



# Burden of Disease of Dietary Exposure to Four Chemical Contaminants in Denmark, 2019

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## Abstract

Exposure to chemical contaminants found in foods has been associated with diverse adverse health effects. The aim of this study was to estimate the burden of disease associated with dietary exposure to four chemicals in Denmark in 2019: lead (Pb), cadmium (Cd), methylmercury (MeHg), and inorganic arsenic (i-As). We collected national food consumption and chemical food monitoring data from Danish databases, dose-response and severity data from the scientific literature, and disease incidence and population numbers from national statistics. We adopted a risk assessment approach to estimate disease burden, quantifying incidence, mortality, and Disability-Adjusted Life Years (DALYs) attributable to dietary exposure to the chemicals. In all models, we propagated uncertainty around the input parameters through the calculations using Monte Carlo simulation. We estimated that, among these chemicals, Pb and MeHg were responsible for the highest disease burden. MeHg led to the loss of nearly 600 healthy life years, or approximately 10 DALYs per 100,000 inhabitants. Dietary exposure to Pb was estimated to cause 383 to 1,261 DALYs, corresponding to 6.6 (lower bound) to 22 (upper bound) DALYs/100,000 per year. The foods contributing most to disease burden were fish (MeHg) and sweets, fruit, and bread and cereals (Pb). The burden attributed to dietary exposure to i-As (5 DALYs) and Cd (0.04 DALY) was substantially lower. Interpretation of estimates needs to consider all underlying uncertainties, linked with data and knowledge gaps. These estimates are useful supplements to traditional risk assessment to guide food safety interventions and inform dietary guidelines for different population groups.

**Keywords** Methylmercury · Arsenic · Cadmium · Lead · DALY · Diet · Health impact

## Introduction

Foods may be contaminated with chemicals of natural origin or resulting from primary production, processing, packaging, or environmental contamination. Numerous adverse health effects are associated with exposure to chemical contaminants found in foods, and well-established associations include various forms of cancer, cardiovascular, neurological, and reproductive disorders (EFSA 2010, 2012a; IARC 2012). Exposure through diet depends on the levels of contamination of the foods one has access to, and on the prevailing dietary patterns. In Denmark, as in many other countries, some chemical contamination of foods is regulated and monitored. For many food-associated chemicals, thresholds of maximum exposure levels are established and enforced based on the available evidence, data, and risk assessments to control the exposure in populations (European Commission 2006).

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Risk assessments compare exposure to chemical contaminants with toxicological data and health-based guidance values (HBGV) to assess if levels of exposure are of health concern to the population (FAO/WHO 2009). However, estimates of the actual public health impact of dietary exposure to chemicals in the population are lacking, as are rankings of the chemical hazards causing the highest burden of disease and of the foods contributing most to this burden. These are useful to inform national-level public health strategies to prevent foodborne exposure and disease.

The aim of this study was to estimate the burden of disease associated with dietary exposure to four chemicals in Denmark in 2019: lead (Pb), cadmium (Cd), methylmercury (MeHg), and inorganic arsenic (i-As). We estimated burden of disease using the Disability-Adjusted Life Year (DALY), a composite health metric, and estimated the relative contribution of different foods to this burden. Additionally, we assessed the population dietary exposure to the contaminants against established health-based guidance values and reference doses.

## Materials and Methods

We adopted a risk assessment approach to estimate disease burden, quantifying the incidence, mortality and DALYs attributable to dietary exposure to the chemical hazards. We describe the detailed methodology for each chemical below. In all models, we propagated uncertainty around the input parameters through the calculations using 1000 Monte Carlo simulations. When information on the variability of input parameters was available, this was included in the model but separated from uncertainty by applying two-dimensional Monte Carlo simulation (100,000 iterations for variability). We reported the number of cases, deaths, total DALYs and DALYs per 100,000 individuals as the mean of the variability dimension and the median of the uncertainty dimension with 2.5th and 97.5th percentiles reflecting the 95% uncertainty interval (UI). All calculations were conducted in R version 4.0.3 (R Core Team 2018). We used R's `mc2d` package to define probability distributions. To assess how exposure to each contaminant compares to the health-based guidance values and reference doses, we compared the estimated dietary exposure of the population to each contaminant against the reference values established by the European Food Safety Authority (EFSA).

### Chemical contaminants and health outcomes

We included four chemicals on the basis of available data and of the chemical contaminant's presumed public health impact in the population: Pb, Cd, MeHg and i-As.

Pb occurs naturally in the environment, but mainly as a consequence of anthropogenic activities. The inorganic form of Pb predominates in the environment (EFSA 2010). Foods are contaminated with Pb via different routes such as contaminated water or atmospheric deposition on agricultural crops, but also during food processing, handling or packaging (EFSA 2010; Carrington et al. 2019). Exposure to Pb may affect renal function, hematopoiesis, and the developing central nervous system (Carrington et al. 2019). Exposure to Pb may also increase the systolic blood pressure (EFSA 2010). The neurotoxic effects of Pb in exposed children below the age of seven are well established and have been found to increase the risk of intellectual disability, measured in terms of lowering the intelligence quotient (IQ) (Lanphear et al. 2005; EFSA 2010; Carrington et al. 2019). The EFSA's Panel on Contaminants in the Food Chain (CONTAM) determined the benchmark dose lower confidence limit for a 0.1% increased incidence of intellectual deficits in children, measured by the Full Scale IQ score (BMDL01) of 0.50 µg Pb/kg of body weight (bw) per day. At slightly higher doses, effects on the kidney and systolic blood pressure have been observed.

Like Pb, Cd is naturally occurring in the environment in its inorganic form, with anthropogenic activities adding to the pollution in soil, water and living organisms. Smoking may contribute considerably to exposure in humans; however, in non-smoking individuals, food is the primary source (EFSA 2009a). The primary target of Cd toxicity are the kidneys, where it accumulates over a lifetime. Human studies on Cd exposure in workers and individuals living in areas with a low, moderate, or high Cd pollution have found increased exposure to be associated with a lower glomerular filtration rate (GFR), a measure of kidney function that describes the flow rate of filtered fluid through the kidney (Järup et al. 1995; Åkesson et al. 2005). The established tolerable weekly intake (TWI) for cadmium is 2.5 µg/kg b.w (EFSA 2009a).

Mercury (Hg) occurs in the environment, both naturally and via anthropogenic activities. The most prevalent form of Hg in foods is MeHg, which is also the most toxic form. MeHg may contaminate fish and other seafood as a consequence of environmental contamination of waters (EFSA 2004, 2012a). The EFSA CONTAM Panel evaluated that other foods than fish and seafood mostly contain inorganic Hg and that the contribution from these sources to MeHg exposure is negligible (EFSA 2004). MeHg is a known neurotoxin and the association between in utero exposure to MeHg and the compromised neurodevelopment is well established, mostly using IQ as a measure for neurodevelopment (EFSA 2012a). For MeHg, epidemiological studies from the Seychelles Child Developmental Study Nutrition Cohort have indicated that n-3 long-chain polyunsaturated fatty acids in fish may counteract negative effects from MeHg exposure (Strain et al. 2008, 2012; Stokes-Riner et al.

