



## **Review and evidence synthesis of data needed to estimate the global burden of disease caused by foodborne exposure to cadmium, methylmercury, arsenic and lead**

### **Preliminary Terms of Reference**

Reference Number: CTTF-002

#### **Purpose**

Specific purpose of the work: Please note that applicants of this expression of interest are welcomed to indicate interest either in all or specific purpose(s) from the list below:

- a. To collect data that are most suitable for estimating the disease burden of chronic kidney disease caused by dietary exposure to cadmium (Cd)
- b. To collect data that are most suitable for estimating the disease burden of intellectual disability caused by dietary exposure to methylmercury (MeHg)
- c. To collect data that are most suitable for estimating the disease burden of lung, bladder and skin cancer caused by dietary exposure to inorganic arsenic (iAs)
- d. To collect data that are most suitable for estimating the disease burden of intellectual disability and cardiovascular diseases (CVD) caused by dietary exposure to lead (Pb).

#### **Background**

- a. General: Please refer to the accompanying Concept Note.<sup>1</sup>
- b. Cadmium, methylmercury, lead and inorganic arsenic are metals that occur in the environment either naturally or by anthropogenic activities. These metals are associated to the risk of a range of adverse health effects. Among those, cadmium causes chronic kidney disease, exposure to methylmercury and lead impairs neurodevelopment in the fetus and young children and lead increase systolic blood pressure and inorganic arsenic is classified as carcinogenic to humans<sup>2</sup>. In 2007-2015, estimates of the global burden of diseases from three chemical hazards and toxins were generated (WHO 2015). The Chemicals and Toxins Taskforce (CTTF) in the first iteration of WHO's technical advisory group, "Foodborne Disease Burden Epidemiology Reference Group for 2007-2015 (FERG1)" considered that evidence to estimate the disease burden caused by the above-mentioned four metals was available, and global estimates for intellectual disability due to methylmercury and lead, chronic kidney disease caused by cadmium, and lung, bladder and skin cancer and coronary heart disease caused by inorganic arsenic were later published in the scientific literature<sup>3</sup>. Various

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<sup>1</sup> [https://cdn.who.int/media/docs/default-source/foodborne-diseases/ferg/call-for-expressions-of-interest-ferg-concept-note.pdf?sfvrsn=e01eebbc\\_6](https://cdn.who.int/media/docs/default-source/foodborne-diseases/ferg/call-for-expressions-of-interest-ferg-concept-note.pdf?sfvrsn=e01eebbc_6)

<sup>2</sup> <https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono87.pdf>

<sup>3</sup> <https://www.sciencedirect.com/science/article/abs/pii/S0013935118306959?via%3Dihub>

models and data were used to generate the global estimates, but all applied a risk assessment approach.

- c. The CTTF under the FERG for 2021-2025 (FERG2) has developed a workplan agreed with WHO that prioritizes various chemicals and toxins for systematic reviews to identify the global burden associated with the individual specific hazards and how much disease associated with the relevant hazard was due to contaminated food. In this second iteration of FERG, the CTTF has prioritized the inclusion of the disease burden of the four metals in the global estimates for 2025.

## Objectives and specific tasks

### a. Objective 1 – Cadmium

- To conduct a systematic review of literature published between 1990 and the commencement date of the successful contractor to collect data to enable country specific dietary cadmium exposure estimation. This review should include, but is not limited to national/subnational total diet studies, biomonitoring data, national/subnational food consumption data, or published national/subnational cadmium exposure assessments (see specific scope below).
- To conduct a systematic review of literature published between 1990 and the commencement date of the successful contractor to collect data of country specific glomerular filtration rates of the general population.
- To collect country specific case-fatality rates of chronic kidney disease stage 5 from relevant sources.

### b. Objective 2 – Methylmercury

- To update the systematic literature review by Bellinger et al. (2016)<sup>4</sup> so that it follows the standardized approach developed by the FERG2 (e.g. review of literature published between 1990 and the commencement date of the successful contractor) to collect data to enable country specific MeHg exposure of the general population using biomonitoring data and information to link to intellectual disability.

### c. Objective 3 – Inorganic arsenic

- To conduct a systematic review of literature published between 1990 and the commencement date of the successful contractor to collect data to enable country specific dietary iAs exposure estimation. This review should include, but is not limited to national/subnational total diet studies, biomonitoring data, national/subnational food consumption data, biomonitoring data or published national/subnational cadmium exposure assessments (see specific scope below).
- To provide information to the FERG2 on which dose response relationships between iAs exposure and lung, bladder and skin cancer are appropriate to use for disease burden estimation.

