Technical Support Document for Derivation of Health-Based Guidance Values for Metals in Spices

Bureau of Toxic Substance Assessment

Center for Environmental Health

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Introduction

At the request of the New York State Department of Agriculture & Markets (NYS A&M), we derived health-based guidance values for arsenic, cadmium, chromium, and lead in spices used in food preparation. To derive these health-based guidance values, we used procedures that are consistent with the general risk assessment paradigm (NRC, 1983; US EPA, 2019). A basic overview of the risk assessment paradigm and how it was applied to the task of developing health-based guidance values from metals in spices follows.

- **Hazard Identification**

  Hazard identification determines the types of adverse health effects that can be caused by exposure to a chemical, and characterizes the quality and weight of evidence supporting this identification. We reviewed and summarized information on the long-term health effects of arsenic, cadmium, chromium, and lead based on animal and human toxicity studies. These summaries are presented in Appendix A.

- **Dose-response Assessment**

  Dose-response assessment quantifies the likelihood and severity of adverse health effects (the responses) in relation to the amount and condition of exposure to an agent (the dose). To accomplish this, we obtained oral toxicity values from published assessments for arsenic, cadmium, chromium, and lead. These values are based on quantitative dose-response relationships between oral exposure to these metals[1] and the incidence or severity of adverse health effects reported in animal or human toxicity studies. We evaluated oral toxicity values based on the strength of their underlying data and the quality of methods used in their derivation. Separate toxicity values were selected for cancer and noncancer

[1] We use "metals" throughout for convenience to refer to the four elements that are the focus of this report, recognizing that, strictly speaking, arsenic is a metalloid.

health effects if both were available. Dose-response assessment details are presented in Appendix B.

- **Exposure Assessment**

  Exposure assessment is the process of measuring or estimating the magnitude, frequency, and duration of human exposure to an agent in the environment. To characterize the potential for oral exposure to the metals of concern in spices used for food preparation, we estimated rates of daily consumption of spices for children, adults and different race/ethnic(ity) groups using available data from the scientific literature and other authoritative sources. We estimated central tendency and high-end consumption rates based on daily oral exposure to multiple spices. Exposure assessment details are presented in Appendix C.

- **Risk Characterization**

  Risk characterization summarizes and integrates information from the hazard identification, dose-response assessment, and exposure assessment components of the risk assessment process to synthesize an overall conclusion about risk. In this case, risk characterization involved deriving health-based guidance values for the metals of concern in spices by choosing a target degree of minimal or insignificant risk, and then working "backwards" to obtain an associated concentration of each metal in spices.[2] This involves using information obtained about spice consumption from the exposure assessment with toxicity values for each metal from the dose-response assessment to calculate the concentration of each metal in spices that would result in a daily dose equal to the corresponding toxicity value. The resulting health-based guidance values correspond to the concentration of metals in spices that are expected to be without an appreciable risk of deleterious non-cancer effects, or at a *de minimis* level (commonly one-in-one-million) for cancer risk, given average or high-end daily consumption of spices in foods. We calculated health-based guidance values using the cancer and noncancer toxicity values selected in the dose-response assessment (Appendix B), and the estimated daily spice consumption rates for

[2] As opposed to the situation where there is a known concentration of a contaminant in an environmental medium and the degree of risk represented by exposure to the contaminant at that concentration is evaluated.

children, adults and different race/ethnic(ity) groups calculated in the exposure assessment (Appendix C). The health-based values are expressed as a concentration of each metal in any spice. Long-term daily consumption of food prepared with spices containing metals at or below these guidance values is expected to be without significant risk of adverse effects.

Calculation of Health-Based Guidance Values for Metals in Spices

As mentioned, a health-based guidance value is derived from the integration of a dose-response assessment with an exposure assessment. Dose-response assessments can be developed for noncancer and cancer health effects. Because of underlying assumptions about the different toxicological processes that cause cancer versus noncancer effects, the corresponding dose-response assessment results differ. A noncancer dose-response assessment results in what is known as a Reference Dose. The analogous cancer assessment results in a dose associated with a lifetime cancer risk of one-in-one-million.[3] We calculated noncancer and cancer health-based guidance values using the equations below. These equations are also represented in schematic diagrams shown in Appendix D (Supplementary Figures 1 and 2).

Equation 1.

Noncancer Health-Based Guidance Value

$$= \left(\frac{\text{Reference Dose}}{\text{Total Spice Consumption Rate}}\right) \times \text{Relative Source Contribution} \times \text{Conversion Factor}$$

Where:

Reference Dose = a noncancer toxicity value expressed in units of milligrams of chemical ingested, per kilogram body weight, per day (mg_{chem}/kg_{bw}/day). A reference dose is an estimate of chronic daily oral exposure in humans (including sensitive groups) that is likely without appreciable risk of adverse noncancer health effects.

Total Spice Consumption Rate = an estimate of the amount of spices eaten daily per kilogram of body weight and is expressed in units of mg_{spice}/kg_{bw}/day. The total

[3] By long-held convention, one-in-one-million lifetime cancer risk is considered to a *de minimis* or insignificant risk level

spice consumption rate represents the sum of the central tendency or high-end spice consumption rates of multiple spices based on individual spice consumption data from the Food Commodity Intake Database (FCID, 2019), and body weight data from the Exposure Factors Handbook (US EPA, 2011) for adults and children. See *Appendix C Equation 1* for additional details.

Relative Source Contribution = a fraction of the reference dose for a given metal that is assigned to a particular exposure source (such as spices), acknowledging that other exposure sources (e.g., water, soil, consumer products) can also be present and contribute to overall exposure. A default relative source contribution of 20% of the reference dose for each metal was assumed, effectively lowering the health-based guidance value an additional 5-fold below the value that would correspond to the reference dose itself.

Conversion Factor = (1×10^6 milligrams$_{spice}$ / 1 kilogram$_{spice}$)

Equation 2.

Cancer Health-Based Guidance Value

$$= \left(\frac{10^{-6}\ \text{Cancer Risk Level}}{\text{Total Spice Consumption Rate}}\right) \times \text{Conversion Factor}$$

Where:

10^{-6} Cancer Risk Level = the oral dose (in units mg$_{chem}$/kg$_{bw}$/day) corresponding to an excess lifetime cancer risk of one-in-one million and is calculated from a Cancer Potency Factor (expressed in units of per (mg/kg$_{bw}$/day) or (mg/kg$_{bw}$/day)$^{-1}$) as follows:

$$= \frac{1 \times 10^{-6}}{\text{Cancer Potency Factor}}$$

Total Spice Consumption Rate = an estimate of the amount of spices eaten daily per kilogram of body weight and is expressed in units of mg$_{spice}$/kg$_{bw}$ /day. The total spice consumption rate represents the sum of the central tendency or high-end spice consumption rates of multiple spices based on spice consumption data from the Food Commodity Intake Database (FCID), and body weight data from the Exposure Factors Handbook (US EPA, 2011) for adults. See *Appendix C Equation 2* for additional details.

Conversion Factor = (1×10^6 milligrams$_{spice}$ / 1 kilogram$_{spice}$)

Using the equations shown above, and the cancer and noncancer toxicity values selected in Appendix B (Table B.1), we calculated several candidate health-based guidance values for metals in spices using total spice consumption rates for different age groups (adults and children), race/ethnic(ity) groups, and different groupings of spices (i.e., including or excluding sesame seed). In the exposure assessment (Appendix C), we identified 8 spices for calculating total spice consumption rates. The total spice consumption rates we used to calculate candidate health-based guidance values for metals in spices are central tendency (mean) estimates summed across multiple spices, and high-end (90th percentile) estimates summed across multiple spices. To evaluate average spice consumers, high-end consumers (i.e., individuals at the upper end of the exposure distribution), sensitive subgroups (e.g., children), as well as specific subpopulations (e.g., race/ethnic(ity) groups), we used a total of 16 exposure scenarios in the development of candidate health-based guidance values for metals in spices (summarized in Appendix D Supplementary Tables 3, 4, 5 and 6). As described in the exposure assessment (Appendix C), central tendency and high-end total spice consumption rates are generally higher in young children (less than 7 years of age) compared to older children and adults.[4] In addition, certain race/ethnic(itcy) groups (e.g., classified in the FCID database as "other, Hispanic", "non Hispanic Black", "Mexican American" and "other races") had higher central tendency and upper-end total spice consumption rates than the estimated rates for all races combined. The exposure assessment also showed that sesame seed was the spice with the highest consumption rate across all age groups. Therefore, we calculated total spice consumption rates including sesame seed and excluding sesame seed in order to evaluate the influence of sesame seed consumption on total spice consumption rates.

After considering differences in spice consumption rates across the various exposure scenarios, we selected central tendency consumption estimates for children (averaged from birth to < 7 years of age) for all race/ethnic(ity) groups and genders, and central tendency consumption estimates for adults (all race/ethnic(ity) groups, all genders) as the basis for calculating

[4] The average total consumption rate for children age 0 to < 7 for all spices (including sesame seed) is 114 mg/kg-BW/day. For comparison, inclusion of older children in the calculation of the average total consumption (i.e., for children 0 to < 8 years of age, all spices) would result in a total spice consumption rate of 106.4 mg/kg-BW/day, which would have resulted in slightly higher (less conservative) noncancer health-based values for spices.

recommended cancer and noncancer health-based guidance values (Table 1) for metals in spices. Among the key factors we considered in selecting these consumption estimates were the population sample size and the number of spices with adequate data to contribute to total spice consumption rates. Central tendency estimates for all races and all genders provided the most robust exposure estimates in terms of having the largest sample sizes for each spice and allowing for the inclusion of all 8 of the evaluated spices in the calculations of total spice consumption rates. Larger datasets are less likely to be highly influenced by small numbers of unusually high or low consumers of spices, and therefore, may provide more stable and representative estimates of total spice consumption rates. Upper percentile spice consumption rates for children have adequately large datasets for some spices (Appendix D, Supplementary Tables 3 and 4), but high-end estimates of total spice consumption rates are more limited compared to the central tendency estimates because upper percentile estimates were only available in the FCID database for 4 of the 8 considered spices.

In addition to considering the age groups and race/ethnic(ity) groups upon which to base final selected health-based guidance values for metals in spices, we also considered whether to include sesame seed in calculations of total spice consumption rates because of its large contribution to most spice consumption estimates. Based on preliminary sampling data collected by NYS A&M and studies in the scientific literature showing that sesame seed can contain measurable levels of metals (Angelova et al., 2005; Hao et al., 2011), the recommended cancer and noncancer health-based values were calculated using total spice consumption rates that included sesame seed consumption data (Table 1). Basing guidance values on all spices with robust consumption rate data (including sesame seed) addresses the potential for people to have concurrent daily exposure to several different spices and spice mixtures, and for those spices to contribute to the overall total daily dose of metals from spice consumption.

Table 1. Summary of Recommended Noncancer and Cancer Health-Based Values

for Metals in Spices

Chemicals	Noncancer Health-Based Spice Comparison Values (mg/kg)[a]		Cancer Health-Based Guidance Value (mg/kg)[a]
	Child Exposure Scenario[b]	Adult Exposure Scenario[c]	
arsenic (inorganic)	0.53	2.4	0.0030
cadmium	0.019	0.61	0.45
chromium (hexavalent form only)[d]	1.6	5.5	0.058
lead	0.21	--	2.64

[a]Units in mg/kg represent milligrams of metal per kilogram of spice (mg_{metal}/kg_{spice}), which is equivalent to units expressed in parts per million (ppm).

[b]Total spice consumption rate (114 $mg_{spice}/kg\text{-}_{bw}/day$) is based on the sum of mean spice consumption rates for 8 spices with available estimates (hereafter referred to as "available spices") for children ages 0 to < 7 for all races, all genders.

[c]Total spice consumption rate for adults (32.9 $mg_{spice}/kg\text{-}_{bw}/day$) is based on the sum of mean spice consumption rates for 8 available spices.

[d]hexavalent chromium or chromium (VI) is the more toxic form of chromium; trivalent chromium [chromium (III)] is an essential dietary element and is substantially less toxic than chromium (VI).

Recommendations

- In order to be protective of cancer and noncancer health effects for children and adults from consumption of spices, we recommend that the lower end of the range of possible health-based values for each metal (shown in Table 1) be considered when adopting screening or action levels for metals in spices. For example, selection of the lowest value for cadmium (i.e., 0.019 mg/kg), which is a noncancer health-based value calculated using a child exposure scenario, is also health-protective of cancer effects as well as noncancer effects in adults from the daily consumption of spices.

- From a strictly health-based perspective, the lowest value for each metal in Table 1 would be considered the most protective. However, some of the calculated health-based guidance values could be lower than typical background levels of those metals in spices. Therefore, we recommend that NYS A&M rely upon the distribution of background metal levels in spices that NYS A&M has compiled and that might be available from other sources. This

information will help inform NYS A&M's implementation of action levels for metals in spices based on health-based guidance values or backround levels as appropriate.

- We recommend that NYS A&M consider the need to speciate the forms of chromium and arsenic that are present in spices. Different forms of these metals differ significantly in their toxic potency. Inorganic arsenic and hexavalent chromium are the more toxic forms compared to organic arsenic or trivalent chromium, respectively. Therefore, analysis that specifically reports chromium (VI)[5] and inorganic arsenic in spices would be more appropriate for comparison with recommended health-based guidance values than analysis reporting total arsenic or total chromium.

- Although we evaluated lead in this assessment (Appendix A and B), and proposed a noncancer health-based guidance value (Table 1), it is important to recognize that this assessment differs from other noncancer assessments because of the absence of a threshold for the human health effects of lead; in particular, for effects on the developing central nervous system of children. While the health-based guidance value we developed is based on health protective methods and assumptions, the absence of a threshold means that we cannot assume that exposure below the health-based guidance value is without appreciable risk as we would for other noncancer health-based guidance values. Due to absence of a threshold for the toxicological effects of lead, and the presence of many other potential sources of exposure to lead (e.g., air, soil, indoor dust, water), it is prudent to manage risks for lead in spices by adopting screening or action levels as low as achievable relative to background levels in spices.

- As with the neurodevelopmental effects of lead exposure, a threshold is assumed to be absent for cancer effects from arsenic and hexavalent chromium exposure. Given the lack

[5] For comparison, we calculated noncancer health-based values using toxicity values for chromium (III) soluble salts and these values are several fold higher (i.e., 8.8 mg/kg and 30.4 mg/kg based on child and adult exposure scenarios, respectively) than health-based values based on chromium (VI) (Table 1), and orders of magnitude higher for chromium (III) insoluble salts (i.e., 2632 mg/kg and 9119 mg/kg based on child and adult exposure scenarios, respectively). In addition, chromium (III) is an essential dietary element and this analysis does not address recommendations for minimum daily intake. The health effects of chromium (III) and chromium (VI) compounds are summarized in Appendix A. Toxicity values are summarized in Appendix B.

of a threshold for the cancer effects of these metals, and evidence for increased cancer risk from oral exposure to inorganic arsenic during early life-stages (see health effects summary in Appendix A), it is prudent to manage risks from exposure to arsenic and hexavalent chromium by adopting screening or action levels close to the one-in-one million *de minimis* risk level, if feasible, or at levels consistent with background concentrations of arsenic and hexavalent chromium in spices.

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Summary of the Health Effects of Inorganic Arsenic, Cadmium, Chromium Compounds and Lead

1. Health Effects of Arsenic

Arsenic and arsenic compounds are naturally occurring and widely distributed in the environment. Arsenic compounds can be found in all environmental media including soil, water, plants and air from both natural sources (e.g., volcanic action, erosion of rocks, and forest fires) as well as human activities such as mining, ore smelting and industrial uses. Arsenic compounds can be found in environmental media in organic and inorganic forms. The more common form of arsenic found in the environment is inorganic arsenic such as arsenic trioxide, arsenate, arsenite and arsenic sulfide compounds. Inorganic arsenic compounds have been used in paint pigment, wood preservatives, and commercial pesticides. When arsenic is combined with carbon and hydrogen, it is referred to as organic arsenic. Foods can contain organic and inorganic arsenic compounds from both natural and human-made sources (ATSDR, 2007a, 2015; CDC, 2017, IARC, 2012).

In studies of human populations exposed via drinking water, a characteristic effect of long-term oral exposure to high levels of arsenic was the development of hyperpigmentation and hyperkeratosis (i.e., darkening and thickening) of the skin on the hands and feet. Long-term oral exposure to arsenic is also associated with cardiovascular effects, including increased incidences of peripheral vascular effects such as cyanosis and Blackfoot Disease, cerebrovascular disease, ischemic heart disease, and high blood pressure (ATSDR, 2007a; NRC, 1999). Other effects linked to chronic oral exposure to arsenic include gastrointestinal, neurological, hematological, hepatic, and endocrine effects, developmental and reproductive effects (miscarriages, stillbirths, preterm births, and low birth weights) and reduced IQ in children (ATSDR, 2007a; NRC, 1999).

