

STATEMENT

Statement on the use and interpretation of the margin of exposure approach

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The declarations of interest of all scientific experts active in EFSA's work are available at <https://open.efsa.europa.eu/experts>

Abstract

The margin of exposure (MOE) is a risk assessment tool used to evaluate the safety of substances in food and feed. Adopted by the European Food Safety Authority (EFSA) in 2005, the MOE is calculated as the ratio between a Reference Point (RP) and the estimated exposure. While some regulatory bodies use 'margin of safety' (MOS) interchangeably with MOE, others define it differently, leading to inconsistencies in interpretation. To address this, EFSA has standardised its terminology, establishing MOE as a primary metric for safety assessments across human and animal health evaluations. In addition, the meaning and interpretation of terms used to qualify a 'concern' is elaborated. The EFSA definitions will come into force from when this statement is published. By refining these definitions and ensuring consistent terminology across sectors, EFSA aims to improve clarity and transparency in its risk assessments, facilitating effective communication.

KEYWORDS

benchmark, risk assessment, risk management, toxicology

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1 | INTRODUCTION

1.1 | Background and Terms of Reference as requested by EFSA

In 2005, the European Food Safety Authority (EFSA) proposed a harmonised approach for the risk assessment of chemical substances which are both genotoxic and carcinogenic which are present in food and feed (EFSA, 2005). Prior to this, the advice to risk managers had been to reduce the exposure to such substances to a level that is as low as reasonably achievable (known as the ALARA principle). However, it was recognised that this did not provide risk managers a basis for setting priorities for action. Therefore, the EFSA Scientific Committee, recommended using the Margin of Exposure (MOE) approach (EFSA, 2005).

The MOE is a ratio determined by comparing a reference point (RP) on an in vivo dose–response curve (such as a benchmark dose lower confidence limit (BMDL) derived from a rodent carcinogenicity study) with the estimated human exposure to the substance.

The interpretation of the adequacy of the magnitude of an MOE for chemical substances which are both genotoxic and carcinogenic includes consideration of the following uncertainties (EFSA, 2005):

- (i) *Inter-species differences (extrapolation from experimental animals to humans) and intra-species differences (interindividual human variability). Species differences and human variability are based on the fundamental processes of toxicokinetics and toxicodynamics. A default 100-fold factor is typically adopted to accommodate these uncertainties in the risk assessment of non-genotoxic substances; similar uncertainties would apply to substances that are both genotoxic and carcinogenic.*
- (ii) *The nature of the carcinogenic process. There are further uncertainties specifically for substances that are both genotoxic and carcinogenic, due to the inter-individual human variability in cell cycle regulation and DNA repair, which impact the carcinogenic process.*
- (iii) *The type of RP selected, e.g. a BMDL for 10% extra risk or T25.¹ The relationship between dose and effect below the RP, as well as the dose below which cancer incidence does not increase, are unknown, presenting additional uncertainties.*

In essence, a 100-fold factor between the RP and human exposures would account for species differences and human variability as described in (i) above. An additional factor of 100 would address the additional uncertainties outlined in (ii) and (iii) if it is based on the BMDL₁₀ from an animal study, resulting in 10,000 value for substance that are both genotoxic and carcinogenic.

If not otherwise indicated by detailed knowledge of the dose–response curve at dose levels below the RP, a smaller MOE (< 10,000) indicates a higher level of concern, while a larger MOE (> 10,000) suggests a lower level of concern. Risk Managers often use the MOE as a basis for making decisions. It is important to note that the MOE does not directly equate to risk, but it does assist in prioritising substances for further research or regulatory action, as well as serving as a basis for public communication.

The following conclusions were reported by the Scientific Committee in the EFSA 2005 Opinion:

- *The MOE approach is proposed for the risk assessment of substances that have both genotoxic and carcinogenic properties. The MOE is defined as the RP on the dose–response curve (usually based on animal experiments in the absence of human data) divided by the estimated intake by humans.*
- *For genotoxic substances which interact with DNA, directly or after metabolic transformation (direct-acting genotoxic chemicals), the absence of a threshold in their mechanism of action is generally assumed. In contrast, threshold-based mechanisms conceivable for genotoxic agents which do not react with DNA, or which indirectly cause DNA damage are not to be considered further.*
- *The use of a BMDL10 (benchmark dose lower confidence limit 10%), representing the lower bound of a 95% confidence interval on a BMD (benchmark dose) corresponding to a 10% tumour incidence is recommended as an RP on the dose–response curve. The T25, representing the dose corresponding to a 25% tumour incidence in animals (corrected for spontaneous incidence), should be used if the data are inadequate for estimation of a BMDL.*
- *A range of human intake estimates relevant to different exposure scenarios and groups of the population should be used to calculate margins of exposure.*
- *Margins of exposure, calculated for different substances and intake scenarios, can vary broadly. A small margin of exposure represents a higher risk than a larger margin of exposure. Consequently, risk management can use this information for priority setting.*
- *The EFSA Scientific Committee is of the view that in general a margin of exposure of 10,000 or higher, if it is based on the BMDL10 from an animal study, and considering overall uncertainties in the interpretation, would be of low concern from a public health point of view and might be reasonably considered as a low priority for risk management actions. However, such a judgement is ultimately a matter for the risk managers. Moreover, a margin of exposure of that magnitude should not preclude the application of risk management measures to reduce human exposure.*

¹The chronic dose rate expected to produce a 25% increase in tumour incidence at a specific tissue site in animal studies, after correcting for spontaneous tumour incidence.

- *The EFSA Scientific Committee is of the opinion that the margin of exposure approach can be applied in cases where substances that are both genotoxic and carcinogenic have been found in food, irrespective of their origin, and where there is a need for guidance on the possible risks to those who are, or have been, exposed.*
- *The EFSA Scientific Committee is of the opinion that, in principle, substances which are both genotoxic and carcinogenic should not be deliberately added to foods or used earlier in the food chain if they leave residues in food which are both genotoxic and carcinogenic.*

In 2012, the EFSA Scientific Committee 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 present in substances added to food or feed (EFSA Scientific Committee, 2012). The EFSA Scientific Committee acknowledged that analytical methodology is continuously improving, and an increasing number of impurities (both residuals and reaction products), including some substances which are both genotoxic and carcinogenic, can now be detected at low levels in, e.g. food/feed additives or food contact materials. In that statement, the EFSA Scientific Committee agreed that the MOE approach can be applied to impurities which are both genotoxic and carcinogenic, irrespective of their origin. In 2022, the EFSA Scientific Committee discussed the possibility to revise the opinion published in 2005 where the concept of the MOE was presented.

TERMS OF REFERENCE

The EFSA Scientific Committee (SC) suggested to undertake a revision of the 2005 opinion on the Margin of Exposure (MOE) for chemicals that are both genotoxic and carcinogenic and clarify its application in the EFSA remit. This self-tasked mandate shall include the following Terms of Reference (ToR):

Terms of Reference 1: Clearly define terminology for the use of Margin of Exposure (MOE) and Margin of Safety (MOS) and explain how EFSA and other EU/international agencies have used them and will use these terms. Define the expressions currently used such as “high/low concern or unlikely to be of safety concern”.

Terms of Reference 2: Revision of the 2005 opinion on the use of MOE for chemicals which have both genotoxic and carcinogenic properties. The objective is to create a comprehensive guidance document that builds upon the original text while incorporating updated approaches and methodologies that have emerged since 2005 for calculating, applying, and interpreting the MOE. This guidance will also address ambiguities that have arisen over the nearly two decades since the publication of the 2005 EFSA MOE opinion.

Terms of Reference 3: Guidance on the use of MOE for substances that do not have both genotoxic and carcinogenic properties. The underlying principles of MOE will be equivalent to the abovementioned guidance (ToR 2), however further elaboration will be provided for chemicals with other modes of action (MoAs), excluding those that are both genotoxic and carcinogenic. This work will be aligned and performed together (or by) the working group presently revising the guidance on the use of default values in the absence of actual data.

1.2 | Scope and objectives

This document provides the definition and use of the terminology margin of exposure (MOE) and maps how EFSA and other EU/international agencies have been using this term. In addition, it defines the meaning and interpretation of the terms used to qualify for a ‘concern’. This document will only cover the Terms of Reference 1 of the mandate.

