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**SPECIAL ISSUE**

# Risk assessment of contaminants in food and feed

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## ABSTRACT

The EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) carries out risk assessment on contaminants in food and feed. The presence of hazardous chemical contaminants or undesirable substances in food and feed is often unavoidable as these substances may occur ubiquitously or are of natural origin. Therefore, human and animal exposure to such substances is also unavoidable. The task of the CONTAM Panel is to assess whether or not exposure to a chemical contaminant in food is likely to be associated with adverse health effects in the European population. Similarly, the Panel assesses if the exposure to a contaminant in feed is likely to be associated with adverse health effects in farm animals, fish and pets in Europe, or to represent a risk to the consumer of foods of animal origin. In contrast to EFSA Panels dealing with regulated substances where *inter alia* applications are taken into account, the CONTAM Panel relies on scientific information that is in the public domain. EFSA often launches calls for data on occurrence of contaminants in food and feedstuffs where Member States and other interested stakeholders are invited to submit data. Whenever possible and required the CONTAM Panel establishes for a substance a health-based guidance value such as tolerable daily intake. For substances that are both genotoxic and carcinogenic, or for which the data are inadequate to establish a health-based guidance value, the margin of exposure approach is used. Recently the CONTAM Panel also used the threshold of toxicological concern approach. In addition, the CONTAM Panel considers inherent uncertainties in relation to objectives, exposure and hazard characterisation in its risk assessments. During 2003-2012, the CONTAM Panel published 107 scientific outputs (55 on food, 43 on feed, 9 on food and feed).



## KEY WORDS

CONTAM Panel, risk assessment, contaminants, human health, animal health

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## INTRODUCTION

The mandate of the EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) is to deliver scientific opinions on "contaminants in food and feed, associated areas and undesirable substances such as natural toxicants, mycotoxins and residues of non-authorised substances not covered by another Panel". The European Union (EU) Food Law (Regulation (EC) No 178/2002[3]) aims not only to ensure a high level of protection of human health but also the protection of animal health. Within this context the CONTAM Panel, over the nine years since its inception, has assessed human and animal health risks related to the presence of persistent organic pollutants, natural toxins and plant toxicants, metals and metalloids, reaction products from thermal food processing, cross-contamination of feed for non-target animals with chemicals authorised for use such as feed additives, or non-authorised substances such as hormones, and complex mixtures such as mineral hydrocarbons in food and/or feed. During this period the CONTAM Panel has published 107 scientific outputs of which 55 address contaminants in food, 43 address contaminants in feed and 9 comprise a combined assessment of contaminants in food and feed. The division of the scientific outputs according to the different areas is presented in Figure 1. The majority of the requests were received from the European Commission (EC) (95 %) a smaller amount of requests came from Member States (1 %) and the European Parliament (1 %). In addition the CONTAM Panel carried out three self tasking activities during this period.

The scientific output of the CONTAM Panel has helped risk managers, in most of the cases the EC but also the Member States (MSs), to decide on the need for setting of maximum levels of contaminants in food and feed and other revisions of the legislation or other possible follow-up measures in relation to the presence of contaminants in food and feed.

This paper aims to provide an overview of the working principles used by the CONTAM Panel and gives an outlook for future perspectives of risk assessments of contaminants in food and feed.