Long-term exposure to high levels of arsenic in drinking water is associated with increased risk of skin, lung and bladder cancer (NTP, 2016). Based on convincing evidence for arsenic carcinogenicity in human epidemiological studies, IARC (2004, 2012), NTP (2016) and US EPA IRIS (2019a) identify inorganic arsenic compounds as carcinogenic to humans. Human epidemiological studies also show an association between early-life exposures to arsenic in drinking water and increased risk for cancer in adulthood (NYS HHFS, 2015a; Marshall et al., 2007; Smith et al., 2006, 2012). Studies on adult (post-weaning) exposures of animals have not clearly demonstrated the carcinogenicity of arsenic and several studies report negative findings (ATSDR, 2007a; US EPA IRIS, 2019). However, in animal studies where exposures occurred during early life stages (i.e., transplacental exposures (in utero only) or whole-life exposures (in utero, throughout lactation, and post-weaning through adulthood)), arsenic caused cancer in adult mice (NYS HHFS, 2015a; Ahlborn et al., 2009; Tokar et al., 2011; Waalkes et al., 2003, 2006, 2007, 2009). Overall, evidence from human and animal studies indicates that exposure to arsenic during childhood poses a greater lifetime oncogenic risk than exposure during adulthood.

2. Health Effects of Cadmium

Cadmium is a soft silver-white metal that is naturally present in the earth's crust in zinc, lead and copper ores (ATSDR, 2012a). Cadmium compounds can be found the environment from both natural sources (e.g., weathering of rocks and volcanic emissions) and human activities (EFSA, 2009a). Releases of cadmium into the environment from industrial and agricultural sources (such as waste incineration, metal production activities, fossil fuel combustion, sewage sludge disposal and fertilizer use) are the main sources of cadmium in air, water and soil. Wet and dry deposition of cadmium released in air contributes to cadmium concentrations in both soil and water. Cadmium is also found in a variety of foods (meats, nuts, cereals, and vegetables) and can get into plants via uptake from cadmium-containing soil (ATSDR, 2012a).

The primary target organ for the long-term effects of oral exposure to cadmium is the kidney. In human epidemiological studies of workers occupationally exposed to cadmium and in studies of long-term dietary exposure to cadmium in general populations, urinary concentrations of cadmium have been associated with increased urinary excretion of several biomarkers for renal tubular dysfunction (EFSA, 2009a). In studies of laboratory animals, oral exposure to high levels of cadmium caused effects on the kidneys, blood, liver, heart and the immune and nervous systems and had effects on the unborn offspring of animals exposed during pregnancy (ATSDR, 2012a).

The weight of evidence for the carcinogenicity of cadmium from oral exposure comes from studies in laboratory animals. In two long-term studies of oral exposure to high levels of cadmium (via the diet or drinking water), increased incidences in testicular tumors were reported in male rats from two different strains (NYS HHFS, 2015b; Waalkes and Rehm, 1992; Waalkes et al., 1999b). The evidence that exposure to cadmium causes testicular cancer in male rats is strengthened by several studies showing that subcutaneous exposure to single or multiple cadmium doses caused interstitial-cell testicular tumors in several strains of male rats (NYS HHFS, 2015b; Waalkes et al., 1988, 1989, 1997, 1999a, 2000).

3. Health Effects of Chromium

Chromium is a naturally occurring metal found in rocks, plants, and soil. Chromium can exist in the environment in several different forms and can occur from both natural sources and human activities. Industrial releases constitute the largest source of chromium in environmental media such as air, water and soil. The two primary forms of chromium found in the environment are hexavalent chromium (chromium (VI)) and trivalent chromium (chromium (III)). Chromium (VI) and chromium (III) compounds have several industrial and commercial uses such as chrome plating, production of dyes and pigments, leather tanning, and wood preserving. Chromium (VI) typically occurs in the environment from industrial sources, whereas chromium (III) can be found from both natural and industrial sources. Chromium (III) is also an essential dietary nutrient (NIH, 2018). Small amounts of chromium (III) are required by the human body for normal energy metabolism. Low levels of chromium (III) compounds are found naturally in several foods such as fruits, vegetables, nuts and meats (ATSDR, 2012b).

The oral toxic potency of chromium (III) and chromium (VI) differs. Chromium (VI) is the more toxicologically potent form of chromium. In humans chronically exposed to chromium (VI) through ingestion of drinking water, effects on the gastrointestinal system (e.g., oral ulcers, diarrhea, abdominal pain, indigestion, and vomiting) have been reported. Chronic and subchronic oral exposures to chromium (VI) caused effects on the gastrointestinal system, reproductive system, hematological system, liver, and kidneys of laboratory animals. Chromium (VI) also caused developmental effects in the offspring of dams orally exposed during gestation. In studies of laboratory animals, long-term oral exposure to chromium (VI) via drinking water caused increased incidence of tumors in the oral cavity of rats and tumors in the gastrointestinal tract of mice (ATSDR, 2012b; EFSA, 2014).

By contrast, the available chronic oral toxicity studies on chromium (III) in laboratory animals are largely negative for effects including gastrointestinal, hematological, hepatic and renal effects. Conflicting results have been reported in reproductive and developmental toxicity studies of oral exposure to chromium (III) with some studies reporting effects, and other studies reporting an absence of effects (ATSDR, 2012b; EFSA, 2014).

4. Health Effects of Lead

Lead is a naturally occurring metal that is found in the earth's crust. Because of its physical/chemical properties (e.g., malleability, corrosion resistance, high density, and low melting point), lead and lead compounds have been widely used in a variety of products including gasoline, paints, ceramics, pipes, solders, batteries and cosmetics. Due primarily to human activity, such as burning of fossil fuels, mining and manufacturing, lead and lead compounds are ubiquitous in the environment. Lead can be found in both indoor and outdoor environments in media including air, water, soil, and dust. Lead can also be found in foods, such as vegetables, through uptake from contaminated soils or from atmospheric deposition onto plant surfaces. Lead can also leach into foods that are stored in improperly glazed pottery or ceramic dishes, and from leaded-crystal glassware (ATSDR, 2007b).

It has been well established in the scientific literature that children are the most sensitive to the health effects of lead. Long-term exposure to lead in children can cause several developmental effects, particularly on cognition, such as decreases in intelligence quotient (IQ) scores and academic achievement, as well as increases in behavioral effects such as hyperactivity and decreased attention. There is no threshold for the health effects of lead in children, meaning there is no level of exposure to lead in children below which there are no risks for adverse health effects. Health effects in children can occur even at low blood lead levels (BLLs), and some effects have been reported at BLLs less than 5 micrograms per deciliter (mcg/dL) (NIEHS, 2013). In pregnant women, exposure to lead is associated with reduced postnatal growth and height, and delayed puberty in offspring (ATSDR, 2017; NIEHS, 2013). High levels of exposure to lead in pregnant women is also associated with miscarriage (ATSDR, 2007b). Long-term exposure to lead in adults is associated with kidney, cardiovascular, reproductive, hematological and central nervous system effects (ATSDR, 2017; NIEHS, 2013).

In studies of laboratory animals, repeated exposure to lead causes effects on several biological systems such as the kidneys and the cardiovascular, hematological, reproductive and central

nervous systems. Lifetime exposure to lead via the diet caused kidney tumors in male and female rats. In addition, exposure to lead during gestation and lactation caused developmental effects in offspring. (ATSDR, 2007b; CA EPA, 2009).

Selection of Noncancer and Cancer Toxicity Values

1. Introduction

Previous toxicological assessments of arsenic, cadmium, lead and chromium (trivalent and hexavalent compounds) have been performed by New York State Department of Health (NYS DOH), wherein available oral cancer and noncancer toxicity values were identified, summarized, evaluated, and in some cases derived (NYS HHFS, 2015a,b,c,d and NYS DEC/DOH, 2006). These assessments recommended the use of specific oral cancer and noncancer toxicity values for evaluating the human health risks of long-term exposure to arsenic, cadmium, lead and chromium (trivalent and hexavalent forms) in environmental media such as water and soil. These recommended oral cancer and noncancer toxicity values were considered in this toxicological assessment of metals in spices. We also performed an updated internet search of oral cancer and noncancer toxicity values from national and international authoritative bodies. Examples of authoritative body sources for toxicity values are provided in Appendix D (Supplementary Table 1). Toxicity values were selected based on an evaluation of the technical aspects of derivations such as the scientific quality of the key studies, choice of the critical health effect(s) (i.e., points-of-departure), methods used to extrapolate from high doses to low doses, application of uncertainty factors (UFs), or other key factors of the derivations. A summary table of selected values is provided below.

Appendix Table B.1.
Summary of Selected Noncancer and Cancer Toxicity Values[a]

Chemicals	Noncancer Toxicity Value (mg/kg/day)	Cancer Potency Factor (per mg/kg/day)
arsenic (inorganic)	3.0×10^{-4}	10.3
cadmium	1.1×10^{-5}	0.067
chromium III (soluble salts)	5.0×10^{-3}	--
chromium III (insoluble salts)	1.5	--
chromium VI	9.0×10^{-4}	0.53
Lead[b]	1.2×10^{-4}	0.012

[a]Units in mg/kg/day represent milligrams of metal per kilogram body weight per day.

[b]There is no threshold for the health effects of lead. This comparison value is presented for screening purposes to assist in the identification of lead contaminated spices, and thus, to minimize potential exposure to lead.

1.1 Selection of Noncancer Toxicity Values

1.1.1 Selection of a Noncancer Toxicity Value for Inorganic Arsenic

The available noncancer toxicity values for arsenic are summarized in Appendix D (Supplementary Table 2). US EPA IRIS (2019a), ATSDR (2007a) and CA EPA (2004) based noncancer toxicity values on human health effects reported in epidemiological studies of Taiwanese populations. US EPA and ATSDR derived the same RfD (3×10^{-4} mg/kg/day) based on increased incidence of hyperpigmentation, keratosis, and possible vascular complications observed in ecological studies of Taiwanese populations chronically exposed to high levels of arsenic in contaminated drinking water wells (Tseng et al., 1968; Tseng, 1977). The US EPA and ASTDR identified the arithmetic mean arsenic concentrations in water corresponding to the NOEL[6] and LOEL[6] for these effects as 0.009 milligrams per liter (mg/L) and 0.17 mg/L, respectively. Using exposure assumptions for Taiwanese populations (i.e., water consumption rate, body weight, and dietary intake of arsenic from staple foods in the Taiwanese diet),[7] US EPA and ASTDR estimated daily oral doses of 0.0008 mg/kg/day (NOEL) and 0.014 mg/kg/day (LOEL), respectively.

The key study selected as the basis of the CA EPA's noncancer public health goal for arsenic in drinking water (Chiou et al., 1997) evaluated the relationship between prevalence of cerebrovascular disease and oral exposure to arsenic in residents of Lanyang Basin on the northeast coast of Taiwan using logistic regression. Chiou et al. (1997) reported a statistically significant dose-response relationship between exposure to arsenic (i.e., drinking water concentrations of arsenic, and cumulative exposure estimates) and prevalence of cerebrovascular disease and cerebral infarction after adjusting for age, sex, hypertension, diabetes mellitus, cigarette smoking, and alcohol consumption. CA EPA's (2004) public health goal for the noncancer effects of arsenic was based on benchmark dose modeling to determine the 95% lower confidence limit on the cumulative dose [3.0 (mg/L)yr] associated with a 1% increase in cerebrovascular disease in the exposed population (the LED_{01} or $BMDL_{01}$).[6] CA EPA (2004) calculated a health-based value of 0.9 mcg/L for arsenic in drinking water by applying a total UF of 10 (an UF of 3 for inter-human variation and an UF of 3 to "extrapolate to a level of negligible risks") to the LED_{01}, assuming a 70-year exposure duration, and a relative source contribution of 0.2, which allocates 20% of the cumulative lifetime dose to drinking water. CA EPA's derivation of a public health goal in drinking water, did not specifically include derivation an RfD. However, in a previous risk assessment, the New York State Department of Health calculated an RfD (4.0×10^{-4} mg/kg/day) from CA EPA's health-based water value for arsenic using exposure estimates for Taiwanese populations (i.e., drinking water consumption rate, body weight, and arsenic daily dose from food)[8] (NYS HHFS, 2015a).

Overall, the toxicity values derived by US EPA IRIS (2019a), ATSDR (2007a) and CA EPA (2004) are of similar quality with respect to the methods used to derive values, including

[6] Definition of terms: Lower-bound on the benchmark dose (BMDL); Lower-bound effective dose (LED); No-observed-effect level (NOEL); Lowest-observed-effect level (LOEL);

[7] US EPA and ATSDR daily dose estimates based on water concentrations at the LOEL and NOEL assume that a Taiwanese adult weighs 55-kg, consumes 4.5 L of water per day (3.5 L from drinking water and 1 L from cooking/food preparation), and has an arsenic intake of 0.002 mg/day from food such as rice and sweet potatoes.

[8] To calculate an RfD from CA EPA's health-based value for arsenic in drinking water, we used the same exposure assumptions as US EPA and ATSDR (i.e., assuming a Taiwanese adult weighs 55-kg, consumes 4.5 L of water per day (3.5 L from drinking water and 1 L from cooking/food preparation), and has an arsenic intake of 0.002 mg/day from food such as rice and sweet potatoes).

the selection of key studies and toxicity endpoints used for dose-response assessment. The toxicity values are both suitable for use in deriving health-based guidance values for arsenic in spices. CA EPA's derivation is strengthened by use of a human study with individual estimates of cumulative exposure and the use of benchmark dose modeling (rather than point estimates such as a LOEL or NOEL). The key study used in CA EPA's derivation also accounted for potential confounding factors (i.e., age, gender, hypertension, diabetes mellitus, cigarette smoking, and alcohol consumption), which strengthens confidence in the dose-response relationship between cumulative arsenic exposure and the incidence of cerebrovascular disease. However, there is some uncertainty in the documentation of the uncertainty factors used in CA EPA's calculation.[9] Therefore, we selected US EPA's RfD of 3.0×10^{-4} mg/kg/day for use in deriving noncancer health-based guidance values for arsenic in spices.

1.1.2 Selection of Noncancer Toxicity Values for Cadmium

The available oral noncancer toxicity values for cadmium (summarized in Appendix Table D, Supplementary Table 2) are all based on the relationship between internal measures of exposure (e.g., urinary cadmium concentrations or cadmium levels in the renal cortex) and sensitive biomarkers for kidney effects in humans.[10] The two most robust and well documented values were derived by ATSDR (2012a) and EFSA (2009a) and are based on meta-analyses of observed dose-response relationships from several human studies (NYS DEC/DOH, 2006; NYS HHFS, 2015b).

ATSDR performed a meta-analysis of seven key studies that evaluated the dose-response relationship between urinary cadmium concentrations in European, Japanese or Chinese populations and an increased prevalence of abnormal levels of biomarkers for kidney toxicity (i.e., beta-2-microglobulin and human complex forming glycoprotein). In total, benchmark dose estimates from eleven datasets stratified by geographic location and separated by gender, when possible, were considered in ATSDR's analysis. ATSDR selected the lowest of the eleven lower-bound benchmark internal dose estimates as the point of departure for deriving an RfD for cadmium. The lowest estimated 95% lower confidence limit on the urinary cadmium dose associated with a 10% excess risk of low molecular weight renal proteinuria ($UCDL_{10}$)) is 0.5 micrograms of cadmium per gram of creatinine (mcg cadmium/g creatinine) based on studies of cadmium exposure in European populations. ATSDR then used a multicompartment pharmacokinetic model to estimate the chronic dietary cadmium doses (0.33 mcg/kg/day and 0.70 mcg/kg/day in females and males, respectively) corresponding to the cadmium urinary concentration at the point of departure (0.5 mcg cadmium/g creatinine). Although the pooled-analysis is based on seven large-scale population-based studies that may have included sensitive subpopulations, ATSDR applied a UF of 3 for human variability based on the concern that people with diabetes may be more sensitive to the kidney effects of cadmium and may have been underrepresented in the dose-response analysis as some of the studies excluded people with

[9] In the equation showing the calculation of the public health goal for arsenic, CA EPA used a total uncertainty factor of 10. However, in the text, the total UF is cited as 30 (10 for human variability and 3 to "extrapolate to a level of negligible risks".

[10] Human biomarkers for kidney effects include urinary beta-2-microglobulin or human complex forming glycoprotein.

diabetes. Using the UF of 3 and the dietary cadmium dose corresponding to the $UCDL_{10}$ in females (0.33 mcg/kg/day), ATSDR calculated an RfD of 1 x 10^{-4} mg/kg/day.

EFSA conducted a meta-analysis of the dose-response relationship between urinary cadmium levels and urinary beta-2-microglobulin levels based on group averages from 35 human studies. EFSA estimated lower confidence limit benchmark doses for a 5 percent increase in prevalence of elevated urinary beta-2-microglobulin ($BMDL_{05}$ values) for whole study populations and for non-occupationally exposed people over 50 years of age. In addition, EFSA used both statistical and biological cut-offs for identifying elevated levels of urinary beta-2-microglobulin for use in dose-response modeling.[11] Taking into consideration the range of $BMDL_{05}$ values obtained using the four modeling approaches, EFSA selected an overall group-based $BMDL_{05}$ of 4 mcg cadmium/g creatinine as the point of departure for calculating a noncancer toxicity value for cadmium. EFSA applied a chemical-specific adjustment factor[12] of 3.9 to account inter-individual variation in urinary clearance of cadmium within study populations, resulting in an internal cadmium dose of 1 mcg cadmium/g creatinine. Using a one-compartment pharmacokinetic model, EFSA calculated the average daily dietary intake (i.e., an RfD of 3.6 x 10^{-4} mg/kg/day) that would result in 95% of the exposed population having a urinary cadmium concentration not exceeding the internal cadmium dose of 1 mcg cadmium / g creatinine in urine.

