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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 (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:

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

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 ($\mu\text{g/g}$), f_{abs} is the gut absorption fraction, and BW is body weight (kg). Daily intake (DI_i) of food in group i in contact with the chemical is:

$$DI_i = m_i \times CF_i \times f_{Ci}$$

where m_i is the daily mass (g) consumed of food group i , CF_i is a “consumption factor” - the fraction of the consumed mass of food in group i packaged in polymers, and f_{Ci} is the fraction of polymer packaging in food group i containing the chemical (i.e., market penetration or prevalence of the chemical). We define 12 food groups for use in this framework by combining the four food type categorizations used by the FDA in migration exposure calculations (fatty, aqueous, acidic, and alcoholic) (U.S. FDA, 2007) with three

temperatures associated with room, refrigerated, and frozen storage temperatures (27, 4, and 0 °C, respectively).

Eqs. (1) and (2) were implemented in a population-based manner within EPA's HT Stochastic Human Exposure and Dose Simulation (SHEDS-HT) model (Isaacs et al., 2014). SHEDS-HT uses U.S. census data to generate a simulated population of individuals, and assigns each a diary of food consumed based on age and gender. Dietary intake data for this application were developed from the National Health and Examination Survey (NHANES) What We Eat in America (WWEIA) food diaries (U.S. Department of Agriculture, n.d.-a). The NHANES-WWEIA two-day diaries for the years 2009–2010 (9651 diary-days) were downloaded from the NHANES website (U.S. Department of Agriculture, n.d.-a). These diaries contain individual food intakes (g), indexed by over 7000 unique food codes (U.S. Department of Agriculture, n.d.-b). Food codes correspond to different food and food form (e.g., frozen, canned) combinations; individual codes were assigned to one of the 12 food/temperature groups (examples given in Table 1) according to their food and form descriptions. All foods were categorized into a group irrespective as to whether they were in polymer packaging; the consumption factors and food type distribution factors quantify consumption not packaged in polymers. The mass of chemical m_i and daily intakes DI_i for each food group were calculated for every individual. Dry foods were not assigned to a food group, as migration into these foods was assumed to be negligible. Values for f_{Ci} , f_{abs} , and CF_i were obtained as described in Table 2.

To estimate chemical concentration C_i in each of the 12 food groups, an HT empirical model for chemical migration was developed from measured migration data as described in the next section.

2.2. High throughput model for chemical migration

A screening-level empirical model for equilibrium chemical migration was developed by fitting an existing FDA database of migration measurements from polymer or plastic food FCSs as a function of migrant properties, food properties, initial migrant concentration in the packaging, and storage temperature. Full details of the chemical migration database, development of the predictors, and the regression methods are provided in the Supplemental Information (SI).

The migration database is public and is available by email request from FDA (U.S. FDA, 2002). A linear model for migration at equilibrium (M , mg/in²) was fit to the measured data. The criteria for identifying measurements associated with equilibrium are given in the SI. Model selection (identification of the optimal predictor subset) was performed using the least absolute shrinkage and selection operator (LASSO) method, a type of linear regression that simultaneously mitigates overfitting and performs model selection by identifying an optimal reduced set of predictors (Tibshirani, 1996). The LASSO regression was implemented using the least angle regression and shrinkage (LARS) algorithm with the R (The R Project for Statistical Computing, 2017) package *lars* (Hastie and Efron, 2007); the optimal set of predictors was identified by the minimum value of the Mallows' C_p statistic (Mallows, 1973). All parameters considered as potential predictors are given in Table 3. We chose to include water solubility (S), log of the octanol-water partition coefficient ($\log K_{ow}$),

and molecular weight (MW) as predictors, as they are known to influence the partition coefficient between food and packaging and thus migration (non-polar and soluble compounds have lower partition coefficients, while higher MWs result in higher coefficients) (Tehrany and Desobry, 2004). These are properties for which estimates are readily available for thousands of chemicals; here they were obtained from EPA's CompTox Chemistry Dashboard (The U.S. EPA's Chemistry Dashboard, n.d.). Measured values were used where available, otherwise predictions from EPA's OPEn (quantitative) structure-activity Relationship Application (OPERA) models were used (Mansouri et al., 2016). The optimal set of predictors identified by the LASSO method were used to fit the data to a linear model using the R stats package (R, n.d.) for estimation of final parameter estimates, coefficient uncertainty, and residual model error. This combination LASSO/least-squares approach has been recommended for reducing bias in coefficient estimates (Hastie et al., 2009). Food concentration (mg/kg) was calculated from migration as

$$C_i = M_i \times r_{am}$$

where r_{am} is surface area-to-mass of food ratio. Here, we used the standard assumption that 6 dm² (93 in²) of packaging material impacts 1 kg of food (Robertson, 2016).

