EU-FORA SERIES 2

APPROVED: 31 July 2019

doi: 10.2903/j.efsa.2019.e170905

Joint venture on the further development of chemical exposure assessment by use of probabilistic modelling

Austrian Agency for Health and Food Safety (AGES),
Christina Vlachou and Daniela Hofstädter

Abstract

Exposure assessment is a fundamental component of the risk assessment process and has a significant contribution to the overall uncertainty of the risk estimates. The aim of the present project, implemented within the framework of the EU-FORA Fellowship, was to develop a structured approach for probabilistic modelling of the dietary exposure to chemical contaminants, which shall be used as a refined alternative to the more conservative deterministic approach or as part of a Tier 2 assessment. The fellow received training and worked in close cooperation with the project team on three case studies of contaminants in food (cadmium, acrylamide and deoxynivalenol). The modelling of the dietary intake was based on relevant EFSA Guidance and employed the Monte Carlo simulation methodology with the use of a standard software tool (Monte Carlo Risk Assessment (MCRA) platform) and/or a tailor-made risk model in the programming language *R*. The strengths and the limitations of every approach were explored and discussed. The conclusion from the critical comparison of the outputs was that the former can be a tool for the generation of fast preliminary estimates of the usual dietary exposure, whereas the latter may be used by the risk assessors as a more sophisticated, 'state-of-the-art' strategy, which will lead to more realistic estimates of the exposure. The outcomes of the project are being currently incorporated in a Guidance Document on probabilistic exposure assessment, which will highly contribute to more informed risk management decisions and to more effective risk communication.

Keywords: risk assessment, probabilistic modelling, dietary exposure

Correspondence: eu-fora@efsa.europa.eu

Acknowledgements: This report is funded by EFSA as part of the EU-FORA programme.

Suggested citation: Austrian Agency for Health and Food Safety (AGES), Vlachou C and Hofstädter D, 2019. Joint venture on the further development of chemical exposure assessment by use of probabilistic modelling. EFSA Journal 2019;17(S2):e170905, 12 pp. https://doi.org/10.2903/j.efsa.2019.e170905

ISSN: 1831-4732

The EFSA Journal is a publication of the European Food Safety Authority, an agency of the European Union.

Table of contents

1. Introduction

This Technical Report presents the workflow and the outcomes of the project 'Joint venture on the further development of chemical exposure assessment by use of probabilistic modelling', which has been implemented within the framework of the EFSA's 2018–2019 EU-Food Risk Assessment Fellowship Programme (EU-FORA). The project was a joint-cooperation among the Austrian Agency for Health and Food Safety (AGES), the German Federal Institute for Risk Assessment (BfR), the Croatian Food Agency (HAH) and the Croatian University of Osijek (UniOS).

The fellow, whose home institution is the General Chemical State Laboratory of Greece, was hosted by AGES and was placed in the Data, Statistics and Risk Assessment Department, where she had the opportunity to exchange views and knowledge with the Austrian experts and gain new skills, more expertise and hands-on experience in chemical risk assessment. During a short hosting period in BfR, she had also the opportunity for a collaboration with the German experts.

2. Description of work programme

2.1. Aims

The aim of this joint initiative was the further development of chemical risk assessment methodologies in food safety, with focus on the probabilistic modelling of dietary exposure. The project included case studies, in which the exposure assessment of a chemical hazard in food would be performed through probabilistic modelling with different software tools, using defined data sets from the participating countries. Critical comparison of the methodologies and of the results and compilation of a Guideline Document on probabilistic exposure assessment including gap analysis were the expected short-term outcomes of the project. As a long-term goal, these results shall be used for capacity building in the participating institutions and in programming tailor-made solutions for the risk assessment of chemical substances in food. Further objectives of the fellowship were to offer relevant training sessions to the fellow, to support her participation in the activities of the hosting organisation and to encourage scientific contributions related to the project.

2.2. Activities/Methods

All chemical risk assessment case studies were conducted with respect to the general principles of Regulation (EC) No 178/2002 and the WHO Human Health Risk Assessment Toolkit (WHO, 2010a) and included the following steps: (i) Problem formulation, (ii) Hazard identification, (iii) Hazard characterisation, (iv) Exposure assessment and (v) Risk characterisation.

