Risk assessment related to food additives and food processing-derived chemical contaminants exposure for the Portuguese population

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Abstract
The European Food Risk Assessment Fellowship Programme (EU-FORA) is an initiative by EFSA, aimed at building scientific capacity in food safety risk assessment in the EU. Current paper reports on the activities of this fellow, undertaken in participation of the third, 2019–2020 cycle of the EU-FORA programme while placed at the University of Porto, Faculty of Nutrition and Food Sciences, in Portugal. The work programme offered by the hosting site was related to risk assessment on food additives and contaminants. The fellow’s hands-on work consisted of two practical exercises, which aimed to assess the exposure to the 10 intense sweeteners authorised in the EU and a process contaminant, acrylamide, for the Portuguese general population.

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Keywords: food additives, intense sweeteners, process contaminants, acrylamide, dietary exposure

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1. Introduction

The European Food Risk Assessment (EU-FORA) Fellowship Programme is an initiative by the European Food Safety Authority (EFSA), aimed at building scientific capacity in food safety risk assessment in the European Union. During a 12-month period, the fellows enrolled in the programme are placed in a food safety risk assessment organisation outside their own country, to be integrated in the hosting site’s activities for a hands-on work experience. Additionally, the fellows benefit from four dedicated training modules that cover a wide range of topics related to risk assessment.

Current paper reports on the activities of this fellow, undertaken in participation of the third, 2019–2020 cycle of the EU-FORA programme. The fellow, whose home institution is the National Institute for Health Development in Estonia, was placed at the University of Porto, Faculty of Nutrition and Food Sciences, in Portugal. The work programme offered by the hosting site was related to risk assessment on food additives and contaminants.

Food additives are substances that are intentionally added to food for a specific technological purpose, e.g. to prevent spoilage, preserve the food’s structure or improve its organoleptic properties. In the European Union (EU), rules for the use of food additives are laid down by the European Parliament and Council Regulation (EC) No 1333/2008 (European Union, 2008), and only substances that are listed in Annex II to that regulation may be placed on the market. Food additives must be safe when used and therefore should be kept under continuous observation (European Union, 2010), considering not only new scientific information but also potential changes in their intake by the population.

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The functional class ‘sweeteners’ includes food additives used to impart a sweet taste to foods or in table-top sweeteners (European Union, 2008). The class may be further divided into two groups: bulk and intense sweeteners. The former group consists of sugar alcohols (or polyols) that are usually slightly less sweet than sucrose and that are therefore used in similar volume to sugars for achieving the desired sweetness and texture of the food (Grembecka, 2015). Intense sweeteners, also referred to as non-nutritive sweeteners, are in contrast hundreds to thousands of times sweeter than sucrose and include substances with diverse chemical structures and of both synthetic and natural origin (Mortensen, 2006; Carocho et al., 2017).

In the recent decades, the prevalence of obesity has increased both among adults and children in most countries around the world, and excessive body weight contributes to the escalating public health burden of non-communicable diseases such as diabetes, cardiovascular disease and many cancers (GBD 2015 Obesity Collaborators, 2017). One of the main drivers of this obesity pandemic is an easy access to energy-dense foods in the modern food environment (Swinburn et al., 2011). This realisation had led to an array of intervention strategies (Sisnowski et al., 2017), including the taxation of sugary foods. This, however, may considerably change the exposure to sugar substitutes in the population.

In contrast to additives that are intentionally added to food, contaminants are unwanted chemical substances that may be introduced into food during various stages of production, processing, transport or storage (European Union, 1993). Process contaminants are formed when food components undergo chemical changes due to the processing of food, either at home or by the industry – for example, when foods are smoked, cured, fermented or heated. Some examples of process contaminants include heterocyclic aromatic amines, acrylamide and polycyclic aromatic hydrocarbons that are formed when starchy and protein-rich foods are subjected to high heat, e.g. fried, roasted or grilled (Koszuka and Nowak, 2019). This leads to an appealing flavour and texture and consequently to the popularity of such foods; however, many process contaminants have been identified as possible or probable human carcinogens (Jägerstad and Skog, 2005). Therefore, efforts are needed to monitor and minimise the intake of such contaminants by the population.

