7th SKLM Symposium

New Challenges and Developments in Food/Consumer Safety

Program and Abstracts

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DFG Senate Commission on Food Safety (SKLM)

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Preface

Food safety has a long tradition which can be traced back far into the past. The first written records of “food safety or quality” are mentioned in the Code of Hammurabi dating from the 18th century BC. Since then, the legislation and control regarding foodstuffs has continuously evolved, reaching near-modern era standards in the early 19th century AD. Of course, these emerging legislative frameworks led to the development of different institutions, whose role it was and still is to critically assess, implement and monitor the newly-adopted laws.

The history of a DFG commission dealing with food safety goes back to 1949, with the establishment of the so-called „Farbstoffkommission“ (“Commission on colouring agents”). After several successful years and structural changes, the „Fremdstoffkommission“ (“Commission on xenobiotics”) chaired by Konrad Lang was founded in 1961. In 1972 Karl Joachim Netter became the commission’s chair and was succeeded by Gerhard Eisenbrand from 1995 until 2013. Over the years, the activity profile and thereby the name of the SKLM substantially changed. Finally, the commission was named “Senatskommission zur gesundheitlichen Bewertung von Lebensmitteln” (SKLM; Senate Commission on Food Safety) in 2007.

Today, the scientific members of the SKLM are: Pablo Steinberg (chair), Patrick Diel, Gerhard Eisenbrand, Karl-Heinz Engel, Bernd Epe, Volker Heinz, Hans-Ulrich Humpf, Hans-Georg Joost, Dietrich Knorr, Theo de Kok, Doris Marko and Rudi F. Vogel as well as Peter Fürst, Sabine Kulling, Alfonso Lampen, Gerhard Rechkemmer, Richard H. Stadler and Stefan Vieths as permanent guests. Topics regarding food safety are worked out in special working groups, whose role it is to elaborate preliminary outlines or drafts, which are then further discussed and finally adopted in the plenary meetings of the SKLM.

In the light of a growing globalization and intensified international trade, the topic of food safety increasingly requires attention and gains importance. Moreover, the development of new technological

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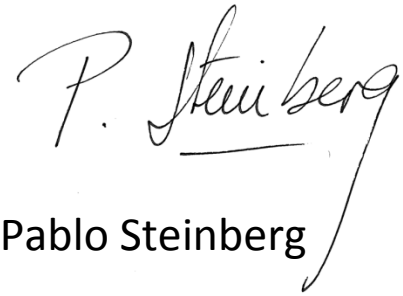
and analytical methods used in food production as well as to monitor the entire food chain add a higher level of complexity, further complicating the risk and quality assessment of foodstuffs. Consequently, the requirements for institutions dealing with food safety increase as well, making an awareness of new challenges and consideration of developments in food and consumer safety mandatory in order to guarantee food/consumer safety.
We have tried to address this issue by organizing the present symposium and by incorporating a wide range of topics divided into three sessions. The first session thereby deals with food/consumer safety in the context of globalization. The next session focuses on novel approaches in risk assessment, while the third and last session, dealing with emerging challenges, tries to proactively identify future issues and developments relevant to risk assessment.

This symposium will hopefully represent an excellent forum to discuss topics of particular relevance with experts in their fields, and we are looking forward to welcome you all in Bonn. Of course, the SKLM is very grateful to the DFG for ongoing support regarding the realization of high-quality scientific symposia.



Pablo Steinberg

Chair of the DFG Senate Commission on Food Safety

Session 1

Session 1	**Introductory session** **Food/consumer safety:** **A global challenge** **Chair:** Eisenbrand, G. (D)
09:00 – 09:30	**Welcome and introduction** *Steinberg, P. - Hannover (D)*
09:30 – 10:10	**Keynote lecture:** **New challenges in the risk assessment of chemicals in food** *Benford, D. - London (UK)*
10:10 – 10:45	**Food safety assessment in the European and global context** *Hensel, A. - Berlin (D)*
10:45 – 11:15	**Coffee break**