The methods used by ATSDR and EFSA to derive RfDs are robust and are of similar quality in that both values are based on analyses of multiple human studies that included direct measurements of urinary cadmium and kidney biomarker concentrations. The EFSA derivation included a larger number of studies, but the pooled analysis is based on study group means and statistical adjustment (i.e., the chemical specific UF of 3.9) to account for inter-individual variation in the urinary cadmium concentration at the estimated $BMDL_{05}$. Although the ATSDR derivation is based on fewer total studies than EFSA's derivation, it included use of data points from individual study participants from each study, and the results were aggregated geographically and separated by gender (when possible) in order to choose the most sensitive point of departure. EFSA and ATSDR both used pharmacokinetic models to extrapolation from an internal measure of exposure (i.e., urinary cadmium concentrations) to oral doses corresponding to the BMDLs. However, EFSA used a one-compartment model, while ATSDR used a multi-compartment model. Although the overall method is similar for the two derivations, ATSDR's use of individual study-participant data for dose-response modeling in their pooled analysis and the use of a multi-compartment pharmacokinetic model are slightly preferred analytical approaches. Therefore, we selected ATSDR's RfD (1 x 10^{-4} mg/kg/day) for use in deriving noncancer health-based guidance values for cadmium in spices.

ATSDR's derivation used pharmacokinetic modeling assumptions based on adults[13]. Therefore, we also selected the CA EPA (2005) child-specific reference dose (chRfD) of (1.1 x

[11] EFSA used a urinary level of 300 mcg beta-2-microglobulin per gram creatinine as the biologically based cut-off for estimating $BMDL_{05}$ values. The statistically based cut-off value was the 95th percentile of the beta-2-microglobulin distribution at background urinary cadmium concentrations.

[12] The chemical-specific adjustment factor assumes lognormal distribution of urinary cadmium and an inter-individual coefficient of variation of 100%.

[13] Absorption of ingested cadmium was assumed to be 5% in males and 10% in females.

10^{-5} mg/kg/day) for use in deriving noncancer health-based guidance values for cadmium. CA EPA (2005) chRD is the only child-specific oral toxicity value for cadmium derived by an authoritative body. The point-of-departure is kidney toxicity[14] (1 x 10^{-3} mg/kg/day) observed in a cross-sectional study of Belgium populations (Buchet et al., 1990).[15] CA EPA used of a total UF of 90 (10 for intrahuman variability, 3 for use of a LOEL based on minimal effect, and an additional factor of 3 to account for differences in gastrointestinal absorption between children and adults)[16]. CA EPA used an additional UF for children-based Alexander et al. (1974), which reported an average gastrointestinal absorption of 55% in children from early infancy to 8 years of age.

1.1.3 Selection of a Noncancer Toxicity Value for Chromium (III)

The available oral noncancer toxicity values for chromium (III) are summarized in Appendix D (Supplementary Table 2). US EPA IRIS (2019b) and EFSA (2014) derived RfDs for chromium (III) based on the absence of toxicological effects in chronic studies in rats exposed to cadmium through the diet. We selected the US EPA RfD of 1.5 mg/kg/day as the basis of health-based guidance values for insoluble chromium (III) salts in spices, and the RIVM RfD of 5.3 x 10^{-3} mg/kg/day for deriving health-based guidance values for water-soluble chromium III compounds and for chromium III compounds of unknown form (i.e., when it is not known whether chromium III compounds are soluble or insoluble). The selection of RfDs derived by US EPA and EFSA for deriving noncancer health-based guidance values for chromium (III) in spices is consistent with previous recommendations by the NYS Department of Health (NYS DEC/DOH, 2006).

1.1.4 Selection of a Noncancer Toxicity Value for Chromium (IV)

The available oral noncancer toxicity values for chromium VI are summarized in Appendix D (Supplementary Table 2). Only two of the available reference doses, from ATSDR (2012b) and CA EPA (2011), are based on observed effects in animal studies. The other available RfDs are based on studies in animals that did not report any toxicological effects, and are thus, less preferred for selection as the basis of health-based guidance values for chromium (VI) in spices.

Overall, the toxicity values from ATSDR (2012b) and CA EPA (2011) are of similar quality with respect to the methods used to derive values, including the selection of key studies, and toxicity endpoints used as the point of departure for high to low dose extrapolation. Both RfDs are based on liver effects (i.e., chronic inflammation and fatty changes in the livers or

[14] The LOEL is the 50-year oral intake (in non-smokers) corresponding to an increased risk (10% probability) of abnormal kidney biomarker levels when cadmium excretion levels exceed 2 to 4 mcg/ 24 hour from which a mean renal cortex concentration of 50 mcg/g (wet weight) was estimated, assuming a gastrointestinal absorption rate of 5%, and a daily excretion rate of 0.005 percent body burden.

[15] Buchet et al. (1990) was also used in ATSDR's pooled analysis.

[16] As part of the justification for the use of an additional uncertainty factor of 3 to address higher gastrointestinal absorption rates in children, CA EPA ran a pharmacokinetic model using an approach similar to Buchet et al, (1990) but assuming a gastrointestinal absorption rate of 55 % for the first 8 years of life. Using these assumptions, the daily oral dose at the LOEL was approximately two-fold lower (0.51 mcg/kg).

indications of diffuse epithelial hyperplasia of the duodenum) in lifetime studies in rats or mice. CA EPA selected a LOEL as the point of departure and applied a total UF of 1000 (10 fold for interspecies extrapolation, 10-fold for intraspecies variability and 10-fold for the use of a LOEL). ATSDR performed benchmark dose modeling of several health endpoints from key studies on oral exposure to chromium (VI). ATSDR selected the lowest $BMDL_{10}$ as the point of departure and used a total uncertainty factor of 100-fold (10 fold for interspecies extrapolation and 10-fold for intrahuman variability) uncertainty factor to compensate for animal-to-human extrapolation (10) and human variation (10). Use of a BMDL (which is estimated based on multiple points on the dose-response curve) as the point of departure for derivation of an RfD is generally a more preferred analytical approach than use of point estimates such as NOELs or LOELs. Therefore, we selected ATSDR's reference dose of 9×10^{-4} mg/kg/day for use in deriving noncancer health-based guidance values for chromium (VI) in spices.

1.1.5 Selection of a Noncancer Toxicity Value for Lead

The available noncancer toxicity values for lead are summarized in Appendix D (Supplementary Table 2). The most sensitive toxicological effect of lead is on the developing central nervous system in children; specifically, there is an inverse dose-response relationship between blood lead levels (BLLs) in young children and performance on Intelligence Quotient (IQ) tests. Therefore, the available toxicological assessments on the effects of lead focus on the relationship between BLLs in children and effects on IQ.

In 1992, the United States Food and Drug Administration (US FDA) derived provisional total tolerable intake levels (PTTILs) for lead in food: 6 mcg/day for small children, 25 mcg/day for pregnant women, and 75 mcg/day for adults (Carrington and Bolger, 1992; US FDA, 1994). The PTTILs derived for children and pregnant women correspond to BLLs of 10 micrograms per deciliter (mcg/dL), which the US FDA (1994) considered to be an effect level based on evidence from studies in children and infants that showed associations between neurodevelopmental effects and BLLs at and below 10 mcg/dL. The US FDA also noted the lack of an apparent threshold for these effects (i.e., a level below which neurodevelopmental effects do not occur). To calculate PTTILs, US FDA estimated the daily doses associated with BLLs of 10 mcg/dL in children and pregnant women (60 mcg/day and 250 mcg/day, respectively) and applied a 10-fold uncertainty factor to account for intra-human variability. The PTTILs derived for adults correspond to a BLL of 30 mcg/dL, a dietary intake level of 750 mcg/day, and application of a 10-fold uncertainty factor for intraspecies variability. However, as part of its efforts to monitor lead in food, foodwares and dietary supplements, the US FDA (2018a) recently derived maximum daily intakes of lead in food (called Interim Reference levels (IRLs)) based on the United States Centers for Disease Control and Prevention (CDC, 2019) reference level for lead in children's blood, which was lowered in 2012 from a BLL of 10 mcg/dl to 5 mcg/dL (FDA, 2018a). The US FDA (2018a) derived an IRL of 3 mcg/day for children and 12.5 mcg/day for adults, which is intended to be protective of potential fetal exposure in women of childbearing age who are unaware of pregnancy. Although specific details of the derivation are not provided in the available documentation, US FDA (2018a) states that IRLs "allow for differences across populations and are set nearly ten-times less than the actual amount of intake from food required to reach the CDC's blood reference level." Based on this information, it can be inferred that the IRLs of 3 mcg/day and 12.5 mcg/day (corresponding to BLLs of 5 mcg/dL) were based on daily

intakes of approximately 30 mcg/day and 125 mcg/day in children and adults, respectively, and application of a 10-fold uncertainty factor for intra-human variability.

In 1987, the Joint Food and Agriculture Organization of the United Nations/World Health Organization Expert Committee on Food Additives (JECFA) (WHO, 1987) derived a Provisional Tolerable Weekly Intake (PTWI) of 25 mcg/kg for lead based on "evidence that a mean daily intake of 3-4 mcg/kg of body weight of lead by infants and children is not associated with an increase in blood lead levels." Specific details about the quantitative basis of derivation were not provided in the documentation of the value (WHO, 1987). In 2011, JECFA conducted a re-evaluation of the toxicity of lead based on more recent studies and a dose-response assessment of neurodevelopmental effects in children at BLLs below 10 mcg/dL (WHO, 2011). JECFA (WHO, 2011) estimated that dietary exposure to lead in children at the previously derived PTWI of 25 mcg/kg (approximately equivalent to 3.6 mcg/kg/day) is associated with a decrease of at least 3 IQ points.[17] The assessment of the dose-response relationship between blood lead levels in children and effects on IQ is based on a pooled analysis (Lanphear et al., 2005) of seven longitudinal cohort studies of 1333 children from the US, Mexico, Kosovo and Australia. Children in the studies were followed from birth or early infancy until 5 to 10 years of age. Full scale IQ tests were administered on children between 4 years and 10 months of age and 7 years of age. Based on the estimated decreases in IQ at the PWTI, JECFA (WHO, 2011) concluded that the PTWI "could no longer be considered health protective" and the value was withdrawn. JECFA (WHO, 2011) further concluded that it was not possible to derive a new PTWI that could be considered health protective due to the absence of evidence suggesting a threshold for the human health effects of lead.

The European Food Safety Authority (EFSA, 2013) Panel on Contaminants in the Food Chain (CONTAM) evaluated the scientific literature on the toxicity of lead and identified neurodevelopmental effects in children, and kidney and cardiovascular effects in adults, as the most sensitive toxicological endpoints for assessing the human health risks associated with exposure to lead. Given the absence of evidence suggesting a threshold for the toxicological effects of lead in humans, the CONTAM panel concluded that the PTWI of 25 mcg/kg derived by JECFA (WHO, 1987) is no longer appropriate. The CONTAM panel did not derive an updated toxicity value for lead. To assess the human health risks associated with dietary exposure to lead, the CONTAM panel used a margin-of-exposure approach, which involved comparisons between estimates of dietary exposure to lead within European populations and "critical reference points" for neurodevelopmental effects in children and kidney and cardiovascular effects in adults. The critical reference point for neurodevelopmental effects in children is the 95% lower confidence limit on the benchmark dose ($BMDL_{01}$) of 1.2 mcg/dL blood lead. The BMDL is based on linear regression modeling[18] of the quantitative relationship between full scale IQ test outcomes and concurrent blood lead levels in 6 year old children from the Lanphear et al. (2005) pooled analysis. The BMDL is estimated at a benchmark response (BMR) of 1%, which is a population level shift in IQ distribution that corresponds to a decrease

[17] JECFA (WHO, 2011) also estimated that dietary exposure to lead at the PTWI of 25 mcg/kg is associated with an increase in systolic blood pressure of approximately 3 mmHg (0.4 kPa) in adults.

[18] Linear regression modeling included a piecewise linear function at a breakpoint of 10 mcg/dL and adjustments for multiple covariates that significantly effect IQ such as study location, birth weight, maternal education and IQ, and Home Observation for Measurement of the Environmental (HOME) Inventory score.

of 1 IQ point in children.[19] Using Integrated Exposure Uptake Biokinetic (IEUBK) modeling, the CONTAM panel estimated the daily oral dose of lead through dietary exposure (0.5 mcg/kg/day in 6 year old children)[20] corresponding to a BLL of 1.2 mcg/dL, assuming negligible exposure to lead from air and soil. Using the margin-of-exposure approach, the CONTAM panel compared the daily oral dose at the BMDL (0.5 mcg/kg/day) to estimated daily dietary exposure to lead in European children and found that dietary exposure for most age groups considered exceeded the daily oral dose corresponding to the BMDL. Although the CONTAM panel did not derive a reference dose for lead, it concluded that "a margin of exposure of 10 or greater should be sufficient to ensure that there was no appreciable risk of a clinically significant effect on IQ." For comparison purposes, assuming an intra-human uncertainty factor of 10-fold would result in a reference dose of 5×10^{-5} mg/kg/day based on the daily oral dose at the BMDL of 1.2 mcg/dL derived by the CONTAM panel. This hypothetical value is within similar range of other toxicity values based on a 1-point decrease in IQ in children (Appendix D, Supplementary Table 2).

The CONTAM panel also considered BMDLs based on cardiovascular and kidney endpoints in adults (i.e., changes in systolic blood pressure and glomerular filtration rates) and calculated MOEs based on dietary exposure to lead in European adults. However, the panel "concluded that the risk of clinically important effects on either the cardiovascular system or kidneys of adult consumers, at current levels of lead exposure is low to negligible. In infants, children and pregnant women, there is potential concern at current levels of exposure to lead for effects on neurodevelopment. Protection of children and women of child-bearing age against the potential risk of neurodevelopmental effects should be protective for all other adverse effects of lead, in all populations."

In developing a Public Health Goal for lead in drinking water, CA EPA (2009) evaluated the noncancer health effects of lead and identified a blood lead "level of concern" of 1 mcg/dL based on a dose-response assessment performed by Carlisle and Dowling (2006), which estimated that an incremental (lower-bound) increase in BLL of 1 mcg/dL is associated with an incremental decrease of 1 point in the average IQ of children. CA EPA considered a decrease of 1 IQ point shift in the population mean IQ in children to be a critical effect and used it as a starting point (or point-of-departure) for calculating its drinking water public health goal for lead. Using IEUBK modeling, CA EPA estimated that consumption of 2.86 mcg/day of lead in drinking water in children between 12 and 24 months of age would increase the BLL by 1 mcg/dL and would therefore be associated with a 1 IQ point decrease in average IQ within a population of children. CA EPA (2009) then applied a UF of 3 "to account for the uncertainty with regard to the degree of protection offered at this level, considering the lack of a threshold," and to compensate for the relatively small sample size used in the Lanphear et al. (2005) study. CA EPA's derivation of a public health goal for lead in drinking water, did not specifically include derivation an RfD. However, assuming a body weight of 11.4 kg for children 12 to 24 months of age, CA EPA's derivation can be converted to an RfD of 8.4×10^{-5} mg/kg/day.

[19] The BMR of 1 percent assumes that the mean IQ score in children is 100 with a standard deviation of 15 IQ points.

[20] Assuming a 6-year-old child weighs 18.6 kg (US EPA, 2011), the daily oral dose can be converted to a lead intake of 9.3 mcg/day.

Given the absence of a threshold for the noncancer effects of lead, and the potential for exposure to lead in children from multiple pathways including media such as air, soil, indoor dust (e.g., dust from lead paint), drinking water, food and consumer products, we selected the estimated one-point decrease in average IQ at a BLL of 1 mcg/dL in children, as identified in the CA EPA (2009) derivation, as the basis of an oral noncancer health-based value for lead in spices. However, since CA EPA's estimate is based on IEUBK modeling of the relationship between drinking water exposure to lead and BLLs in children, we performed IEUBK modeling to determine the relationship between dietary exposure to lead and blood lead concentrations in children (as this is a more relevant exposure pathway for assessing exposure to lead from consumption of spices). IEUBK modeling provides age specific BLL estimates for children ages 6 month to 1 year up to 7 years of age. The results of IEUBK modeling showed that the highest BLL corresponding to a dietary exposure of 1 mcg/day of lead is for children 6 months to 1 year of age (0.3 mcg/dL). Using this estimate, we calculated a daily intake of 3.33 mcg lead/day corresponding to a BLL of about 1 mcg/dL in children age 6 months to 1 year of age. This estimated daily lead intake is similar to the daily intake used as the point-of-departure by CA EPA (2009) to calculate its public health goal for drinking water (2.86 mcg/day corresponding to a BLL of 1 mcg/dL); it is about 3-fold lower than the daily intake calculated by EFSA (9.3 mcg/day assuming 0.5 mcg/kg/day at a BLL of 1.2 mcg/dL in a 6 year old child weighing 18.6 kg), and is approximately 9-fold lower than the daily intake likely used by US FDA (2018a) for assessing dietary exposure to lead (30 mcg/day corresponding to a BLL of 5 mcg/dL). The results of our IEUBK modeling and the values obtained from other authoritative bodies are shown in the table below.