Acrylamide is formed when starch food is subjected to temperatures above 120°C at low moisture, mainly due to the Maillard reaction involving asparagine (Zhang and Zhang, 2007). Acrylamide is a probable genotoxic carcinogen in humans and a neurotoxicant (EFSA CONTAM Panel, 2015) that was highlighted as a food-related health risk in the early 2000s (Tareke et al., 2002). Subsequently, several risk assessments on acrylamide have been carried out in different countries (e.g., Mojska et al., 2010; Hirvonen et al., 2011; Claeys et al., 2016), including an extensive scientific opinion by EFSA (EFSA CONTAM Panel, 2015) that identified exposure to acrylamide as a concern for neoplastic effects in the European population.
2. Description of work programme

2.1. Aims

Although the general topic for the fellow’s hands-on exercises remained unchanged – namely, risk assessment on food additives and contaminants, the particulars of the work programme underwent several developments during the roll-out. First, changes were proposed due to delays in field work for the population-based birth-cohort Generation XXI, the source of food intake data according to the initial work programme which was titled ‘Risk assessment related to food additives and contaminants exposure during infancy and adolescence’. Later, the focus for food contaminants shifted from heterocyclic amines and polycyclic aromatic hydrocarbons to acrylamide. This was prompted by the University of Porto being asked to assist in the analysis of epidemiological data from the COVID-19 outbreak in support of the national health authorities, which required a prioritisation of the university’s resources. Consequently, the work programme that was realised included the following two parts: a risk assessment on the intense sweeteners currently authorised in the EU and a risk assessment on a process contaminant, acrylamide, both of which were concerned with the Portuguese general population.

In support of the practical exercises, the fellow also followed additional learning objectives. For instance, as the practical work consisted mainly of computational tasks, the fellow worked through several handbooks to improve her data wrangling skills and ability to write clean script in the R programming language, attended an online course on R Markdown for creating dynamic documents with R, and familiarised herself with some of the available software for the assessment of habitual dietary intake. Furthermore, by a combination of onsite and online classes and seminars, the fellow gained knowledge on a wide range of other relevant topics, such as the concepts of epidemiology, conducting systematic reviews and meta-analysis, food security, One Health, etc. In addition, the fellow benefited from the four EU-FORA dedicated training modules: the induction training on 2–20 September 2019 in Parma, module 1 on 25–29 November 2019 in Vienna, and modules 2 and 3 on 10–14 and 24–28, 31 August 2020 as online events due to restrictions related to the COVID-19 outbreak.

2.2. Activities/methods

2.2.1. Practical exercise: risk assessment on intense sweeteners

This practical exercise aimed to assess the exposure to intense sweeteners authorised in the EU and to characterise the risk for the Portuguese general population. In Portugal, a tax on sugar-sweetened beverages was introduced in February 2017 (Diário da Republica, 2016); consequently, changes in consumer preferences and the reformulation of products by the food industry may have led to an increased intake of intense sweeteners in the recent years.

There are currently 10 intense sweeteners authorised for the use in food in the EU (European Union, 2008). Approved food additives, including intense sweeteners, have been subject to a safety assessment by EFSA or its predecessor, the Scientific Committee on Food (SCF). Therefore, as the first step of the risk assessment, the fellow located and read the latest safety assessment for each of these sweeteners, to gain an overview of their toxicology and to extract their acceptable daily intake (ADI). The results from this literature survey are listed in Table 1. No ADI is specified for thaumatin as no adverse health effects are known. The safety of aspartame-acesulfame salt has not been separately assessed as its constituent moieties are covered by the safety assessments for aspartame and acesulfame K; therefore, aspartame-acesulfame salt was also considered contributing to the exposure to aspartame and acesulfame K in the current risk assessment.

Subsequently, the fellow carried out an exposure assessment that utilised individual-level food consumption data from the Portuguese National Food, Nutrition and Physical Activity Survey (Lopes et al., 2017). The survey collected high-resolution food intake data, including the specific brand of the consumed food products, from a nationally representative sample of the Portuguese population aged three months to 84 years. The exposure assessment was based on 24-h food intake data collected on two non-consecutive days from a total of 5,811 respondents.

As occurrence data, maximum usage levels for each permitted food category were extracted from the Regulation (EC) No 1333/2008 on food additives (European Union, 2008). The fellow was also provided with some auxiliary databases, including one that mapped the food items of the Portuguese
food composition database, that were consumed by the respondents of the dietary survey, to the legislative food categories.

Since the hosting organisation had compiled a database of label information for brand products reported in the dietary survey, the exposure assessment on intense sweeteners was further refined – namely, the presence of a sweetener in each food item consumed by each respondent was determined by the ingredients list of the reported brand product. Missing product information had been filled in by multiple imputations, and the fellow was given the food consumption database that included five imputations for each sweetener. The label information database was also the source of the usage levels for the sweetening agents in table-top sweeteners, since the use of intense sweeteners in table-top products is permitted quantum satis (i.e. at a level that is needed to achieve the intended purpose), meaning that no numerical maximum limit is specified by the legislation.