2.3. HT FCS exposure predictions for chemicals in polymer FCSs

Exposures were estimated for a set of chemicals (unique Chemical Abstract Registration Numbers, CASRN) identified from several U.S. and European data sources as potentially present in polymer FCS (plastics, coatings, or silicones) (U.S. FDA, n.d.-a; European Commission, 2011; Council of Europe and Council of Ministers, 1999; Commission of European Communities, 2002; Council of Europe and Consumer Health Protection Committee, 2004), including the US FDA's Inventory of Effective Food Contact Substance (FCS) Notifications (U.S. FDA, n.d.-a) and List of Indirect Additives Used in Food Contact Substances (U.S. FDA, n.d.-c). Estimated (or measured, when available) chemical properties for chemicals were obtained from EPA's CompTox Chemistry Dashboard (The U.S. EPA's Chemistry Dashboard, n.d.). A total of 3291 unique chemicals were identified from the data sources; property predictors required by the migration model (e.g., log K_{ow}) could be obtained for 1009 chemicals. Any reported functional role (e.g. "plasticizer," "monomer," "polymer additive") was extracted from the data sources. Data collection methods are described in the SI. Equilibrium migration and concentration estimates were made for all chemicals for all 12 food groups using the regression model, and population exposures generated using SHEDS-HT as described below.

2.3.1. HT estimates of C_0 —The assumption was made that the initial concentration of a chemical in the packaging (C_0) is determined primarily by the function (e.g., plasticizer) that the chemical performs in FCS. We have previously used function to predict screening-level chemical concentrations in consumer products (Isaacs et al., 2016). The functional role in FCSs of each chemical in the migration database was determined from information included with the data, from the literature, or from other public data sources (Isaacs et al., 2016) (see SI Table S1). Mean C_0 values for each function across all experiments in the migration database were calculated (SI Table S2). The possible functions of the 1009 FCS chemicals

were determined from information reported in the data sources. If a data source only identified a chemical as a polymer additive (i.e., not a specific function like “plasticizer” or “monomer”) the chemical was assigned the mean of the C_0 values for all polymer additives (e.g., antioxidants, stabilizers, etc.) in the migration database. Each chemical was assigned the median of the mean C_0 values associated with its possible functions (SI Table 3), and variability in C_0 for use in estimating concentrations was assumed as described in the next section.

2.3.2. Migration and concentration predictions—Distributions of concentration C_i were calculated for each food group i (combination of food storage temperature and food type, e.g., as in Table 1) for each chemical using a Monte Carlo (MC) simulation to incorporate uncertainty in C_0 . For each chemical, C_0 was sampled from a normal distribution with a mean equal to its HT C_0 estimate (SI Table 3) and a coefficient of variation of 50%. Migrations were estimated using the regression model and converted to concentrations as described in the Methods section. The resulting distributions for C were lognormal; a total of 10,000 samples were required to ensure convergence of medians and percentiles. Distribution parameters for C (median, coefficient of variation, 5th and 95th percentiles) were calculated for use in estimating exposures. Predictions were compared with published measured concentrations in foods for 11 chemicals (Schecter et al., 2013; Cao et al., 2014; Cao et al., 2011; Lorber et al., 2015) as described in the SI.

2.3.3. Dietary intakes and exposures—A simulated population of 35,000 people representative of the U.S. population in terms of age and gender was generated using SHEDS-HT; each simulated individual was randomly assigned a food intake diary (comprised of daily intakes for all 12 food groups), matching age and gender. Daily dietary exposures for each chemical were calculated using Eqs. (1) and (2). Resulting population mean, median, and percentile exposures (mg/kg-BW/day) were calculated for each chemical.