Table B.2. Comparison of Exposure Metrics for Available Noncancer Points-of-Departure for Lead

	Points-of-Departure			
	BLL (mcg/dL)	Daily Intake (mcg/day)	Daily Oral Dose (mcg/kg/day)	Modeled Age Interval
CA EPA (2009)	1	2.86	0.25[a]	12 to 24 months
EFSA (2013)	1.2	9.3[b]	0.5	6-year-old
US FDA (1994)[c]	10	60	6.5[d]	infants, age not specified
US FDA (2018a)	5	30	3.3[d]	infants, age not specified
IEUBK results	1	3.33	0.36	6 to 12 months

[a]CA EPA's daily intake corresponds to IEUBK modeling of BLLs for children ages 12 to 24 months. Assuming a 1 year old child weighs 11.4 kg (US EPA, 2011), we calculated a daily oral dose of 0.25 mcg/kg/day.
[b]EFSA's daily oral dose corresponds to IEUBK modeling of BLLs for 6-year-old children. Assuming a 6-year-old child weighs 18.6 kg (US EPA, 2011), the daily oral dose can be converted to a lead intake of 9.3 mcg/day.
[c]Carrington and Bolger, 1992; US FDA, 1994
[d]Daily lead intakes of 60 and 30 mcg/day can be converted to daily oral doses of 6.5 and 3.3 mcg/kg/day, respectively assuming an infant body weight of 9.2 kg (US EPA, 2011).

Using an analogous approach to CA EPA's (2009) derivation of its noncancer public health goal for lead, we used the daily intake estimated from IEUBK modeling of dietary

exposure to lead (3.33 mcg/day) corresponding to a BLL of 1 mcg/dL in infants and applied a 3-fold UF to account for intra-human variability. Assuming an infant (6 to 12 month of age) weighs 9.2 kg (US EPA, 2011), we calculated a noncancer toxicity value of 1.21×10^{-4} mg/kg/day. We selected this toxicity value for use in the derivation of an oral noncancer health-based guidance value for lead in spices.

1.2 Selection of Cancer Toxicity Values

1.2.1 Selection of a Cancer Toxicity Value for Inorganic Arsenic

In a previous risk assessment (NYS HHFS, 2015a), the New York State Department of Health derived a unit risk of 3.5×10^{-4} per mcg/L based on cancer potency estimates derived by US EPA (2000a,b, 2001), NRC (2001) and CA EPA (2004). All derivations are based on dose-response modeling of lung and bladder cancer mortality data from studies of southwestern Taiwanese populations exposed to high levels of arsenic in drinking water. CA EPA's cancer potency estimate also includes lung and bladder cancer mortality data from studies of South American populations exposed to arsenic in drinking water. The unit risk of 3.5×10^{-4} per mcg/L represents the median of the available cancer potency estimates derived by authoritative bodies[21] and can be converted into a cancer potency factor of 10.3 per mg/kg/day. We selected this cancer potency factor for use in the derivation of a cancer health-based guidance value for arsenic in spices.

1.2.2 Selection of a Cancer Toxicity Value for Cadmium

In a previous risk assessment, the New York State Department of Health derived a cancer potency factor of 0.067 per mg/kg/day based on a $BMDL_{10}$ obtained from benchmark dose modeling of interstitial-cell testicular tumor incidence in male rats orally exposed to cadmium via the diet for 77 weeks (NYS HHFS, 2015b). We selected this cancer potency factor for use in the derivation of a cancer health-based guidance value for cadmium in spices.

1.2.3 Selection of a Cancer Toxicity Value for Chromium (VI)

CA EPA (2011) derived a cancer potency factor of 0.5 per mg/kg-day for chromium (VI) based on the increased incidences of adenomas and carcinomas in the small intestine of male mice exposed via drinking water in a 2-year study. This cancer potency factor has been previously evaluated by the NYS Department of Health and recommended for use in deriving health-based guidance values for chromium (VI) in other environmental media (NYS HHFS 2015c). CA EPA's interspecies scaling approach[22] used an adult body weight of 70 kg. In a previous risk assessment, the NYS Department of Health, (NYS HHFS, 2015c) adjusted CA EPA's cancer potency factor to 0.53 per mg/kg/day to correspond to an adult body weight of 80

[21] All unit risks were normalized to correspond to the same the same adult body weight and drinking water consumption rate of 0.034 L/kg/day.

[22] CA EPA (2011) used the following equation to calculate a human equivalent dose at the $BMDL_{10}$: 1.2 mg/kg-day x $(0.05 \text{ kg}/70 \text{ kg})^{1/4} = 0.196$ mg/kg-day. NYS DOH adjusted the human equivalent dose by substituting the 70 kg in the equation with 80 kg.

kg. We selected this adjusted cancer potency factor for use in the derivation of a cancer health-based guidance value for chromium (VI) in spices.

An oral cancer potency factor for chromium (III) is not available. US EPA IRIS (1998) evaluated available cancer studies in animals and humans and classified the overall weight-of-evidence on the carcinogenicity of trivalent chromium as Group D (i.e., "not classified as to its human carcinogenicity").

1.2.4 Selection of a Cancer Toxicity Value for Lead

In a previous risk assessment, the New York State Department of Health derived a cancer potency factor of 1.15×10^{-2} per mg/kg/day based on a $BMDL_{10}$ obtained from benchmark dose modeling of increased incidence of kidney tumors in male rats fed a diet containing lead acetate for two years (NYS HHFS, 2015d). We selected this cancer potency factor for use in the derivation of a cancer health-based guidance value for lead in spices.

1. Introduction

In risk assessment, "exposure assessment is the process of measuring or estimating the magnitude, frequency, and duration of human exposure to an agent in the environment" (US EPA, 1992). To estimate exposure to a contaminant in an exposure medium (e.g., air, water or food) it is necessary to have an estimate of the ingestion rate for the medium, frequency and duration of exposure, and the body weight of exposed individuals. In this section, we define spices more specifically for the purpose of exposure assessment, identify body weight assumptions and describe the process used to derive quantitative estimates of spice consumption rates that will be used to derive health-based guidance values for arsenic, lead, cadmium and chromium in spices.

The United States Food and Drug Administration (US FDA, 2018b) considers a spice "any aromatic vegetable substance in the whole, broken, or ground form, except for those substances which have been traditionally regarded as foods, such as onions, garlic and celery; whose significant function in food is seasoning rather than nutritional; that is true to name; and from which no portion of any volatile oil or other flavoring principle has been removed." In this exposure assessment, the term spice is more narrowly defined as any edible, dried vegetable, herb, bark, bud, root or seed, or plant material derived from natural sources that is used in food preparation, other than dehydrated onion or garlic, that is added to food to enhance aroma and taste.

2. Literature Review of Spice Consumption Rates

We conducted a search for spice consumption rate data from both the scientific literature and from reports of national and international authoritative agencies involved in the evaluation of human exposure media, including food for human consumption.

2.1 Scientific Literature

We used the PubMed and PubMed-Advanced Search Builder to find peer-reviewed publications that contained the following keywords: 1) "spice," or the name of various individual spices, such as "turmeric," "chili" or "pepper," and 2) "consumption" or "intake" or "ingestion rate." We initially retrieved more than 250 citations. We excluded those studies reporting only intake of specific compounds isolated or derived from spices and studies reporting intake of spices used for any purposes other than food preparation (such as home remedies and folk medicine.) We also excluded articles in languages other than English or those referring only to spices rarely available or used in the United States, such as carom and nigella seeds. We then reviewed publications to determine if actual spice consumption rates were reported and excluded any publications that did not report these rates. Although we tried to include primary or original sources of information, in a few cases, we included consumption data cited in secondary sources if the original article was not available.

We found that especially during the last decade, there have been efforts to estimate daily spice consumption for individual spices and for total spices. However, the available studies are small in number and limited in terms of providing quantitative estimates of spice consumption. In this report, "ingestion rate" is defined as the amount of spice eaten in one day and is expressed in grams per day (g/d), unless stated otherwise. "Total ingestion rate" refers to the sum of individual spice ingestion rates and is also expressed in g/d. "Consumption rate" is the body weight normalized ingestion rate, or total ingestion rate and is expressed in milligrams of spice per kilogram of body weight per day (mg/kg-BW/day).[23] Supplementary Table 7 summarizes the results of eight study estimates and two authoritative body estimates (see next section) of adult ingestion rates for individual or mixtures of spices. Average ingestion rates for individual and total spices in these studies vary, ranging from 0.2 g/d to 45 g/d, with a mean ingestion rate of 3.3 g/d across all studies. Using estimates of body weight that were reported in the studies, or using assumed body weights based on country of origin, we normalized the adult ingestion rates to body weight, and estimated consumption rates which ranged from 2.7 mg/kg-BW/d to 642.9 mg/kg-BW/d with a mean of 50.6 mg/kg-BW/d.

Among the available studies (see Supplementary Table 7), two recent studies use robust methods, to estimate not only consumption rate, but also consumption frequency. One study is a food survey conducted in Norway with 146 adults over 28 days. The study reported that the median dietary ingestion rate of spices (sum of 27 herbs and spices) was 2.7 g/day (range 0.19 to 45 g/d) (Carlsen et al., 2011). The second study was conducted in urban India with 100 surveyed households and determined the ingestion rates and frequency of 17 spices routinely used in Indian cuisine. The study reported that the average daily ingestion rate of total spices from meals was estimated to be 10.4 g/d. The spices with the highest daily ingestion rates were chilies (mean 2.1 g/d ± 1.3 g/d), and cumin (mean 1.22 g/d ± 1.14 g/d). With exception of chilies and cumin, the ingestion rate for more than 50% of the spices was below 1 g/d. The study also showed a great variability in the mean ingestion rates and frequency of use by spice (Siruguri and Bhat, 2015). Despite their robust method, neither of these studies provided quantitative estimates of spice ingestion in children. The estimates for adults, while potentially informative for subpopulations, may be less informative for evaluating the overall US population.

2.2 **Authoritative Body Estimates of Spice Consumption**

US FDA (2013, 2017) has recommended that to improve spice safety, it is necessary to "determine the distribution and variability of spice consumption servings among general and susceptible U.S. populations. This information cannot be accurately determined with the National Health and Nutrition Examination Surveys (NHANES) data. Such data are needed to quantitatively characterize the public health risk associated with spice ingestion and would be most useful if it included additional data about high consumers and susceptible populations."

As reported by US FDA (2013), the USDA estimated an annual *per capita* total spice ingestion in the United States of 1,575 grams based on annual food availability and the U.S. population in 2010. Assuming that spices are consumed on a daily basis, the estimated *per capita* ingestion rate would have been 4.32 g/d, which is higher than the 2.7 g/d estimated for the Norwegian population (Carlson et al., 2011) and higher than our estimated mean ingestion rate

[23] The term "consumption" is sometimes used generically and may not necessarily imply a rate.

(3.3 g/d) from the available studies (Supplementary Table 7). The same US FDA report also indicated that *per capita* spice ingestion rate in the United States, as measured by food availability, had been increasing by approximately 0.62 g/d/decade since 1966.

The US FDA and the US Center for Disease Control and Prevention (CDC), through the NHANES, estimated that total daily spice ingestion for consumers in the United States based on survey data collected from 2003-2006 was 1 g/d, excluding *Capsicum* (chili peppers), and 5 g/d including *Capsicum* (US FDA, 2013). These estimates included ingestion of fresh herbs and chili peppers used in standard recipes for foods consumed and reported in the What We Eat in America Survey (WWEIA) (Dwyer *et al.*, 2003). US EPA Office of Pesticide Programs used NHANES 2003−2006 data to update the Food Commodity Intake Database (FCID) that was developed in a 1994-96 analysis of data from the USDA's Continuing Survey of Food Intake among Individuals (CSFII) (US EPA, 2000; USDA, 2000).

The FCID provides distributions of food ingestion rates for various ages and populations. The FCID uses information from recipes to translate food ingestion as reported in the WWEIA survey (2005-2010 survey cycles) into ingestion rates of US EPA-defined food commodities. Food commodity intakes are expressed as grams of food commodity consumed per day (g/d) or grams per kg body weight per day (g/kg-BW/d) for over 500 commodities derived from more than 7000 different foods and beverages reported in the two surveys. In addition to data on food ingestion, the database also includes demographic data that are available through CDC's National Center for Health Statistics.

2.3 Summary of Data Sources and Recommendations for Exposure Assessment

Estimating daily intake of spices is difficult because spices are generally consumed in small amounts and often as integrated parts of prepared dishes, which can lead to measurement error. The mass of spices used in food preparation often falls within the range of 0.5-1.0% of the total mass of the food (Carlsen et al., 2011.) There are only a few studies reporting spice ingestion in the scientific literature (Supplementary Table 7) and most of them are based only on adults, or for a single spice, or conducted in populations with a more homogeneous cultural background than the more diverse population in New York State. Moreover, some reports include data on consumption of plants not considered spices in this study, such as shallots or garlic, or fresh herbs such as lemon grass or tamarind pods. Therefore, these reported spice ingestion estimates were not used for use in this analysis.

For this exposure assessment, we used the WWEIA-FCID 2005-10 to estimate spice total ingestion rates among US populations, because it contains survey-based values expressed as grams of individual spice ingested per day (ingestion rates) for different groups, genders and ethnicities. We did not use estimates of spice ingestion *per capita* in the United States developed by USDA (FDA, 2013) because this approach includes those individuals that reported no ingestion, thereby underestimating levels of ingestion among individuals who do consume spices. The FCID database provides means, as well as measures of ingestion variability (e.g., range of variance) that can be retrieved for the whole population ("all races") or by race/ethnicity, by age, and by gender. Although FCID has some limitations (See Section 1.3.4), it

provides the most comprehensive approach to estimating spice consumption among various populations within the U.S.

3. Data Analysis

3.1 Description of Methodology

Central tendency (mean) and high-end (90th percentile) total daily consumption rates for children were estimated according to the following equation:

Appendix C Equation 1.

$$CR = \sum_{i=1}^{m} \left(\sum_{j=1}^{n} \left(\frac{\bar{I}R \times ED}{AT \times BW \times CF} \right) \right)$$

Where,

CR = total daily consumption rate (mg/kg-BW/day)
i = spice (unitless)
m = maximum number of spices considered
j = age (in one-year intervals)
n = maximum number of age intervals considered
$\bar{I}R$ = ingestion rate of spice (g/d); mean for central tendency estimates and 90th percentile for high-end estimates.
ED = exposure duration for interval *j* (one year)
BW = assumed body weight (kg) at year *j* based on Appendix Table C.1.
AT = averaging time (seven years)
CF = conversion factor (10^{-3} g/mg)

For adults, we assumed ED and AT were equal and that BW and IR were constant throughout all adult life.

Appendix C Equation 2.

$$CR = \sum_{i=1}^{m} \left(\left(\frac{\bar{I}R}{BW \times CF} \right) \right)$$

Where,

CR = total daily consumption rate (mg/kg-BW/day)
i = spice (unitless)
m = maximum number of spices considered

$\bar{I}R$ = FCID adult (age 21 to <78) ingestion rate of spice (g/d)
BW = 80 kg
CF = conversion factor (10^{-3} g/mg)

3.1.1 Selection of Spices Considered in the Calculation of Total Spice Ingestion Rate.

The most recent version of the WWEIA-FCID 2005-10 contains approximately 558 unique commodity names grouped in 36 food groups. The "Herbs and Spices" group (code 19) contains data for 22 spices and herbs. From this food group, we excluded *a priori* spices listed as "Herbs" and "Fresh", as well as those labeled as "Baby Food." The FCID also contains data for other spices that are not included in the "Herbs and Spices" category, such as "Turmeric" and "Cinnamon"; therefore, we also searched for the individual spice names. For the search, we used common spice names from the lists compiled by: a) FDA (2018b) in the Specific Food Labeling Requirements; b) the USDA report on imported spices (USDA, 1995); and c) the European Spice Association (ESA, 2018). We searched for more than 60 individual spice names. We applied the following four inclusion/exclusion criteria to the list of spice names found in the FCID (Supplementary Table 8):

1. Availability of reliable ingestion rate data: The lack of reliable ingestion rate data was a major limitation for spice inclusion in the calculation of total spice consumption rate. For example, ingestion rates of spices commonly used in food preparation such as oregano and cumin are not included in the FCID. Another reason for exclusion was the low number of eaters within the total population for some spices, which rendered the reported ingestion rates statistically unreliable.

2. Sufficient evidence that the spice is imported: Imported spices are believed to be more commonly contaminated with heavy metals than domestic spices. Most of the U.S. spice supply is imported, with some exceptions. According to USDA data from 1995, the U.S. imported more than 40 separate spices, seven of which (vanilla beans, black and white pepper, chili peppers, sesame seed, cinnamon, mustard and oregano) accounted for more than 75% of the total annual value of spices imports. There is no consumption rate data specifically for domestically produced spices, but it is estimated that most of the dehydrated onion used in the U.S. is produced domestically. U.S. farms also produce significant amounts of the U.S. supply of dehydrated garlic, chili peppers and mustard seed (US FDA, 2018c).

3. Spice is dried and/or powdered: Although spices can be ingested in the form of crude plant material, oral infusions or tinctures, in this assessment, we only included consumption data for powdered, dried plant material that is ingested as part of daily meals. We also excluded from this analysis dehydrated vegetables used as spices such as onion, garlic and celery.

4. Potential for adulteration: Numerous cases in recent reports suggest that certain spices, such as turmeric, saffron and chili powder have a higher potential for being adulterated than other spices and, therefore, for becoming a potential source of metal exposure

(Marieschi et al., 2012; Gleason et al., 2014; Zhu et al., 2016 and Cowell et al., 2017). Therefore, efforts were made to include data for these spices in the analysis.

