The use of meta-analysis in food contact materials risk assessment

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ABSTRACT

As materials intended to be brought into contact with food, food contact materials (FCMs) – including plastics, paper or inks – can transfer their constituents to food under normal or foreseeable use, including direct or indirect food contact. The safety of FCMs in the EU is evaluated by the European Food Safety Authority (EFSA) using risk assessment rules. Results of independent, health-based chemical risk assessments are crucial for the decision-making process to authorize the use of substances in FCMs. However, the risk assessment approach used in the EU has several shortcomings that need to be improved in order to ensure consumer health protection from exposure arising from FCMs. This article presents the use of meta-analysis as a useful tool in chronic risk assessment for substances migrating from FCMs. Meta-analysis can be used for the review and summary of research of FCMs safety in order to provide a more accurate assessment of the impact of exposure with increased statistical power, thus providing more reliable data for risk assessment. The article explains a common methodology of conducting a meta-analysis based on meta-analysis of the dose-effect relationship of cadmium for benchmark dose evaluations performed by EFSA.

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Introduction

Food comes into contact with many materials and articles during its production, processing, storage, preparation and serving. Food contact articles are made from various FCMs such as plastics, paper and board, ceramics, glass, metal, adhesives, and printing inks. More than several thousand chemical substances are used in the production of materials and articles for contact with food, including starting substances, such as monomers, substances used in polymer processing and additives. The chemicals that are used in the production of FCMs are subject to risk assessment by the European Food Safety Authority (EFSA) and then regulated by relevant European Union legislation. Materials and articles intended for contact with food may release intentionally added substances, which are included in the material. Examples of these substances include antioxidants, fillers, foaming and anti-foaming agents, plasticizers, stabilizers, auxiliary...
substances used in the production of plastics such as dispersing agents aimed at obtaining specific technological effects and nonintentionally added substances (NIASs) such as impurities and reaction products, e.g. oligomers, polymers, and by-products converted during processing such as, carcinogenic primary aromatic amines (Ćwiek-Ludwicka et al. 2011).

By far the majority of food packaging and processing equipment are made of plastics, e.g. polyethylene, polypropylene, polyethylene terephthalate, and polyamide, or they contain a polymeric coating or layer in direct contact with food in multi-layer plastic packaging (laminates). Due to the complex chemistry of polymers and the use of a wide variety of materials in food packaging production, many substances can migrate into food: both known or unknown NIASs (Geueke et al. 2014; Grob et al. 2006). The amount and rate of release of a given substance from the material in contact with food depends on the type of food, storage temperature and thermal processing of the food, storage time and exposure to UV radiation.

Many chemical compounds used as ingredients in materials and products intended for contact with food, including substances used in the production and processing of plastics and organic protective coatings intended for contact with food, exert endocrine disrupting properties. These compounds include bisphenol A (Gray et al. 2004) and bisphenol S, or esters of phthalic acid, such as di(2-ethylhexyl)phthalate (Fasano et al. 2012). In addition, endocrine disrupting substances occur in printed food packaging and in recycled paper and cardboard as a residue of UV-stabilized printing inks, e.g. benzophenone and 4-methylbenzophenone (Suciu et al. 2013). Other examples of such substances are perfluorooctane sulfonate (PFOS) and perfluorooctane acid (PFOA), belonging to the group of per- and polyfluoroalkyl substances (PFASs), which are used in grease-resistant waxed paper and in anti-stick coatings used in cooking, frying and baking vessels. However, the most recent risk assessment performed by EFSA shows that human epidemiological studies for endocrine outcomes provide insufficient support for causal associations between exposure to PFOS/PFOA and the timing of puberty, menopause, menstrual cycle changes, endometriosis, duration of breastfeeding, semen quality, levels of sex hormones or thyroid function (EFSA 2018).

Understanding the migration of chemicals from FCMs into food is an important part of FCMs risk assessment. Risk assessment of chemicals migrating from FCMs has two major objectives: to establish acceptable exposure levels for humans and to assess the health risk associated with a particular type of exposure.