2.4. Comparison of HT exposure estimates with biomarker data

The resulting dietary exposures were compared with exposure values previously inferred from NHANES biomarker concentrations (Wambaugh et al., 2013; Wambaugh et al., 2014) and to consumer product pathway exposures generated with SHEDS-HT (Isaacs et al., 2014). A calibrated linear model for population median aggregate exposure including both contributing pathways (food contact and consumer product) was generated by treating the pathway-specific exposures as predictors and regressing on the NHANES inferences. Calibrated exposures were estimated with the aggregate model for 1931 chemicals and compared to exposures associated with in-vitro bioactivities for 51 chemicals. These oral equivalent doses (mg/kg/day) were previously estimated from ToxCast assays using in vitro-to-in vivo (IVIVE) extrapolation and reverse dosimetry, and have been used in conjunction with exposure estimates to calculate ranking metrics for chemical prioritization (Shin et al., 2015).

2.5. Assumptions and caveats

We highlight here key assumptions on which this exposure framework and its initial application rely. In many cases, these assumptions highlight where improvements to the methods could be made by obtaining new data (e.g., on inclusion levels of chemicals in different types of polymers).

1. The steady-state, screening-level empirical model for migration does not account for any chemical gradients in the polymer FCS or food.
2. The migration database obtained from FDA included many experiments performed under conditions (higher temperatures) designed to exaggerate migration. We assume that our regression model allows us to linearly extrapolate the results of these experiments to normal conditions.
3. In estimating exposures, we assumed all food within each food group consumed by the individual had the same concentration (i.e., one concentration per person was sampled for each group).
4. Due to data gaps in packaging-specific properties, all FCSs were assumed to be monolayer and in direct contact with packaged foods.
5. The model represents maximum migration during storage only, and does not explicitly take into account chemical migration during heating of a FCS (e.g., microwavable containers).
6. The migration model considers solely polymer FCSs, and is not applicable to chemicals in non-plastic packaging such as metal or paper. The model is appropriate for polymer food containers or coated cans, and was not applied to chemicals in inks, adhesives, or films.
7. Migration of chemicals into dry foods was assumed to be negligible in this study.

3. Results

3.1. Empirical model for chemical migration

In building the regression model for migration, different transformations of C_0 were tested; a cubed-root transformation was selected based on the results of a Box-Tidwell test (Pardoe, 2012) for optimal power transformations (optimal exponent = 0.31). An optimal predictor subset was identified using LASSO. Only the “fatty” categorical variable was eliminated as a predictor, this indicates the overall mean of the migration data was not different than that for fatty foods. A linear regression on the remaining predictors yielded an $R^2 = 0.71$ ($p < 0.0001$). C_0 was the most influential predictor (largest absolute standardized regression coefficient), followed by molecular weight (MW), aqueous and acidic food types, $\log K_{ow}$, and temperature (T). C_0 , $\log K_{ow}$, T, and S had positive coefficients and thus were indicative of increased migration; all other coefficients were negative. A comparison of predicted versus measured migration for the optimal model and a plot of the regression coefficients are given in Fig. 1; details of the model fit are provided in SI Table S4.

The influence of C_0 , T , and substrate type are expected; migration is known to be correlated with C_0 (O'Brien et al., 1997) and increased temperature (Bhunja et al., 2013), and fatty substrates have higher migration than others due to the higher solubility of migrating organic compounds in fat (Baner et al., 1992). The influence of MW , S , and $\log K_{ow}$ were also consistent with a mechanistic understanding of their influence on migration; higher MW compounds have higher K_p , while less polar and more soluble compounds have lower K_p (higher concentration in foods at equilibrium).