2011). Together with the information that beneficial nutrients in fish may have confounded previous adverse outcomes in child cohort studies from the Faroe Islands, the Panel established a TWI for MeHg of 1.3 µg/kg bw, expressed as Hg.

i-As is the inorganic form of arsenic, a metalloid naturally present in the earth's crust, as well as an anthropogenic pollutant, thus widely distributed in the environment (soil, air and water). Humans are mainly exposed to I-As, the form that is toxic to humans, through drinking water and cereal-based foods as a consequence of contaminated soil and irrigation waters (Hughes et al. 2011; IARC 2012; European Food Safety Authority (EFSA) 2014). i-As is classified as carcinogenic to humans and the association between dietary exposure to i-As and the risk of developing cancers of the lung, bladder, and skin (non-melanoma) is well established, based on evidence from prospective cohort studies performed in populations of both high- and low i-As exposure from water and foods (IARC 2012). The EFSA CONTAM Panel identified a BMDL<sub>01</sub> for risk of cancer of the lung, skin and bladder, as well as skin lesions between 0.3 and 8 µg/kg bw/day (European Food Safety Authority (EFSA) 2014).

## Exposure assessment

We used data on food consumption for Danish individuals aged 4–75 years from the Danish National Survey of Diet and Physical Activity (DANSDA), 2011–2013—a 7-day nation-wide, cross-sectional survey of diet and physical activity in a representative sample of individuals in the Danish population, drawn from random sampling from the civil population registration system (Petersen et al. 2015). Participants of the survey answered a pre-coded semi-closed food diary consisting of categories with common foods and dishes in the Danish diet (Knudsen et al. 2011).

Data on the concentrations of the four heavy metals were collected from Danish food monitoring of foods of both Danish and non-Danish origin on the Danish market in the period between 2004 and 2011 (Petersen et al. 2015). Foods were selected based on the presence of each metal in collected samples. When information on the number of samples from different sources of food sampling was available, we applied a mean weighted by the number of samples across food sampling sources. If the number of samples was not available, all data sources were given the same weight. The concentration of the four chemicals in food categories is presented in Supplementary Material 1.

We estimated the observed individual mean (OIM) dietary exposure to each chemical as a measure for long-term average daily exposure,  $y_{mi}$  (µg/kg bw/day), in the Danish population as:

$$y_{mi} = \frac{\sum_f x_{fi} \cdot c_{fm}}{bw_i} \quad (1)$$

where  $x_{fi}$  is the mean daily intake of food  $f$  in g/day (average over seven days) for individual  $i$ ,  $c_{fm}$  is the mean concentration of heavy metal  $m$  in food  $f$  (in µg/g) and  $bw_i$  is the body weight in kg for individual  $i$  (Bingham et al. 1994). Different aggregations of exposure to the chemicals were used depending on the subgroups (age, gender) affected and the associated health outcomes (cf. Sections "Lead", "Cadmium", "Methylmercury", "Inorganic Arsenic").

## Lead

Exposure to Pb was calculated for 5-year-old children with no gender differentiation by computing the mean daily exposure given the mean daily consumption and the concentration per ingredient. We focused on this age group to ensure coherence with dose–response evidence (see section "Lead"). The forty six individuals in this age group were extracted from DANSDA with a body weight ranging from 15 to 28 kg. We converted the estimated mean daily dietary Pb exposure (expressed in µg/day, thus not scaled by body-weight as in Eq. 1) to lead concentration in blood (µg/dL) using a conversion factor censored within a lower [0.052 µg/dL (µg Pb/day)<sup>-1</sup>] and an upper [0.16 µg/dL (µg Pb/day)<sup>-1</sup>] limit by multiplying the conversion factor with the mean daily dietary Pb exposure (WHO 2011).

## Cadmium

Mean exposure to Cd was calculated for the whole population with no gender differentiation based on consumption data for 3669 individuals of 4–75 years from DANSDA. The mean lifetime exposure to Cd from 4 to 75 years was assumed to also represent exposure at 75+ years of age. We converted dietary exposure to Cd into cadmium concentration eliminated through urine (UCd) using the one-compartment toxicokinetic model described in (Amzal et al. 2009). The half-life of Cd in the body is estimated to be between 3 and 35 years. A physiological parameter and elimination factor (FKFU) was set to be 0.005 (Amzal et al. 2009).

## Methylmercury

Exposure to MeHg from fish and seafood consumption was calculated for women in fertile age (15–49 years old). Females in childbearing age were subdivided in seven 5-year groups. MeHg has been estimated to constitute 80–100% of total mercury in fish and 50–80% in other seafood (EFSA 2012a). Total Hg concentration data were converted to

**Table 1** Disability weights [95% Uncertainty Interval (UI)] of all health outcomes considered to estimate disability-adjusted life years attributed to exposure to lead, methylmercury, cadmium, and inorganic arsenic through foods in Denmark

Health outcome	Disability weight (95% UI) <sup>a</sup>
Chronic kidney disease—stage 4	0.104 (0.070–0.147)
Chronic kidney disease—stage 5 (on dialysis)	0.571 (0.398–0.725)
Borderline intellectual functioning (IQ 70–84)	0.011 (0.005–0.020)
Mild intellectual disability (IQ 50–69)	0.043 (0.026–0.064)
Moderate intellectual disability (IQ 35–49)	0.100 (0.066–0.142)
Severe intellectual disability (IQ 20–34)	0.160 (0.107–0.226)
Profound intellectual disability (IQ <20)	0.200 (0.133–0.283)
Cancer diagnosis and primary care	0.288 (0.193–0.399)
Cancer remission	0.18–0.47 <sup>b</sup>
Metastatic carcinoma	0.451 (0.307–0.600)
Terminal cancer	0.540 (0.377–0.687)
Bladder cancer sequelae—impotence	0.019 (0.010–0.034)
Bladder cancer sequelae—incontinence	0.142 (0.094–0.204)

<sup>a</sup>All disability weights are obtained from the Global Burden of Disease 2010 study (Salomon et al. 2015), except when stated otherwise. Pert distributions were applied to propagated uncertainty in disability weights

<sup>b</sup>Disability weight obtained from the Australian Burden of Disease Study. A uniform distribution is applied to propagate uncertainty for this disability weight

MeHg concentrations by assuming that 100% and 80% of total Hg in fish and other seafood, respectively, is MeHg to avoid underestimating the MeHg attributable health impact. We calculated mean daily exposure per kilogram of bw per age group.

