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High-throughput dietary exposure predictions for chemical migrants from food contact substances for use in chemical prioritization

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ABSTRACT

Under the ExpoCast program, United States Environmental Protection Agency (EPA) researchers have developed a high-throughput (HT) framework for estimating aggregate exposures to chemicals from multiple pathways to support rapid prioritization of chemicals. Here, we present methods to estimate HT exposures to chemicals migrating into food from food contact substances (FCS). These methods consisted of combining an empirical model of chemical migration with estimates of daily population food intakes derived from food diaries from the National Health and Nutrition Examination Survey (NHANES). A linear regression model for migration at equilibrium was developed by fitting available migration measurements as a function of temperature, food type (i.e., fatty, aqueous, acidic, alcoholic), initial chemical concentration in the FCS (C_0) and chemical properties. The most predictive variables in the resulting model were C_0, molecular weight, log K_{ow}, and food type ($R^2 = 0.71$, $p < 0.0001$). Migration-based concentrations for 1009 chemicals identified via publicly-available data sources as being present in polymer FCSs were predicted for 12 food groups (combinations of 3 storage temperatures and food type). The model was parameterized with screening-level estimates of C_0 based on the functional role of chemicals in FCS. By combining these concentrations with daily intakes for food groups derived from NHANES, population ingestion exposures of chemical in mg/kg-bodyweight/day (mg/kg-BW/day) were estimated. Calibrated aggregate exposures were estimated for 1931 chemicals by fitting HT FCS and consumer product exposures to exposures inferred from NHANES biomonitoring ($R^2 = 0.61$, $p < 0.001$); both FCS and consumer product pathway exposures were significantly predictive of inferred exposures. Including the FCS pathway significantly impacted the ratio of predicted exposures to those estimated to produce steady-state blood concentrations equal to *in-vitro* bioactive concentrations. While these HT methods have large uncertainties (and thus may not be appropriate for assessments of single chemicals), they can provide critical refinement to aggregate exposure predictions used in risk-based chemical priority–setting.

1. Introduction

Assessing the risks posed to human health from exogenous chemicals requires estimates of both toxicity and potential for exposure (Committee on Human and Environmental Exposure Science in the 21st Century et al., 2012). A recent report from the National Academy of Sciences (NAS) on improving risk-based chemical evaluations notes that exposure information plays a particularly high-value role in chemical priority-setting (National Academies of Sciences, Engineering, and Medicine, 2017). To develop risk-based metrics for prioritizing thousands of chemicals for targeted study, the United States Environmental Protection Agency (EPA) has developed methods that combine high-throughput (HT) estimates of both hazard and exposure (U.S. EPA, 2014a). These metrics incorporate bioactivities from a variety of HT in-vitro assays generated by the Toxicity Forecaster (ToxCast) (Dix et al., 2007) and the interagency Tox21 (Tice et al., 2013) programs with analogous HT exposure predictions developed under the Exposure Forecasting (ExpoCast) project (Cohen Hubal et al., 2010). A challenge faced by ExpoCast is the integration of multiple models covering different exposure pathways. To address this, EPA developed a high-throughput (HT) statistical framework, called the Systematic Empirical Evaluation of Models (SEEM), for developing consensus aggregate

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(multi-pathway) exposure predictions and concomitant estimates of uncertainty from multiple models (Wambaugh et al., 2013; Wambaugh et al., 2014; U.S. EPA, 2014b). The NAS report recommended that continued development of such computational tools for estimating exposures to thousands of chemicals be high priority, and should incorporate near-field exposure pathways (i.e., from sources or products near humans) that are known to be important (National Academies of Sciences, Engineering, and Medicine, 2017). While EPA has developed HT models for incorporating near-field exposures from consumer product and pesticide sources into the SEEM framework (Isaacs et al., 2014), HT models covering ingestion exposures to chemicals in food packaging are needed.

Migration of organic chemicals into foods from packaging may be a significant contributor to aggregate near-field exposures (Von Goetz et al., 2010; Wormuth et al., 2006); dietary exposures via this pathway may be orders of magnitude greater than those from environmental sources or pesticides (Grob et al., 2006). Chemicals used in packaging include potential endocrine disruptors (e.g., bisphenols, benzophenones, organotins, parabens, phthalates) (Muncke, 2009; Muncke, 2011). Chemicals may migrate from different packaging components; compounds used in inks, plastics, sealants, and coatings have all been found in packaged foods (Muncke, 2011). Classes of chemicals found in foods due to migration include polymer additives (e.g. plasticizers, thermal and light stabilizers, antioxidants) and unreacted monomers and oligomers (Bhunia et al., 2013), in addition to processing agents and unintentionally added chemicals (Lau and Wong, 2000). The total number of chemicals potentially present in food packaging is unclear, but inventories of registered compounds in the U.S. and Europe (U.S. FDA, n.d.-a; European Commission, 2011; European Food Safety Authority, 2012) alone comprise thousands of chemicals. Methods are needed for rapidly parameterizing this exposure pathway for large numbers of chemicals present in food packaging, hereafter referred to by the preferred U.S. Food and Drug Administration (US FDA) term "food contact substance," (FCS) via intentional or non-intentional addition (e.g., contamination or degradation products).