Session 2

Session 2	**Novel approaches in risk assessment** **Chair:** Joost, H.G. (D)
11:15 - 11:50	**The application of toxicogenomics in the risk assessment of food constituents** *De Kok, T. - Maastricht (NL)*
11:50 - 12:25	**Large scale *in vitro* molecular measurements of the human cellular response to chemicals from food: Overview and examples** *Sturla, S. - Zürich (CH)*
12:25 - 13:45	**Lunch**
13:45 - 14:20	**Exploring biomarkers for the risk assessment of food constituents** *Eisenbrand, G. - Kaiserslautern (D)*

Session 3

Session 3	**Emerging challenges in risk assessment** **Chair:** Steinberg, P. (D)
14:20 - 14:55	**Risk assessment of genotoxic carcinogens in the low dose range** *Hartwig, A. - Karlsruhe (D)*
14:55 - 15:30	**The use of PBK models in the risk assessment of plant genotoxins** *Rietjens, I. M.C.M.- Wageningen (NL)*
15:30 - 16:00	**Coffee break**
16:00 - 16:35	**Novel developments in the risk assessment of food allergens** *Houben, G.F. - Zeist (NL)*
16:35 - 17:10	**Novel technologies in food processing** *Knorr, D. - Berlin (D)*
17:10 - 17:15	**Concluding remarks** *Steinberg, P. - Hannover (D)*

25th Anniversary of the Permanent Senate Commission on Food Safety (SKLM) of the German Research Foundation (DFG): Introductory remarks

Pablo Steinberg

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The Senate Commission on Food Safety (SKLM) of the Deutsche Forschungsgemeinschaft (DFG; German Research Foundation) provides scientific advice to the Senate of the DFG as well as to parliaments, government and public authorities on various food safety aspects. To do so, the SKLM works independently and includes highly qualified experts from Germany and other European countries with expertise in a range of fields, which are relevant for the risk assessment of food (e.g. toxicology and pharmacology, (food) chemistry, biochemistry and nutrition sciences, human and veterinary medicine, food technology and microbiology as well as immunology).

Topics may be proposed by the SKLM, if they are considered to be of particular importance for consumer health protection, or may result from requests issued by the German Federal Ministries. These topics include for example the safety and nutritional benefit of food ingredients and additives, of novel and functional food, as well as of innovative technologies in food production. The SKLM sets up working groups involving also external scientists with topic-specific expertise to discuss scientific matters and to prepare scientific opinions, which are published on the DFG homepage (http://www.dfg.de/sklm) and in peer-reviewed scientific journals. At present, working groups focus on safety issues regarding food constituents and new food technologies and on the development of new strategies to evaluate genotoxic carcinogens present at human-relevant concentrations in food. In recent years, the SKLM has

critically evaluated thermally induced/process-related contaminants such as acrylamide and acrolein, dietary supplements on the basis of red mould rice or isoflavones, functional food containing phytosteryl esters and phytosterol oxidation products as well as novel food processing technologies such as the use of plasma and ohmic heating. Meanwhile, the assessment of risks and benefits of certain food constituents is also in the focus of the scientific discussion. As a first example, the SKLM has evaluated the benefits and risks of dietary nitrate and nitrite for human health. At the present time, statements on new strategies to evaluate the toxic effects of low doses of genotoxic carcinogens being present in foods and at the working place (together with the Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, the so-called MAK-Commission of the DFG), on the effects of isoflavones on the female breast and on the thyroid gland in humans and on safety issues regarding insects as a novel source of proteins and lipids are in preparation.

At the national level, there is an extensive exchange with the Federal Institute for Risk Assessment (BfR), the Federal Institute for Drugs and Medicinal Devices (BfArM), the Paul-Ehrlich-Institute (PEI) and the Max Rubner-Institute (MRI). Since risk assessment and consumer protection are also dependent on transnational activities, the SKLM is in close contact with international expert scientific committees such as various panels of the European Food Safety Authority (EFSA) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

New challenges in the risk assessment of chemicals in food

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The objective of risk assessment of chemicals in food is to provide the evidence to support protection of consumer health. Some of the key challenges to this objective are financial, related to austerity measures in various areas of the world, or technological, both with respect to innovation in food production and detection of previously unknown chemicals in food. We also need to deal with increasing internet sales and public perceptions that often differ from the expert view.

