SciCom

SCIENTIFIC COMMITTEE
established at the
Belgian Federal Agency for
the Safety of the Food Chain

OPINION 15-2019

Subject:

Use of the 'margin of exposure' (MOE) approach for deriving risk-based action limits for carcinogens unintentionally present in food

(SciCom 2018/12)

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Background & Terms of reference

When legal standards or maximum limits are absent for a given chemical substance in a food, the competent authority may act if too high levels are identified which endanger public health (Regulation (EC) n° 178/2002). To evaluate if a level is too high from a public health point of view, the Belgian Federal Agency for the Safety of the Food Chain (FASFC) applies action limits for a number of substance-food combinations. Exceedance of the action limit calls for follow-up action such as an investigation, withdrawal from the market, recall or legal consequences.

If a health-based guidance value (HBGV) such as the tolerable or the acceptable daily intake (TDI or ADI) exists, an action limit for a chemical substance in a food is defined as the maximum concentration of the substance the food may contain without exceeding the TDI or ADI in the case of daily large consumption of the food (i.e. the 97.5th percentile of consumption) (eq. 1).

$$action\ limit = \frac{tolerable/acceptable\ daily\ intake}{consumption\ at\ percentile\ 97.5} \quad \text{(eq. 1)}$$

However, a HBGV is not always available. Moreover, for chemical substances having a non-threshold toxicological effect (genotoxic carcinogens) it is impossible to establish such HBGV below which the exposure is without appreciable health risk. If it concerns an unavoidable genotoxic contamination, the action limit is established by the FASFC based on the ALARA principle ('as low as reasonable achievable') and in consultation with the sector, the Scientific Committee (SciCom) and the Directorate General Laboratories of the FASFC. Risk assessment of such substances is usually based on the margin of exposure (MOE) approach. The MOE corresponds to the ratio between a defined point on the dose-response curve for the adverse effect (reference point or RP) and the estimated exposure. The MOE indicates if exposure should be considered of 'concern for public health'.
Although the MOE does not quantify the risk of exposure to a substance, the MOE approach could be considered for deriving an intake of low public health concern as an alternative to the tolerable / acceptable daily intake, to be used for establishing an action limit (see further). It is in this context that the SciCom has been asked to evaluate if the MOE approach can be used for determining action limits for genotoxic carcinogens in food.

To clearly delineate the question, firstly the difference between genotoxic and non-genotoxic carcinogens, as well as between threshold and non-threshold carcinogens is discussed. Based on the carcinogenic Mode of Action (MoA), in essence a distinction can be made between (i) non-threshold carcinogens with a DNA-reactive (and thus direct) genotoxic MoA, and (ii) threshold carcinogens having (a) a non-genotoxic MoA or (b) a non-DNA reactive (and thus indirect) genotoxic MoA. If the MoA of a carcinogen has not been identified, or when available data are inadequate for a threshold to be identified, the default or starting assumption is that it concerns a non-threshold genotoxic carcinogen. Therefore, as well as for simplicity sake, this opinion considers principally the distinction between genotoxic (non-threshold) and non-genotoxic (threshold) carcinogens only. Moreover, given that genotoxic carcinogens should not deliberately be added to food, the question is delimited to genotoxic carcinogens unintentionally present in food (i.e. contaminants, impurities). Secondly, it is important to clearly differentiate between toxicological, risk-based and legal thresholds. A toxicological threshold corresponds to a reference point (RP) or dose below which there is no appreciable

adverse health effect in the test population under experimental conditions. Examples are the benchmark dose lower confidence level or $BMDL_{10}$ (i.e. the lower confidence limit on the dose that produces a 10% change in adverse response relative to background response) and the T25 (i.e. chronic dose causing tumours in 25% of the animals). A risk-based threshold is a health-based guidance value (or HBGV) and corresponds to a level of human intake at which it is confidently expected that there would be no appreciable adverse health effects, taking into account uncertainty and variability related to the toxicological data. Examples are the TDI and the ADI (i.e. the estimated amount of a substance that can be consumed daily over a lifetime without presenting an appreciable risk to health). Legal thresholds are maximum concentrations that are partly determined based on the risk for public health, but for which also other factors (such as socio-economic, political) are taken into account. They rely in principle on risk management decisions. Action limits triggering a control policy action belong in principle to the field of risk management and should therefore be considered as 'legal' thresholds.

To avoid possible ambiguity in interpretation of the term "action limit" when SciCom, a consultative body on risk assessment, is asked to propose an "action limit" (i.e. a purely risk-based concentration limit) to be applied in a risk management context (i.e. a control-oriented concentration limit that may be stricter or less strict than the risk-based concentration limit), the SciCom is in favour of an alternative terminology. Therefore, the term "estimated acceptable concentration" (EAC) is introduced. The EAC is a risk-based concentration limit that corresponds to the concentration of a substance a food may contain without the exposure to the substance through the food posing an appreciable risk or a concern for public health. The EAC can serve as a basis for the risk manager to establish an action limit.

Methodology

The evaluation of the applicability of the MOE approach for deriving action limits for genotoxic carcinogens is based on information available from scientific literature, and on expert opinion.

Discussion

MOE approach

The MOE is defined as the ratio of the reference point (RP) on the dose-response curve for the critical effect, preferentially the $BMDL_{10}$, to the theoretical, predicted or estimated exposure. When this calculated MOE is larger than the product of uncertainty factors (UF) addressing the differences between experimental data and the human situation, the nature of the carcinogenic process and the type of RP selected, the risk can be assumed to be of low concern from a public health point of view. This product of UF can be considered as a theoretical MOE, indicated in this opinion as "MOE_{UF}" (eq. 2).
Case-dependent, different uncertainties can be considered (i.e. based on expert opinion), but the default product of UF of 100 (accounting for intraspecies variability and individual human variability) is generally applied for substances with a threshold effect (non-genotoxic carcinogens) and of 10 000 (accounting for additional uncertainties related to the MoA) for substances with a non-threshold effect (genotoxic carcinogens).

$$MOE = \frac{dose - response\ reference\ point}{estimated\ exposure} > UF_1 x UF_2 x \ldots x UF_n = MOE_{UF}$$

⬇

"low concern for public health"

(MOE approach; eq. 2)

Low-dose extrapolation (virtually safe dose)

Besides the MOE approach, the risk associated with human exposure to carcinogens can also be evaluated by extrapolation of a RP, such as the T25 or $BMDL_{10}$, to lower doses or concentrations. The risk may in this case be expressed either as the calculated additional cancer risk arising from different levels of exposure or as the level of exposure associated with a predefined level of lifetime risk. The extrapolated low dose which after lifelong exposure results in an additional cancer case in a certain population of individuals, is often referred to as the "virtually safe dose" (VSD).
Providing that the calculated low-dose risk numbers are seen as an upper bound of risk and not interpreted as a realistic risk estimate, low-dose linear extrapolation and MOE calculations can be considered as basically similar approaches. An exposure level estimated via linear extrapolation from a RP will be calculated by dividing the RP by the UF, i.e. by the MOE_{UF}. For instance, linear extrapolation of the T25 or $BMDL_{10}$ to a risk of 1 per 100 000 is equivalent to dividing the T25 by the MOE_{UF} of 25 000 and the $BMDL_{10}$ by the MOE_{UF} of 10 000. Although the choice of UF to be considered in the MOE_{UF} is a risk assessment issue, the choice of an acceptable cancer risk cut-off point (e.g.. a risk for cancer in 1 per 10^5 or in 10^6 exposed) is a decision to be taken by the risk manager.

Action limits for (non-)genotoxic carcinogens

By means of a number of examples from scientific literature, it is illustrated in this opinion that the MOE approach is not only used to evaluate the risk of genotoxic carcinogens, but also of non-genotoxic carcinogens when for instance toxicological data are insufficient to set a HBGV. Additionally, it is pointed out that MOEs also have been calculated for validating a change of the maximum limit or so-called reference points for action (RPA) for genotoxic carcinogens.

Based on the field of application of the MOE approach in scientific literature, the SciCom regards the MOE approach to be appropriate for deriving action limits for genotoxic (non-threshold) as well as for non-genotoxic (threshold) carcinogens. Although the MOE does not quantify the risk of exposure to a substance, particularly in case of non-threshold effect substances, the MOE approach can be used for deriving a 'low concern' intake – comparable to the VSD - to be used for establishing an 'estimated acceptable concentration' (EAC) (eq. 3), which can serve as a basis for the determination of an action limit.

$$'low\ concern'intake = \frac{dose\text{–}response\ reference\ point}{MOE_{UF}}$$

$$\Downarrow$$

$$estimated\ acceptable\ concentration\ (EAC) = \frac{'low\ concern'\ intake}{consumption\ at\ percentile\ 97.5} \quad \text{(eq. 3)}$$

When toxicity data are absent, the 'Threshold of Toxicological Concern' (TTC) approach could be considered as an alternative for the MOE approach for the derivation of an EAC and determination of an action limit for both genotoxic and non-genotoxic carcinogens, on the condition that also in this case it is kept in mind that the TTC concerns a threshold of "low concern".

It should be emphasized that for any genotoxic carcinogen, there may be a carcinogenic risk at any exposure, although this may be very small. An EAC derived for (non-threshold) genotoxic carcinogens only indicates a "low concern" for public health. Ideally, the action limit established for a carcinogenic contaminant or impurity should be as low as possible (i.e. lower than the EAC).

Worthwhile considering in the context of action limits for genotoxic carcinogens, is the approach that the European Food Safety Authority (EFSA) has put forward for establishing Reference Points for Action (RPAs)

for non-allowed pharmacologically active substances. The step-wise approach is based on a comparison between toxicological properties of the substance and the reasonably achievable lowest residue concentration that can be unequivocally determined by official control laboratories, i.e. the reasonably achievable lowest decision limit (CCα).

Uncertainties

Similarly to action limits based on a HBGV, MOE-based EACs or action limits are accompanied with a number of uncertainties, related to e.g. the consideration of sensitive populations, the dose-response curve and the toxic potency of the substance, and consumption data. These uncertainties are however, generic to all EACs and action limits and not only to the ones derived by means of the MOE approach.

Although the definition of 'action limit' implies the maximum concentration of the substance in the food at large consumption of the food (i.e. the 97.5 percentile of consumption), it is recommended that different exposure scenarios should be provided, e.g. for the whole population and for specific groups of the population, depending on the substance considered and its distribution in the diet. Different exposure scenarios result in a broad range of EACs for a substance-food combination. Whilst this makes it difficult to generalize about the health risks related to the EACs and the action limits derived, such different scenarios have the potential to be informative for decisions and prioritisation regarding risk management actions (e.g. withdrawal from the market, recall, investigation, etc.).

At present, an action limit is defined based on the chronic risk. However, when a legislative maximum limit is exceeded, mostly acute risk assessment is performed to determine the extent of measures to be taken (e.g. a recall of the food). Therefore, a reflection on 'acute' action limits could be made. Regarding certain carcinogens, there are indications that short-term or single exposure can indeed give rise to tumour formation. A number of methodologies addressing less-than-lifetime exposure or peak exposure to genotoxic carcinogens, which can occur following accidents or calamities, is briefly discussed but a common framework does not exist.

Conclusions

The MOE approach allows establishing a relation between a dose and an effect (for substances with a threshold) or between a dose and a probability of effect (for substances without a threshold) for substances without an HBGV. Based on this principle and the field of application of the MOE approach in scientific literature, the SciCom is of the opinion that from a scientific point of view, the MOE approach can also be applied for deriving action limits for genotoxic (non-threshold) as well as for non-genotoxic (threshold) carcinogens.

Determination of action limits from a EAC based on the MOE approach should, however, be viewed in an appropriate framework. It should be recognized that respective EACs imply an upper bound of risk related to an exposure of low concern for public health and cannot be considered as safety limits. EACs based on the MOE approach are derived on a case-by-case basis taking into account uncertainties associated with the underlying toxicological data (and expressed by the MOE_{UF}). Because a genotoxic carcinogens might pose a risk at any exposure, ideally the action limit for a carcinogenic contaminant or impurity should be set as low as possible (i.e. lower than the EAC).

Samenvatting

Advies 15-2019 van het Wetenschappelijk Comité van het FAVV betreffende : Gebruik van de 'margin of exposure' (MOE) benadering voor het afleiden van risicogebaseerde actielimieten voor carcinogenen die onbedoeld in levensmiddelen aanwezig zijn

Context & Referentietermen

Als er geen wettelijke normen of maximum limieten voor een bepaalde chemische stof in levensmiddelen zijn, kan de bevoegde overheid toch optreden wanneer er te hoge gehalten vastgesteld worden die de volksgezondheid in gevaar kunnen brengen (Verordening (EG) nr. 178/2002). Om te beoordelen of een gehalte te hoog is vanuit het oogpunt van de volksgezondheid hanteert het Belgisch Federaal Agentschap voor de Veiligheid van de Voedselketen (FAVV) actielimieten voor een aantal levensmiddel-chemische stof combinaties. Het overschrijden van de actielimiet leidt tot een actie of opvolging, zoals een onderzoek, het uit de handel halen, terugroeping ('recall') of juridische gevolgen.

Indien een gezondheidsgerelateerde referentiewaarde ('health-based guidance value' of HBGV), zoals de aanvaardbare of de toelaatbare dagelijkse inname (ADI of TDI) bestaat, wordt een actielimiet voor een chemische stof in levensmiddelen gedefinieerd als de maximale concentratie van de stof die het levensmiddel kan bevatten zonder dat de ADI of de TDI overschreden wordt bij dagelijkse hoge consumptie van het levensmiddel (i.e. het 97,5^{e} consumptie percentiel) (vgl. 1).

$$actielimiet = \frac{toelaatbare/aanvaardbare\ dagelijkse\ inname}{consumptie\ bij\ percentiel\ 97{,}5} \qquad \text{(vgl. 1)}$$

Een HBGV is echter niet altijd beschikbaar. Bovendien is het onmogelijk om voor chemische stoffen met een toxicologisch effect zonder drempelwaarde (genotoxische carcinogenen) een dergelijke HBGV vast te stellen waaronder de blootstelling geen noemenswaardig gezondheidsrisico vormt. Indien het een onvermijdelijke genotoxische verontreiniging betreft, wordt de actielimiet door het FAVV op grond van het ALARA-beginsel ('as low as reasonably achievable' of 'zo laag als redelijkerwijs haalbaar') en in overleg met de sector, het Wetenschappelijk Comité (SciCom) en het Directoraat-generaal Laboratoria van het FAVV vastgelegd. De risicobeoordeling van dergelijke stoffen is gewoonlijk gebaseerd op de blootstellingsmarge of 'margin of exposure' (MOE) benadering. De MOE stemt overeen met de verhouding tussen een bepaald punt op de dosis-responscurve voor het schadelijk effect (referentiepunt of RP) en de geraamde blootstelling. De MOE geeft aan of de blootstelling beschouwd moet worden als ' zorgwekkend voor de volksgezondheid'.
Ofschoon de MOE het risico van blootstelling aan een stof niet kwantificeert, zou de MOE-benadering kunnen overwogen worden om een inname die weinig zorgwekkend is voor de volksgezondheid af te leiden als alternatief voor de toelaatbare / aanvaardbare dagelijkse inname die wordt aangewend om een actielimiet vast te stellen (zie verder). Het is in deze context dat aan het SciCom gevraagd wordt om na te gaan of de MOE-benadering gebruikt kan worden om actielimieten te bepalen voor genotoxische carcinogenen in levensmiddelen.