3.2. Migration and food concentration predictions

Equilibrium migration levels and food concentrations were predicted for 1009 chemicals in the FCS dataset with the migration model, using chemical-specific properties and HT C_0 estimates as described in the Methods section; 10,000 estimates per chemical per food group were made by sampling from the HT C_0 distributions. Median equilibrium concentrations for the 1009 chemicals for 12 food groups (in $\mu\text{g/g}$) are shown in SI Fig. S1. Nearly all (99.5%) of the predicted concentrations fell within the range in the training set; the medians ranged over 7 orders of magnitude across chemicals, and over 2 orders of magnitude across food groups within chemicals. The majority of the small number of predictions outside the training set range were very low concentrations that were predicted for higher MW chemicals under chilled or frozen conditions. Within a single food group, the range of the 5th to 95th percentile was also approximately 2 orders of magnitude. The highest concentrations were for plasticizers in fatty foods (with median equilibrium concentrations ranging up to nearly 1500 $\mu\text{g/g}$ for a few chemicals). The lowest concentrations were for additives and monomers in aqueous or acidic foods. Concentration predictions generated with the migration model were compared to 258 reported measurements for 9 phthalates (Schechter et al., 2013), bis(2-ethylhexyl) adipate (DEHA) (Cao et al., 2014), and bisphenol A (BPA) (Cao et al., 2011; Lorber et al., 2015) (Fig. 2; SI Table S5). Results are presented using the HT C_0 estimates (which were based on the function of each chemical in food packaging) and using limited measured C_0 data from the literature. DnHP, DEP, DEHA, BBzP, and DEHP were identified in at least one data source as plasticizers, so their predicted concentrations were higher. The other chemicals were either monomers and/or polymer additives in the data sources. As the predicted concentrations are equilibrium values, it was expected that observed concentrations would range from the limit of detection to the predictions. Given that they represent equilibrium concentrations, the median food concentrations predicted with HT C_0 are reasonably consistent with measurements for DEHA, BBzP, DEHP, BPA, DBP, DCHP, DiBP, DnOP. Even considering the use of equilibrium concentrations, concentrations were overestimated for the plasticizers DnHP and DEP, and DMP (an additive). It was hypothesized that these differences are due to overestimating C_0 for these chemicals. Comparing the limited data available for C_0 in the literature for these chemicals (Cao et al., 2014; Shen, 2005) demonstrated that C_0 can range over several orders of magnitude within plasticizers, resulting in widely differing predicted concentrations (green bars), for example, for DEHA versus DEP. This finding reflects the limitations of the HT parameterization of C_0 used here. Future efforts should seek to characterize more completely the initial concentrations of different plasticizers (and other chemicals) in packaging used in the U.S. to further discriminate among chemicals. However,

since the literature C_0 values were based on a single study per chemical, we chose to use the HT C_0 (with uncertainty) for estimating exposures in this study.

3.3. High throughput exposure predictions for chemicals in polymer FCS

Dietary exposure predictions for 1009 chemicals in FCSs were estimated in SHEDS-HT by combining the food group concentrations predicted with the HT migration model with food group intakes for individuals. The predicted population exposure percentiles (SI Fig. S2) spanned 9 orders of magnitude; the distributions were long tailed, with the distribution means falling close to the 75th percentiles. The population median intakes ranged from 8.4×10^{-8} to 33.7 mg/kg-BW/day. The exposure distributions for each chemical reflect both variability in chemical concentration within a food group and variability in food intakes (amount and food type distributions) among individuals. As expected from the food concentration predictions, the highest dietary exposure estimates were found for plasticizers; the largest exposure was for dihexyl azelate, (CASRN 109-31-9). The largest exposures were seen for children age 0–5 (due to smaller body weights).

3.4. Comparison of food contact exposures with NHANES data and development of calibrated aggregate predictions

Median population exposures consistent with NHANES biomarker measurements have been previously inferred for 106 chemicals (Wambaugh et al., 2013; Wambaugh et al., 2014). These inferences were compared (Fig. 3A) to the dietary FCS exposure predictions ($N = 17$) and to consumer product (CP) pathway exposures previously calculated using SHEDS-HT ($N = 26$); 9 NHANES chemicals had both FCS and consumer product pathways and 17 chemicals had solely CP pathways. The FCS predictions overestimated the inferred exposures by approximately two to three orders of magnitude, which was not unexpected given the conservative nature of the equilibrium concentration estimates, consumption factors, and FCS chemical prevalences (f_{ci}). In general, NHANES chemicals possessing FCS pathways had higher inferred exposures: the chemicals with the 5 highest inferred exposures (including three phthalates) had FCS pathways, and 13 of 17 chemicals with FCS pathways had inferred exposures higher than the second-highest value for a chemical having only a CP pathway (malathion).