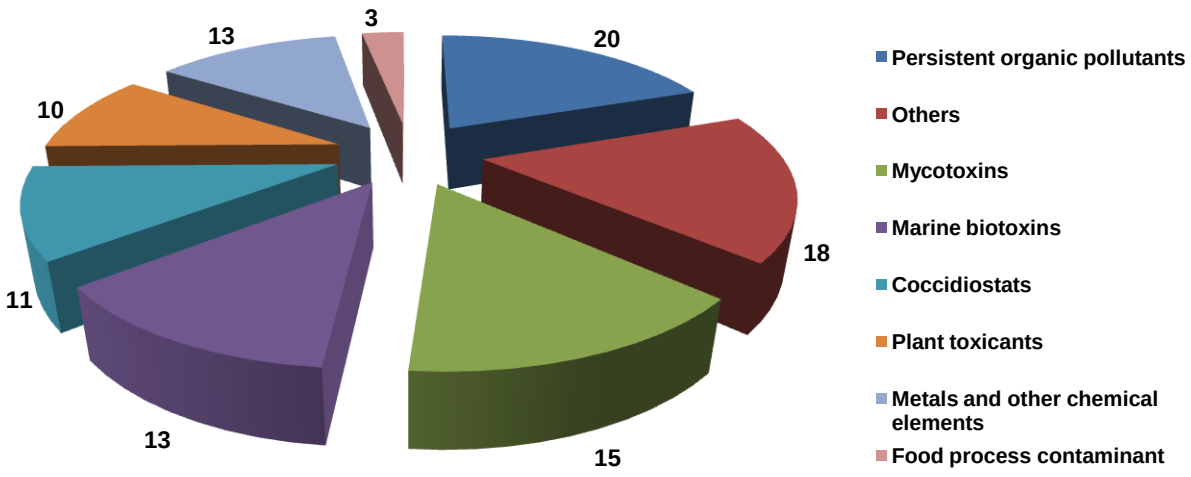


**Figure 1:** Overview of risk assessments provided by the CONTAM Panel between 2003 and 2012.

[3] Regulation (EC) No 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. OJ L 31, 1.2.2002, p. 1–24.

## 1. DATA SOURCES AND DATA MINING IN RISK ASSESSMENT – ASSUMPTIONS AND UNCERTAINTY

In contrast to many other Panels, the CONTAM Panel does not base its risk assessments on an application presented to EFSA, e.g. in the framework of a marketing authorisation procedure, but relies on scientific information that is in the public domain. That holds for data on the toxicological effects of the substances under investigation, for occurrence data in the relevant food and/or feed matrices and for food or feed consumption data. These data are usually collected from publicly available sources such as peer-reviewed papers published in scientific journals, official national reports from EU MSs or risk assessment evaluations from international organisations such as the World Health Organization. To complement these open data sources, the Data Collection and Monitoring (DCM) Unit of EFSA regularly launches a call for data on occurrence of the substance(s) of interest and collects food consumption data.

In response to these calls, mainly competent authorities of European countries but also other stakeholders submit occurrence data in a specific format as requested by EFSA. Depending on the substance(s) for which information is requested, the number of countries providing data and the total number of submitted results may differ considerably. While for some contaminants (e.g. some marine biotoxins and mycotoxins) only a small number of results was submitted, for other substances, such as cadmium, the number of submitted results exceeded 100 000 (EFSA, 2004a; EFSA Panel on Contaminants in the Food Chain (CONTAM), 2009a, 2010a, 2012a). It should be noted that normally occurrence data submitted to EFSA do not stem from samples that were intended for risk assessment purposes, but originate from samples that were analysed within the framework of official food and feed control with the objective to check whether food and feed commodities comply with legal limits. As a consequence, the data submissions often contain a high number of left-censored data, i.e. data below the limit of detection (LOD) or the limit of quantification (LOQ). In addition, the LOD and LOQ of the analytical methods are sometimes adjusted to the legal limits and not to the actual background of the respective contaminants in food and feed. These issues may introduce considerable uncertainty in the occurrence data and the submitted data are therefore thoroughly checked by the DCM Unit to provide all relevant information and as reliable estimate as possible of the distribution of the respective substance(s) in food and feed.

Human exposure is a key element in the risk assessment of contaminants. For this purpose, occurrence levels in food are combined with consumption patterns across European populations to estimate human exposure to the respective contaminants. In addition to the general population, the risk assessments generally also consider the exposure of specific consumer groups, such as infants, children, and people following specific diets (e.g. vegetarians). Information on consumption for all these groups stems from national consumption surveys submitted to EFSA and combined in the Comprehensive European Food Consumption Database. This database includes information from more than 30 national dietary surveys from 22 European countries. In combination with the occurrence data, it forms the basis for the estimation of human exposure to contaminants from food. Depending on the nature of the toxicity of the contaminant of interest, chronic and/or acute exposure assessments are performed, using probabilistic models where possible to provide some insight into the uncertainties around the exposure estimate.