2 | EFSA's DEFINITIONS

The following definitions are recommended for use in EFSA upon publication of this statement in the EFSA Journal.

Note that EFSA differentiates between substances that are carcinogenic due to direct interaction with DNA versus other substances that are carcinogenic by a different mode of action (MoA) or have a different critical toxicological effect.

2.1 | The margin of exposure approach in EFSA

The Scientific Committee has agreed that the term ‘MOE’ approach will be used to assess possible safety concerns arising from the presence of substances in food and feed. The use of the term MOE, instead of Margin of Safety (MOS, see [Appendices A and C](#)), will be applicable in all EFSA remits and will be used for both human and animal health assessment.

EFSA Scientific Committee defines the MOE as the ratio between the Reference Point (RP) and the estimated exposure.

The Reference Point (RP) is defined as a dose derived from an experimental/observational dose–response relationship (e.g. BMDL/NOAEL/LOAEL) which reflects the critical toxicological effect. The Scientific Committee decided that EFSA should continue to use the term RP rather than Point of Departure (PoD). The choice of which RP to use (NOAEL, LOAEL or BMDL) depends on the data available, the nature of the substance and the specific risk assessment context (for further information see [Appendix A](#)).

The margin of exposure (total), MOET, is used specifically for evaluating the safety of combined exposures to multiple chemicals in food and animal feed (EFSA Scientific Committee, 2019). The MOET is the reciprocal of the sum of reciprocals of the individual substances' MOEs² (OECD, 2018).

2.2 | Current interpretation of margin of exposure – Human health

Currently, based on the EFSA Opinion, for substances that have the potential to be carcinogenic by direct DNA reactivity (mutagenic mode of action), an MOE of 10,000 or higher, if it is based on the BMDL₁₀ from an animal carcinogenicity study, and considering overall uncertainties in the interpretation, would be of low concern from a public health point of view and might be reasonably considered as a low priority for risk managers actions (EFSA, 2005).

For other substances, when a health-based guidance value (HBGV) cannot be derived from the available data, an MOE can be calculated. Considerations for inter- and intra-species differences include default values and/or chemical specific adjustments, where data is sufficient. Depending on the MOE, EFSA may conclude that the substance does not raise a safety concern to human health at the estimated exposure.

When a substance MOE results in 'concern', this indicates a need for action by risk managers.

2.3 | Current interpretation of margin of exposure – Animal health

Adverse animal health effects are evaluated by both the EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) and the EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP Panel).

For contaminants, the CONTAM Panel derives a RP for adverse animal health effects and directly compares it to an estimated exposure (not applying uncertainties factors). For animal health, when a substance MOE results in 'concern', this indicates a need for action by risk managers, with 'no concern' indicating lower priority for risk manager action.

The MOE approach has been applied by the FEEDAP Panel to assess the safety for the target species of botanical feed additives containing substances that have the potential to be carcinogenic by a DNA reactive or mutagenic mode of action. In particular, the MOE has been applied to perform a quantitative risk assessment of compounds belonging to the class of *p*-allylalkoxybenzenes (e.g. methyleugenol, estragole), present in many feed additives of botanical origin (EFSA FEEDAP Panel, 2021). In line with the principles of the EFSA Scientific Committee documents (EFSA, 2005; EFSA Scientific Committee, 2012), the wording 'low concern' has been used by the FEEDAP Panel, as of 2023, in the conclusions on the safety for the target species, when an MOE ≥ 10,000 is obtained comparing the exposure of long-living and reproductive animals with the BMDL₁₀ from an animal carcinogenicity study. For short living animals (species for fattening), a comparison of the exposure to these substances with a RP based on other (non-neoplastic) endpoints could be more appropriate to assess the safety of the target animals (EFSA FEEDAP Panel, 2024).

To address the request of risk managers to clarify the wording 'low concern' (associated in FEEDAP assessments with an MOE ≥ 10,000) in terms of the likelihood that the use of an additive with genotoxic and carcinogenic properties would have adverse effects on animal health, the Panel stated that '*following the terminology of the EFSA Statement on the Margin of Exposure (2012), the use of an additive in feed is considered of low concern for long-living target species if the MOE is ≥ 10,000. Consequently, the FEEDAP Panel considers it very unlikely that the use of that feed additive will induce adverse effects during the lifetime of the long-living target species*' (EFSA FEEDAP Panel, 2024).

In this context the term 'very unlikely' is used independently of the approximate probability ranges recommended for harmonised use in the EFSA Guidance on Uncertainty Analysis in Scientific Assessments (EFSA Scientific Committee, 2018).

2.4 | Conclusions

In conclusion, the Scientific Committee has agreed that the MOE approach will be used to assess possible safety concerns arising from the presence of substances in food and feed when it is not appropriate to derive a HBGV. The size of the MOE will provide risk managers with a basis for setting priorities for action.

For animal and human health, an MOE-based 'concern' indicates a need for action by risk managers.

For human health, 'low concern' for substances that have the potential to be carcinogenic by direct DNA reactivity indicates lower priority for risk manager action. For all other substances, depending on the magnitude of the MOE, EFSA may conclude that the substance does not raise a safety concern to human health at estimated exposure levels.

For animal health, 'no concern' indicates lower priority for risk manager action. For feed additives of botanical origin, 'low concern' in long-living target species is considered as 'very unlikely' to induce adverse animal health effects.

² MOET = $\left(\sum_{i=1}^n \frac{1}{\text{MOE}_i} \right)^{-1}$ where MOE_i is the MOE of the *i*th individual substance.

ABBREVIATIONS

AHAW	Animal Health and Welfare (EFSA Panel)
ALARA	as low as reasonably achievable
ANS	Food Additives and Nutrient Sources added to Food (former EFSA Panel)
APVMA	Australian Pesticides and Veterinary Medicines Authority
BASF	Badische Anilin- & Soda-Fabrik (Chemical company, Germany)
BIOHAZ	Biological Hazards (EFSA Panel)
BMDL	Benchmark Dose Lower Confidence Limit
CEF	Food Contact Materials, Enzymes, Flavourings and Processing Aids (former EFSA Panel)
CEP	Food Contact Materials, Enzymes and Processing Aids (EFSA Panel)
CONTAM	Contaminants in the Food Chain (EFSA Panel)
EMA	European Medicines Agency
EPA	Environmental Protection Agency (U.S.)
FAF	Food Additives and Flavourings (EFSA Panel)
FCM	Food Contact Materials
FEEDAP	Additives and Products or Substances used in Animal Feed (EFSA Panel)
FEZ	Food Enzymes (EFSA Panel, informal designation)
FSAI	Food Safety Authority of Ireland (Ireland)
FSSAI	Food Safety and Standards Authority of India
GMO	genetically modified organisms
HBGV	health-based guidance value
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IFCSLG	International Food Chemical Safety Liaison Group
ILMERAC	International Liaison Group on Methods for Risk Assessment of Chemicals in Food and Feed
IPCS	International Programme on Chemical Safety (WHO)
ISS	Istituto Superiore di Sanità (Italy)
LOAEL	lowest observed adverse effect level
MoA	mode of action
MOE	margin of exposure
MOET	margin of exposure total (used for combined exposures)
MOS	margin of safety
NAMs	new approach methodologies (animal-free toxicity testing approaches)
NDA	Nutrition, Novel Foods and Food Allergens (EFSA Panel)
NIFDS	The National Institute of Food and Drug Safety Evaluation (South Korea)
NOAEL	no observed adverse effect level
OPP	Office of Pesticide Programs (U.S. EPA)
PAH	polycyclic aromatic hydrocarbon
PLH	Plant Health (EFSA Panel)
PoD	Point of Departure
PPR	Plant Protection Products and their Residues (EFSA Panel)
RIVM	National Institute for Public Health and the Environment (Netherlands)
RP	Reference Point
SC	Scientific Committee (EFSA)
SCCS	Scientific Committee on Consumer Safety (European Commission)
SCE	sister chromatid exchange
SCHEER	Scientific Committee on Health, Environmental and Emerging Risks (European Commission)
T25	tumorigenic dose 25 (used as an alternative rp in carcinogenicity assessment)
UDA	unscheduled DNA Synthesis
US EPA	United States Environmental Protection Agency
WHO	World Health Organization

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AMENDMENT

The names of the authors were updated according to the authors' preferences. An editorial correction was carried out that does not materially affect the contents or outcome of this scientific output. To avoid confusion, the original version of the output has been removed from the EFSA Journal, but is available on request.