A linear regression model was built for median population aggregate exposure, E_{Agg} , by fitting the median CP and dietary exposures to the inferred NHANES exposure. This model provides a calibrated estimate of aggregate exposure that corrects for the overestimation of both exposure pathways. The model was of the form:

$$\log(E_{Agg}) = A + FCS(A_{FCS} + B_{FCS} \log(E_{FCS})) + CP(A_{CP} + B_{CP} \log(E_{CP})) + \epsilon$$

FCS and CP are binary variables which are equal to 1 when a chemical has the corresponding pathway and 0 otherwise, and ϵ is the residual error. B_{FCS} and B_{CP} are the regression coefficients determining the significance of pathways, while the intercept A is the global bias term, and A_{FCS} and A_{CP} can be interpreted as additional corrections for each contributing pathway. The regression here is specific to the models being evaluated; if other

HT models were used the regression would not be valid. The regression coefficients (SI Table 6) for both the FCS pathway (BFCS = 1.11, $p = 0.009$) and CP (BCP = 0.60, $p = 0.005$) pathways were significant predictors of inferred exposures; the intercept terms indicate overestimation (as expected). In Fig. 3B, we note that approximately 60% of the chemical-to-chemical variance in median exposure was captured by the aggregate model ($R^2 = 0.61$, $p = 0.00018$). Aggregate exposures were calculated using the calibrated model for 1931 chemicals with CP and/or FCS pathway exposure predictions (SI Table S7).

To demonstrate the impact of including the FCS pathway in aggregate exposures, the calibrated aggregate predictions were compared to exposures estimated to cause bioactivity in HT assays. Oral equivalent bioactive doses (OEDs) for 54 chemicals were previously estimated from ToxCast bioactivity assay results using reverse HT toxicokinetics, and combined them with exposure predictions to calculate a bioactivity quotient (BQ, Exposure/OED) for use as a chemical prioritization metric (Shin et al., 2015). Here, a similar BQ was calculated as:

$$BQ = \frac{E_{95}}{OED_{min}}$$

where OED_{min} was the minimum OED (across ToxCast assays) (Shin et al., 2015), and E_{95} was the 95th percentile confidence bound on the median calibrated exposures estimated using the linear regression model. For the 18 chemicals with both pathways, BQ was calculated using aggregate exposure (by setting both FCS and CP = 1 in Eq. (4)) and CP exposures only (by setting FCS = 0) (SI Fig. S3). BQ ratios for 6 chemicals increased by a factor of at least 100 when FCS pathways were included and BQ for one chemical (DEHA, CASRN 103-23-1) increased by a factor of > 1000. BQ ratios for all other chemicals increased by at least one order of magnitude.

4. Discussion

Rees and Tennant (Rees and Tennant, 1993) summarized a set of guiding principles for developing estimates of consumer intake of chemicals from foods. The first principle was that any estimate of chemical intake should be appropriate for its intended purposes. The modeling system described here is appropriate for developing high-throughput predictions of exposure for thousands of chemicals for use in prioritization of chemicals for further study. It would not necessarily be appropriate for developing exposure estimates for single chemicals for use in regulatory exposure, risk, or safety assessments, given the likely level or uncertainty imposed by the assumptions and limitations of both the migration and exposure modeling components. We introduce stochastic variability in some parameters (e.g., food concentration predictions) where it could be quantified (e.g., based on uncertainty in migration model predictions), whereas for some parameters only point estimates could be made due to lack of current information. Developing new data for these parameters (e.g., consumption factors) could improve estimates of variability in exposures across chemicals, as well as across individuals. However, the statistical approaches described here, while high-throughput, provide a defensible means of categorizing or binning large numbers of

chemicals in FCSs in terms of their potential for exposure. The introduction of large uncertainties is expected, and does not necessarily preclude the use of the exposure estimates in chemical priority-setting frameworks. When data are available, the exposure modeling framework presented here could be used with refined concentration predictions (e.g., from mechanistic migration models) to estimate exposures for individual chemicals for higher-tier applications.

