



# REVISION OF THE EFSA MARGIN OF EXPOSURE DOCUMENT (2005)

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# EFSA MOE DOCUMENT (2005)

In 2005, EFSA published an opinion proposing a harmonised approach for the risk assessment of **substances that have both genotoxic and carcinogenic properties**.

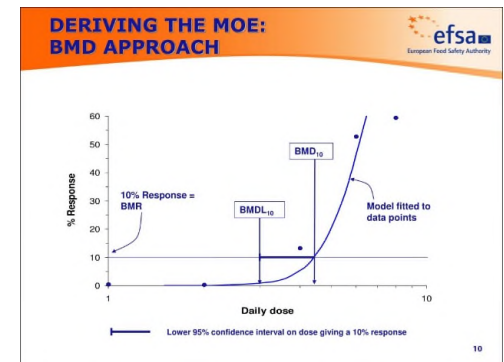
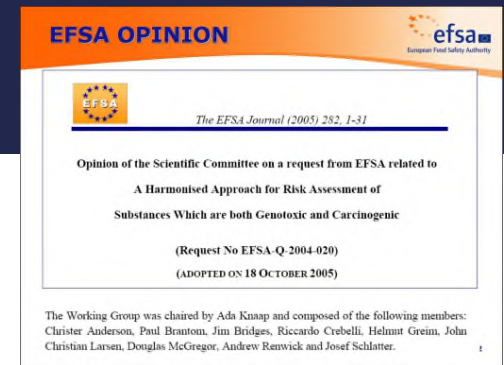
- The Scientific Committee (SC) recommended using the Margin of Exposure (MOE) approach.

In 2012, the SC was asked to deliver a statement on the applicability of the MOE approach for the safety assessment of impurities which are both genotoxic and carcinogenic in substances added to food or feed.

- The SC concluded that the MOE approach can be applied to impurities which are both genotoxic and carcinogenic, irrespective of their origin.

There has been a **growing trend** in utilizing the **MOE approach** to evaluate the potential risk of substances which are both genotoxic and carcinogenic; to this end **the 2005 EFSA document** turn out to be **very helpful**.

However, due to the continuous evolution, improvement, and refinement of science (analytics) and risk assessment methodologies, the 2005 EFSA document **needs to be updated**.



CALCULATING THE MOE

$$\text{MOE} = \frac{\text{BMD}_{10}}{\text{Human exposure}}$$

# PROCEDURE STEPS TAKEN

## Self-task mandate.

- ✓ Drafted Areas of Revision of the 2005 Margin of Exposure Opinion
- ✓ Drafted a Scoping paper
- ✓ Scoping paper approved for public consultation
- ✓ Public consultation during summer 2024
  - Currently refining the Terms of Reference
  - Terms of Reference to be presented at the 122<sup>nd</sup> Scientific Committee Open Plenary

**To participate as observer to the 122<sup>nd</sup> SC Open plenary**



<https://www.efsa.europa.eu/en/events/122nd-plenary-meeting-scientific-committee-open-observers>



# PROPOSED AREAS OF REVISION

✓ Drafted Areas of Revision of the 2005 Margin of Exposure opinion

## State of the art, definitions, terminology.

- a. Areas of application of the MoE approaches outside of EFSA
- b. Definitions and terminologies
- c. Insight on Mode of Action for chemicals which are both genotoxic and carcinogenic

## Application of the MoE

- a. The applicability of the MoE approach to assess safety for the target species, taking into account the relevance of the endpoints (genotoxicity and carcinogenicity) in relation to the lifespan of the different target animal species - e.g. short-lived animals vs long-lived companion animals
- b. Include how to assess mixtures for chemicals which are both genotoxic and carcinogens using the total Margin of Exposure (MoET)
- c. Application of an internal MoE when using Physiologically Based Kinetic (PBK) modelling ([Troutman 2015](#), [Bessems 2017](#))

## Other issues

- a. The use of in vitro and in silico methodologies (e.g. QSARs) (BER Bioactivity: Exposure Ratio elaborated by US EPA - [Paul Friedman et al., 2020](#))
- b. The applicability of biomarkers of effect related to the process of genotoxicity and carcinogenicity
- c. Extension of the MoE approach to include Non dietary exposure

## Revision of the opinion on the Margin of Exposure for chemicals which are both genotoxic and carcinogenic

### Calculation of the MoE

- a. Discussion of the most appropriate RP for genotoxic chemicals when carcinogenicity data are, or are not, available, considering the BMD Guidance Document ([EFSA 2022](#)) on dose-response modelling, and whether the T25 is still considered appropriate
- b. Discussion of the types of genotoxicity data (endpoint, in vivo/in vitro) that can be used in calculation of a BMDL
- c. How to define a Benchmark Response (BMR) for different types of genotoxicity data (continuous) as compared to carcinogenicity data (quantal) for which the BMR of 10% is considered appropriate by EFSA

### Interpretation of the MoE

- a. Guiding principles on MoE interpretation and use will be revised accordingly. For instance, the interpretation of the magnitude of a MoE and the uncertainties included
- b. To rephrase and precisely define the expressions currently used such as "high-, low- concern or unlikely to be of safety concern"
- c. Assessing the potential direct action of extremely low potency chemicals with DNA

**Uncertainties** in the overall approach will be included and discussed





## SCOPING PAPER

✓ Drafted a Scoping paper

✓ Scoping paper approved for public consultation

EFSA is interested to implement a transparent process by reaching out to our stakeholders to provide feedback on the proposed revision of the EFSA opinion on the Margin of Exposure (MoE) for chemicals that are both genotoxic and carcinogenic (EFSA 2005) and the preliminary action plans.