**Food contact chemicals risk assessment in the EU**

In the European Union, substances used in the manufacture of plastic FCMs are subject to authorization that includes starting substances and additives (EFSA 2017). According to the EFSA Administrative Guidance for the preparation of applications for the safety assessment of substances to be used in plastic Food Contact Materials, any applicant who applies for authorization for a particular substance that will be used in FCMs shall provide EFSA with all available data that can be used in its assessment. Any toxic properties of the substance and its migration to food simulants, and the conditions of the proposed use of the material have to be taken into account. The general principle is: the
greater the exposure through migration, the more toxicological information will be required to evaluate the substance.

According to the EFSA risk assessment process, in the case of high substance migration levels, in the range of 5–60 mg kg\(^{-1}\) of food, a full range of toxicological data is required. When the migration of the substance is in the range of 0.05–5 mg kg\(^{-1}\) of food or below 0.05 mg kg\(^{-1}\) then the range of necessary data can be reduced. However, these data have to enable the assessment of the risks associated with the use of the substance in FCMs.

The full data set comprises at least two in vitro genotoxicity tests, a 90-day oral toxicity study, studies on absorption, distribution, metabolism and excretion, studies on reproduction and developmental toxicity, and studies on long-term toxicity/carcinogenicity.

In cases where migration is in the range from 0.05 to 5 mg kg\(^{-1}\) of food or food simulant, at least two genotoxicity tests as indicated above are needed, a 90-day oral toxicity study and data to demonstrate the absence of potential for accumulation in humans.

In cases where migration is below 0.05 mg kg\(^{-1}\) of food/food simulant at least two genotoxicity tests as indicated above are needed. In short, only three in vitro mutagenicity and genotoxicity tests are mandatory for all substances authorized in plastics, regardless of the estimated level of exposure. Only if the estimated level of exposure exceeds 5 mg kg\(^{-1}\) of food/food simulant are tests for developmental and reproductive toxicity are required.

EFSA takes the default exposure assumptions that a person (60 kg body weight, bw) consumes daily throughout his/her whole life-time up to 1 kg of food packaged in 6 dm\(^2\) food contact materials constantly releasing substances at the full specific migration limit (SML).

One major area to revisit is the estimation of consumer exposure (EFSA CEF Panel 2016) as this does not take into account infants and toddlers who have the highest consumption per kg bw; toxicological tiers should also take this into account.

Certain substances, however, are not subject to authorization and listing on the European Union list. These substances include: nonintentionally added substances, impurities present in authorized substances, reaction products generated during the production of plastic materials and articles and resulting from the contact with food, degradation products generated during the production or storage of plastic materials and articles, aids used in the polymerization process, polymer production aids including solvents that are not included in the EU list, colorants, and substances used behind a functional barrier. For these substances, it is the responsibility of the business operators to ensure compliance and be able to demonstrate the absence of risk to human health by performing a risk assessment based on internationally recognized scientific principles. These principles are, however, extremely difficult to use in practice by business operators.

Moreover, a business operator using an authorized substance or materials and articles containing the authorized substance is obliged to immediately inform the European Commission of any new scientific or technical information which might affect the safety assessment of the substance in relation to human health.
**Omissions in the food contact chemicals risk assessment**

**General**

Currently, one of the major problems is the lack of harmonization between national risk assessment mechanisms for substances migrating from FCMs and also the lack of guidelines and transparency in risk assessment across the Member States (MSs). This situation causes difficulties in the free trade of goods and creates major problems in safety assessment and enforcement activities by control services. Also, different protocols for the authorization of substances between MSs not in line with EFSA standards can be problematic. The second important shortcoming in FCM area is the lack of action with respect to technological and scientific developments.

Moreover more attention should be paid to the final article rather than the starting substances, due to the possibility of the presence of chemicals such as break-down products, impurities from starting materials, unwanted side-products and various contaminants from recycling processes. It is not possible to evaluate all the substances present in FCMs, mainly due to EFSA and national risk assessment authorities’ limited capacity to cope with substance authorization. Thus, it seems necessary to focus on substances that can migrate from FCMs into food and not on starting substances in risk assessment process (Muncke et al. 2017).

