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Commentary

Estimates of the 2015 global and regional disease burden from four foodborne metals – arsenic, cadmium, lead and methylmercury

Herman J. Gibb[a,b], Aaron Barchowsky[c], David Bellinger[d], P. Michael Bolger[e], Clark Carrington[f], Arie H. Havelaar[g], Shilpi Oberoi[c], Yu Zang[h], Keri O'Leary[a], Brecht Devleesschauwer[i,j,*]

[a] Gibb Epidemiology Consulting, Arlington, VA 22201, USA
[b] George Washington University Milken Institute School of Public Health, Washington, DC 20052, USA
[c] Department of Environmental and Occupational Health, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA 15261, USA
[d] Departments of Neurology and Psychiatry, Harvard Medical School; Department of Environmental Health, Harvard T.H. Chan School of Public Health; Boston Children's Hospital, Boston, MA 02115, USA
[e] Exponent, Washington, DC 20036, USA
[f] Spoiled Hike LLC, Gaithersburg, MD 20882, USA
[g] Institute for Sustainable Food Systems, Emerging Pathogens Institute and Department of Animal Sciences, University of Florida, Gainesville, FL 32611, USA
[h] Food and Drug Administration, College Park, MD 20740, USA
[i] Department of Epidemiology and Public Health, Sciensano, Brussels, Belgium
[j] Department of Veterinary Public Health and Food Safety, Faculty of Veterinary Medicine, Ghent University, Merelbeke, Belgium

A R T I C L E I N F O

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A B S T R A C T

The impact of foodborne metals on the burden of disease has been largely overlooked, in comparison to the attention on acute diseases associated with infectious foodborne agents. Four articles in this special section describe in detail the burden of disease from foodborne lead, methylmercury, arsenic, and cadmium. Ingested lead and methylmercury are causally associated with lifelong intellectual disability. Long term ingestion of arsenic is causally associated with an increased risk of cancer. Long term ingestion of cadmium is causally associated with an increased risk of late stage chronic kidney disease. This article presents an overview of the burden of disease from these four foodborne metals and discusses them in the context of the World Health Organization's initiative to estimate the global burden of foodborne disease. The results indicate that in 2015, ingestion of arsenic, methylmercury, lead, and cadmium resulted in more than 1 million illnesses, over 56,000 deaths, and more than 9 million disability-adjusted life years (DALYs) worldwide. The greatest impact on DALYs was in the Western Pacific B subregion. All of the metals were found to have high DALYs per case in comparison with other foodborne disease agents, including infectious and parasitic agents. In addition, lead, arsenic, and methylmercury were found to have high DALYs per 100,000 population in comparison to other foodborne disease agents.

1. Background

In September 2006 the World Health Organization (WHO) organized a consultation to develop a strategy to estimate the global burden of foodborne disease (World Health Organization, 2006). This led to the formation of the WHO Foodborne Disease Burden Epidemiology Reference Group (FERG). General meetings of the FERG were held in Geneva (World Health Organization, 2007, 2008, 2010, 2013). FERG originally included three hazard-based task forces: Enteric Disease Task Force, Parasitic Disease Task Force, and the Chemical and Toxins Disease Task Force (CTTF). A Country Studies Task Force, a Source Attribution Task Force, and a Computational Task Force were subsequently added. The results of four chemicals (dioxin, aflatoxin, cyanide in cassava, and peanut allergy) were described by Gibb et al. (2015). Three of these chemicals were also included in the global overview described by Havelaar et al. (2015). Methods and results on the burden of disease of four foodborne metals (methylmercury, lead, arsenic, and cadmium) are described elsewhere in this special section (Bellinger

Abbreviations: CKD, Chronic kidney disease; CTTF, Chemical and Toxins Disease Task Force; DALY, Disability-adjusted life year; FERG, Foodborne Disease Burden Epidemiology Reference Group; ID, Intellectual disability; IQ, Intelligence quotient; UI, Uncertainty interval; YLD, Year lived with disability; YLL, Year of life lost; WHO, World Health Organization

* Correspondence to: Department of Epidemiology and Public Health, Sciensano, Rue J Wytsmanstraat 14, 1050 Brussels, Belgium.
E-mail address: brecht.devleesschauwer@sciensano.be (B. Devleesschauwer).

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Table 1
World Health Organization (WHO) Member States by subregion.