Based on the four criteria above, we selected eight spices for the exposure assessment: "cinnamon," "pepper, black and white," "spices, other," "turmeric," "pepper, bell, dried," "pepper non-bell, dried," "sesame seed," and "ginger, dried." For each of these spices, we filtered the information in the FCID to retrieve single day ingestion estimates of "eaters only" for descriptors of spice ingestion distribution (e.g., mean, maximum, and percentiles from 5 to 99.5) by age and race/ethnicity.

3.1.2 Evaluation of Various Available Consumption Rates

3.1.2.1 Central Tendency vs. Upper-End Ingestion Estimates

For any specific exposure medium, there is a range of intake rates for individuals within a population. Some individuals may have a high rate of spice intake[24] while other individuals may have a lower rate of intake. US EPA policy for exposure assessment recommends consideration of "central tendency" to "high-end" exposure. High-end exposure represents individuals within the upper end of the exposure distribution, which is commonly stated as a range of population distributions including and above the 90th percentile (EPA, 1992).

The FCID provides mean ingestion rates, and ingestion estimates for various percentiles for each sample. Some of the percentiles are marked with a '†' to indicate that the estimates are less statistically reliable, and therefore were not considered in the calculation of total ingestion rate. For the most robust estimation for each spice ingestion rate, we used the mean ingestion rate as a measure of central tendency. We used the 90th percentile as a measure of high-end exposure because we compared the number of reliable values for age-specific mean ingestion percentiles in the high-end (e.g., 75th, 80th, 90th, 95th and 99th percentiles) and found that the 90th percentile had the highest number of reliable values compared with the other high-end percentiles examined (Supplementary Tables 9A and 9B). Therefore, in this report, we considered two spice consumption rates: mean and 90th percentile.

Different approaches have been used in the scientific literature to estimate total spice ingestion rates. One study used the sum of all herbs and spices to estimate the total spice intake in grams/day (Carlsen et al., 2011). Another study found that spice intake varies with frequency of consumption of spice-containing dishes and therefore, estimating the spice amount ingested per dish as well as the frequency of consumption of that dish may facilitate the quantification of individual spice intake (Siruguri and Bhat, 2015). The USDA estimated annual *per capita* spice consumption based on annual food availability data and the US population (US FDA, 2013). We considered that using the sum of spices might be reasonable, given that spices are rarely consumed individually in a given meal or day. Spices consumed with meals are usually part of a larger group of spices used for food preparation. For example, in Indian cuisine, a curry dish may contain up to 11 different spices, while other dishes such as rice, chutney and dhal may contain 10, 5 and 5 spices, respectively (Siruguri and Bhat, 2015). Therefore, in this assessment,

[24] Intake in this case is being used as a synonym of ingestion.

we estimated the total spice ingestion rate using the mean and 90th percentile ingestion rate of eight selected spices by race.

3.1.2.2 Age-specific Spice Ingestion Rates (Children vs. Adults)

Children are more vulnerable to the effects of metal poisoning than adults due to their anatomy, physiology and behavior. Physiologically, children's metabolic rates and activity levels tend to be greater than those of adults. Accordingly, children consume more water and food per unit of body weight than adults (US EPA, 2005, 2006). For this exposure assessment, we assumed that people consume spices in food during their lifetime, although consumption rates may vary with age. We considered two exposed population age categories: children and adults. Children encompass all early postnatal life stages from birth until adolescence, which occurs approximately between 12 and 21 years of age (EPA, 2006), while adults were considered those individuals from 21 to <78 years old.

Because children may be particularly vulnerable to the health effects of metals during early life stages, and because ingestion rates per kg of body weight can be higher at early ages, we determined the ages at which ingestion rates were the highest. To determine the age range in children at which daily ingestion rates were the highest, we evaluated ingestion rates for one-year age intervals from 0 to < 21 years of age. In order to estimate total consumption of spices, for each age interval, we summed the age-specific ingestion rates for each of eight spices as reported by FCID and divided the result by the age-specific body weight (BW) (Appendix C Equation 1 and Appendix Table C.1). We used the average BW from US EPA recommended values in the Exposure Factors Handbook (US EPA, 2011).

Appendix Table C.1. US EPA Recommended Values for Body Weight

Age Class *j*	Mean (kg)		Age Class *j*	Mean (kg)
Birth to < 1 month	4.8		2 to < 3 years	13.8
1 to < 3 months	5.6		3 to < 6 years	18.6
3 to < 6 months	7.4		6 to < 11 years	31.8
6 to < 12 months	9.2		11 to < 16 years	56.8
Birth to < 1 year[25]	7.8		16 to < 21 years	71.6
1 to < 2 years	11.4		Adults	80.0

Source: Table ES-1, US EPA, 2011

An examination of the consumption rates, or body-weight-normalized total ingestion rates, for the first 21 years of life (Supplementary Figures 3A and 3B), shows that high consumption rates occur during the first years of life and decrease with age. There is a substantial year-to-year difference between 7 and 8 years of age in consumption rate (for estimates that included sesame seed). However, when averaging across age groups, the average total consumption rates from birth to < 7 years of age resulted in the higher rates of total spice consumption rates than rates that include spice consumption in older children. In addition, our selection of the age range of 0 to < 7 years of age is supported by previous risk assessments performed by NYS DOH due to the

[25] In the estimation of consumption rates for a one-year-old child, we calculated a BW of 7.8 kg, which is the time weighted average of the BW for the first 12 months of life using the US EPA recommended body weights shown in Appendix Table C.1.

inclusion of early life periods that are marked by rapid growth, weight gain, and other physiological changes (US EPA, 2005). (0 to < 3 years), as well as a period in which anatomy and physiology are relatively stable (3 to < 8/9 years) and their sources of food diversify (e.g., they start eating lunch at school) (US EPA, 2005). In addition, the toxicity of metals evaluated herein (such as lead, for which the most sensitive health effects occur in young children (see Appendix A)) further supports the selection of this age range. Therefore, we selected the range of 0 to < 7 years of age as the most representative life stage of potential concern for children.

As expected, body-weight normalized spice ingestion rates (consumption rates) in children were higher than in adults because children consume more spice per unit body weight than adults. Unexpectedly, the consumption rates of sesame seed were higher than the consumption rates of other spices in both children and adults. As shown in Supplementary Figure 3A, the consumption rate of 379.5 mg/kg/day observed during the first year of life of children decreased rapidly as body weight increased. "Sesame, seed" was the main driver of the high total consumption rates observed in children of less than one year old, due to an extremely high mean value of 323.1 mg/kg/d observed in a group of few individuals (n=5) at age 0 to < 1. Because of the low sample size ("N"), and uncertainty about the plausibility of high consumption of sesame seed during the first year of a child's life, we compared the effect of excluding "sesame, seed" from the sum of consumption rates (Supplementary Figure 3B). Excluding "sesame, seed" from the total would reduce total consumption rates to 56.4 mg/kg/d during the first year, and to 20.0 mg/kg/d at age 21, with a maximum of 56 mg/kg/d at age 4 to < 5 years, and with "pepper, non-bell, dried" as the main driver of consumption.

Total ingestion rates for adults (ages 21 to < 78 years) were normalized assuming an adult weighs 80 kg.

3.1.2.3 Race/Ethnic(ity) Groups Considerations

Spice consumption as part of traditional ethnic cuisine is a cultural expression. Therefore, people of different races and cultures differ in spice preferences for food preparation. Furthermore, some reports indicate that children from immigrant populations can be more vulnerable to metal poisoning from spices than children from non-immigrant populations, due to their culture-specific spice consumption (Woolf et al., 2005; Lin et al., 2010; Cowell et al., 2017). To determine whether certain race/ethnic(ity) groups have higher consumption rates of spices, we compared daily mean ingestion rates of the eight selected spices in children and adults of the five race/ethnicity categories as reported in FCID[26]: "Mexican-American", "Non-Hispanic", "Non-Hispanic-white", "Other-Hispanic", "Other-races, including multiple" and the grouped category of "All races," which includes all five of the aforementioned groups.

[26] The race/ethnic(ity) group categories used in this report are the the same race/ethnic(ity) group categories for spice consumption as the FCID. The categories used in the FCID come from NHANES survey data. In the survey, race/ethnicity categories are based on self-identification. Respondents who self-identified as "Mexican American" are coded separately regardless of their race. All other respondents who self-identified as "Hispanic" ethnicity are coded "Other Hispanic". All "non-Hispanic" participants are categorized based on their self-reported races: "non-hispanic-white", "non-Hispanic black", "non-Hispanic Asian", and "other non-Hispanic races including multiracial".

We found that daily spice consumption in children (0 to < 7 years old) of all races occurs in the following order (from the highest consumed to the least consumed): sesame, seed > pepper, non-bell, dry > spices, other > cinnamon > pepper, bell, dried = turmeric > pepper, black and white > ginger, dried (Supplementary Figure 4). Spice consumption rates in children across races/ethnicities appear to be similar, except for sesame seed, where Mexican American and Other Hispanic showed higher spice consumption rates

Total consumption rates in children, including sesame seeds, by race/ethnicity ranged from 56.1 mg/kg/d in "Non-Hispanic Whites" to 224.2 mg/kg/d in "Other Hispanic," while in adults, consumption rates ranged from 21.3 mg/kg/d in "Non-Hispanic Blacks" to 59 mg/kg/d in "Mexican-Americans" (Supplementary Table 10). Excluding sesame seeds from the sum of spices had a dramatic effect on children's total consumption rates, which ranged from 42.5 mg/kg/d in "Other races, including multiple" to 56.1 mg/kg /day in "Non-Hispanic Whites". In adults, total consumption rate ranges from and from 16.3 mg/kg/d in "Non-Hispanic Blacks" to 19.3 mg/kg/d in Mexican-Americans. (Supplementary Table 11)

3.2 Comparison of Results to Existing Literature Estimates

As a check on our analysis, we sought to compare our ingestion rate estimates with comparable estimates in the literature. Certain limitations apply to these comparisons. In our analysis, we found that children consume more spice per unit body weight than adults. However, in order to compare intake of spices across different studies, authoritative body documents, and estimates from the FCID, we compared estimated ingestion rates (in g/day) because body weight normalized consumption rates (in mg/kg_{bw} /day) were not provided in some studies and reports. Comparing estimates of spice ingestion based on the FCID with other estimates from the scientific literature is difficult because most studies report individual spice consumption and only a few studies have calculated total spice consumption (Supplementary Table 7). Even though some studies report total spice consumption, they included or excluded certain common plants or spices such as garlic, onion or chili peppers which affect the total amount reported.

In this assessment, the estimated total spice ingestion rate calculated using central tendency values for all race/ethnic(ity) groups is 1.5 g/d and 2.6 g/d in children and adults, respectively (Supplementary Table 10).[27] Our estimates for all races fall within the average daily ingestion of 1 g for spices other than chili peppers and 5 g for spices including chili peppers reported in the US FDA Draft Risk Profile on spices (US FDA, 2013). Also, our highest estimate (4.7 g/d) is slightly higher than the 4.3 g/d *per capita* determined by the USDA in 2010, which excluded onion and garlic (US FDA, 2013). The NYS A&M uses 0.5 g/d as a reference amount of total spice per eating occasion, which if we assume that people consume three meals a day and with each meal they consume 0.5 g/d, the resulting per day ingestion is lower than our estimated 2.6 g/d in adults for all races. Our ingestion estimates are also within the range of 0.19 to 45 g/d that Carlsen's study (2013) estimated as the median total spice ingestion (sum of all 27 herbs and spices) in Norway. Finally, our estimate for all races (2.6 g/d) is lower than those reported for

[27] When normalizing based on body weight, the total spice ingestion rates of 1.5 g/day in children and 2.6 g/day in adults, results in total spice consumption rates of 114 mg/kg-BW/day (children) and 32.9 mg/kg-BW/day (adults), respectively.

countries with a tradition of high spice consumption such as Thailand with ingestion ranging from 4.9 to 26.1 g/d (Tantipopipat et al, 2010).

3.3 Limitations of the Consumption Rate Estimations

To estimate how much spice people may consume, we used the ingestion rate estimates in the WWEIA-FCID database. The developers of this database indicated that the database has some limitations that should be considered. The main reported limitations are:

- Many of the recipes in the current version of FCID were originally developed for the USDA's Continuing Survey of Food Intake among Individuals (CSFII) in 1994-1996 and have not been updated since then to reflect changes in commercial food products.

- Ingredient amounts for recipes entered in the WWEIA that were not in the original 1994-1996 database were estimated based on available older recipes, professional judgment, mathematical algorithms or regional/specialty cookbooks.

- The uncertainty around estimated ingestion of some food commodities with very few survey responders can be quite large and therefore ingestion estimates based on small numbers can be less statistically reliable.

As users of FCID, we also identified the lack of data for spices commonly used in the US (e.g., oregano and cumin) as a limitation.

Aside from database limitations, our assessment may have some additional limitations, for example:

- Total ingestion rate of eight spices is the sum of mean spice reported to be consumed by a certain race/ethnic(ity) or age group and not the sum of the amount of eight spices consumed individually, which may overestimate ingestion rates in certain non-spice consuming populations. However, we considered that by using the mean ingestion rate values for "all races" instead of higher values for a certain race/ethnic(ity) group, we could take into account some of the different race/ethnic(ity) spice preferences.

- Our calculations assume that the same eight spices are eaten in the same amount on a daily basis and it does not consider variability in the amount and frequency of spice consumption. The Siruguri and Bhat's study (2015) showed a great variability in the mean consumption and frequency of used spices in Indian cuisine, even in the surveyed households who lived in the same Indian region with an assumed similar cultural background. While this may be a minor limitation for long-term, central-tendency ingestion estimates, it could suggest our high-end estimates are very conservative.

- The estimated total spice consumption may not include spices that people unknowingly consume in restaurants or as part of processed foods.

Appendix C: Exposure Assessment

Tables and Figures

Supplementary Table 1. Authoritative Body Sources Searched for Cancer and Noncancer Toxicity Values

Agency for Toxic Substances and Disease Registry
California Environmental Protection Agency
European Food Safety Authority
Joint Food and Agriculture Organization of the United Nations/World Health Organization Expert Committee on Food Additives (JECFA)
Health Canada
National Institute of Public Health & Environmental Protection, Netherlands (RIVM)
National Research Council
New Jersey Department of Environmental Protection
New York State Department of Environmental Conservation
New York State Department of Health
RIVM (Netherlands National Institute of Public Health & Environmental Protection).
United States Environmental Protection Agency
United States Food and Drug Administration
World Health Organization

Supplementary Table 2. Summary of Available Oral Noncancer Toxicity Values for Inorganic Arsenic, Cadmium, Chromium Compounds and Lead

Source	RfD (mg/kg/day)	Toxicity Endpoint (species)	Point of Departure (mg/kg/day unless otherwise noted)	Uncertainty Factors							Additional Comments
				Total	UF_A	UF_H	UF_L	UF_S	UF_D	Other	
Arsenic											
US EPA IRIS (2019); ATSDR (2007a)	3×10^{-4}	skin, vascular (humans)	8×10^{-4} (NOEL)	3	-	3	-	-	-	-	
CA EPA (2004)	3.9×10^{-4}	vascular (humans)	3.0 (mg/L)yr cumulative dose (LED_{01})	10	-	3	-	-	-	3	CA EPA applied a total UF of 10 (a UF of 3 for inter-human variation and a UF of 3 to extrapolate to a level of negligible risks).
NYS HHFS (2015a)	4×10^{-4}	vascular (humans)	3.0 (mg/L)yr cumulative dose (LED_{01})	10		3	-	-	-	3	Estimated RfD is based on the point of departure and UFs used by CA EPA (2004a) shown above. RfD was adjusted to include estimated arsenic dose from staples foods in Taiwanese populations (e.g., rice, sweet potatoes). This daily dose (0.002 mg/person-day or 0.000036 mg/kg-day for a 55-kg person.
RIVM (2001)	1×10^{-3}	skin (humans)	2.1×10^{-3} (NOEL)	2	-	2	-	-	-	-	RIVM applied a UF of 2 "to compensate for the observation errors that are inevitable in epidemiological studies."

Source	RfD (mg/kg/day)	Toxicity Endpoint (species)	Point of Departure (mg/kg/day unless otherwise noted)	Uncertainty Factors							Additional Comments
				Total	UF_A	UF_H	UF_L	UF_S	UF_D	Other	
Cadmium											
ATSDR (2012a)	1.0×10^{-4}	kidney biomarker (humans)	3.3×10^{-4} (females) 7.0×10^{-4} (males) ($UCDL_{10}$)	3	-	3	-	-	-	-	
CA EPA (2006)	6.3×10^{-4}	kidney biomarker (humans)	3×10^{-4} (NOEL)	50	-	5	-	-	-	10	A UF of 10 was applied to account for the carcinogenicity of cadmium by the oral route.
CA EPA (2005)	1.1×10^{-5} (child specific)	kidney biomarker (humans)	1.0×10^{-3} (LOEL)	90	-	10	3	-	-	3	CA EPA used an additional UF of 3 to account for gastrointestinal absorption differences between children and adults. CA EPA documentation indicated total UF is 90.
EFSA (2009a)	3.6×10^{-4}	kidney biomarker (humans)	4 mcg cadmium / g creatinine ($BMDL_{05}$, one-compartment model)	3.9	-	3.9	-	-	-	-	EFSA applied a UF of 3.9 to the $BMDL_{05}$, resulting in a urinary cadmium concentration of 1 mcg cadmium /g creatinine. Using a one-compartment model, EFSA calculated the daily dose from dietary exposure that would result in 95% of the exposed population having a urinary cadmium concentration not exceeding the adjusted $BMDL_{05}$.