**Nonintentionally added substances (NIASs)**

Not all chemicals migrating from FCMs are assessed by third party authorities for their risk to human health. Only intentionally added substances are subject to EFSA authorization in the EU. NIASs not added for technical reasons during the production of FCMs process are exempted from such authorization and inclusion in the EU list. NIASs originate from different sources in food contact materials and include side-products (such as primary aromatic amines from polyurethane adhesives), break-down products (such as nonanal, glyoxal, methylglyoxal from PET), impurities from starting materials, unwanted side-products and various contaminants from recycling processes (PET oligomers, diethylene glycol dibenzoate from recycled PET) (Félix et al. 2012; Alin and Hakkarainen 2011; Bignardi et al. 2017). Break-down products are a major part of NIASs, but it should be noted that NIASs do not include those break-down products that lead to the original monomer. Generally, it is accepted that only compounds with a molecular weight of more than 1000 Da are not further identified during the analysis of NIASs (Schaefer et al. 2004). In principle, nonintentionally added substances will have to comply with general safety requirements and are subject to risk assessment in line with European Commission Regulation EC 10/2011.

Although the European Commission mentioned NIASs in the EU regulation, no clear advice is provided as to how to handle the complex issue of their risk assessment. Different approaches are discussed, such as a tiered-approach or methods including a combination of bioanalytical and analytical techniques. Moreover, the awareness of the presence of NIASs and their availability as pure chemicals in sufficient quantity is quite often limited and this is a significant obstacle in risk assessment.
Endocrine disrupting chemicals (EDCs)

Food contact materials are an important source of chemical food contaminants, including endocrine disrupting chemicals (EDCs). After entering human or animal organisms, EDCs can interfere with the endocrine system by, for example, interaction with relevant receptors or affecting the hormonal metabolism. Recent results of scientific research have confirmed an association between chronic exposure to EDCs and adverse health effects, such as hormonal cancers (breast, prostate, testes), reproductive problems (genital malformations, infertility), metabolic disorders (diabetes, obesity), asthma and neuro-developmental conditions (learning disorders, autism spectrum disorders) (Muncke 2009).

Muncke (2011) pointed out that at least 50 chemical substances authorized under EU and USA legislation for use in FCMs are known or suspected endocrine disruptors. However, this is not a final list, since there are materials other than plastics which are intended to come into contact with food for which a positive list of permitted substances has not been established. Materials such as paper and cardboard, for the composition of which there are no specific requirements in the EU, can release contaminants into food that may include EDCs. Examples of such substances include diisopropyl-naphthalenes (DiPN, CAS 24157-81-1), dibutylphthalate (DiBP, CAS 84-74-2), and per- and polyfluoroalkyl substances (PFASs). EDCs may also migrate into foods from external printed paper and cardboard packaging. The large pore size of paper-based materials permits smaller molecules to migrate from the outside and into the food.

Van Den Houwe et al. (2016) found several photoinitiators in dry foods packaged in printed cartons and cardboard packaging, including benzophenone (BP), ethyl-4-dimethylnaminobenzoate (EDMAB), 2-dimethoxy-2-phenyl acetophenone (DMPA). These compounds are used as an additive (UV photo-initiator) for printing inks. Van Den Houwe et al. (2016) detected the highest concentration of benzophenone in a rice sample – 0.262 mg kg\(^{-1}\) – and this reveals the extent of the problem with endocrine disrupting chemical substances in paper and cardboard and printing inks.

Due to human exposure to EDCs originating from different sources, not only dietary ones, the European Commission has prepared a strategy for endocrine disruptors which includes a collective EU list of potential endocrine disruptors. In order to prioritize efforts, over 432 candidate substances have been subdivided into 3 main categories (Commission Staff Working Document Impact Assessment 2016):

- Category 1: Substances for which endocrine activity has been documented in at least one study of a living organism. These substances are given the highest priority for further studies.
- Category 2: Substances without sufficient evidence of endocrine activity, but with evidence of biological activity relating to endocrine disruption.
- Categories 3a and 3b: Substances for which there are no indications of endocrine-disrupting properties or which cannot be evaluated due to a lack of data.