Exposure assessment is a fundamental and crucial component of the risk assessment process, as the risk characterisation outcome and any consequent risk management decisions and measures depend largely on the calculated exposure estimates, which should be as close as possible to the 'true' exposure of the population. Deterministic calculation of the dietary intake through generation of point estimates with use of single input data sets is until now the most frequently used methodology for exposure assessment purposes, as it is considered simple to use and understand. However, deterministic methodologies have several limitations, the most important being that they result in substantially more conservative estimates. Probabilistic modelling is a valuable alternative concept, as it utilises distributions for both the occurrence and the consumption data, results in more realistic and precise estimates of the distribution of intake and allows the determination of the primary sources of variability and uncertainty. Despite the unquestionable advantages, probabilistic methodologies have their limitations, such as complexity and data, time and software requirements (Kroes et al., 2002).

The development of probabilistic analysis skills constitutes a strategic decision for the future activities of an organisation, which perform risk assessments with public health relevance. Therefore, the common interest of the participating agencies in this project was to explore as many options as possible, in order to develop and maintain the capacity for scientific modelling, preferably using open source software. A systematic review on the available free of charge software that can be used as a tool for probabilistic exposure assessment and risk modelling was conducted by a postgraduate student from the Croatian University of Osijek. The main functionalities, the possibility of control over the procedures and the availability of technical and support documentation were the main criteria used for the evaluation. Three main categories of non-licenced software for probabilistic modelling of exposure are available: (i) Standard tools, such as the Monte Carlo Risk Assessment (MCRA) software, provided by the Wageningen University (WUR/FERA/RIVM, 2016), (ii) programming languages, such as

R, and (iii) *Excel*-based tools. The first type operates as a 'black box' system, not allowing knowledge or control on the data processing. Non-standard data sets or completely new assessment tasks cannot be handled by those tools. The lack of technical transparency may also pose problems concerning full model documentation, comparison and validation of results. The second type requires expertise on programming, but allows case-specific tailoring and control on the procedures performed in means of a code. *R* packages such as '*fittdistrplus*' and '*mc2d*' provide additional functionalities for probabilistic risk assessment and Monte Carlo simulation. Another *R*-based free software, *rrisk*, falls also in this category. *rrisk* is under development by the BfR as a prototype for quantitative risk assessment and provides all necessary functionalities from model development to documentation of the risk assessment output. The third category includes some *Excel* add-in tools, which suffer from disadvantages regarding lack of info on the usage of certain functionalities or algorithms.

The case studies included in this project comprise exposure assessment based on a standard software tool (MCRA) and/or comparison to a risk model in *R*, according to the EFSA Guidance on the Use of Probabilistic Methodology for Modelling Dietary Exposure. This Guidance recommends the generation of a pessimistic and an optimistic scenario (EFSA, 2012b), constructed according to the upper bound (UB) and lower bound (LB) substitution approach, respectively (EFSA, 2010).

Uncertainty and sensitivity analysis were based on the EFSA Guidance for case-specific assessments (EFSA Scientific Committee, 2018), which requires a systematic identification of all sources of uncertainty, including both the inputs (data, estimates, other evidence) and the methods (statistical methodologies, calculations or models, reasoning) used for the assessment.

2.2.1. Case study 1. Risk assessment on cadmium in food

Cadmium is a toxic heavy metal, which occurs naturally in the earth's crust, accumulates in soils (Tóth et al., 2016) and plants (Shahid et al., 2017), bioconcentrates and bioaccumulates in aquatic organisms (Rubio-Franchini et al., 2016) and occurs ubiquitously as a contaminant in numerous food categories (EFSA, 2009a). Diet and tobacco smoking are the primary sources of human exposure to cadmium (WHO, 2010b), which then accumulates in the body, as it has a half-time of over of 26 years (ATSDR, 2012). The deleterious effects include carcinogenicity (IARC, 2012), end-stage renal failure (Kobayashi et al., 2008), bone demineralisation, (Kjellström, 1992), reproductive and developmental toxicity (Gupta, 2011) and disturbance of metabolism (Edward and Ackerman, 2016) and macro- and micronutrients homeostasis (Kim et al., 2007).

Problem formulation

The objectives of this case study were to estimate whether the chronic dietary exposure of the Austrian adult population to cadmium exceeds the relevant health-based guidance value (tolerable weekly intake (TWI)) and to identify the food categories that mostly contribute to the intake.