### Inorganic Arsenic

Exposure to i-As was calculated as a mean over the population (4–75 years of age) by computing the observed mean daily exposure per kg/bw across age groups, and was interpreted as the mean daily exposure over a lifetime. Like for Cd, we assumed that the mean lifetime exposure to Cd from 4 to 75 years also represents exposure at 75+ years of age. Data on i-As concentration in foods on the Danish market were available and no assumption of As/i-As ratio was needed. However, we assumed a 100% bioavailability of i-As.

### Burden of Disease Estimation

We estimated the annual number of cases (AC) attributable to exposure to each chemical by combining the estimated exposure with dose-response models. We then estimated incidence-based DALYs for each health outcome as the sum of the Years Lived with Disability (YLD) and the Years of Life Lost (YLL) due to premature mortality caused by the disease (Devleeschauwer et al. 2014).

YLD was estimated as:

$$YLD = AC \cdot D \cdot DW \quad (2)$$

where  $D$  is the duration of the health outcome, and  $DW$  its disability weight (Salomon et al. 2015). Disability weights and associated uncertainty intervals (UI) used to calculate YLD are listed in Table 1. We described the uncertainty around the disability weights by either a PERT (Pb, Cd, MeHg, i-As) or uniform (i-As) distribution. YLL was calculated as:

$$YLL = AD \cdot SEYLL \quad (3)$$

where  $AD$  is the number of deaths due to the health outcome and  $SEYLL$  is the Standard Expected Years of Life Lost, i.e., the projected frontier life expectancy for 2050 published by the World Health Organization (World Health Organization 2018). The attributable disease burden per 100,000 inhabitants was calculated by dividing the total DALYs by the total population number for Denmark in 2019 (Statistics Denmark 2020) and multiplying by 100,000.

### Lead

The dose-response relationship derived by JECFA was used to estimate IQ loss in Danish children as a result of dietary Pb exposure (JECFA 2011). The model describes an IQ loss of 0.48 (95% CI 1.19–0.0) IQ points/ $\mu\text{g}/\text{dL}$  Pb in the blood (BPb) based on a pooled meta-analysis of seven cohort studies on 5–10-year-old children (Lanphear et al. 2005). The slope of the dose-response relationship was derived from a low dose bilinear model. Therefore, we assumed that the uncertainty around the dose-response curve follows a triangular distribution where the CI represents the maximum and minimum IQ decrease/ $\mu\text{g}/\text{dL}$  BPb. Concurrent blood lead level (defined as the blood lead measured closest to the IQ

test) was used as a measure for exposure when deriving the dose-response model (JECFA 2011). With the lowest age of IQ test performance among the studies included in the meta-analysis by Lanphear et al. (2005) being 4.8 years and a half-life of lead in the blood of approx. 30 days (JECFA 2011), we considered only the exposure of 5-year-old Danish children for the burden of disease estimation. However, the adverse effects are likely a consequence of the cumulative exposure to Pb up to the age of 5 years. We multiplied BPb estimates ( $\mu\text{g/dL}$ ) by the dose-response model (IQ loss per  $\mu\text{g/dL}$ ) to estimate the lead-attributable IQ loss in Danish children, describing the uncertainty around the dose-response by a triangular distribution.

We estimated the risk of shifting to an IQ associated with a higher level of intellectual disability due to dietary Pb exposure in children. The IQ distribution in a population is by definition normally distributed with a mean of 100 IQ points and a standard deviation (SD) of 15. An IQ above 85 is considered as normal intellectual functioning and not associated with disability. We estimated the risk of shifting to an IQ associated with a higher level of disability due to maternal MeHg exposure, considering five different IQ classes: mild (IQ 50–69), moderate (IQ 35–49), severe (IQ 20–34) and profound (IQ < 20) intellectual disability, as defined by the International Classification of Diseases (ICD-10-CM). Furthermore, we also considered borderline intellectual functioning (IQ 70–84), which may also be associated with disability (Salomon et al. 2015). The Pb-attributable incidence was estimated by combining the estimated risk of shifting to a higher level of intellectual disability by the number of individuals of age 5 years in the Danish population in 2019 ( $n = 58,352$ ) (Statistics Denmark 2020).

We estimated Pb-attributable DALYs under the assumption that the onset of Pb-attributable intellectual disability is at 5 years of age (corresponding to the lowest age of IQ test performance in the studies included in (Lanphear et al. 2005), and that IQ loss due to Pb exposure is lifelong and not associated with increased mortality (i.e., DALY = YLD). Thus, total DALYs were estimated by combining the attributable incidence for each level of intellectual disability with the respective disability weights (Table 1) and Danish remaining life expectancy at 5 years of age (Statistics Denmark 2020).

## Cadmium

We used the dose-response model derived by Ginsberg (Ginsberg 2012) to estimate the increased risk of CKD due to dietary Cd exposure in the Danish population. The dose-response model describes a 7.8% decrease in glomerular filtration rate (GFR) per  $\mu\text{g/L}$  Cd in the urine (UCd) based on a study of long-term dietary exposed adults (53–64 years) (Åkesson et al. 2005). Based on this model, it

was also suggested that a steady state is reached after around 40 years of exposure. Thus, we considered only individuals > 40 years in our calculations.

We estimated the disease burden associated with stage 4 and stage 5 CKD, which are considered to lead to losses in quality of life (Salomon et al. 2015). Patients are diagnosed with stage 4 and 5 CKD when their GFR is 15–29 ml/min/1.73 m<sup>2</sup> and < 15 ml/min/1.73 m<sup>2</sup>, respectively (National Kidney Foundation, 2002). We estimated the decrease in GFR among Danish individuals due to dietary Cd exposure by combining the dose-response model by Ginsberg (2012) with dietary exposure to Cd in the Danish population in terms of UCd. We used the mean and SD of the GFR reported for a Swedish cohort with a mean age of 49.6 years and described the distribution of GFR at a given age by a normal distribution (Zang et al. 2018). We accounted for a 0.8 ml/min/1.73 m<sup>2</sup> decrease in GFR per year after the age of 40 years (Zang et al. 2018) and separated it by the Cd attributable decrease in GFR when estimating the risk of developing CKD stage 4 and 5. We did this by taking the difference between the age- and Cd-dependent risk of CKD stage 4 and 5 and the age-dependent and Cd-independent risk of CKD stage 4 and 5 (Zang et al. 2018). We assumed no remission. For CKD stage 4, we assumed no increased risk of mortality and therefore estimated duration as the difference between the Danish life expectancy for the given age and sex for the year 2019 and current age. We assumed a case fatality of 20% for CKD stage 5, and lifelong duration for surviving cases (Zang et al. 2018).