Mixtures of chemicals

Another shortcoming of the risk assessment process for food contact materials is its focus only on individual substance risk assessment, not on the overall risk of a mixture.
Plastic FCMs can leach mixtures of substances into food at low concentrations, e.g. monomers, additives, processing production aids, impurities, printing inks, adhesives or other unknown substances. The mixture toxicity of the overall migrate in food is not assessed for its risk to human health, which is a great concern due to consumers’ total exposure to mixtures rather than single substances. Moreover, consumers are exposed to chemicals from different sources other than food, which may cause a stronger toxic effect. According to Kortenkamp et al. (2007), joint effects of mixtures are noticeable even when all mixture components are present at doses below acceptable levels of exposure, which raises doubts regarding the traditional chemical-by-chemical approach to risk assessment.

**Oligomers**

Oligomers consist of 2 to 40 monomeric units and can be linear, branched or cyclic. They are formed as a result of either incomplete polymerization or subsequent degradation (thermal or hydrolytic) of polymeric material. The variety of possible oligomers is constantly increasing with the introduction onto the FCM market of new types of plastics made from novel monomers and monomer combinations. Such a diversity, accompanied by the lack of appropriate analytical standards, makes both qualitative and quantitative characterization of oligomeric migrants, as well as evaluation of their toxicity, a challenging task. Hoppe et al. (2016) stressed that oligomers are not specifically regulated in regulation EU 10/2011 and are, therefore, in practical terms located in a legal ‘gray area’. The permanent extension of the EU positive list with new co-monomers as a consequence of industrial developments principally gives rise to an exponentially growing amount of new oligomers which might be present in food contact polymers as potential migrants. Safety assessment for oligomers has been traditionally based on their respective monomers, since physiological degradation of oligomers to monomers is assumed. However, polycondensate-type cyclic oligomers may need to be considered separately; their susceptibility to hydrolysis in the gastrointestinal tract and their toxic properties are as yet incompletely understood.

**Substance of very high concern (SVHCs)**

Many chemicals used in FCMs were identified in REACH as SVHCs due to endocrine disrupting properties (e.g. phthalates as BBP, DBP, DEHP and DiBP) (Geueke and Muncke 2018). There is a noticeable lack of overlap between REACH and FCM legislation. A chemical can be identified as a substance of very high concern (SVHC) in REACH, but this then generates no automatic action in FCM legislation. There is no effective link between data gathered in REACH and FCM laws and no pressure to substitute SVHCs in FCM regulations.

**Prioritization before risk assessment**

The prioritization approach is a highly important part preceding the risk assessment process for FCMs. Thousands of chemicals can migrate from FCMs into foods,
including intentionally added substances and NIASs and also migration from outside food packaging, from printing inks; hence, risk assessment is a very costly and time-consuming process. Prioritization can serve as a tool for selecting those chemicals with highest exposure estimates and toxicity data for subsequent detailed risk assessment.

Pieke et al. (2018) proposed a method to convert the obtained concentration estimates into tentative exposure assessments and to evaluate the predicted chemical structures by quantitative structure-activity relationship (QSAR) models for carcinogenicity, mutagenicity, and reproductive toxicity. These authors further describe a decision tree that uses assessment results to assign the evaluated NIAS into “high priority,” “low priority,” or “unclassified” groups.

Van Bossuyt et al. (2017) proposed a new prioritization strategy for identifying potentially mutagenic substances developed based on the combination of multiple (quantitative) structure-activity relationship ((Q)SAR) tools. Nonevaluated substances used in printed paper and cardboard food contact materials were selected for a case study. As a result of this study, 106 out of the 1723 substances were assigned “high priority” as they were predicted to be mutagenic by 4 different (Q)SAR models. Van Bossuyt et al. (2017) concluded that, for further prioritization, additional support could be obtained by applying local, i.e. specific, models.

**Methodology of meta-analysis**

Meta-analysis refers to the statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating these findings (Glass 1976). Meta-analysis is indeed the analysis of analyses and provides an approach for the joint evaluation of the results of several studies.

Meta-analysis consists of the following steps: systematic review of primary research, evaluation of heterogeneity between primary studies, collation of relevant primary data, estimation of effect size, calculation of effect size for each study, choice of random-effects or fixed effects model, subgroup specification, calculation of the summary effect (per subgroup and overall), conduct of sensitivity analysis, checking for the presence of publication bias and interpretation of meta-analysis results (Borenstein 2009). Meta-analysis results are commonly displayed graphically as ‘forest plots’. A meta-analysis is often part of a systematic review, but – as mentioned – this is not always possible. Figure 1 presents the steps to be taken in meta-analysis of an animal study proposed by Hooijmans et al. (2014).