**Table 1:** Toxicological characteristics of the 10 intense sweeteners currently authorised for the use in food in the European Union

| Name                              | E-number | Critical adverse health effect                      | ADI, mg/kg bw | Reference                  |
|-----------------------------------|----------|-----------------------------------------------------|---------------|---------------------------|
| Acesulfame K                      | E 950    | Not specified                                       | 9             | SCF (2000a)               |
| Aspartame                         | E 951    | Reproductive and developmental toxicity             | 40            | EFSA ANS Panel (2013)     |
| Cyclamic acid and its calcium and sodium salts | E 952 | Reproductive toxicity                               | 7(a)          | SCF (2000b)               |
| Saccharin and its sodium, calcium, and potassium salts | E 954 | Carcinogenicity (non-genotoxic)                     | 3.8(b)        | SCF (1997)                |
| Sucralose                         | E 955    | Reduced body weight gain                             | 15            | SCF (2000c)               |
| Thaumatin                         | E 957    | None that are known                                  | Not specified | EFSA ANS Panel (2015)     |
| Neohesperidin DH                  | E 959    | Not specified                                       | 5             | SCF (1989)                |
| Steviol glycosides                | E 960    | Changes in organ weights                             | 4(c)          | EFSA ANS Panel (2010)     |
| Neotame                           | E 961    | Potential hepatotoxicity                             | 2             | EFSA (2007)               |
| Aspartame-acesulfame salt         | E 962    | Not specified                                       | Not specified | Not available             |

ADI: acceptable daily intake; bw: body weight.
(a): As cyclamic acid.
(b): As free acid.
(c): As steviol equivalents.

Before proceeding to exposure estimation, the fellow combined the various input databases to obtain each respondent’s intake of each sweetener per kg bw per each of the two survey days. To improve the transparency and reproducibility of the assessment, this preparatory data wrangling as well as subsequent calculations were organised as computational notebooks that provided a comprehensive and thoroughly annotated description of the workflow, detailing also any assumptions and data corrections made during this process. The computations were carried out using the R statistical programming language (R Core Team, 2018) and formatted as R notebooks. An R notebook is a document in the R Markdown language that contains plain text with independently and interactively executable code chunks and that can be rendered to a shareable format such as html, pdf or a Word document (Xie et al., 2018).

The mean and the 75th and 95th percentiles of sweeteners’ habitual intake were estimated using the two-part model for episodically consumed food components implemented in the SPADE (Statistical Program to Assess Dietary Exposure) software, for the general population and by specific age groups. SPADE is an R-based program developed at the National Institute for Public Health and the Environment of the Netherlands (Dekkers et al., 2014), which aims to estimate the habitual (i.e. long-term) population intake based on short-term measured intake data. To estimate the within-person variability of intake, which is necessary for this kind of modelling, a sufficient number of respondents...
with non-zero intakes on both of the two survey days is required. Therefore, the observed individual means (OIM; EFSA PPR Panel, 2012) model was used instead habitual intake estimation for some of the more rarely consumed sweeteners. Furthermore, mean intakes by food category were calculated using the OIM model to characterise the main sources of exposure. For each sweetener, exposure was estimated based on each of the five imputations of the food consumption database, applying survey weights to better approximate the results to the Portuguese population. Later the estimates were combined using Rubin’s rules (Marshall et al., 2009).

Besides the computational notebooks, the fellow compiled a short summary that presented the main results of the exposure assessment, characterised the risk for the Portuguese population and discussed the uncertainties. According to the brand database of product label information, two sweeteners, thaumatin and neotame, were not consumed by the respondents of the dietary survey. The mean intake of the rest of the sweeteners (acesulfame K, aspartame, cyclamic acid, saccharin, sucralose, neohesperidin DC and steviol glycosides) by the general population aged 0–84 years and for each of the five imputed datasets is presented in Figure 1. Dietary exposure remained far below the ADI in the general population as well as in the 0- to 9-, 10- to 17-, 18- to 64- and 65- to 84-year age groups. The 75th and 95th percentiles did not exceed the ADI, either, further suggesting that the population is not at risk. The main source of intake for most of the intense sweeteners was the food category ‘flavoured drinks’ that mainly referred to soft drinks in the Portuguese food consumption database. Further results are not presented in this report in order not to compromise any future scientific publications by the hosting site.