## Methylmercury

We used the dose-response model derived by (Zeilmaker et al. 2013) to estimate the impact of maternal MeHg exposure on fetal neurodevelopment as measured in loss of IQ points later in life. The model describes a linear relationship with a mean IQ change of  $-8.5$  IQ points (95% CI  $-1.5$ ;  $-19.5$ ) per  $\mu\text{g}$  maternal exposure to MeHg/kg bw/day with no lower or upper thresholds of the effect. We described the uncertainty around the dose-response by a triangular distribution.

The adverse effects of MeHg on neurodevelopment are associated with maternal exposure. Thus, we estimated the mean exposure to MeHg in seven subgroups of Danish women of childbearing age (15–49 yrs.) in the sample population. Subgroups were defined based on age: 15–19 yrs., 20–24 yrs., 25–29 yrs., 30–34 yrs., 35–39 yrs., 40–44 yrs., and 45–49 yrs. To estimate attributable incidence, the risk of increased level of intellectual disability, estimated by the same approach as for lead, was combined with age-dependent fertility rates for 2019 (Statistics Denmark 2020). We assumed that the loss of IQ points due to maternal MeHg exposure is lifelong and not associated with increased

mortality risk. Thus, duration of intellectual disability was set to the Danish life expectancy at birth of 80.9 years (Statistics Denmark 2020).

### Inorganic Arsenic

We applied dose-response models describing the risk of cancer of the lung and bladder upon i-As exposure published in US FDA (2016) to estimate the risk of cancer in these tissues resulting from dietary exposure to i-As in the Danish population. The dose-response relationships were derived from epidemiological studies (Chen et al. 2010a, b) identified by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) as the pivotal studies for risk assessment, which were based on i-As exposures via drinking water. In its report, FDA adjusted exposure to account for dietary exposure, and adjusted the follow-up time in the epidemiological studies to express a lifetime risk (US FDA 2016). Both dose-response relationships were empirically reported in the FDA iRisk Tool (Food and Drug Administration Center for Food Safety and Applied Nutrition (FDA/CFSAN) 2021) (Table S9). For skin cancer, we used an oral cancer slope factor (CSF) of 0.0015 describing the lifetime risk of skin cancer per  $\mu\text{g/L}$  i-As in drinking water, as reported by the Integrated Risk Information System (IRIS) (Integrated Risk Information System (IRIS) 1995). To estimate the risk of skin cancer due to dietary i-As exposure in Denmark, the CSF was converted to be expressed per  $\mu\text{g/kg}$  bw/day by assuming a daily water intake of 2 L and a bw of 70 kg (EFSA 2009b). We estimated the population lifetime average daily dose in Denmark as the mean of the observed individual mean dietary exposure to i-As estimated in 2.1 across all agegroups for men and women, respectively.

The attributable incidence ( $I_{iAs,c,s}$ ) of specific cancer type  $c$  [ $c = (\text{lung, bladder, skin})$ ] and sex  $s$  was estimated as follows:

$$I_{iAs,c,s} = \frac{N_{pop,s} \cdot r_{c,s}}{LE_s}$$

where  $N_{pop,s}$  is the number of individuals of sex  $s$  in the sample population,  $r$  is the extra lifetime cancer risk of tissue  $c$ , and  $LE_s$  is the observed life expectancy in Denmark for each sex. We took an incidence-based approach and estimated the attributable DALYs using the disease models described in (Jakobsen et al. 2019).

## Results

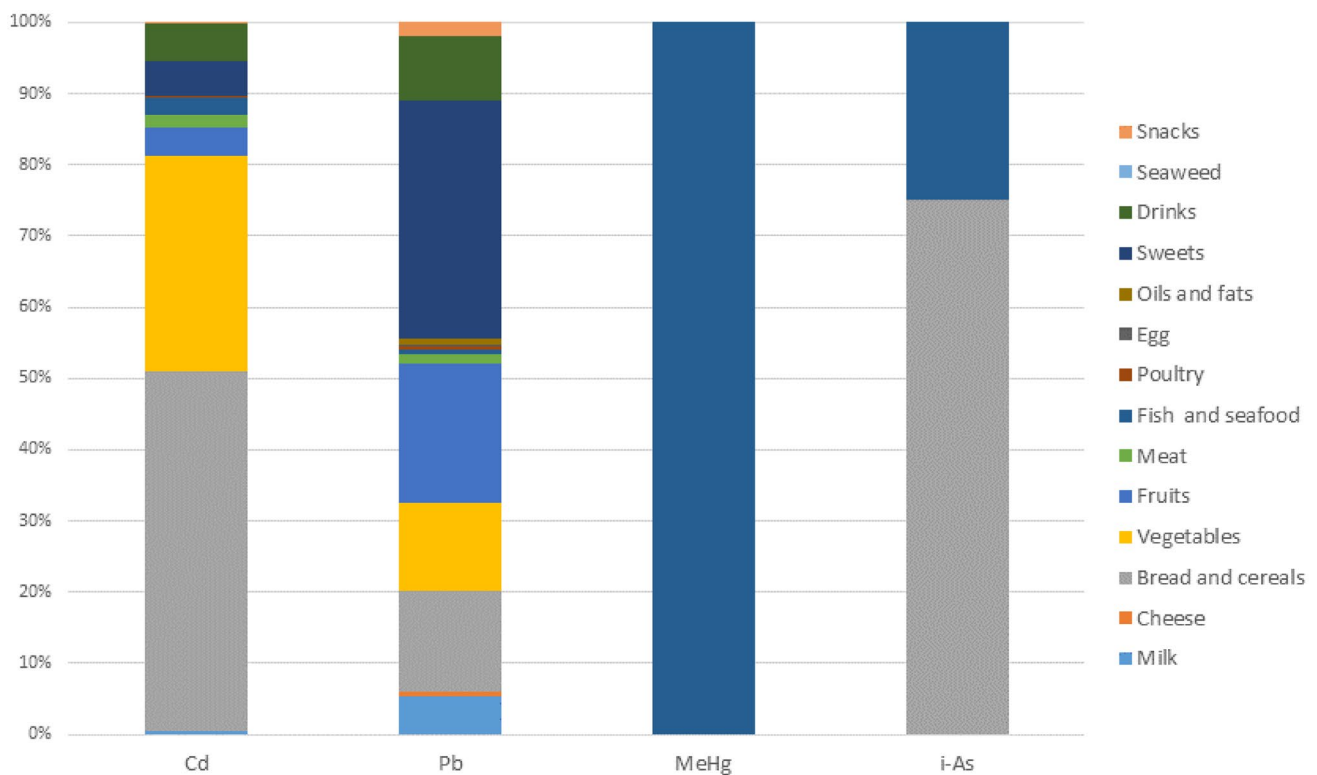
### Exposure Assessment

The estimated mean daily exposure to Pb among Danish 5-year-olds was  $0.45 \mu\text{g/kg}$  bw/day, ranging from  $0.20 \mu\text{g/kg}$  bw/day in the 2.5th percentile to  $1.04 \mu\text{g/kg}$  bw/day in the 97.5th percentile. Among the 5-year-old children, 28% exceeded the  $\text{BMDL}_{01}$  for the neurodevelopmental effects of Pb of  $0.50 \mu\text{g/kg}$  bw/day (EFSA CONTAM Panel 2010). The Margin of Exposure (i.e.,  $\text{MOE} = \text{BMDL}/\text{exposure}$ ) based on the mean Pb exposure in 5-year-old children was 1.10. The foods contributing most to exposure to Pb were sweets, fruit, and bread and cereals (Fig. 1).