Om de vraag duidelijk af te lijnen, wordt allereerst het verschil tussen genotoxische en niet-genotoxische carcinogenen besproken, evenals het verschil tussen carcinogenen mét en zonder drempelwaarde. Op basis van het carcinogene werkingsmechanisme ('Mode of Action' of MoA), kan in essentie een onderscheid gemaakt worden tussen (i) carcinogenen zonder drempelwaarde met een DNA-reactieve (en dus directe) genotoxische MoA, en (ii) carcinogenen mét drempelwaarde met (a) een niet-genotoxische MoA of (b) een niet DNA-reactieve (en dus indirecte) genotoxische MoA. Als de MoA van een carcinogeen niet

geïdentificeerd is of wanneer de beschikbare data onvoldoende zijn om een drempelwaarde vast te stellen, wordt standaard aangenomen dat de stof een genotoxisch carcinogeen zonder drempelwaarde is. Daarom, alsook ter vereenvoudiging, wordt in dit advies hoofdzakelijk enkel het onderscheid tussen genotoxische (zonder drempelwaarde) en niet-genotoxische (met drempelwaarde) carcinogenen beschouwd. Aangezien genotoxische carcinogenen niet bewust aan levensmiddelen mogen worden toegevoegd, wordt de vraag verder afgelijnd tot genotoxische carcinogenen die onbedoeld in levensmiddelen aanwezig zijn (bv. contaminanten, onzuiverheden).
Daarnaast is het belangrijk om een duidelijk onderscheid te maken tussen toxicologische, risicogebaseerde en wettelijke drempelwaarden. Een toxicologische drempelwaarde stemt overeen met een referentiepunt (RP) of een dosis waaronder er geen noemenswaardige nadelige gezondheidseffecten zijn in de testpopulatie onder experimentele omstandigheden. Voorbeelden zijn de 'benchmark dose lower confidence level' of $BMDL_{10}$ (i.e. de lagere betrouwbaarheidslimiet op de dosis die leidt tot 10% verandering in schadelijke respons relatief ten opzichte van de achtergrondrespons) en de T25 (i.e. de chronische dosis die bij 25% van de dieren tumoren veroorzaakt). Een risicogebaseerde drempelwaarde is een gezondheidsgerelateerde referentiewaarde (of HBGV) en stemt overeen met een inname van de mens waarbij met een zeker vertrouwen verwacht wordt dat er geen noemenswaardige nadelige gezondheidseffecten zullen zijn, rekening houdende met de onzekerheid en variabiliteit verbonden aan de toxicologische data. Voorbeelden zijn de TDI en de ADI (i.e. de geschatte hoeveelheid van een stof die levenslang dagelijks geconsumeerd kan worden zonder dat dit een noemenswaardig gezondheidsrisico vormt). Wettelijke drempelwaarden zijn maximumgehalten die deels bepaald worden op basis van het risico voor de volksgezondheid, maar waarvoor ook andere factoren (zoals socio-economische, politieke factoren) in aanmerking genomen worden. Ze steunen in principe op risicomanagementbeslissingen. Actielimieten die kunnen leiden tot een actie op het vlak van controlebeleid, behoren in principe tot het domein van risicomanagement en zouden derhalve beschouwd moeten worden als 'wettelijke' drempelwaarden.

Om mogelijke dubbelzinnigheid in interpretatie van de term "actielimiet" te vermijden wanneer het SciCom, een adviesorgaan inzake risicobeoordeling, gevraagd wordt om een "actielimiet" (i.e. een louter op het risico gebaseerde concentratielimiet) voor te stellen die in een risicomanagement context toegepast zal worden (i.e. een controlegerichte concentratielimiet die strikter of minder strikt kan zijn dan de op het risico gebaseerde concentratielimiet), is het SciCom voorstander van een alternatieve terminologie. Derhalve wordt de term 'estimated acceptable concentration' (EAC of "geschatte aanvaardbare concentratie") geïntroduceerd. De EAC is een op het risico gebaseerde concentratielimiet die overeenstemt met de concentratie van een stof die een levensmiddel kan bevatten zonder dat de blootstelling aan de stof via het levensmiddel een noemenswaardig risico inhoudt of zorgwekkend is voor de volksgezondheid. De EAC kan als basis dienen voor de risicomanager om een actielimiet vast te leggen.

Methodologie

De beoordeling van de toepasbaarheid van de MOE-benadering om actielimieten voor genotoxische carcinogenen af te leiden is gebaseerd op beschikbare informatie uit de wetenschappelijke literatuur en op de opinie van experten.

Bespreking

MOE-benadering

De MOE wordt gedefinieerd als de verhouding tussen het referentiepunt (RP) op de dosis-responscurve voor het kritisch effect, bij voorkeur de $BMDL_{10}$, en de theoretische, voorspelde of geraamde blootstelling.

Wanneer deze berekende MOE groter is dan het product van de onzekerheidsfactoren ('uncertainty factor' of UF) die verschillen tussen de experimentele data en de situatie bij de mens, de aard van het carcinogene proces en het type van geselecteerd RP in rekening brengen, kan aangenomen worden dat het risico voor de volksgezondheid van gering belang is. Het product van de UF kan beschouwd worden als een theoretische MOE, en wordt in dit advies aangeduid als "MOE_{UF}" (vgl. 2).
Van geval tot geval kunnen verschillende onzekerheden in overweging genomen worden (i.e. op basis van expertopinie), maar in het algemeen wordt als product van de UF standaard 100 (om rekening te houden met intraspecies variabiliteit en individuele variabiliteit bij de mens) toegepast voor stoffen met een drempelwaarde effect (niet-genotoxische carcinogenen) en 10.000 (om rekening te houden met bijkomende onzekerheden m.b.t. de MoA) voor stoffen met een niet-drempelwaarde effect (genotoxische carcinogenen).

$$MOE = \frac{dosis - respons\ referentiepunt}{geschatte\ blootstelling} > UF_1 x UF_2 x \ldots x UF_n = MOE_{UF}$$

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"weinig zorgwekkend voor de volksgezondheid"

(MOE-benadering; vgl. 2)

Lage-dosis extrapolatie (virtueel veilige dosis)

Naast de MOE-benadering kan het risico van de blootstelling van de mens aan carcinogenen ook geëvalueerd worden door extrapolatie van een RP, zoals de T25 of $BMDL_{10}$, naar lagere dosissen of concentraties. Het risico kan in dit geval uitgedrukt worden als het berekende bijkomende kankerrisico bij verschillende niveaus van blootstelling of als het blootstellingsniveau dat overeenkomt met een vooraf bepaald niveau van levenslang risico. De geëxtrapoleerde lage dosis die na levenslange blootstelling resulteert in een bijkomend kankergeval in een bepaalde populatie van personen, wordt veelal aangeduid als de "virtueel veilige dosis" ('virtually safe dose' of VSD).
Op voorwaarde dat de berekende lage-dosis risicowaarden gezien worden als een bovengrens van het risico en niet geïnterpreteerd worden als een realistische risico-inschatting, kunnen de lage-dosis lineaire extrapolatie en de MOE-berekeningen in feite als gelijkaardige benaderingen beschouwd worden. Een blootstellingsniveau dat geschat wordt via lineaire extrapolatie van een RP zal berekend worden door het RP te delen door de UF, d.w.z. door de MOE_{UF}. Zo komt lineaire extrapolatie van de T25 of de $BMDL_{10}$ naar een risico van 1 op 100.000 bijvoorbeeld overeen met het quotiënt van de T25 met een MOE_{UF} van 25.000 en van de $BMDL_{10}$ met een MOE_{UF} van 10.000. Hoewel de keuze van UF die voor de MOE_{UF} in aanmerking genomen moeten worden, een risicobeoordelingskwestie is, is de keuze van een grenswaarde (of 'cut-off' punt) voor het te aanvaarden kankerrisico (bv. het risico op kanker bij 1 per 10^5 of per 10^6 blootgestelde personen) een beslissing die dient genomen te worden door de risicomanager.

Actielimieten voor (niet-)genotoxische carcinogenen

Aan de hand van een aantal voorbeelden uit de wetenschappelijke literatuur wordt in dit advies geïllustreerd dat de MOE-benadering niet enkel gebruikt wordt om het risico van genotoxische carcinogenen te beoordelen, maar ook van niet-genotoxische carcinogenen, bijvoorbeeld wanneer toxicologische data onvoldoende zijn om een HBGV te bepalen. Bijkomend wordt erop gewezen dat MOE's eveneens berekend worden om een verandering van de maximum limiet of zogenoemde referentiedrempels voor actie ('reference point for action' of RPA) voor genotoxische carcinogenen te valideren.

Op basis van het toepassingsgebied van de MOE-benadering in de wetenschappelijke literatuur, meent het SciCom dat de MOE-benadering geschikt is om zowel voor genotoxische (zonder drempelwaarde) als voor niet-genotoxische (drempelwaarde) carcinogenen actielimieten af te leiden. Ofschoon de MOE het blootstellingsrisico van een stof niet kwantificeert, in het bijzonder van stoffen zonder drempelwaarde effect,

kan de MOE-benadering gebruikt worden om een 'weinig zorgwekkende' inname -vergelijkbaar met de VSD- af te leiden die aangewend kan worden om een geschatte aanvaardbare concentratie of een 'estimated acceptable concentration' (EAC) af te leiden (vgl. 3), die als basis kan dienen voor het bepalen van een actielimiet.

$$'weinig\ zorgwekkende' inname = \frac{dosis-respons\ referentiepunt}{MOE_{UF}}$$

$$\Downarrow \qquad \text{(vgl. 3)}$$

$$geschatte\ aanvaardbare\ concentratie\ (EAC) = \frac{'weinig\ zorgwekkende'\ inname}{consumptie\ bij\ percentiel\ 97{,}5}$$

Wanneer toxiciteitsgegevens ontbreken, kan de 'Threshold of Toxicological Concern' (TTC) benadering beschouwd worden als een alternatief voor de MOE-benadering bij het afleiden van een EAC en het bepalen van een actielimiet voor zowel genotoxische als niet-genotoxische carcinogenen, op voorwaarde dat hierbij eveneens voor ogen gehouden wordt dat de TTC een drempelwaarde "van weinig zorgwekkende aard" betreft.

Het dient benadrukt te worden dat er voor elk genotoxisch carcinogeen een carcinogeen risico bij eender welke blootstelling kan bestaan, hoewel dit risico zeer klein kan zijn. Een voor genotoxische carcinogenen (zonder drempelwaarde) afgeleide EAC wijst enkel op "weinig zorgwekkend" voor de volksgezondheid. Idealiter zou de vastgestelde actielimiet voor een carcinogene contaminant of onzuiverheid zo laag mogelijk moeten zijn (i.e. lager dan de EAC).

Zinvol om te overwegen in de context van actielimieten voor genotoxische carcinogenen, is de benadering die de Europese Autoriteit voor Voedselveiligheid (EFSA) naar voren geschoven heeft voor de bepaling van 'Reference Points for Action' (RPAs) voor niet-toegelaten farmacologisch actieve stoffen. De stapsgewijze benadering is gebaseerd op en vergelijking tussen de toxicologische eigenschappen van de stof en de laagste redelijkerwijs haalbare residuconcentratie die onweerlegbaar bepaald kan worden door officiële controlelaboratoria, i.e. de laagste beslissingslimiet (CCα) die redelijkerwijs haalbaar is.

Onzekerheden

Net zoals actielimieten die op een HBGV gebaseerd zijn, gaan ook MOE-gebaseerde EACs of actielimieten gepaard met een aantal onzekerheden, zoals m.b.t. het in aanmerking nemen van gevoelige populaties, de dosis-responscurve en toxische potentie van de stof, en consumptiegegevens. Deze onzekerheden zijn echter generiek voor alle EACs en actielimieten en niet enkel voor deze die afgeleid zijn op basis van de MOE-benadering.

Hoewel de definitie van 'actielimiet' de maximum concentratie van de stof in het levensmiddel inhoudt bij hoge consumptie van het levensmiddel (i.e. 97,5^{e} consumptiepercentiel), wordt aanbevolen om verschillende blootstellingsscenario's te beschouwen, bv. voor de hele populatie en voor specifieke groepen van de populatie, afhankelijk van de in aanmerking genomen stof en de verspreiding ervan in het dieet. Verschillende blootstellingsscenario's resulteren in een brede waaier aan EACs voor een levensmiddel-chemische stof combinatie. Ofschoon dit het moeilijk maakt om de gezondheidsrisico's die met de EACs en de afgeleide actielimieten gepaard gaan te veralgemenen, hebben dergelijke, verschillende scenario's het potentieel om informatie te geven voor beslissingen en prioritisering met betrekking tot risicomanagementacties (bv. uit de handel nemen, recall, enquête, enz.).

Momenteel wordt een actielimiet gedefinieerd op basis van het chronisch risico. Wanneer echter de wettelijke maximum limiet overschreden wordt, wordt meestal een acute risicobeoordeling uitgevoerd om de omvang van de te treffen maatregelen te bepalen (bv. recall van het levensmiddel). Daarom kan er worden

nagedacht over ‘acute’ actielimieten. Met betrekking tot bepaalde carcinogenen zijn er aanwijzingen dat eenmalige blootstelling of blootstelling op korte termijn inderdaad kan leiden tot tumorvorming. Een aantal methodologieën betreffende minder-dan-levenslange blootstelling of piekblootstelling aan genotoxische carcinogenen, wat zich kan voordoen na een ongeval of ramp, wordt kort besproken. Een algemeen kader bestaat evenwel niet.

Conclusies

De MOE-benadering laat toe om een verband te leggen tussen een dosis en een effect (voor stoffen met drempelwaarde) of tussen een dosis en een kans op effect (voor stoffen zonder drempelwaarde) voor stoffen zonder een HBGV. Op basis van dit principe en het toepassingsgebied van de MOE-benadering in de wetenschappelijke literatuur, is het SciCom van mening dat de MOE-benadering vanuit wetenschappelijk oogpunt toegepast kan worden om EACs en actielimieten af te leiden voor zowel genotoxische (zonder drempelwaarde) als niet-genotoxische (drempelwaarde) carcinogenen.