Subregion	WHO member states
AFR D	Algeria; Angola; Benin; Burkina Faso; Cameroon; Cape Verde; Chad; Comoros; Equatorial Guinea; Gabon; Gambia; Ghana; Guinea; Guinea-Bissau; Liberia; Madagascar; Mali; Mauritania; Mauritius; Niger; Nigeria; Sao Tome and Principe; Senegal; Seychelles; Sierra Leone; South Sudan; Togo.
AFR E	Botswana; Burundi; Central African Republic; Congo; Côte d'Ivoire; Democratic Republic of the Congo; Eritrea; Ethiopia; Kenya; Lesotho; Malawi; Mozambique; Namibia; Rwanda; South Africa; Swaziland; Uganda; United Republic of Tanzania; Zambia; Zimbabwe.
AMR A	Canada; Cuba; United States of America
AMR B	Antigua and Barbuda; Argentina; Bahamas; Barbados; Belize; Brazil; Chile; Colombia; Costa Rica; Dominica; Dominican Republic; El Salvador; Grenada; Guyana; Honduras; Jamaica; Mexico; Panama; Paraguay; Saint Kitts and Nevis; Saint Lucia; Saint Vincent and the Grenadines; Suriname; Trinidad and Tobago; Uruguay; Venezuela (Bolivarian Republic of).
AMR D	Bolivia (Plurinational State of); Ecuador; Guatemala; Haiti; Nicaragua; Peru.
EMR B	Bahrain; Iran (Islamic Republic of); Jordan; Kuwait; Lebanon; Libyan Arab Jamahiriya; Oman; Qatar; Saudi Arabia; Syrian Arab Republic; Tunisia; United Arab Emirates.
EMR D	Afghanistan; Djibouti; Egypt; Iraq; Morocco; Pakistan; Somalia; Sudan; Yemen.
EUR A	Andorra; Austria; Belgium; Croatia; Cyprus; Czech Republic; Denmark; Finland; France; Germany; Greece; Iceland; Ireland; Israel; Italy; Luxembourg; Malta; Monaco; Netherlands; Norway; Portugal; San Marino; Slovenia; Spain; Sweden; Switzerland; United Kingdom.
EUR B	Albania; Armenia; Azerbaijan; Bosnia and Herzegovina; Bulgaria; Georgia; Kyrgyzstan; Montenegro; Poland; Romania; Serbia; Slovakia; Tajikistan; The Former Yugoslav Republic of Macedonia; Turkey; Turkmenistan; Uzbekistan.
EUR C	Belarus; Estonia; Hungary; Kazakhstan; Latvia; Lithuania; Republic of Moldova; Russian Federation; Ukraine.
SEAR B	Indonesia; Sri Lanka; Thailand.
SEAR D	Bangladesh; Bhutan; Democratic People's Republic of Korea; India; Maldives; Myanmar; Nepal; Timor-Leste.
WPR A	Australia; Brunei Darussalam; Japan; New Zealand; Singapore.
WPR B	Cambodia; China; Cook Islands; Fiji; Kiribati; Lao People's Democratic Republic; Malaysia; Marshall Islands; Micronesia (Federated States of); Mongolia; Nauru; Niue; Palau; Papua New Guinea; Philippines; Republic of Korea; Samoa; Solomon Islands; Tonga; Tuvalu; Vanuatu; Viet Nam.

Table 2
Median global number of foodborne illnesses, deaths, years lived with disability (YLDs), years of life lost (YLLs) and disability-adjusted life years (DALYs), with 95% uncertainty intervals, 2015.

Metal	Illnesses	Deaths	YLDs	YLLs	DALYs
Arsenic	241,195 (54,665–431,463)	52,220 (11,885–93,363)	86,362 (19,649–154,412)	1,333,204 (303,761–2,383,273)	1,419,566 (323,409–2,537,685)
Cadmium	12,224 (3,330–114,626)	2,064 (403–22,641)	18,352 (4,889–173,416)	50,911 (10,602–586,428)	70,513 (19,113–742,340)
Lead	583,569 (0–3,382,588)	0 (0–0)	5,243,184 (0–30,790,070)	0 (0–0)	5,243,184 (0–30,790,070)
Methylmercury	226,655 (87,386–633,509)	0 (0–0)	1,963,869 (780,769–5,272,924)	0 (0-0)	1,963,869 (780,769–5,272,924)
Total	**1,122,436 (333,683–3,899,318)**	**56,192 (14,299–98,806)**	**7,657,416 (1,351,788–32,995,822)**	**1,434,849 (363,536–2,521,337)**	**9,164,162 (2,498,509–34,232,298)**

et al., 2019; Carrington et al., 2019; Oberoi et al., 2019; Zang et al., 2019). The current article summarizes the results for the four metals and discusses them in the context of the FERG estimates of the global burden of foodborne disease.