Mean daily Cd exposure in the general Danish population (4–75 yrs) was estimated to be  $0.19 \mu\text{g/kg}$  bw/day, ranging from  $0.074 \mu\text{g/kg}$  bw/day in the 2.5th percentile to  $0.48 \mu\text{g/kg}$  bw/day in the 97.5th percentile. A high level of variability between age groups was observed, with the highest mean daily exposure (relative to bodyweight) estimated for 4–9-year-olds ( $0.39 \mu\text{g/kg}$  bw/day) and the lowest estimated for the 20–29-year-olds ( $0.16 \mu\text{g/kg}$  bw/day). Among the general population, 7% exceeded the tolerable weekly intake (TWI) of  $2.5 \mu\text{g/kg}$  bw/week (corresponding to approximately  $0.36 \mu\text{g/kg}$  bw/day) (EFSA 2012b). However, our stratified analysis showed large variation between age groups; 55% of the 4–9-year-olds and 12% of the 10–14-year-olds exceeded the TWI. In the remaining population groups considered, this number was  $\leq 2\%$ . The foods contributing most to exposure to Cd were bread and cereals, and vegetables (Fig. 1).

We estimated that the average Danish woman of childbearing age is exposed to  $0.035 \mu\text{g MeHg/kg}$  bw/day with an exposure of  $0 \mu\text{g/kg}$  bw/day in the 2.5th percentile and  $0.14 \mu\text{g/kg}$  bw/day in the 97.5th percentile. In the age stratified analysis, the highest exposure among the women of childbearing age was estimated for the 20–24-year-olds ( $0.042 \mu\text{g/kg}$  bw/day). Among all women of childbearing age, 0.9% exceeded the TWI of  $1.3 \mu\text{g/kg}$  bw/week (corresponding to approx.  $0.18 \mu\text{g/kg}$  bw/day). This percentage differed between age groups with the highest found for women of 20–29 yrs of age (3%) and the lowest for women of 30–39 yrs of age (0%). Among the general population, 2% exceeded the TWI with an average exposure of  $0.04 \mu\text{g/kg}$  bw/day. The stratified analysis showed that the 4–9-year-olds had the highest average exposure relative to bw ( $0.0576 \mu\text{g/kg}$  bw/day) and the highest fraction of individuals exceeding the TWI (5%). All exposure was attributed to fish and seafood consumption.

The estimated average daily exposure to I-As in the population was  $0.056 \mu\text{g/kg}$  bw, with an exposure of  $0.001 \mu\text{g/kg}$  bw in the 2.5th percentile and  $0.217 \mu\text{g/kg}$  bw in the



**Fig. 1** Relative contribution of specific food categories to dietary exposure to Cadmium (Cd), lead (Pb), methyl mercury (MeHg), and inorganic arsenic (I-As) in Denmark

97.5th percentile. The mean daily exposure to I-As varied across agegroups with an exposure of 0.14  $\mu\text{g}/\text{kg}$  bw in age 4–9 years and 0.03 in age 65–69. The MoE considering the population average exposure and the lower bound of the  $\text{BMDL}_{01}$  range of 0.3  $\mu\text{g}/\text{kg}$  bw/day is 5.4.; considering MoE among agegroups, children aged 4–9 have a MoE of 2.1 and the highest MoE of 9.0 is observed among the 60–64-year-olds. The food group contributing most to the i-As exposure was cereals (excluding rice), followed by crustaceans and rice (sum of polished, white and parboiled rice) (Fig. 1).

### Attributable Incidence and Mortality

We estimated that up to approximately 1000 Danish children fell into an IQ class of increased intellectual disability due to Pb exposure in 2019, i.e., approximately 17 per 100,000 general Danish population experience a higher intellectual disability due to dietary Pb exposure. Table 2 shows the extra number of cases of intellectual disability within the respective IQ classes attributable to Pb exposure in Danish 5-year-olds, total and per 100,000 general population per year. The table also illustrates the uncertainty around the estimates associated with the choice of the lower or upper bound of the conversion factor used for translating dietary Pb exposure into Pb blood concentrations.

We estimated that 0.09 and 0.04 cases of CKD stage 4 and stage 5, respectively, were attributable to dietary Cd exposure in Denmark. This corresponds, in total, to 0.0026 number of cases per 100,000 individuals (Table 2).

In utero exposure to MeHg was estimated to cause increased intellectual disability in approximately 400 children, corresponding to approximately 7 per 100,000 general Danish population. Table 2 shows the extra number of cases of intellectual disability within the respective IQ classes attributable to in utero exposure to MeHg, total and per 100,000 general population per year.

Dietary exposure to i-As was estimated to cause less than 1 case of cancer in total (lung, bladder, skin) and approximately 0.01 per 100,000 per year. Table 2 lists the i-As attributable number of cases and deaths [total and per 100,000 individuals (general population)] for cancer of the lung, bladder, and skin.

### Disability-Adjusted Life Years

According to our estimates, Pb and MeHg were responsible for the highest disease burden in Denmark among the four chemicals assessed (Table 3). We estimated that MeHg causes nearly 600 DALYs per year, corresponding to approximately 10 DALYs per 100,000. The mean

**Table 2** Attributable number of cases and deaths (total and per 100,000 individuals of the general population) of health outcomes associated with exposure to lead, methylmercury, cadmium, and inorganic arsenic through foods in Denmark, 2019

