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Directorate-General for Health & Food Safety

Genotoxic compounds in EU food safety policy

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General principles for feed and food safety legislation in the EU

General Food Law (Regulation (EC) 178/2002)

- * a **high level of protection of human health and animal health** has to be pursued
- * **free movement** within the European Union of feed and food compliant with EU legislation
- * **international standards** to be taken into account.
- * **feed and food placed on the market shall be safe**

General principles for feed and food safety legislation in the EU

- In order to achieve the general objective of a high level of protection of human health and animal health, **EU feed and food legislation shall be based on risk analysis** (process consisting of three interconnected components: risk assessment-risk management-risk communication)
- Risk assessment shall be based on the **available scientific evidence** and undertaken in an **independent, objective and transparent manner** → **risk assessment performed by EFSA**
- **Risk management shall take into account the results of risk assessment, other factors legitimate** to the matter under consideration and the precautionary principle where appropriate



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Assessment/prioritisation tools for genotoxic compounds

Threshold of toxicological concern (TTC)

Increasing numbers of substances present at low and very low concentrations in food and feed are now detectable due to improved analytical methods.

For many such substances there are little or no toxicological data available.

There is an increased need to assess the potential health significance of these previously undetectable trace substances but it is not always possible to generate toxicological data on every single substance found in the diet.

Assessment/prioritisation tools for genotoxic compounds

Threshold of toxicological concern (TTC)

The approach can be used when

- the chemical structure of the substance is known,
- limited chemical-specific toxicity data are available, and
- the exposure can be estimated.

Assessment/prioritisation tools for genotoxic compounds

Threshold of toxicological concern (TTC)

The TTC approach is not applicable for substances

- for which EU food/feed legislation requires the submission of toxicity data, or
- when sufficient data are available for a risk assessment or if the substance under consideration falls into one of the exclusion categories.



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Assessment/prioritisation tools for genotoxic compounds

Threshold of toxicological concern (TTC)

The TTC approach has been excluded for a number of categories of substances:

- high potency carcinogens (i.e. aflatoxin-like, azoxy- or N-nitroso-compounds),
- inorganic substances, metals and organometallics,
- proteins,
- steroids,
- substances that are known or predicted to bioaccumulate, nanomaterials,
- radioactive substances, and
- mixtures of substances containing both known and unknown chemical structures.

Assessment/prioritisation tools for genotoxic compounds

Threshold of toxicological concern (TTC)

For substances that have the potential to be DNA-reactive mutagens and/or carcinogens based on the weight of evidence, **the relevant TTC value is 0.0025 µg/kg body weight (bw) per day**

Assessment/prioritisation tools for genotoxic compounds

Margin of Exposure (MOE)

The margin of exposure (MOE) is a tool used by risk assessors to consider possible safety concerns arising from the presence in food and feed of chemical substances when they deem it inappropriate or unfeasible to establish a health-based guidance value (HBGV; a 'safety threshold ') such as an Acceptable Daily Intake (ADI) or a Tolerable Daily Intake (TDI).

Assessment/prioritisation tools for genotoxic compounds

Margin of Exposure (MOE)

- The two main situations in which this occurs are:
 - when assessing substances that are neither genotoxic nor carcinogenic but for which uncertainty about their effects, e.g. due to insufficient toxicological data, does not allow for establishing a HBGV;
 - when assessing substances that are both genotoxic and carcinogenic, in which case no HBGV can be established as any level of exposure could theoretically lead to cancer.

Assessment/prioritisation tools for genotoxic compounds

Margin of Exposure (MOE)

For genotoxic carcinogens, the use of the BMDL10 (benchmark dose lower confidence limit 10%) is recommended to obtain the MOE. In general, an MOE of 10,000 or higher, if it is based on the BMDL10 from an animal study, would be of low concern from a public health point of view and **might be considered as a low priority for risk management actions.**

Such a judgment is ultimately a matter for the risk managers.

An MOE of that magnitude should not preclude the application of risk management measures to reduce human exposure.

Risk management approach to genotoxic compounds

Difference in approach between

- substances and their residues requiring authorisation before use in or on food « regulated substances »
- contaminants

Regulated products

Substance to be authorised is genotoxic → no « safe dose » can be established → no authorisation –no use in food

Substance to be authorised is not genotoxic **but the impurities might be genotoxic carcinogen** → for these impurities the MOE approach can be used ([EFSA statement](#))

In general, a margin of exposure of 10,000 or higher, if it is based on the BMDL10 from an animal study, and taking into account overall uncertainties in the interpretation, would be of low concern from a public health point of view;

Regulated products

The magnitude of an MOE **however only indicates a level of concern and does not quantify risk.**

When using the MOE approach for assessing impurities, the derivation of the MOE, its magnitude, and the uncertainties regarding its derivation should be described.