Hazard identification and characterisation

A literature review was conducted by the fellow. Due to resources and time limitations, data from the last EFSA Opinion (EFSA, 2009a) on cadmium as well as from the toxicological profiles released by other institutions (ATSDR, 2012, IARC, 2012) were enriched with recent references, in order to account for any new scientific evidence regarding the toxicity of cadmium.

Exposure assessment

The exposure assessment was based on the occurrence levels of cadmium analysed within the framework of the Austrian Official Food Control 2010–2017 and the consumption data from the most recent Austrian dietary survey of 2016. The determination and quantification of cadmium was performed either with inductively coupled plasma mass spectrometry (ICP-MS) or with atomic absorption-graphite furnace technique (GF-AAS) in the ISO 17025 accredited AGES laboratories. The food categories were standardised under EFSA's FoodEx2 hierarchical classification system. The fellow had active participation in the evaluation of the occurrence data for relevance and quality, performed a preliminary summary and delivered descriptive statistics on the analytical results with the programming language *R*. The obtained results provided further insights into the identification of the most contaminated food categories (Vlachou et al., 2019b). The consumption data were available from the national 2-day dietary survey of 2016, conducted by the University of Vienna according to the General principles for the collection of national food consumption data provided by EFSA (2009b). The food categories were coded under FoodEx2. The same data sets of the occurrence and the consumption data were used for the modelling of the intake both for the MCRA and for the *R* application. The results for the optimistic and pessimistic

scenarios with the use of the MCRA software are summarised on Table 1. The model-based usual exposure distribution for the pessimistic scenario is presented in Figure 1.

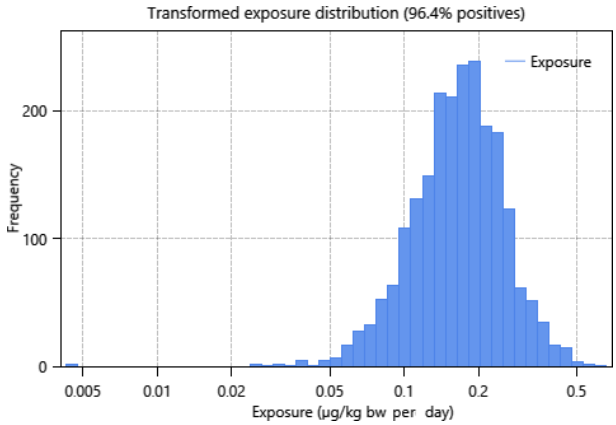

Figure 1: The model-based usual exposure distribution to cadmium for the pessimistic scenario with the use of the MCRA software

In order to account for the other major source of exposure of the general population to cadmium, which is the inhalational exposure to tobacco smoking (WHO, 2010b), the fellow conducted a literature review, summarised the results of the Austrian official control on cadmium in tobacco products, and applied a methodology used by EFSA (2009a) to estimate the magnitude of exposure. The minimum estimated weekly deposition of cadmium in the lungs of a heavy smoker (≥ 20 cigarettes/day) with a body weight of 60 kg b.w. was 0.3 µg cadmium/kg b.w. (Vlachou et al., 2019a). The findings of this study are very important for risk assessment and risk management purposes, as 26% of men and 22% of women > 15 years in Austria are daily smokers, while the percentages for heavy smokers are 12.1% and 6.7%, respectively (EUROSTAT, 2014).

Risk characterisation

The TWI of 2.5 µg/kg b.w. adopted by EFSA was the selected health-based guidance value for the risk characterisation (EFSA, 2009a, 2012a). The results are presented on Table 1. Taking into account, the lack of occurrence data for cadmium in many important food categories and the contribution from the inhalational exposure through tobacco smoking, along with the contribution from other sources, which were not considered for this assessment, we could suggest that the exposure estimates are likely higher, and might be close or even exceeding the TWI.

Table 1: Estimates and 95% CIs for the mean and upper tail (P95) exposure of the Austrian adult population to cadmium (µg/kg b.w. per week) and % contribution to the TWI for the optimistic and the pessimistic scenario with the use of the MCRA software

Scenarios	Mean exposure (µg/kg b.w. per week)	Contribution to the TWI (%)	P95 exposure (µg/kg b.w. per week)	Contribution to the TWI (%)
Optimistic	1.05 (0.9639–1.1389)	42.0 (38.6–45.6)	2.01 (1.7969–2.2267)	80.4 (71.9–89.1)
Pessimistic	1.19 (1.1522–1.3118)	47.6 (46.1–52.5)	2.20 (2.0293–2.3828)	88.1 (81.2–95.3)

CI: confidence interval; TWI: tolerable weekly intake; MCRA: Monte Carlo Risk Assessment; b.w.: body weight.