Hazard, health outcome	Total attributable incidence (95% UI)	Attributable incidence/100,000 (95% UI)	Total attributable mortality (95% UI)	Attributable mortality/100,000 (95% UI)
<b>Lead<sup>a</sup></b>				
Borderline ID	LB: 247 (54; 478)	LB: 4 (0.9; 8)		
70 < IQ < 85	UB: 805 (173; 1583)	UB: 14 (3; 27)	–	–
Mild ID	LB: 56 (12; 108)	LB: 1 (0.2; 2)	–	–
50 < IQ < 70	UB: 184 (39; 373)	UB: 3 (0.7; 6)		
Moderate ID	LB: 2 (0.3; 3)	LB: 0.03 (0.006; 0.05)	–	–
35 < IQ < 50	UB: 5 (1; 11)	UB: 0.09 (0.02; 0.2)		
Severe ID	LB: 0.04 (0.007; 0.07)	LB: 0.0006 (0.0001; 0.001)	–	–
20 < IQ < 35	UB: 0.1 (0.02; 0.3)	UB: 0.002 (0.0004; 0.005)		
Profound ID	LB: 0.0003 (0.00006; 0.0006)	LB: 0.000005 (0.000001, 0.00001)	–	–
IQ < 20	UB: 0.001 (0.0002; 0.002)	UB: 0.00002 (0.000003; 0.00004)		
<b>Cadmium<sup>b, d</sup></b>				
CKD stage 4	0.09	0.002	4	0
CKD stage 5	0.04	0.0006	5	0.0001
<b>Methylmercury<sup>c</sup></b>				
Borderline ID	338 (114; 614)	5.8 (2.0; 11)	–	–
70 < IQ < 85				
Mild ID	76 (26; 140)	1.3 (0.44; 2.4)	–	–
50 < IQ < 70				
Moderate ID	2.2 (0.74; 4.1)	0.038 (0.013; 0.071)	–	–
35 < IQ < 50				
Severe ID	0.049 (0.016; 0.091)	0.00084 (0.00028; 0.0016)	–	–
20 < IQ < 35				
Profound ID	0.00039 (0.00013; 0.00074)	6.7e-06 (2.2e-06; 1.3e-05)	–	–
IQ < 20				
<b>Inorganic arsenic<sup>d</sup></b>				
Lung cancer	0.225	0.004	0.186 (0.185; 0.187)	0.00321 (0.00319; 0.00322)
Bladder cancer	0.090	0.002	0.026 (0.026; 0.027)	0.00045 (0.00044; 0.00046)
Skin cancer	0.339	0.006	0.029 (0.027; 0.03)	0.000496 (0.000467; 0.000525)

<sup>a</sup>Borderline intellectual disability (ID), mild ID, moderate ID, severe ID and profound ID due to exposure to Pb in Danish 5-year-olds. Calculations were made using lower bound (LB) and upper bound (UB) estimates for the conversion factor relating dietary Pb exposure ( $\mu\text{g}/\text{day}$ ) to Pb in the blood ( $\mu\text{g}/\text{dL}$ ). Associated 95% Uncertainty Intervals (UI), propagated from the uncertainty around the dose–response relationship, are given in parenthesis

<sup>b</sup>Chronic kidney disease (CKD) stage 4 and stage 5 due to dietary Cd exposure in Denmark. Uncertainty was not quantified

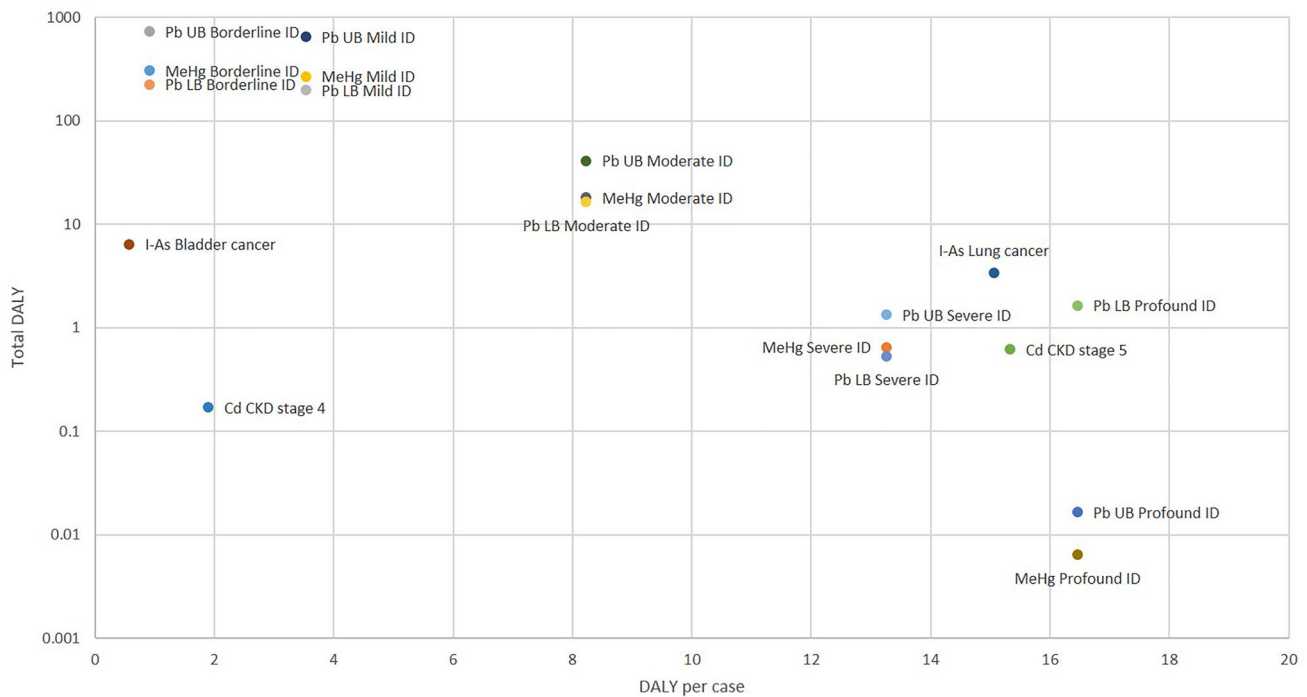
<sup>c</sup>Borderline intellectual disability (ID), mild ID, moderate ID, severe ID and profound ID due to in utero exposure to MeHg of the fetuses of Danish pregnant women. Associated 95% Uncertainty Intervals (UI) are given in parenthesis

<sup>d</sup>Uncertainty was not quantified when estimating incidence, only mortality

**Table 3** Disability-adjusted life years (DALYs) attributable to dietary exposure to MeHg, Pb, Cd, and i-As (total and per 100,000 individuals of the general population). Associated 95% Uncertainty Intervals (UI) are given in parenthesis

	Total DALY (95% UI)	YLD (95% UI)	YLL (95% UI)	DALY/100,000 (95% UI)
MeHg—intellectual disability	592 (200; 1181)	592 (200; 1181)	0 (0; 0)	10 (3.4; 20)
Pb—intellectual disability	LB: 383 (86; 787) UB: 1261 (277; 2658)	LB: 383 (86; 787) UB: 1261 (277; 2658)	0 (0; 0)	LB: 6.6 (1.5; 14) UB: 22 (4.8; 46)
Cd—chronic kidney disease	0.040 (0.035; 0.044)	0.029 (0.025; 0.034)	0.010 (0.010; 0.010)	0.0007 (0.0006; 0.0008)
iAs—lung, bladder and skin cancer	5.05 (4.72; 5.39)	1.12 (0.81; 1.47)	3.82 (3.76; 3.88)	0.087 (0.081; 0.093)