A conclusion on whether the **MOE is of high concern, low concern, or unlikely to be of safety concern** should also be provided.

Contaminants

- **Definition:**
- 'Contaminant' means any substance not intentionally added to food which is present in such food as a result of the production (including operations carried out in crop husbandry, animal husbandry and veterinary medicine), manufacture, processing, preparation, treatment, packing, packaging, transport or holding of such food, or as a result of environmental contamination.

Contaminants

Regulatory framework :

[Council Regulation \(EEC\) No 315/93](#) of 8 February 1993 laying down Community procedures for contaminants in food

(this Regulation does not apply to contaminants which are the subject of more specific Union rules, such as pesticide residues, veterinary drug residues, food contact materials, ...)

- **Further reference to contaminants refers to contaminants within the scope of Regulation (EEC) 315/93**

Contaminants

Contaminants in food can be unavoidably present :

- from their natural presence (plant toxins)
- from toxicogenic fungi (mycotoxins)
- from environmental pollution
- from the unintended consequences of cooking or other manufacturing processes

Risk management approach to contaminants

- Contaminant levels shall be kept as low as can reasonably be achieved by following good practices at all stages of the production chain (the so-called ALARA principle)→ Maximum levels are established following the ALARA principle.
- This principle also applies to genotoxic carcinogens
- From a risk assessment point of view, generally the MOE approach is used for contaminants that are genotoxic carcinogen (Only for *Alternaria* toxins the TTC approach was used)

Experiences and challenges regulating genotoxic carcinogenic contaminants

- aflatoxins:

- before the use of MOE as assessment tool
as low as possible (from an analytical point of view)
- after the use of MOE as assessment tool:

Experiences and challenges regulating genotoxic carcinogenic contaminants aflatoxins

- Opinion of the scientific panel on contaminants in the food chain [CONTAM] related to the potential increase of consumer health risk by a possible increase of the existing maximum levels for aflatoxins in almonds, hazelnuts and pistachios and derived products (March 2007)

The CONTAM Panel concluded that changing the maximum levels for total aflatoxins from 4 to 8 or 10 µg/kg in almonds, hazelnuts and pistachios would have minor effects on the estimates of dietary exposure, cancer risk and the calculated MOEs

Experiences and challenges regulating genotoxic carcinogenic contaminants

- aflatoxins

Effect on public health of a possible increase of the maximum level for 'aflatoxin total' from 4 to 10 µg/kg in peanuts and processed products thereof, intended for direct human consumption or use as an ingredient in foodstuffs (February 2018): *The calculated cancer risks indicate that an increase of the ML would further increase the risk by a factor of 1.6–1.8.*

Experiences and challenges regulating genotoxic carcinogenic contaminants

- aflatoxins

Risk assessment of aflatoxins in food (March 2020)

MOE values for AFB1 exposure ranged from 5,000 to 29 and for AFM1 from 100,000 to 508.

The calculated MOEs are below 10,000 for AFB1 and also for AFM1 where some surveys, particularly for the younger age groups, have an MOE below 10,000. This raises a health concern

→ Challenge for risk manager

Experiences and challenges regulating genotoxic carcinogenic contaminants

- polycyclic aromatic hydrocarbons

The resulting MOEs for average consumers were 17,900 for benzo[a]pyrene, 17,500 for PAH4. For high level consumers, the respective MOEs were 10,800, 9,500, 9,900 and 9,600. These MOEs indicate a low concern for consumer health at the average estimated dietary exposures. However, for high level consumers the MOEs are close to or less than 10,000, which as proposed by the EFSA Scientific Committee indicates a potential concern for consumer health and a

Experiences and challenges regulating genotoxic carcinogenic contaminants

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- Challenge for risk manager

Experiences and challenges regulating genotoxic carcinogenic contaminants - acrylamide

Comparison of the data on human exposure levels to AA across surveys and age groups reported above to this BMDL10 of 0.17 mg/kg b.w. per day, reveals MOE values that range from 425 (minimum LB) to 89 (maximum UB) for the mean exposure estimates, and from 283 (minimum LB) to 50 (maximum UB)

Although the epidemiological associations have not demonstrated AA to be a human carcinogen, the margins of exposure (MOEs) indicate a concern for neoplastic effects based on animal evidence.

- Challenge for risk manager



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Challenges

When regulating contaminants,, following other legitimate factors among otherhave to be taken into account

- Feasibility/achievability by applying good practices (**challenges** *regional differences in the EU, impact climate change*)
- Balance risks of contaminants – benefits of consumption of certain foods (health risk – health benefit considerations)



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FINAL CONSIDERATION

How can risk assessment for genotoxic carcinogens improve/evolve to provide more guidance for the risk manager



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**Thank you for
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attention !**