Financial challenges include reduced capacity for testing of foods at import or on the EU market. We need new rapid and economical testing methods for food chemicals to support risk assessment and food controls. Linked to this is the potential for food fraud or deliberate adulteration of foods as unscrupulous producers try to increase their profit margin. Examples of adulteration over the past decade include Sudan dyes in chilli products, melamine in feed and in milk powder from China, horsemeat in products labelled as beef, mislabeled fish species, almond shell in ground cumin, and olive and myrtle leaves in dried oregano. In some instances these issues are food fraud and not a food safety concern. However if commodities are not intended for the food chain, then it is necessary to consider possible risks. The challenge is to try to predict future adulterants.

Other challenges relate to developing technologies in the food industry – are our current approaches to risk assessment adequate to address engineered nanomaterials released to the environment as contaminants, use of synthetic biology, 3D printing, etc? Commercial sensitivities can mean that information on new processes is not readily available to the risk assessor. Efforts to increase economic

growth in the EU are encouraging innovation. There is also increasing focus on securing the adequacy of the food supply. We need to ensure that these developments do not compromise food safety. Developments in analytical methodology can reveal increasing numbers of chemicals that were previously unknown in food. It is more than 10 years since acrylamide was discovered in cooked food as a product of the Maillard reaction. Maillard reaction products include multiple chemicals that contribute to flavour and colour of cooked food; like acrylamide they could have undesirable toxicological properties but many have not been tested. They are likely to have been present in food for generations, but detection leads to a call for risk assessment. New analytical approaches are also resulting in very large datasets. Furthermore there are moves towards using other sources of information, such as from social media. We need the robust approaches to analyse and interpret such "big data".

Potential emerging risks include the impact of climate change, which could alter distributions of natural toxins contaminating food, such as mycotoxins, marine biotoxins, and new plant species being introduced to the European Union. We have limited toxicological information on many of these toxins. For complex molecules that cannot easily be synthesized, the production of sufficient purified material for traditional toxicological testing is unlikely to be feasible. We need alternative *in vitro* or *in silico* approaches for the risk assessment of multiple process contaminants and toxins.

Many food products are now purchased over the internet, which provides challenges for risk managers. An example is dietary supplements, such as "fat burners" that are popular with individuals wanting to decrease body fat, for sport or slimming aids. 2,4-Dinitrophenol (DNP) marketed as a fat burner has caused the death of several young adults in the UK, and its toxicity is well known. Other supplements marketed as fat burners are poorly characterized, but at best are likely to be ineffective and some could be toxic.

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Some consumers have the perception that natural is healthy and synthetic is bad, leading them to seek out products marketed as natural and to be alarmed by reports of chemicals in food and in our bodies resulting from dietary exposure, even when at very low levels. Risk assessment needs to address these concerns, including possible “low dose” effects and combined effects of mixtures of chemicals.
Finally, with emerging information on multiple chemicals in food in the face of limited resources, we need risk ranking and risk benefit tools to support prioritisation on risks to consumer health in a manner that is risk proportionate without imposing unnecessary burden on food industry (and hence the consumer) or on public funds.

Food safety assessment in the European and global context

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The public agencies that are legally entrusted with safeguarding food safety face similar issues all over the world. Therefore, it is straightforward to take a closer look at solutions found, tested, and implemented elsewhere, in order to learn from each other. A concomitant benefit of such an approach is that it serves as a peer review of applied methods, thus ensuring that a high scientific level is maintained. While agencies that have similar tasks often have to cope with comparable problems, their interests may differ markedly from those of other players in the field, e. g. industry or agencies on other organisational levels, such as national versus regional or local level.