**Fig. 2** Scatterplot of the DALY per incident case and total mean DALY estimated for of each type of health outcome included in the assessment. Methyl mercury (MeHg) and Lead (Pb) are shown with points for each class of intellectual disability (ID); Pb are shown with

points for both the mean upper (UB) and lower (LB) bounds; Cadmium (Cd) is shown with points for chronic kidney disease (CKD) stage 4 and 5, respectively; inorganic arsenic (i-As) is shown with points for lung, bladder, and skin cancer

burden caused by Pb depends on the conversion factor used for translating dietary Pb into Pb blood concentrations in the exposure assessment for Pb. If the mean upper bound of the conversion factor is applied, the DALYs attributable to dietary Pb exposure in Danish children amounts to 1261 total DALYs and 22 DALYs/100,000. However, if the mean lower bound of the conversion factor is applied, the DALYs attributable to dietary Pb exposure amount to approximately 400 DALYs total, corresponding to around 7 DALYs per 100,000 individuals (general population). However, the 95% UI around the mean lower and upper bounds are overlapping; likewise, the UI of the mean lower and upper bounds of Pb are overlapping with the UI of the mean DALY caused by MeHg.

The attributable burden due to Cd and i-As were much lower than for Pb and MeHg. i-As was estimated to be responsible for 5 DALYs total per year, while Cd caused less than 1 DALY per year.

In Fig. 2, the burden at the individual level (DALY per incident case) of each health outcome included for each chemical contaminant is plotted against the burden at population level (mean total DALY) attributed to each chemical contaminant. The health outcomes for which the burden on the individual level is low (e.g., borderline and mild ID caused by Pb and MeHg) but total burden is high

are in the upper left corner. In the lower right corner are the health outcomes where burden on the individual level is high (e.g., lung cancer caused by i-As, CKD stage 5 caused by Cd, and profound ID caused by MeHg and Pb) but total burden is low.

## Discussion

We estimated the population-level health impact of dietary exposure to four chemicals in Denmark for the reference year 2019 using national food consumption and food monitoring data and a harmonized burden of disease approach. Among these chemicals, Pb and MeHg were estimated to be responsible for the highest disease burden. MeHg led to the loss of nearly 600 healthy life years, or approximately 10 DALYs per 100,000 inhabitants. Exposure to Pb through foods was estimated to cause 383 (86; 787) (LB) to 1261 (277; 2658) (UB) DALYs per year, corresponding to 6.6 (1.5; 14) (LB) to 22 (4.8; 46) (UB) DALYs/100,000 per year. The uncertainty intervals of the disease burden attributed to exposure to Pb and MeHg overlapped, and thus interpretations of the ranking of these two chemicals on the basis of estimated DALYs should be made with care. The adverse health effects of both chemicals are experienced by young children and are

of lifelong duration. Our results also show that i-As and Cd cause a considerably lower burden of disease. In contrast to MeHg and Pb, the adverse health consequences of these two chemicals occur in adults upon lifelong and repeated exposure.

These differences are also reflected in the proportion of the chemicals' DALY estimates that is explained by premature mortality (i.e., YLL) and by disability (i.e., YLD). Although intellectual disability caused by exposure to MeHg and Pb was assumed to not lead to increased mortality (YLL = 0), these chemicals caused the highest burden in the population, because effects are lifelong. On the contrary, i-As' attributable cancer and Cd attributable late-stage CKD are both associated with an increased mortality. Comparing the DALY per case (which is a reflection of how severe the disease outcomes associated with exposure to each chemical are, on average, for each individual affected), with the estimated total DALY illustrated how the relation between number of individuals affected, the severity of the disease and associated total disease burden differ. For example, lung cancer led to 15 years of healthy life lost per individual, but the estimated number of individuals with lung cancer due to i-As was low.

The ranking based on DALYs did not necessarily align with the results of traditional risk assessment approaches for all chemicals, i.e., calculating the MoE or fraction of the population exceeding the TWIs. Only a small fraction of women of childbearing age were found to have exposures that exceeded the TWI for MeHg (0.9% on average, maximum proportion found for 20–29-year-old women), but the burden of disease associated with MeHg was the highest. On the other hand, while the calculated population MoE for I-As was very low, indicating a health risk of high concern, the estimated burden of disease attributable to i-As was low compared to that of MeHg and Pb. One of the reasons for these discrepancies between the ranking based on DALYs and on the MoE and fraction exceeding the TWIs is the fact that the DALY not only takes into account the probability of an adverse effect, but also integrates the severity and duration of that effect. Furthermore, traditional risk assessment approaches are particularly concerned with the fractions of the population for which exposure levels are of concern, whereas burden estimates account for the burden of the entire population.

The relative contribution of specific foods to the exposure and burden of each chemical varied. The only significant source of MeHg is fish and seafood, and thus 100% of that exposure and burden was attributed this food category. The most important sources of Pb were sweets, fruits and bread and cereals. The latter category was also an important source of Cd (along with vegetables), and of I-As (along with rice). Knowledge on the sources contributing most to the disease burden in the population is important to identify

and prioritize food safety prevention strategies to reduce exposure in the population. Since Cd and I-As combined led to approximately 6 DALY, our results suggest that interventions in the foods contributing to the dietary exposure to Pb and MeHg are of higher priority to reduce disease burden. Likewise, the evidence provided by burden of disease studies provides evidence to target policies to the population groups at higher risk. For example, policies to prevent disease associated with MeHg, by e.g., advising limiting the consumption of large predatory fish species, should be targeted primarily to women of childbearing age and pregnant women. Furthermore, knowledge on food sources contributing most to the disease burden may also reveal areas of the food sector that need a higher level of control measures to limit contaminated foods on the consumers' plates.

Recent global studies have provided estimates of the 2015 disease burden attributed to these four chemicals at global and regional level, including for the European region to which Denmark belongs (Zang et al. 2018; Oberoi et al. 2019; Carrington et al. 2019). The results of these studies differed from ours in terms of ranking and estimated burden. They indicated that Pb caused the highest burden [41 DALY/100,000 inhabitants (95% CI 0–162)], followed by I-As [14 DALY/100,000; (3–35)], MeHg [12 DALY/100,000; (5–28)] and Cd [0.2 DALY/100,000; (0.09–2)] (Gibb et al. 2018). These differences in estimates are partly explained by differences in the methodologies and health outcomes included, and largely by differences in the data sources used for the exposure assessment. In contrast to these studies, we have used detailed national data on food consumption and were able to estimate exposure based on national-representative and robust data set. Albeit not recent, data on the concentration of chemical hazards in foods were the best available, and collected from national monitoring that samples foods that are available in the Danish market (Petersen et al. 2011). When compared to regional and global efforts, national burden of disease studies have the advantage of using national data and relying on national relevant experts, thus reducing uncertainties in the models and estimates (Lake et al. 2015; Pires et al. 2021). National studies are also easily updated when new data or evidence become available.