2.2.2. Case study 2. Risk assessment on acrylamide in food

Acrylamide occurs as a processing contaminant in food, resulting from the Maillard reaction between amino acids and reducing sugars (Mottram et al., 2002). Fried or baked carbohydrate-rich foods are the most contaminated food categories. High levels of acrylamide have been reported in fried potato products, breads, biscuits, breakfast cereals, coffee, cocoa and baby foods (EFSA CONTAM Panel, 2015). Once ingested, acrylamide is readily absorbed and largely distributed in the body. Detoxification after glutathione conjugation and epoxidation to glycidamide (Doerge et al., 2005) are the main metabolic pathways, the latter suggested to be associated with the genotoxicity (COM, 2009) and carcinogenicity (Hogervorst et al., 2010) of acrylamide observed in animal studies. Other deleterious effects include neurotoxicity and reproductive and developmental toxicity (EFSA CONTAM Panel, 2015).

Problem formulation

The objectives of this case study were to estimate the chronic dietary exposure of the Croatian adult population to acrylamide and to identify the food categories that mostly contribute to the intake.

Hazard identification and characterisation

This stage of the risk assessment process has been implemented by the Croatian Food Agency.

Exposure assessment

The exposure assessment was based on data from the Official Croatian Food Control Plan 2014–2016 on acrylamide occurrence in black and espresso coffee, French fries, chips, breakfast cereals, bread & rolls, cookies and snacks, and the Croatian National Food Consumption Survey on adults (NIPNOP 2011–2012, three 24-hours recall, conducted according to EFSA's guidelines (EFSA, 2009b)). The intake estimates were generated with a tailor-made model based on *R* and are summarised on Table 2.

Table 2: Estimates and 95% CIs for the mean and upper tail (P95) exposure of the Croatian adult population to acrylamide (μg/kg b.w. per day) and for the respective MOEs calculated for neurotoxic and neoplastic effects (*R* model, optimistic scenario)

Evaluated risk	Mean exposure (μg/kg b.w. per day)	MOE	P95 exposure (μg/kg b.w. per day)	MOE
Neurotoxic effects	0.0947 (0.0841–0.1060)	4,541 (5,113–4,057)	0.360 (0.316–0.413)	1,194 (1,361–1,041)
Neoplastic effects		1,795 (2,021–1,604)		472 (538–412)

CI: confidence intervals; b.w.: body weight; MOE: margin of exposure.

Risk characterisation

Since acrylamide and its main metabolite, glycidamide, are genotoxic, no safe level and thus no health-based guidance value has been established. The margin of exposure (MOE) approach was used for risk characterisation. The benchmark dose for a 10% response (BMDL10) values of 0.43 and 0.17 mg/kg b.w. per day were used for non-neoplastic effects (neurotoxicity) and for neoplastic effects, respectively (EFSA CONTAM Panel, 2015). All MOEs calculated for neurotoxic effects within the optimistic scenario (Table 2) and the pessimistic scenario are above the adjusted MOE of 125, indicating no health concern for neurotoxicity. However, all MOE values calculated for neoplastic effects are lower than 10 000, indicating a health concern.

2.2.3. Case study 3. Risk assessment on DON in food

Deoxynivalenol (DON) is a trichothecene-mycotoxin, which is produced by *Fusarium* fungi in cereal grains. DON is relatively heat stable and some industrial processing of the grains can result in increases in concentrations (Abbas et al., 1985; EFSA CONTAM Panel, 2017). Contamination of food and feed with DON is a global issue. Acute intoxication cases have been reported in many countries, mostly in Asia. DON inhibits protein synthesis through binding to ribosomes, and is associated with acute effects on the gastrointestinal system as well as with chronic effects such as intestinal function disruption, immunotoxicity (Antonissen et al., 2014), developmental and reproductive toxicity (SCF, 2002), skeletal abnormalities and postnatal mortality (EFSA CONTAM Panel, 2017). Anorexia and reduced body weight were observed in animal studies following ingestion of feed contaminated with DON. Pigs are the most sensitive species (Rotter et al., 1996; EFSA CONTAM Panel, 2017).