Comparable databases for feed consumption do not exist in Europe. Therefore the assessment of animal exposure is based on the submitted occurrence data and/or the data collected from the literature and from typical European feed regimes for various animal species.

Compared to the assessment of individual substances, additional uncertainties are introduced when the risk assessment concerns mixtures of substances such as polychlorinated biphenyls (PCBs) and flame retardants such as polybrominated diphenylethers (EFSA, 2005a; EFSA Panel on Contaminants in the Food Chain (CONTAM), 2011a,b). Due to their different physical-chemical properties, the different components of these mixtures vary with respect to their behaviour in the environment and their appearance in the food chain. Consequently the composition of the original technical mixture which

was tested in toxicity studies generally does not resemble the composition of the mixture of substances to which humans are exposed via food.

The evaluation of the inherent uncertainties in the assessment of exposure to contaminants is performed following the guidance of the Opinion of the Scientific Committee related to Uncertainties in Dietary Exposure Assessment (EFSA, 2006a). According to this guidance document, uncertainties in assessment objectives, exposure scenario, exposure model, and model input (parameters) are generally considered. In addition, uncertainties in the scientific basis of the hazard characterisation are qualitatively considered. In this way the CONTAM Panel provides an overall assessment of the uncertainties inherent in the risk assessments.

## 2. RISK ASSESSMENT PRINCIPLES

The presence of chemical contaminants or other undesirable substances in food and feed is often unavoidable as these substances may occur ubiquitously (e.g. dioxins and dioxin-like PCBs or heavy metals such as lead and cadmium) or are of natural origin (e.g. inherent plant constituents such as alkaloids, or mycotoxins such as aflatoxins (EFSA, 2004a-d, 2005a, 2006b, 2007a,b, 2008a, 2009a; EFSA Panel on Contaminants in the Food Chain (CONTAM), 2011c)). Therefore, human exposure to such substances is also unavoidable. The risk assessment of chemical contaminants in food relies on the integration of two components: knowledge about the human exposure to these substances via food and other routes, and their potential to cause adverse health effects (i.e. the hazard). The risk is the likelihood of the occurrence of adverse health effects at a given exposure. The task of the CONTAM Panel is to assess whether or not exposure to a chemical contaminant in food is likely to be associated with adverse health effects in the European population or in certain sub-groups. Whenever possible, the CONTAM Panel establishes an exposure level at which there is no appreciable health risk, called a health-based guidance value (HBGV) such as a tolerable daily intake. In the identification and characterisation of the hazard the Panel takes into account all toxicological information available, including studies on humans, experimental animals, cell- and other systems. In the absence of toxicity data from humans, the HBGV is usually based on data from repeated-dose studies on experimental animals, such as chronic toxicity or multigeneration studies in rats and mice. For the establishment of an HBGV, a reference point (RP) needs to be identified, based, if possible, on mathematical modelling of the dose-response relationship. The EFSA Scientific Committee recommended the use of a benchmark dose lower confidence limit (BMDL) as the RP (EFSA, 2009b). The BMDL is an estimate of the lowest dose that is 95 % certain to cause no more than a specified change in response over background. If modeling is not considered appropriate, another RP may be used such as the no-observed-adverse-effect level (NOAEL), which is the highest dose not causing a statistically significant adverse effect compared to the controls. The HBGV is established by dividing the RP by uncertainty factors to account for extrapolation from animals to humans and for variability in human sensitivity. In some cases the CONTAM Panel has been able to model human data and to incorporate information from biomarkers of exposure or of effect in the characterisation of the hazard, e.g. cadmium and lead (EFSA, 2009b,c; EFSA Panel on Contaminants in the Food Chain (CONTAM), 2010b). This allows the use of a body burden approach, where an estimate of systemic exposure (body burden), rather than external dose, is used in the risk characterisation.