REQUESTOR

EFSA

QUESTION NUMBER

EFSA-Q-2025-00033

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APPENDIX A

The state of art of the Margin of Exposure approach

The MOE informs risk managers to decide on the need to implement health-protective measures.

In 2005, the EFSA published an Opinion (EFSA, 2005) proposing a harmonised approach for the risk assessment of chemical substances which are both genotoxic and carcinogenic and which are present in food and feed. The EFSA Scientific Committee recommended using the MOE approach, where the MOE equals the reference point (RP) divided by the estimated human exposure for chemicals with both genotoxic and carcinogenic properties (EFSA, 2005; Larsen, 2006). The MOE concept is also used by EFSA for regulated chemicals (EFSA CEP Panel, 2021) and other substances which cause (i) effects not driven by a mutagenic mode of action linked to carcinogenicity, (ii) for which a health-based guidance value (HBGV) cannot be derived or is not set as in the example of novel foods (EFSA NDA Panel, 2024) or (iii) when there are deficiencies in the toxicological database that preclude establishment of a robust HBGV (EFSA FAF Panel, 2022).

For some regulatory bodies, the Margin of Safety (MOS) is synonymous with the MOE, and for others it refers to the ratio between a HBGV and the exposure (see Table C2 Appendix C). This has created confusion between the definitions and their application. EFSA has historically employed both the MOE and MOS concepts to evaluate potential risks to human health and the environment. In the assessment of animal safety of feed additives, the MOS was defined as the ratio of the highest tolerated additive concentration in feed and the highest use level proposed, both tested in tolerance trials in the target animal species (EFSA FEEDAP Panel, 2017).

In EFSA, the RP is defined by the Scientific Committee (2021) as a dose derived from an experimental or observational dose–response relationship for the critical toxicological effect, which is the biologically relevant adverse effect occurring at the lowest exposure compared to other adverse effects or the highest dose where no adverse effects were observed. RPs include the lowest or no observed adverse effect level (LOAEL/NOAEL) or a benchmark dose lower confidence limit (BMDL). Internationally, the RP is commonly referred to as the Point of Departure (PoD). EFSA used the term RP in its 2005 MOE Opinion (instead of the term PoD); since it reflects a point of reference on the dose–response relationship that can be used in different ways that does not always involve extrapolation (departure), for example if the estimated exposure is in the region of the RP as may occur with some contaminants.

The NOAEL is the highest dose or exposure level at which no statistically or biologically significant adverse effects were observed. The LOAEL is the lowest dose or exposure level at which adverse effects were observed. The BMDL is a statistically derived dose associated with a predetermined level of effect (benchmark response, BMR) on a dose–response curve (EFSA Scientific Committee, 2022). The BMDL is the preferred RP for chemical risk assessments by EFSA as it considers all dose–response data providing more reliable estimates. Estimation of a BMDL value is described in the EFSA BMD guidance (EFSA Scientific Committee, 2022).

The use of the T25 (a simplified carcinogenic potency index) in the MOE approach was indicated in the 2005 EFSA opinion as the alternative to BMDL₁₀, when the data set is inadequate to develop a BMDL. However, as the T25 is calculated from one data point on the dose–response relationship whereas the BMD approach considers all available information on the dose–response relationship, the latter has been preferred.

EFSA predefined the required magnitude of an MOE which would indicate whether a substance is of concern for human and animal health. A distinction is made between substances that have effects not driven by a mutagenic mode of action linked to carcinogenicity and those with both genotoxic and carcinogenic properties (Chapter 2.2).

The application of the MOE approach is widespread across various panels within EFSA, each using it to assess specific risks associated with different substances in the food chain (a summarising Table A1).

The **Food Contact Materials (FCM) Panel** applies MOE to evaluate the potential risks of genotoxicity and carcinogenicity associated with impurities and contaminants in food contact materials (EFSA, 2009).

The **Food Enzymes (FEZ) Panel**, the **Food Additive and Flavourings (FAF) Panel** and the **Nutrition, Novel Foods and Food Allergens (NDA) Panel** use MOE to assess the safety of these regulated products. In the absence of an HBGV for food enzymes, which are typically a complex mixture of an enzyme and other constituents, an MOE, calculated from oral toxicity data in rodents, is used by the FEZ Panel to assess safety. In the FAF Panel, MOE is used in the absence of an HBGV to conclude on the safety of the substance under evaluation, and is also applied to assess the risk of impurities of toxicological concern, such as aniline in indigo carmine (E 132) or polycyclic aromatic hydrocarbons (PAHs) in smoke flavourings (EFSA FAF Panel, 2023a, 2023b). For novel foods, an MOE may be calculated to evaluate the safety of a novel food under the proposed conditions of use (EFSA NDA Panel, 2024). In the context of requests for exemptions from labelling for food allergens subject to mandatory labelling, the MOE is used to estimate the likelihood that allergic reactions are observed in food allergic individuals (EFSA NDA Panel, 2023).

The **Plant Protection Products and their Residues (PPR) Panel** applies MOE both for impurities and for cumulative exposure assessments (Total Margin of Exposure, MOET).

The Margin of Safety (MOS) was used in the past by the EFSA Panel on Food Additives and Nutrient Sources added to Food (EFSA ANS Panel, 2012) and by the EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (EFSA CEF Panel, 2010).

The **Additives and Products or Substances used in Animal Feed (FEEDAP) Panel** uses MOE (and the combined margin of exposure, MOET) to assess the safety of botanical feed flavourings components – both genotoxic and carcinogenic and non-genotoxic – for target animals (EFSA FEEDAP Panel, 2021; EFSA Scientific Committee, 2012).

The **Contaminants in the Food Chain (CONTAM) Panel** applies MOE and MOET for both genotoxic and non-genotoxic contaminants (EFSA CONTAM Panel, 2021).

The **Genetically Modified Organisms (GMO) Panel** establishes MOE as a safety margin for consumers, while the **Scientific Committee (SC)** defined MOE for both genotoxic and non-genotoxic substances (EFSA, 2005; EFSA Scientific Committee, 2012). The **Biological Hazards (BIOHAZ) Panel** only reports the MOE values established by other EFSA's panels. Finally, the **Animal Health and Welfare (AHAW)** and **Plant Health (PLH)** Panels do not currently apply the MOE approach.

TABLE A1 Summary of MOE uses by EFSA panels.

EFSA's Panel name	Description	References
Food Contact Materials (FCM)	Applies MOE to evaluate potential risks of genotoxicity and cancer from impurities and contaminants in food contact materials	EFSA (2009)
Food Enzymes (FEZ)	Uses MOE to assess the safety of food enzymes, particularly when no HBGV is available. MOE is based on oral toxicity in rodents	Not specified
Food Additives and Flavourings (FAF)	Uses MOE to assess safety of substances and impurities of toxicological concern, including genotoxic impurities such as aniline and PAHs	EFSA FAF Panel (2023a, 2023b)
Nutrition, Novel Foods and Food Allergens (NDA)	Uses MOE to assess the safety of novel foods and exemptions from mandatory allergen labelling	EFSA NDA Panel (2024)
	MOE is used to estimate the likelihood of an allergic reaction	EFSA NDA Panel (2023)
Plant Protection Products and their Residues (PPR)	Applies MOE to assess impurities and cumulative exposures (MOET)	Not specified
Food Additives and Nutrient Sources added to Food (ANS)	Previously used Margin of Safety (MOS) in risk assessments	EFSA ANS Panel (2012)
Food Contact Materials, Enzymes, Flavouring and Processing Aids	Previously used MOS	EFSA CEF Panel (2010)
Additives and Products or Substances used in Animal Feed (FEEDAP)	Uses MOE and MOET to assess safety of botanical feed flavourings for animals	EFSA FEEDAP Panel (2021); EFSA Scientific Committee (2012)
Contaminants in the Food Chain (CONTAM)	Applies MOE for genotoxic contaminants and both MOE and MOET for non-genotoxic ones; does not use MOS	EFSA CONTAM Panel (2021)
Genetically Modified Organisms (GMO) Scientific Committee (SC)	Establishes MOE as a consumer safety margin	Not specified
	Defines MOE for both genotoxic and non-genotoxic substances	EFSA (2005); EFSA Scientific Committee (2012)
Biological Hazards (BIOHAZ)	Reports MOE values established by other EFSA panels	Not specified
Animal Health and Welfare (AHAW)	Does not apply MOE	Not applicable
Plant Health (PLH)	Does not apply MOE	Not applicable