Based on a 1995 FAO / WHO recommendation, scientifically based risk assessment - as performed by BfR - is clearly separated from risk management - i. e. decisions of the executive - in Germany. This mirrors the situation in Europe where risk assessment is carried out by the EFSA. This sharp separation is fully implemented in France, Denmark, and Germany, whereas Austria, Hungary, Italy, Lithuania, Poland, and Slovakia employ related systems. However, all 28 member states feature varying set-ups of their food safety structures. Especially small member states are obviously unable to simply copy the structures utilised by the large ones. The talk addresses these issues by exemplifying different approaches, such as those followed by Greece, the Netherlands, the Czech Republic, and Germany. Population size is only one determining criterion of institutional food safety structure, with the extent of centralisation and historic traditions being no less important.

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The citizens' fundamental right to safe food needs to be safeguarded using (1) administrative acts - such as regulations, control mechanisms, and potentially decisions about product recalls -, (2) penal convictions in case of breaches of law, and (3) civil jurisdiction among businesses, producers, and traders, e. g. concerning questions of liability. Beyond this traditional line, the talk also takes a view at standards that are not set by legislative or governmental authorities, but by professional associations or individual enterprises. Examples are ISO norms, guidelines, or voluntary commitments. This not only requires new ways of communicating such non-conventional basis of risk assessment, but also opens up new possibilities for consumers to actively participate in the process.

The application of toxicogenomics in the risk assessment of food constituents

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Traditionally, toxicology has relied on the use of laboratory animals to evaluate potential health risks associated with environmental exposure or dietary intake of chemical compounds. Also potential toxic effects of natural ingredients of food, food additives and contaminants originating from food production, processing, storage or preparation have been evaluated in this way. Considering that apart from food related exposures also newly developed drugs and industrial chemicals have to be evaluated for toxicity, the total effort put into safety evaluation has become expensive, time-consuming and uses an impressive number of laboratory animals.
During the last decade, several large initiatives in the EU and US have stimulated the development of alternatives to animal testing, based on *in vitro* systems and the application of new genomic techniques, including whole genome gene expression analyses, epigenetic changes, proteomics and metabolomics analyses. As these information-dense approaches are applied to studies in human cells, the outcome can be regarded as more relevant to human biology and also provides information at the molecular level of the toxicological mode of action. Knowledge of these molecular mechanisms is crucial for the understanding of the interactions between the chemical and the biological system and the resulting perturbations of the normal cell physiology, ultimately leading to adverse health outcomes. Molecular 'omics' signatures that have been established for different types of toxic compounds can be used for toxicity prediction and screening of new or existing food ingredients (1).

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Apart from *in vitro* screening for toxicity of individual compounds or combinations of food constituents, toxicogenomics approaches can also be applied in human studies in the context of risk assessment of dietary factors. Gene expression profiles can for instance be evaluated in relation to the intake of food contaminants in order to understand the biological consequences of such exposures. As an example, transcriptome profiles have been established in a large Norwegian cohort, relating gene expression levels to dietary intake of polychlorinated biphenyls and dioxins. The outcome of these studies suggested immunosuppressive effects of maternal exposure to TCDD and PCB at the transcriptomic level in neonates (2). Also the potential health impact of dietary habits can be evaluated using toxicogenomics approaches. Both cross-sectional studies and dietary intervention studies have demonstrated that gene expression changes induced by exposure to N-nitroso compounds, related to high intake of red and processed meat products, are indicative for increased colon cancer risk. These data have been generated both in peripheral lymphocytes and in colonic biopsies indicating that also genomics approaches using blood samples originating from archived samples in biobanks can be used for this purpose, as was also demonstrated by the Envirogenomarkers Project (3).

