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

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### Abstract

1  
2  
3 Specialty software and simplified models are often used to estimate migration of potentially toxic chemicals  
4 from packaging into food. Current models, however, are not suitable for emerging applications in decision-  
5 support tools, e.g. in Life Cycle Assessment and risk-based screening and prioritization, which require rapid  
6 computation of accurate estimates for diverse scenarios. To fulfil this need, we develop an accurate and rapid  
7 (high-throughput) model that estimates the fraction of organic chemicals migrating from polymeric packaging  
8 materials into foods. Several hundred step-wise simulations optimised the model coefficients to cover a range  
9 of user-defined scenarios (e.g. temperature). The developed model, operationalised in a spreadsheet for future  
10 dissemination, nearly instantaneously estimates chemical migration, and has improved performance over  
11 commonly used model simplifications. When using measured diffusion coefficients the model accurately

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12 predicted ( $R^2 = 0.9$ , standard error ( $S_e$ ) = 0.5) hundreds of empirical data points for various scenarios. Diffusion  
13 coefficient modelling, which determines the speed of chemical transfer from package to food, was a major  
14 contributor to uncertainty and dramatically decreased model performance ( $R^2 = 0.4$ ,  $S_e = 1$ ). In all, this study  
15 provides a rapid migration modelling approach to estimate exposure to chemicals in food packaging for  
16 emerging screening and prioritization approaches.

17 **Keywords:** risk; life cycle assessment; low-tier; exposure modelling; product intake fraction; food contact  
18 materials

## 19 1. Introduction

20 Food contact materials (FCM) are a source of consumer exposure to potentially hazardous chemicals,  
21 such as bisphenol A, phthalates and fluorinated compounds (Begley et al. 2005b; Tittlemier et al.  
22 2007; Apelberg et al. 2007; Cao 2010; Geens et al. 2012). In addition, thousands of other chemicals  
23 are legally acceptable in FCM and can lead to human exposure (Geueke et al. 2014; FDA 2015a).  
24 Concern over consumer risks are bolstered by data gaps in FCM safety assurance as well as recent  
25 hazard information generated by *in silico* and *in vitro* high-throughput toxicity and bioactivity  
26 screening studies (Biedermann and Grob 2013a; Neltner et al. 2013; Muncke et al. 2014; Price and  
27 Chaudhry 2014; Evans et al. 2016; Karmaus et al. 2016). To estimate potential risks posed by  
28 chemicals in FCM, hazard and exposure must be quantified. Empirical exposure data, however, are  
29 scarce and analytically challenging to obtain (Rudel et al. 2011). Modelling the migration of chemicals  
30 from materials into food is therefore critical to fill empirical data gaps and quantify exposure.  
31 Chemicals in food packaging in particular have been a major focus of consumer exposure assessments  
32 that build on migration modelling. The *Cumulative Estimated Daily Intake* (CEDI) database of the

33 United States Food and Drug Administration (FDA 2015a) and the *Flavourings, Additives, and food*  
34 *Contact materials Exposure Tool* (FACET) (Oldring et al. 2014b) of the European Commission's Joint  
35 Research Center (JRC) are recent large-scale advances to estimate realistic exposure to chemicals in  
36 food packaging, for 1,302 and 6,499 chemicals, respectively (although only 5 chemicals are pre-  
37 installed in FACET as of May 2017). In both cases, exposure estimates (expressed in mg/kg/d) are a  
38 function of *undisclosed data e.g. based on an annual country-specific market survey*. By fixing  
39 exposure estimates based on undisclosed market-wide occurrences of a chemical in package-food  
40 combinations combined with a food consumption estimate, CEDI and FACET cannot be used to  
41 estimate exposure to chemicals in packaging per unit(s) of product use, such as one packaged food  
42 consumed by one person. Comparing different unit(s) of product use or unit(s) of chemical use (e.g.  
43 kilogram of chemical used as a plasticizer in many different polymers) is a main application of  
44 emerging exposure screening tools such as SHEDS-HT (Isaacs et al. 2014), ECETOC TRA (Delmaar et al.  
45 2013), USEtox (Rosenbaum et al. 2008), and the PiF framework (Fantke et al. 2016). A per-unit  
46 assessment structure facilitates comparing products on a per use basis (regardless of total market  
47 volume), or comparing extrapolated uses (e.g. to the entire population or a company-specific  
48 production volume). Therefore, in order to be coupled or incorporated within emerging assessment  
49 tools, a chemical exposure model for food packaging should have the flexibility to assess various units  
50 of packages used by consumers. A major research gap remains, as no peer reviewed tool or method  
51 exists to facilitate high-throughput, transparent and flexible estimation of exposure to chemicals in  
52 food packaging to support applications in screening and prioritization tools.

53 With millions of product-chemical combinations on the market, screening has emerged as a  
54 resourceful approach to prioritize chemicals and/or products that require further scrutiny. High-  
55 Throughput Risk-based Screening (HTRS), and environmental Life Cycle Assessment (LCA) are distinct  
56 screening and prioritization tools that can consider potential impacts on human health related to  
57 chemical exposure. HTRS combines low-tier high-throughput exposure modelling with risk-based  
58 indicators, such as high-throughput screening bioassays (Wambaugh et al. 2013; Isaacs et al. 2014;  
59 Wetmore et al. 2015; Shin et al. 2015; Karmaus et al. 2016). LCA is an established sustainability  
60 assessment framework that combines multiple modelling approaches to screen product systems and  
61 their potential impacts on human health, ecosystems, and natural resources (Hauschild 2005; Hellweg  
62 and Milà i Canals 2014). Both HTRS and LCA rely on practical, high-throughput models that require  
63 limited parameterization and computational capacity. Exposure models can thereby be designed for  
64 both tools despite their different applications (Wambaugh et al. 2013; Shin et al. 2015; Huang et al.  
65 2017a).

66 High-throughput models, compatible with LCA and HTRS, to estimate exposure to chemicals in food  
67 packaging are specifically needed to complement fast-paced advances towards sustainability and  
68 resource management targets. Concern over chemicals in food packaging is a barrier to the rising  
69 interest in circular economy and use of recycled or re-used materials (Biedermann and Grob 2013b;  
70 Lee et al. 2014; European Bureau for Conservation and Development 2015; FDA 2015b; Leslie et al.  
71 2016). Furthermore, bio-based packaging designs (Yuan et al. 2016), or designs to reduce food waste  
72 (Siracusa et al. 2014), can also influence packaging materials, their contained chemicals, and their  
73 environmental impacts. LCA is extensively used to inform decision making regarding more sustainable

74 food packaging design (Hunt and Franklin 1996; Flanigan et al. 2013). However, LCA methods  
75 traditionally only consider *environmental* exposure pathways, and not indoor exposure pathways  
76 related to product use, such exposure to chemicals that have migrated from a package into a food. .  
77 To address this inconsistency, there are recent modelling efforts to make LCA more comprehensive  
78 and include exposure to chemicals in products (Shin et al. 2012; Jolliet et al. 2015a; Fantke et al. 2016;  
79 Ernstoff et al. 2016; Csiszar et al. 2016b; Huang et al. 2017a), although LCA-compatible models do not  
80 yet exist to estimate exposure through food packaging.

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

94 the developed approach against other models and empirical migration data available from the United  
95 States Food and Drug Administration (US FDA).

## 96 **2. Methods**

### 97 **2.1 Product intake fraction framework**

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

111 Values for  $f_c$  can be estimated through studies quantifying consumer food waste,  $f_w$ , where  $f_c = 1 - f_w$ .  
112 Various country-specific studies have found consumer-level wastes between 9-45% depending on the  
113 food category (Beretta et al. 2013; Buzby et al. 2014). Accounting for food waste could be especially

114 important in assessments of packaging designs that result in different food spoilage rates (Williams  
 115 and Wikström 2011; Williams et al. 2012). This study will focus on providing methods to estimate the  
 116 second parameter  $f_t$  through mathematical modelling for various chemical- package-food  
 117 combinations and scenarios, as  $f_t$  is not a value that can be typically obtained from prior studies.