Problem formulation

The objectives of this case study were to estimate the chronic dietary exposure of the Croatian adult population to DON and to identify the food categories that mostly contribute to the intake.

Hazard identification and characterisation

This stage of the risk assessment process has been implemented by the Croatian Food Agency.

Exposure assessment

The exposure assessment was based on Croatian occurrence data on DON and consumption data from the Croatian National Food Consumption Survey. The intake estimates were generated with a tailor-made model based on *R*.

Risk characterisation

The risk characterisation was based on the **group tolerable daily intake (TDI)** of 1 μg/kg b.w. per day established by EFSA CONTAM Panel (2017) for the sum of DON, 3-Ac-DON, 15-Ac-DON and DON-3-glucoside. The selected critical effect was the reduced body weight gain observed in animal studies.

2.2.4. Uncertainty and sensitivity analysis

The uncertainty and sensitivity analysis was based on the recent EFSA Guidance (EFSA Scientific Committee, 2018) and comprises a systematic identification of all potential sources of uncertainty regarding the data and the methods used and of the key factors influencing the output. The main sources of uncertainty associated with the inputs were the absolute lack of occurrence data for some important food categories, the left censoring of the analytical results and the small sample size for some other commodities, the targeted sampling plans, the lack of accepted processing factors, the precision of the description and standardisation in FoodEx2 and the underreporting or misreporting of the consumption in the dietary survey. The main sources of uncertainty associated with the methods were the lack of control on the selection and validation of the model in the MCRA software and potential pitfalls in the structure of the *R* model because no package was available with ready-made functions that would cover all the needs for a risk assessment model. The selection of the statistical methodology of the Monte Carlo simulation was one of the strengths of the project, as this approach allows for the quantification of the uncertainty components and delivers the required estimates accompanied by the respective confidence intervals at a predetermined significance level.

The conclusions of the uncertainty and sensitivity analysis will provide valuable information to the risk managers and will enable prioritisation of uncertainties and decision about the needs for future data collection or research.

2.3. MCRA & R – Comparison of experiences and results

The MCRA software is a web-based platform for probabilistic dietary and/or non-dietary, acute or chronic exposure assessment, which implements the recommendations of EFSA on probabilistic modelling about generation of optimistic and pessimistic scenarios (EFSA, 2012b), or offers the possibility for a custom-made scenario and supports many additional functionalities such as sensitivity analysis, cumulative and aggregated exposure assessment and use of processing factors. It offers a user-friendly interface and is compatible with food categorisation in FoodEx2. The output is very detailed and is presenting the exposure estimates, the uncertainty and the food categories most contributing to the intake. There are some practical limitations: the data shall be prepared in a specific format, which requires some additional effort, and the upload of the files can be challenging. The main detriment is that the user cannot have any knowledge or control over the ongoing procedures.

R is an open source and thus a cost-effective programming language, which is rapidly evolving within a huge community of developers. Learnability and availability of learning resources, extensibility and availability of specified packages (*R* libraries), appropriateness for the handling of large data sets, control over the procedures described through the algorithms are the main advantages of the use of *R* for risk assessment purposes. On the other hand, modelling with *R* is substantially time-demanding and requires the employment of specific skills. The realistic objective of this project was the construction of a tailor-made *R* code under the guidance of the experienced statisticians of AGES, which could be modified and used on demand for probabilistic risk assessment tasks within the current project and in the future. The fellow had introductory and advanced training sessions on R and was able to understand and use the basic functions that are needed in data analysis, algorithms generation and risk simulation. Still, using *R* requires good programming skills. Since no package is available that could cover all the requirements for performing the simulation model, many functions have to be programmed by the user himself.

Comparison of the results on cadmium generated either with the MCRA platform or with *R* revealed that the estimates of the exposure were similar and provided an opportunity for a cross-validation of the two models.

2.4. EU-FORA Fellowship supporting programme

Apart from her participation in the training modules in Parma, Vienna, Berlin and Athens, which were included in the curriculum of the EU-FORA Fellowship programme, the fellow was provided by the hosting organisation AGES with additional training sessions, was enabled to participate in other

activities and benefit from her interaction with colleagues and experts. These supporting activities are presented in Appendix A.