As some substances the CONTAM Panel assesses could give rise to acute health effects in relation to short periods of intake (e.g. certain metals, opium alkaloids, some mycotoxins or marine biotoxins), the Panel establishes, if possible, an acute reference dose (ARfD) as the HBGV for such substances (EFSA, 2008b-d, 2009d-h; EFSA Panel on Contaminants in the Food Chain (CONTAM), 2009a, 2011d). This is usually based on short-term toxicity data from experimental animals (e.g. acute toxicity or developmental toxicity), but also based on human data when available (e.g. pharmacological activity of opium alkaloids, outbreaks of food poisoning caused by some marine biotoxins). Conversely, when a substance shows a long biological half-life, tends to accumulate in the human body and exposure over a longer time period therefore matters, the CONTAM Panel usually establishes a tolerable weekly intake as the HBGV (e.g. for cadmium or the mycotoxin ochratoxin A (EFSA, 2006b, 2009a)). If human exposure to the substance from food and other sources is below the

HBGV, the CONTAM Panel usually concludes that such exposure does not pose an appreciable risk to human health.

This "classical" approach for risk assessment needs sufficient knowledge on human exposure (i.e. occurrence data in food and food consumption data), a sufficiently sound toxicological database and the absence of genotoxic potential. This is because the HBGV approach, which assumes a dose threshold for toxicity, is not considered applicable to substances that are genotoxic. In contrast to the situation for substances that are intentionally used for specific purposes in food production (e.g. food additives and plant protection products), for food contaminants there is no manufacturer to provide additional toxicological information. This is a particular challenge for the CONTAM Panel as, unfortunately, the toxicity database on contaminants is often incomplete and limited (e.g. certain marine biotoxins and many mycotoxins).

Many substances that the CONTAM Panel has to assess show genotoxic potential (e.g. aflatoxins, ethyl carbamate, pyrrolizidine alkaloids or polycyclic aromatic hydrocarbons (PAHs) (EFSA, 2004c, 2007a-c, 2008e; EFSA Panel on Contaminants in the Food Chain (CONTAM), 2009a, 2011c)). For substances that cause genotoxicity by a mechanism involving reaction with DNA, it is not possible to identify a dose threshold of effect. Until 2005, the advice given by the risk assessor to the risk manager was to reduce exposure to such substances to a level that is as low as reasonably achievable (known as the ALARA principle). However, it was long recognised that such advice does not provide risk managers with a basis for setting priorities for action, either with regard to the urgency or to the extent of measures that may be necessary. To overcome this, the EFSA Scientific Committee proposed the margin of exposure (MOE) approach[4] (EFSA, 2005b) as a harmonised approach for the risk assessment of substances that are both genotoxic and carcinogenic. The MOE approach takes into account the fact that carcinogens differ in their potency, that is, they differ in their likelihood of inducing a tumor at a given dose over time. Information about potency is mostly derived from laboratory studies on rodents (e.g. acrylamide or furan (EFSA, 2004e, 2005c)), since with few exceptions (e.g. arsenic (EFSA Panel on Contaminants in the Food Chain (CONTAM), 2009b)), human data are rarely available. The MOE approach, similar to the derivation of a HBGV, uses an RP on the dose-response relationship often taken from an animal study, corresponding to a dose that causes a low, but measurable cancer incidence in animals (usually the BMDL for a 10 % extra risk). This RP is then compared with various dietary exposure estimates in humans, taking into account differences in consumption patterns. The CONTAM Panel used this approach in several of its assessments of substances that are both genotoxic and carcinogenic (e.g. ethyl carbamate, pyrrolizidine alkaloids and PAHs (EFSA, 2007c, 2008e; EFSA Panel on Contaminants in the Food Chain (CONTAM), 2011c)). Furthermore, the benchmark dose (BMD) approach can also be applied to human data, which was done by the CONTAM Panel in its assessment of aflatoxin B1 (EFSA, 2007b).