## 118 2.2 Analysis of migration model behaviour and needs for a high-throughput model

119 Various migration models exist to estimate migration of a chemical from FCM into food. Models tend  
 120 to be computationally complex, require empirical input data for parameterization, or only be valid for  
 121 specific scenarios (Pocas 2008; Piringer and Baner 2008; Pocas et al. 2012). We focused on widely  
 122 used migration models that have also been empirically validated and require a limited amount of  
 123 empirically-derived input parameters (Begley et al. 2005a; Piringer and Baner 2008; Oldring et al.  
 124 2014b, a; Hoekstra et al. 2015; FDA 2016). The most commonly used migration model is derived from  
 125 a mass-balance equation based on Fick's second law (Crank 1975). Arranging the terms to solve for  
 126 the fraction of the initial chemical mass  $m_{i,0}$  that has migrated from a package into a food after a  
 127 contact duration of  $t$  results in

$$128 \quad f_t = \frac{m_{i,t}}{m_{i,0}} = \left( \frac{\alpha}{1+\alpha} \right) \left[ 1 - \sum_{n=1}^{\infty} \frac{2\alpha(1+\alpha)}{1+\alpha+\alpha^2 q_n^2} \exp\left(-D_p t d \frac{q_n^2}{d_p^2}\right) \right] \quad (1)$$

129 where

$$130 \quad \alpha = \frac{1}{K_{P,F}} \frac{V_F}{V_P}.$$

131 Migration of chemical  $i$  is modelled as a function of the partition coefficient  $K_{P,F}$  between package and  
 132 food; the ratio of food to package volumes  $V_F/V_P$  ( $\text{cm}^3 \text{cm}^{-3}$ ) the diffusion coefficient for a chemical in



133 a package,  $D_p$  ( $\text{cm}^2\text{s}^{-1}$ ); the duration of food-package contact,  $t_d$  (s); the thickness of the package,  $d_p$   
 134 (cm); and the infinite solutions of  $q_n$ , where  $q_n$  are the positive roots of the transcendental equation  
 135  $\tan(q_n) = -\alpha q_n$ .

136 The complexity of eq (1) requires specialty software or model simplification which can lead to over or  
 137 underestimation. A common approach is to obtain values of  $q_n$  from a look-up table of 6-50 solutions  
 138 for pre-specified values of  $\alpha$  (Crank 1975; Piringer and Baner 2008; Hoekstra et al. 2015). Another  
 139 common approach is using short-term diffusion-dominated and long-term partitioning-dominated  
 140 models, respectively eq (2) and eq (3), where

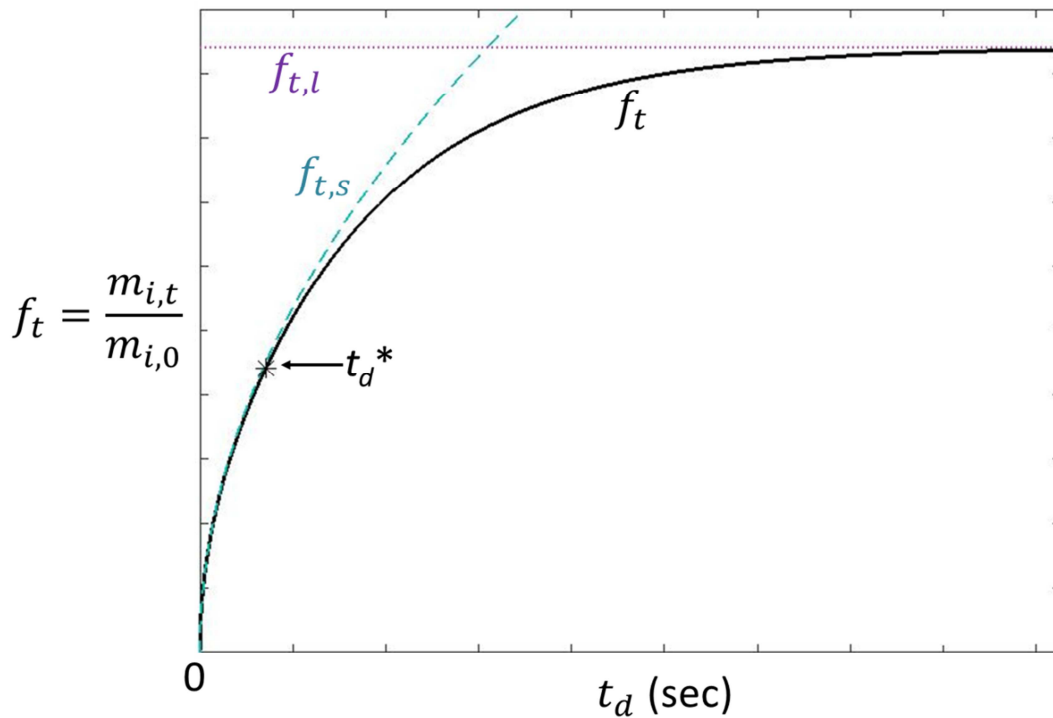
141 
$$f_{t,s} = \frac{m_{i,t}}{m_{i,o}} = 2/d_p \times (D_p t_d / \pi)^{1/2} \quad (2) \text{ and}$$

142 
$$f_{t,l} = \frac{m_{i,t}}{m_{i,o}} = \frac{\alpha}{1+\alpha} \quad (3).$$

143 The parameters are defined above with eq (1). Eq (2) and (3) are computationally simple, but only  
 144 valid for restricted timescales, for example eq (3) is valid when  $D_p t_d / d_p^2 \gg 0.001$  (Piringer and Baner  
 145 2008). To apply eqs (1)-(3), the parameters are either fixed or estimated. For example, regulatory  
 146 models often fix  $K_{p,f} = 1$  as a claimed “worst-case” scenario, and fix the volume of food to 1000 mL (1  
 147 kg) in Europe or 10 g of food in the US. When applying the formulas in regulatory settings, the  
 148 packaging volume is determined by the typical reference surface area of 6  $\text{dm}^2$  in Europe and 1  $\text{in}^2$  the  
 149 US, and assuming packaging thickness generally between 0.001-0.1 cm (Oldring et al. 2014b; Hoekstra  
 150 et al. 2015; FDA 2016). Regardless of the input parameters, eq (2) always surpasses eq (1) at a food-  
 151 package contact duration referred to in this study as the *deviation time*,  $t_d^*$ . Using eq (2) beyond  $t_d^*$

152 can result in surpassing the ultimate equilibrium value achieved according to eq (3), and grossly over-  
153 estimating migration. Quantification of when  $t_d^*$  occurs has not been to our knowledge defined, and  
154 changes according to the model input parameters.

155 We programmed simulations in Matlab R2015a to elucidate the behaviour of eq (1) in order to  
156 understand the needs for operationalizing HT models. To begin, we investigated the feasibility of  
157 using eq (1) and associated simplifications for HT modelling. Specifically, we elucidated the  
158 consequences on the model behaviour when simulations of eq (1) were performed a) with a limited  
159 number of  $q_n$  roots or b) using a fixed value for input parameter  $K_{p,f}$ . We also compared the  
160 behaviour of eq (1) with eq (2) and eq (3). Figure 1 is a generic representation of the model system  
161 with a sufficient number of  $q_n$  roots to achieve eq (1) with accuracy; the required number of  $q_n$  roots  
162 as well as the shape of the  $f_t$  curve and values on the X and Y axes will differ depending on input  
163 parameters.



164

165 Figure 1. Representation of model behaviour through an undefined package-food contact duration.

166 Eqs (1)  $f_t$  (solid line) with sufficient  $q_n$  roots, (2)  $f_{t,s}$  (dashed line), and (3)  $f_{t,l}$  (dotted line), are  
 167 demonstrated. The point at which the short term simplification deviates from the model with >99%  
 168 accuracy,  $t_d^*$ , is indicated with a star.

169 Preliminary simulations demonstrated that the number of  $q_n$  roots needed to estimate eq (1) with  
 170 high accuracy (e.g. up to 99%) cannot easily be predetermined; in addition to the relationship  
 171  $D_p t_d / d_p^2$  (Piringer and Baner 2008), the number of  $q_n$  roots required to accurately estimate eq (1) is  
 172 also dependent on  $\alpha$ . We found as  $\alpha$  decreases the number of roots required to obtain eq (1) increases  
 173 (Figure S1A-B). The number of roots and thus iterative calculations affected the required computation  
 174 time. We found generally when  $\alpha$  was high (> 10) computation time was rapid and few roots were

175 needed (e.g. 5 - 50,000). For very low  $\alpha$  ( $< 0.001$ ) even 1 million roots resulted in several orders of  
176 magnitude overestimation during short time scales (i.e. in the first 24 hours). Taking 1 million roots  
177 substantially lengthened the computation time. Restricting the number of  $q_n$  values to rapidly solve  
178 eq (1) always led to overestimation of the model  $f_t$  at short time scales (supporting information (SI),  
179 Figure S1A-B), typically by several orders of magnitude. This suggests using a limited number of  $q_n$  can  
180 be appropriate for safety assessments, but does not provide a realistic estimation, especially at short  
181 time scales and for low values of  $\alpha$ . In all, using eq (1) is not practical for rapid and accessible HT  
182 methods that are operational across all time scales and values of  $\alpha$ . Iterative calculation steps can  
183 lengthen computation time and furthermore poses a computational barrier to pragmatically coupling  
184 of the model to spreadsheet-based tools.