At its first meeting, the CTTF identified broad groups of chemicals and toxins (e.g., mycotoxins, pesticides, elemental contaminants, etc.) to be considered in estimating the burden of foodborne disease; hazards within each of these groups were then ranked on: (1) the severity of potential health effects, (2) the prevalence of exposure, and (3) sufficiency of data to support burden estimates (Gibb et al., 2015). The CTTF considered the four metals described herein and the four chemicals discussed in Gibb et al. (2015) to be the highest priorities among those for which the task force believed that burdens could be estimated. Despite the large number of chemicals and toxins that are known to be present in the global food supply, little effort has been made to quantify these risks.

2. Materials and methods

To make estimates of incidence, an exposure response approach was used for each of the four metals. The disease endpoints for lead and methylmercury are mild, moderate, and severe intellectual disability caused by a population shift in intelligence quotient (IQ). The disease endpoint for cadmium is late stage (stage 4 and 5) chronic kidney disease (CKD). The disease endpoints for arsenic described in this summary article are lung, bladder, and skin cancer. An estimate for arsenic and cardiovascular disease is also described in the article on arsenic (Oberoi et al., 2019). Because the uncertainty intervals for cardiovascular disease illnesses, deaths, and DALYs are very wide, it was decided not to include these outcomes in this summary. Other endpoints have also been associated with arsenic ingestion such as neurotoxicity (Vahidnia et al., 2007; Tyler and Allan, 2014), but there is not enough information to derive burden of disease estimates for these endpoints. Similarly, while there is considerable evidence of an association between lead ingestion and hypertension (Navas-Acien et al., 2007), there was not enough information to derive burden estimates of foodborne lead and cardiovascular disease. Thus the disease burden estimates in this summary reflect only those disease endpoints that could be reliably quantified.

The methods used to express burden in this review are those of Devleesschauwer et al. (2015). Estimates of the number of incident cases were produced using United Nations country-level population data for 2015. This differs from the population data used for Havelaar et al. (2015) and Gibb et al. (2015) in which 2010 population data were used. Because population has an effect on the absolute numbers of illnesses, deaths, years lived with disability (YLDs), years of life lost (YLLs), and disability-adjusted life years (DALYs), comparison of the absolute numbers were made only among the four metals. Some comparisons of the results of this study with Havelaar et al. (2015) and Gibb et al. (2015), however, were done using rates per 100,000.

The estimates in this study are for foodborne exposure only. However, exposure to three of the metals described in this study can also occur through media other than food (e.g., exposure to cadmium can occur via inhalation of cigarette smoke, exposure to arsenic can occur via consumption of arsenic-contaminated water, exposure to lead

Table 3
Median rates of foodborne disability-adjusted life years per 100,000 population, by subregion, with 95% uncertainty intervals, 2015.

HAZARD	Global	AFR D	AFR E	AMR A	AMR B	AMR D	EMR B
TOTAL	**125 (34–466)**	**157 (30–776)**	**152 (30–787)**	**22 (9–40)**	**111 (30–541)**	**160 (50–823)**	**113 (36–534)**
Arsenic	19 (4–35)	11 (2–20)	14 (3–25)	9 (2–16)	14 (3–25)	16 (4–29)	23 (6–42)
Bladder cancer	*4 (1–8)*	*4 (1–8)*	*5 (1–10)*	*2 (0.5–4)*	*3 (0.8–6)*	*4 (0.8–7)*	*9 (2–15)*
Lung cancer	*12 (3–22)*	*5 (1–9)*	*7 (2–13)*	*6 (1–11)*	*9 (2–16)*	*10 (2–17)*	*13 (3–23)*
Skin cancer	*3 (0.6–5)*	*1 (0.3–3)*	*1 (0.3–3)*	*0.3 (0.06–0.5)*	*1 (0.3–3)*	*3 (0.7–5)*	*2 (0.4–3)*
Cadmium	1 (0.3–10)	0.1 (0.02–2)	1 (0.1–12)	0 (0–0)	1 (0.1–10)	6 (0.2–278)	4 (0.6–18)
CKD Stage 4	*0.2 (0.05–2)*	*0.03 (0.003–0.6)*	*0.1 (0.007–2)*	*0 (0–0)*	*0.3 (0.01–3)*	*0.5 (0.02–29)*	*2 (0.1–13)*
CKD Stage 5	*0.7 (0.2–8)*	*0.07 (0.01–0.9)*	*0.9 (0.06–11)*	*0 (0–0)*	*0.9 (0.04–8)*	*5 (0.2–249)*	*1 (0.1–8)*
Lead	71 (0–420)	86 (0–690)	82 (0–707)	5 (0–22)	64 (0–499)	67 (0–573)	57 (0–491)
ID, Mild	*67 (0–382)*	*80 (0–632)*	*77 (0–648)*	*4 (0–21)*	*60 (0–454)*	*62 (0–525)*	*54 (0–449)*
ID, Moderate	*5 (0–36)*	*6 (0–56)*	*5 (0–58)*	*0.3 (0–2)*	*4 (0–48)*	*4 (0–47)*	*4 (0–40)*
ID, Severe	*0.1 (0–1)*	*0.2 (0–2)*	*0.2 (0–2)*	*0.008 (0–0.05)*	*0.1 (0–2)*	*0.1 (0–2)*	*0.1 (0–1)*
Methylmercury	27 (11–72)	44 (11–235)	37 (9–210)	7 (2–16)	27 (10–61)	54 (21–146)	24 (9–60)
ID, Mild	*23 (8–66)*	*36 (6–221)*	*30 (5–197)*	*5 (2–12)*	*24 (8–54)*	*49 (18–138)*	*20 (8–54)*
ID, Moderate	*4 (2–7)*	*8 (4–13)*	*7 (4–13)*	*2 (0.7–5)*	*3 (1–7)*	*5 (3–8)*	*3 (2–6)*