![Figure 1: Mean intake of intense sweeteners by the 0- to 84-year age group, results from five imputed data sets per sweetener](image)

2.2.2. Practical exercise: risk assessment on acrylamide

The other practical exercise aimed to assess the dietary exposure to acrylamide and characterise the risk for the Portuguese general population. The exposure assessment again utilised the individual-level food consumption data from the Portuguese National Food, Nutrition and Physical Activity Survey, and occurrence data corresponding to the lower, medium and upper bound scenarios for various food groups were extracted from the EFSA scientific opinion on acrylamide (EFSA CONTAM Panel, 2015). The BMDL\textsubscript{10} (benchmark dose lower confidence limit 10%) for the neurotoxic effects (430 μg/kg bw) and neoplastic effects (170 μg/kg bw) of acrylamide were similarly obtained from the scientific opinion.

As for the previous practical exercise, the fellow first combined the input databases to calculate each respondent’s intake of acrylamide per kg bw per each of the two survey days, and the workflow
was detailed in a computational notebook. Subsequently, the mean and the 75th and 95th percentiles of habitual intake were estimated using the one-part model for daily consumed food components in the SPADE software. Intakes were estimated for the lower, medium and upper bound scenario and for the general population aged 0–84 years as well as by age group and sex. Mean intakes by food category were calculated using the OIM model to characterise the main sources of exposure.

Again, the fellow compiled a summary of the assessment that described the results of the exposure assessment, calculated the margins of exposure (MOE) to characterise the risk, and briefly discussed the uncertainties. For genotoxic effects, such as the neoplastic effects of acrylamide, an MOE of 10,000 could be considered of low concern from a public health perspective, and an MOE of 100 is considered safe for non-genotoxic effects (EFSA, 2005). Regardless of the population group and scenario, MOEs for both neurotoxic and neoplastic were far below these safe margins, and the main sources of dietary exposure to acrylamide proved to be various cereal-based products such as soft bread, biscuits and crackers, etc. This indicates the need for a more refined exposure assessment on acrylamide for the Portuguese population; however, such assessment fell out of the scope of this fellowship.

3. Conclusions

The EU-FORA programme offered this fellow an opportunity to familiarise herself with risk assessment on two classes of substances found in food: additives and contaminants. This included both reviewing literature, to gain an understanding of the type of substances, their health effects, and the regulatory framework, as well as practical, hands-on exercises on risk assessment. The latter also provided the fellow an opportunity to develop her data science related skills, which will benefit her professional development as a data analyst. In addition, the fellow gained an overview of various topics related to food safety risk assessment by attending the EU-FORA dedicated training modules.

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Abbreviations

- **ADI**: acceptable daily intake
- **BMDL<sub>10</sub>**: benchmark dose lower confidence limit 10%
- **bw**: body weight
- **EU-FORA**: The European Food Risk Assessment
- **OIM**: observed individual means
- **MOE**: margin of exposure
- **SCF**: Scientific Committee on Food
- **SPADE**: Statistical Program to Assess Dietary Exposure
## Appendix A – Additional learning activities

| Type of activity | Title | Organised by | Date/Duration |
|------------------|-------|--------------|---------------|
| **On-site courses** | Fundamentals of Epidemiology | University of Porto, part of Master's in Public Health | 31.10.2019–8.1.2020 |
| | Systematic Review and Meta-Analysis | University of Porto, part of Doctoral program in Public Health | 9.1.2020–30.1.2020 |
| **On-site seminars** | Institute of Public Health open seminars | University of Porto, Institute of Public Health | October 2019–February 2020, monthly |
| | Institute of Public Health PhD Students’ seminars | University of Porto, Institute of Public Health | October 2019–February 2020, monthly |
| | Nutrition and Obesity Epidemiology research group's seminars | University of Porto, Institute of Public Health | October-December 2019, monthly |
| **Online courses** | Reproducible Templates for Analysis and Dissemination | Emory University, at Coursera | ~20 h |
| | Estimation of Measurement Uncertainty in Chemical Analysis | University of Tartu, MOOC | ~26 h |
| | Sustainable Food Security: Crop Production | Wageningen University and Research, at edX | ~42 h |
| | Sustainable Food Security: Food Access | Wageningen University and Research, at edX | ~42 h |
| | Sustainable Food Security: The value of systems thinking | Wageningen University and Research, at edX | ~54 h |
| | Julia Scientific Programming | University of Cape Town, at Coursera | ~21 h |
| **Online conferences and seminars** | One Health EJP Annual Scientific Meeting | The One Health European Joint Programme | 27–29.5.2020 |
| | Getting to know the Global Dietary Database | The Global Nutrition and Policy Consortium | 11.6.2020 |