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Review

Use of bioassays to assess hazard of food contact material extracts: State of the art

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ABSTRACT

This review focuses on the use of *in vitro* bioassays for the hazard assessment of food contact materials (FCM) as a relevant strategy, in complement to analytical methods. FCM may transfer constituents to foods, not always detected by analytical chemistry, resulting in low but measurable human exposures. Testing FCM extracts with bioassays represents the biological response of a combination of substances, able to be released from the finished materials. Furthermore, this approach is particularly useful regarding the current risk assessment challenges with unpredicted/unidentified non-intentionally added substances (NIAS) that can be leached from the FCM in the food. Bioassays applied to assess hazard of different FCM types are described for, to date, the toxicological endpoints able to be expressed at low levels; cytotoxicity, genotoxicity and endocrine disruption potential. The bioassay strengths and relative key points needed to correctly use and improve the performance of bioassays for an additional FCM risk assessment is developed. This review compiles studies showing that combining both chemical and toxicological analyses presents a very promising and pragmatic tool for identifying new undesirable NIAS (not predicted) which can represent a great part of the migrating substances and/or “cocktail effect”.

Contents

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1. Introduction

The majority of food distributed in developed countries is packed. Packages are barriers to prevent the chemical and microbiological contamination of food, and to prolong their shelf-life maintaining food quality and safety. Packaging contributes also actively to decrease food waste. Food Contact Material (FCM) is a general term to define materials intended to come directly or indirectly into contact with foodstuff. It includes kitchen utensils, packaging, containers, machines and materials used during the production chain, but also the storage and the transport of foodstuff.

The European framework Regulation (EU) No 1935/2004 for materials and articles intended to come into contact with food lists 17 groups of materials and articles which have to be in compliance with the requirements of the EU regulation (authorization of substance, labelling of materials, traceability, declaration of compliance and safeguard/control measures) and may be covered by specific measures. Among the 17 groups of the materials, only 5 are currently covered by specific measures. Depending on FCM physical/chemical parameters and food composition, FCM may interact with food and transfer some constituents (phenomenon called migration) that lead to low but measurable human chemical exposure (FACET project, 2012). Then, migration may cause a potential risk for human health that must be measured and controlled.

Regarding food safety, general requirements are set by article 3 of the regulation: “Material and articles in contact with food do not transfer substances in amounts which could endanger human health, or change food composition and/or organoleptic characteristics”.

FCM are manufactured from different base materials and Intentionally Added Substances (IAS) such as monomers, additives, and polymer production aids, essential in the manufacturing or FCM use since they enhance e.g. processibility, shelf life or mechanical properties. However, in addition to these substances of known origin, substances that are Non-Intentionally Added (NIAS) may be released from FCM and it has been pointed out that they can represent a large part of migrating substances (Grob et al., 2006, 2010). The article 3 of the “Plastic” Regulation (EU) No 10/2011 defines them as impurities, reaction intermediates or decomposition/reaction products. This text points out that the risk assessment of a substance should cover the substance itself but also relevant impurities and foreseeable reactions or degradation products that could be formed under intended use. However, not only plastics but all FCM types are concerned by NIAS presence; (recycled) paper and board, coatings, metal, cork ….

If some NIAS are already known and controlled, some others are difficult to predict with no available toxicological data. Furthermore, for some of them, it is difficult to analytically characterize, identify, quantify and make a risk assessment (Skjevrak et al., 2005) especially for mixture (eg MOAH in mineral oils from recycled paperboard). It is also important to notice that during these last few years, incidents reported by media were mainly due to NIAS.

1.1. Why is risk assessment difficult regarding NIAS?

The example of mineral oils found in recycled paper and board is characteristic of the problematic of NIAS. In terms of identification and quantification of NIAS, among specific techniques, GC-MS (detection of volatile molecules) or LC-MS (detection of non-volatile molecules) are the most popular analytical tools performed to characterize a FCM extract composition. Unfortunately, a single method is not able to give exhaustive information on molecules present in an extract (each of them can analyze a defined number of compounds present in FCM matrixes). Thus, a battery of analytical methods is complementary and need to be coupled (Nerin et al., 2013). The different reaction products of polymers, their corresponding degradation products (breakdown compounds), the presence of minor impurities, the degradation of IAS during FCM processing or food packaging storage, lead to the so-called 'forest of peaks' in chromatography (Grob et al., 2010). These chromatograms are extremely difficult to analyze and it should be emphasized that, if the GC-MS databases are rich, databases concerning LC-MS only begin to be implemented.

Due to the complex nature of FCM and the evolution of formulations (novel polymers, additives and uses), chemical analysis cannot be exhaustive, and structural identification of all FCM substances could not be achievable since they are present sometimes at trace levels (Nerin et al., 2013; Biedermann et al., 2014).

Predictive approaches of additive and polymer degradation have also been attempted to identify NIAS, but are often hindered by the non-disclosure of the initial composition of the material. Reaction schemes are often complex and function of specific process conditions. Moreover, one reaction intermediate can be the product of the degradation of various molecules recombined with others. Therefore, the prediction of reaction scheme in undefined chemical mixtures is very difficult to achieve completely (Castillo et al., 2013) and is time-consuming (Castle, 2013).

In term of risk assessment, the scientific literature may help to predict hazard. Quantitative Structure-Activity Relationship (QSAR) software programs, as statistical and expert methods, are able to predict the physicochemical properties and some biological effects of a substance as a function of its molecular structure such as alerts in genotoxicity (Ashby and Tennant, 1988). However, these *in silico* toxicological prediction tools require the full characterization of the substance chemical structure and then cannot be applied with unidentified NIAS or with a complex mixture such as FCM extract.

The “threshold of toxicological concern” (TTC) is also an interesting predictive risk assessment tool to use. TTC has been developed to assess potential human health concerns for chemicals of unknown toxicity present at low levels in the diet. However, to apply TTC, the defined chemical structure and the accurate exposure is needed (EFSA, 2012). Furthermore, the applicability of the TTC as a tool for mixture evaluation, not fully characterized, is only endorsed if sufficient information or analysis are available to confirm the absence in the mixture of compounds of exclusion classes (EFSA, 2016).

Regarding toxicological data, EFSA requires, whatever the level