Genomics approaches can also be used for risk-benefit assessment of food ingredients such as bioactive phytochemicals, like polyphenols, vitamins and indoles. In a recent dietary intervention study, we evaluated the impact of intake of a blueberry juice containing a complex mixture of phytochemicals using transcriptomics signatures (4). Relevant cellular processes and genetic pathways were identified that are indicative for the preventive effect against oxidative DNA damage observed in this study. Using gene networks in which the complex set of connections between the genes was visualised, gene expression changes were linked to changes in the biological processes immune response, cell adhesion, lipid metabolism and apoptosis. Additional evaluation of the impact of 34 polymorphisms in genes involved in metabolism, handling of oxidative stress and

DNA-repair showed to have a large impact on the study outcome, demonstrating that individuals with specific genetic variants may respond differently to potentially toxic of preventive food constituents. As a consequence, the use of genetic information can help to understand inter-individual differences in responses to food constituents or even complete diets, and further advance the concept of personalized nutrition. Although there are still many scientific challenges to overcome before our understanding of gene-diet interactions and their impact on multifactorial diseases is sufficiently robust to be widely used for guiding of dietary advice, the nutrigenomics field is slowly making advances in this direction (5).
Overall, it can be concluded that genomics techniques provide valuable tools to establish mechanistic pathways involved in both induction and prevention of disease induced by dietary factors.

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Large scale *in vitro* molecular measurements of the human cellular response to chemicals from food: Overview and examples

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Future global food needs and emerging food technologies present a considerable challenge for ensuring food safety as well as promoting health through food into the future. It requires a dramatic increase in the capacity to characterize and predict the effects of bioactive food components (nutrients, additives or chemical residues/contaminants) on human health (1). A systems-based approach in addressing this challenge is based on the concept that chemical exposures lead to changes that may be described on a molecular level, and that some of these changes induce morphological or functional alterations at the cellular and the organism level, ultimately contributing to beneficial or toxic outcomes (2). At the same time, society and regulations drive a need for alternative *in vitro* models that avoid or limit the use of animals in toxicity studies.

Over the past decade, there has been unprecedented development in technologies that enable the collection of large datasets composed of quantitative information regarding molecular responses on the basis of changes in all major classes of biomolecules in living organisms, including human cells (*2*). Such datasets are derived using data-rich methodologies such as transcriptomics, proteomics, metabolomics and lipidomics. Such methodologies can be used to quantify exposure to chemicals in food as well as resulting effects at the molecular level. For example, NMR spectroscopy and/or mass spectrometry (MS)-based methods can be used to quantify xenobiotic substances and their metabolites in cells and at the same time interrogate resulting

changes in the endogenous chemical species metabolome. On the other hand, MS-based methods that use isotope tagging for relative and absolute quantification and data-independent analysis or selected reaction monitoring can allow one to quantify changes in the levels of proteins and/or their posttranslational modifications in whole cell lysates or in selected subcellular compartments. Furthermore, high content imaging techniques allow quantitative measurement of changes at the cellular level, and phenotypic assessment of human cells in culture following chemical exposure (*2*). Combined with recent advances in bioinformatics that allow mining and interpretation of very large, complex datasets, systems-based approaches provide an unprecedented opportunity to causally link food-related exposures to quantifiable outcomes on human health, and can inform the development of *in silico* models that can be useful for risk assessment.

Notwithstanding the vast potential of systems-based approaches in the assessment of human health effects of chemicals in food, implementation of these approaches remains largely theoretical. Key issues to be addressed arise mainly from the inherent complexity of real-life exposures that may be acute or chronic, combined exposures with benefits to be weighed against toxicity, low concentrations, and potential functional interactions amongst different chemicals (*3*). In addition, a critical requirement is the identification and characterization of *in vitro* phenotypes that are relevant to *in vivo* outcomes (*4*). This talk will present a framework for current advances with a focus on enabling technologies involving systems-based approaches to large-scale assessment of molecular responses in human cells exposed to chemicals found in food, and will further highlight recent representative examples.

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Exploring Biomarkers for the Risk assessment of Food Constituents

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Food constituents of relevance for food safety comprise compounds present in minor to trace concentrations, including chemicals of natural origin, such as polyphenols, alkaloids, saponins, steroidal and other organic and inorganic compounds. In addition, food is invariably at risk to become contaminated throughout the food chain as a consequence of various production, storage, transport and processing techniques or of migration from food contact/packaging materials into food.