APPENDIX B

Definitions as reported in the EFSA guidance on genotoxicity testing strategies

Mutagenicity refers to the induction of permanent transmissible changes in the amount or structure of the genetic material of cells or organisms. These changes may involve a single gene or gene segment, a block of genes or chromosomes. The term clastogenicity is used for agents giving rise to structural chromosome aberrations. A clastogen can cause breaks in chromosomes that result in the loss or rearrangements of chromosome segments. Aneugenicity (aneuploidy induction) refers to the effects of agents that give rise to a change (gain or loss) in chromosome number in cells. An aneugen can cause loss or gain of chromosomes resulting in cells that do not have an exact multiple of the haploid number. For example, three number 21 chromosomes or trisomy 21 (characteristic of Down syndrome) is a form of aneuploidy (EFSA Scientific Committee, 2011).

Genotoxicity is a broader term and refers to processes which alter the structure, information content or segregation of DNA and are not necessarily associated with mutagenicity. Thus, tests for genotoxicity include tests which provide an indication of induced damage to DNA (but not direct evidence of mutation) via effects such as unscheduled DNA synthesis (UDS), sister chromatid exchange (SCE), DNA strand-breaks, DNA adduct formation or mitotic recombination, as well as tests for mutagenicity (EFSA Scientific Committee, 2011).

APPENDIX C

Use of the MOE/MOS concept in other organisations – Results from EFSA survey

Basic Introduction

To clearly define terminology for the use of MOE and MOS and explain how other EU/international agencies have used them, a survey was created by EFSA named *Understanding the terms 'Margin of Exposure' and 'Margin of Safety' in hazard/risk assessment of chemicals*.

The survey was announced on 31 March 2025 and remained open for 6 weeks (closing date 11 May 2025). The survey was conducted using an online questionnaire via the European tool EUSurvey (<https://ec.europa.eu/eusurvey>) and comprised 12 primary questions: one with multiple choice answers, one dichotomous, one closed and 9 questions in free text format. The questions and the format were agreed among the members of the MOE working group. The survey was in five sections: Demographics (organisation name, country of organisation, contact details of responders); Definition of MOE/MOS; Application of MOE/MOS; use of the term RP/PoD; interpretation of MOE and Final Remarks. The full questionnaire is available in Table C1. For the purposes of this analysis, most responses to the questionnaire are reported by individual institutes and a few were aggregated. Contact details of responders were not shared.

TABLE C1 EU SURVEY- Understanding the terms 'Margin of Exposure' and 'Margin of Safety' in hazard/risk assessment of chemicals.

<p>Demographics</p> <p>Name of your Institute/Organisation</p> <p>Institution/Organisation Country</p> <p>Respondent/Contact Name and Surname</p> <p>Respondent/Contact person email</p> <p>In which sector do you work?</p>
<p>Definition of MOE/MOS</p> <p>Please provide the definitions of Margin of Exposure (MOE) and Margin of Safety (MOS) as used by your institute/organisation. Please also provide references if possible. If you do not use it and have not defined it, please report 'N/A'</p>
<p>Application of MOE/MOS</p> <p>Which term(s) do you generally use in your assessment(s)?</p> <p>Please provide examples of where/when/why Margin of Exposure (MOE) is used in your assessment(s). Please specify the domain and the type of endpoint (e.g. contaminant/carcinogenicity)</p> <p>Please provide examples of where/when/why Margin of Safety (MOS) is used in your assessment(s). Please specify the domain and the type of application</p>
<p>Use of the terms RP/PoD</p> <p>EFSA prefers to use the term Reference Point (RP) for the value used to establish health-based guidance values (HBGVs) and calculation of MOEs in risk assessment (e.g. NOAEL, BMDL). The equivalent term PoD is used by some other bodies such as US EPA. What term do you prefer/use</p>
<p>Interpretation of MOE & Final Remarks</p> <p>If applied, what are the principal aspects, factors or considerations considered in interpreting the adequacy of margins of exposure by your Institute/Agency?</p> <p>This is the end of the questionnaire. We would like to thank you kindly for your participation. If you have any further comments or experiences that you would like to share related to the use of MOE/MOS, please feel free to do so in the text field below:</p>

The target group for this survey was European and International agencies, however replies were also received from industry and academia due to their involvement in the networks selected to share the invitation to the survey. To this end, the survey was shared with:

- EFSA Member States via Advisory Forum/Focal Points
- Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) and Scientific Committee on Consumer Safety (SCCS) secretariat
- EU and international agencies (list prepared by the MOE working group)
- The ILMERAC network – International Liaison Group on Methods for Risk Assessment of Chemicals in Food and Feed (ILMERAC)
- The IFCSLG network – International Food Chemical Safety Liaison Group
- The World Health Organization (WHO) network on Chemical Risk Assessment

The aim was to reach as many organisations in the field as possible, as well as to understand the various geographic locales in which the organisations operate. However, the authors did not receive feedback on the degree to which the survey was forwarded within networks, and thus, it was not possible to determine the exact number of recipients of this survey.

The answers collected by the EUSurvey tool were exported to a Microsoft Excel file for analysis and interpretation. Data analysis and graphical representation analysis were conducted using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA) or taken directly from the EU Survey tool. The results are presented by individual organisation.

Results

A total of 25 survey recipients filled out the online survey from the EUSurvey tool. In addition, two organisations provided their replies via email. The 27 replies were received from 21 countries: Australia ($N=1$, 3.7%), Austria ($N=2$, 7.4%), Belgium ($N=1$, 3.7%), Bulgaria ($N=1$, 3.7%), Canada ($N=2$, 7.4%), Croatia ($N=1$, 3.7%), Czech Republic ($N=2$, 7.4%), Denmark ($N=1$, 3.7%), Finland ($N=1$, 3.7%), Germany ($N=2$, 7.4%), Greece ($N=1$, 3.7%), India ($N=1$, 3.7%), Ireland ($N=1$, 3.7%), Italy ($N=1$, 3.7%), Japan ($N=2$, 7.4%), Luxembourg ($N=1$, 3.7%), Netherlands ($N=2$, 7.4%), Singapore ($N=1$, 3.7%), South Korea ($N=1$, 3.7%), United States ($N=1$, 3.7%), Zambia ($N=1$, 3.7%). The European Medicines Agency (EMA) provided their replies via email before the survey was published. The Food Safety and Standards Authority of India (FSSAI) provided their replies via email after closing of the survey. More than half ($N=17$) of the responses came from the European geographical area.

Survey participants represented experts from governmental organisations ($N=16$, 56%), industries ($N=1$, 3.7%), academia ($N=1$, 3.7%), national institutes ($N=8$, 29.6%) and other institutions ($N=2$, 7.4%; EMA and SCCS of the EC). Their representative sectors were in: Food and Feed ($N=19$, 57.6%), Consumer Products ($N=4$, 12.1%), Drug development ($N=2$, 6.1%), Agrochemicals ($N=5$, 15.2%), Industrial Chemicals ($N=1$, 3%) and Veterinary ($N=2$, 6.1%). The SCCS covering consumer product safety, mainly for cosmetic ingredients' safety assessment.

Of the 27 respondents, 17 use MOE (63%), 1 MOS (4%), 1 both MOE and MOS interchangeably (4%), 6 both MOE and MOS but in different contexts (22%) and 2 use neither (7%).

Based on replies it was found that 'Point of Departure' is the most used term, preferred by 52% of respondents, while 'Reference Point' is used by 37% of the respondents. Finally, 11% of respondents use both terms interchangeably, indicating that while some distinction may exist (based on context), the terms are often treated as synonymous in practice.