We invite the stakeholders to provide comments related to:

1. proposed areas of revision,
2. work plan & timelines, and
3. engagement activities.



Scoping paper on the revision of the opinion on the Margin of Exposure for chemicals which are both genotoxic and carcinogenic

Scientific Committee (SC) - Methodology and Scientific Support (MESE)

# THE PUBLIC CONSULTATION

✓ Public consultation during summer 2024

Received comments from 7 institutions and 1 individual.

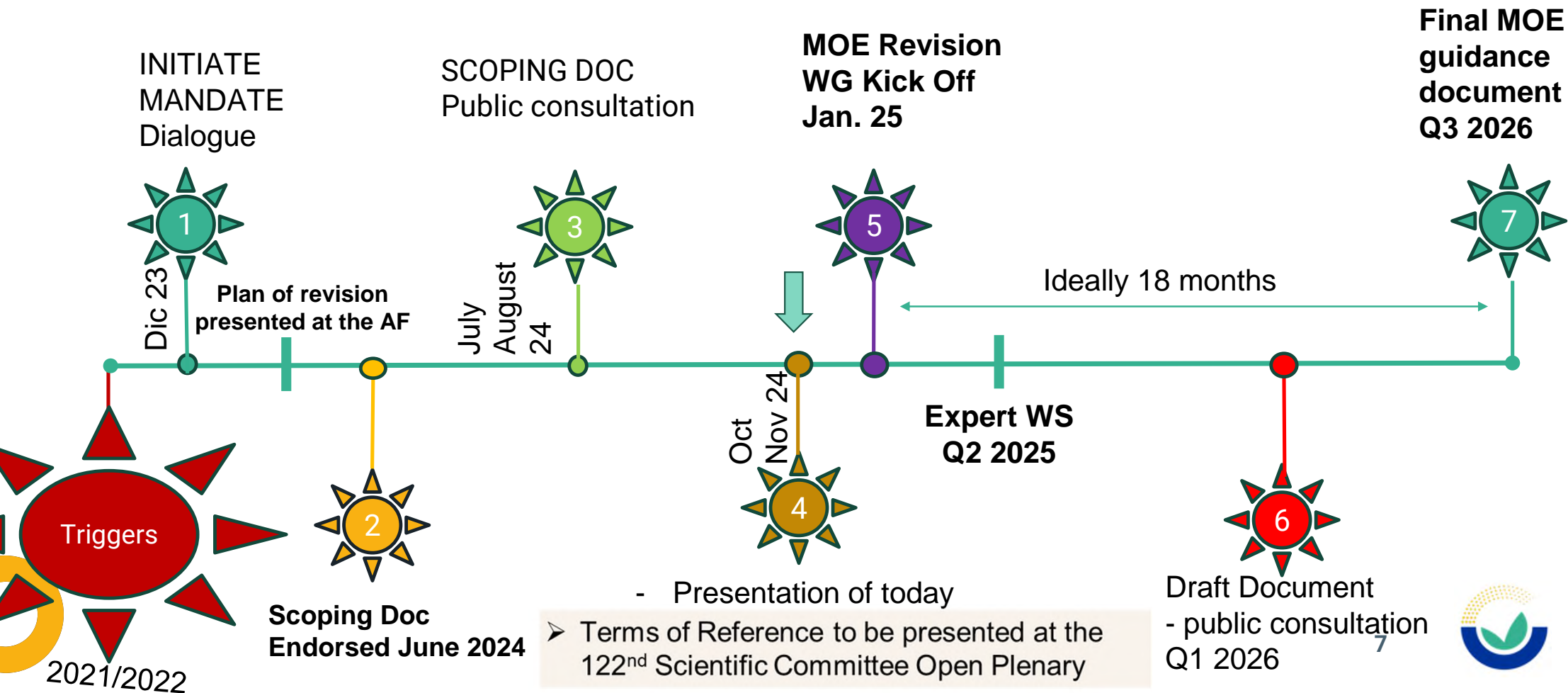
Organisation Name	Country	Section Title
FoodDrinkEurope	Belgium	PROPOSED AREAS OF REVISION
FoodDrinkEurope	Belgium	ENGAGEMENT ACTIVITIES
German Federal Institute for Risk Assessment (BfR)	Germany	PROPOSED AREAS OF REVISION
UK Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC)	United Kingdom (excluding Northern Ireland)	PROPOSED AREAS OF REVISION
PETA Science Consortium International e.V.	Germany	PROPOSED AREAS OF REVISION
PETA Science Consortium International e.V.	Germany	WORK PLAN & TIMELINES
PETA Science Consortium International e.V.	Germany	ENGAGEMENT ACTIVITIES
International Organization of the Flavor Industry	United States	PROPOSED AREAS OF REVISION
Kerry, LLC	Ireland	PROPOSED AREAS OF REVISION
RIVM	Netherlands	PROPOSED AREAS OF REVISION
RIVM	Netherlands	WORK PLAN & TIMELINES
RIVM	Netherlands	ENGAGEMENT ACTIVITIES
Not Applicable (Submission on Personal Capacity)	Unknown	PROPOSED AREAS OF REVISION
Not Applicable (Submission on Personal Capacity)	Unknown	WORK PLAN & TIMELINES

➤ Currently refining the Terms of Reference



# TIMELINE

+/- 2 years



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