185 The partition coefficient between packaging and food for a migrant,  $K_{p,F}$ , is an important parameter  
186 influencing the behaviour of eq (1) and eq (3). When  $K_{p,F}$  is high the chemical has higher affinity for  
187 the package, and when  $K_{p,F}$  is low (e.g.  $K_{p,F} < 1$ ) the compound has higher affinity for the food  
188 (Tehrany and Desobry 2004; Ozaki et al. 2010). When analysing model behaviour to inform method  
189 development we found *no evidence* that the simplification of  $K_{p,F} = 1$  is a “worst-case” scenario as  
190 claimed by regulatory documents and publications (e.g. Brandsch et al. 2002; Begley et al. 2005a;  
191 Hoekstra et al. 2015). We found that setting  $K_{p,F} < 1$  can lead to migration estimates greater than the  
192 model outcome when  $K_{p,F} = 1$ , especially when the food and packaging volume are of similar  
193 magnitude.  $K_{p,F} < 1$  have also been observed empirically (Tehrany and Desobry 2004; Piringer and  
194 Baner 2008; Ozaki et al. 2010). Quantitatively,  $K_{p,F} = 1$  corresponds to the chemical concentration  
195 being *equal* in the package and the food. Our simulations demonstrated that setting  $K_{p,F} = 1$  can

196 underestimate the migrated chemical mass at equilibrium, e.g. by a factor of  $\approx 2$  when  $K_{p,F} \leq 0.1$   
197 when the volumes of food and packaging material are equivalent (SI Figure S2A versus S2B when  $K_{p,F} =$   
198 1), and this factor increases if the ratio between the package and food increases above 1. Therefore,  
199 in situations when the mass of packaging material approaches the mass of the food (e.g. for small  
200 candies, capsules, and single-serving condiments) and equilibrium can be approached or reached—  
201 e.g. due to a long contact time, small package thickness, and/or due to rapid diffusion— $K_{p,F}$  cannot be  
202 set to 1 to obtain a realistic *or* worst-case value for chemicals with  $K_{p,F} < 1$ . Using the default  
203 regulatory values for the amounts of packaging and food, the assumption  $K_{p,F} = 1$  provides *nearly* an  
204 upper-bound (worst-case) estimate of eq (1) (SI Figure S2B). There is substantial empirical evidence  
205 that chemicals in polymers can have  $K_{p,F} < 1$ , and  $< 0.01$ , (Mercea 2008), however, we cannot  
206 determine the frequency such chemicals occur in situations where packaging and food volumes are  
207 similar. Nevertheless, we recommend that regulatory documents and other publications do not state  
208 that  $K_{p,F} = 1$  is a “worst-case” scenario. Instead, we recommend stating that setting  $K_{p,F} = 1$  is a  
209 pragmatic approximation of a worst-case scenario when the volume ratio of food to package is  $> 100$ .  
210 Moreover analysing the consequence of setting  $K_{p,F} = 1$  points to a need for a model to estimate  $K_{p,F}$  to  
211 be used in HT estimates of realistic exposure, as setting  $K_{p,F} = 1$  can overestimate exposure when  $K_{p,F} >$   
212 1, and underestimate exposure when  $K_{p,F} < 1$ .

213 To summarize, analysing the behaviour of existing modelling approaches demonstrated that using  
214 too few  $q_n$  roots can lead to drastic overestimation of eq (1), but that using more  $q_n$  roots slows  
215 computation times; eq (2) is a simple and accurate method suitable for HT estimates of migration for  
216 short timescales ( $< t_d^*$ ), but this timescale is not well defined; and setting  $K_{p,F} = 1$  does not provide

217 either representative or worst-case estimates for all scenarios. These findings informed the research  
218 needs for developing an HT model that can rapidly provide representative migration estimates across  
219 all timescales and for a variety of chemical-package-food combinations. Specifically, the identified  
220 needs are to 1) design a model that does not require iterative calculations based on  $q_n$  roots, 2)  
221 identify package-food contact duration,  $t_d^*$ , where eq (2) is no longer valid and 3) more accurately  
222 estimate  $K_{p,F}$ .

### 223 **2.3 Development of a high-throughput model for migration estimation**

224 To address these three needs, we aimed to develop a parsimonious approach valid for all time-scales  
225 and a large range of input parameters.

226 First we defined  $t_d^*$  (Figure 1) as the contact duration between package and food when the solution  
227 to eq (2) deviates from the solution of eq (1) by more than >1% of the ultimate equilibrium value. At  
228 contact durations  $< t_d^*$  eq (2) is valid, compares well with eq (1) ( $R^2 \approx 1$ ) and thus eq (2) can be directly  
229 used for HT approaches in this time range. To determine  $t_d^*$  as an explicit function of main  
230 parameters, we hypothesized that it is a function of  $\alpha$ ,  $D_p$ , and  $d_p$  due to the influence of these  
231 parameters on the function behaviour. To test this hypothesis we obtained  $t_d^*$  from several hundred  
232 simulations for random permutations of the input parameters  $D_p$  ( $10^{-10}$ ,  $10^{-20}$  cm<sup>2</sup>/sec),  $\alpha$  (values  
233 randomly generated between  $10^{-6}$  and  $10^5$ ), and  $d_p$  (0.01, 0.1, 1 cm), using up to 1 million roots in eq  
234 (1) to ensure high accuracy. Next, we plotted the resulting values of  $t_d^*$  as function of  $\alpha$ ,  $D_p$ , and  $d_p$   
235 and used the Matlab 2015a Curve Fitting Toolbox™ to determine an explicit function of these  
236 variables and enabling prediction of  $t_d^*$  with reasonable accuracy.

237 After determining a predictive function for  $t_d^*$ , we aimed to develop an HT migration model valid  
238 after  $t_d^*$ . The model theory is based on recent work by Huang & Jolliet (2016) where a parsimonious  
239 model was developed for HT prediction of volatile organic compound releases from solid materials.  
240 This approach demonstrated a Fickian-based differential equation requiring the infinite sum of  $q_n$   
241 roots, similar to eq (1), can be approximated as a two-term exponential decay model (Huang and  
242 Jolliet 2016). The first exponential term captures short-term diffusion-dominated behaviour and the  
243 second exponential term captures long-term partitioning-dominated behaviour (Chang and Guo  
244 1992). A model of this form relates the mass transferred (lost from the material) through time,  $m(t)$ ,  
245 as a function of the initial mass,  $m_0$ , in the material multiplied by an exponential decay with constant  
246  $k$ ,  $m(t) = m_0 e^{-kt}$ . When estimating the fraction of chemical mass initially in the material (i.e. the  
247 package) that has transferred (i.e. into the food) this results in the form  $1 - e^{-kt}$ . We therefore  
248 hypothesized that a 2-term decay model in the form of  $1 - e^{-kt}$  could capture the behaviour of eq (1).  
249 Furthermore, since the shape of eq (1) through time is determined by input parameters  $\alpha$ ,  $D_p$ , and  $d_p$ ,  
250 likewise the exponential shape parameters (analogous to the decay constant) could be predicted as a  
251 function of  $\alpha$ ,  $D_p$ , and  $d_p$ . We found that one exponential term sufficed ( $R^2 > 0.99$ ) when  $\alpha \approx > 10$  and  
252 there were no partitioning constraints (given infinite time nearly all of the chemical will have  
253 transferred from package to food), however, in order to obtain high values of  $R^2$  ( $R^2 > 0.97$ ) when  
254 comparing the simplification to eq (1) across values of  $\alpha$  two exponential terms were needed (SI  
255 Figure S3) (eq 4). We therefore followed a two exponential form in order to provide a model valid for  
256 all values of  $\alpha$ . The resulting model form for all contact durations and values of  $\alpha$  was determined as

$$f_{t,p} = \begin{cases} \frac{2}{d_p} \times (D_p t_d / \pi)^{\frac{1}{2}} \text{eq}(2) & \text{if } t_d \leq t_d^*, \text{ else} \\ y_{t_d} + \left(\frac{\alpha}{1+\alpha} - y_{t_d}\right) \times \left(A \times (1 - e^{-B \times \beta \times (t_d - t_d^*)}) + (1 - A) \times (1 - e^{-C \times \beta \times (t_d - t_d^*)})\right) \end{cases}, \quad (4)$$

$$\text{where } \beta = \frac{D_p N_{t_d^*}}{d_p^2},$$

and where A, B, and C are varying coefficients discussed further below; slope factor  $N_{t_d}$  is the derivative of eq (2) at the contact duration  $t_d^*$  to train the slope towards the slope of eq (2) at that point;  $y_{t_d}$  is the vertical shift to begin the double exponential model at contact duration  $t_d^*$  and is equal to the value of eq (2) at  $t_d^*$ ; other equation parameters are defined within eq (1).

