



## **Review and evidence synthesis of data needed to estimate the global burden of disease caused by foodborne exposure to aflatoxin B1 and aflatoxin M1**

### **Terms of Reference**

**Reference Number: CTTF-001**

### **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 Aflatoxin B1 (AFB1) and Aflatoxin M1 (AFM1) exposure assessment from maize/peanuts and ruminant milk, respectively at country and/or WHO (sub-) regional level.
- b. To collect data on country specific hepatitis B virus (HBV) prevalence and/or WHO (sub-) regional level.
- c. To collect and synthesize the evidence necessary to estimate acute aflatoxicosis disease burden and advise if burden estimation is possible.
- d. To review current knowledge on the association between aflatoxin exposure and growth impairment, and advise if burden estimation is possible.

### **Background**

- a. General: Please refer to the accompanying Concept Note.<sup>1</sup>
- b. AFB1 is a mycotoxin produced by the *Aspergillus* fungus in certain crops intended for human consumption and animal feed. AFM1 is a metabolite of AFB1, and occurs mainly in milk from cattle fed AFB1 contaminated crops. Aflatoxins are classified as carcinogenic to humans (group 1) by International Agency for Research on Cancer (IARC) (IARC, 2012, 2015); sufficient evidence in humans exist for the carcinogenicity of aflatoxins and sufficient evidence in experimental animals for the carcinogenicity of naturally occurring mixtures of aflatoxins, and of aflatoxin B1, G1 and M1 (IARC, 2012). AFB1 and AFM1 cause hepatocellular carcinoma (HCC), a leading cause of cancer deaths worldwide. However, the carcinogenicity of AFM1 has been documented only in experimental animals. AFB1 interacts with hepatitis B virus (HBV), increasing the risk of HCC (JECFA, 2002). It is not known if AFM1 interacts with HBV in a similar manner. In 2007-2015, estimates of the global burden of diseases from seven chemical hazards were generated including the 2010 global burden of hepatocellular cancer (HCC) caused by dietary exposure to AFB1 (WHO 2015). AFB1-induced HCC was estimated by a multiplicative approach where a population attributable fraction was estimated from the combination of a cancer slope factor (JECFA, 2002) and exposure of AFB1 from maize and peanuts.

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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\\_5](https://cdn.who.int/media/docs/default-source/foodborne-diseases/ferg/call-for-expressions-of-interest-ferg-concept-note-.pdf?sfvrsn=e01eebbc_5)

- c. The chemical and toxins taskforce (CTTF) has developed a workplan 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 the first iteration of the FERG, it was estimated that there was an annual global burden of approximately 637,000 disability-adjusted life years (DALYs) from about 21,800 cases of HCC caused by aflatoxin (Gibb, 2015).

## Objectives and specific tasks

a. Specific objectives of the work

i. Purpose A – Exposure assessment

- To conduct a systematic review of literature published between 1990 and the commencement date of the successful contractor to collect data to enable country and WHO (sub-)regional specific AFB1 and AFM1 exposure estimation from maize/peanuts and ruminant milk, respectively. This review should include, but is not limited to national/subnational total diet studies, biomonitoring data, national/subnational maize, peanuts and ruminant milk consumption data, biomonitoring data or published national/subnational AFB1 and AFM1 exposure assessments (see specific scope).
- To collect and assess data from GEMS/Food contaminants database<sup>2</sup>; the literature review should supplement occurrence data obtained from GEMS/Food contaminants database.
- To collect, if available, other relevant data (other than published literature) including data from national surveillance systems.
- Assess the representativeness, completeness, pros and cons of different data sources and advise FERG and WHO on which data are most suitable for exposure assessment.

ii. Purpose B – HBV prevalence

- To conduct a systematic review of literature published between 1 January 1990 and the commencement date of the successful contractor on country and WHO (sub-)regional specific prevalence of HBV in the general population assessed by HBV surface antigen (HBVsAg+).