A case in point that has met with great attention in the last decade is the process related contaminant acrylamide (AA). AA is known to be generated during various food heating processes from reducing carbohydrate constituents and asparagine. It is genotoxic and classified a probable human carcinogen.

Exposure to AA has been thoroughly investigated. It is well amenable to biomonitoring, since biomarkers of longer term exposure, as well as those reflecting short term exposure are available. Adducts to the N-terminal valine amino group of hemoglobin (Hb) have evolved as long term exposure biomarkers, based on a lifetime of human red blood cells of approximately 120 days. Formation of Hb adducts by the oxidative genotoxic key metabolite, 2,3-epoxypropanamide (glycidamide, GA) has been found to parallel formation of N7-glycidamide-guanine- (N7-GA-Gua) DNA adducts in animal experiments. Therefore, GA-Hb adducts have been proposed as surrogate biomarkers of DNA adduct formation.

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AA and GA can be detoxified by coupling to the thiol group of glutathione (GSH). The resulting GSH-thioethers undergo metabolic processing to yield the mercapturic acids (MA), N-acetyl-S-(carbamoylethyl)-L-cysteine (AAMA) and N-acetyl-S-(2-carbamoyl-2-hydroxyethyl)-L-cysteine (GAMA), respectively. MA excreted in the urine may be considered end products of the GSH mediated detoxification pathway. They reflect recent exposure because they are excreted practically completely within 72 h. Both, Hb adducts and MA have been used in human studies to monitor AA exposure. Largely similar results have been obtained by monitoring these exposure biomarkers and calculating the associated AA exposure based on established human biokinetics. In an intervention study in 14 healthy non-smoking volunteers the dietary AA intake in duplicates of their total daily diet was exactly determined. Urinary AAMA and GAMA output was monitored for up to 72 h. Dietary exposure to AA in the range of 0.6 - 1.8 µg/kg bw resulted in a MA output corresponding to 58% of the respective AA intake, based on total AAMA excretion and to 7% - 10%, based on that of GAMA. In a comprehensive rat study, AA was given orally in single dosage of 0.1 - 10,000 µg/kg bw and MA output as well as formation of N7-GA-Gua DNA adducts in several organs were monitored. In the dose range of 0.1 - 100 µg AA/kg bw, no dose dependent increase of N7-GA-Gua adducts above background was observed in liver, lung and kidney (<2 adducts/10^8 nucleotides), although the MA output clearly increased in a dose related fashion. In contrast, at higher dose range (>500 µg/kg bw) a clear dose response of N7-GA-Gua DNA adduct formation was observed in all organs, in parallel to dose related increase of MA excretion in the urine.

For genotoxic agents, DNA lesions are considered the first key element in the complex chain of events that eventually leads to a mutation and potential malignant cell transformation. The advent of adequate analytical methodology now provides the perspective to monitor DNA adducts or other surrogate biomarkers in order to measure the impact of an exposure to a given food borne genotoxic

agent on human background levels. To achieve this, it will be mandatory to expand the data base relating to background DNA lesions/surrogate biomarkers in human tissues or body fluids. A read-across approach for groups of similar DNA lesions should also be explored. Altogether, the determination of a potential impact on steady state background of human DNA damage may become a key element to inform case by case evaluations of human health risk to a given genotoxic carcinogen.