De bepaling van actielimieten uit een EAC die gebaseerd is op de MOE-benadering moet echter in een geschikt kader geplaatst worden. Er dient te worden onderkend dat de respectievelijke EACs een bovengrens van het risico betreffen bij een blootstelling die weinig zorgwekkend is voor de volksgezondheid en dat deze niet als veiligheidslimieten beschouwd kunnen worden. Op de MOE-benadering gebaseerde EACs worden geval per geval afgeleid, rekening houdende met de onzekerheden verbonden aan de onderliggende toxicologische data (en uitgedrukt door de MOE_{UF}). Omdat een genotoxische carcinogeen bij eender welke blootstelling een risico kan vormen, zou een actielimiet voor een carcinogene contaminant of onzuiverheid idealiter zo laag mogelijk vastgesteld dienen te worden (i.e. lager dan de EAC).

Résumé

Avis 15-2019 du Comité scientifique établi auprès de l'AFSCA concernant : Utilisation de l'approche de la 'marge d'exposition' (MOE) pour dériver des limites d'action basées sur le risque pour des cancérogènes involontairement présents dans l'alimentation

Contexte et termes de référence

Lorsque des normes légales ou des limites maximales sont absentes pour une substance chimique donnée dans une denrée alimentaire, l'autorité compétente peut agir si des niveaux trop élevés pouvant mettre la santé publique en danger sont identifiés (Règlement (CE) n°178/2002). Afin d'évaluer si un niveau est trop élevé d'un point de vue de santé publique, l'Agence fédérale pour la Sécurité de la Chaîne alimentaire (AFSCA) applique des limites d'action pour un nombre de combinaisons substance-aliment. Un dépassement de la limite d'action requiert une action de suivi telle qu'une enquête, un retrait du marché, un rappel ou des conséquences juridiques.

S'il existe une valeur indicative pour la santé ('health-based guidance value' ou HBGV) telle que la dose journalière tolérable ou la dose journalière admissible (DJT ou DJA), une limite d'action pour une substance chimique dans un aliment est définie comme la concentration maximale de la substance que l'aliment peut contenir sans dépasser la DJT ou la DJA en cas de consommation journalière importante de l'aliment (c'est-à-dire le 97,5^{e} centile de consommation) (éq. 1).

$$limite\ d'action = \frac{dose\ journalière\ tolérable/admissible}{97{,}5\ centile\ de\ consommation} \quad \text{(éq. 1)}$$

Toutefois, une HBGV n'est pas toujours disponible. De plus, pour les substances chimiques exerçant un effet toxique sans seuil (cancérogènes génotoxiques), il est impossible d'établir une telle HBGV en dessous de laquelle l'exposition ne présente pas de risque appréciable pour la santé. S'il s'agit d'un contaminant génotoxique inévitable, la limite d'action est fixée par l'AFSCA sur base du principe ALARA ('as low as reasonably achievable' ou 'aussi faible que raisonnablement possible') et en concertation avec le secteur, le Comité scientifique (SciCom) et la Direction générale Laboratoires de l'AFSCA. L'évaluation des risques de telles substances se base habituellement sur l'approche de la marge d'exposition ('margin of exposure' ou MOE). La MOE correspond au rapport entre un point défini sur la courbe dose-réponse pour l'effet indésirable (point de référence ou PR) et l'exposition estimée. La MOE indique si l'exposition devrait être considérée comme « une préoccupation pour la santé publique ».
Bien que la MOE ne quantifie pas le risque d'exposition à une substance, l'approche MOE pourrait être prise en considération pour déduire un apport peu préoccupant pour la santé publique, comme alternatif à la dose journalière tolérable / admissible, à utiliser pour définir une limite d'action (voir plus loin). C'est dans ce contexte qu'il a été demandé au SciCom d'évaluer si l'approche MOE peut être utilisée pour définir des limites d'action pour les cancérogènes génotoxiques présents dans l'alimentation.

Pour délimiter clairement la question, la différence entre des cancérogènes génotoxiques et non-génotoxiques, ainsi qu'entre des cancérogènes à effet avec et sans seuil est d'abord discutée.

Sur la base du mode d'action ('Mode of Action' ou MoA) cancérogène, une distinction peut surtout être faite entre (i) des cancérogènes exerçant un effet sans seuil avec un MoA génotoxique impliquant une réaction avec l'ADN (et donc direct) et (ii) des cancérogènes exerçant un effet avec seuil ayant (a) un MoA non-génotoxique ou (b) un MoA génotoxique n'impliquant pas de réaction avec l'ADN (et donc indirect). Si le MoA

d'un cancérogène n'a pas été identifié ou lorsque les données disponibles sont insuffisantes pour identifier un seuil, l'affirmation par défaut est qu'il s'agit d'un cancérogène génotoxique sans seuil. Pour cette raison, et aussi par souci de simplicité, cet avis prend principalement en considération la distinction entre cancérogènes génotoxiques (sans seuil) et non génotoxiques (avec seuil). De plus, étant donné que des cancérogènes génotoxiques ne devraient pas être délibérément ajoutés aux aliments, la question se limite aux cancérogènes génotoxiques involontairement présents dans l'aliment (c.-à-d. contaminants, impuretés).

Ensuite, il est important de différencier clairement les seuils toxicologiques, les seuils basés sur le risque et les seuils légaux.

Un seuil toxicologique correspond à un point de référence (PR) ou une dose en dessous de laquelle il n'y a pas d'effet néfaste appréciable pour la santé dans une population test et dans des conditions expérimentales. Des exemples sont la 'benchmark dose lower confidence level' ou $BMDL_{10}$ (c.-à-d. la limite de confiance inférieure de la dose qui produit un changement de 10% de la réponse néfaste par rapport à la réponse de fond) et la T25 (c.-à-d. la dose chronique causant des tumeurs chez 25% des animaux).

Un seuil basé sur le risque est une valeur indicative pour la santé (soit une HBGV) et correspond à un niveau d'ingestion humaine auquel on s'attend à ce qu'il n'y ait pas d'effets néfastes appréciables pour la santé, compte tenu de l'incertitude et de la variabilité liées aux données toxicologiques. La DJT et la DJA en sont des exemples (c.-à-d. la quantité estimée d'une substance pouvant être consommée quotidiennement durant toute sa vie sans présenter de risque appréciable pour la santé).

Les seuils légaux sont des teneurs maximales déterminées en partie sur base du risque pour la santé publique mais pour lesquelles d'autres facteurs (tels que des facteurs socio-économiques et politiques) sont également pris en compte. Ils se basent, en principe, sur des décisions de gestion des risques. Les limites d'action entraînant une action de politique de contrôle appartiennent en principe au domaine de la gestion des risques et devraient par conséquent être considérées comme des seuils « légaux ».

Pour éviter toute ambiguïté dans l'interprétation du terme « limite d'action » lorsqu'il est demandé au SciCom, un organe consultatif d'évaluation des risques, de proposer une « limite d'action » (c.-à-d. une limite de concentration purement basée sur le risque) à utiliser dans un contexte de gestion des risques (c.-à-d. une limite de concentration visant au contrôle et pouvant être plus stricte ou moins stricte que la limite de concentration basée sur le risque), le SciCom est en faveur d'une terminologie alternative. Par conséquent, le terme **'estimated acceptable concentration' (EAC ou concentration acceptable estimée)** est introduit. L'EAC est une limite de concentration basée sur le risque qui correspond à la concentration d'une substance que l'aliment peut contenir sans que l'exposition à la substance via l'aliment n'entraîne un risque appréciable ou une préoccupation pour la santé publique. L'EAC peut servir de base au gestionnaire des risques pour établir une limite d'action.

Méthode

L'évaluation relative à la possibilité d'appliquer l'approche MOE pour dériver des limites d'action pour des cancérogènes génotoxiques se base sur des informations disponibles dans la littérature scientifique ainsi que sur l'avis d'experts.

Discussion

Approche MOE

La MOE est définie comme le rapport entre le point de référence (PR) sur la courbe dose-réponse pour l'effet critique, de préférence la $BMDL_{10}$, et l'exposition théorique, prédite ou estimée. Lorsque cette MOE calculée est supérieure au produit de facteurs d'incertitude ('uncertainty factor' ou UF) portant sur les différences entre les données expérimentales et la situation humaine, la nature du processus cancérogène et le type de PR sélectionné, on peut supposer que le risque est peu préoccupant du point de vue de la santé publique. Ce produit de UF peut être considéré comme une MOE théorique, indiquée dans le présent avis comme "MOE_{UF}" (éq. 2).
Selon le cas, des incertitudes différentes peuvent être prises en considération (à savoir sur la base de l'opinion d'expert), mais le produit par défaut du UF de 100 (représentant la variabilité intra-espèce et la variabilité individuelle au niveau humain) est généralement appliqué pour les composés à effet avec seuil (cancérogènes non-génotoxiques) et de 10.000 (en tenant compte des incertitudes complémentaires liées au MoA) pour les composés à effet sans seuil (cancérogènes génotoxiques).

$$MOE = \frac{point\ de\ référence\ dose - réponse}{exposition\ estimée} > UF_1 x UF_2 x \ldots x UF_n = MOE_{UF}$$

(approche MOE ; éq. 2)

« faible préoccupation pour la santé publique »

Extrapolation d'une faible dose (dose virtuellement sûre)

Outre l'approche MOE, le risque associé à l'exposition humaine à des cancérogènes peut aussi être évalué par extrapolation d'un PR, tel que la T25 ou la $BMDL_{10}$, aux doses ou concentrations plus faibles. Le risque peut en l'occurrence être exprimé soit comme le risque additionnel de cancer calculé résultant de différents niveaux d'exposition, soit comme le niveau d'exposition associé à un niveau prédéfini de risque. La faible dose extrapolée qui, après une exposition à vie, résulte en un cas de cancer additionnel dans une population donnée d'individus, est souvent appelée la «dose virtuellement sûre» (DVS).
Pour autant que les chiffres calculés de risque à faible dose sont perçus comme une limite supérieure du risque et ne sont pas interprétés comme une estimation réaliste du risque, l'extrapolation linéaire à faible dose et les calculs de la MOE peuvent être considérés comme des approches, *in fine*, similaires. Un niveau d'exposition humaine estimé extrapolé de manière linéaire à partir d'un PR se calculera en divisant le PR par le UF, c'est-à-dire par la MOE_{UF}. Par exemple, l'extrapolation linéaire de la T25 ou $BMDL_{10}$ en un risque de 1 sur 100.000 équivaut à diviser la T25 par la MOE_{UF} de 25.000 et la $BMDL_{10}$ par la MOE_{UF} de 10.000. Bien que le choix de UF à prendre en considération dans la MOE_{UF} soit une question d'évaluation des risques, le choix d'un point limite acceptable pour le risque de cancer (par ex. un risque de cancer de 1 sur 10^5 ou de 1 sur 10^6 personnes exposées) est une décision qui doit être prise par le gestionnaire de risque.

Limites d'action pour des cancérogènes (non) génotoxiques

A l'aide d'un certain nombre d'exemples de la littérature scientifique, on illustre dans le présent avis que l'approche MOE n'est pas uniquement utilisée pour évaluer le risque des cancérogènes génotoxiques mais également des cancérogènes non génotoxiques lorsque, par exemple, les données toxicologiques sont insuffisantes pour définir une HBGV. De plus, il est signalé que les MOE ont aussi été calculées pour valider une modification de la limite maximale ou de soi-disant valeurs de référence ('reference point for action' ou RPA) pour des cancérogènes génotoxiques.

Sur la base du champ d'application de l'approche de la MOE dans la littérature scientifique, le SciCom considère que l'approche de la MOE convient pour dériver des limites d'action pour les cancérogènes

génotoxiques (sans seuil) et non génotoxiques (avec seuil). Bien que la MOE ne quantifie pas le risque d'exposition à une substance, particulièrement dans le cas de substances à effet sans seuil, elle peut être utilisée pour dériver un apport « peu préoccupant » - comparable à la DVS - à utiliser pour définir une concentration acceptable estimée, soit une 'estimated acceptable concentration' (EAC) (éq. 3) qui peut servir de base pour déterminer une limite d'action.

$$apport\ 'peu\ préoccupant' = \frac{point\ de\ référence\ dose-réponse}{MOE_{UF}}$$
$$\Downarrow \qquad \text{(éq. 3)}$$
$$concentration\ acceptable\ estimée\ (EAC) = \frac{apport\ 'peu\ préoccupant'}{consommation\ à\ centile\ 97{,}5}$$

En l'absence de données sur la toxicité, l'approche du 'Treshold of Toxicological Concern' (TTC) pourrait être considérée comme une alternative à l'approche MOE pour dériver une EAC et déterminer une limite d'action pour les cancérogènes génotoxiques et non génotoxiques, à condition de garder aussi dans ce cas à l'esprit que le TTC concerne un seuil « peu préoccupant ».

Il conviendrait de souligner que pour tout cancérogène génotoxique, il peut y avoir un risque cancérogène pour n'importe quel niveau d'exposition, même très faible. Une EAC, mais aussi la limite d'action dérivée pour des cancérogènes génotoxiques (sans seuil) indique seulement une « faible préoccupation » pour la santé publique. Idéalement, la limite d'action établie pour un contaminant ou une impureté cancérogène devrait être aussi faible que possible (c.-à-d. inférieure à l'EAC)

L'approche mise en avant par l'Autorité européenne de sécurité des aliments (EFSA) pour définir des (Reference Points for Action' (RPA) pour les substances pharmacologiquement actives non autorisées vaut la peine d'être prise en considération dans le contexte des limites d'actions pour des cancérogènes génotoxiques. L'approche par étapes est basée sur une comparaison entre les propriétés toxicologiques de la substance et la plus faible concentration de résidus que l'on peut raisonnablement atteindre pouvant être déterminée sans équivoque par des laboratoires officiels de contrôle, c.-à-d. la plus faible limite de décision que l'on peut raisonnablement atteindre (CCα).

Incertitudes

De façon similaire aux limites d'action basées sur une HBGV, les EACs ou les limites d'action basées sur la MOE sont accompagnées d'un certain nombre d'incertitudes liées par ex. à la prise en compte de populations sensibles, à la courbe dose-réponse et au degré de toxicité de la substance ainsi qu'aux données de consommation. Ces incertitudes sont cependant génériques à toutes les EACs et limites d'action et pas seulement à celles dérivées au moyen de l'approche MOE.