3. Conclusions

3.1. Conclusions from the probabilistic assessments

The EU-FORA Fellowship programme has to a large extent reached the goals predetermined by the participating institutions. The fellow has participated in the establishment of a structured probabilistic risk assessment approach, which is based on a selected standard software tool (MCRA) and a risk model in *R*. The former may be used by the risk assessors as a tool to achieve fast estimates of the usual dietary exposure, whereas the latter shall be used as a refined, state-of-the-art strategy following the commonly used deterministic methodology. The critical comparison of the outputs among the three approaches will contribute to decision-making and risk management. The results of the project are being currently incorporated in a Guidance Document on probabilistic exposure assessment including the gap analysis.

3.2. Conclusions from the participation in the fellowship programme

The fellowship provided the fellow with a unique opportunity to apply and extend her knowledge and elaborate her skills in chemical risk assessment according to European and international guidelines and standards and to widen her hands-on experience in probabilistic assessment of the dietary exposure to contaminants in food through various frameworks. The fellow was fully integrated, had active participation in the activities of the hosting institution, received targeted training, gained valuable insights in methodologies on systematic extraction, evaluation, standardisation, combination and modelling of scientific data and was encouraged to communicate the programme results in poster presentations in conferences, in workshops and in peer-reviewed scientific journals. Furthermore, the fellow had benefit from the dedicated induction training at EFSA and the three further modules offered in Vienna, Berlin and Athens. The outcomes of the programme will contribute to the harmonisation of food risk assessment methodologies and to the capacity building in both the sending and the hosting organisations and could be the basis for future networking and collaborations between them and with EFSA.

3.3. Future goals

Further development and progress of the probabilistic risk assessment methodology, as well as iterative review and refinement of the Guidance Document are the future goals of both the hosting site and the fellow. Meetings and workshops will be scheduled for communication of the results and knowledge transfer to the project team and to the staff of the participating institutions. Publication of the outputs in administrative reports and scientific journals will further contribute to the dissemination of knowledge and experience.

4. Disclaimer

The risk assessment process for the case studies is still ongoing during the last months of the fellowship programme. Therefore, only some limited interim results are included in this report, in order to avoid copyright claims, in case of publication of the final results in other scientific journals.

References

Abbas HK, Mirocha CJ, Pawlosky RJ and Pusch DJ, 1985. Effect of cleaning, milling and baking on deoxynivalenol in wheat. Applied and Environment Microbiology, 50, 482–486.

Antonissen G, Martel A, Pasmans F, Ducatelle R, Verbrugghe E, Vandenbroucke V, Li S, Haesebrouck F, Van Immerseel F and Croubels S, 2014. The impact of fusarium mycotoxins on human and animal host susceptibility to infectious diseases. Toxins, 6, 430–452.

ATSDR, 2012. Toxicological profile for Cadmium. Department of Health and Human Services, Public Health Service, U.S https://www.atsdr.cdc.gov/toxprofiles/tp5.pdf

COM (UK Committee on Mutagenicity of Chemicals in Food, Consumers Products and the Environment), 2009. Statement on the Genotoxicity of Acrylamide. COM/09/S1. Available online: http://www.iacom.org.uk/statements/documents/COM09S1Acrylamide.pdf