Respondents were asked to provide how they define and apply MOE and MOS. The raw replies are reported in [Table C2](#). The MOE is commonly defined as the ratio between a toxicological reference point (e.g. NOAEL, BMDL or LOAEL) and the estimated human exposure. Primarily used in risk assessment, it is particularly used when a health-based guidance value (HBGV) cannot be established. The interpretation: A higher MOE generally indicates lower concern. For genotoxic carcinogens, an MOE above 10,000 is typically considered to be of low public health concern. On the other hand, the MOS is defined as the ratio between a health-based guidance value (such as ADI, TDI, or NOAEL) and the actual or estimated exposure. The MOS is more commonly applied in cosmetics, pharmaceuticals and veterinary product assessments, as well as in crop/animal safety considerations. Like the MOE, a higher MOS indicates greater safety and is often used when a known safe dose is established.

[Table C3](#) reports the applications of MOE and MOS by organisations. Briefly, MOE is widely used, especially for genotoxic/carcinogenic substances and contaminants when health-based guidance values (HBGVs) cannot be established. On the other hand, MOS is less commonly used and often depends on the domain or regional practices (main areas of use in cosmetics), with some authorities avoiding or rarely using MOS, instead relying on direct comparison with HBGVs or using other descriptors (e.g. Health Canada, Netherlands, FSAI). [Table C5](#) reports the replies from the industrial company.

From the information reported in [Tables C2](#) and [C3](#), a summary of how different organisations use the MOE and MOS in risk assessment is provided in [Tables C4](#).

TABLE C2 Raw replies to the survey reported by individual organisation on the definition of MOE and MOS.

Organisation	Definition of margin of exposure	Definition of margin of safety
Australian Pesticide and Veterinary Medicine Authority (APVMA) (Australia)	The margin between the relevant toxicological endpoint (no observed adverse effect level) and the measured or estimated repeated exposure	Margin between the proposed use rate and the rate at which unacceptable effects are observed (used primarily in efficacy considerations of crop or target animal safety)
Austrian Agency for Health and Food Safety (Austria)	We use the MOE in the field of food safety according to the EFSA guidelines and opinions	We use the MOS in the field of cosmetics according to the SCCS Notes of guidance for the testing of cosmetic ingredients and their safety evaluation (https://health.ec.europa.eu/latest-updates/sccs-notes-guidance-testing-cosmetic-ingredients-and-their-safety-evaluation-12th-revision-2023-05-16_en)
Federal Agency for the Safety of the Food Chain (Belgium)	Ratio between the toxicological dose–response reference point (e.g. NOAEL, BMDL, T25) for the critical effect of the substance under consideration and the theoretical, predicted or estimated exposure. If the calculated MOE is higher than the product of the uncertainties related to the differences between the experimental data and the human situation, the nature of the carcinogenic process and the type of selected dose–response reference point, the exposure is presumed to be of low public health concern. For genotoxic substances, an MOE higher than 10,000 is generally regarded as of low concern	N/A
Risk Assessment Center of Food Chain (Bulgaria)	Margin of exposure (MOE) is the ratio of no observed adverse effect level (NOAEL) obtained from animal toxicology studies to the predicted, or estimated human exposure level or dose	Margin of Safety (MOS) is the ratio of the lethal dose to 1% of population to the effective dose to 99% of the population
Health Canada (Pre-Market Toxicology) (Canada)	Generally defined as the margin between a study NOAEL and exposure estimate (working definition)	N/A
Health Canada (Food & Nutrition Directorate) (Canada)	ratio of the PoD (e.g. BMDLx, NOAEL, LOAEL) to the estimated exposure dose	Ratio of the TDI or ADI to the estimated exposure dose
Croatian Agency for Agriculture and Food (Croatia)	It is value to which consumers are exposed	This is the vale bellow which contamination will not do harm to consumers health
National Institute of Public Health (Státní zdravotní ústav) (Czech Republic)	MoE is a tool to consider possible safety concerns arising from the presence in food and feed of chemical substances when they deem it inappropriate or unfeasible to establish a 'safety threshold' – EFSA	N/A
National Institute of Public Health (Státní zdravotní ústav) (Czech Republic)	MOE – 10,000	Rozdíl mezi skutečným příjmem látky danou populací a odhadovanou denní dávkou za celý život, kterou odborníci považují za bezpečnou... [<i>'The difference between the actual intake of a substance by a given population and the estimated daily dose over a lifetime that experts consider safe...'</i>]
Technical University of Denmark (Denmark)	BMDLxx/Exposure	TDI or similar/exposure
European Medicines Agency (EMA) (European Commission)*	The MOE is also explicitly defined in the Guideline on user safety for pharmaceutical veterinary medicinal products as 'The ratio of the No Observed (Adverse) Effect Level (NO(A)EL) to an estimated exposure level' (EMA, 2010)	Human Health and Veterinary divisions, MOS is sometimes applied or mentioned (as margin of safety/safety margin/safety factor), it is never clearly defined in any publications
Scientific Committee on Consumer Safety (SCCS) (European Commission)	MOE: a definition is not explicitly taken in the SCCS Notes of Guidance	MOS: ratio between PoD and actual amount of systemic exposure

TABLE C2 (Continued)

Organisation	Definition of margin of exposure	Definition of margin of safety
Ruokavirasto (Finland)	We use the definition of EFSA (https://www.efsa.europa.eu/en/press/news/120330) and have additionally given examples in risk assessment reports: 'BMDL/exposure or NOAEL/exposure'. Example in Finnish in report https://doi.org/10.5281/zenodo.5647279 in definitions, page 8	N/A
German Federal Institute for Risk Assessment (Germany)	The Margin of Exposure (MOE) is obtained by dividing the value of a relevant point of departure (PoD, also reference point) by the estimated exposure. The PoD used is not necessarily a health-based value and can be a NOAEL, LOAEL and BMD(L). Accordingly, the MOE may rather indicated the level of concern associated with a certain exposure than safety. The MOE is applied in particular when a toxicological reference value (TRV)/health-based guidance value (HBGV) could not be derived or agreed	N/A
German Federal Institute for Risk Assessment (Germany)	Under REACH/CLP: N/A	Under REACH/CLP: N/A
Hellenic Food Authority (Greece)	We follow EFSA's definition: A tool used in risk assessment to explore safety concerns arising from the presence of a potentially toxic substance in food or animal feed	We follow EFSA's definition: The gap between the actual intake of a substance by a given population and the estimated daily dose over a lifetime that experts consider to be safe
Food Safety and Standards Authority of India (FSSAI), (New Delhi, India)*	It is the estimating human exposure of a certain population against the benchmark dose, for example, BMDL10, which is the lower confidence limit of the dose that causes 10% response in animal studies	It is the ratio of the NOAEL derived from the animal studies and the human exposure level
Food Safety Authority of Ireland (FSAI) (Ireland)	A ratio of the dose at which a low but measurable adverse effect is observed i.e. reference point and the level of exposure to the substance for a given population. EFSA 2005 – https://www.efsa.europa.eu/en/efsajournal/pub/282 and EFSA, 2023 – https://www.efsa.europa.eu/en/topics/topic/margin-exposure	This definition is less clear in our view But would point to the definition of margin of safety as the ratio between a safe threshold e.g. health-based guidance value (HBGV) and the actual or estimated exposure It could also be defined as the gap between the actual intake of a substance by a given population and the estimated daily dose over a lifetime that experts consider to be safe In the EFSA 2005 (https://www.efsa.europa.eu/en/efsajournal/pub/282) opinion it suggests that it relates only to genotoxic carcinogens Would an update of the 2005 opinion perhaps be warranted?
Istituto Superiore di Sanità (Italy)	It is a risk characterisation concept used by definition for substances that are both genotoxic and carcinogenic, or for which no clear health-based guidance value can be established. It is calculated by the ratio between a reference point (BMDL or NOAEL) and the estimated dietary human exposure. Following EFSA references (<i>EFSA Journal</i> 2012;10(3):2578), for genotoxic and carcinogenic substances an MOE above 10,000 indicates a low concern for public health	It is a risk characterisation concept used for substances that have known safe dose. It is calculated by the ratio between a reference point (NOAEL) and the estimated dietary human exposure. An MOE above 100 indicates a low concern for public health
Food Safety Commission (Japan)	Our organisation defines MOE (margin of exposure) as the ratio obtained by dividing toxicity evaluation values, such as NOAEL (no observed adverse effect level), LOAEL (lowest observed adverse effect level) and BMDL (benchmark dose lower confidence limit) derived from toxicity tests, by the actual human exposure level (intake) or estimated human intake. MOE is sometimes used as a means of prioritisation in our organisation's risk management (Reference: Glossary ' https://www.fsc.go.jp/yougoshu.data/yougoshu.pdf ' *In Japanese only)	N/A