Bien que la définition de « limite d'action » implique la concentration maximale de la substance dans l'aliment lorsque celui-ci est consommé en grandes quantités (c.-à-d. au 97,5^{e} centile de consommation), il est recommandé de fournir différents scénarios d'exposition, par ex. pour l'ensemble de la population et pour des groupes spécifiques de la population, selon la substance prise en considération et sa répartition dans le régime alimentaire. Différents scénarios d'exposition peuvent résulter en une large gamme des EACs pour une combinaison substance-aliment. Alors que cela rend difficile toute généralisation à propos des risques pour la santé liés aux EACs et aux limites d'action dérivées, des tels scénarios différents ont le potentiel d'être informatifs pour les décisions et la priorisation en ce qui concerne les actions de gestion des risques (par ex. retrait du marché, rappel, enquête, etc.).

Actuellement, une limite d'action est définie sur la base du risque chronique. Toutefois, lorsqu'une limite légale maximale est dépassée, une évaluation des risques aigus est généralement réalisée pour déterminer l'étendue des mesures à prendre (par ex. un rappel de l'aliment). C'est pourquoi une réflexion pourrait être menée sur les limites d'action « aiguës ». En ce qui concerne certains cancérogènes, il y a des indications qu'une exposition de courte durée ou une seule et unique exposition peut en effet donner lieu à la formation de tumeur. Un certain nombre de méthodologies portant sur l'exposition durant toute la vie ou sur un pic d'exposition à des cancérogènes génotoxiques, pouvant se produire suite à des accidents ou des calamités, sont brièvement abordées mais un cadre commun n'existe pas.

Conclusions

L'approche MOE permet d'établir une relation entre une dose et un effet (pour des composés avec seuil) ou entre une dose et une probabilité d'effet (pour des composés sans seuil) pour les substances sans HBGV. Sur la base de ce principe et du champ d'application de l'approche MOE dans la littérature scientifique, le SciCom considère que d'un point de vue scientifique, l'approche MOE peut être appliquée pour dériver des EACs et des limites d'action pour les cancérogènes génotoxiques (sans seuil) et non génotoxiques (avec seuil).

La détermination de limites d'action d'une EAC basée sur l'approche MOE devrait cependant être considérée dans un cadre approprié. Il devrait être admis que les EACs respectives supposent une limite supérieure du risque en lien avec une exposition peu préoccupante pour la santé publique et qu'elles ne peuvent pas être considérées comme des limites de sécurité. Les EACs basées sur l'approche de la MOE sont définies au cas par cas, compte tenu des incertitudes associées aux données toxicologiques sous-jacentes (et exprimées par la MOEUF). Étant donné qu'une substance cancérogène génotoxique peut présenter un risque à toute exposition, idéalement la limite d'action pour un contaminant ou une impureté cancérogène devrait être établie aussi faible que possible (c.-à-d. inférieure à l'EAC).

1. Terms of reference

1.1. Question

When legal standards or maximum limits are absent for a given chemical substance in a food, the FASFC might establish an action limit (FASFC, 2019 & 2014). Exceedance of the action limit calls for further action such as an investigation, withdrawal of the food from the market or legal measures.

The Scientific Committee has been asked to evaluate if the 'margin of exposure' (MOE) approach can be used for determining action limits for genotoxic carcinogens.

The SciCom delimits the question to genotoxic carcinogens unintentionally present in food (i.e. contaminants, impurities) since substances which are both genotoxic and carcinogenic are not approved for deliberate addition to foods or for use earlier in the food chain, if they leave residues which are both genotoxic and carcinogenic in food (EFSA, 2005).

1.2. Methodology

This opinion is based on information available from scientific literature and on expert opinion.

2. Abbreviations

Following abbreviations are used (definitions are given in Appendix 1):

ADI	acceptable daily intake
ALARA	as low as reasonable achievable
BMD	benchmark dose
BMDL	benchmark dose 95% lower confidence limit
BMR	benchmark response
CCα	reasonably achievable lowest residue concentration
DNA	deoxyribonucleic acid
DRCF	dose-rate correction factor
EAC	'estimated acceptable concentration'
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
FASFC	Belgian Federal Agency for the Safety of the Food Chain
HBGV	health-based guidance value
LOAEL	lowest observed adverse effect level
MoA	mode of action
MOE	margin of exposure
MOE_{UF}	"theoretical" MOE
MON	moniliformin
MRL	maximum residue limit
NOAEL	no observed adverse effect level
RACE	'Rapid Assessment of Contaminant Exposure'
RASFF	Rapid Alert System for Food & Feed
RP	reference point or reference dose (equivalent to the term 'Point of Departure' or PoD)
RPA	reference point for action
SciCom	Scientific Committee of the FASFC
SCOEL	European Commission's Scientific Committee on Occupational Exposure Limits
T25	chronic dose causing tumours in 25% of the animals

TDI	tolerable daily intake
TSV	toxicological screening value
TTC	threshold of toxicological concern
UF	uncertainty factor
US EPA	Environmental Protection Agency of the U.S.
VSD	virtually safe dose

Considering the discussions during the working group meeting on 19 October 2018 and during the plenary sessions of the Scientific Committee on 6 July 2018, 22 February 2019 and 21 June 2019,

the Scientific Committee gives the following scientific opinion:

3. Introduction

To protect consumers' health European and Belgian legislation establishes standards or maximum limits for chemical substances, including contaminants, residues of pesticides and of veterinary medicines, migrating substances from packaging and other materials in contact with food, allergens, food and feed additives. When a maximum limit is exceeded, the competent authority (i.e. the FASFC) decides upon a withdrawal of the food from the market (i.e. preventing the distribution and sale of the product and the offering thereof to the consumer) whether or not in combination with a recall, depending on the outcome of a risk assessment.

However, legal standards or maximum limits are not (yet) available for all substance-food combinations. In the absence of legal standards or maximum limits, the competent authority may act if too high values are identified which endanger public health (cf. Article 14 of Regulation (EC) n° 178/2002 [1]). To evaluate whether a value is too high from a public health point of view, the FASFC applies action limits for a number of substance-food combinations.

An action limit is defined as a value established by the Directorate General Control Policy of the FASFC and validated by the Scientific Committee (SciCom) established at the FASFC when no official standard or maximum limit is available, and that - if exceeded - calls for an action (FASFC, 2019). The action taken might involve a RASFF (Rapid Alert System for Food and Feed) notification, withdrawal of the food from the market, a legal consequence (warning, report) or an investigation (FASFC, 2014).
If a health-based guidance value (HBGV) such as the tolerable or the acceptable daily intake (TDI or ADI) is available, the action limit for a chemical substance in a food corresponds to the maximum concentration of the substance the food might contain without exceeding the TDI or ADI of the substance at daily large consumption of the food (i.e. the 97.5th percentile of consumption) (eq. 1) (FASFC, 2019). This simplified approach does not consider background exposure from other foodstuffs or from other sources than food, e.g. the environment.

[1] Regulation (EC) n° 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety

$$action\ limit = \frac{tolerable/acceptable\ daily\ intake}{consumption\ at\ percentile\ 97.5} \quad \text{(eq. 1)}$$

However, a HBGV is not always available. Moreover, for substances having a non-threshold toxicological effect (genotoxic carcinogens) it is impossible to establish a HBGV below which the exposure is without appreciable health risk. If it concerns an unavoidable genotoxic contamination, the action limit is established by the FASFC based on the ALARA principle ('as low as reasonable achievable') and in consultation with the sector, the Scientific Committee (SciCom) and the Directorate General Laboratories of the FASFC (FASFC, 2019).

Risk assessment of genotoxic carcinogens is usually based on the margin of exposure (MOE) approach. The MOE corresponds to the ratio between the toxicological dose-response reference point for the substance concerned and the estimated exposure (eq. 2). The MOE is used to evaluate if exposure can be considered of 'low concern for public health'.

$$MOE = \frac{dose{-}response\ reference\ point}{estimated\ exposure} \quad \text{(eq. 2)}$$

Although the MOE does not quantify the risk of exposure to a substance, it could be considered for deriving an intake of 'low concern' to be used for establishing an action limit. It is in this context that the SciCom has been asked to evaluate if the MOE approach can be used for determining action limits for genotoxic carcinogens (unintentionally present in food).

To clearly delineate this question, the difference between non-genotoxic and genotoxic carcinogens, as well as between threshold and non-threshold carcinogens is discussed. Given that action limits are based on risk but can trigger a policy control action, the differentiation between toxicological, risk-based and legal thresholds is given as well.

3.1. Non-genotoxic and genotoxic carcinogens, threshold and non-threshold carcinogens

3.1.1. Genotoxicity

Genotoxic substances are agents that are known to damage genetic information or DNA within a cell causing mutations, which may lead to cancer. Based on the Mode of Action (MoA), following distinction can be made (ECHA/RAC-SCOEL Joint Task Force, 2017):

- Non-DNA reactive (indirect) genotoxic substances:
  - Chemical agents that increase the extent of gene mutations and decrease genomic stability due to indirect mechanisms, e.g. by increasing the level of oxidative DNA damage, by interfering with the cellular response to DNA damage or by epigenetic mechanisms;
  - Chemical agents that act on the chromosomal level alone, e.g. leading to numerical chromosomal aberrations but not increasing the frequency of gene mutations, or modifying the assembly or functioning of the cell division spindle.

- DNA-reactive (direct) genotoxic substances: Chemical agents (or their metabolites) that interact directly with DNA, leading to gene mutations.

3.1.2. Carcinogenicity

Carcinogens are substances or agents capable to cause the development or to increase the incidence of cancer. Carcinogens can be further classified into non-genotoxic carcinogens and genotoxic carcinogens. A non-genotoxic carcinogen differs from a genotoxic carcinogen by the MoA of carcinogenesis (O'Brien *et al.*, 2006; US EPA, 2005):

- Non-genotoxic carcinogens: Chemical substances or agents causing tumours by non-genotoxic mechanism (e.g. peroxisome proliferators, hormones and local irritants). Such substances do not have genotoxicity as a primary biological activity and are believed to cause tumours by disrupting cellular structures and by changing the rate of either cell proliferation or of processes that increase the risk of genetic error. Non-genotoxic carcinogens have been shown to act as tumour promoters (e.g. 1,4-dichlorobenzene), endocrine-modifiers (e.g. 17β-estradiol), receptor-mediators (e.g. 2,3,7,8-tetrachlorodibenzo-p-dioxin), immunosuppressers (e.g. cyclosporine) or inducers of tissue-specific toxicity and inflammatory responses (e.g. metals such as arsenic and beryllium) (Hernández *et al.*, 2009).

- Genotoxic carcinogens: Chemical substances or agents causing tumours by affecting the genetic material (e.g. DNA, chromosomes), being either DNA-reactive or non-DNA reactive. Such substances can induce gene mutations, structural chromosome mutations and genome mutations. Genotoxic carcinogens include organic compounds that induce mutations directly, organic compounds that alter DNA after metabolic activation, and inorganic compounds and metals that can alter DNA.

If the carcinogenic MoA has not been identified, the carcinogenic substance will usually be assumed to be a genotoxic carcinogen (i.e. a default position of a genotoxic MoA based on a lack of information) (EFSA, 2005).

3.1.3. Threshold and non-threshold carcinogens

The risk assessment approach for carcinogenic substances varies depending on whether or not a health-based threshold can be assumed. The threshold for carcinogens is the level of exposure below which there is no cancer risk. It is generally agreed that a threshold exists for non-genotoxic carcinogens, since the mechanism leading to carcinogenesis has an "effect level".

For genotoxic carcinogens, it is commonly assumed that there is no threshold and that even a very small dose may cause adverse effects so that a "no effect level" (i.e. no observed adverse effect level or NOAEL) cannot be derived.
However, it has been shown that there are thresholds for some genotoxic carcinogens (EC DG Health & Consumer Protection, 2009). A joint task force from the European Commission's Scientific Committee on Occupational Exposure Limits (SCOEL) and the European Chemicals Agency's Committee for Risk Assessment (ECHA RAC) has agreed on an approach towards the risk assessment of carcinogens, where MoA is the key for deciding whether health-based thresholds for chemical risk assessment exist (ECHA/RAC-SCOEL Joint Task Force, 2017). A differentiation is made between non-threshold carcinogens with a DNA-reactive (and thus direct) genotoxic MoA at one hand, and threshold carcinogens having (a) a non-genotoxic MoA or (b) a non-DNA reactive (and thus indirect) genotoxic MoA at the other hand (Table 1).
It has to be noticed however, that for most threshold genotoxic carcinogens the available data are likely to be inadequate for a threshold to be identified with sufficient confidence. The default assumption for these carcinogens is that there is no threshold for the carcinogenic hazard (ECHA/RAC-SCOEL Joint Task Force, 2017).

Table 1. Approach towards the risk assessment of carcinogens
(ECHA/RAC-SCOEL Joint Task Force, 2017)

Category	Mode of Action (MoA)		Thresholds exist? (*)
Non-genotoxic carcinogen	Non-genotoxic mechanism (e.g., peroxisome proliferators, hormones and local irritants). Genotoxicity is not a primary biological activity.		Yes
Genotoxic carcinogen	Indirect genotoxicity: Genotoxicity is caused by indirect mechanisms that cause damage to DNA or chromosomes: - Toxic to non-DNA targets: interactions with proteins such as aneugens[2] - Substances that overload the system/change metabolism and exceed natural protective mechanisms: ROS (reactive oxygen species)	*Non-DNA reactive*	Yes
	Direct genotoxicity: Genotoxicity is caused by direct interaction of the respective substance or its metabolites with the DNA leading to gene mutations.	*DNA reactive*	No

(*) i.e. substances for which a threshold mechanism can be assumed for the effect

Based on the default assumptions that (i) a carcinogen can be considered genotoxic when the carcinogenic MoA has not been identified, and (ii) to have no-threshold effect when available data are inadequate for a threshold to be identified, but also for simplicity sake, this opinion considers principally the distinction between genotoxic (non-threshold) and non-genotoxic (threshold) carcinogens only.

3.2. Toxicological, risk-based and legal thresholds

A toxicological threshold corresponds to a reference point (RP) or dose without appreciable adverse health effects in the test population under experimental conditions. This RP is used to establish a risk-based threshold or a level of human intake at which it is confidently expected that there would be no appreciable adverse health effects, taking into account uncertainty and variability such as inter- and intraspecies differences, suboptimal study characteristics or missing data. Legal thresholds rely in principle on risk management decisions, considering not only the risk for public health but also other factors such as socio-economic or political factors.

3.2.1. Toxicological thresholds

A toxicological threshold refers to a reference point (RP) or dose obtained by extrapolation from a toxicological dose-response curve established from experimental or observational data. Examples of toxicological thresholds often applied are the NOAEL (no observed adverse effect level), the LOAEL (lowest observed adverse effect level), the T25 (chronic dose causing tumours in 25% of the animal) and the BMD(L) (benchmark dose (lower confidence level)) (Figure 1).