HAZARD	EMR D	EUR A	EUR B	EUR C	SEAR B	SEAR D	WPR A	WPR B
TOTAL	**143 (33–659)**	**69 (18–191)**	**112 (30–353)**	**68 (16–191)**	**120 (36–490)**	**83 (22–247)**	**59 (16–167)**	**182 (44–647)**
Arsenic	18 (4–33)	14 (3–25)	25 (6–44)	17 (4–30)	46 (11–83)	23 (5–42)	10 (2–18)	20 (5–36)
Bladder cancer	*6 (1–11)*	*4 (0.7–6)*	*8 (2–14)*	*5 (1–8)*	*5 (1–9)*	*4 (0.9–7)*	*3 (0.8–6)*	*4 (0.8–6)*
Lung cancer	*9 (2–16)*	*10 (2–17)*	*15 (3–27)*	*10 (2–19)*	*37 (8–66)*	*16 (4–28)*	*6 (1–10)*	*12 (3–21)*
Skin cancer	*3 (0.7–6)*	*0.7 (0.1–1)*	*1 (0.3–3)*	*2 (0.4–3)*	*5 (1–8)*	*3 (0.8–6)*	*1 (0.2–2)*	*5 (1–8)*
Cadmium	0.02 (0.006–0.2)	0.2 (0.09–2)	7 (0.4–137)	0.02 (0.006–0.1)	0.01 (0.003–0.05)	0.009 (0.003–0.04)	0.2 (0.008–24)	0.5 (0.1–7)
CKD Stage 4	*0.008 (0–0.1)*	*0.06 (0.03–1)*	*1 (0.04–26)*	*0.005 (0–0.03)*	*0.002 (0–0.01)*	*0.002 (0–0.01)*	*0.08 (0–12)*	*0.08 (0.01–1)*
CKD Stage 5	*0.01 (0.004–0.06)*	*0.1 (0.05–1)*	*5 (0.2–111)*	*0.02 (0.005–0.08)*	*0.009 (0.003–0.03)*	*0.008 (0.002–0.03)*	*0.1 (0.001–12)*	*0.4 (0.08–6)*
Lead	81 (0–609)	41 (0–162)	57 (0–223)	42 (0–164)	52 (0–449)	47 (0–218)	34 (0–137)	117 (0–584)
ID, Mild	*75 (0–558)*	*39 (0–150)*	*54 (0–207)*	*39 (0–151)*	*49 (0–411)*	*44 (0–201)*	*31 (0–127)*	*109 (0–525)*
ID, Moderate	*5 (0–49)*	*3 (0–12)*	*4 (0–16)*	*3 (0–12)*	*3 (0–37)*	*3 (0–16)*	*2 (0–10)*	*8 (0–55)*
ID, Severe	*0.2 (0–2)*	*0.08 (0–0.4)*	*0.1 (0–0.5)*	*0.08 (0–0.4)*	*0.1 (0–1)*	*0.09 (0–0.5)*	*0.06 (0–0.3)*	*0.3 (0–2)*
Methylmercury	32 (11–147)	12 (5–28)	14 (5–50)	9 (3–19)	17 (6–40)	12 (4–26)	12 (5–30)	41 (14–93)
ID, Mild	*25 (7–137)*	*10 (4–24)*	*11 (4–46)*	*6 (2–15)*	*14 (5–33)*	*8 (3–19)*	*11 (4–27)*	*37 (13–85)*
ID, Moderate	*6 (4–10)*	*2 (0.8–4)*	*3 (2–5)*	*2 (0.8–5)*	*3 (1–7)*	*3 (1–8)*	*2 (0.8–3)*	*4 (1–9)*