(Continues)

TABLE C2 (Continued)

Organisation	Definition of margin of exposure	Definition of margin of safety
Pharmaceuticals and Medical Devices Agency (Japan)	We will answer with prescription drugs in mind (1) Systemic exposure (C_{max} , AUC) when administered at a non-toxic dose to animals/(2) systemic exposure (C_{max} , AUC) when administered at the proposed approved dosage in humans. That it, (1) divided by (2) As a safety net, the exposure margin is usually taken to be several times this value	Same as above
National Institute for Public Health and the Environment (RIVM) (Netherlands)	We define the MOE as the margin between the exposure and a point of departure/reference point (BMDL, NOAEL, LOAEL, when no health-based guidance value can be established). This is similar to the definition in 'Environmental health criteria 240' (chapter 5.4.1), written by the WHO and FAO, which reads: 'It should be noted that in this chapter', the terms 'margin of safety' and 'margin of exposure' are both used. They are not synonymous. https://cdn.who.int/media/docs/default-source/food-safety/publications/chapter5-dose-response.pdf	We define the MOS as the margin between the exposure and the health-based guidance value A margin of safety is defined as the margin between an HBGV and the actual or estimated exposure dose or concentration. An MOE is defined as the ratio of the NOAEL or BMDL for the critical effect to the theoretical, predicted or estimated exposure dose or concentration https://cdn.who.int/media/docs/default-source/food-safety/publications/chapter5-dose-response.pdf
Singapore Food Agency (Singapore)	Ratio of the NOAEL or BMDL for the critical effect to the theoretical, predicted or estimated exposure dose or concentration	Margin between an HBGV and the actual or estimated exposure dose or concentration
The National Institute of Food and Drug Safety Evaluation (NIFDS) (South Korea)	It means the value obtained by dividing the toxicity starting value, such as BMDL, PoD, etc. of evaluated substance by the daily exposure amount	N/A
National Food Laboratory (Zambia)	N/A	N/A
United States Environmental Protection Agency (United States)	The MOE is a risk estimate calculated for risk assessment by dividing the point of departure (e.g. a no observed adverse effect level (NOAEL)) derived from a toxicity study by an estimate of anticipated exposure based on the intended use. Each MOE is compared against a composite uncertainty factor (i.e. level of concern) to determine whether there are potential risks of concern	Please note that the term margin of safety is not used in EPA's Office of Pesticide Program (OPP) pesticide risk assessments. We would consider this term to be synonymous with 'level of concern', which refers to the composite uncertainty factor used for comparison to MOEs to determine whether there are potential risks of concern

*Replies provided via email.

TABLE C3 Raw replies to the survey questions on the application of Margin of Exposure (MOE) and Margin of Safety (MOS).

Organisation	Examples of MOE use	Examples of MOS use
Australian Pesticide and Veterinary Medicine Authority (APVMA) (Australia)	Dietary exposures (acute and chronic) based on comparison with an appropriate NOAEL. The margin is a standard of 100, but can be varied depending on the endpoint selected and the completeness of the database. Occupational exposure based on comparison with an appropriate NOAEL (including route and duration of exposure) Environmental assessment, in comparison with an appropriate NOAEL The assessment is compared with a NOAEL without consideration of how close the LOAEL is	Used for target animal/target crop assessments (i.e. if phototoxicity was seen at 1.5 times label rate, it may not have a sufficient margin of safety) Also used in descriptive text in situations where, for example, an acceptable daily intake or acute reference dose is not required because there is a large margin of safety between NOAELs and anticipated consumption values
Austrian Agency for Health and Food Safety (Austria)	We use the MOE according to EFSA guidelines; mainly in context with genotoxic and carcinogenic substances; mainly food contaminants; but also if EFSA opinions recommend the MOE in other circumstances (e.g. when no HBGV can be derived for substances due to a lack of data)	For ingredients in cosmetics we use the MoS as recommended by the SCCS

TABLE C3 (Continued)

Organisation	Examples of MOE use	Examples of MOS use
Federal Agency for the Safety of the Food Chain (Belgium)	The MOE is for example used for estimating the risk for the public health of a food product contaminated with a both genotoxic and carcinogenic chemical contaminant; in that case, the MOE was evaluated against a reference value of 10,000	N/A
Risk Assessment Center of Food Chain (Bulgaria)	I use Margin of Exposure when assessing the risk of various chemical contaminants in feed for carcinogenicity	The term Margin of Safety is less commonly used in the assessments mentioned above
Health Canada (Pre-Market Toxicology) (Canada)	Margin of Exposure is sometimes used, but we also use descriptive statements such as 'e margin between the NOAEL and the highest exposure estimate'. Our domain is the pre-market assessment of mandatory regulatory submissions to the Food and Nutrition Directorate for food additives, novel foods, new infant formula ingredients and supplemented food ingredients	Not used
Health Canada (Food & Nutrition Directorate) (Canada)	In general, for the assessments of contaminants, natural toxins and process-induced chemicals, we take a MOE approach for risk assessments of genotoxic carcinogens and when uncertainty in the toxicological database precludes establishing a HBGV (e.g. TDI)	We rarely find it helpful to incorporate a MoS in our assessments, since we would typically indicate that the exposure is less than the HBGV and may indicate by what order of magnitude
Croatian Agency for Agriculture and Food (Croatia)	in risk assessment for acrylamide-because it is a substant that cannot be eliminated from food, but also this substance is cancerogenic	N/A
National Institute of Public Health (Státní zdravotní ústav) (Czech Republic)	MOE approach is applied for the risk assessment of substances where no HGBV is set. It is used the most often in contaminants with carcinogenic effect like mycotoxins, lead, arsenic	Most of the risk assessment in our institution are provided in the Czech language where translation or original English term MoS is not used
National Institute of Public Health (Státní zdravotní ústav) (Czech Republic)	Margin expozice	Margin of safety
Technical University of Denmark (Denmark)	MOE is used to assess a risk when there is calculated a BMDL. The lowest tolerable MOE is a case-by-case decision	N/A
European Medicines Agency (EMA) (European Commission)*	According to EMA's Human Medicines Division, the literal formulations 'margin of exposure' and 'margin of safety' are not often used as such. Some EMA publications mention terms such as 'exposure margin' and 'safety margin'. According to EMA's Veterinary Medicines Division, MOE and MOS are typically used as 'uncertainty factors', i.e. numerical factors intended to account for uncertainties in safety assessments	According to EMA's Human Medicines Division, the literal formulations 'Margin of Exposure' and 'Margin of Safety' are not often used as such. Some EMA publications mention terms such as 'exposure margin' and 'safety margin'. According to EMA's Veterinary Medicines Division, MOE and MOS are typically used as 'uncertainty factors', i.e. numerical factors intended to account for uncertainties in safety assessments
Scientific Committee on Consumer Safety (SCCS) (European Commission)	Contaminant/carcinogenicity; for certain contaminants like Pb also contaminant/neurotoxicity, or for Ni contaminant/acute effects	N/A
Ruokavirasto (Finland)	Database insufficient or existence of threshold not demonstrated	N/A
German Federal Institute for Risk Assessment (Germany)	N/A	N/A
German Federal Institute for Risk Assessment (Germany)	In case of contaminants	In case of Food Additives

(Continues)

TABLE C3 (Continued)