EPA's HT exposure framework, the Systematic Empirical Evaluation of Models (SEEM) is a Bayesian linear regression that involves joint estimation of both the inferred exposures and model regression coefficients (U.S. EPA, 2014b). An advantage of the SEEM framework is the ability to independently calibrate pathway or source specific estimates against monitoring data, allowing for the evaluation of the chemical-to-chemical influence of multiple estimates having different levels of uncertainty. A goal of the prioritization framework is to develop methods that discriminate among chemicals, based on mechanistic or empirical model prediction. Multiple models are combined into a regression-based consensus model that is used to develop calibrated aggregate exposures for use in prioritization. Thus, a model with relatively low R^2 but a significant relationship between predicted and inferred exposures is much more meaningful than a set of worst case assumptions (e.g. assuming 100% migration). The aggregate regression model presented here can be interpreted as an initial standard application of this approach (that uses previously-developed NHANES inferences). The SHEDS-HT consumer product and food contact pathway exposures should be further evaluated with SEEM (and updated inferences estimated) along with other available exposures for thousands of chemicals, including far-field model exposures and food contact exposures reported by FDA in their Cumulative Estimated Daily Intake database (U.S. FDA, n.d.-b) for ultimate determination of final consensus exposures for use in chemical priority-setting.

The strong dependence of predicted food concentrations on C_0 and variability in function-specific C_0 values (especially plasticizers) illustrates the need for better quantitative data describing the composition of individual chemicals in different types of food packaging (different polymers, packaging configurations, and food types). Under the ExpoCast project, new HT analytical methods using high resolution mass spectrometry are being developed to characterize thousands of chemicals in environmental media, consumer product formulations, articles, and foods (Rager et al., 2016). These methods can also provide HT quantitative estimates of concentrations of chemicals in packaging, which could improve C_0 estimates for individual chemicals and chemical classes. In addition, the food contact chemicals simulated here are all known polymer additives or other production aids. Non-intentionally added contaminants such as additive or monomer breakdown products may also migrate to foods. New analytical methods, combined with growing databases of chemical use information, will potentially enable identification of new classes of chemicals for which HT food contact exposure estimates are needed.

The HT estimates here could be refined by additional data with little or no alteration of the overall framework. While variability in C_0 was modeled to account for variation in function within chemicals, other conservative or point-value assumptions were made due to lack of information. The overestimation of FCS pathway exposures was likely a combination of

conservative concentration predictions with an assumption of a universal polymer consumption factor that is applied to all food groups, and most markedly the assumption of a 100% chemical presence in polymer packaging. Better consumption factor information (e.g., development of CF values for each NHANES food code) and improved f_C values that capture detail on the prevalence of use of individual chemicals within different packaging and polymer formulations will improve characterization of both the magnitude of exposures and population and between-chemical variability. Finally, biomarker data for additional chemicals beyond the NHANES set, especially for chemicals known to have both FCS and CP pathways, would improve confidence in the calibrated aggregate exposure model.

The current model predicts exposures to chemicals due to migration into foods during storage. As better data become available for chemicals contained in different types of packaging (e.g., those intended for heating) the model could be refined by adding additional estimates of migration during heating, as this could add significant additional migration into foods (Bhunia et al., 2013). These additional exposures could even be evaluated independently within SEEM (as the strength of the framework lies in its ability to evaluate contributions from different pathways or mechanisms).

5. Conclusions

In summary, the methods presented here allow for the incorporation of the potentially significant food contact pathway into aggregate exposure predictions for thousands of chemicals. Estimates of dietary exposures for chemicals with FCS pathways were overestimated yet predictive of exposures inferred from NHANES biomarker data; these exposures were significant in relation to contributions from consumer product pathways. Predictions of chemical migration and resulting exposures could be significantly improved by additional data on concentrations of chemicals in different types of packaging, market penetration of individual chemicals in packaging, and improved estimates of packaging-specific food consumption. We believe that these methods will be useful in supporting the prediction of aggregate chemical exposures for thousands of existing or new commercial chemicals with food contact pathways for use in chemical priority-setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Results of the HT model for migration, and regression coefficients for 436 measurements of 24 chemicals. A. Initial concentration C_0 , $\log K_{ow}$, water solubility (S), and temperature (T) were predictive of higher migration, whereas molecular weight (MW) was predictive of reduced migration. B. Aqueous, acidic, and alcoholic substrates resulted in lower migration (i.e., fatty substrates had highest predicted migration).