[2] mutagenic agent that affects the number of chromosomes

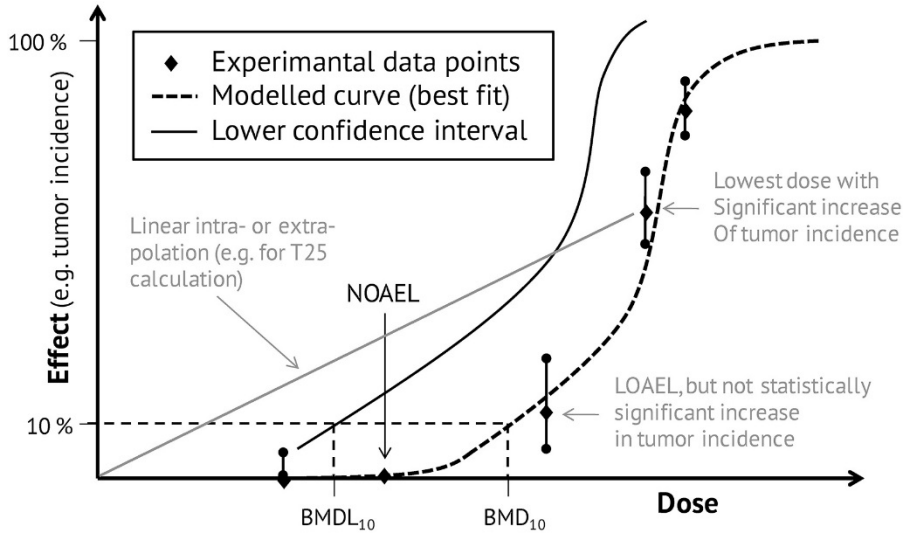

Figure 1. Modelling of experimental data to derive the lower confidence level of a benchmark dose with 10% effect ($BMDL_{10}$, black) and data used for linear intra- or extrapolation (grey) ('no observed adverse effect level' of NOAEL & 'lowest observed adverse effect level' of LOAEL) (remark: the effect in case of genotoxic carcinogens may be very low or even not detectable/measurable but not necessarily zero at low doses; source: Cartus & Schrenk, 2017)

For threshold substances, the NOAEL has long been considered the gold standard. Now, benchmark dose (BMD) modelling is generally the preferred approach and is fast becoming the standard for dose-response analysis.[3] The BMD is a standardised reference point derived from animal (or from epidemiological) data by mathematical modelling. It estimates the minimum dose of a substance that produces a clear, but low level health risk, usually in the range of a 1-10% change in a specific toxic effect such as cancer induction. The BMD is applicable to all chemicals in food, irrespective of their category or origin, and to all toxicological effects, whether or not having a threshold.

The NOAEL corresponds to the highest level of a substance at which no detectable adverse effects occur in an exposed population. It is a dose level where generally no significant differences in response are observed, compared with the background response. This implies that the NOAEL could reflect a dose level where effects are too small to be detected in that particular study, and therefore, the size of the possible effect at the NOAEL remains unknown. The NOAEL approach is only applicable to substances with a toxicological effect considered to have a threshold.

Main limitations and advantages of BMD and NOAEL are given in Table 2.

In the EFSA updated BMD guidance (2017a) it has been noted that the default values of the benchmark response (BMR) are such that the BMDL on average coincides with the NOAEL. Moreover, it was illustrated in the guidance that the potential magnitude of the effect at the NOAEL can be even greater than the specified response size (BMR) associated with the BMDL.

[3] EFSA (2017). Workshop confirms BMD approach as the best method for dose-response modelling in risk assessment (Brussels, 1 March 2017). https://www.efsa.europa.eu/en/events/event/170301-0

Table 2. Advantages and limitations of the NOAEL and the BMD

(based on EFSA, 2017a & Davis *et al.*, 2011)

BMD advantages	NOAEL limitations
• Not limited to experimental doses • Less dependent on dose spacing • Appropriately accounts for variability and uncertainty resulting from study quality • Takes into account the shape of the dose–response curve and other related information • Corresponds to consistent response level and can be used to compare results across chemicals and studies • Flexibility in determining biologically significant rates • Applicable to all toxicological effects	• Highly dependent on dose selection • Highly dependent on sample size • Does not account for variability and uncertainty in the experimental results (e.g. does not account for study quality appropriately) • Dose–response information (e.g. shape of dose–response curve) not taken into account • Does not correspond to consistent response levels for comparisons across studies • A LOAEL cannot be used to derive a NOAEL • Only applicable to toxicological effects considered to have a threshold
BMD limitations	**NOAEL advantages**
• Ability to estimate BMD may be limited by the format of data presented • Requires preferentially a robust dataset and additional knowledge of statistical modelling • Time consuming • More complicated decision-making process	• Can be used when data is not amenable for BMD modelling • Easy to derive • Has been the standard method for deriving a toxicological threshold for decades (e.g. is familiar to most risk assessors)

3.2.2. Risk-based thresholds

A risk-based threshold is a health-based guidance value (or HBGV) corresponding to an exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of harmful effects at one eating moment (acute) or during a lifetime (chronic). Common risk-based thresholds are the acute reference dose (ARfD) and the acceptable or tolerable daily intake (ADI/TDI) for assessing acute and long-term risks respectively. A risk-based threshold is derived from a RP taking several uncertainty factors into account (Table 3). Uncertainty factors (UF) are used to address the differences between the experimental data and the human situation, considering uncertainties in the extrapolation.

Historically, the NOAEL has been used as the RP (see 3.2.1) for deriving risk-based thresholds or HBGV for substances with a threshold effect. The NOAEL is divided by an appropriate UF to take account of potential interspecies and intraspecies (interindividual) differences in susceptibility. A default UF of 100 (based on a factor of 10 for interspecies variation and a factor of 10 for interindividual variation) is often used when extrapolating data from toxicity studies in experimental animals. Other factors may also be included, on a case-by-case basis (Table 3).
Alternatively, the BMD(L) can be used as RP (see 3.2.1) for deriving the risk-based threshold (WHO, 2009). It has been suggested that larger or additional UF might be appropriate when a BMDL is used as the RP. The argument is that the BMDL does not reflect a 'no effect' dose, in contrast to the NOAEL. This argument is based on the assumption that a NOAEL is associated with the complete absence of any adverse effect (EFSA, 2017a; see 3.2.1). The default UF values currently applied to the NOAEL are equally applicable to the BMDL (EFSA, 2017a; WHO, 2009).

If all UF are applied, one can end up with an overall UF of 100 000 (or more), which is considered to be too important to have confidence in the derived HBGV. The final numerical value of UF is considered an indicator

of confidence given to the source study from which the HBGV has been derived. If the product of UF applied exceeds 1 000, an indicative HBGV will rather be proposed (Anses, 2017).

Risk-based thresholds cannot be derived for substances without an identifiable threshold of effect such as genotoxic carcinogens. Exposure to such substances should be as low as reasonably achievable (ALARA; see 3.2.3). The degree of public health concern related to the exposure to genotoxic carcinogens can generally be assessed by means of the MOE approach (see 4.1). Because there is in theory no "safe dose" for non-threshold genotoxic carcinogens, alternatively a so-called "virtually safe dose" (VSD) can be defined (4.1.4). This VSD however, depends on the risk that is accepted or tolerated (see 4.2.3).

Table 3. Standard uncertainty factors (UF) considered for risk assessment of threshold and non-threshold carcinogens (EFSA, 2012a; IPCS, 1994; US EPA, 1993)

		Account for …	UF
non-threshold carcinogens	threshold carcinogens	interspecies differences; the uncertainty when extrapolating from animal data to humans *= kinetic and dynamic differences between animal species and humans*	10 [(a)] *= factor 4 × 2.5*
		intraspecies differences; the variation in sensitivity among members of the human population *= kinetic and dynamic differences within the human population*	10 [(b)] *= factor 3.2 × 3.2*
		differences in duration of exposure; the uncertainty when extrapolating from sub-chronic NOAELs to chronic NOAELs	10 [(c)] (default is 1)
		issues related to the dose-response relation; the uncertainty when using LOAEL instead of NOAEL or BMD (e.g. factor of 2,5 when T25 is used instead of BMD)	10 (default is 1)
		additional uncertainty factor (also referred to as 'modifying factor' or MF) to account for data quality and confidence in data set	0 < UF ≤ 10 (default is 1)
	additional uncertainties specifically for substances that are both genotoxic and carcinogenic; (i) inter-individual human variability in cell cycle control and DNA repair, which influence the carcinogenic process; (ii) the reference point is not equivalent to a NOAEL and effects can occur at lower doses. The dose-response relationship below the reference point, and the dose level below which cancer incidence is not increased are unknown, representing additional uncertainties.		100

[(a)] The interspecies uncertainty factor is not necessary if the NOAEL or LOAEL is based on human data (IPCS, 1994).

[(b)] For some substances, it may be that a subset of the population would be particularly sensitive, for example due to deficiencies in detoxication processes. Many of the enzymes involved in xenobiotic biotransformation are polymorphically distributed in the human population, which should be taken into account where the enzymatic differences result either in a marked change in bioavailability or clearance of the parent compound or in a major change in the extent of formation of the toxic entity. In cases where the default factor will not adequately cover this additional variability, the default UF should be modified. Alternatively, special strategies for health protection may be implemented for these groups. In cases where the risk assessment is based on *in vivo* data in the sensitive subgroup, the factor of 10 should be reduced to a lower value. A value of 1 could be used if there is an extensive database in humans and the database adequately addresses any identified sensitive subgroups (IPCS, 1994).

[(c)] Uncertainty factors of 3, 5 or 10 have been used previously to extrapolate from a LOAEL to a NOAEL depending on the nature of the effect(s) and dose-response relationship. Instead, a BMD may be modelled as an alternative to the UF in extrapolating to the NOAEL (IPCS, 1994).

3.2.3. Legal thresholds

Legal thresholds are maximum levels set according to good practices and ALARA. Often, legal thresholds are more stringent than risk-based thresholds given that besides possible risks also Good Agricultural Practices or Good Manufacturing Practices are amongst others accounted for. An example are maximum residue levels (MRL), which are the highest levels of a pesticide residue that is legally tolerated in or on food or feed when pesticides are applied correctly. Foods which contain residues at or below the legally established MRLs are considered safe for consumers. Nevertheless, pesticide residue concentration may also be above the MRL without representing an appreciable risk to the consumer (Claeys *et al.*, 2011).

In some cases, such as e.g. in the case of genotoxic carcinogens, legal thresholds cannot meet the risk-based threshold and are, in other words, less stringent than risk-based thresholds. A balance must thus be made between toxicological and other factors, including social, technical and economic factors. Legal thresholds have been established for several genotoxic carcinogen-food combinations, such as for inorganic arsenic [4], cadmium, polycyclic aromatic hydrocarbons and aflatoxin B1 (Commission Regulation (EC) No 1881/2006 of 19 December 2006 setting maximum levels for certain contaminants in foodstuffs).

Legal thresholds, including in fact action limits, thus rely in principle on risk management decisions, considering not only the risk for public health but also other factors.

ALARA principle

The ALARA principle ('as low as reasonable achievable') is a management measure used by advisory bodies and national regulatory authorities to keep the risk of exposure to genotoxic carcinogens as low as possible. The ALARA principle is a qualitative management tool, not applicable for risk assessment (EC DG Health & Consumer Protection, 2009). It has the advantage that only hazard identification data are needed to confirm that the substance is either genotoxic (*in vivo*) and so assumed to be carcinogenic, or that studies have shown that the compound is both genotoxic and carcinogenic. The disadvantage of the ALARA approach is that it does not make any distinction between high potency and low potency carcinogens, nor does it relate the potential hazard to the extent of exposure. Also, it does not give any guidance on the magnitude of any residual risk that might remain despite successful risk management control that results in a 'reasonably achievable' low exposure level (Dybing *et al.*, 2008).

Action limits

In the absence of legal standards or maximum limits, the FASFC applies action limits for several substance-food combinations. Exceedance of an action limit triggers a control policy action, including a RASFF notification, withdrawal of the food from the market, a legal consequence (warning, report) or an investigation.
Action limits should therefore be considered as 'legal' thresholds belonging in principle to the field of risk management. Risk management and risk assessment are two separate, but closely related pillars of risk analysis and it is recognised that scientific risk assessment alone cannot, in some cases, provide all the information on which a risk management decision should be based (Regulation (EC) n° 178/2002 [5]). Therefore and given that the SciCom is a consultative body on risk assessment, it is recommendable to use a different

[4] It is likely, but not proven, that the genotoxicity of arsenic is a threshold effect, however, the available data do not allow the identification of threshold exposure levels (ECHA, 2013)
[5] Regulation (EC) n° 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety

terminology for action limits derived by the SciCom (i.e. a purely risk-based concentration limit) and action limits for control policy (i.e. a control-aimed concentration limit that may be stricter or less strict than the risk-based concentration limit).
To avoid possible ambiguity in terminology, the term "estimated acceptable concentration" (EAC) is introduced. The EAC is a risk-based concentration limit that corresponds to the concentration of a substance a food may contain without the exposure to the substance through the food posing an appreciable risk or a concern for public health. The EAC can serve as a basis for the action limit applied by control policy.

4. Discussion

4.1. Risk characterization by means of the margin of exposure (MOE)

The MOE approach is used when it is inappropriate to derive a HBGV owing to the nature of the effect, such as for substances that are genotoxic and carcinogenic. Additionally, the MOE-approach is also used when limited toxicological or human data exist and hazard identification and characterization data are insufficient to set a HBGV. The MOE is defined as the ratio of the RP on the dose-response curve for the critical effect to the theoretical, predicted or estimated exposure (WHO, 2009; US EPA, 2005).

4.1.1. Reference point

Reference points (RP) considered for calculating the MOE are the NOAEL and the BMDL, but the BMDL is considered the most appropriate RP (Benford *et al.*, 2010; EFSA, 2005). Furthermore, it is scientifically not valid to identify a NOAEL for genotoxic carcinogens, and more specifically for carcinogenic processes mediated via a DNA-reactive MoA as there may be no threshold in the dose-response relationship (3.2.1).