To operationalize eq (4), coefficients A, B, C, must be determined as explicit function of main parameters. Based on observations from the initial simulations, we hypothesized each coefficient is interdependent and a function of  $\alpha$ . To test this hypothesis, we ran simulations of  $f_t$  as well as the predicted function  $f_{t,p}$  using random permutations of input parameters to cover range of potential migration scenarios, i.e. for  $D_p (10^{-10}, 10^{-20} \text{ cm}^2/\text{sec})$ ,  $\alpha$  (values randomly generated between  $10^{-6}$  and  $10^5$ ) and  $d_p$  (0.01, 0.1, 1 cm) with up to 1 million roots to ensure accuracy. These simulations were used to develop predictive models for the coefficients A, B, and C, applying the following stepwise procedure to iteratively restrict noise due to interactions between these parameters:

The first step was to investigate values of A, B, and C as a function of  $\alpha$  as completely “free” variables, optimised by minimizing the residual squares between eq (4) and eq (1) using the Matlab 2015a pre-existing function *fminsearch*. From this exercise we observed that values of A were being optimised to force the equation towards a 1-exponential (e.g. A approaches 1) when  $\alpha \approx > 10$ . We then fixed A as a



275 piece-wise function of  $\alpha$  and ran simulations to predict values of B and C. Again seeing that B was  
 276 forced towards 1 at high values of  $\alpha$ , we then also fixed B as piece-wise functions of  $\alpha$  to finally obtain  
 277 a predictive function of C.

278 Finally we tested the accuracy of eq (4) at estimating  $f_t$  eq (1) when using the final resulting  
 279 predictions of  $t_d$ , A, B, and C. Because  $f_{t,s}$  eq (2) and  $f_{t,l}$  eq (3) model short and long-term behaviour,  
 280 we also compared our modelling approach to a simple approach using  $f_{t,s}$  until it is equal to  $f_{t,l}$  and  
 281 then switching to  $f_{t,l}$ . Nine simulations were run to cover the range of  $\alpha$  from ( $10^{-4}$ - $10^3$ ), where the  
 282 simulation time for low values of  $\alpha$  was extensive due to the number of  $q_n$  roots required.

#### 283 2.4 Model parameterization

284 **Chemical diffusion coefficient:** Chemical diffusion is influenced by material and chemical properties  
 285 (e.g. molecular size) as well as the ambient temperature. Diffusion coefficients are commonly  
 286 estimated using eq (5) (Brandsch 2000; Mercea 2000; Begley et al. 2005a; Hoekstra et al. 2015)

$$287 \quad D_p = D_o \exp \left( A_p - 0.1351 MW^{\frac{2}{3}} + 0.003 MW - \frac{10454}{T} \right) \left( \frac{cm^2}{s} \right) \quad (5)$$

288 where  $A_p = A'_p - \frac{\tau}{T}$ ,  $D_o = 1 \text{ m}^2/\text{s} = 10^4 \text{ cm}^2/\text{s}$  and  $R = 8.3145 \text{ J mol}^{-1} \text{ K}^{-1}$ .

289 Molecular weight (MW g/mol) is specific to the migrant;  $A_p$  is a dimensionless polymer-specific  
 290 diffusivity parameter that is sensitive to the ambient temperature,  $T$  (K) of the food-material system;  
 291  $\tau$  and the constant 10,454 are polymer-specific and account for the diffusion activation energy (where  
 292 10,454 is the reference constant for polyethylene) (Barnes et al. 2006). When applying this model in  
 293 regulatory settings typically “worst case” values of  $A_p$  are used. LCA compatible models do not

294 typically estimate worst case scenarios but aim to estimate average scenarios, therefore to estimate  
295  $A_p$  we used average values (*not 'upper-bound' or worst case*) of  $A'_p$  (a standard polymer-specific  
296 diffusivity parameter) which we calculated from data listed in Begley et al. 2005a as listed in SI Table  
297 S1. The diffusion coefficient is highly sensitive to  $A'_p$  where a 10% change in  $A'_p$  can lead to a 300%  
298 change in the diffusion coefficient. The full model, eq (1), however, is less sensitive to changes in the  
299 diffusion coefficient (e.g. a 10% change in the diffusion coefficient leads to a <5% change in model  
300 output), where the level of sensitivity depends on the contact duration and if this is in the diffusion-  
301 dominated timescale.

302 **Package-food partition coefficient:** As discussed in Section 2.2 the partition coefficient  $K_{p,F}$  influences  
303 model behaviour after contact duration  $t_d^*$  and  $K_{p,F}$  cannot be set to a fixed value to obtain realistic  
304 estimates. Therefore, we focus on developing HT methods to estimate  $K_{p,F}$  for various scenarios.  
305 Previous works (Tehrany and Desobry 2005; Tehrany et al. 2006; Ozaki et al. 2010) to this aim have  
306 developed correlations of  $K_{p,F}$  with the chemical and food lipophilicity, where the octanol-water  
307 partition coefficient,  $K_{ow}$ , is used as a the chemical proxy and the simulant ethanol-equivalency EtOH-  
308 eq is used as the food proxy.  $K_{p,F}$  is also temperature sensitive but the relationship is not known to be  
309 easily predictable (Tehrany and Desobry 2004). In this study we do not attempt to predict the  
310 temperature-dependency of  $K_{p,F}$ . We build on more recent empirical work by Ozaki et al. 2010  
311 correlating  $K_{p,F}$  with a range of chemical log  $K_{ows}$  and across a range of food EtOH-eqs. The FACET  
312 project (Seiler et al. 2014) also built on this work and performed experiments to extend the  
313 correlation range of  $K_{p,F}$ , but the experimental data and subsequent correlations are not available to  
314 our knowledge.

315 Therefore, we developed a method to estimate  $K_{p,F}$  as a function of a chemical  $K_{ow}$  and food EtOH-eq  
316 by generalizing the three log-log linear EtOH-eq correlations in Ozaki et al. 2010 to all potential  
317 combinations of EtOH-eq and  $K_{ow}$ . We assumed the gradient between the slopes of these log-log  
318 linear curves would be uniformly distributed across EtOH-eqs and therefore follows the format  
319  $\log K_{p,F} = m(\text{EtOH} - \text{eq}) \times \log(K_{ow}) - b$ , with  $m$  a linear function of EtOH-eq. The solver add-in in  
320 Microsoft Excel 2010 was used to optimize the parameters of a log-log linear model while minimizing  
321 the residual error between our predicted values and the measured values from Ozaki et al. 2010. We  
322 restricted the applicability range of the  $K_{p,F}$  correlations according to the  $K_{ow}$  values empirically

323 measured in Ozaki et al. 2010, e.g. data were not available for chemicals with  $\log K_{ow} > \approx 5, 8, 18$  when  
324 the EtOH-eq is  $\approx 10, 50, 95\%$  respectively. Finally, to test the accuracy of our modelling approach by  
325 external validation, we obtained a separate dataset of 163 different experiments that measured  
326 partition coefficients between LDPE and HDPE polymers and 13 different foods at ambient  
327 temperature 296 K (Mercea 2008). We assigned these 13 different foods to EtOH-eq according to SI  
328 Table S2.

### 329 **2.5 Applying the high-throughput estimation approach – external validation**

330 We ran the developed HT model to predict migration for various chemical, package, and food  
331 combinations that have empirical data available. The empirical data were provided by request from  
332 the US FDA (FDA 2016). These requested data are used to provide industrial guidance for pre-market  
333 submissions, and the data set contains 12,773 independent measurements for migration.