Source	RfD (mg/kg/day)	Toxicity Endpoint (species)	Point of Departure (mg/kg/day unless otherwise noted)	Uncertainty Factors							Additional Comments
				Total	UF_A	UF_H	UF_L	UF_S	UF_D	Other	
Health Canada (1986)	6×10^{-4} to 7×10^{-4}	kidney biomarker (humans)	--	-	-	-	-	-	-	-	
NYS DEC (1997)	7.0×10^{-4}	kidney biomarker (humans)	--	-	-	-	-	-	-	-	
RIVM (2001)	5.0×10^{-4}	kidney biomarker (humans)	0.001 (LOEL)	2	-	-	-	-	-	-	
US EPA (2019c)	5×10^{-4} (water)	kidney biomarker (humans)	0.005 (NOEL)	10	-	10	-	-	-	-	
US EPA (2019c)	1×10^{-3} (food)	kidney biomarker (humans)	0.01 (NOEL)	10	-	10	-	-	-	-	
WHO (2011)	8×10^{-4}	kidney biomarker (humans)	8×10^{-4} (NOEL)	-	-	-	-	-	-	-	
Chromium (III)											
EFSA (2014)	0.3	no toxicological effects observed	286 (NOEL)	100	10	10			10		The database UF of 10 was to "an additional factor of 10 to account for the absence of adequate data on reproductive and developmental toxicity."
US EPA (2019b)	1.5 (insoluble salts)	no toxicological	1468 (NOEL, adjusted)	1000	10	10	-	-	-	10	US EPA applied a modifying factor of 10 to account for database deficiencies including

Source	RfD (mg/kg/day)	Toxicity Endpoint (species)	Point of Departure (mg/kg/day unless otherwise noted)	Uncertainty Factors							Additional Comments
				Total	UF_A	UF_H	UF_L	UF_S	UF_D	Other	
		effects observed									lack of a studies evaluating reproductive toxicity.
RIVM (2001)	5.3×10^{-3} (water soluble chromium compounds)	no toxicological effects observed	2.5 (NOEL)	500	10	10	-	-	-	5	RIVM applied a UF of 5 for limitations in the study used as the basis of the Rfd.
			0.46 (NOEL)	100							
	5 (insoluble chromium compounds)	--	--	-	-	-	-	-	-	-	
Chromium (VI)											
ATSDR (2012b)	9×10^{-4}	stomach (mice)	0.09 ($BMDL_{10}$)	100	10	10	-	-	-	-	
CA EPA (2011)	2×10^{-4}	liver (rats)	0.2 (LOEL)	1000	10	10	10	-	-	-	
RIVM (2001)	5×10^{-3}	no toxicological effects (rats)	2.5 (NOEL)	500	10	10	-	5	-	-	
US EPA (2019d)	3×10^{-3}	no toxicological effects (rats)	2.5 (NOEL)	900	10	10	-	3	-	3	US EPA applied a modifying factor of 3 to account for gastrointestinal effects observed in a study of a Chinese population exposed to approximately 20 mg/L hexavalent chromium in drinking

Source	RfD (mg/kg/day)	Toxicity Endpoint (species)	Point of Departure (mg/kg/day unless otherwise noted)	Uncertainty Factors							Additional Comments
				Total	UF_A	UF_H	UF_L	UF_S	UF_D	Other	
											water (exposure duration not reported).
Lead											
CA EPA (2009)	8.4×10^{-5} (estimated for comparison)	neuro-developmental (humans)	1 mcg/dL blood lead from drinking water	3	-	3	-	-	-	-	The CA EPA point-of-departure of 1 mcg/dL blood lead can be converted into 2.86 mcg/day or 0.25 mcg/kg/day assuming an 11.4 kg child. For comparison purposes, we used this daily dose to estimate an RfD using the same UF as CA EPA in their public health goal derivation (also see Appendix B Section 1.1.5).
EFSA (2013)	--	neuro-developmental (humans)	1.2 mcg/dL blood lead ($BMDL_{01}$) 0.5 mcg/kg/day EFSA-estimated dietary exposure from IEUBK	-	-	-	-	-	-	-	EFSA (2013) did not derive a reference dose for lead.
US FDA (1994); Carrington and Bolger (1992)	6 mcg/child-day	neuro-developmental (humans)	10 mcg/dL blood lead from ingestion 60 mcg/day	10	-	10	-	-	-	-	

Source	RfD (mg/kg/day)	Toxicity Endpoint (species)	Point of Departure (mg/kg/day unless otherwise noted)	Uncertainty Factors							Additional Comments
				Total	UF_A	UF_H	UF_L	UF_S	UF_D	Other	
US FDA (2018a)	3 mcg/child-day	neuro-developmental (humans)	5 mcg/dL blood lead from ingestion	10	-	10	-	-	-	-	Details on the derivation were not provided. However, it appears likely that US FDA used the dose-response modeling from its previous derivation based on a BLL of 10 mcg/dL in children and adjusted the dose to correspond to a lower BLL of 5 mcg/L (i.e., BLL at 5 mcg/dL = (60 mcg/day (at BLL of 10 mcg/dL) ÷ UF of 10 ÷ 2) = 3 mcg/day.
WHO (1987)	25 mcg/kg-week 3.6	neuro-developmental (humans)	-	-	-	-	-	-	-	-	

BLL = blood lead level; BMDL = benchmark dose, lower 95% confidence limit; IEUBK = Integrated Exposure Uptake Biokinetic model; LED = lower bound on effective dose; LOEL = lowest-observed-effect level; NOEL = no-observed-effect-level; RfD = reference dose; UCDL = lower bound urinary cadmium dose; UF_A = animal-to-human uncertainty factor; UF_H = uncertainty factor for intrahuman variability; UF_L = NOEL-to-LOEL uncertainty factor; UF_S = subchronic to chronic; UF_D = database uncertainty factor.

Supplementary Table 3. Child-specific Spice Consumption Rates Used to Calculate Potential Noncancer Health-Based Guidance Values for Spices (All Available Spices)[a]

	Central Tendency Estimates[b]		Upper Percentile Estimates[c]	
	Highest Consuming Race/Ethnic Group	All	Highest Consuming Age Group	All
Total Spice Consumption Rate (mg/kg/day)	601.8[d]	114.0[d]	131.6[d]	96.0[d,e]
Receptor Age (in years)	1 to < 2	0 to < 7	1 to < 2	0 to < 7
Receptor Race/Ethnic(ity) Groups (includes both males and females)	Other Hispanic,	all races	all races	all races
Number of spices included in Total Consumption Rate	8	8	4	4
Highest Contributing Spice to Total Spice Consumption Rate	sesame seed	sesame seed	pepper, non-bell, dried	pepper, non-bell, dried
Sample Size (n) for Highest Contributing Spice	3	251	326	1737

[a]All spices included in calculation of total spice consumption rates met the inclusion criteria described in Appendix C.

[b]Total spice consumption rate is based on the sum of mean spice consumption rates for 8 available spices.

[c]Total spice consumption rate is based on the sum of 90th percentile spice consumption rates for 4 available spices.

[d]Since central tendency and upper percentile estimates are shown side by side for comparison purposes. However, these estimates represent different data sets as they are based on different groupings of number of spices included, different receptor age and race/ethnic(ity) groups, and different sample sizes. For example, the upper percentile estimate for all races/ethnic(ity) groups (96.0 mg_{spice}/kg_{bw}/day) is based on a smaller number of available spices than the central tendency estimate of 114.0 mg_{spice}/kg_{bw}/day for Non-Hispanic Black. These data groupings are compared to show that several exposure assumptions were considered in deriving health-based guidance values based on different central tendency and high-end exposure estimates.

[e]90th percentile sesame seed consumption rates were not available for children age 0 to < 7 years of age.

Supplementary Table 4. Child-specific Spice Consumption Rates Used to Calculate Potential Noncancer Health-Based Guidance Values for Spices (Excludes Sesame Seeds)[a]

	Central Tendency Estimates[b]		Upper Percentile Estimates[c]	
	Highest Consuming Race/Ethnic Group	All	Highest Consuming Age Group	All
Total Spice Consumption Rate ($mg_{spice}/kg_{bw}/day$)	97.4[d,e]	47.0[d]	131.6[d]	96[d,e]
Receptor Age (in years)	0 to < 1	0 to < 7	1 to < 2	0 to < 7
Receptor Race/Ethnic(ity) Group (includes males and females)	Non Hispanic Black	all races	all races	all races
Number of spices included in Total Consumption Rate	7	7	4	4
Highest Contributing Spice to Total Spice Consumption Rate	pepper, non-bell, dried	pepper, non-bell dried	pepper, non-bell, dried	pepper, non-bell, dried
Sample Size (n) for Highest Contributing Spice	15	1737	326	1737

[a]All spices included in calculation of total spice consumption rates met the inclusion criteria described in Appendix C. When available, consumption rates for sesame seeds were excluded from consumption rates.

[b]Total spice consumption rate is based on the sum of mean spice consumption rates for 7 available spices.

[c]Total spice consumption rate is based on the sum of 90th percentile spice consumption rates for 4 available spices.

[d]Sesame seed consumption rates were not available for these data sets.

[e]Since central tendency and upper percentile estimates are shown side by side for comparison purposes. However, these estimates represent different data sets as they are based on different groupings of number of spices included, different receptor age and race/ethnic(ity) groups, and different sample sizes. For example, the upper percentile estimate for all races/ethnic(ity) groups (96 $mg_{spice}/kg_{bw}/day$) is based on a smaller number of available spices than the central tendency estimate of 97.4 $mg_{spice}/kg_{bw}/day$ for Non-Hispanic Black. These data groupings are compared to show that several exposure assumptions were considered in deriving health-based guidance values based on different central tendency and high-end exposure estimates.

Supplementary Table 5. Adult Spice Consumption Rates Used to Calculate Potential Cancer and Noncancer Health-Based Guidance Values for Spices (All Available Spices)[a]

	Central Tendency Estimates[b]		Upper Percentile Estimates[c]	
	Highest Consuming Race/Ethnic Group	All	Highest Consuming Race/Ethnic Group	All
Total Spice Consumption Rate mg/kg/day	59[d]	32.9[d]	212.5[d]	76.3[d]
Receptor Age (in years)	21 to < 78	21 to < 78	21 to < 78	21 to < 78
Receptor Race/Ethnic(ity) Group (includes both males and females)	Mexican-American	all races	Mexican-American	all races
Number of spices included in Total Consumption Rate	8	8	7	7
Highest Contributing Spice to Total Spice Consumption Rate	sesame seed	sesame seed	sesame seed	sesame seed
Sample Size (n) for Highest Contributing Spice	268	1572	268	1572

[a]All spices included in calculation of total spice consumption rates met the inclusion criteria described in Appendix C.

[b]Total spice consumption rate is based on the sum of mean spice consumption rates for 8 available spices.

[c]Total spice consumption rate is based on the sum of 90th percentile spice consumption rates for 7 available spices.

[d]Since central tendency and upper percentile estimates are shown side by side for comparison purposes. However, these estimates represent different data sets as they are based on different groupings of number of spices included, different receptor age and race/ethnic(ity) group, and different sample sizes. These data groupings are compared to show that several exposure assumptions were considered in deriving health-based guidance values based on different central tendency and high-end exposure estimates.

Supplementary Table 6. Adult Spice Consumption Rates Used to Calculate Potential Cancer and Noncancer Health-Based Guidance Values for Spices (Excludes Sesame Seeds)[a]

	Central Tendency Estimates[b]		Upper Percentile Estimates[c]	
	Highest Consuming Race/Ethnic Group	All	Highest Consuming Race/Ethnic Group	All
Total Spice Consumption Rate mg/kg/day	19.4[d]	17.9[d]	50.0[d,e]	47.5[d]
Receptor Age (in years)	21 to < 78	21 to < 78	21 to < 78	21 to < 78
Receptor Race/Ethnic(ity) Group (includes both males and females)	other races	all races	other races	all races
Number of spices included in Total Consumption Rate	7	7	6	6
Highest Contributing Spice to Total Spice Consumption Rate	pepper, non-bell, dried	pepper, non-bell, dried	pepper, non-bell, dried	pepper, non-bell, dried
Sample Size (n) for Highest Contributing Spice	228	6287	228	6287

[a]All spices included in calculation of total spice consumption rates met the inclusion criteria described in Appendix C.

[b]Total spice consumption rate is based on the sum of mean spice consumption rates for 7 available spices.

[c]Total spice consumption rate is based on the sum of 90th percentile spice consumption rates for 6 available spices.

[d]Since central tendency and upper percentile estimates are shown side by side for comparison purposes. However, these estimates represent different data sets as they are based on different groupings of number of spices included, different receptor age and race/ethnic(ity) group, and different sample sizes. These data groupings are compared to show that several exposure assumptions were considered in deriving health-based guidance values based on different central tendency and high-end exposure estimates.

[e]Sesame seed consumption rates were not excluded from the analysis. In this case, the data were not available.

Supplementary Table 7. Reported Spice Consumption in Adults

Spice(s)	Study Location	N	Population	Ingestion Rate g/day	Body weight (BW) kg	Reported/ Assumed BW	BW-Normalized Ingestion Rate mg/kg BW-d	Notes on Method/Results	Ref.
Total spices Excl. Capsicum (chili)	USA	N/A	N/A	1	80		12.5	Recipe-derived, commodity-specific intake, 2003-06, included fresh herbs and compared intake including and excluding chili peppers.	US FDA, 2013
Total spices incl. Capsicum	USA	N/A		5	80		62.5		
Total spice	USA	N/A	N/A	0.9	80		11.3	Low-end intake/eating occasion x 3	
	USA	N/A	N/A	5.1	80		63.8	High-end intake/eating ocassion x 3	
Turmeric	India	156	adult	0.6	60	Assumed	10.0	Mean daily intake per portion size. Mean BW of 60 kg for all studies in India that do not report BW, was assumed after Thimmayamma's report (1983) and Mungreiphy's study (2012) who reported an average body weight of 54.4 kg in Indian males and females.	Siruguri and Bhat, 2015
		156		0.66	60		11.0		
Chillies		157		2.1	60		35.0		
		157		1.8	60		30.0		
Cumin		61		1.22	60		20.3		
		61		1	60		16.7		
Coriander		27		0.8	60		13.3		
		27		0.5	60		8.3		
Mustard		34		0.55	60		9.2		
		34		0.5	60		8.3		
Cardamon		6		0.67	60		11.2		
		6		0.63	60		10.5		
Black pepper		28		0.69	60		11.5		
		28		0.5	60		8.3		
Asafoetida		17		0.37	60		6.2		
		17		0.4	60		6.7		
Herbs & spices	Norway		adult	2.7	70		38.6	Median from Food frequency questionnaire incl. 27 herbs & spices	Carlsen et al., 2011
				0.19	70		2.7	Low-end from Food frequency questionnaire incl. 27 herbs & spices	
				45	70		642.9	High-end from Food frequency questionnaire incl. 27 herbs & spices	
Turmeric	India		adult	0.2	60	Reported	3.3	Low-end intake	Thimmayamma et al., 1983 in Srinivasan, 2014
				4.8	60		80.0	High-end intake	
Red pepper				2.4	60		40.0	Low-end intake	
				4.1	60		70.0	High-end intake	
Fenugreek				0.3	60		5.0	Low-end intake	
				0.6	60		10.0	High-end intake	
Turmeric	India	N/A	adult	0.24	60	Assumed	4.0	High-income household.	Krishnaswamy, 2006, in Hutchins-Wolfbrandt and Mistry, 2011
		N/A		0.49	60		8.2	Low-income household.	
		N/A		0.73	60		12.2	Rural India. Assumed	
Turmeric	India	N/A	adult	4	60		66.7		Tapsell et al., 2006 in Hutchins-Wolfbrand and Mistry, 2011
Turmeric	Nepal	N/A	adult	0.5	60		8.3	Low-end daily serving (estimated)	Eigner and Scholz, 1999 in Hutchins-Wolfbrand and Mistry, 2011
		N/A		1.5	60		25.0	High-end daily serving (estimated)	
Turmeric	India	N/A	adult	4	60		66.7		Thatte and Dahanukar, 1986 in Tantipopipat et al., 2010
Herbs & spices	Thailand	551	adult	4.9	60		81.7	Low-end in g/traditional dish, includes garlic and tamarind	Tantipopipat et al., 2010
		551		26.1	60		435.0	High-end in g/traditional dish, includes fresh chilies, garlic and shallots	

Supplementary Table 8. List of Spices in the FCID Category Group 19, or Other Categories, that Were Included or Excluded from Data Analysis and Reasons for their Inclusion or Exclusion[a]

Spice name [(a)]	Included/ Excluded.	Reason for Inclusion				Reasons for Exclusion			
		Imported	Dried/ Powdered	Potential for Adulteration	High N	Unlikely Imported	Fresh	Potential for Adulteration	Low N
Basil, fresh leaves	Excluded						✓		
Basil, dried leaves	Excluded					✓			
Chive, dried leaves	Excluded								✓
Herbs, other	Excluded						✓		
Lemongrass	Excluded					✓	✓		
Marjoram	Excluded								
Parsley, dried leaves	Excluded					✓			
Savory	Excluded								
Cinnamon	Included	✓			✓				
Coriander, seed	Excluded								
Dill, seed	Excluded					✓			✓
Pepper, black and white	Included	✓							
Spices, other	Included	✓			✓				
Sesame, seed	Included	✓							
Ginger, dried	Included	✓							
Turmeric	Included	✓		✓					
Pepper, bell	Excluded						✓		
Pepper, bell, dried	Included	✓		✓	✓				
Pepper, non-bell	Excluded						✓		
Pepper, non-bell dried	Included	✓		✓	✓				
Peppermint	Excluded					✓			

[a] FCID, 2019. All commodities listed as "Fresh" and "Baby Food" were excluded.