The MOE approach is not confined to substances that are genotoxic and carcinogenic and it can also be applied to cases where the data are insufficient or otherwise considered inappropriate to establish a HBGV. As an example of this, the CONTAM Panel considered it appropriate to calculate MOEs to support the risk characterisation of lead (EFSA Panel on Contaminants in the Food Chain (CONTAM), 2010b). The CONTAM Panel identified developmental neurotoxicity in young children and cardiovascular effects and nephrotoxicity in adults as the critical effects for the risk assessment. The Panel then calculated respective BMDLs for these effects from blood lead levels, which were then extrapolated to external exposure levels for comparison to estimated dietary exposure in various human population subgroups.

There are, however, situations in which the available data on a substance occurring in food do not allow either the establishment of a HBGV or calculation of a BMDL for use as an RP in the MOE approach. This was the case when the CONTAM Panel had to assess the *Alternaria* toxins (EFSA

[4] The MOE is the ratio between a defined point on the dose-response curve for the adverse effect and the human intake, and therefore it makes no implicit assumptions about a "safe" intake.

Panel on Contaminants in the Food Chain (CONTAM), 2011e). In this case, the CONTAM Panel explored the use of the "threshold of toxicological concern (TTC) approach", which is a screening tool that has been developed in order to assess substances with known structures of unknown toxicity present at very low levels in the diet (EFSA Scientific Committee (SC), 2012). Application of the TTC approach requires only knowledge of the chemical structure of the substance concerned and information on human exposure, for which there is confidence that it is not an underestimate. It utilises generic human exposure threshold values (also called TTC values) that have been established for substances grouped according to their chemical structure and likelihood of toxicity. The human exposure threshold values developed are based on data from extensive toxicological testing in animals. There are a number of different threshold values and these can be used for substances either with or without a structural alert for genotoxicity, respectively. At exposures below the generic human exposure threshold values, the probability of adverse effects on human health is considered to be very low. For *Alternaria* toxins there are few or no relevant toxicity data, but the chemical structure of several of them is known and in addition dietary exposure data exist for some of them. In using the TTC approach, the CONTAM Panel was able to assess the relative level of concern for dietary exposure of humans to these mycotoxins (EFSA Panel on Contaminants in the Food Chain (CONTAM), 2011e).

## 3. ANIMAL RISK ASSESSMENT

A general principle of the EU food safety policy is the integrated "farm to fork approach" which includes the protection of human as well as animal health (Regulation (EC) No 178/2002). Within this context the EC tasked EFSA to provide the scientific bases for the revision of the European Directive 2002/32/EC[5] which regulates undesirable substances in feed. Subsequently, the CONTAM Panel has addressed over the nine years of its existence the risks to animal health due to the presence of many substances, including toxic plant secondary metabolites (EFSA 2008a,f-i, 2009i; EFSA Panel on Contaminants in the Food Chain (CONTAM), 2011c, 2012b), mycotoxins (EFSA, 2004c,d,f, 2005d,e; EFSA Panel on Contaminants in the Food Chain (CONTAM), 2011e,f, 2012a,c), persistent organic pollutants (EFSA, 2005a,f-j, 2006c,d, 2007d,e), toxic metals (EFSA, 2004a,b, 2005k, 2008j) and other substances, e.g. melamine and nitrite in feedstuffs (EFSA, 2009h; EFSA Panel on Contaminants in the Food Chain (CONTAM), 2010c). Moreover, hazards related to feed production technologies (cross-contamination of feed) for non-target animals from coccidiostats authorised in Europe (EFSA, 2007f, 2008k-t) and by-products of biofuel production (EFSA Panel on Contaminants in the Food Chain (CONTAM), 2010d) for farmed animals (ruminants, poultry, pigs and rabbits), fish, and companion animals such as cats, dogs and horses were assessed. Within this mandate, the CONTAM Panel also determined the possible impact on human health from the carry-over of undesirable substances or contaminants into food of animal origin such as meat, milk, eggs and honey.