334 Most of the migration measurements in the database also included the parameters needed for  
335 modelling, e.g. according to eq (4), specifically the tested chemical's MW and  $K_{ow}$ , the food or  
336 simulant tested, the polymer tested and its thickness, the duration and temperature of the test.  
337 Entries reporting a "0" starting concentration of a chemical in a polymer, or reporting that the final  
338 migrated mass into a simulant or food exceeded the initial mass in the tested material (perhaps due  
339 to experimental uncertainty) were disregarded. Diffusion coefficients are also provided for each  
340 experiment in the spreadsheet. Several parameters required for modelling were also not reported in  
341 the database, for example  $A'_p$  which is required to model the diffusion coefficient, and EtOH-eq of the  
342 food or simulant which is required to model the partition coefficient. We therefore matched the  
343 database to the available polymer-specific average  $A'_p$  (Section 2.4.1; SI Table S1) and a list of EtOH-eq

344 matched to food or simulants (SI Table S2) in order to simulate each applicable experimental value.  
345 4,492 applicable experimental values remained with available  $A'_p$ , and EtOH-eq. Migration modelling  
346 was then performed using three different approaches: A) the HT model (Table 1) and *using measured*  
347 *diffusion coefficients from the database*, B) applying the HT model (Table 1) and using *modelled*  
348 *diffusion coefficients estimated with eq (5)*, and finally C) using a combination of eq (2) (diffusion-  
349 dominated model) and (3) (partition denominated model) and taking the minimum value, i.e. the  
350 value of eq (2) until it intersects with eq (3), and then the value of eq (3). . The two first modelling  
351 approaches A and B were employed to elucidate the contribution of the estimated diffusion  
352 coefficient to model uncertainty. The final approach C, is the most simple and was tested against the  
353 first two approaches A and B.

### 354 **3. Results and discussion**

#### 355 **3.1 Development of an accurate model for high-throughput migration modelling**

356 **Model development:** The operationalised form of the HT migration model eq (4), including estimates  
357 for  $t_d^*$ , A, B, and C is compiled in Table 1. Predicting  $t_d^*$  first is important for knowing the contact  
358 duration after which the simplified diffusion eq (2) is no longer valid, and also to serve as input for eq  
359 (4). To avoid over-estimating  $t_d^*$ , which would jeopardize the predictive ability of the model, we  
360 determined two equations to predict  $t_d^*$  as a function of  $\alpha$ , i.e. one for  $\alpha \leq 0.2$  and one for  $\alpha > 0.2$  as  
361 described by eq (6) in Table 1, with a high accuracy ( $R^2 \approx 1$ , Figure S4C). The coefficients A, B, and C of  
362 the HT migration model are obtained as a direct function of alpha as defined by equation (8a,b,c) of  
363 Table 1 and the stepwise procedure to determine these is further detailed in SI Figure S5.

364  $t_d^*$  is proportional to the ratio  $d_p^2/D_p$  which we have defined as a characteristic time of migration  
 365 (CTM (s), see SI Figure S4) as a function of the thickness of the diffusive path length and the diffusion  
 366 coefficient. . CTM can range from a few hours to thousands of years depending on the packaging  
 367 thickness and diffusion coefficient (Figure 2).  $t_d^*$  may only be a small fraction of CTM, and the fraction  
 368 lessens as  $\alpha$  and the equilibrium value decrease.

369 Table 1. Final high-throughput estimation model and required parameters.

Model	$f_{t,p} = \begin{cases} \frac{2}{d_p} \times (D_p t_d / \pi)^{\frac{1}{2}} \text{ eq(2)} & \text{if } t_d \leq t_d^* \text{, else} \\ y_{t_d^*} + \left(\frac{\alpha}{1+\alpha} - y_{t_d^*}\right) \times \left(A \times (1 - e^{-B \times \beta \times (t_d - t_d^*)}) + (1 - A) \times (1 - e^{-C \times \beta (t_d - t_d^*)})\right) & \end{cases} \quad (4)$ <p>where <math>y_{t_d^*} = \frac{2}{d_p} \times (D_p t_d^* / \pi)^{\frac{1}{2}}</math></p>
Diffusion coefficient	$D_p = D_o \exp\left(A_p - 0.1351 MW^{\frac{2}{3}} + 0.003 MW - \frac{10454}{T}\right) \left(\frac{cm^2}{s}\right) \quad (5)$ <p>where <math>A_p = A'_p - \frac{\tau}{T}</math>, <math>D_o = 1 \text{ m}^2/s = 10^4 \text{ cm}^2/s</math> and</p> <p><math>R = 8.3145 \text{ J mol}^{-1} \text{ K}^{-1}</math>.</p>
Contact time when eq (2) deviates from eq (1) >1%	$t_d^* = \begin{cases} \left(\frac{d_p^2}{D_p} \left(\frac{r_1}{1+r_2 e^{r_3 \times \log(\alpha)}}\right)\right) & \text{for } \alpha \leq 0.2 \\ \left(\frac{d_p^2}{D_p} r_4 e^{r_5 \times \log(\alpha)}\right) & \text{for } \alpha > 0.2 \end{cases} \quad (6)$ <p><math>R^2=0.99</math> when the values and the 95% confidence interval (CI) are:  <math>r_1(95\% \text{ CI})=0.3552 (0.3549, 0.3555)</math>  <math>r_2 (95\% \text{ CI})=85.88 (83.99, 87.77)</math>,  <math>r_3(95\% \text{ CI})=-3.506 (-3.524, -3.488)</math>,</p>

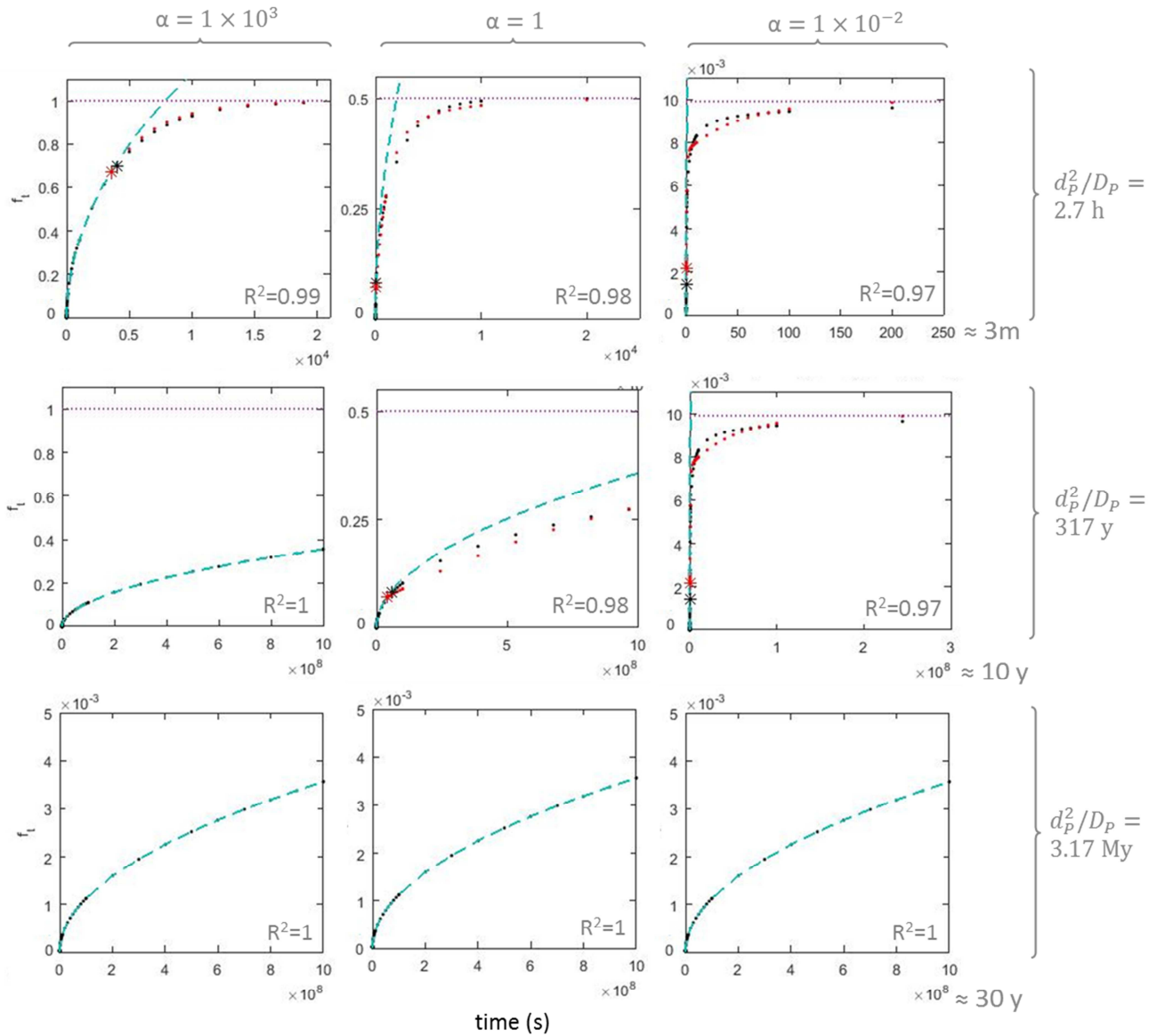
	$r_4(95\% \text{ CI})=8.495^E-3 (8.375^E-3, 8.616^E-3)$ $r_5(95\% \text{ CI})=4.458 (4.445, 4.47).$
Slope factor ( $\beta$ ), approximation of the slope (derivative) of eq (2) at time $t_d^*$	$\beta = \frac{1}{d_p} \sqrt{\frac{D_p}{\pi t_d^*}} \times \left( \frac{\alpha}{\frac{1+\alpha}{eq (3)}} - \frac{2}{d_p} \times \underbrace{(D_p t_d^*/\pi)^{\frac{1}{2}}}_{eq (2) \text{ at } t_d^*} \right)^{-1} \quad (\text{s}^{-1}) \quad (7)$
Coefficients A, B, and C	$A(x_1) = \begin{cases} 0.7 & \text{for } x_1 < 0.7 \\ 1 & \text{for } x_1 > 1 \\ x_1 & \text{elsewhere;} \end{cases} \quad \text{where } x_1 = 10^{0.12 \log(\alpha) + \log 0.8} \quad (8a)$ $B(x_2) = \begin{cases} 0.3 & \text{for } x_2 < 0.3 \\ 0.9 & \text{for } x_2 > 0.9 \\ x_2 & \text{elsewhere;} \end{cases} \quad \text{where } x_2 = 10^{0.22 \log(\alpha) + \log 0.5} \quad (8b)$ $C(x_3) = \begin{cases} 0.004 & \text{for } x_3 < 0.3 \\ 1 & \text{for } x_3 > 1 \\ x_3 & \text{elsewhere;} \end{cases} \quad \text{where } x_3 = 10^{0.7 \log(\alpha) + \log 0.08} \quad (8c)$
Partition coefficient between package and food.	$\log K_{P,F} = m \times \log(K_{ow}) - b \quad (9)$ <p>where <math>m = -0.0085 \times \text{EtOH} - \text{eq} + 0.876</math>, and <math>b = 1.05</math>.<sup>#</sup></p>