CKD Chronic Kidney Disease; *ID* Intellectual Disability

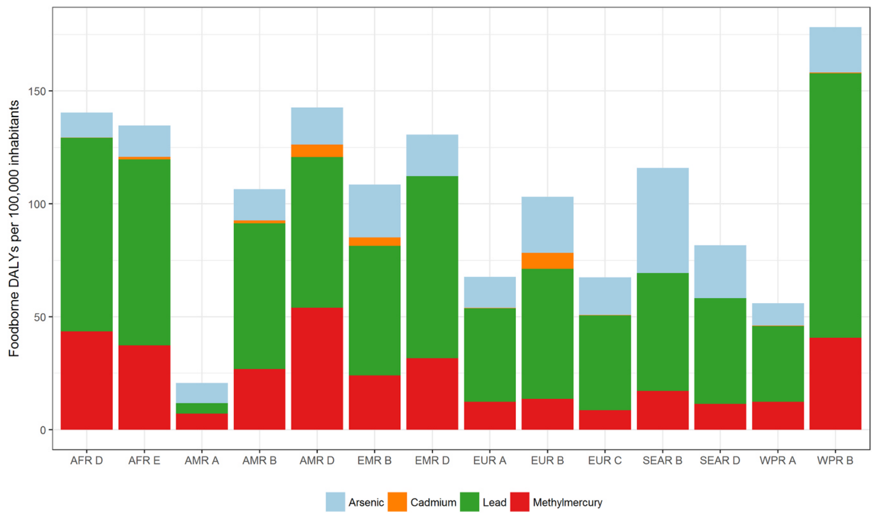

Fig. 1. The relative contribution to the disability-adjusted life year (DALY) incidence from each of the metals for each World Health Organization subregion.

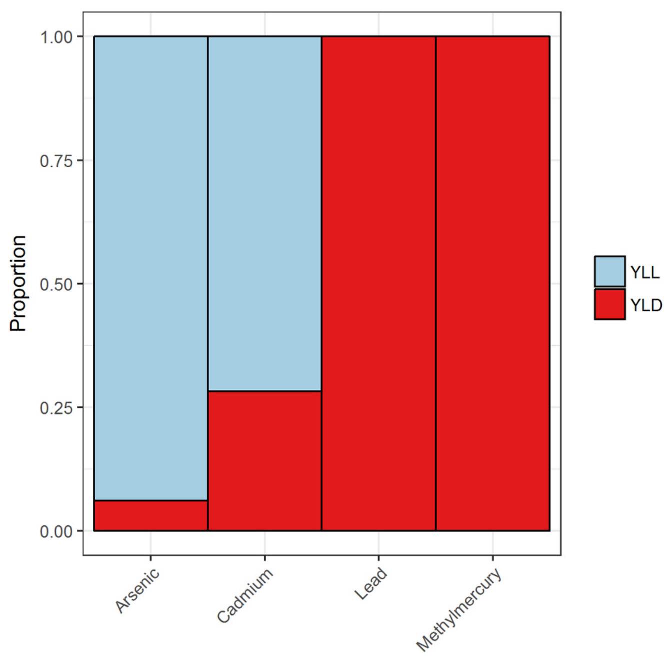

Fig. 2. The relative contributions from years of life lost (YLLs) and years lived with disability (YLDs) for each of the four metals.

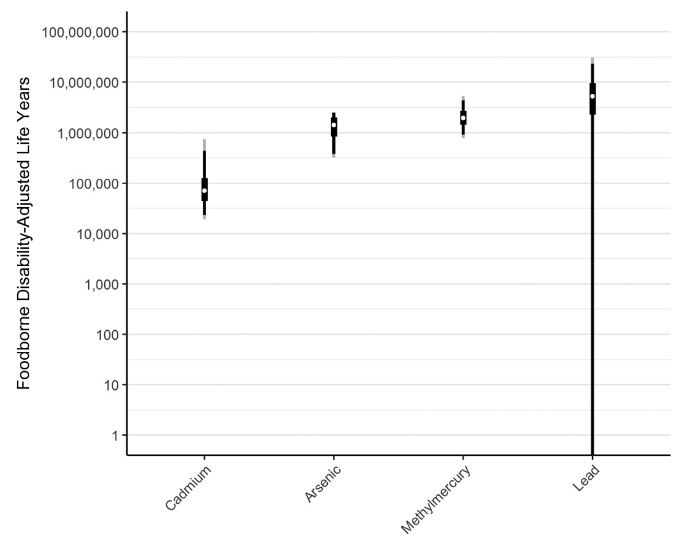

Fig. 3. Disability-adjusted life years (DALYs) for each of the four metals from lowest to highest with 95% uncertainty interval (UI). The dot in the middle of each box represents the median, the box the 50% UI, the dark line the 90% UI, and the light line the 95% UI.