### d. Objective 4.1 – Lead (using the approach developed by FERG1)

- To conduct a systematic review of literature published between 1990 and the commencement date of the successful contractor to collect data to enable country specific dietary lead exposure estimation in children below age of 5, and information to link to intellectual disability. This review should include, but is not limited to national/subnational

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<sup>4</sup> <https://doi.org/10.1016/j.envres.2015.10.006>

- total diet studies, biomonitoring data, national/subnational food consumption data, biomonitoring data or published national/subnational cadmium exposure assessments (see specific scope below).
- To conduct a literature review and evidence synthesis of data needed to estimate the burden of CVD caused by dietary exposure to lead.
- e. Objective 4.2 – Lead (in line with the approach developed by Institute for Health Metrics and Evaluation (IHME))
  - To collect country specific population attributable fractions (PAF) of intellectual disability caused by lead exposure from relevant databases (i.e. IHME database).
  - To collect country specific PAF of systolic blood pressure and/or CVD (the relevant specific outcomes under CVD) caused by lead exposure from relevant databases (i.e. IHME database).

## Scope of work

- a. The protocol for the systematic reviews must be developed in line with the PRISMA-P guidelines (<http://www.prisma-statement.org/documents/PRISMA-P-checklist.pdf>). For full transparency, protocols must be registered in Prospero (<https://www.crd.york.ac.uk/prospero/>).
- b. Inclusion and exclusion criteria in addition to the minimum requirements in the Concept Note:
  - For all purposes: include studies/sources from 1990 until current time and geographic locations; peer reviews and grey literature sources including government and institutional reports or other databases. If not else is stated below, include only studies representative of the general population. Where relevant, data in the GEMS Food Contamination Database should be collected in addition to literature search.
  - For purpose 2 Follow at least the same inclusion/exclusion criteria as described in Bellinger et al. 2015.
  - For purpose 4.1 and 4.2: Data to dietary exposure to lead must cover, to the extent possible, data to enable assessment of children below 5 years of age as well as the adult population.
- c. Databases
  - Systematic searches are required to consider both peer-reviewed and grey literature
    - Peer-reviewed literature needs to be searched for in at least the following repositories: PubMed, Web of Science, Embase, Scopus, and [INASP Journals Online project](#).
    - Grey literature needs to be searched for in at least the following repositories: IRIS (WHO), Oaister, Google Scholar
  - Where relevant, national surveillance data can be collected from individual country sources
- d. Language requirements
  - Systematic searches are required to include both English and non-English papers
- e. Requirements for extracted/compiled data:

The final data extracted from each identified study/source must be captured in a standard spreadsheet (to be provided, see example template in Appendix A). For this work, the spreadsheet will capture the following:

All purposes:

- Study Design and Study Population Information:
  - Reviewer assigned identification number of the input source
  - Full name of the first author of input source
  - Year of publication
  - Language of publication
  - DOI of publication, or name of journal/website/etc. if DOI is unavailable
  - Full title of the input source
  - Country source of data in separate column
  - For the data/values extracted from the input source (note, may require separate rows if multiple different values are extracted from one source:
    - The starting date of the data (e.g., the beginning of data collection)
    - The end date of the data collection
    - The geographic location from which the data came
    - The type of population from which the data came (if relevant) (such as national population or subgroups)
    - The age distribution in the study population (if relevant)
    - The proportion of males, females, and 'other' in the study population from which the data came (if relevant)

Purposes where exposure assessments are included:

- Exposure assessment data:
  - Unit of exposure (e.g., ng/kg bw/day)
  - Type of assessment (such as external exposure (deterministic/probabilistic dietary exposure, internal exposure (biomarkers))
  - Foods analyzed/contributing to exposure
  - Relevant descriptive statistics of population exposure.
- Occurrence data specified:
  - Analytical method
  - Sampling approach (such as random, targeted)
  - Individual or pooled samples, if so number of subsamples by composite sample
  - Unit
  - LOD/LOQ
  - Foods analyzed and state (as consumed or raw agricultural commodity)
  - Number of samples, number < LOD/LOQ
  - Concentration in samples (mean and other statistics if concentration in single samples are not reported)
- Food consumption data specified:
  - Type of food record (Individual quantitative food consumption data (24h recalls, weighted diet, food record), FFQ, food consumption estimates derived household budget surveys, food balance sheets).
  - Meta data of food record (if anything additional than included under "all purposes" such as number of days of food records, mean bodyweight of age groups/genders), unit of intake).
  - Relevant descriptive statistics of population intake of relevant foods (peanuts, maize, ruminant milk).

