Food and Chemical Toxicology 109 (2017) 428–438

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

High-throughput migration modelling for estimating exposure to chemicals in food packaging in screening and prioritization tools

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A R T I C L E I N F O

Article history:
Received 4 May 2017
Received in revised form
9 June 2017
Accepted 14 September 2017
Available online 20 September 2017

Keywords:
Risk
Life cycle assessment
Low-tier
Exposure modelling
Product intake fraction
Food contact materials

A B S T R A C T

Specialty software and simplified models are often used to estimate migration of potentially toxic chemicals from packaging into food. Current models, however, are not suitable for emerging applications in decision-support tools, e.g. in Life Cycle Assessment and risk-based screening and prioritization, which require rapid computation of accurate estimates for diverse scenarios. To fulfil this need, we develop an accurate and rapid (high-throughput) model that estimates the fraction of organic chemicals migrating from polymeric packaging materials into foods. Several hundred step-wise simulations optimised the model coefficients to cover a range of user-defined scenarios (e.g. temperature). The developed model, operationalised in a spreadsheet for future dissemination, nearly instantaneously estimates chemical migration, and has improved performance over commonly used model simplifications. When using measured diffusion coefficients the model accurately predicted ($R^2 = 0.9$, standard error (S_e) = 0.5) hundreds of empirical data points for various scenarios. Diffusion coefficient modelling, which determines the speed of chemical transfer from package to food, was a major contributor to uncertainty and dramatically decreased model performance ($R^2 = 0.4$, $S_e = 1$). In all, this study provides a rapid migration modelling approach to estimate exposure to chemicals in food packaging for emerging screening and prioritization approaches.

1. Introduction

Food contact materials (FCM) are a source of consumer exposure to potentially hazardous chemicals, such as bisphenol A, phthalates and fluorinated compounds (Begley et al., 2005b; Tittlemier et al., 2007; Apelberg et al., 2007; Cao, 2010; Geens et al., 2012). In addition, thousands of other chemicals are legally acceptable in FCM and can lead to human exposure (Geueke et al., 2014; FDA, 2015a). Concern over consumer risks are bolstered by data gaps in FCM safety assurance as well as recent hazard information generated by *in silico* and *in vitro* high-throughput toxicity and bioactivity screening studies (Biedermann and Grob, 2013; Neltner et al., 2013; Muncke et al., 2014; Price and Chaudhry, 2014; Evans et al., 2016; Karmaus et al., 2016). To estimate potential risks posed by chemicals in FCM, hazard and exposure must be quantified. Empirical exposure data, however, are scarce and analytically challenging to obtain (Rudel et al., 2011). Modelling the migration of chemicals from materials into food is therefore critical to fill empirical data gaps and quantify exposure.

Chemicals in food packaging in particular have been a major focus of consumer exposure assessments that build on migration modelling. The *Cumulative Estimated Daily Intake* (CEDI) database of the United States Food and Drug Administration (FDA, 2015a) and the *Flavourings, Additives, and food Contact materials Exposure Tool* (FACET) (Oldring et al., 2014b) of the European Commission's Joint Research Center (JRC) are recent large-scale advances to estimate realistic exposure to chemicals in food packaging, for 1302 and 6499 chemicals, respectively (although only 5 chemicals are pre-installed in FACET as of May 2017). In both cases, exposure estimates (expressed in mg/kg/d) are a function of *undisclosed data* e.g. *based on an annual country-specific market survey.* By fixing exposure estimates based on undisclosed market-wide occurrences of a chemical in package-food combinations combined with a food consumption estimate, CEDI and FACET cannot be used to estimate exposure to chemicals in packaging per unit(s) of product use, such

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https://doi.org/10.1016/j.fct.2017.09.024

as one packaged food consumed by one person. Comparing different unit(s) of product use or unit(s) of chemical use (e.g. kilogram of chemical used as a plasticizer in many different polymers) is a main application of emerging exposure screening tools such as SHEDS-HT (Isaacs et al., 2014), ECETOC TRA (Delmaar et al., 2013), USEtox (Rosenbaum et al., 2008), and the PiF framework (Fantke et al., 2016). A per-unit assessment structure facilitates comparing products on a per use basis (regardless of total market volume), or comparing extrapolated uses (e.g. to the entire population or a company-specific production volume). Therefore, in order to be coupled or incorporated within emerging assessment tools, a chemical exposure model for food packaging should have the flexibility to assess various units of packages used by consumers. A major research gap remains, as no peer reviewed tool or method exists to facilitate high-throughput, transparent and flexible estimation of exposure to chemicals in food packaging to support applications in screening and prioritization tools.