iii. Purpose C – Acute aflatoxicosis

- To conduct a systematic review of literature published between 1 January 1990 and the commencement date of the successful contractor on national or WHO (sub-)regional evidence of incidence and mortality of acute aflatoxicosis (see specific scope).
- In collaboration with CTTF and WHO, on the basis of the above, assess if evidence is available to estimate the burden of acute aflatoxicosis.
- If relevant, to characterize through scientific literature the health state(s) associated with acute aflatoxicosis including estimates of disease duration.

iv. Purpose D – Association between growth impairments and aflatoxin exposure

- To update the review on association between growth impairments and aflatoxin exposure published by Khlangwiset et al (2011).
- To synthesize the data collected, compare with findings in FERG1 and assess in collaboration with CTTF and WHO if sufficient evidence is available to estimate the burden of growth impairments induced by aflatoxin exposure.

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<sup>2</sup> <https://extranet.who.int/gemsfood/?DisplayFormat=1>

## Scope of work

- a. Inclusion and exclusion criteria in addition to the minimum requirements in the Concept Note:
  - i. 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. Data in the GEMS Food Contamination Database should be collected in addition to literature search.
  - ii. For purpose A – Exposure assessment: Exclude studies not reporting exposure assessments relating to consumption of peanuts/maize or ruminant milk or studies not reporting AFB1 and/or AFM1 occurrence data in peanut/maize and ruminant milk, respectively.
  - iii. For purpose B – HBV prevalence: Exclude studies not reporting prevalence in the general population.
  - iv. For purpose C – Acute aflatoxicosis: Include studies reporting on incidence and/or mortality of acute aflatoxicosis, both sporadic and outbreak data.
  - v. For purpose D – Growth impairments: Include studies/sources to update review by Khlangwiset et al. (2011).
- b. Databases
  - i. Systematic searches are required to consider both peer-reviewed and grey literature
    - o 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](#).
    - o Grey literature needs to be searched for in at least the following repositories: IRIS (WHO), Oaister, Google Scholar
  - ii. Where relevant, national surveillance data can be collected from individual country sources
- c. Language requirements
  - i. Systematic searches are required to include both English and non-English papers
- d. 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:
  - o Reviewer assigned identification number of the input source
  - o Full name of the first author of input source
  - o Year of publication
  - o Language of publication
  - o DOI of publication, or name of journal/website/etc. if DOI is unavailable
  - o Full title of the input source
  - o Country source of data in separate column
  - o 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)

Purpose A - Exposure assessment:

- 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).

Purpose B – HBV prevalence in the general population

- Sample size of the population for which the prevalence of HBV was estimated
- Number of individuals with chronic HBV assessed by HBsAg
- Relevant descriptive statistics of HBsAg prevalence

Purpose C– Acute aflatoxicosis

- Acute aflatoxicosis incidence information
  - Type of study (case reports, outbreak data, cross sectional)
  - Sample size of the population from which incidence of acute aflatoxicosis was derived
  - Numerator for the incidence rate of acute aflatoxicosis
  - Denominator for the incidence rate of acute aflatoxicosis
  - Relevant descriptive statistics of acute aflatoxicosis incidence rate

- Acute aflatoxicosis mortality/case fatality rate information
  - Sample size of the population from which mortality of acute aflatoxicosis was derived
  - Numerator for the mortality/case fatality rate of acute aflatoxicosis
  - Denominator for the mortality/case fatality rate of acute aflatoxicosis
  - Relevant descriptive statistics of acute aflatoxicosis mortality/fatality rate.

#### Purpose D – Aflatoxin and stunting

- As stated under All purposes and under specific purposes of the work.
- e. WHO Regions/Sub-Regions:
- i. See Concept Note

## Timeframe

**Start date:** November 2022 **End date:** April 2023 (6 months)

## Deliverables and timeline for delivery

The contractors will deliver a final dataset and report documenting results, to be further analyzed 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>3</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.

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<sup>3</sup> <https://www.who.int/about/policies/publishing/open-access>

## *Report content, quality and style*

### Components of the final report

1. Abstract
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 mycotoxins, 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 or individual 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. Scientists will participate in their individual capacity rather than as a representative of their employer. Once shortlisted, 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 individual or 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.