The BMDL, corresponding to a dose that causes a low but measurable response, is applicable for threshold as well as for non-threshold substances. The EFSA recommends the use of the $BMDL_{10}$ which is in case of carcinogens an estimate of the lowest dose which is 95% certain to cause no more than a 10% cancer incidence in rodents, or in humans when human data are available (EFSA, 2005). A benchmark response (BMR) of 10% was preferred to 5%, since the modelling of lower responses generally results in greater uncertainty (Benford *et al.*, 2010). If data are unsuitable for deriving a BMD, use of the T25, representing the dose corresponding to a 25% incidence of tumours, is recommended (EFSA, 2005). The BMDL is preferred to the T25 as a reference point because the BMDL takes into account uncertainty regarding the shape of the dose-response relationship, within the observed dose range of carcinogenicity studies (Figure 1).

4.1.2. Estimated exposure

In the context of the present opinion there is no need for a detailed discussion on the choice of exposure estimates because the exposure assessment for a substance that is both genotoxic and carcinogenic is not different to the exposure assessment performed for substances with another toxicological profile. Ideally, various exposure estimates are considered, taking into account differences in consumption patterns, in order to provide risk managers with extensive information (Benford *et al.*, 2010; EFSA, 2005).

The need to estimate acute and/or chronic exposure is dependent on the nature of the toxicity of the contaminant of interest and the duration of exposure. The main concern regarding the presence of genotoxic carcinogens however, is chronic exposure (EFSA, 2005). The issue of assessing the carcinogenic risk following less-than-lifetime or peak exposure to genotoxic carcinogens, which can occur following accidents or

calamities, has been considered by scientists and policy makers, but a common framework does not exist (Felter *et al*., 2011; Bos & van Raaij, 2002) (see 4.1.4).

4.1.3. Interpretation of the margin of exposure

Following aspects have to be considered for the interpretation of a MOE (EFSA, 2005):

- interspecies differences and intraspecies differences (human variability),
- nature of the carcinogenic process,
- type of RP selected, e.g. $BMDL_{10}$ or T25.

The uncertainty related to these factors is accounted for by means of UF. Table 3 summarizes standard UF considered for the risk assessment of threshold and non-threshold carcinogens.

When the calculated MOE or ratio of the RP to the exposure is larger than the product of UF, the risk can be assumed to be of low concern from a public health point of view. The product of UF can be considered as a theoretical MOE, indicated in this opinion as "MOE_{UF}" (eq. 3). An MOE smaller than the product of UF or MOE_{UF} indicates a potential public health concern.

$$MOE = \frac{dose - response\ reference\ point}{estimated\ exposure} > UF_1 x UF_2 x \dots x UF_n = MOE_{UF}$$

"low concern for public health"

(MOE approach; eq. 3)

The magnitude of the MOE gives an indication of the level of concern, but is not a precise quantification of risk; the larger the MOE, the smaller the potential risk posed by exposure to the substance under consideration. For example, a carcinogen with an MOE of 1 000 cannot be assumed to represent 10 times the cancer risk of a different carcinogen with an MOE of 10 000 (Benford *et al.*, 2010).

MOE approach for substances with a threshold effect

For most non-genotoxic carcinogens, it is accepted that there is a threshold dose, below which no effect occurs. Where there is adequate evidence for a plausible, non-genotoxic MoA which supports a threshold for carcinogenicity, a HBGV can be derived at or below which no risk of carcinogenicity in humans can be assumed (3.2.2). However, when the available information on adverse health effects are too limited to establish a HBGV, the MOE can be applied for the risk assessment of chemical substances with a threshold effect. To illustrate, reference can be made to the EFSA risk assessment of the mycotoxin moniliformin (MON) (EFSA, 2018b). The limited information available on toxicity and on toxicokinetics indicated haematotoxicity and cardiotoxicity as major adverse health effects of MON. MON causes as well chromosome aberrations *in vitro* but no *in vivo* genotoxicity data and no carcinogenicity data were identified. Because the available information on chronic and acute adverse health effects of MON was considered too limited to establish a TDI or an ARfD, EFSA assessed the chronic and acute health risk of exposure to MON by means of the MOE approach. Chronic health risks were evaluated based on a comparison of the $BMDL_{05}$ for haematotoxicity in pigs with the estimated chronic exposure of humans. Acute health risks were evaluated based on a comparison of the NOAEL from a subacute study in rats with the estimated acute exposure of humans (EFSA, 2018b). In the same EFSA opinion, the MOE approach was also applied for the farm and companion animal health risk evaluation of MON exposure through feed.

The default uncertainty factor of 100 (accounting for intraspecies and human variability) has a long history of use for threshold effects and is generally regarded as the MOE_{UF} that would be without appreciable health

risk. Because the calculated MOE is based on a NOAEL or a BMDL, the MOE is equivalent to a 'margin of safety', and there would be negligible risk providing that the exposure is at or less than the ADI/TDI (WHO, 2009).

Case-dependent, different UF can be considered for calculating the MOE_{UF} to which the margin of exposure ('actual' MOE) between the NOAEL or the BMDL and the intake is compared. For example, for the risk assessment of the chronic oral exposure to nickel (Ni), the EFSA derived a TDI based on a $BMDL_{10}$ derived through modelling of the dose-response data regarding reproductive and developmental toxicity in rats and by applying a default UF of 100 to account for interspecies differences and human variability. For the acute risk characterization, a $BMDL_{10}$ was selected based on modelling of the dose-response data regarding systemic contact dermatitis elicited in sensitive humans after acute oral exposure to Ni. As the selected $BMDL_{10}$ for acute toxicity was derived based on data obtained in a highly sensitive group of individuals and was assumed to be conservative, only the large interindividual variability in the immune response was taken into account as an uncertainty and a UF of 10 was considered. For the risk assessment it was therefore decided that an MOE of 10 or higher would be indicative of a "low public health concern" at acute exposure (EFSA, 2015a).

Another example is the incident with 4-methylbenzophenone, a photo-initiator that migrated from the packaging in breakfast cereals. Due to lack of toxicological data and the urgency of the risk assessment, an MOE was calculated based on an LOAEL value for the structurally related benzophenone. Besides the UF of 100 for inter- and intraspecies variability, additional UF of 3 for use of a LOAEL instead of a NOAEL and of 2 for read-across from benzophenone to 4-methylbenzophenone were applied. Hence, the estimated MOE had to be higher than 600 to conclude that the exposure unlikely posed a public health concern (EFSA, 2009a).

MOE approach for substances with no identifiable threshold of effect

In the case of adverse effects that are considered not to show a biological threshold in their dose-response relation, the margin between the BMDL and the estimated human intake/exposure (or the MOE) cannot be considered a margin of safety, and this in contrast to substances with a threshold effect.

For genotoxic carcinogens, uncertainties related to their MoA are considered in addition to the uncertainties related mainly to interspecies differences and human variability. In general, substances with a MOE of 10 000 or higher, if based on the $BMDL_{10}$ from an animal study, would be a low concern from a public health point of view and might reasonably be considered as a low priority for risk management actions (EFSA, 2005). A MOE smaller than 10 000 indicates a public health concern. There is no further banding of the MOE value to expand the interpretation of its magnitude.

Under circumstances where there are greater uncertainties, for example if the MOE is calculated using a T25 or if the RP is based on a poor animal database, a MOE of an order of magnitude of 10 000 is no longer considered of low public health concern and an additionally UF should be accounted for (EFSA, 2005). The T25 approach is inherently less conservative than $BMDL_{10}$ modelling, in that the former considers a level of tumour incidence of 25% and the latter of 10%. Therefore, a MOE_{UF} 2.5 times higher is considered (i.e. 25 000) when the RP is based upon a T25 and not upon a $BMDL_{10}$ (Dybing *et al.*, 2008).

4.1.4. Low-dose (linear) extrapolation to a "virtually safe dose" (VSD)

Numerical estimates of the risk associated with the human exposure can also be derived by extrapolation of the animal dose-response data or from a RP, such as the T25 or $BMDL_{10}$ to lower doses or concentrations. These estimates may be expressed either as the calculated additional cancer risk arising from different levels of exposure or as the exposure associated with a predefined level of risk. The extrapolated low dose which

after lifelong exposure results in an additional cancer case in a certain population of individuals (in others words, the risk considered to be negligible or acceptable), is often referred to as the "virtually safe dose" (VSD) (Boobis *et al.*, 2013b).

Consider for instance a VSD which, after lifelong exposure, results in one additional cancer case in a population of one million exposed individuals. This VSD is estimated applying linear extrapolation from the lowest significant dose producing relevant tumours in an animal experiment (RP) to the dose theoretically resulting in one cancer case after lifelong exposure of one million humans. The method corrects for exposure duration and life expectation of the particular experimental animal. No correction is made for extrapolating from animals to humans, as the general feeling is that this way of linear extrapolation is already rather conservative (Bos *et al.*, 2004).

However, an exposure level estimated via linear extrapolation from a RP will be calculated by dividing the RP by the UF, i.e. by the MOE_{UF} (Figure 2). For instance, linear extrapolation of the T25 or $BMDL_{10}$ to a risk of 1 per 100 000 is equivalent to dividing the T25 by 25 000 and the $BMDL_{10}$ by 10 000. Providing that the calculated low-dose risk numbers are seen as an upper bound of risk and not interpreted as a realistic risk estimate, low-dose extrapolation and MOE calculations should be considered as basically similar approaches (ECHA, 2012; Dybing *et al.*, 2008; O'Brien *et al*., 2006).

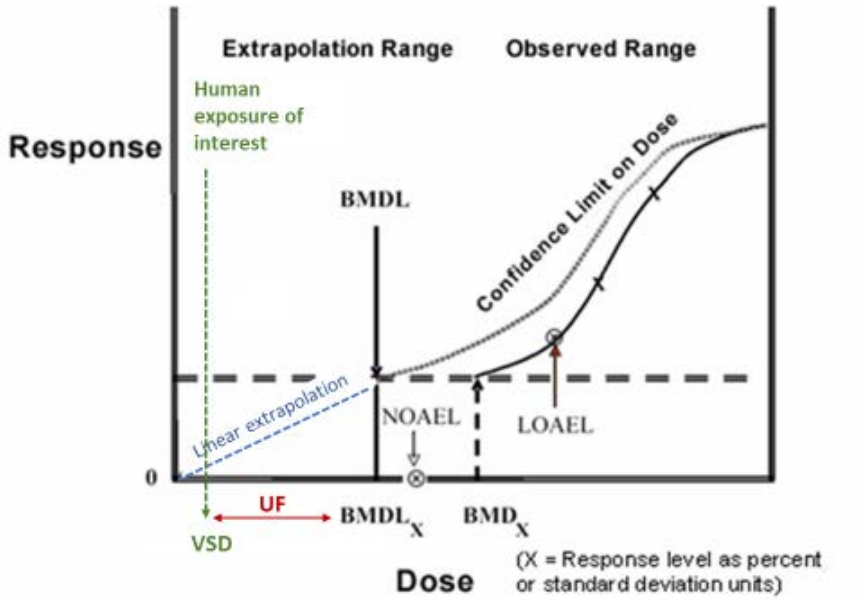

Figure 2. Virtually safe dose (VSD) and benchmark dose (lower confidence limiet) (BMD(L)) extrapolated from a hypothetical dose-response curve, with indication of the no observed adverse effect level (NOAEL) and the lowest observed adverse effect level (LOAEL) (adapted from EPA, source: https://toxtutor.nlm.nih.gov/06-003.html)

Different extrapolation methods are applied to derive a VSD, but at present there is no scientific consensus or harmonized decision regarding certain methodological aspects (Anses, 2017; WHO, 2009; Mullot *et al*., 2006; US EPA, 2005). The default approach used by several regulatory bodies as a precautionary approach, is linear extrapolation to some prefixed exposure, representing the preferred risk level of "low concern", or to actual human exposures for estimating associated risks (ECHA, 2012). According to the US Environmental Protection Agency (US EPA, 2005) linear extrapolation should be used when there is sufficient information about the MoA to indicate that the dose-response curve is likely to have a linear component below the RP. This includes substances that are DNA-reactive and have direct mutagenic activity. Linear extrapolation is also appropriate as a default extrapolation approach where the MoA is not established as the approach is generally considered to be a health-protective approach.

The use of quantitative low-dose extrapolation of dose-response data from an animal bioassay raises however numerous scientific uncertainties related to the selection of mathematical models and extrapolation down to levels of human exposure (Figure 3). It does not reflect the underlying biological processes and there is potential for significant non-linearity in the intake-response relationship outside the observable domain (Boobis *et al.*, 2013; Dybing *et al.*, 2008). There is consensus that the margin of exposure (MOE) is the preferred approach because it is based on the available animal dose-response data, without extrapolation, and on human exposures (EFSA, 2006). Similarly to extrapolating to a VSD however, interpretation of the MOE requires implicit or explicit consideration of the shape of the dose–response curve at human relevant exposures (Boobis *et al.*, 2013 a & b). Comparison of the on the $BMDL_{10}$ based calculated MOE with a MOE_{UF} of e.g. 10 000 implies confidence that this cut-off of 10 000 generally applied for genotoxic carcinogens is adequately protective for humans (see 4.2.4).

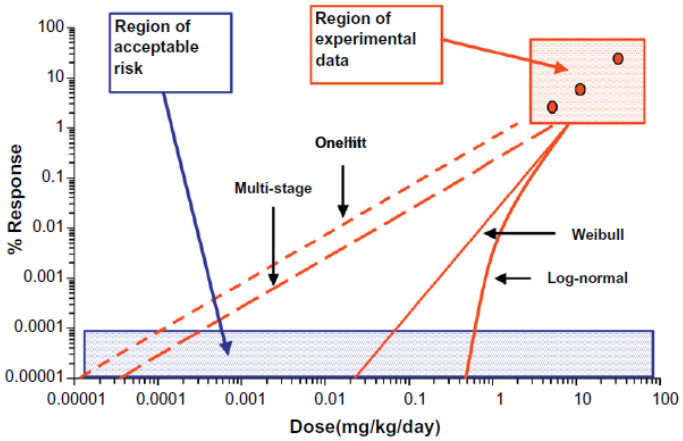

Figure 3. Dose-response extrapolation; a few examples of possible dose–response curves for genotoxic carcinogens at human relevant exposures with indication of the region of the risk level that is generally accepted (see 4.2.3) (the figure is reproduced and modified by Boobis *et* al. (2013b) based on EFSA (2005))

4.1.5. 'Threshold of Toxicological Concern' (TTC) when carcinogenicity data are absent/limited

The 'Threshold of Toxicological Concern' (TTC) concept is applicable to substances for which the chemical structure is known but for which there are few or no relevant toxicity data. It provides a practical screening tool either for priority setting or for deciding whether exposure to a substance is so low that the probability of adverse health effects is low, and no further data are necessary (EFSA, 2016 & 2012b). The TTC approach should not be used for the following (categories of) substances: high potency carcinogens (i.e. aflatoxin-like, azoxy- or N-nitroso-compounds, benzidines, hydrazines), inorganic substances, metals and organometallics, proteins, steroids, substances that are known or predicted to bioaccumulate, nanomaterials, radioactive substances, and mixtures of substances containing unknown chemical structures.