can occur via ingestion and inhalation of lead dust). Exposure to methylmercury is believed to be through food only.

The burden estimates for the four metals are compared globally and by WHO region and subregion. The six WHO regions are Africa ("AFR"), the Americas ("AMR"), Eastern Mediterranean ("EMR"), Europe ("EUR"), Southeast Asia ("SEAR"), and the Western Pacific ("WPR"). Countries within a region are classified into subregions by mortality levels: A: Very low child, very low adult mortality; B. Low child, low adult mortality; C. Low child, high adult mortality; D High child, high adult mortality; and E: High child, very high adult mortality (Ezzati et al., 2002). The subregions and the member states in the subregions are described in Table 1.

3. Results

Of the over 1 million illnesses estimated to be caused by the four metals in 2015, 54% are due to lead, 22% are due to methylmercury, 20% are due to arsenic, and 1% are due to cadmium. The overwhelming majority of deaths (96%) were due to arsenic; 4% of deaths were due to cadmium. No deaths were attributed to lead and methylmercury, which is a function of the disease endpoint that was evaluated (intellectual disability). With regard to DALYs, 60% were attributed to lead, 23% to methylmercury, 14% to arsenic, and 1% to cadmium. A comparison of the numbers of foodborne illnesses, deaths, YLDs, YLLs, and DALYs, with 95% uncertainty intervals (UIs), for the four metals can be found in Table 2. Median rates of foodborne DALYs per 100,000 for each of the metals, by WHO subregion, are reported in Table 3. The complete set of estimates is given in the Appendix.

Fig. 1 provides the DALYs per 100,000 by global region. The subregion with the highest burden is the Western Pacific Region B. The subregion with the lowest burden is the Americas Region A. Lead and/or methylmercury have the greatest impact on all subregions with the exception of the Americas Region A where the greatest impact is arsenic. Fig. 2 contrasts the proportion of DALYs due to YLL and YLD for each of the four metals. All of the DALYs for lead and methylmercury are due to YLDs. For arsenic, the YLLs contribute the largest source of DALYs. Fig. 3 shows the uncertainty around the DALY estimates for each of the four metals. The metal with the least uncertainty is