**Systematic review**

Systematic review is the first step in performing meta-analysis and performed in order to gain an overview of all available studies, and assess them for relevance, quality and reported findings. The results of all individual studies are reported and compared in each systematic review as the last step, but only when it is possible to perform a meta-analysis. However, some systematic reviews are also published without meta-analyses, especially when the included studies are too heterogeneous or seem to be seriously biased (Hooijmans et al. 2014). Results from a meta-analysis may be more robust than
results from a systematic review including only the analysis and comparison results of individual studies.

Generally, systematic reviews consist of eight steps: phrase the research question; define the study in- and exclusion criteria; search for all original papers and abstracts; select all relevant abstract and papers; assess the study quality and validity of the included studies; extract the relevant data from all included papers; analyze and compare the results of all individual studies; and present and interpret data.

**Software packages**

Dedicated software is available to perform meta-analyses; the most popular are: Comprehensive Meta-analysis (CMA), MetAnalysis, MetaWin, MIX, Revman and WEasyMA. According to Bax et al. (2007), the most suitable meta-analysis software for a given user depends on his demands; no single program may be best for everybody.

**Steps in meta-analysis**

Key elements and steps which are necessary to take in performing a meta-analysis are presented below, based on the Cochrane Handbook (Higgins and Green 2008):
Check whether the included studies are homogenous

It is critical to assess whether heterogeneity is present, and to what extent, when pooling studies using meta-analysis, as the presence of heterogeneity can affect the conclusions that can be drawn from a meta-analysis. Any statistical heterogeneity that is detected in results must also be taken into account when interpreting the results, as this can affect the generalizability of the conclusions that can be drawn. Thus, an important part of a meta-analysis is to include only systematic reviews that have been assessed for variability across studies in order to make sensible decisions about pooling data or making particular comparisons. Statistical heterogeneity can be assessed by using statistical tests for variation. Most dedicated software automatically generates statistics that test for heterogeneity when performing a meta-analysis. There are different statistical approaches for investigating heterogeneity, including the standard chi-squared test, the I square statistic, and Tau squared.

Assemble the relevant study data

Study design and study results are important to gather relevant study results, they may be used in the meta-analysis. Study results may be expressed on different scales of measurement and mean values.

Choose and calculate the effect size measure

Effect sizes refer to quantitative indicators of the direction and magnitude of the effects of the interventions on outcomes. Common effect sizes reported in meta-analyses include the risk ratio (RR), risk difference (RD), odds ratio (OR), weighted mean difference (WMD), and standardized mean difference (SMD). It is important to calculate a weighted average of the results, in which larger trials have more influence than smaller ones. The statistical techniques to tackle this can be classified into two broad models: “fixed effects” model and “random effects” model.

Choose a random-effects or fixed-effects meta-analysis model

The choice between these two models will depend on the way the variability of the results between the chosen studies is treated. The first model suggests that random variation is the sole cause for this variability, meaning that the size of the studies is irrelevant to the type of results they give. The second, “random effects”, model considers different underlying effects in each study as sources of variation, leading to larger confidence intervals than in the “fixed effects” model.

Calculate the summary effect, per subgroup and overall

The summary effect size is generally based on the effect sizes and the weights of the individual studies. It can be calculated by hand, but there is also software that will perform the calculations and provide forest plots.
Conduct a sensitivity analysis

To assess the robustness of the findings from the meta-analysis, a sensitivity analysis is conducted. For example, one sensitivity analysis may explore the impact of using different meta-analysis models. Another sensitivity analysis may explore the impact of excluding or including studies in a meta-analysis based on sample size, methodological quality, or variance. If results remain consistent across the different analyses, the results can be considered robust as even with different decisions they remain the same/similar. If the results differ across sensitivity analyses, this is an indication that the results may need to be interpreted with caution.

Minimize publication bias

Publication bias occurs when the results of a published study differ from the results of the entire pool of research conducted in that field. This can happen if research that is statistically significant is published while neutral results remain unpublished. Publication bias can also encompass other dissemination biases; for example, selectively reporting only significant outcomes.