Doerge DR, Young JF, McDaniel LP, Twaddle NC and Churchwell MI, 2005. Toxicokinetics of acrylamide and glycidamide in Fischer 344 rats. Toxicology and Applied Pharmacology, 208, 199–209.
Edward J and Ackerman C, 2016. A Review of Diabetes Mellitus and Exposure to the Environmental Toxicant Cadmium with an Emphasis on Likely Mechanisms of Action. Current Diabetes Reviews, 12, 252–258. https://doi.org/10.2174/1573399811666150812142922
EFSA (European Food Safety Authority), 2009a. Scientific Opinion of the Panel on Contaminants in the Food Chain on a request from the European Commission on cadmium in food. EFSA Journal 2009;7(3):980, 139 pp. https://doi.org/10.2903/j.efsa.2009.980
EFSA (European Food Safety Authority), 2009b. General principles for the collection of national food consumption data in the view of a pan-European dietary survey. EFSA Journal 2009;7(12):1435, 51 pp. https://doi.org/10.2903/j.efsa.2009.1435
EFSA (European Food Safety Authority), 2010. Management of left-censored data in dietary exposure assessment of chemical substances. EFSA Journal 2010;8(3):1557, 96 pp. https://doi.org/10.2903/j.efsa.2010.1557
EFSA (European Food Safety Authority), 2012a. EFSA Panel on Contaminants in the Food Chain (CONTAM); Scientific Opinion on tolerable weekly intake for cadmium. EFSA Journal 2011;9(2):1975, 19 pp. https://doi.org/10.2903/j.efsa.2011.1975
EFSA (European Food Safety Authority), 2012b. EFSA Panel on Plant Protection Products and their Residues (PPR); Guidance on the Use of Probabilistic Methodology for Modelling Dietary Exposure to Pesticide Residues. EFSA Journal 2012;10(10):2839, 95 pp. https://doi.org/10.2903/j.efsa.2012.2839
EFSA CONTAM Panel, 2015. Scientific Opinion on acrylamide in food. EFSA Journal 2015;13(6):4104, 321 pp. https://doi.org/10.2903/j.efsa.2015.4104
EFSA CONTAM Panel, 2017. Scientific Opinion on the risks to human and animal health related to the presence of deoxynivalenol and its acetylated and modified forms in food and feed. EFSA Journal 2017;15(9):4718, 345 pp. https://doi.org/10.2903/j.efsa.2017.4718
EFSA Scientific Committee, 2018. Guidance on Uncertainty Analysis in Scientific Assessments. EFSA Journal 2018;16(1):5123, 39 pp. https://doi.org/10.2903/j.efsa.2018.5123
EUROSTAT, 2014. Tobacco Consumption Statistics from the European Health Interview Survey 2014. Available online: https://ec.europa.eu/eurostat/statistics-explained/index.php/Tobacco_consumption_statistics
Gupta CR, 2011. Reproductive and Developmental Toxicology, 1st edition. Acad. Press. pp. 424–426.
Hogervorst JG, Baars BJ, Schouten LJ, Konings EJ, Goldbohm RA and van den Brandt PA, 2010. The carcinogenicity of dietary acrylamide intake: a comparative discussion of epidemiological and experimental animal research. Critical Reviews in Toxicology, 40, 485–512.
IARC, 2012. Monograph: Cadmium and Cadmium Compounds. Available online: https://monographs.iarc.fr/wp-content/uploads/2018/06/mono100C-8.pdf
Kim D-W, Kim K-Y, Choi B-S, Youn P, Ryu D-Y, Klaassen CD and Park J-D, 2007. Regulation of metal transporters by dietary iron, and the relationship between body iron levels and cadmium uptake. Archives of Toxicology, 81, 327–334.
Kjellström T, 1992. Mechanism and epidemiology of bone effects of cadmium. IARC Scientific Publications, 118, 301–310.
Kobayashi E, Suwazono Y, Dochi M, Honda R, Nishijo M, Kido T and Nakagawa H, 2008. Estimation of benchmark doses as threshold levels of urinary cadmium, based on excretion of beta2-microglobulin in cadmium-polluted and non-polluted regions in Japan. Toxicology Letters, 179, 108–112.
Kroes R, Müller D, Lambe J, Löwik MRH, van Klaveren J, Kleiner J, Massey R, Mayer S, Urieta I, Verger P and Visconti A, 2002. Assessment of intake from the diet. Food and Chemical Toxicology, 40, 327–385.
Mottram DS, Wedzicha BL and Dodson AT, 2002. Food chemistry: Acrylamide is formed in the Maillard reaction. Nature, 419, 448–449.
Rotter BA, Prelusky DB and Pestka JJ, 1996. Invited review: Toxicology of deoxynivalenol (vomitoxin). Journal of Toxicology and Environment Health, 48, 1–34. https://doi.org/10.1080/009841096161447
Rubio-Franchini I, López-Hernández M, Ramos-Espinosa MG and Rico-Martínez R, 2016. Bioaccumulation of Metals Arsenic, Cadmium, and Lead in Zooplankton and Fishes from the Tula River Watershed, Mexico, Water. Air & Soil Pollution, 227, 5.
SCF, 2002. Opinion of the Scientific Committee on Food on Fusarium toxins. Part 6: Group evaluation of T-2 toxin, HT-2 toxin, nivalenol and deoxynivalenol. SCF/CS/CNTM/MYC/27. Available online: https://ec.europa.eu/food/sites/food/files/safety/docs/cs_contaminants_catalogue_fusarium_out123_en.pdf
Shahid M, Dumat C, Khalid S, Niazi N and Antunes PMC, 2017. Cadmium Bioavailability, Uptake, Toxicity and Detoxification in Soil-Plant System. Reviews of Environmental Contamination and Toxicology, 241, 73–137.
Tóth G, Hermann T, Da Silva MR and Montanarella L, 2016. Heavy metals in agricultural soils of the European Union with implications for food safety. Environment International, 88, 299–309.
Vlachou C, Wolf J and Hofstädter D, 2019a. Non-Dietary Exposure to Cadmium: Tobacco Smoking. Scientific Symposium of the Austrian Society of Toxicology (ASTOX), Vienna, Austria, 25-26/04/2019.
Vlachou C, Wolf J, Mihats D and Hofstädter D, 2019b. Cadmium levels in foods from the Austrian market: Results of the Official Food Control 2010-2017. 74. ALVA-Jahrestagung, Vienna, 27-28/05/2019.