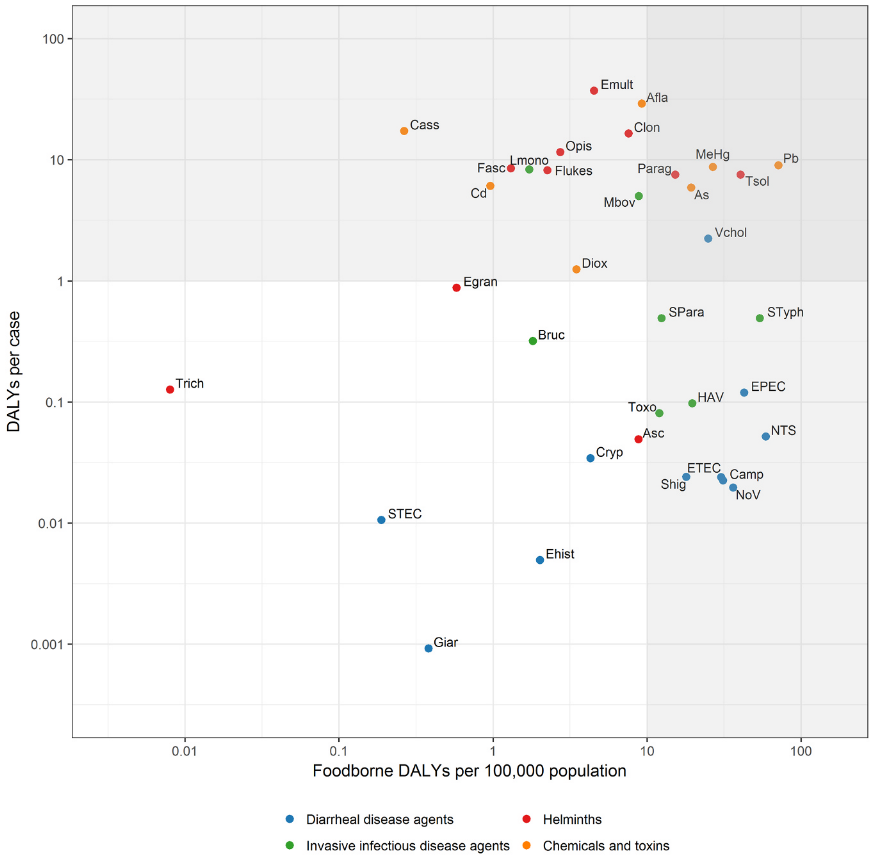

Fig. 4. Foodborne disability-adjusted life years (DALYs) per 100,000 population and DALYs per case for diarrheal disease agents, invasive infectious disease agents, helminths, and chemicals and toxins. The grey-shaded areas indicate arbitrary cut-offs between high or low population burden (> or ≤ 10 DALYs per 100,000 population) and high or low individual burden (> or ≤ 1 DALY per case). Abbreviations: NoV: Norovirus; Camp: *Campylobacter* spp.; EPEC: Enteropathogenic *Escherichia coli*; ETEC: Enterotoxigenic *E. coli*; STEC: Shiga toxinproducing *E. coli*; NTS: non-typhoidal *Salmonella enterica*; Shig: *Shigella* spp.; Vchol; *Vibrio cholerae*; Ehist: *Entamoeba histolytica*; Cryp: *Cryptosporidium* spp.; Giar: *Giardia* spp.; HAV: Hepatitis A virus; Bruc: *Brucella* spp.; Lmono: *Listeria monocytogenes*; Mbov: *Mycobacterium bovis*; SPara: *Salmonella* Paratyphi A; STyph: *Salmonella* Typhi; Toxo: *Toxoplasma gondii*; Egran: *Echinococcus granulosus*; Emult: *E. multilocularis*; Tsol: *Taenia solium*; Asc: *Ascaris* spp.; Trich: *Trichinella* spp.; Clon: *Clonorchis sinensis*; Fasc: *Fasciola* spp.; Flukes: Intestinal flukes; Opis: *Opisthorchis* spp.; Parag: *Paragonimus* spp.; Diox: Dioxins; Afla: Aflatoxin; Cass: Cyanide in cassava; Pb: Lead; Cd: Cadmium; As: Arsenic; MeHg: methylmercury. Rates for all substances with the exception of lead, cadmium, arsenic, and methylmercury are adapted from Havelaar et al. (2015).

methylmercury; the metal with the most uncertainty is lead. Fig. 4 compares the number of DALYs per case for various foodborne agents, including the four metals.

4. Discussion

Recently, the WHO published first-ever estimates of the global burden of foodborne disease. These estimates captured the health impact of 31 foodborne hazards, including diarrheal disease agents, invasive infectious disease agents, helminths, and chemicals and toxins (Havelaar et al., 2015). The current study adds four metals to our knowledge of the global burden of disease from foodborne chemicals. Even with the addition of the four metals, the greatest contribution to the burden of disease appears to be the diarrheal disease agents (Havelaar et al., 2015). The estimate of the disease burden for the chemicals, however, remains incomplete. Other chemicals and toxins for which estimates would be important include seafood toxins, pesticide residues, food additives (e.g., sulphites, nitrites, etc.), mycotoxins other than aflatoxin, process contaminants (e.g., acrylamide, polycyclic aromatic hydrocarbons, etc.), and natural contaminants (e.g., aminoglycosides, aristolochic acid, etc.). Furthermore, for the four metals described in this study and for the four chemicals/toxins described in Gibb et al. (2015), not all disease endpoints were included (e.g., lead and hypertension, arsenic and heart disease). Indeed, disease caused by chemical hazards is typically chronic and appears a long time after exposure, resulting in more and larger uncertainties than for health endpoints caused by biological hazards. The burden estimates for the four metals described in this study and the four chemicals/toxins described in Gibb et al. (2015) are thus a "tip of the iceberg" with respect to the impact of chemicals and toxins on the foodborne burden of disease.

Burden estimates for the four metals were all determined using an exposure response ("bottom-up") approach. Another method would be to use a "top-down approach" in which an existing estimate of the morbidity and mortality from all causes ("envelope") becomes the starting point. An attributable fraction is then determined for the specific hazard and applied to the envelope to estimate the fraction due to the hazard (Gibb et al., 2015). There is uncertainty with both the "bottom-up" and "top-down" approaches. For the "top-down approach," an envelope may be inadequately determined (e.g., less developed countries where health statistics may be limited or nonexistent). For the "bottom-up" approach, the exposure response relationship from one set of data may not be applicable to another population or to all exposures.