Supplementary Table 9A. Ingestion Rates from FCID and Estimated Daily Consumption Rates of Selected Spices by Age (All Races, All Genders)

Age Range	Mean BW (kg)	Cinnamon					Pepper, Black and White				
		N	Ingestion rate (g/d)		Cons. Rate (mg/kg/d)		N	Ingestion rate (g/d)		Cons. Rate (mg/kg/d)	
			Mean	90th Pctl.	Mean	90th Pctl.		Mean	90th Pctl.	Mean	90th Pctl.
Birth to < 1 year	7.8	80	0.05	0.1†	6.4	-	198	0.02	<0.05	2.6	-
1 to < 2 years	11.4	240	0.06	0.2	5.3	17.5	628	0.02	<0.05	1.8	-
2 to < 3 years	13.8	263	0.08	0.3	5.8	21.7	705	0.02	0.1	1.4	7.2
3 to < 4 years	18.6	172	0.12	0.3†	6.5	-	431	0.02	0.1	1.1	5.4
4 to < 5 years	18.6	199	0.12	0.3	6.5	16.1	488	0.02	<0.05	1.1	-
5 to < 6 years	18.6	185	0.17	0.5†	9.1	-	436	0.02	0.1	1.1	5.4
6 to < 7 years	31.8	176	0.13	0.4†	4.1	-	481	0.02	0.1	0.6	3.1
7 to < 8 years	31.8	204	0.14	0.4	4.4	12.6	467	0.02	0.1	0.6	3.1
8 to < 9 years	31.8	187	0.16	0.5†	5.0	-	484	0.02	0.1	0.6	3.1
9 to < 10 years	31.8	182	0.14	0.4†	4.4	-	484	0.03	0.1	0.9	3.1
10 to < 11 years	31.8	197	0.15	0.4	4.7	12.6	458	0.02	0.1	0.6	3.1
11 to < 12 years	56.8	231	0.31	0.7	5.5	12.3	528	0.03	0.1	0.5	1.8
12 to < 13 years	56.8	204	0.21	0.5	3.7	8.8	500	0.02	0.1	0.4	1.8
13 to < 14 years	56.8	196	0.16	0.5	2.8	8.8	468	0.03	0.1	0.5	1.8
14 to < 15 years	56.8	199	0.2	0.6	3.5	10.6	480	0.04	0.1	0.7	1.8
15 to < 16 years	56.8	223	0.17	0.6	3.0	10.6	443	0.02	0.1	0.4	1.8
16 to < 17 years	56.8	244	0.21	0.6	3.7	10.6	502	0.03	0.1	0.5	1.8
17 to < 18 years	71.6	217	0.15	0.5	2.1	7.0	436	0.03	0.1	0.4	1.4
18 to < 19 years	71.6	189	0.2	0.6†	2.8	-	393	0.04	0.1	0.6	1.4
19 to < 20 years	71.6	185	0.2	0.7†	2.8	-	416	0.03	0.1	0.4	1.4
20 to < 21 years	71.6	95	0.24	0.7†	3.4	-	221	0.03	0.1	0.4	1.4
21 to < 78 years	80.0	6679	0.14	0.5	1.8	6.3	11756	0.05	0.1	0.6	1.3

Age Range		Spices, Other					Turmeric				
		N	Ingestion rate (g/d)		Cons. Rate (mg/kg/d)		N	Ingestion rate (g/d)		Cons. Rate (mg/kg/d)	
			Mean	90th Pctl.	Mean	90th Pctl.		Mean	90th Pctl.	Mean	90th Pctl.
Birth to < 1 year	7.8	382	0.08	0.2	10.3	25.6	38	0.04	0.1†	5.1	-
1 to < 2 years	11.4	959	0.13	0.4	11.4	35.1	115	0.03	0.1†	2.6	-
2 to < 3 years	13.8	1046	0.16	0.4	11.6	29.0	164	0.03	0.1†	2.2	-
3 to < 4 years	18.6	661	0.2	0.6	10.8	32.3	120	0.03	0.1†	1.6	-
4 to < 5 years	18.6	719	0.22	0.5	11.8	26.9	122	0.04	0.1†	2.2	-
5 to < 6 years	18.6	655	0.22	0.6	11.8	32.3	122	0.03	0.1†	1.6	-
6 to < 7 years	31.8	690	0.29	0.8	9.1	25.2	128	0.04	0.1†	1.3	-
7 to < 8 years	31.8	678	0.23	0.7	7.2	22.0	118	0.04	0.1†	1.3	-
8 to < 9 years	31.8	703	0.27	0.7	8.5	22.0	136	0.04	0.1†	1.3	-
9 to < 10 years	31.8	699	0.35	0.8	11.0	25.2	118	0.03	0.1†	0.9	-
10 to < 11 years	31.8	695	0.33	0.8	10.4	25.2	145	0.05	0.1†	1.6	-
11 to < 12 years	56.8	766	0.43	1.1	7.6	19.4	146	0.05	0.1†	0.9	-
12 to < 13 years	56.8	742	0.43	0.9	7.6	15.8	124	0.04	0.1†	0.7	-
13 to < 14 years	56.8	723	0.39	0.9	6.9	15.8	125	0.04	0.1†	0.7	-
14 to < 15 years	56.8	743	0.36	0.9	6.3	15.8	128	0.05	0.1†	0.9	-
15 to < 16 years	56.8	729	0.44	1	7.7	17.6	163	0.04	0.1†	0.7	-
16 to < 17 years	56.8	786	0.41	0.9	7.2	15.8	145	0.05	0.1†	0.9	-
17 to < 18 years	71.6	721	0.47	1.2	6.6	16.8	165	0.05	0.1†	0.7	-
18 to < 19 years	71.6	654	0.47	1.2	6.6	16.8	170	0.04	0.1†	0.6	-
19 to < 20 years	71.6	655	0.53	1.6	7.4	22.3	159	0.04	0.1†	0.6	-
20 to < 21 years	71.6	340	0.46	1.1	6.4	15.4	88	0.08	0.2†	1.1	-
21 to < 78 years	80.0	18411	0.51	1.2	6.4	15.0	3752	0.05	0.1	0.6	1.3

† Some values in the Food Commodity Intake Database (FCID, 2019) were marked as "less statistically reliable" and therefore were not considered in the estimation of the consumption rates.

Supplementary Table 9B. Ingestion Rates from FCID and Estimated Daily Consumption Rates of Selected Spices by Age (All Races All Genders)

Age Range	Mean BW (kg)	Pepper, Bell, Dried					Pepper, Nonbell, Dried				
		N	Ingestion rate (g/d)		Cons. Rate (mg/kg/d)		N	Ingestion rate (g/d)		Cons. Rate (mg/kg/d)	
			Mean	90th Pctl.	Mean	90th Pctl.		Mean	90th Pctl.	Mean	90th Pctl.
Birth to < 1 year	7.8	17	0.02	0.1†	2.6	-	92	0.22	0.7†	23.7	-
1 to < 2 years	11.4	51	0.02	<0.05†	1.8	-	326	0.32	0.9	28.1	78.9
2 to < 3 years	13.8	61	0.02	<0.05†	1.4	-	362	0.34	1	25.2	72.5
3 to < 4 years	18.6	48	0.03	0.1†	1.6	-	243	0.4	1	25.2	53.8
4 to < 5 years	18.6	51	0.03	0.1†	1.6	-	258	0.55	1.5	29.7	80.6
5 to < 6 years	18.6	32	0.05	0.1†	2.7	-	226	0.38	1.1	18.4	59.1
6 to < 7 years	31.8	53	0.05	0.1†	1.6	-	230	0.37	1.4	16.4	44.0
7 to < 8 years	31.8	63	0.05	0.1†	1.6	-	250	0.66	1.9	24.1	59.7
8 to < 9 years	31.8	39	0.04	0.1†	1.3	-	230	0.46	1.4	14.7	44.0
9 to < 10 years	31.8	54	0.09	0.1†	2.8	-	243	0.51	1.9	14.1	59.7
10 to < 11 years	31.8	56	0.05	0.2†	1.6	-	284	0.53	2.1	13.4	66.0
11 to < 12 years	56.8	57	0.05	0.1†	0.9	-	263	0.49	1.3	11.0	22.9
12 to < 13 years	56.8	49	0.04	0.1†	0.7	-	240	0.63	1.9	12.5	33.5
13 to < 14 years	56.8	49	0.05	0.1†	0.9	-	245	0.54	1.9	9.5	33.5
14 to < 15 years	56.8	51	0.12	0.2†	2.1	-	236	0.62	2.1	10.1	37.0
15 to < 16 years	56.8	56	0.08	0.1†	1.4	-	234	0.61	1.9	9.3	33.5
16 to < 17 years	56.8	80	0.18	0.3†	3.2	-	240	0.59	1.5	8.7	26.4
17 to < 18 years	71.6	59	0.14	0.3†	2.0	-	247	0.74	2.1	11.1	29.3
18 to < 19 years	71.6	69	0.07	0.1†	1.0	-	225	0.63	1.9	9.0	26.5
19 to < 20 years	71.6	64	0.06	0.1†	0.8	-	241	0.56	1.5	7.5	20.9
20 to < 21 years	71.6	51	0.09	0.3†	1.3	-	135	0.52	1.9†	7.0	-
21 to < 78 years	80.0	3513	0.11	0.2	1.4	2.5	6287	0.54	1.7	6.8	21.3

Age Range	Mean BW (kg)	Sesame, Seed					Ginger, Dried				
		N	Ingestion rate (g/d)		Cons. Rate (mg/kg/d)		N	Ingestion rate (g/d)		Cons. Rate (mg/kg/d)	
			Mean	90th Pctl.	Mean	90th Pctl.		Mean	90th Pctl.	Mean	90th Pctl.
Birth to < 1 year	7.8	5	2.52	8.4†	271.0	-	97	0.01	<0.05†	1.1	-
1 to < 2 years	11.4	34	0.53	0.3†	46.5	-	467	0.01	<0.05	0.9	-
2 to < 3 years	13.8	59	0.21	0.5†	15.6	-	566	0.01	<0.05	0.7	-
3 to < 4 years	18.6	28	0.36	1.1†	22.6	-	358	0.01	<0.05	0.6	-
4 to < 5 years	18.6	55	0.53	1.7†	28.6	-	392	0.01	<0.05	0.5	-
5 to < 6 years	18.6	27	0.38	0.2†	18.4	-	379	0.01	<0.05	0.5	-
6 to < 7 years	31.8	43	0.51	0.4†	22.7	-	410	0.01	<0.05	0.4	-
7 to < 8 years	31.8	32	0.55	0.3†	20.1	-	397	0.01	<0.05	0.4	-
8 to < 9 years	31.8	45	0.57	0.5†	18.2	-	425	0.01	<0.05	0.3	-
9 to < 10 years	31.8	42	0.9	1.7†	24.9	-	427	0.01	<0.05	0.3	-
10 to < 11 years	31.8	73	0.75	1.3†	19.0	-	391	0.01	<0.05	0.3	-
11 to < 12 years	56.8	56	0.13	0.3†	2.9	-	459	0.02	<0.05	0.4	-
12 to < 13 years	56.8	43	0.73	1.3†	14.5	-	431	0.01	<0.05	0.2	-
13 to < 14 years	56.8	58	0.29	0.6†	5.1	-	409	0.01	<0.05	0.2	-
14 to < 15 years	56.8	57	0.41	0.3†	6.7	-	427	0.04	<0.05	0.7	-
15 to < 16 years	56.8	77	0.49	1.1†	7.4	-	389	0.03	<0.05	0.5	-
16 to < 17 years	56.8	91	0.68	3.6†	10.0	-	452	0.02	<0.05	0.3	-
17 to < 18 years	71.6	63	1.1	3.1†	16.5	-	376	0.02	<0.05	0.3	-
18 to < 19 years	71.6	60	2.55	12.5†	36.3	-	330	0.02	<0.05	0.3	-
19 to < 20 years	71.6	57	1.17	1.3†	15.7	-	358	0.02	<0.05	0.3	-
20 to < 21 years	71.6	27	0.44	0.4†	5.9	-	185	0.01	<0.05†	0.1	-
21 to < 78 years	80.0	1572	1.2	2.3	15.0	28.8	9244	0.03	<0.05	0.4	-

† Some values in the Food Commodity Intake Database (FCID, 2019) were marked as "less statistically reliable" and therefore were not considered in the estimation of the consumption rates.

Supplementary Table 10. Total Spice Consumption Rates (Including Sesame Seeds) in Children and Adults

Exposure Level	Race/Ethnic(ity)	Total Ingestion Rate (g/d)		Total Consumption Rate[a] (mg/kg-BW/d)		Number of Reliable Values[b]
		Children	Adults	Children	Adults	
Central Tendency (Mean)	All races	1.5	2.6	114.0	32.9	64
	Mexican -Americans	2.6	4.7	186.5	59.0	63
	Non-Hispanic Black	1.0	1.7	62.5	21.3	63
	Non-Hispanic White	0.9	2.5	56.1	30.6	46
	Other Hispanic	2.7	3.7	224.2	46.1	63
	Other Races Inc. Multiple	1.5	3.2	102.3	40.5	61
High-end (90th Pctl.)	All races	1.7	6.1	96.0	76.3	27
	Mexican -Americans	0.4	17.0	22.7	212.5	12
	Non-Hispanic Black	-	3.6	-	45.0	6
	Non-Hispanic White	0.4	5.3	26.3	66.3	10
	Other Hispanic	-	3.8	-	47.5	6
	Other Races Inc. Multiple	-	4.1	-	50.0	6

[a]Includes: children (0 to < 7 years old) and adults (21 to <78 years old)
[b]Some values in the Food Commodity Intake Database (FCID, 2019) were marked as "less statistically reliable" and therefore were not considered in the estimation of the consumption rates.

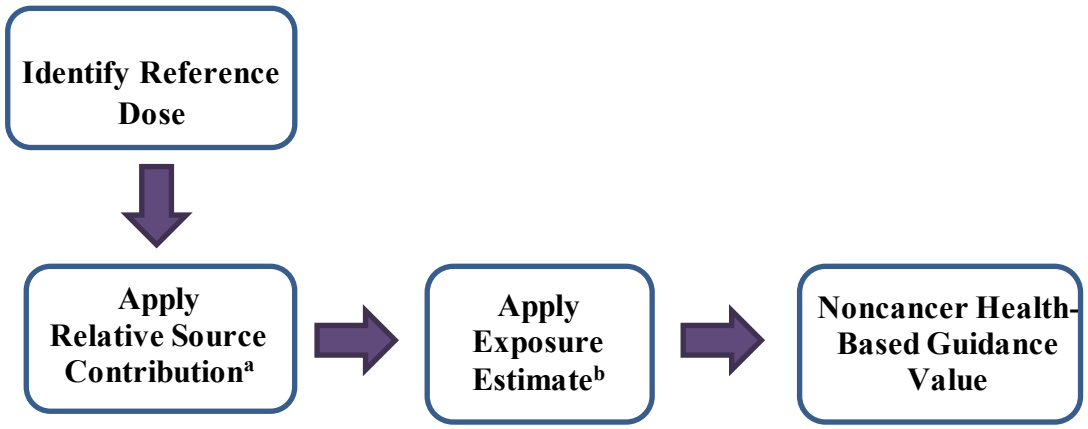
Supplementary Table 11. Total Spice Consumption Rates (Excluding Sesame Seeds) in Children and Adults

Exposure Level	Race/Ethnic(ity)	Total Ingestion Rate (g/d)		Total Consumption Rate[a] (mg/kg-BW/d)		Number of Reliable Values[b]
		Children	Adults	Children	Adults	
Central Tendency (Mean)	All races	0.8	1.5	47.0	17.9	56
	Mexican -Americans	0.8	1.54	49.9	19.3	55
	Non-Hispanic Black	0.7	1.3	43.8	16.3	56
	Non-Hispanic White	0.9	1.44	56.1	18.0	55
	Other Hispanic	0.7	1.41	43.8	17.6	55
	Other Races Inc. Multiple	0.8	1.55	42.5	19.4	7
High-end (90th Pctl.)	All races	1.7	3.8	96.0	47.5	26
	Mexican -Americans	0.4	3.5	22.7	48.9	11
	Non-Hispanic Black	0.0	1.7	0.0	45.0	6
	Non-Hispanic White	0.4	3.8	22.5	47.5	13
	Other Hispanic	0.0	3.8	0.0	47.5	6
	Other Races Inc. Multiple	0.0	4.1	0.0	50.0	5

[a]Includes: children (0 to < 7 years old) and adults (21 to <78 years old)
[b]Some values in the Food Commodity Intake Database (FCID, 2019) were marked as "less statistically reliable" and therefore were not considered in the estimation of the consumption rates.