Organisation	Examples of MOE use	Examples of MOS use
Hellenic Food Authority (Greece)	<p>Where/When:</p> <ol style="list-style-type: none"> Chemicals with non-threshold adverse health effects such as genotoxic carcinogens, lead, etc. Chemicals with threshold mechanism of action but inadequate toxicological database to allow for establishment of a (HBGV) such as sulphites for example <p>Why:</p> <p>The Margin of Exposure approach alerts risk managers that there is some level of uncertainty around the health-based threshold. Noting that even with Margin of Exposures, which are greater than the respective assessment factor there may still be some concern for health</p>	<p>The approach to risk assessment taken by the FSAI follows the approach taken in the respective EFSA risk assessments and FSAI do not use margin of safety terminology</p>
Food Safety and Standards Authority of India (FSSAI), (New Delhi, India)*	<p>It is most frequently used in the context of carcinogenic genotoxins (where no safe threshold is assumed) or where the substance's toxicological profile is lacking</p> <p>Reliability:</p> <p>Advantages: For assessing risks when setting a threshold is not possible, it is very useful (e.g. aflatoxins, acrylamide)</p> <p>Limitations: 'Safety' is not defined directly but is rather assumed (e.g. an MOE > 10,000 might be judged as low risk for genotoxic carcinogens as per expert opinion)</p>	<p>Used for non-genotoxic chemicals which are assumed to have a threshold such as pesticides and food additives</p> <p>Reliability:</p> <p>Advantages: Directly evaluates NOAEL Levels and Incorporates safety margins (e.g. a 100-fold for inter- and intra-species variability)</p> <p>Disadvantages: Assumes there is a threshold; may not include cumulative exposures or sensitive sub populations without modification</p>
Food Safety Authority of Ireland (FSAI) (Ireland)	<p>We conduct risk assessment evaluations for our Competent Authority concerning the presence of mycotoxins and plant toxins in food and feed. In our most recent opinion on the presence of ochratoxin A (OTA) in peanuts, we estimated exposure based on a specific contamination level and developed possible risk characterisation scenarios. These scenarios considered both the neoplastic effects of OTA (using a BMDL10 of 14.5 µg/kg bw/day) and the non-neoplastic effects (using a BMDL10 of 4.74 µg/kg bw/day). For the neoplastic effects, a margin of exposure (MOE) threshold of 10,000 was applied, while for the non-neoplastic effects, a threshold of 100 was used for risk characterisation</p>	<p>Actually, we do not use MoS as such, but we measure the percentage of the ratio between the calculated exposure and the HBGV. Values < 100 mean no concern, values > 100 mean exceedance of the HBGV. This is done for risk assessment done, for example, for DON, FBs, ZEN, T-2/HT-2 toxins</p>
Istituto Superiore di Sanità (ISS) (Italy)	<p>In our risk characterisation of processing aids – some of which we define as substances that are removed from the food before final packaging – when their estimated intake is more than 90 µg/person per day and not judged to be genotoxic, MOE is to be evaluated in principle</p> <p>Additionally, in risk characterisation of food apparatus, containers and packaging (ACP), MOE is to be evaluated in the following cases:</p> <ol style="list-style-type: none"> When the dietary concentration of a target substance is above 0.05 mg/kg but not more than 1 mg/kg, and the substance is assessed to be neither genotoxic nor necessary to set a Health-Based Guidance Value HBGV (ADI/TDI), the health risk from the substance shall be determined based on the level of MOE (a) When the dietary concentration of a target substance is more than 1 mg/kg, and it is assessed to be a genotoxic carcinogen, but is non-intentionally contained in the materials of ACP (such as impurities, by-products and decomposition products), the health risk from the substance shall be comprehensively determined based on the MOE approach (b) When the dietary concentration of a target substance is more than 1 mg/kg, and it is assessed to be neither a genotoxic carcinogen nor necessary to set a HBGV (ADI/TDI), the health risk from the substance shall be determined based on the level of MOE <p>There are also cases where MOE is evaluated for veterinary medicinal products and feed additives for which provisional standards are established</p>	<p>N/A</p>

TABLE C3 (Continued)

Organisation	Examples of MOE use	Examples of MOS use
Food Safety Commission (Japan)	Active ingredients of prescription drug/repeated dose toxicity studies, reproductive and developmental toxicity studies, genotoxicity study (in vivo micronucleus study), carcinogenicity studies	Same as above
Pharmaceuticals and Medical Devices Agency (Japan)	The SCCS has only rarely used MOE approach for safety assessment of cosmetic ingredients. One example is the SCCS Opinion on acetaldehyde (SCCS/1468/12 – Revision of 11 December 2012)	The SCCS generally uses MoS in safety assessment of cosmetic ingredients were permitted by the availability of data
National Institute for Public Health and the Environment (RIVM) (Netherlands)	Genotoxic carcinogens, or in assessment where toxicity information is lacking an no HBGV can be established (i.e. contaminants, herbal preparations etc.)	This term is not often used in our assessment
Singapore Food Agency (Singapore)	Contaminants that are genotoxic and carcinogenic or when HBGVs cannot be established, novel foods	Hardly used. Used only for consistency of communication with risk assessors that use margin of safety
The National Institute of Food and Drug Safety Evaluation (NIFDS) (South Korea)	We apply MOE to such substances for which HBGVs cannot be established among substance with threshold values or to substances without threshold values	N/A
National Food Laboratory (Zambia)	N/A	N/A
United States Environmental Protection Agency (United States)	Margins of exposure may be calculated for potential residential/non-occupational, occupational, aggregate and cumulative non-cancer risk assessments based on the intended use pattern of the pesticide. If necessary, MOEs could be calculated for dietary non-cancer risk assessments; however, EPA's Office of Pesticide Program (OPP) currently uses the RfD/PAD approach for dietary risk non-cancer assessments	This term is not used in EPA's Office of Pesticide Program (OPP) pesticide risk assessment

*Replies provided via email.

TABLE C4 Summary table comparing the definitions and use of Margin of Exposure (MOE) and Margin of Safety (MOS) across various organisations, by domain and application.

Organisation	MOE use (where/when/why) – definition	MOS use (where/when/why) – definition
Australian Pesticide and Veterinary Medicine Authority (APVMA) (Australia)	Dietary, occupational and environmental risk assessment using NOAELs MOE = NOAEL/exposure	Used for target animal/crop safety; where high margins indicate low risk MOS relates to safe use levels in crops or animals
Austrian Agency for Health and Food Safety (Austria)	Genotoxic/carcinogenic food contaminants; where HBGV cannot be set MOE (EFSA guidance 2005)	Cosmetics, as per SCCS recommendations
Federal Agency for the Safety of the Food Chain (Belgium)	Genotoxic/carcinogenic contaminants in food; uses MOE of 10,000. MOE = reference point/exposure	Not specified
Risk Assessment Center of Food Chain (Bulgaria)	Carcinogenic contaminants in feed	Rarely used
Health Canada (Pre-Market Toxicology) (Canada)	For food additives, novel foods, contaminants with uncertain toxicity	Not used
Health Canada (Food & Nutrition Directorate) (Canada)	Genotoxic carcinogens and uncertain toxicological datasets MOE = reference point/exposure	Rarely used; exposure typically compared with HBGVs directly MOS = reference point/exposure

(Continues)

TABLE C4 (Continued)