370 <sup>#</sup>Data were not available for chemicals with  $\log K_{ow} > \approx 5, 8, 18$  when the EtOH-eq is  $\approx 10, 50, 95\%$   
371 respectively, and the model accuracy in this range is thus unknown.

372 **HT Model performance:** Figure 2 demonstrates the resulting model performance across a wide range  
373 of permutations of  $\alpha$ ,  $D_p$ , and  $d_p$ , where the model behaviour is specific to combinations of  $\alpha$  and  
374 CTM, within a feasible contact duration between package and food (i.e.  $< 30y$ ). Simulations were  
375 chosen within realistic values of  $\alpha$  and CTM based on observed ranges of partition coefficients,  
376 diffusion coefficients and packaging thicknesses (Piringer and Baner 2008). Figure 2 is organised in  
377 rows and columns, where alpha decreases from the first to third column, and where the CTM  
378 increases from first to third row. When alpha is large the potential migrated fraction approaches 1,  
379 and as alpha decreases (see first to third column) so does the migrated fraction. As CTM increases  
380 between the first and third rows, the time to reach full migration (seen as the curve flattening at a

381 plateau) also increases. For each CTM (see first to third column for each row) the model plateaus at  
382 earlier contact times when there is a lower  $\alpha$  value which corresponds to a lower equilibrium value.  
383 For each CTM (rows) the model plateaus earlier with low  $\alpha$  values and subsequent equilibrium value  
384 (columns). Figure 2 also demonstrates that the HT model (in red) fits very well the original model (in  
385 black) with  $R^2$  between 0.97 and 1, across a wide range of relevant time scales from a few minutes to  
386 30 years and input parameter combinations. The HT model represents a substantial improvement  
387 compared to the combination of the minimum value of the short-term diffusion dominated model (in  
388 green) and the long-term equilibrium value (pink dotted line) that may over-estimates  $f_t$  by a factor of  
389 3 (Figure 3). The points plotted in the figure represent the maximum over-estimation which always  
390 occurs when eq (2) intersects eq (3) (also see Figure 1). SI Table S3 provides example combinations of  
391  $D_p$ , and  $d_p$  (infinite combinations are possible) to obtain the CTMs that were simulated.

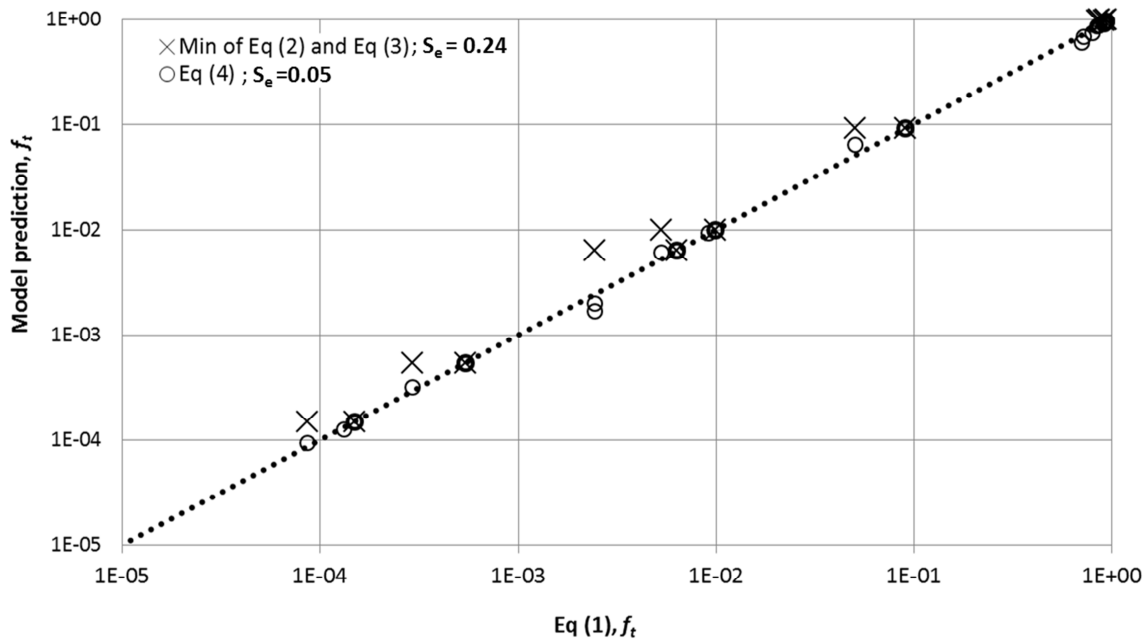




392

393 Figure 2. Comparison between the migrated fraction,  $f_t$ , predicted by the HT model (Table 1) after the  
 394 deviation point,  $t_d^*$  (red solid line), with  $f_t$  predicted by the original model, eq (1) (black solid line). A  
 395 range of combinations of  $\alpha$  and characteristic times ( $d_p^2/D_p$ , converted to relevant units, where My is  
 396 millions of years) were simulated to cover a feasible span of scenarios and  $R^2$  were obtained. The  
 397 diffusion-based model, eq (2) (turquoise dashed line), and the equilibrium-based model, eq (3) (pink

398 dotted line) are also shown. Eq (2) and eq (1) are >99% equal until  $t_d^*$  (black asterisk); the red asterisk  
 399 is the predicted  $t_d^*$  where the double exponential form begins.