## References

IARC (2012). Chemical agents and related occupations. IARC Monogr Eval Carcinog Risks Hum. 100F:1–599. PMID:23189753. Available from: <http://monographs.iarc.fr/ENG/Monographs/vol100F/index.php>

IARC (2015). Mycotoxin control in low- and middle-income countries. Edited by Christopher P. Wild, J. David Miller, John D. Groopman. IARC Working Group Reports; 9. Available from: <https://publications.iarc.fr/Book-And-Report-Series/Iarc-Working-Group-Reports/Mycotoxin-Control-In-Low--And-Middle-income-Countries-2015>

Joint FAO/WHO Expert Committee on Food Additives (2002). Meeting. (57th: 2001: Rome, Italy). (2002). Safety evaluation of certain food additives and contaminants / prepared by the fifty-seventh meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). World Health Organization. Available from: <https://apps.who.int/iris/handle/10665/42501>

Khlangwiset P, Shephard GS, Wu F (2011). Aflatoxins and growth impairment: a review. Crit Rev Toxicol. 41(9):740–55. <http://dx.doi.org/10.3109/10408444.2011.575766> PMID: 21711088

## HOW TO APPLY

Please note the following requirements before proceeding with your application.

To complete the application an applicant or the team leader of applying team must provide responses to questions explicitly detailed in the application portal linked below. It is important to have all information prepared prior to applying online, as it is not possible to return to the portal to modify your submission:

- 1) Reference number (found in the Terms of Reference)
- 2) Contact information from the main focal point only (such as the 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) Proposed fee for undertaking the work (in USD)
- 5) Ideal start date and completion dates to undertake the work
- 6) ONE document (ideally in PDF format) that includes every Curriculum Vitae (CV) of the proposed research team or an individual applicant.
- 7) ONE document (ideally in PDF format) that includes a brief biography of an applicant or each research team member (max 150 words per person).

Apply here:

<https://extranet.who.int/dataformv3/index.php/998268?lang=en>

Contact: WHO secretariat [fbd-burden@who.int](mailto:fbd-burden@who.int)

**APPENDIX A – template of data extraction spreadsheet**

<b>SOURCE_ID</b>	Identification number of the input source
<b>SOURCE_AUTHOR</b>	First author of input source
<b>SOURCE_YEAR</b>	Year of publication
<b>SOURCE_TITLE</b>	Title of source
<b>SOURCE_DOI</b>	DOI of source (if available)
<b>SOURCE_URL</b>	URL of source, other than DOI (if available)
<b>REF_YEAR_START</b>	Starting year of the data derived from the input source
<b>REF_YEAR_END</b>	End year of the data derived from the input source
<b>REF_LOCATION</b>	Geographic location for which the input source was used
<b>REF_AGE_START</b>	Numerical value of starting age of the population of the data derived from the input source
<b>REF_AGE_END</b>	Numerical value of ending age of the population of the data derived from the input source
<b>REF_SEX</b>	Sex of the population of the data derived from the input source
<b>REF_SAMPLE_SIZE</b>	Sample size of data derived from input source
<b>VALUE_MEAN</b>	Mean estimate of the data derived from the input source
<b>VALUE_MEDIAN</b>	Median estimate of the data derived from the input source
<b>VALUE_SE</b>	Standard error of the data derived from the input source
<b>VALUE_P0</b>	0th percentile (minimum) of the data derived from the input source
<b>VALUE_P2_5</b>	2.5th percentile of the data derived from the input source
<b>VALUE_P5</b>	5th percentile of the data derived from the input source
<b>VALUE_P10</b>	10th percentile of the data derived from the input source
<b>VALUE_P25</b>	25th percentile of the data derived from the input source
<b>VALUE_P75</b>	75th percentile of the data derived from the input source
<b>VALUE_P90</b>	90th percentile of the data derived from the input source
<b>VALUE_P95</b>	95th percentile of the data derived from the input source
<b>VALUE_P97_5</b>	97.5th percentile of the data derived from the input source
<b>VALUE_P100</b>	100th percentile (maximum) of the data derived from the input source
<b>VALUE_X</b>	Number of events in data derived from input source
<b>VALUE_N</b>	Sample size of data derived from input source