

Topic: Development of non targeted profiling approaches for the detection of emerging chemical hazards: application to the identification of new internal exposure markers in Human to support biomonitoring and environmental health studies

Research Unit: Laboratoire d'Etude des Résidus et Contaminants dans les Aliments (LABERCA)

UMR 1329 INRA-Oniris

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Planned start: September/October 2017

Context and challenge:

The reality of human exposure to chemical compounds is various and complex. First from a descriptive point of view, due to the wideness and variety of the substances involved. Secondly from a dynamic point of view, issued from the evolution over time induced by regulatory dispositions and/or practices at the production and use levels of these substances (for example via the introduction of substitutes to certain compounds and/or new substances). Thus, the number of substances which are conventionally monitored by targeted chemical analyses is not wide enough to allow a comprehensive vision of this Human chemical exposome. In particular, the current biomonitoring programs are centered around a limited number of internal exposure markers, which are already known, and for which data are already available in terms of characterization of the associated hazard. Thus these programs do not allow to take into account, let alone anticipate, the issue of emerging substances which have not been described yet as markers of interest from an exposure point of view or studied for their toxicological impact. The new non targeted phenotyping technological capabilities today offer new perspectives for addressing this issue. In particular, the profiling of biological samples using High Resolution Mass Spectrometry techniques, coupled to adapted bioinformatics data processing tools, constitutes a current research avenue in this field and falls within the domains of both science and innovation.

This issue is an integral part of a major European initiative to which this PhD project proposal is linked. This initiative, launched in the framework of a Cofund H2020 project (733032 Project « European Human Biomonitoring Initiative », HBM4EU) ambitions to provide Europe with a consortium able to address the current issues at stake around biomonitoring and the link between environment and health, on a scale which would make it competitive and visible alongside similar structures present in the American or Asian continents. Support to public policies is one of the main objectives of this project, which includes a research aspect in addition to an objective of structuring a reference network for the generation of these internal exposure data. This particularly ambitious project gathers more than 100 partner structures. It has been allocated a total of 50 million Euros over 5 years, as from January 2017. Within a French Hub gathering the main national research institutes, INRA (represented by LABERCA and Toxalim Units) is member of its management board, as leader of the « Emerging Substances » dedicated workpackage 16 (17 partners, 3m€). The work plan of this PhD project proposal will be set in the framework of this WP16, more precisely within Tasks T16.2 « Method

development and harmonisation of methods for non-targeted screening of yet unknown compounds » and T16.3 « Generation of new human biomonitoring data ».

Objectives and methods:

The purpose of this PhD work is to develop new analytical strategies and new bioinformatics supporting tools allowing a more comprehensive characterization of the Human internal chemical exposome. The finalized objective will be the detection and identification of new exposure markers concerning emerging contaminants. This topic associates both a state-of-the-art methodological research based on advanced technologies (high resolution mass spectrometry) and a thematic framework calling on high level and innovative scientific concepts and knowledge (exposome, data exploration, link between environment and health). In parallel to this content, which bears an interest as a training by and for research, the ambition of this PhD work is to contribute significantly to support public policies via the generation of data and knowledge which will guide the future biomonitoring programs and more widely to feed the risk assessment work.

The detection of exposure markers which have not yet been described can be implemented using several of strategies. A first approach consists in looking for particular signatures within the descriptive signals generated, based for example on the isotopic patterns observed in high resolution mass spectrometry. Some initial developments have already been done within LABERCA on this approach, the feasibility and proof of concept elements being achieved for certain environmental and food matrices [1]. From this methodological basis, the objective will consist to develop a similar non targeted analytical strategy destined to characterise halogenated contaminants in various human biological matrices, by coupling a spectrometric fingerprinting at high resolution (last generation instrumentation including orbitrap and hybride Q-TOF devices) to semi automated bioinformatics tools for data filtration and analysis (R, xcms, Shiny), focused on mass defect as discriminant feature. This “fishing” strategy will permit to screen and identify new internal exposure markers related to halogenated substances, possibly corresponding to various classes of compounds of interest for human biomonitoring and environmental health. The untargeted analysis will be performed according to several techniques for chromatographic separation (GC, LC, SFC) and ionization (ESI, APCI), for covering complementary fractions accessible to the analysis and then extending the range of possibly revealed markers. This PhD thesis work will include components of sample preparation (fractioning, concentration,...), bioinformatics, and structural elucidation work.

[1] Cariou R, Omer E, Léon A, Dervilly-Pinel G, Le Bizec B. Screening halogenated environmental contaminants in biota based on isotopic pattern and mass defect provided by high resolution mass spectrometry profiling. *Analyta Chimica Acta* 2016;936:130-138.

Hosting laboratory :

The Laboratoire d'Etude des Résidus et Contaminants dans les Aliments (LABERCA) is a mixed research unit of the National Institute for Agronomic Research (INRA) and Nantes Atlantic College of Veterinary Medicine, Food Science and Engineering (Oniris), belonging to the French Ministry of Agriculture. The Unit is also the French Reference Laboratory (NRL) of the General Directorate for Food (DGAI) for various classes of drug residues and environmental chemical contaminants. From a scientific point of view, the general domain of activity of the laboratory is chemical food safety and environmental health. The various research projects conducted by the laboratory are then referred to the generation and interpretation of exposure data (external and internal dose human), including the study of the investigated chemicals from their environmental sources to the consumers throughout the food chain. The Unit is also involved for years in the development and application of metabolomic and lipidomic approaches for characterizing the biological signatures associated to chemicals for

studying their potential link with clinical health parameters. LABERCA also developed an international teaching engineering with the implementation of a continuous education school specialized in food safety (www.saraf-educ.org). All these activities (assays and research) are carried out fulfilling basic management, e.g. accreditation and certification according to the ISO 17025 and ISO 9001:2008 standards, respectively.

Expected background and profile : Solid competences in analytical chemistry and experience with mass spectrometry and metabolomic.

Procedure : CV, motivation letter and master results. Reference letter may be joined.

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