For substances with a structural alert for genotoxicity, the TTC value of 0.0025 µg/kg bw/day is considered sufficiently conservative, provided the structures already designated as high potency carcinogens are excluded from the TTC approach. Substances without structural alerts for genotoxicity can proceed down the TTC decision tree to be considered in relation to the higher TTC values for organophosphates and carbamates (0.3 µg/kg bw/day), for Cramer Classes II and III (1.5 µg/kg bw/day) or for other substances (30 µg/kg bw/day) (EFSA, 2016 & 2012b).

TTC values should be expressed in terms of µg/kg body weight per day (rather than on a per person basis) to allow for application of the TTC approach to the whole population, including infants and children. For infants under 3 months of age, case-by-case considerations are needed if the estimated exposure approaches the TTC value (see also 4.2.4). Additional considerations might include prediction of metabolic routes for the structure concerned and other issues such as frequency and duration of the exposure (EFSA, 2016 & 2012b).

When the TTC approach is used, it is important for both risk assessors and risk managers to keep in mind that it is a probability-based screening tool and, in common with other risk assessment approaches, it does not offer complete certainty (EFSA, 2012b). The probability that a substance with an exposure below the relevant TTC value may still pose a potential risk when using either the cancer or non-cancer TTC values, is estimated to lie between zero and 5%.

4.2. Action limits for non-genotoxic and genotoxic carcinogens

4.2.1. Action limits based on the MOE approach

The MOE approach was initially established by the EFSA to consider possible safety concerns arising from the presence in food and feed of contaminants which are both genotoxic and carcinogenic (EFSA, 2005). The presence of such substances in food and feed, while not desirable, could result from environmental pollution or manufacturing processes. The MOE is not used to assess the safety of regulated substances deliberately added to the food chain (for instance food and feed additives or food contact materials). However, EFSA's Scientific Committee advised in a statement published in 2012 that the MOE approach could be useful in assessing the safety of any genotoxic and carcinogenic impurities present in such substances at very low levels. Use of the MOE can in this way help support risk managers in defining possible actions required to keep exposure to such substances as low as possible (EFSA, 2012c).
Moreover, the EFSA technical report regarding the risk assessment of chemical contaminants in the context of RASFF notifications recommends the MOE approach for substances for which no toxic threshold can be defined (i.e. genotoxic carcinogens), but for which an RP is available. The MOE approach is also implicitly put forward in this EFSA report for the risk assessment of substances for which a toxic threshold can be assumed (i.e. non-genotoxic substances), but for which no HBGV but an RP (e.g. BMDL, NOAEL) is available (see: 'Rapid Assessment or Contaminant Exposure' or RACE tool; EFSA, 2019).

The MOE approach has also been used in a number of EFSA opinions to evaluate the risk of substances with a non-genotoxic critical effect (e.g. EFSA, 2018b; 2015a; 2011 a & b; 2009a – see 4.1.3). Additionally, it is remarked that both the WHO (2009) and US EPA (1993) consider a larger field of application for the MOE than solely the risk assessment of genotoxic carcinogens. For instance, the MOE approach has been put forward by the US EPA as "an alternative measure that may be useful to some risk managers, and which is the magnitude by which the NOAEL of the critical toxic effect exceeds the estimated exposure dose, where both are expressed in the same units. When the MOE is equal to or greater than the product of UF, the need for regulatory concern is likely to be small" (US EPA, 1993).

The MOE approach can thus be used for deriving action limits for non-genotoxic carcinogens.

Given that a HBGV cannot be derived for genotoxic carcinogens, it is theoretically not possible to calculate an action limit corresponding to a maximum concentration of the substance a food might contain without appreciable health risk. The most precautionary approach to reduce the risk from such chemicals would be to prevent exposure completely. However, under specific circumstances, e.g. very low exposures to genotoxic contaminants or impurities, a pragmatic action limit may be identified to aid risk management decisions. In this respect, the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and

the Environment, an advisory committee of the UK government and government agencies, suggests the derivation of a 'minimal risk level'. The derivation of a minimal risk level for a genotoxic carcinogen involves assessment of all available dose-response data for carcinogenicity to identify an appropriate point of departure (i.e. a RP), and the use of expert judgement to derive an appropriate UF to apply to it (COC, 2012), which is in essence the MOE approach.

Additionally, it is pointed out that MOEs have been calculated for validating a change of the maximum limit or so-called reference points for action (RPA) for genotoxic carcinogens (see also 4.2.2). For example, EFSA concluded that changing the maximum limit for the sum of the aflatoxins B1, B2, G1 et G2 (mycotoxins), from 4 to 8 or 10 µg/kg in almonds, hazelnuts and pistachios would have minor effects on estimates of dietary exposures, of cancer risk as well as of MOEs that are calculated based on current and increased maximum limits and for a chronic dietary exposure (EFSA, 2018c). Similarly it was concluded that a reference point for action (RPA) of 0.3 µg/kg for chloramphenicol, an antibiotic not authorised for use in food-producing animals in the European Union (EU), is adequate to protect public health given among others the MOE values calculated based on a hypothetical worst-case human dietary exposure, for which the RPA of 0.3 µg/kg was considered as occurrence value of chloramphenicol in food (EFSA, 2014).
From this point of view, it can be assumed acceptable to derive an action limit for genotoxic carcinogens based on the MOE approach. It could however be considered to rephrase the question as "what is the impact of the proposed action limit on the MOE?" (i.e. to evaluate the impact on the risk of different maximum limits for a chemical in food) instead of approaching the issue from the perspective of "deriving an action limit from the MOE approach".

The MOE approach allows establishing a relation between a dose and an effect (for substances with a threshold) or between a dose and a probability of effect (for substances without a threshold) for substances without an HBGV, including genotoxic carcinogens. So, although the MOE does not quantify the risk of exposure to a substance, particularly in case of non-threshold effect substances, the MOE-approach can be used for deriving a 'low concern' intake – comparable to the VSD (see 4.1.4) - to be used for establishing an EAC (eq. 4) that can be used as a basis for the action limit.

$$'low\ concern'\ intake = \frac{dose\text{–}response\ reference\ point}{MOE_{UF}}$$

$$\Downarrow$$

$$estimated\ acceptable\ concentration\ (EAC) = \frac{'low\ concern'\ intake}{consumption\ at\ percentile\ 97.5} \quad \text{(eq. 4)}$$

It should still be recognised that, for any genotoxic carcinogen, there may be a carcinogenic risk at any exposure, although this may be very small. An EAC for (non-threshold) genotoxic carcinogens only indicates a "low concern" for public health or a "low probability of increased incidence" and not that there is "no appreciable risk". When toxicological data and thus an RP are lacking, the TTC approach could be considered as an alternative for the MOE approach for the derivation of an EAC, on the condition that also in this case it is kept in mind that it concerns a threshold of low concern.

4.2.2. 'Reference Points for Action' for non-allowed pharmacologically active substances

An action limit could alternatively be derived according to the approach that has been put forward for establishing Reference Points for Action (RPAs) for non-allowed pharmacologically active substances (EFSA, 2018a). RPAs are based on the reasonably achievable lowest residue concentration that can unequivocally be determined by official control laboratories, i.e. the reasonably achievable lowest decision limit (CCα). The

proposed step-wise approach applies toxicological screening values (TSVs), based on genotoxic potential, pharmacological activity, as well as other effects of the substance, with the aim to check whether the CCα is low enough to adequately protect the consumers. The highest dietary exposure corresponding to the reasonably achievable lowest CCα for the substance has to be estimated and compared with the TSV. Where equal to or lower than the TSV, the reasonably achievable lowest CCα can be accepted as the RPA. If higher, the sensitivity of the analytical method needs to be improved.

The action limit to be derived for genotoxic carcinogens would then correspond to reasonably achievable lowest CCα and the TSV to the $BMDL_{10}$ divided by the MOE_{UF}. This approach for establishing RPAs for non-allowed pharmacologically active substances is more in line with the reasoning that ALARA remains the overriding principle even when the VSD or the EAC suggest there is unlikely to be a concern for public health.

4.2.3. Acceptable level of risk

The acceptability or tolerability of risk depends on scientific data, social, economic, and political factors (IPCS, 2004). It could be reasoned by analogy with the concepts of ADI and TDI, that "acceptable" risk level refers in principle to chemical substances deliberately added to food (e.g. food additives, pesticides) and "tolerable" risk level to chemical contaminants or impurities. However, no clear distinctive definitions were found. Although the choice of a cut-off point is a risk management decision, the SciCom wishes to take the opportunity to highlight this issue as the tolerable risk level determines the "tolerable" intake of a carcinogen and as such the choice of an appropriate action limit.

Different institutions and countries may make different risk management decisions based on different perceptions of the risk that is deemed to be acceptable to society. The ADI and TDI, which usually incorporate a composite UF of 100 when based on animal studies, have been accepted by international institutions and countries as HBGV (WHO, 2009).

According to low-dose linear extrapolation, the default MOE_{UF} of 10 000 set by the EFSA for genotoxic carcinogens and relative to the dose associated with a 10% cancer response ($BMDL_{10}$), equates to lifetime cancer risks of 10^{-5} (i.e. a risk for cancer in 1 per 100 000 exposed). Likewise, MOE_{UF} of 100, 100 000 and 1 000 000 equate to lifetime cancer risks of 10^{-3}, 10^{-6} and 10^{-7}. Although there is no European legislation setting the 'tolerable' risk level for carcinogens, cancer risk levels have been set and used in different contexts. Based on these experiences, cancer risk cut-off points used for lifetime exposure of the general population are generally in the range of 10^{-5} to 10^{-6} (ECHA, 2012).

4.2.4. Uncertainties

Sensitive populations

The intraspecies variability UF takes into account the potential variability of the response in the human population. This variability may be the result of differences in genetic makeup, age, sex, lifestyle or health status. As a result, this factor accounts for general differences in response between the average person and a sensitive person in the population. In absence of data demonstrating a particular sensitivity of children, the default UF of 10 accounting for intraspecies variability should be sufficient. If however, data show that children are more susceptible than adults, an additional UF could be considered case-by-case (Anses, 2017).

Very young infants (< 16 weeks) are considered to be a particularly sensitive subgroup because their metabolic capacities are not yet fully developed. Most differences between infants and adults are of a quantitative nature, i.e. the effects may occur at lower or higher doses than in adults. It is often assumed

that the young infant is generally more sensitive than the adult, but this may not always be true. Current understanding of the toxicodynamic variability in infants is nevertheless insufficient to make general quantitative and qualitative predictions of adverse effects in infants or to identify appropriate additional toxicodynamic default UFs. Additional considerations on a case-by-case basis are needed to decide whether there is a health concern (EFSA, 2017b).

This consideration related to sensitive population groups applies however, to all action limits whether derived from a HBGV or based on the MOE approach.

Dose-response & Toxic potency

A MOE-derived EAC is based on a 'low concern' intake calculated from the ratio of a dose-response RP (preferentially the BMDL) to the MOE_{UF} (being the product of UF) (eq. 4). It is however, important to be aware that similar MOE-based EACs for different chemicals do not necessarily represent the same magnitude of risk because of the different uncertainties in the potency data and because of possible differences in the shape of the dose-response curve.

When the RP is a BMDL, the modelled BMDL reflects the shape of the dose–response curve. Nevertheless, application of a different statistical methodology for establishing a BMDL, might result in different risk-based thresholds (e.g. 3-MCPD; EFSA, 2018d).
Moreover, and as already addressed in 4.1.4, interpretation of the MOE based on a RP in experimental animals implies confidence that the MOE_{UF} is adequately protective for humans (and the assumption of a linear relationship below the RP). It has generally been accepted that MOEs above 10 000 for genotoxic carcinogens indicate exposure levels of low concern, but a robust scientific rationale for this is lacking. This issue has been addressed by Boobis *et al.* (2013a), who reviewed evidence from large-scale animal studies on genotoxic carcinogens at low doses and gathered information on the factors influencing extrapolation from animal studies to effects at low exposures in humans. They also compared risk estimates based on animal data and the MOE approach with estimates of excess cancer risk in humans from epidemiological studies for both known human carcinogens and for chemicals with no clear evidence of carcinogenicity in humans. The different lines of evidence revealed considerable uncertainty regarding the relationship between the BMD in experimental animals and levels causing increased cancer incidences in either animals or humans. Very little direct information was available on the dose–response relationship at human relevant exposures. Hence, a clearer understanding is needed of mode or mechanism of action and the quantitative implications of this for the dose–response relationship and interpretation of the MOE.

For the sake of completeness, it should be mentioned that uncertainties related to potency data and the shape of the dose-response curve, are also relevant for action limits set for threshold substances and determined by means of a HBGV.

Consumption data

Other aspects are the variability and uncertainties in consumption data, which are country-specific and depend on consumption patterns and methodology used (Barlow *et al.*, 2010). This variability and these uncertainties in consumption data are generic to all EACs and action limits, not only to the ones derived by means of the MOE approach.

Different consumption scenarios can result in a broad range of EACs or action limits for a substance-food combination. Whilst this makes it difficult to generalize about the risks to health related to the action limits derived, such different scenarios have the potential to be informative for decisions and prioritisation regarding risk management actions (e.g. withdrawal from the market, recall, investigation, etc.).

Although the definition of 'action limit' implies the maximum concentration of the substance in the food at large consumption of the food (i.e. the 97.5 percentile of consumption) (FASFC, 2019), it is recommended that different exposure scenarios are elaborated, e.g. for the whole population and for specific groups of the population, depending on the substance considered and its distribution in the diet. The choice of exposure scenarios from the range of estimates provided is a decision to be made by the risk manager, but these should be provided by the risk assessor with a description of the relevant inherent uncertainties related to the different estimates (EFSA, 2005).

Less-than-lifetime risk

At present, an action limit is defined based on the chronic risk (see eq. 1) (FASFC, 2019). However, when the legislative maximum limit or the MRL is exceeded, mostly acute risk assessment is performed to determine the extent of measures to be taken (e.g. a recall of the food). Therefore, a short reflection on assessing the acute risk of genotoxic carcinogens is made.

Carcinogenicity is an endpoint that is normally observed and studied only in long-term animal experiments with the aim of establishing a RP that can be used for deriving the MOE or the VSD. In other words, such an MOE or VSD is based on a lifetime daily exposure scenario. Published data however, suggest that short-term or single exposure can also give rise to tumour formation in animal experiments (Bos *et al.*, 2004; Bos & van Raaij, 2002).