Organisation	MOE use (where/when/why) – definition	MOS use (where/when/why) – definition
Croatian Agency for Agriculture and Food (Croatia)	Acrylamide (carcinogenic contaminant in food)	Not specified
National Institute of Public Health (Czech Republic)	For contaminants without HBGV, e.g. mycotoxins, lead	MOS not typically used or translated
Technical University of Denmark (Denmark)	Case-by-case basis using BMDL for risk assessment	Not specified
European Medicines Agency (EMA) (European Commission)	Not used (Human Medicines Division), MOE used as 'uncertainty factors' (Veterinary Medicines Division)	Not used (Human Medicines Division), MOS used as 'uncertainty factors' (Veterinary Medicines Division)
Scientific Committee on Consumer Safety (SCCS) (European Commission)	Rarely used; e.g. acetaldehyde opinion	Common in cosmetic ingredient safety assessments
Ruokavirasto (Finland)	Contaminants: carcinogenicity, neurotoxicity, acute effects	Not specified
German Federal Institute for Risk Assessment (Germany)	When database is insufficient, or threshold is uncertain. MOE used where no HBGV exists	Not specified
Hellenic Food Authority (Greece)	Contaminants Follows EFSA's definition	Food additives Follows EFSA's definition
Food Safety and Standards Authority of India (FSSAI), (New Delhi, India)	BMDL10/human exposure (for genotoxic, e.g. aflatoxins, acrylamide)	NOAEL/human exposure level (for non-genotoxic chemicals)
Food Safety Authority of Ireland (FSAI) (Ireland)	Genotoxic carcinogens, insufficient data to establish HBGV. Follows EFSA's definition	Not used; follows EFSA approach MOS = ratio between HBGV and exposure
Istituto Superiore di Sanità (ISS) (Italy)	Mycotoxins in food; MOE of 10,000 (neoplastic), 100 (non-neoplastic)	Exposure vs. HBGV ratio used instead of MOS. MOS = NOAEL/exposure with threshold
Food Safety Commission (Japan)	Processing aids, food contact materials, veterinary products – especially if no HBGV is set MOE = NOAEL/LOAEL/BMDL/exposure	Not mentioned
Pharmaceuticals and Medical Devices Agency (Japan)	Prescription drugs – chronic toxicity, carcinogenicity, genotoxicity	Not mentioned
National Institute for Public Health and the Environment (RIVM) (Netherlands)	Genotoxic carcinogens, insufficient toxicity data MOE = NOAEL or BMDL/exposure	Rarely used MOS = HBGV/exposure
Singapore Food Agency (Singapore)	Contaminants and novel foods without HBGV	Used only for communication consistency
The National Institute of Food and Drug Safety Evaluation (NIFDS) (South Korea)	Substances without HBGV or without clear thresholds	Not mentioned
United States Environmental Protection Agency (United States)	Potential residential/non-occupational, occupational, aggregate and cumulative non-cancer risk assessments MOE = NOAEL/exposure	Not used

TABLE C5 Replies received from industries on the definition and use of MOE and MOS.

Organisation	Definition of margin of exposure	Definition of margin of safety
BASF Österreich GmbH (Austria)	Factor in risk assessment that described the fold-distance from the exposure level towards the hazard point of departure	Factor in hazard assessment that describes the fold-distance from the hazard point of departure (NOAEL or BMD) towards the hazard reference value (ADI, AOEL), covers uncertainty factors and kinetic considerations
Organisation	MOE Use (Where/When/Why)	MOS Use (Where/When/Why)
BASF Österreich GmbH (Austria)	Non-dietary risk assessment of agricultural products (outside of Europe)	Derivation of AOEL, ADI

The respondents provided their views on how main aspects, factors or considerations are considered in interpreting the adequacy of the MOE in risk assessment. The results showed a general pattern and practice in using the following default MOE values:

- 100-fold: Common default for threshold-based toxicological effects (e.g. APVMA Australia, BASF Austria, Ireland and Germany).
- 10,000-fold: Widely used for genotoxic and carcinogenic substances (e.g. Belgium, Finland, Germany, SCCS, Ireland and Health Canada).

Many European agencies (Austria, Belgium, Bulgaria, Czech Republic, Finland, Greece, Ireland, Italy and the Netherlands) rely heavily on the EFSA recommendations, including default MOE values and guidance on PoDs/RPs (Points of Departure/Reference Points) (EFSA, 2005, 2023).

Japan and South Korea apply MOE for genotoxicity, carcinogenicity, or in absence of reliable thresholds. Japan provided the link to their glossary where terminologies are defined (<https://www.fsc.go.jp/youngoshu.data/youngoshu.pdf>) which also references EFSA.

Zambia did not provide any information on the use of either MOE or MOS. So, it is currently unclear whether Zambia uses these approaches.

For carcinogenic and genotoxic substances an MOE $\geq 10,000$ is typically considered of low concern (e.g. Belgium, Finland, Health Canada and the SCCS). The ALARA principle (as low as reasonably achievable) is used in some cases where thresholds are not applicable (e.g. SCCS for cosmetic products).

Factors considered when assessing MOE adequacy were:

- Toxicological Data Quality & Uncertainty (e.g. Canada, Italy, Netherlands and South Korea).
- Nature of the Effect (threshold vs. non-threshold; severity) (e.g. Germany, Denmark and Australia APVMA).
- Vulnerability of Populations (e.g. children, elderly) (e.g. Italy, Czech Republic and Australia APVMA).
- Mode of Action and Dose–Response Curve (e.g. Denmark, Germany).
- Relevance of Animal Data to Humans (e.g. APVMA, Singapore, SCCS).

In summary most organisation use standard MOE thresholds (100 or 10,000) and adjust these based on: toxicity type (e.g. severity), quality and robustness of scientific data, species differences, exposure accuracy, vulnerable population considerations.

Some considerations provided by specific organisations:

- SCCS (EU): Provides detailed distinctions between MOE and MOS and uses modern animal-free methods (NAMs) for new cosmetic ingredients.
- APVMA (Australia): Allows flexible MOEs based on data quality and species sensitivity.
- Health Canada (Canada): Differentiates MOE use between genotoxic carcinogens and other chemicals.
- ISS (Italy): Stresses balancing MOE with exposure data quality and uncertainty.
- European Medicines Agency (EMA): According to EMA's Human Medicines Division, the literal formulations 'margin of exposure' and 'margin of safety' are not often used as such. Some EMA publications mention terms such as 'exposure margin' and 'safety margin'. For example, the Draft reflection paper on the qualification of non-mutagenic impurities explicitly defines 'safety margin' as 'the ratio between the exposure in the animal study at the NOAEL and the maximal clinical exposure' (EMA, 2025). Some guidelines from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), which are used by EMA for assessment of new medicinal products, also mention terms that resemble an 'exposure margin'. For example, while the ICH guideline on testing for carcinogenicity of pharmaceuticals (ICH, 2022) does not define 'exposure margin' explicitly, it is indirectly mentioned, e.g. in the following phrase: 'A no observed adverse effect level for these effects was identified which provided a five-fold margin to human exposure'. According to EMA's Veterinary Medicines Division, MOE and MOS are typically used as 'uncertainty factors', i.e. numerical factors intended to account for uncertainties in safety assessments. However, the MOE is also explicitly defined in the Guideline on user safety for pharmaceutical veterinary medicinal products as 'the ratio of the no observed (adverse) effect level (NO(A)EL) to an estimated exposure level' (EMA, 2010).
- US EPA Office of Pesticide Program (OPP): in pesticide risk assessments, the margin of exposure (MOE) is utilised to determine whether there are any potential risks of concern. A tiered approach is applied where more conservative assumptions are initially used to calculate MOEs, if a potential risk of concern is identified, teams will investigate whether there are potential refinements that can be incorporated into the hazard and/or exposure. If potential risks of concern still exist, then teams will consider whether mitigations can be put into place (e.g. lower application rates, personal protective equipment, restrictions on application equipment, etc.) or if additional data (hazard and/or exposure) would be beneficial for developing additional refinements.
- The India FSSAI provided their definitions and uses of the approaches via email; they concluded that for non-threshold effects, like genotoxic carcinogenesis the MOE approach is more reliable since it does not assume that a safe level exists. On the other hand, for threshold-based toxicants such as additives and pesticides, the MOS is more reliable since it includes safety margins and clearly-defined acceptable exposure.

A similar mapping was conducted by the World Health Organization (WHO) in 2004, as part of development of the International Programme on Chemical Safety (IPCS) Risk Assessment Terminology, where the terminology used in approaches to the assessment of risk from exposure to chemicals were harmonised (WHO, 2004). The results of the survey were published, with the WHO concluding that 'For some experts, margin of safety has the same meaning as margin of exposure, while for others, margin of safety means the margin between the reference dose and the actual exposure'. Due to the 20-year gap since the WHO's published results, the MOE working group decided to conduct this survey.

In conclusion:

- MOE is the preferred term and approach for carcinogenic substances with a DNA reactive mode of action or when toxicological data is incomplete, especially for carcinogens or substances with incomplete toxicological profiles.
- MOE is a safety assessment term applied in a broad context.
- MOS is often tied to specific product types or regulatory expectations (e.g. cosmetics).
- MOE and MOS, while mathematically similar (both are ratios), serve distinct regulatory purposes and should not be used interchangeably.
- MOE provides a numerical value to indicate the level of concern. 10,000 is widely accepted MOE for carcinogenic substances with a DNA reactive mode of action.
- Many agencies follow EFSA or international guidelines, which use MOE rather than MOS, especially for food-related risk.