WHO, 2010a. WHO human health risk assessment toolkit: chemical hazards (IPCS harmonization project document; no. 8).
WHO, 2010b. Exposure to Cadmium: A Major Public Health Concern. Available online: https://www.who.int/ipcs/features/cadmium.pdf?ua=1
WUR/FERA/RIVM, 2016. MCRA 8.2 a web-based program for Monte Carlo Risk Assessment Reference Manual.

Abbreviations

AGES	Austrian Agency for Health and Food Safety
ATSDR	Agency for Toxic Substances and Disease Registry
BfR	German Federal Institute for Risk Assessment
BMDL10	benchmark dose for a 10% response
b.w.	body weight
CI	confidence interval
DON	deoxynivalenol
EU-FORA	European Union Food Risk Assessment
EUROSTAT	The Statistical Office of the European Union
FERA	Food and Environmental Research Agency, The Netherlands
GF-AAS	atomic absorption-graphite furnace technique
HAH	Croatian Food Agency
IARC	International Agency for Research on Cancer
ICP-MS	inductively coupled plasma-mass spectrometry
LB	lower bound
MCRA	Monte Carlo Risk Assessment
MOE	margin of exposure
RIVM	National Institute for Public Health and the Environment, The Netherlands
SCF	Scientific Committee on Food
TDI	tolerable daily intake
TWI	tolerable weekly intake
UB	upper bound
UniOS	University of Osijek
WHO	World Health Organization
WUR	Wageningen University and Research centre

Appendix A – Supporting activities during the EU-FORA Fellowship

	Title	Date
Training sessions	Introduction to Statistics & Software *R*	9–11.10.2018
	Advanced Statistics: Probabilistic Modelling with R	19–23.11.2018
	Strategy-Mission-Tasks of AGES	2.10.2018
	Risk Assessment in AGES	2.10.2018
	FoodEx2 Webinar – Part I	26.9.2018
	FoodEx2 Webinar – Part II	3.10.2018
	Food Control in Austria	11.10.2018
	Literature Search based on 'EndNote'	25.10.2018
	Medical Biometry and Epidemiology	17–18.12.2018
	Introduction to Novel Food	23.1.2019
Other activities	Scientific Symposium (Poster): Vlachou C, Wolf J and Hofstädter D. *Non-Dietary Exposure to Cadmium: Tobacco Smoking*. Scientific Symposium of the Austrian Society of Toxicology (ASTOX), Vienna	25–26.4.2019
	Scientific Conference (Poster and contribution to the proceedings): Vlachou C, Wolf J, Mihats D and Hofstädter D. *Cadmium levels in foods from the Austrian market: Results of the Official Food Control 2010-2017*. 74. ALVA-Jahrestagung, Vienna	27–28.5.2019
	Visit of the AGES Departments in Graz: Data, Statistics and Risk Assessment & Food Safety, Experts Coordination and Fraud Protection Meeting with the experts, exchange of knowledge and views on aspects of food safety and discussions on the course of the fellowship programme with the statisticians.	9–11.10.2018 19–23.11.2018 19.12.2018 27.6.2019
	Visit of the AGES Laboratories in Linz Meeting with the experts, exchange of knowledge and views on aspects of chemical analysis of contaminants in food	25.6.2019