Because of the large number of illnesses associated with foodborne lead and methylmercury (Table 2) and because the effects begin at an early age and last throughout life, lead and methylmercury are responsible for the most DALYs. For both lead and methylmercury, the associated illnesses are mild, moderate, and severe intellectual disability. The increase in the number of illnesses in each category due to exposure to these chemicals is a result of a population shift in IQ. Mild, moderate, and severe intellectual disabilities are considered disease states because each has an International Classification of Disease code. As Bellinger (2018) points out, however, this minimizes the effect that lead and methylmercury have on the population disease burden since exposure to these metals can diminish IQ without shifting an individual into one of the categories of intellectual disability. Even among those not classified as having intellectual disability, the diminution of IQ has a resulting health and social effect.

The vast majority (96%) of deaths are attributed to arsenic. The remainder (4%) is attributed to CKD deaths from cadmium. The majority of deaths being attributed to foodborne arsenic is explained by the large number of potentially life-threatening illnesses attributed to arsenic (Table 2). These include lung, bladder, and non-melanoma skin cancer, lung cancer being particularly fatal (Mathers et al., 2001).

Of the four metals, the fewest number of illnesses and DALYs were attributed to cadmium. Globally, however, foodborne cadmium was estimated to account for 12,224 illnesses, 2064 deaths, 70,513 DALYs, and 1.0 DALY per 100,000 (about 0.2% of the global DALYs of CKD) in 2015.

Havelaar et al. (2015), using 2010 population data, reported on the burden of disease due to 31 foodborne hazards. These 31 agents include: diarrheal disease agents (norovirus, seven types of bacteria, and three types of protozoa); invasive infectious disease agents (hepatitis A virus, five types of bacteria, and one type of protozoa); helminths (three types of cestodes, two types of nematodes, and five types of trematodes); and three chemicals and toxins (dioxin, aflatoxin, and cyanide in cassava). Diarrheal disease agents had the highest foodborne DALYs per 100,000 for all of the subregions with the exception of AMR D (helminths), SEAR B (invasive infectious disease agents), and WPR B (helminths). The geographic presence of two of the three chemicals (aflatoxin and cyanide in cassava) described by Havelaar et al. (2015) is limited with respect to their presence in the food supply, aflatoxin being found primarily in Asia and Africa and global estimates for cyanide in cassava being done only for Africa. It should be noted, however, that cyanide in cassava, aflatoxin, and dioxin were all found to have a high burden per case (high > 1 DALY per case), and of the 31 agents considered, only *Echinococcus multilocularis*, a cestode, was found to have a higher burden per case than aflatoxin and cyanide in cassava.

The number of DALYs per 100,000 for the foodborne metals does not appear particularly high in comparison to the total number of DALYs per 100,000 associated with foodborne viruses, bacteria, protozoa, and parasites reported by Havelaar et al. (2015). Again, however, it must be remembered that Havelaar et al. (2015) described results for 28 viral, bacterial, protozoan, and parasitic agents and only three chemicals/toxins. Only four chemical agents are described in the current study. However, like the three chemicals/toxins described in Havelaar et al. (2015), all four of the metals have a high burden per case (> 1 DALY per case): arsenic – 6 DALYs per case; cadmium – 6 DALYs per case; methylmercury – 9 DALYs per case; and lead – 9 DALYs per case. The high DALYs per case is a reflection of the chronic and some severe diseases caused by these agents. Of the six agents with both a high (> 10) number of DALYs per 100,000 and a high (> 1) number of DALYs per case, three (arsenic, methylmercury, and lead) are metals (Fig. 4).

5. Conclusion

The foodborne metals in this study are estimated to be responsible for over 9 million DALYs, over 1 million illnesses, 7.7 million YLDs, 1.4 million YLLs and over 56,000 deaths globally in 2015. Similar to dioxin, aflatoxin, and cyanide in cassava, the four metals have high DALYs per case; three of the metals (arsenic, methylmercury, lead) have high DALYs per 100,000 population. Cadmium contributed least to the number of foodborne illnesses and DALYs, but among the metals, all of the YLLs and deaths were attributed to cadmium and arsenic.

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Competing interests

The authors declare they have no actual or potential competing financial interests.

Appendix A. Supplementary material

Estimates of the 2015 global and regional disease burden from four foodborne metals – arsenic, cadmium, lead and methylmercury. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.envres.2018.12.062.

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