Figures

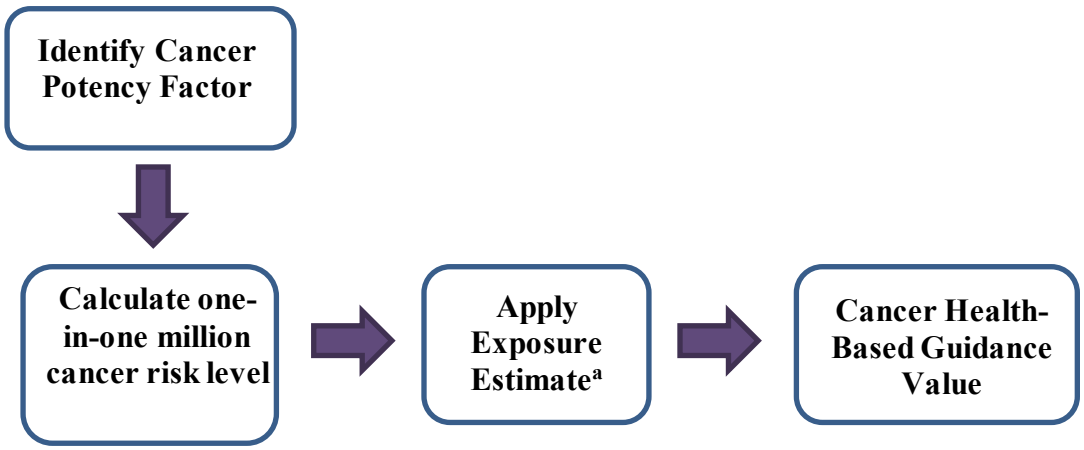
Supplementary Figure 1. Schematic Diagram of Procedure for Calculating Noncancer Health-Based Guidance Values for Spices



[a]Adjustment to the reference dose to account for other potential sources of exposure (e.g., air, water, soil, etc).

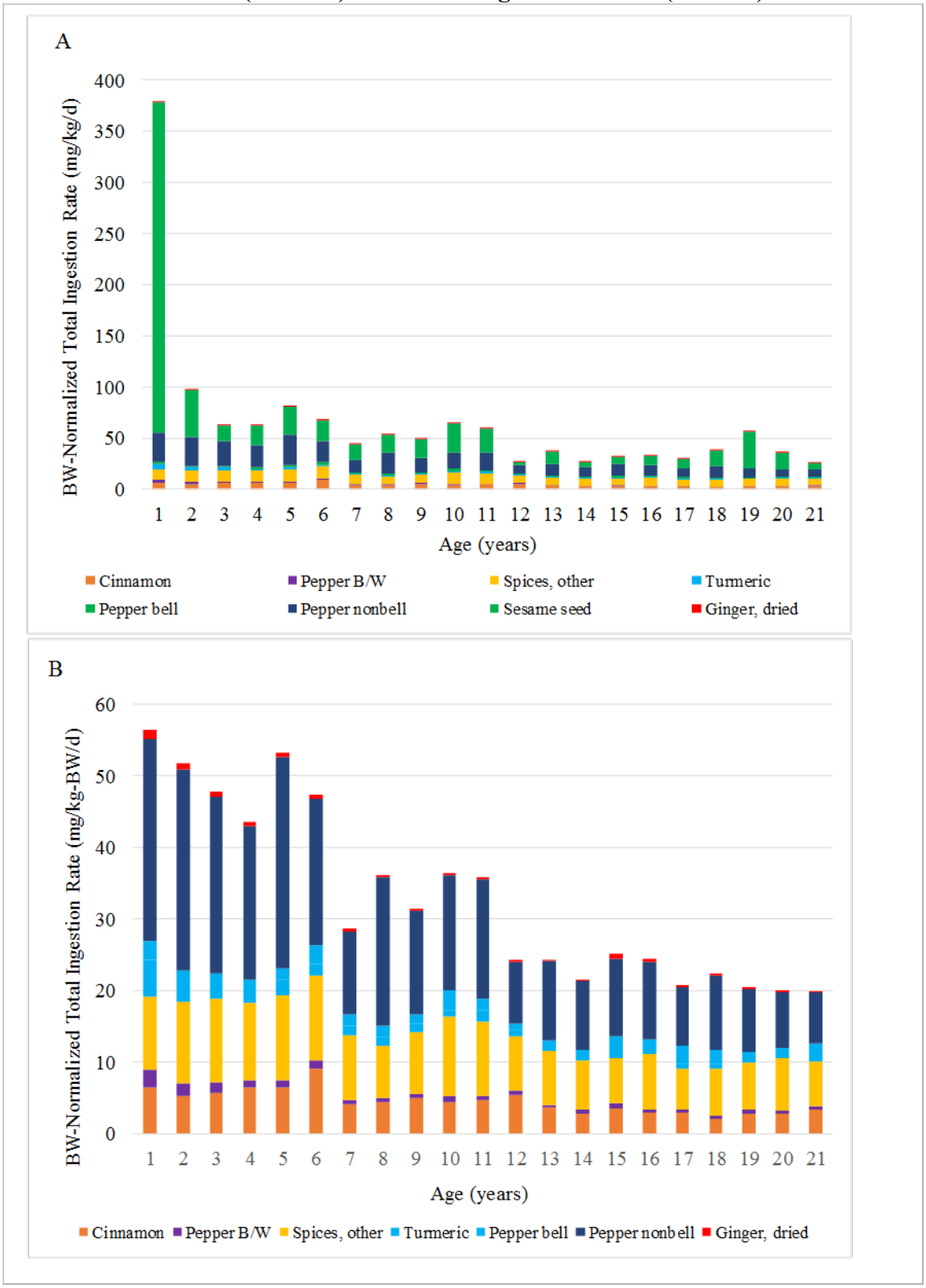
[b]Evaluate available spice consumption data to identify average and high-end exposure estimates for children and adults, across different race/ethnic(ity) groups

Supplementary Figure 2. Schematic Diagram of Procedure for Calculating Cancer Health-Based Guidance Values for Spices

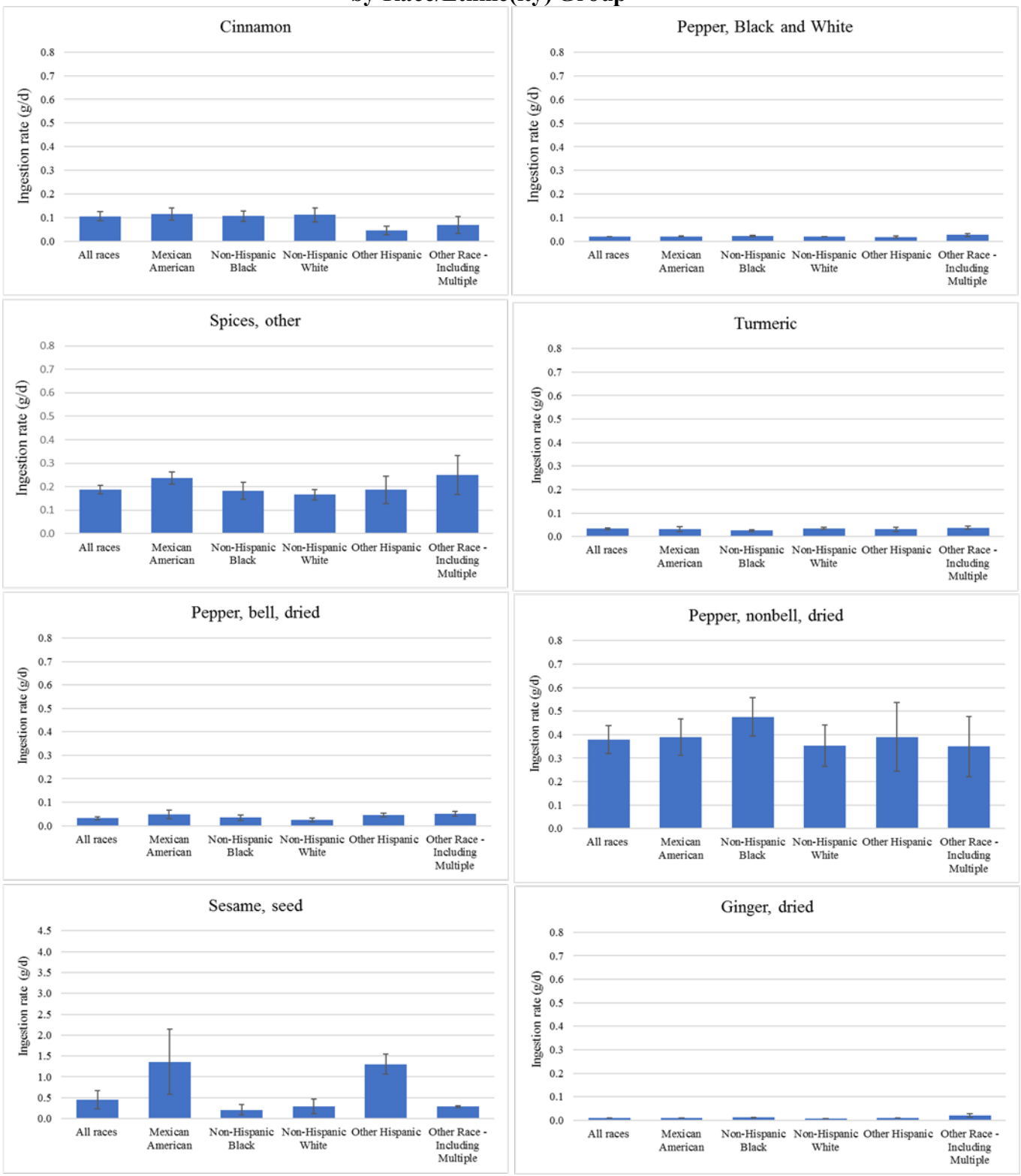


[a]Evaluate available spice consumption data to identify average and high-end exposure estimates for adults, across different race/ethnic(ity) groups

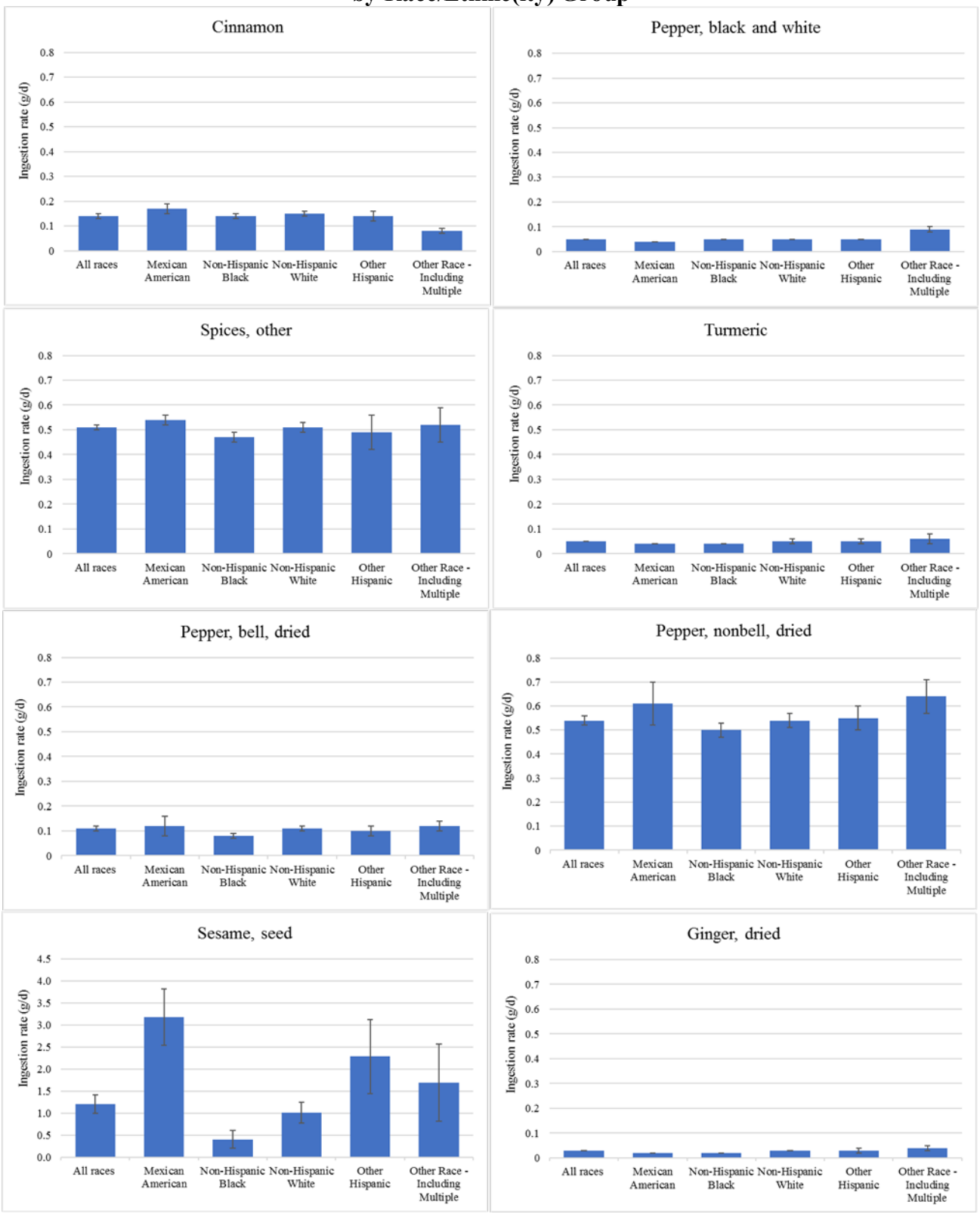
Supplementary Figure 3. Body Weight Normalized Total Ingestion Rate (Consumption Rate) in Children (0 To < 21 Years, All Races, All Genders) Including Sesame Seed (Panel A) and Excluding Sesame Seed (Panel B)



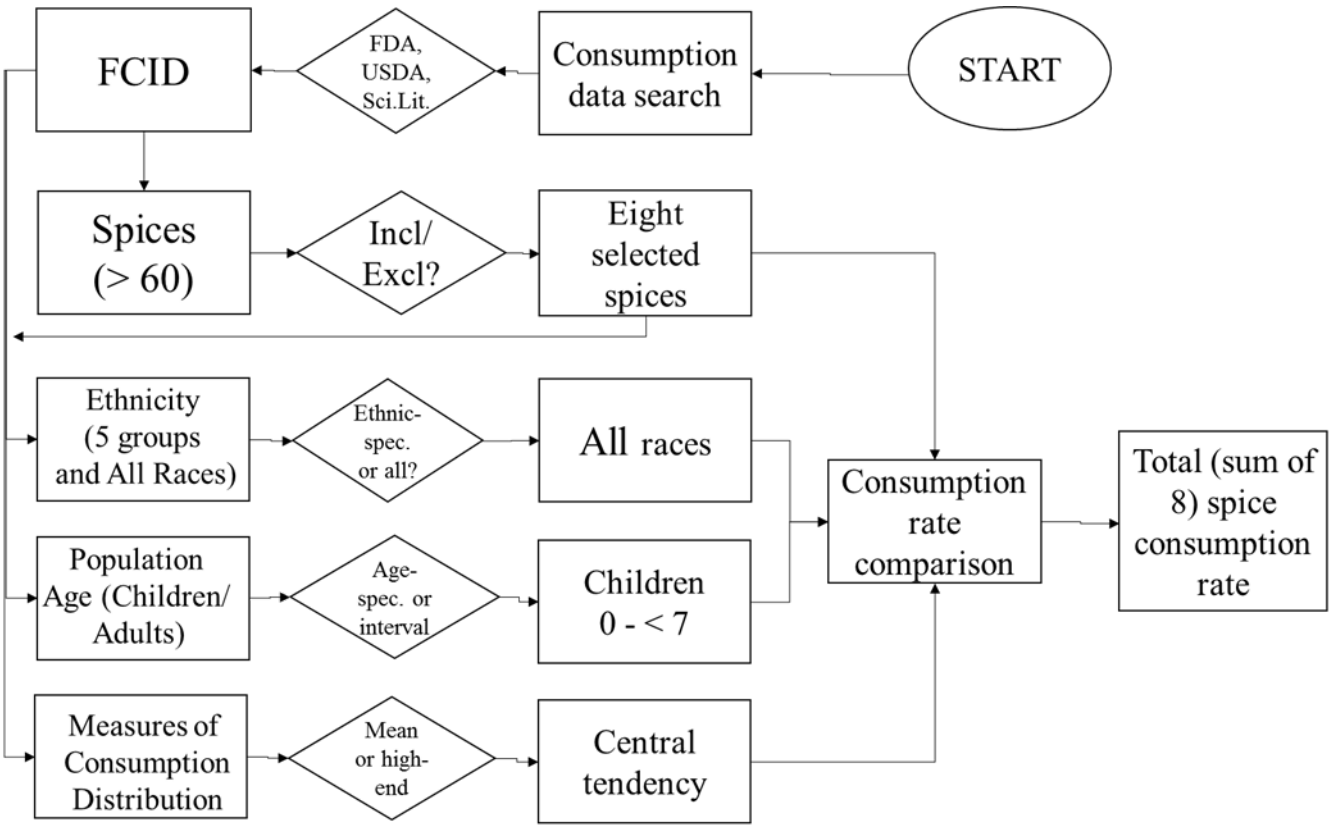
Supplementary Figure 4. Mean Child Ingestion Rates (0 to < 7 years) of Eight Selected Spices by Race/Ethnic(ity) Group



Supplementary Figure 5. Mean Adult Ingestion Rate of Eight Spices by Race/Ethnic(ity) Group



Supplementary Figure 6. Flow Diagram of the Exposure Assessment Process



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