Application of meta-analysis in FCM risk assessment

Gonzales-Barron and Butler (2011) recommended using meta-analysis as a valuable tool for the synthesis of food safety research and in quantitative risk assessment modeling. According to Gonzales-Barron and Butler (2011), a meta-analysis systematic approach comprising a broad range of techniques merits consideration among food safety researchers to integrate the current body of knowledge and data on targeted issues in food safety.

Use of meta-analysis is extremely useful in chronic risk assessment of substances migrating from FCMs into food. It is especially required in the determination of toxicological reference values due to the large variety of chemical food contaminants that can leach from food contact materials and the lack of updated risk assessment for them. The synthesis of information gathered from different studies can explain dose-response and/or dose-effect relationships and estimate the benchmark dose (BMD) and its 95% confidence lower limit (BMDL) for humans using cutoff points relevant to clinical changes in the target organ. To set a reference value for exposure of substances migrating from food contact materials, the levels of exposure that do not cause substantial adverse health effects should be estimated. The no-observed-adverse-effect level (NOAEL) approach was traditionally used to set the point of departure for a guideline value of the human exposure limit. Later, the benchmark dose (BMD) was introduced for the risk assessment of contaminants. A BMDL is a statistical lower confidence limit to a dose producing some predetermined increase in response rate, such as 1% or 10%. The BMD is calculated using a mathematical dose-response model. This approach makes appropriate use of sample size and the shape of the dose-response curve. The BMD will normally not depend strongly upon the mathematical model used, because the method does not involve extrapolation far below the experimental range. Thus, the method sidesteps much of the model dependency often associated with extrapolation of carcinogenicity data to low doses. The method can be applied to either “quantal” data,
in which only the presence or absence of an effect is recorded, or “continuous” data, in which the severity of the effect is also noted. The BMD method is a more advanced approach and competence in the area is limited (Sand et al. 2007).

EFSA used the Bayesian technique of meta-analysis and hierarchical modeling in order to revise the current provisional tolerable weekly intake (PTWI) of cadmium in Europe and evaluated the dose-response and/or dose-effect relationships between urinary cadmium and biomarkers in the Technical Report (EFSA 2009).

Urinary cadmium is a classical cadmium marker of long-term exposure to cadmium. Cadmium is a heavy metal found as an environmental contaminant, both through natural occurrence and from industrial and agricultural sources. Foodstuffs are the main source of cadmium exposure for the nonsmoking general population. Food contact materials, especially ceramic ware, can release cadmium into foodstuffs.

EFSA assessment is based on a meta-analysis of epidemiological studies selected in a systematic review and assessing the concentration-effect relationship between urinary cadmium and beta-2-microglobulin (B2M) levels. Using a hybrid approach for various cutoffs, EFSA evaluated the benchmark dose (BMD) and its 95%-confidence lower bound (BMDL) for humans. A hybrid benchmark dose (BMD) approach, in which the Hill model was fitted to the data, was chosen to estimate the BMD and its lower one-sided 95%-confidence bound for an extra risk of 5% of producing a specified change in the urinary level of the B2M (BMDL5).

In its report, EFSA concluded that the meta-analysis and “key-study” approaches are two complementary steps for robust BMD evaluation in the risk assessment set-up.

**Conclusions**

In this review, we have attempted to propose the use of meta-analysis to improve the FCMs risk assessment mechanism. The major conclusion in defining shortcomings in the current food contact risk assessment mechanism and legislation is that safety of food contact materials is currently less guaranteed due to different risk assessment and authorization processes across the Europe and their problematic enforcement. Due to EFSA and national risk assessment authorities’ limited capacity to cope with substance authorization in FCMs, risk assessment should focus on chemicals that can migrate from FCMs, taking into account in the prioritization process and their toxicological properties. To determine toxicological reference values for chemical food contaminants that can migrate from FCMs, one valuable tool could be meta-analysis, as an approach to the statistical analysis of a large collection of data from individual studies for the purpose of integrating the findings. Use of a meta-analysis can lead to more reliable conclusions than from single study results. The lack of updated risk assessment data for many substances migrating from food contact materials is still a great problem hindering the establishment of action values, which is necessary to harmonize enforcement actions in all MSs.

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