Fig. 2.

Comparison of 258 measured food concentrations with equilibrium concentration ranges predicted with the empirical migration model. Predicted values (in blue) are means across all foods of the median, 5th, and 95th percentile concentrations. Green bars indicate concentrations predicted using limited literature C0 measurements (Cao et al., 2014; Shen, 2005). LOD = limit of detection.

Fig. 3.

A: SHEDS-HT estimated exposures (mg/kg-BW/day) for 34 chemicals with consumer product and/or food contact pathways. B. Predicted aggregate exposures estimated with the calibrated linear model developed from fitting pathway exposures to the NHANES chemicals.

Table 1

Examples of assigning NHANES food codes to 12 migration-specific food groups by storage temperature and food substrate type.

Food Group	Food Type	Storage Temperature	NHANES Food Code	Example NHANES Food/Form Description
Fatty, Chilled	Fatty	4 °C	11111000	Milk, cow's, fluid, whole
Fatty, Room	Fatty	27 °C	11210050	Milk, evaporated
Fatty, Frozen	Fatty	0 °C	11459990	Yogurt, frozen
Aqueous, Chilled	Aqueous	4 °C	75113000	Lettuce, raw
Aqueous, Frozen	Aqueous	0 °C	75233002	Squash, summer, cooked, from frozen, NS as to fat added in cooking
Aqueous, Room	Aqueous	27 °C	75220023	Okra, cooked, from canned
Acidic, Chilled	Acidic	4 °C	61210220	Orange juice, canned, bottled or in a carton
Acidic, Frozen	Acidic	0 °C	61204600	Lemon juice, frozen
Acidic, Room	Acidic	27 °C	63201110	Blackberries, cooked or canned
Alcoholic, Chilled	Alcoholic	4 °C	93101000	Beer
Alcoholic, Room	Alcoholic	27 °C	93201000	Cordial or liqueur
Alcoholic, Frozen	Alcoholic	0 °C	93301500	Frozen daiquiri

Table 2

Exposure parameter values used in the modeling of food contact substance exposures.

Parameter	Value or Equation
Absorption fraction (f_{abs}, unitless)	Estimated with the “log K_{ow} -only” ingestion uptake efficiency model of O’Connor et al. using default parameter values (see SI) (O’Connor et al., 2013).
Consumption factor (fraction of food consumed contacting polymer matrices) for food group i (CF_i)	Estimated as $CF_i = CF \times f_{T,i}$ where CF is a global consumption factor for polymers (fraction of all consumed food packaged in polymer matrices), and $f_{T,i}$ is a food type distribution factor (the fraction of all food contacting polymer that is in a given food group). CF was assumed to be 0.8, the recommended US FDA value for “all polymers,” which includes polymer-coated metal and paper (U.S. FDA, 2007). US FDA recommendations for polymer f_T values for aqueous (0.08), acidic (0.16), alcoholic (0.01), and fatty (0.34) foods (U.S. FDA, 2007) were used for each corresponding group (all three temperatures).
Fraction of polymer packaging in food group i containing the chemical (fC_i)	Assumed to be 1 for all food groups, the value recommended by FDA (U.S. FDA, 2007) in exposure assessments due to the lack of information about market penetration of packaging types and the chemicals they contain.

Table 3

Candidate migration model parameters.

Parameter	Description
C_0	Initial concentration of chemical migrant in the FCS (percent)
Food type (Food or food simulant)	Alcoholic: Products containing alcohol and corresponding food simulants (e.g., 50% ethanol) Aqueous: Nonacidic products that may contain salt or sugar with pH > 5.0 and corresponding food simulant (water). Acidic: Products containing salt or sugar or both, and corresponding food simulant (10% ethanol) Fatty: Products containing fat or oil (i.e., dairy products, bakery products, poultry and meat products) and corresponding food simulants (e.g. food oil, HB307, Miglyol812)
T	Temperature (°C)
MW	Molecular weight (g/mol)
S	Solubility in water (mol/L)
$\text{Log } K_{ow}$	Log of the octanol/water partition coefficient