### Specific for Objective 1 – Cd and Glomerular filtration rate (GFR)

- Characterization of population from which GFR data are collected (type of population, ie. general, occupation, sample size etc.) relevant to identify representativeness of general population
- Age of population from which GFR data are collected.
- Relevant descriptive statistics of population GFR distribution (i.e. mean and SD)

## Timeframe

**Start date:** September 2023 **End date:** February 2024 (6 months)

## Deliverables and timeline for delivery

The contractors will deliver a final dataset and report documenting results, to be further analysed and interpreted by WHO and the FERG, especially the respective taskforces and the computational taskforce. It is expected that this review will result in a manuscript for publication in at least one peer-review journal, that must adhere to the WHO policy on Open Access<sup>5</sup>. Contractors are to lead the writing process, in close coordination with the relevant taskforces, respectively. The publication process will be governed by the existing publication policy, and authorship is subject to the recommendations for defining the role of authors and contributors published by the International Committee of Medical Journal Editors (ICMJE).

### *Interim deliverables*

- a. Protocol development and registration
  - i. The protocol for the systematic reviews needs to be developed in line with the PRISMA-P guidelines (<http://www.prisma-statement.org/documents/PRISMA-P-checklist.pdf>).
  - Protocols need to be registered in Prospero, for full transparency (<https://www.crd.york.ac.uk/prospero/>).
- b. Interim meetings with commissioning TF and CTF
- c. Final report
  - i. Draft report
  - ii. Final report
- d. Electronic copies of all references from which evidence was extracted (organized for easy use and with source identification number included in the file name) f.
- e. Electronic copies of the final data extraction sheets i.
  - i. Data extraction sheet templates at start of review
  - ii. Revised data extraction sheets incorporating FERG feedback
  - iii. Final data extraction sheets containing evidence extracted and estimates calculated.

### *Report content, quality and style*

#### Components of the final report

1. Abstract

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<sup>5</sup> <https://www.who.int/about/policies/publishing/open-access>

2. Introduction
3. Methods
4. Results
5. Discussion
6. Conclusion
7. Annexes

## Qualifications, experience, skills and languages

- a. Educational qualifications
  - Advanced degree in toxicology, food science or public health. A PhD in one of these disciplines will be considered an asset.
- b. Experience
  - 5+ years in the field of chemical risk assessment, preferably pertaining to metals, including dose response characterization and/or exposure assessment through dietary data and/or biomarkers.
  - Experience should include systematic literature reviews, report writing, including peer-reviewed publications in the area under consideration.
  - Experience collaborating with end-knowledge users (such as government agencies) throughout the systematic review process, to ensure the type and format of evidence generated by the review are directly useable by the end-user (here, FERG2).
- c. Languages and level required
  - Strong communication skills in English, especially in scientific written communication
- d. Other essential requirements
  - Teamwork, delivering results, communication

## Other requirements

The study team will be selected from the submitted expressions of interest and based on the qualifications and skills (see specifications in relevant section). Geographical and gender diversity is encouraged for applications from teams. Each individual or team member will also need to complete the standard WHO Declaration of Interest form, which will be assessed for conflict of interests. The team leader may be asked to further elaborate the expression of interest in a virtual video meeting with the WHO Secretariat. The final candidates will be selected through a competitive process in accordance with WHO's policies and procedures.

## Location and travel

The work should be done remotely, and no travel is required.

## How to apply for a call for expressions of interest

Expressions of interest must be delivered electronically to the WHO Secretariat via the following application portal link:

[extranet.who.int/dataformv3/index.php/329293?lang=en](https://extranet.who.int/dataformv3/index.php/329293?lang=en)

**IMPORTANT:** To complete the application you must have the following information collected **prior** to applying. It is not possible to return to the portal and modify your submission.

- 1) Reference number (found in the Terms of Reference)
- 2) Contact information from the main focal point only (i.e. Lead Investigator)
- 3) Cover letter/statement of motivation, including a maximum of 600 words detailing why your team are submitting this Expression of Interest, and why you believe your team is the most suitable to undertake this work. **It is recommended to prepare this in a separate Word document so you can copy and paste text into the application.**
- 4) ONE document (ideally in PDF format) that includes every Curriculum Vitae (CV) of the proposed research team.
- 5) ONE document (ideally in PDF format) that includes a brief biography of each research team member (max 150 words per person).