Risk assessment of genotoxic carcinogens in the low dose range

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Risk assessment for genotoxic carcinogens is an important challenge in toxicology. Even though manifold attempts have been made to substitute carcinogens and to reduce exposures, their complete elimination appears to be not possible. Thus, low concentrations of known or suspected genotoxic carcinogens are present at workplaces, in the environment and in food. In order to deal with this situation and to set priorities for risk management, different concepts have been established such as the ALARA principle (As Low As Reasonably Achievable) and the Margin Of Exposure (MOE), based on the ratio between concentrations being carcinogenic in experimental animals and the actual exposure of humans for example via foodstuff. Other approaches are based on the mode of action of chemical carcinogens. Examples are carcinogen categories 4 and 5 of the German MAK Commission and categories B, C and D by the Scientific Committee on Occupational Exposure Limits (SCOEL) on the European Level. While usually linear dose-response-relationships have been used as default assumption for genotoxic carcinogens, a further discrimination appears possible. Thus, analytical methods are now available to assess the induction, repair and mutagenicity of DNA lesions on low exposure conditions. Also, for some compounds, it is possible to discriminate DNA lesions generated endogenously within normal metabolism from the same type of DNA lesion induced via respective chemical exposure; in these cases, the extent of exposure-induced DNA lesions may be related to endogenous DNA damage. In other cases, proficient detoxification mechanisms including DNA repair may protect from irreversible genetic damage. Finally, results from

genomics may provide additional hints on the mode of action. All these aspects are important prerequisites to establish health-based and/or risk-based limit values for selected genotoxic carcinogens and are currently discussed within a common working group of the SKLM and MAK commissions.

The use of PBK models in the risk assessment of plant genotoxins

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Botanicals and botanical preparations that are part of our modern food chain may contain compounds that are both genotoxic and carcinogenic. In 2009, EFSA published an updated guidance on the scientific data needed to carry out a safety assessment of a botanicals and botanical preparations (1). In cases where a botanical preparation contains substances that are both genotoxic and carcinogenic, assessment of the risk for human health is complicated. Considering the possible uncertainties and existing disadvantages connected to the use of qualitative and quantitative approaches such as ALARA (as low as reasonably achievable) and low-dose cancer risk extrapolation, the use of a Margin of Exposure (MOE) approach was recommended (2-4). The MOE is a dimensionless ratio based on a reference point obtained from epidemiologic or experimental data on tumor incidence, such as for example a BMDL10 (the lower confidence limit of the benchmark dose that give 10% extra tumor incidence above background levels) which is divided by the estimated daily intake (EDI) in humans. The MOE approach is considered a useful and pragmatic tool for risk assessment of substances that may be both genotoxic and carcinogenic.

A recent inventory of botanical ingredients that are of possible concern for human health because of their genotoxic and carcinogenic properties revealed that the majority of the compounds identified belong to the group of alkenylbenzenes or the group of unsaturated pyrrolizidine alkaloids (5). For both groups of compounds tumor data that enable definition of a BMDL10 for risk assessment by the MOE approach are limited to only a few congeners.

In addition, risk assessment of these botanical genotoxins should consider that realistic dietary exposure levels are low while exposure may occur within a complex food matrix and for periods that may be significantly shorter than whole life and that effects of genetic polymorphisms or lifestyle factors may have to be taken into account. To facilitate risk assessment of botanical genotoxins we have pioneered the use of physiologically based (PBK) modelling.

A PBK model is a set of mathematical equations that together describe the absorption, distribution, metabolism and excretion (ADME) characteristics of a compound within an organism (6). PBK models can predict the tissue concentration of a compound or its metabolite(s) in any tissue over time at any dose, allowing analysis of effects at both high but also more realistic low dose levels. Furthermore, PBK models can be developed for different species, which can facilitate interspecies extrapolation. They can also be defined for different congeners in a groups facilitating read across from compounds for which toxicity data are available to analogues for which these data are limited or even absent. In addition, by incorporating equations and kinetic constants for metabolic conversions by individual human samples and/or specific isoenzymes, modelling of interindividual variations and genetic polymorphisms becomes feasible.

In the lecture we will present examples of how PBK modelling can be used to facilitate risk assessment of plant genotoxins, taking the alkenylbenzenes as model compounds, including;

- Prediction of species differences in bioactivation of estragole, methyleugenol and safrole to their ultimate carcinogenic 1'-sulfooxy metabolites and related DNA adduct formation (7-10).
- Quantifying the influence of food matrix derived combination effects on the risk assessment of methyleugenol and estragole (11-14).
- Prediction of interindividual differences in bioactivation and DNA adduct formation by estragole and methyleugenol and consequences for risk assessment (15-17).