With millions of product-chemical combinations on the market, screening has emerged as a resourceful approach to prioritize chemicals and/or products that require further scrutiny. High-Throughput Risk-based Screening (HTRS), and environmental Life Cycle Assessment (LCA) are distinct screening and prioritization tools that can consider potential impacts on human health related to chemical exposure. HTRS combines low-tier high-throughput exposure modelling with risk-based indicators, such as high-throughput screening bioassays (Wambaugh et al., 2013; Isaacs et al., 2014; Wetmore et al., 2015; Shin et al., 2015; Karmaus et al., 2016). LCA is an established sustainability assessment framework that combines multiple modelling approaches to screen product systems and their potential impacts on human health, ecosystems, and natural resources (Hauschild, 2005; Hellweg and Milà i Canals, 2014). Both HTRS and LCA rely on practical, high-throughput models that require limited parameterization and computational capacity. Exposure models can thereby be designed for both tools despite their different applications (Wambaugh et al., 2013; Shin et al., 2015; Huang et al., 2017a).

High-throughput models, compatible with LCA and HTRS, to estimate exposure to chemicals in food packaging are specifically needed to complement fast-paced advances towards sustainability and resource management targets. Concern over chemicals in food packaging is a barrier to the rising interest in circular economy and use of recycled or re-used materials (Biedermann and Grob, 2013; Lee et al., 2014; European Bureau for Conservation and Development, 2015; FDA, 2015b; Leslie et al., 2016). Furthermore, bio-based packaging designs (Yuan et al., 2016), or designs to reduce food waste (Siracusa et al., 2014), can also influence packaging materials, their contained chemicals, and their environmental impacts. LCA is extensively used to inform decision making regarding more sustainable food packaging design (Hunt and Franklin, 1996; Flanigan et al., 2013). However, LCA methods traditionally only consider *environmental* exposure pathways, and not indoor exposure pathways related to product use, such exposure to chemicals that have migrated from a package into a food. . To address this inconsistency, there are recent modelling efforts to make LCA more comprehensive and include exposure to chemicals in products (Shin et al., 2012; Jolliet et al., 2015a; Fantke et al., 2016; Ernstoff et al., 2016; Csiszar et al., 2016b; Huang et al., 2017a), although LCA-compatible models do not yet exist to estimate exposure through food packaging.

The objective of this study is thereby to develop a high-throughput (HT) modelling approach for estimating migration of chemicals from packaging into food for emerging applications in screening and prioritization tools, such as LCA and HTRS. The main criteria for our HT approach was to design a rapid, accurate, and accessible migration model—meaning nearly instantaneous computation, representative of the average and not the worst-case, and easily applicable to existing exposure assessment frameworks. To maximize future applicability, the HT model should be valid across chemical-package-food scenarios sensitive to packaging type, thickness, the food type and quantity, and the time and temperature of contact between the package and the food. Archetypal scenarios can be defined in an assessment framework to minimize required user inputs. As a first step we focus on organic chemicals in a single layer of polymeric packaging directly contacting food. Our goals are to 1) analyze commonly used migration models to identify needs for high-throughput approaches, 2) develop a new HT approach for predicting migration for chemical-food-packaging scenarios (e.g. characteristics of package and food, and contact time and temperature) defined by users, 3) and test the developed approach against other models and empirical migration data available from the United States Food and Drug Administration (US FDA).

2. Methods

2.1. Product intake fraction framework

To quantify exposure to chemicals in food packaging in LCA and HTRS, we propose using the product intake fraction metric (PiF - Jolliet et al., 2015a)—defined as the mass of a chemical taken in by all exposed persons versus the mass of chemical in a product after manufacturing. PiF has been applied to several other groups of consumer products and HT approaches (Shin et al., 2015; Jolliet et al., 2015a; Fantke et al., 2016; Csiszar et al., 2016a; Ernstoff et al., 2016). Assuming that the majority of exposure to chemicals within a manufactured food package occurs via migration into food and not through other pathways (e.g. dermal uptake through contact with package or inhalation via releases into indoor air), $PiF = f_c \times f_t$, where f_t is the time-dependent fraction of the initial mass of chemical in the packaging that has *transferred* (i.e. migrated) into food, and f_c is the fraction of food *consumed* (e.g. not wasted). In the case of food packaging, PiF is specific for each chemical in a given package-food scenario, where a scenario is specified by packaging (material type, thickness, and amount) and food (type and amount) characteristics, and the contact duration and temperature (e.g. according to pasteurization and/or storage).

Values for f_c can be estimated through studies quantifying consumer food waste, f_w, where $f_c = 1 - f_w$. Various country-specific studies have found consumer-level wastes between 9 and 45% depending on the food category (Beretta et al., 2013; Buzby et al., 2014). Accounting for food waste could be especially important in assessments of packaging designs that result in different food spoilage rates (Williams and Wikström, 2011; Williams et al., 2012). This study will focus on providing methods to estimate the second parameter f_t through mathematical modelling for various chemical-package-food combinations and scenarios, as f_t is not a value that can be typically obtained from prior studies.

2.2. Analysis of migration model behaviour and needs for a high-throughput model

Various migration models exist to estimate migration of a chemical from FCM into food. Models tend to be computationally complex, require empirical input data for parameterization, or only be valid for specific scenarios (Pocas, 2008; Piringer and Baner, 2008; Pocas et al., 2012). We focused on widely used migration models that have also been empirically validated and require a limited amount of empirically-derived input parameters (Begley