In the 1980s, statistical models were developed to simulate and compare the risks of chronic versus short-term exposures to carcinogens. These models suggest some variability in excess cancer risk when comparing long versus short durations of exposure with the same cumulative dose. This variability was quantified, and the concept of a dose-rate correction factor or DRCF was developed to correct (or lower) the acceptable exposure to account for this variability. The DRCF is the factor by which the tumour incidence caused by a specific dose of a chemical carcinogen at long-term low-dose rates is to be multiplied to derive the tumour incidence at short-term high-dose rates. It is suggested that a DRCF in the range of 1 (i.e. no adjustment needed) to 7-fold should be considered for cancer risk assessments involving less-than-lifetime and/or intermittent exposures, but there is currently no agreed-upon guidance for the magnitude of the DRCF and under which conditions it should be applied (Felter *et al.*, 2011; Bos & van Raaij, 2002; Verhagen *et al.*, 1994).

Bos *et al.* (2004) proposed a categorical decision tree based on the "standard" VSD for the $1{:}10^6$ additional carcinogenic risk after lifetime exposure, assuming a linear relationship between tumour incidence and cumulative dose. For reasons of simplicity a human lifetime was set at 25 000 days (corresponding to 68.5 years). In the decision tree, a distinction is made between specific situations where the exposure can be clearly limited to no more than 1 day (e.g. in case of chemical release following an accident), and other situations where exposure may last for a few days, by default set to 10 days (e.g. in food contamination). Linear extrapolation of a VSD to a 1- or 10-day exposure resulted in daily dose levels of 25 000 x VSD or 2 500 x VSD, respectively, at which exposures cancer risk is considered as acceptable. If sensitive subpopulations can be identified, an additional factor of 10 is applied resulting in 10-fold lower daily doses (i.e. 2 500 x VSD and 250 x VSD respectively). Up to these dose levels, the additional lifetime cancer risk is considered to be negligible because they are set for susceptible subpopulations. Application of the proposed decision tree on MOE-based EACs for the determination of action limits for genotoxic carcinogens can be taken into consideration, given that a VSD derived by linear extrapolation from a RP to an estimated human exposure level corresponds to dividing the RP by the MOE_{UF} (4.1.4). Although it allows a pragmatic assessment of the carcinogenic risk following short-term exposure to genotoxic carcinogens, further validation with model-substances is required.

There are a variety of studies or methodologies available to address less-than-lifetime exposures (Felter *et al.*, 2011). However, a common framework for evaluating the risk from less-than-lifetime exposures (including short-term and/or intermittent exposures) does not exist, which could result in inconsistencies in risk assessment practice.

5. Conclusions

Since substances that are known to be both genotoxic and carcinogenic are never approved for deliberate addition to foods, or for use earlier in the food chain if their residues that are both genotoxic and carcinogenic remain in final food, the present opinion only addresses the applicability of the MOE approach for deriving an action limit for genotoxic carcinogens unintentionally present in food (i.e. contaminants, impurities).

The MOE approach allows establishing a relation between a dose and an effect (for substances with a threshold) or between a dose and a probability of effect (substances without a threshold) for substances without an HBGV. Based on this principle and the field of application of the MOE approach in scientific literature, the SciCom is of the opinion that from a scientific point of view, the MOE approach can be applied to derive estimated acceptable concentrations (EACs) and action limits for genotoxic (non-threshold) as well as for non-genotoxic (threshold) carcinogens.

Determination of action limits from an EAC based on the MOE approach should, however, be viewed in the right framework. It should be recognized that respective EACs imply an upper bound of risk related to an exposure of low concern for public health and cannot be considered as safety limits. EACs based on the MOE approach are derived on a case-by-case basis taking into account uncertainties associated with the underlying toxicological data (and expressed by the MOE_{UF}). Because a genotoxic carcinogens might pose a risk at any exposure, ideally the action limit for a carcinogenic contaminant or impurity should be set as low as possible (i.e. lower than the EAC).

For the Scientific Committee,
Chairman,

Prof. Dr. E. Thiry (Sgd.)
Brussels, 16/08/2019

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Presentation of the Scientific Committee established at the FASFC

The Scientific Committee is an advisory body established at the Belgian Federal Agency for the Safety of the Food Chain (FASFC) that provides **independent scientific opinions** on risk assessment and risk management in the food chain, and this at the request of the Chief Executive Officer of the FASFC, the Minister competent for food safety or at its own initiative. The Scientific Committee is administratively and scientifically supported by the Staff direction for Risk Assessment of the Agency.

The Scientific Committee consists of 22 members who are appointed by royal decree on the basis of their scientific expertise in areas related to the safety of the food chain. When preparing an opinion, the Scientific Committee can call on external experts who are not a member of the Scientific Committee. Similar to the members of the Scientific Committee, they must be able to work independently and impartially. To ensure the independence of the opinions, potential conflicts of interest are managed transparently.

The opinions are based on a scientific assessment of the question. They express the view of the Scientific Committee which is taken in consensus on the basis of a risk assessment and the existing knowledge on the subject.

The opinions of the Scientific Committee may contain **recommendations** for food chain control policy or for the stakeholders. The follow-up of these recommendations for control policy is the responsibility of the risk managers.

Questions on an opinion can be directed to the secretariat of the Scientific Committee:
Secretariat.SciCom@afsca.be.

Members of the Scientific Committee

The Scientific Committee is composed of the following members:

S. Betrand *, M. Buntinx, A. Clinquart, P. Delahaut, B. De Meulenaer, N. De Regge, S. De Saeger, J. Dewulf, L. De Zutter, M. Eeckhout, A. Geeraerd, L. Herman, P. Hoet, J. Mahillon, C. Saegerman, M.-L. Scippo, P. Spanoghe, N. Speybroeck, E. Thiry, T. van den Berg, F. Verheggen, P. Wattiau **

* member until March 2018
** member until June 2018

Conflict of interest

No conflicts of interest were notified.

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Composition of the workgroup

The workgroup was composed of:

Members of the Scientific Committee:	P. Hoet (reporter), B. De Meulenaer, S. De Saeger, M.-L. Scippo
External experts:	C. Matthys (UZLeuven), L. Pussemier, A. Rajkovic (UGent), C. Vleminckx (Sciensano)
File manager:	W. Claeys

The activities of the workgroup were attended by the following members of the administration (as observers): E. Moons and V. Vromman (FASFC, DG Control Policy)

Legal framework

Law of 4 February 2000 on the creation of the Federal Agency for the Safety of the Food Chain, in particular article 8;
The Royal Decree of 19 May 2000, on the composition and operating procedures of the Scientific Committee, as established at the Federal Agency for the Safety of the Food Chain;
The Internal Rules as mentioned in Article 3 of the Royal Decree of 19 May 2000, on the composition and operating procedures of the Scientific Committee, as established at the Federal Agency for the Safety of the Food Chain, approved by the Minister on 8 June 2017.

Disclaimer

The Scientific Committee at all times reserves the right to modify the opinion by mutual consent, should new information and data become available after the publication of this version.

Appendix 1. Abbreviations & Definitions

acceptable risk	risk management term; the acceptability of the risk depends on scientific data, social, economic, and political factors, and the perceived benefits arising from exposure to an agent (IPCS, 2004)
action limit	value established by DG Control Policy of the FASFC and validated by the SciCom of the FASFC when no official standard or maximum limit is available, and that - if exceeded - calls for an action (FASFC, 2019)
ADI	acceptable daily intake; an estimate of the amount of a substance in food or drinking water (usually expressed as mg/kg body weight) that can be consumed over a lifetime without presenting an appreciable risk to health. It applies to chemical substances such as food additives, pesticide residues and veterinary drugs (IPCS, 2004; EFSA Glossary [6])
adverse effect	a change in the health, growth, behaviour or development of an organism that impairs its ability to develop or survive (EFSA Glossary [6])
ALARA	as low as reasonable achievable (EC DG Health & Consumer Protection, 2009)
BMD	benchmark dose; dose producing a measurable effect corresponding to a response level compared to a control group. The BMD_{01} or the BMD_{10} correspond to the minimum dose of a substance that produces a clear, low level health risk, in the range of a 1 or 10% change respectively in a specific toxic effect such as cancer induction relatively to the control (EFSA, 2005; EFSA Glossary [6])
BMDL	benchmark dose 95% lower confidence limit (EFSA, 2005)
BMR	benchmark response; low but measurable response at BMD, typically chosen at a 5 or 10% incidence above the control (EFSA, 2005)
carcinogen	chemical substance or a mixture of chemical substances that induces cancer or increases its incidence (US EPA, 2005)
carcinogenicity	cancer-causing property of a substance when an animal or human is exposed to it (EFSA Glossary [6])
CCα	In the case of unauthorized pharmacologically active substances, CCα corresponds to the lowest residue concentration that can reasonably be achieved and unequivocally be determined by official control laboratories (EFSA, 2018a), corresponding to the decision limit at and above which it can be concluded with an error probability of α that a sample is non-compliant (Commission Decision 2002/657/EC)[7]
DNA	deoxyribonucleic acid
DRCF	dose-rate correction factor; the factor by which the tumour incidence caused by a specific dose of a chemical carcinogen at long-term low-dose rates is to be multiplied to derive the tumour incidence at short-term high-dose rates (Bos *et al.*, 2004)
EAC	estimated acceptable concentration; a risk-based concentration limit that corresponds to the concentration of a substance a food may contain without the exposure to the substance through the food posing an appreciable risk or a concern for public health. The EAC can serve as a basis for the risk manager to establish an action limit.
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
FASFC	Belgian Federal Agency for the Safety of the Food Chain
genotoxicity	refers to the capability of a substance of damaging the DNA in cells (see also 'mutagenicity') (EFSA Glossary [6])

[6] https://www.efsa.europa.eu/en/glossary-taxonomy-terms, consulted in June 2019

[7] Commission Decision of 12 August 2002 implementing Council Directive 96/23/EC concerning the performance of analytical methods and the interpretation of results

HBGV	health-based guidance value; guidance on safe intake of substances that takes into account current toxicity data, uncertainties in these data, and the likely duration of consumption (EFSA Glossary [6])
LOAEL	lowest observed adverse effect level; lowest level of a substance that has been observed to cause harm in an exposed population (EFSA Glossary [6])
MoA	mode of action; specific sequence of events explaining how a substance causes a toxic effect (EFSA Glossary [6])
MOE approach	approach used in risk assessment to explore safety concerns arising from the presence of a potentially toxic substance in food or animal feed, based on a comparison between the MOE and the "theoretical" MOE_{UF}
MOE	margin of exposure; the ratio of a defined point on the dose-response curve for the critical effect, preferentially the $BMDL_{10}$, to the theoretical, predicted or estimated exposure dose or concentration (EFSA, 2005)
MOE_{UF}	"theoretical" MOE; product of uncertainty factors addressing the differences between experimental data and the human situation, the nature of the carcinogenic process and the type of RP selected to which the MOE (calculated) is compared in order to evaluate if exposure is of concern for public health (based on EFSA, 2005)
MON	moniliformin (i.e. a mycotoxin)
MRL	maximum residue limit; maximum amount of a pesticide residue allowed in foods or animal feeds, expressed as mg/kg (EFSA Glossary [6])
mutagenicity	The capacity to cause permanent, typically negative, changes to an organism and any offspring by altering the structure of its DNA (EFSA Glossary [6]). These changes may involve a single gene or gene segment, a block of genes or chromosomes. The genetic change is referred to as a mutation and the agent causing the change as a mutagen. Genotoxicity is similar to mutagenicity except that genotoxic effects are not necessarily always associated with mutations. All mutagens are genotoxic, however, not all genotoxic substances are mutagenic.
NOAEL	no observed adverse effect level; the highest concentration or amount of a substance at which no detectable adverse effects occur in an exposed population (EFSA Glossary [6])
RACE	'Rapid Assessment of Contaminant Exposure'; web application developed for rapid characterization of the acute or the chronic risk of substances in (categories of) food in the context of RASFF notifications (EFSA, 2019)
RASFF	Rapid Alert System for Food and Feed; allowing European Member States and the European Commission to exchange information rapidly and to coordinate their responses to health threats caused by food or feed (https://ec.europa.eu/food/safety/rasff_en)
RP	reference point or reference dose (equivalent to the term 'Point of Departure' or PoD, used amongst other by the US EPA (Environmental Protection Agency)); a defined point on the dose-response curve for the adverse effect
RPA	reference point for action; may be established for non-allowed pharmacologically active substances when it is deemed necessary to ensure the functioning of controls for food of animal origin (Regulation (EC) No 470/2009[8]). The RPA is based on the lowest residue concentration that can unequivocally be determined in food by official control laboratories (EFSA, 2018a).

[8] Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009 laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin, repealing Council Regulation (EEC) No 2377/90 and amending Directive 2001/82/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council.

SciCom	Scientific Committee of the FASFC
SCOEL	European Commission's Scientific Committee on Occupational Exposure Limits
T25	chronic dose (mg/kg bw per day) causing 25% of the animal tumours at a specific tissue site, after specific correction of the spontaneous incidence within the standard life time of that species (Dybing *et al.*, 2008)
TDI	tolerable daily intake; estimate of the amount of a substance in food or drinking water (usually expressed as mg/kg body weight) which is not added deliberately (e.g. contaminants) and which can be consumed over a lifetime without presenting an appreciable risk to health (EFSA Glossary [6])
Toxicodynamics	the process of interaction of chemical substances with target sites and the subsequent reactions leading to adverse effects (EFSA Glossary [6])
Toxicokinetics	the process of the uptake of potentially toxic substances by the body, the biotransformation they undergo, the distribution of the substances and their metabolites in the tissues, and their elimination from the body (EFSA Glossary [6]). Both the amounts and the concentrations of the substances and their metabolites are studied. The term has essentially the same meaning as pharmacokinetics, but the latter term should be restricted to the study of pharmaceutical substances
TSV	toxicological screening value; value based on genotoxic potential, pharmacological activity, as well as other effects of the substance and used in the context of establishing RPAs for non-allowed pharmacologically active substances (EFSA, 2018a)
TTC	Threshold of Toxicological Concern; screening tool that provides conservative exposure limits in the absence of sufficient chemical-specific toxicological data. It is a science-based approach for prioritising chemicals with low-level exposures that require more data over those that can be presumed to present no appreciable human health risk (EFSA, 2016; EFSA Glossary [6]).
UF	uncertainty factor; used to address the differences between the experimental data and the human situation, considering uncertainties in the extrapolation procedure
US EPA	Environmental Protection Agency of the U.S.
VSD	virtually safe dose; may be determined for those carcinogens not assumed to have a threshold. Virtually safe doses are calculated to represent the level of exposure to such carcinogenic agents at which an excess of cancers greater than that level accepted by risk managers (and society) is not expected (Boobis *et al.*, 2013b; Bos *et al.*, 2004).