- Risk assessment for elemicin, for which tumor data for definition of a BMDL10 are absent, using PBK modelling based read-across to methyleugenol and estragole for which in vivo animal tumor data are available (18).

Together these examples reveal that PBK modelling can facilitate read-across in risk assessment from compounds, exposure regimens or species for which in vivo toxicity studies are available to compounds, exposure regimens, species or even individuals for which no or only limited toxicity data have been described, thus contributing to better risk assessment as well as to the development of alternatives for animal testing.

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Novel developments in the risk assessment of food allergens

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Risk assessment of food allergens has made an enormous development during the last decade. Initially, many questioned whether in food allergy thresholds exist below which allergic responses would not occur. Although we still don't understand how exposure patterns influence sensitization or tolerance inducing processes in food allergy, all stakeholders nowadays agree that thresholds do exist with respect to effect elicitation. Low dose challenge studies have provided insight into dose levels minimally required to elicit allergic reactions in individual patients and into the distribution of these minimal eliciting doses among the allergic population for various major allergens. This has laid a basis for the application of risk assessment approaches to food allergy.
Depending on the risk management question and goal, different approaches can be followed in risk assessment, which is also the case in food allergen risk assessment. A zero risk based approach, as is common in toxicology, may be the top of mind approach for some stakeholders in the case of food allergy. However, a zero risk based approach often results in non-conclusive assessments or impractical conclusions in food allergen risk assessment and therefore is unsuitable for most risk management goals. Particular for population risk management purposes, probabilistic quantitative risk assessment is nowadays considered the most appropriate approach. Probabilistic quantitative risk assessment was first proposed and developed for food allergen risk assessment by TNO, The Netherlands, and has been used in the development of the current Voluntary Incidental Trace Allergen Labeling (VITAL® 2.0) guidance of the Australian-New Zealand Allergen Bureau and for the quantification of risks of

(possible) unintended allergen presence in food products. Besides the advantage of having the best state of the art quantification of risks, probabilistic quantitative risk assessment provides the best opportunities to get insight into the uncertainties in risk assessment and the contribution of the various elements (e.g. estimation of level of contamination of a food product with an allergen, the assumed food intake, or knowledge on the sensitivity of the allergic population) to the uncertainties. Probabilistic quantitative risk assessment can also be used to assess and compare the efficacy of various management options in reducing the risks of allergens in food chains. Databases and methodologies for probabilistic quantitative risk assessment will continuously be further developed and uncertainties in the assessments will decrease over time, but stakeholders generally agree that the approach is ready to be applied for most major food allergens. The most important issue for the applicability of probabilistic quantitative risk assessment in food allergy to be dealt with at this moment is the fact that the approach depends on our ability to deal with risks. A zero risk in food allergy is not feasible and stakeholders need to agree on and accept a chosen balance between reducing risks on the one hand and feasibility, practicability and ensuring food choice for allergic consumers on the other hand.

Novel Technologies in Food Processing

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Novel, or emerging technologies have recently been developed in response to consumer preferences and needs. Key requirements given mainly by consumers included non-thermal, gentle processing technologies with minimum impact on quality and freshness of raw materials while providing safe and functional products with high sensory qualities.
Originally research activities and product and process developments centered around microbial safety especially pasteurization process. More recently product modification techniques, via a better understanding of the processing technologies involved, have emerged and technology transfers to and from other fields such as medicine, biotechnology and pharmacy have taken place. In addition, combination processes to achieve product sterilization, freezing or specific property engineering have been created.
The aim of the presentation is to provide an overview of key emerging technologies such as high hydrostatic pressure, pulsed electric fields, atmospheric plasma and ultrasound. Modes of action, key advantages and challenges will be given and specific examples of recent process developments provided, including product function engineering, sterilization and freezing techniques as well as insights into microbial inactivation mechanisms and kinetics.
The potential for process integration of emerging technologies into existing processes, as well as re-evaluation of existing traditional food processing technologies and combinations of emerging and conventional processes for improved consumer acceptance and preference will be discussed.

Finally future research needs, opportunities and challenges will be provided.

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