Efforts exist in both the US and the European Union to estimate exposures for FCS in support of regulatory chemical safety assessments (European Commission Joint Research Center, n.d.; U.S. FDA, n.d.-b). These exposure assessment methods involve combining population consumption rates for different foods with measured or modeled estimates of chemical migration from packaging material into those foods, scaled by the proportion of the food consumption in contact with packaging containing the chemical (U.S. FDA, 2007; Duffy et al., 2006; Oldring et al., 2014a; Oldring et al., 2014b). Any workflow to estimate population exposures to these chemicals must include methods to estimate migration values for thousands of chemicals into many different kinds of foods, and consider the distributions of consumption and packaging associated with those same foods. In this work, we present a high-throughput, screening-level exposure prediction framework that integrates these data streams.

Several computational and experimental approaches have been used to measure and predict migration, which determines resulting chemical concentrations in foods (Bhunia et al., 2013; Arvanitoyannis and Bosnea, 2004; Arvanitoyannis and Kotsanopoulos, 2014). The kinetics of chemical migration depend on food storage conditions (e.g., temperature and duration of food contact with packaging), FCS-specific properties (e.g., material type, thickness, the initial concentration of the migrant), migrant-specific chemical properties, and properties of the food (e.g., fatty or aqueous) (Bhunia et al., 2013). Experimental migration studies are often used to characterize migration from packaging under different storage conditions for food simulants having different properties (U.S. FDA, 2007; Veraart et al., 2007). However, accurately characterizing migration for chemicals in this manner may require hundreds of expensive and time-consuming tests and analyses (Baner et al., 1996). Therefore, to reduce dependence on migration experiments, some research efforts have focused on developing computational approaches for estimating migration (Baner et al., 1996; Begley et al., 2005; Poças et al., 2008) including mechanistic (Chung et al., 2002; Franz, 2005; Piringer, 1994) probabilistic (Poças et al., 2010) and empirical (Fauconnier et al., 2001; Poças et al., 2012) models. The mechanistic models are often derived from Fick's law of diffusion in order to describe the mass transfer from the FCS into the food, and typically depend on a diffusion coefficient D_p of the migrant in the packaging and a partition coefficient K_p (equal to the ratio at equilibrium of the concentration of the migrant in the packaging to that in the food) (Poças et al., 2008). For polymer FCSs, D_p has been estimated empirically as a function of molecular weight, temperature, and polymer-specific factors (Piringer, 1994) and quantitative relationships have been developed for these parameters in terms of other chemical properties (Shahbazikhah et al., 2011; Vitrac et al., 2006), but no generalized method exists for calculating D_p and K_p (and thus migration) for thousands of chemicals for different packaging, food, and storage conditions.

In this paper, we introduce a HT framework for generating HT exposure predictions for chemicals that may migrate from FCS for incorporation into HT risk-based metrics for chemical prioritization. The framework allows for the integration of multiple factors impacting exposures, including dietary intakes, chemical- and food-specific migration, and (should data become available) market penetration of chemical use. To parameterize a case-study application of this framework, we develop and evaluate a screening-level empirical model for predicting the chemical migration as a function of migrant chemical properties, migrant concentration in the FCS, food storage conditions, and food type (e.g., fatty, aqueous). The model is based on a linear regression on available migration measurements and evaluated with concentration measurements from the literature. We combine the migration predictions with U.S. food consumption data from the National Health and Nutrition Examination Survey (NHANES) (U.S. Department of Agriculture, n.d.-a) to estimate HT dietary exposures (mg/kg-BW/day) for 1009 chemicals identified as potentially present in polymer FCS. We evaluate these dietary exposure predictions and existing consumer product exposures against population exposures previously inferred from NHANES biomarker data (Wambaugh et al., 2014). We develop a calibrated prediction model for aggregate exposure that includes food contact and consumer product pathways, and present aggregate exposure predictions for 1931 chemicals. We demonstrate the impact of including FCS pathways by comparing aggregate predictions to exposures previously estimated to produce blood concentrations equivalent to in-vitro bioactive concentrations. We comment on current critical data gaps, and highlight key information that could improve future exposure predictions..

2. Methods

HT exposure methods should be amenable to rapid application large numbers of chemicals. Here we present an overall framework for rapidly estimating exposures (absorbed intakes) to chemicals in polymer food packaging materials that integrates a screening-level empirical model of chemical migration at equilibrium with existing U.S. food consumption information.

2.1. HT dietary exposures to chemicals in polymer food contact substances

Exposure, E, (mg/kg-BW/day) to a chemical migrant in a polymer FCS is estimated here as:

$$E = \frac{f_{abs}}{BW \times 1000} \sum_{i=1}^{N_{FG}} C_i \times DI_i \quad (1)$$

N_{FG} is the number of foods or food groups having unique concentrations due to differing migration, C_i is the equilibrium concentration of chemical in food group i (μg/g), f_{abs} is the gut absorption