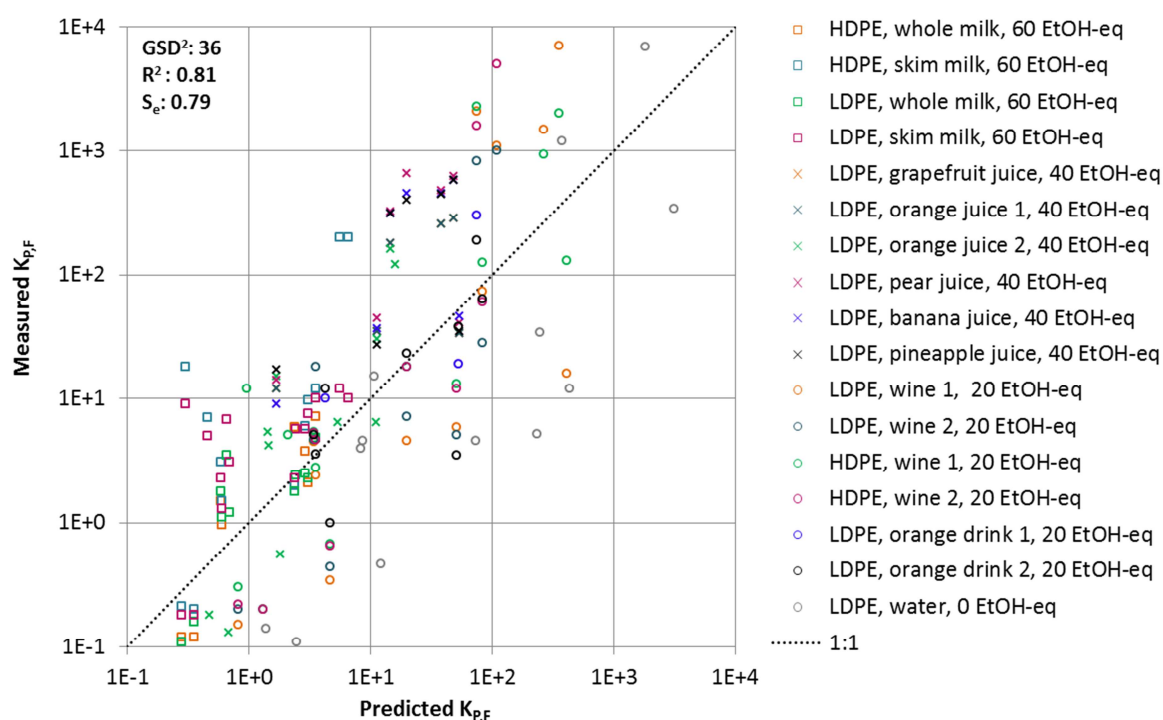
400

401 Figure 3. Comparison between the migrated fraction  $f_t$  predicted by the detailed model eq (1), by the  
 402 HT model (Table 1) and by taking the minimum of the diffusion-based model eq (2) and the  
 403 equilibrium-based model eq (3). Standard error,  $S_e$ , on the logarithmic scale is indicated with the  
 404 legend.

405

**406 3.2 Model parametrization**

407 Determination of the diffusion and partition coefficients,  $D_p$  and  $K_{p,F}$ , are essential to model migration  
408 and key parameters in all model eqs (1) to (3) and in the HT model described in Table 1. For  $D_p$  we  
409 used the established equation presented by Begley et al. (2005) as shown in equation (5), but when  
410 available a measured value or more precise model should be used for this parameter. Eq (9), Table 1,  
411 provides the model to estimate the log-log linear approximation of  $K_{p,F}$ . SI Figure S6 compares this  
412 approximation with the empirical data reported in Table 2 of Ozaki et al. 2010 (Table 2),  
413 demonstrating a good resulting correlation. The performance of the model on the log-scale was  
414 described by standard error ( $S_e$ ), the coefficient of determination ( $R^2$ ), and the squared geometric  
415 standard deviation ( $GSD^2$ ); assuming with a log-normal distribution of uncertainty around the  
416 modelled value, the product of the modelled value and  $GSD^2$  is equal to the 97.5%-ile and the  
417 quotient of the modelled value and  $GSD^2$  is equal to the 2.5%-ile of the expected data uncertainty  
418 distribution (Heijungs and Frischknecht 2004).



419

420 Figure 4. Comparison of the predictions of partition coefficients  $K_{p,F}$  by the HT model with empirical  
 421 data from Mercea 2008; dotted line is the 1:1 diagonal; the squared geometric standard deviation  
 422 ( $GSD^2$ ), standard error ( $S_e$ ) and coefficient of determination ( $R^2$ ) are evaluated on the log-scale.

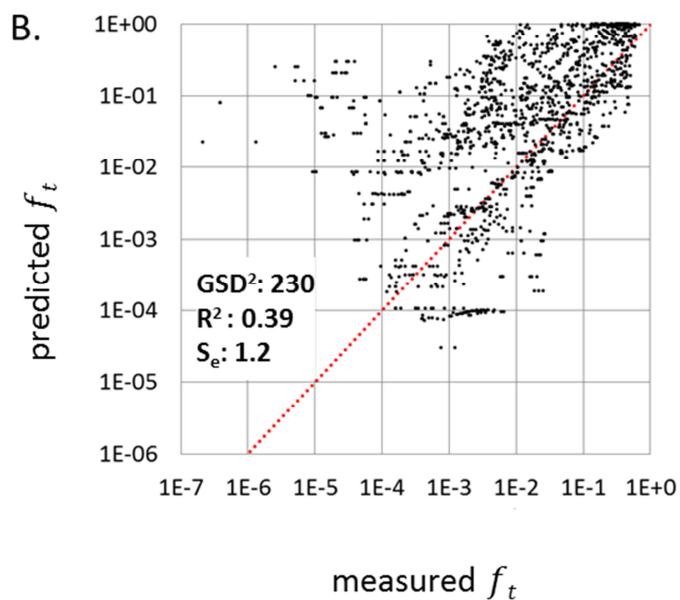
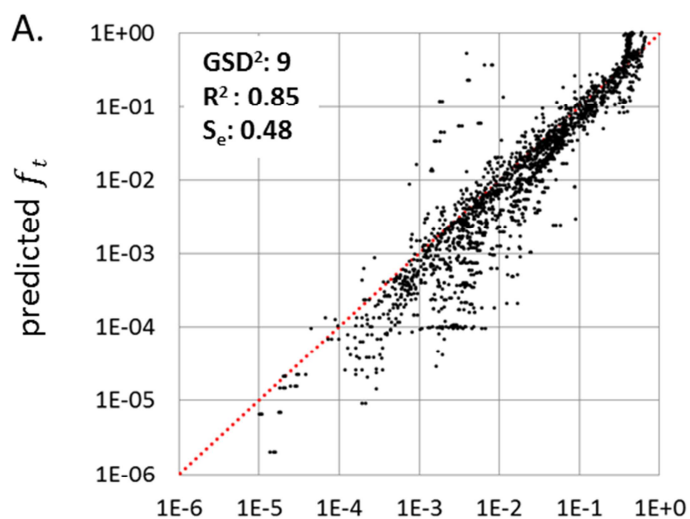
423 Figure 4 demonstrates an external validation of the developed  $K_{p,F}$  model compared with empirical  
 424 data for 17 chemicals from Appendix II Piringer & Baner (2008) (Mercea 2008) with various food types  
 425 and two polymers at 23 °C (Figure 4). The considered chemicals' MWs ranged from 94 to 220 g/mol  
 426 and from log  $K_{ow}$  1.3 to 5.2. The performance of the  $K_{p,F}$  model was reasonable for both LDPE and  
 427 HDPE, likely because these polymers have similar properties influencing partitioning (e.g. polarity)  
 428 (Ozaki et al. 2010). The applicability of the model for polymers other than LDPE and HDPE is unknown  
 429 at this time and should be explored in future work. The influence of  $K_{p,F}$  uncertainty can be

430 understood by examining the influence of  $\alpha$  on the ultimate equilibrium value, where  $\alpha$  is a function  
431 of  $K_{p,F}$  and the volumes of food and packaging material. The sensitivity of the equilibrium value to  $\alpha$   
432 depends on the magnitude of  $\alpha$ . Since equilibrium is determined as  $\alpha / (1 + \alpha)$ , eq (3), there is  
433 maximum a factor 2 difference between the equilibrium values of any  $\alpha \geq 1$  (which range between  
434 0.5 and 1). This means uncertainty of  $K_{p,F}$  becomes less important as the equilibrium value increases.  
435 When  $\alpha \leq 0.1$  the sensitivity of the equilibrium value is mirrored, where a factor 10 difference in  $\alpha$  (or  
436  $K_{p,F}$  holding all else constant) results in nearly a factor 10 difference in the equilibrium value. This  
437 means when equilibrium is low the uncertainty on  $K_{p,F}$  is more important.

### 438 **3.3 High-throughput migration modelling – external validation**

439 The calculation speed for the HT migration model developed in this paper and listed in Table 1 is  
440 nearly instantaneous, and the full model was programmed in a spreadsheet. Of the 4,492 FDA data  
441 points with data available for parameterization 1,428 were excluded due to high  $K_{ow}$  outside of the  
442 range of the empirical data used for determining  $K_{p,F}$ . We first applied the HT model (Table 1) with the  
443 *measured* diffusion coefficients reported in the FDA database (SI Figure S6), considering all data  
444 points ( $GSD^2 = 24$ ,  $R^2 = 0.6$ ,  $S_e = 0.7$ ). Two sets of data points from one experimental data set referred  
445 to as “Models for the Migration of Low Molecular Weight Additives in Polyolefins. National Bureau of  
446 Standards. Report NBSIR 81-2264, April, 1981.”, corresponding to experiments for a chemical called  
447 BHT in DEHP migration to corn oil and ethanol and dotriacontane in corn oil were clear outliers. The  
448 reported diffusion coefficients caused an unexplainable vertical shift (SI Figure S7) from the trend  
449 observed for the rest of the data, including other data for the same chemicals, polymers and  
450 simulants, suggesting analytical issues from this experimental dataset. We therefore also removed

451 these 744 points for these two chemicals of this dataset. Screening was finally performed for the  
452 remaining 2,320 data points (Figure 5) and when using measured data for the diffusion coefficient  
453 (Figure 5A), the uncertainty was minimal ( $GSD^2=8$ ,  $R^2=0.87$ ,  $S_e=0.48$ ).