The assessment of animal health risks associated with the presence of undesirable chemical substances in feed follows the same principles as the human health risk assessment (see Risk assessment principles). However, in the hazard characterisation, species-specific and inter-species differences in animals need to be taken into account. The exposure assessment and risk characterisation are based on the respective animal species and their specific diets. The hazard characterisation aims to identify the most relevant toxicological endpoint for the respective animal species to derive a safe intake level. Most often a NOAEL/lowest-observed-adverse-effect level is identified, at least for major farm animal species, but a BMDL can also be used (EFSA Panel on Contaminants in the Food Chain (CONTAM), 2011f) as an RP. Physiological differences such as the microbiological flora in the forestomach of ruminants and the species-specific rate of absorption and biotransformation have to be taken into account when assessing the toxicokinetics of a chemical substance in target animal species. However, such data are frequently not available and the available information is confined to case reports of intoxications lacking information about the actual dose and time of exposure. The physiological differences referred to above also influence the potential carry-over of toxic substances and/or their

[5] Directive 2002/32/EC of the European Parliament and of the Council of 7 May 2002 on undesirable substances in animal feed. OJ L 140, 30.5.2002, p.10–22.

metabolites into food of animal origin. Therefore, the CONTAM Panel flags such uncertainties when evaluating the effects of contaminants on animal species and, via animal-derived products, in humans.

Exposure estimates for animals take into account the amount of feedstuffs consumed by the respective species, as well as the concentration of the particular contaminant in animal feed. Geographic origin, climatic conditions and plant stress influence the level of many undesirable substances in animal feeds. Analytical data on contaminants in feed are often made available by MSs and/or are taken from the open literature (e.g. *Alternaria* toxins and citrinin in feed (EFSA Panel on Contaminants in the Food Chain (CONTAM), 2011e, 2012a)). In Europe, different husbandry and farming systems for animals exist and consequently the composition of animal diets varies considerably. This constitutes a challenge in risk assessment. In order to address this, the CONTAM Panel has recently developed an exposure assessment approach for animals taking into account common standards in animal nutrition. In practice this means that for individual animal species and production stage (i.e. the age of the animal) a standard consumption pattern per feed category has been defined that is combined with the measured concentrations of the specific contaminant in feedstuffs. Where appropriate, decontamination procedures are taken into account. The CONTAM Panel applied this approach for the first time in the opinion on T-2 and HT-2 toxins in feed (EFSA Panel on Contaminants in the Food Chain (CONTAM), 2011f).

The risk characterisation relates the estimate of animal exposure to the hazard characterisation and concludes on potential animal health risks. However, due to a paucity of data on the shape of the dose-response curve, there is usually considerable uncertainty in the assessment of possible health risks for individual farm animal species, particularly minor species. As a result, animal health risk assessment is still accompanied by a high degree of uncertainty and needs further development.

## CONCLUSIONS AND OUTLOOK

The CONTAM Panel conducts risk assessments on an enormous range of different types of chemicals, adapting its approach depending on the types of data that are available, and the specific question that has been asked. It is anticipated that future work will include instances where previously uninvestigated environmental contaminants have been detected in food or feed. This will require risk assessments to determine whether regulatory action is required. In other instances, the availability of new information will require reassessment of previously reviewed contaminants. The EFSA emerging risks activities are likely to identify topics for future evaluation, including some requiring urgent risk assessments.

The CONTAM Panel will continue to seek ways to improve and refine its human and animal risk assessments. Areas where developments are likely include further integration of animal and human data, greater use of information obtained in mechanistically based *in vitro* assays, linked to mode of action, high content analysis, such as toxicogenomics, quantitative structure-activity relationships and other *in silico* approaches, and their use in read across and category formation. Increasing availability of biomarker data and physiologically based toxicokinetic (PBTK) modelling will support the "margin of body burden" approach. There is likely to be increased use of probabilistic modelling in exposure assessment, including dealing with left-censored data and greater use of harmonised protocols for data collection. Information on mode of action will be used to inform interpretation of dose-response modelling of toxicity data, allowing individual variability to be better addressed. Mathematical approaches will also be extended to other areas, such as the assessment of uncertainty. In instances where it is not possible to provide a quantitative estimate of risk, it might still be possible to provide some indication of relative risk, or to provide better guidance on key research needs. As the range of contaminants broadens even further, it is likely that there will be an increasing workload on EFSA for risk-benefit assessments and for assessments of the effects of combined exposure.

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