Estimating the diet-associated burden of disease of chemical hazards is challenging. It is difficult to establish the link between exposure and occurrence of a disease, primarily due to the often multicausal nature of the health outcomes, and because symptoms may only appear long time following exposure. Consequently, human data linking exposure to effect (i.e., dose-response) are often lacking or have to be extrapolated from *in vitro* or *in vivo* studies, introducing uncertainty. To avoid further uncertainties by such extrapolations, we based our burden of disease estimates on human epidemiological evidence only. Still, comparison of these

estimates with results of other burden of disease studies should be made with care. For example, Jakobsen et al. estimated that the burden of peanut allergy in Denmark was 906 DALYs; Pires et al. estimated the burden of seven foodborne pathogens, with *Campylobacter* causing the highest burden among them (1299 DALYs); and Jakobsen et al. estimated that the burden of acrylamide in the country was 90 DALYs (Jakobsen et al. 2016, 2020; Pires et al. 2019b). These estimates shows that the overall health impact of exposure to MeHg and Pb is high, even when compared with food-associated diseases of a very different nature.

Our study suffered from various limitations associated with data availability and methodological assumptions. The burden of disease models for both MeHg and Pb relied on the assumption that IQ reductions due to MeHg and Pb exposure during fetal development and early childhood, respectively, are lifelong. However, other factors such as socioeconomic environment would also be expected to play a role in cognitive development. Furthermore, our models relies on IQ as the sole measure of neurodevelopment, but there are various others measures that capture other aspects of cognitive development (Debes and Grandjean 2016). Also, we did not include adverse effects that have been associated with exposure to Pb and MeHg, such as cardiovascular effects. Additionally, we used food consumption data from 5-year-olds only to estimate exposure to Pb. We conducted a sensitivity analysis to compare the difference in exposure when applying data for 5-year-olds only and data across the age group 4–6 years, which showed that if we had we used data across more agegroups (4–6-year-olds), the exposure would have been slightly lower than when applying data for 5-year-olds only (results not shown). Although our exposure estimates for Pb were based on a small sample size of individuals (46), we chose the most conservative approach by applying exposure data for the agegroup with the highest Pb exposure. This was also the youngest age group included in the meta-analysis in which the dose-response model we used in our calculations for Pb was based on (Lanphear et al. 2005).

One of the limitations of the Cd model is linked with the assumption of a threshold effect at a UCd level of 1.0 µg/g creatinine, while not accounting for background exposure to Cd, such as from smoking. Smoking is the major source of Cd exposure in the smoking population (Alexander et al. 2009). Thus, excluding Cd exposure from smoking in the exposure assessment may underestimate the burden of CKD due to cadmium exposure.

For i-As, we applied the most recent dose-response relationship for lung and bladder cancer evaluated and found appropriate by JECFA (JECFA 2011). However, there are other studies of the dose-response relation; we observed that if we applied the dose-response relationship for lung cancer derived by EFSA (EFSA 2009b), DALY estimates would have been approximately 16 times larger, demonstrating the uncertainties

associated with the data (Jakobsen et al. 2019). Furthermore, we accounted for three cancer types, but Oberoi et al. also included the burden associated with CHD for countries with an exposure high enough to surpass a threshold of 10 µg/L (Oberoi et al. 2019). The exposure estimated in our study for Denmark was considerable lower (Jakobsen et al. 2019). The foods contributing to exposure in our assessment belong to the food groups “bread and cereals” and “fish and shellfish”. These foods are the ones for which we had national specific data for I-As content. Failure to include other foods is likely to underestimate the exposure. Additionally, in its assessment of dietary exposure to I-As, EFSA estimated that drinking water and other beverages were the main contributors to exposure (EFSA (European Food Safety Authority), et al. 2021). However, we did not include drinking water in the assessment of I-As, which could have resulted in an exposure closer to the threshold of 10 µg/L, as water and beverages is a considerable source to I-As exposure (Petersen et al. 2011). Likewise, the disease burden would be higher. The exposure estimated by EFSA is in the same order of magnitude of the one estimated in our study [between approximately 0.05 µg/kg bw/day in adults and 0.10–0.15 µg/kg bw/day in children] (EFSA (European Food Safety Authority), et al. 2021). Nevertheless, the inclusion of these health effects in future studies would likely increase the burden attributed to I-As considerably.

We disregarded the risk of synergistic effects following exposure to multiple chemical hazards, which may underestimate the overall burden of disease of chemical exposures. Additionally, quantification of all health effects potentially associated with exposure to chemicals might be impossible either due to lack of data or that an identified and toxicological recognized adverse effects is not directly quantifiable in terms of DALY (i.e., subclinical effects such as hormonal changes). Still, the DALY is now the most widely used public health metric for burden of disease studies, and the key measure in the Global Burden of Disease (GBD) studies (Abbfati et al. 2020). It was also the metric used in the World Health Organization’s Global Burden of Foodborne Diseases Report (WHO 2015). Using such an harmonized metric is particularly useful to compare diseases and risk factors within a country and across countries, and thus to prioritize policy. When used to estimate the public health impact of food-associated diseases, it has the added advantage of allowing for a more holistic evaluation of the health effects of foods and diets, considering both beneficial and adverse health effects. For this purpose, risk-benefit assessment approaches are increasingly used to inform food policy globally (Pires et al. 2019a). For example, in Denmark, recent studies have shown that the beneficial effects of fish consumption on e.g., neurodevelopment may counteract the adverse effects of MeHg on neurodevelopment, indicating the importance of accounting for whole diets when addressing food safety issues (Thomsen et al. 2018, 2019).

## Conclusion

We found that, among the four chemicals considered in this study (Pb, Cd, MeHg, I-As), MeHg and Pb caused the highest burden of disease in terms of DALYs. These chemicals cause compromised neurodevelopment in the developing fetus and in small children, respectively. Thus, our estimates show that particular attention should be given to the risk associated with exposure of specific population groups, particularly women in childbearing age and children. The burden of disease for Cd and I-As was estimated to be considerably lower. The ranking of the four chemicals based on DALYs is not necessarily in line with the ranking based on traditional risk assessment approaches. Our results emphasize the importance of assessing the health impact of chemical contamination of foods using multiple measures. Burden of disease studies may help identifying and prioritizing food safety prevention strategies to reduce exposure in the sub-populations at highest risk.

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**Author Contributions** STT, LSJ, and SMP designed the study. STT, LSK, HRG, and FAF analyzed the data. STT, LSJ, and SMP wrote the manuscript. SF, BD, MH, and MO provided critical review and edited the manuscript.

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**Data Availability** All data are available in the manuscript, supplementary documents, or upon request.

**Code Availability** All codes can be made available upon request.

## Declarations

**Conflict of interest** The authors declare no conflict of interest.

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