454

455 Figure 5A-B. Prediction of  $m_{i,t}/m_{i,0}$  using the developed HT model (Table 1) compared to empirical  
456 data from US FDA, where either the measured (Figure 5A) or modelled  $D_p$ , eq (5) was used (Figure  
457 5B). Dotted red line represents the 1:1 diagonal; the squared geometric standard deviation ( $GSD^2$ ),  
458 standard error ( $S_e$ ) and coefficient of determination ( $R^2$ ) values are evaluated on the log-scale.

459 Using eq (2) and eq (3) to model these points yielded the same results as applying the approach in  
460 Table 1, because the experiments in the FDA study were all in the short-term contact duration  
461 range—and in fact are reasonably estimable by only eq (2). The US FDA empirical dataset provides  
462 estimated diffusion coefficients, therefore experiments were likely intentionally restricted to be in the  
463 range of diffusion-dominating behaviour. To our knowledge there is no available empirical dataset to  
464 test the model that covers a full range of measured values shifting from diffusion-dominated to  
465 partition-dominated behaviour (as experiments are usually designed to obtain either of these  
466 parameters).

467 When the HT model (Table 1) was applied with *modelled diffusion coefficients*, eq (5), the 95<sup>th</sup>  
468 percentile distribution increased by more than an order of magnitude on either side of the modelled  
469 point and the goodness of fit fell (Figure 5B) ( $GSD^2 = 230$ ,  $R^2 = 0.49$ ,  $S_e = 1.2$ ). This dramatic increase in  
470 uncertainty is thereby directly attributable to the diffusion coefficient model. To reduce the  
471 uncertainty of diffusion modelling, topological molecular descriptors (e.g. molecular volume) are an  
472 area of interest (Fang and Vitrac 2017); however, more accurate models using topological input  
473 parameters have not yet been operationalised for rapid HT modelling. Therefore, improving HT-  
474 compatible modelling of the diffusion coefficient, for example through quantitative property-property

475 relationship modelling (Huang et al. 2017b), is necessary for future HT models estimating migration of  
476 chemicals from packaging into food.

477 Eq (1) and the resulting HT approach is mathematically valid when the matrix of the food poses no  
478 resistance to diffusion and is continuously mixed, e.g. valid for fluids, which is the most studied and  
479 empirically validated scenario (Pocas 2008; Piringer and Baner 2008). Most of the empirical data used  
480 to validate the model is from liquid foods (e.g. beverages) and only several experiments were  
481 available for non-liquid foods, mayonnaise and chocolate. Given these limited data, there was also  
482 good agreement between the model and the estimates of the migration of chemicals from packaging  
483 into foods (SI Figure S9). Further work would be required to develop and test the model against solid  
484 and dry foods; applying a multiplying ratio of the diffusion coefficients between food and polymer  
485 may be useful in future approaches to adjust the model (Piringer and Baner 2008).

#### 486 **4. Conclusion**

487 High-throughput (HT) modelling approaches were developed to estimate the fraction of an organic  
488 chemical migrating from a polymeric food contact material into a food. The primary aim was to  
489 operationalize migration modelling, e.g. eqs (1)-(3), to be suitable for decision-support tools that  
490 require rapid calculation of best-estimates of migration. Setting the partition coefficient between  
491 packaging and food equal to one (which we found was not a universal “worst-case” scenario) can lead  
492 to grossly misestimating the equilibrium value. Therefore, we also developed methods to estimate  
493 the partition coefficient to ensure more accurate HT methods. A main outcome was furthermore, a  
494 method to more precisely determine the timespan for which an existing simple, diffusion-based  
495 model, eq (2), is valid. We determined this simple model is valid when the contact duration between



496 the food and package is less than the developed prediction for  $t_d^*$  (eq 6, Table 1), which can range  
497 from fractions of a second to several years depending on the input parameters and can be predicted  
498 as a function of  $\alpha$  and CTM – the characteristic time of migration.

499 By providing a method to determine  $t_d^*$ , the timespan where eq (2) is valid, and additionally  
500 developing a method to estimate migration after  $t_d^*$ , the developed HT model (Table 1) is valid over  
501 all relevant timespans. The new HT model also showed good agreement with eq (1) over a full range  
502 of input parameters and agreement improved as the parameter  $\alpha$  increased (meaning the equilibrium  
503 concentration in food increased). The developed HT model offers substantial improvement compared  
504 to the combination of the minimum value of the diffusion-based model eq (2), and the equilibrium  
505 value eq (3), that may otherwise over-estimate  $f_t$  by a factor of 3 after  $t_d^*$  and before equilibrium is  
506 achieved. Additionally, our model was more accurate by several orders of magnitude than using eq (1)  
507 with a limited number of tabulated roots at short time scales; therefore the developed HT model is  
508 preferred to eq (1) for comparative assessments that aim at average rather than conservative  
509 estimates. Furthermore, the model demonstrated good agreement with measured data, especially  
510 when using a measured diffusion coefficient. When a modelled diffusion coefficient was used, there  
511 was a drastic increase in uncertainty, underscoring the importance of improving diffusion coefficient  
512 modelling.

513 The developed model, as well as eq (1), rely on  $\alpha$  which is a direct function of the partition coefficient  
514 between a polymer and a food,  $K_{p,F}$ . The model we developed, eq (9), to estimate  $K_{p,F}$  as a function of  
515 the chemical  $K_{ow}$  and the food's assigned ethanol-equivalency, EtOH-eq, also had good agreement  
516 with the empirical data ( $R^2=0.81$ ) which are limited to LDPE and HDPE polymers. The approach is

517 similar to other models (Seiler et al. 2014), however, we additionally provide the equation to support  
518 application in future uses.

519 The developed model is intended for future use in decision support tools that consider exposure to  
520 chemicals in food packaging materials in a variety of scenarios, for example in Life Cycle Assessment  
521 (LCA) or high-throughput risk-based screening (HTRS) (Shin et al. 2015; Jolliet et al. 2015b). In such  
522 decision support assessments the model could be combined with the initial chemical mass in a food  
523 packaging material in order to estimate the migrated mass and subsequent exposure. Furthermore, in  
524 order to estimate risk exposure estimates can be combined with toxicity information, e.g. if available  
525 through high-throughput screening (Karmaus et al. 2016) and relevant dosimetry adjustments  
526 (Wetmore et al. 2015). The initial concentration of chemicals in various consumer products are  
527 becoming increasingly available through databases (Goldsmith et al. 2014); however, concentrations  
528 of chemicals in packaging are not yet available. Future research is required to fill this concerning data  
529 gap, e.g. through rapid analytical identification methods or function-based chemical concentration  
530 modelling, as has been recently performed for cosmetics (Isaacs et al. 2016).

531 The model was specifically designed to address the need for estimating the product intake fraction  
532 (Jolliet et al. 2015a) (Section 2.1) of food contact materials in LCA. Recent studies have underscored  
533 trade-offs between environmental impacts of food packaging systems and exposure to potentially  
534 toxic chemicals in food packaging materials (Lee et al. 2014; Yuan et al. 2016; Leslie et al. 2016).  
535 Considering exposure to chemicals in packaging within LCA could, for example, help ensure that  
536 system or packaging designs aiming to minimize environmental impacts (e.g. greenhouse gas  
537 emissions or resource use) do not unintentionally increase exposure to hazardous chemicals in

538 packaging, and vice versa that system or product designs to minimize migration and exposure to  
539 hazardous substances do not increase environmental impacts.

540 In all, this study presents a rapid method to provide best-estimates of migration of chemicals from  
541 packaging with a first focus on organic chemicals in polymeric food packaging. Future work could  
542 extend this approach to other food contact materials (e.g. paper and board) and chemical types (e.g.  
543 nanoparticles or inorganic chemicals). Future focus on diffusion coefficient modelling, for polymers  
544 and other material types, should also be a priority to improve the accuracy of migration modelling in  
545 general. Additionally, future work should focus on identifying data availabilities that will be required  
546 for application of the model in decision support tools, such as the initial chemicals in packaging and  
547 toxicity of these chemicals.

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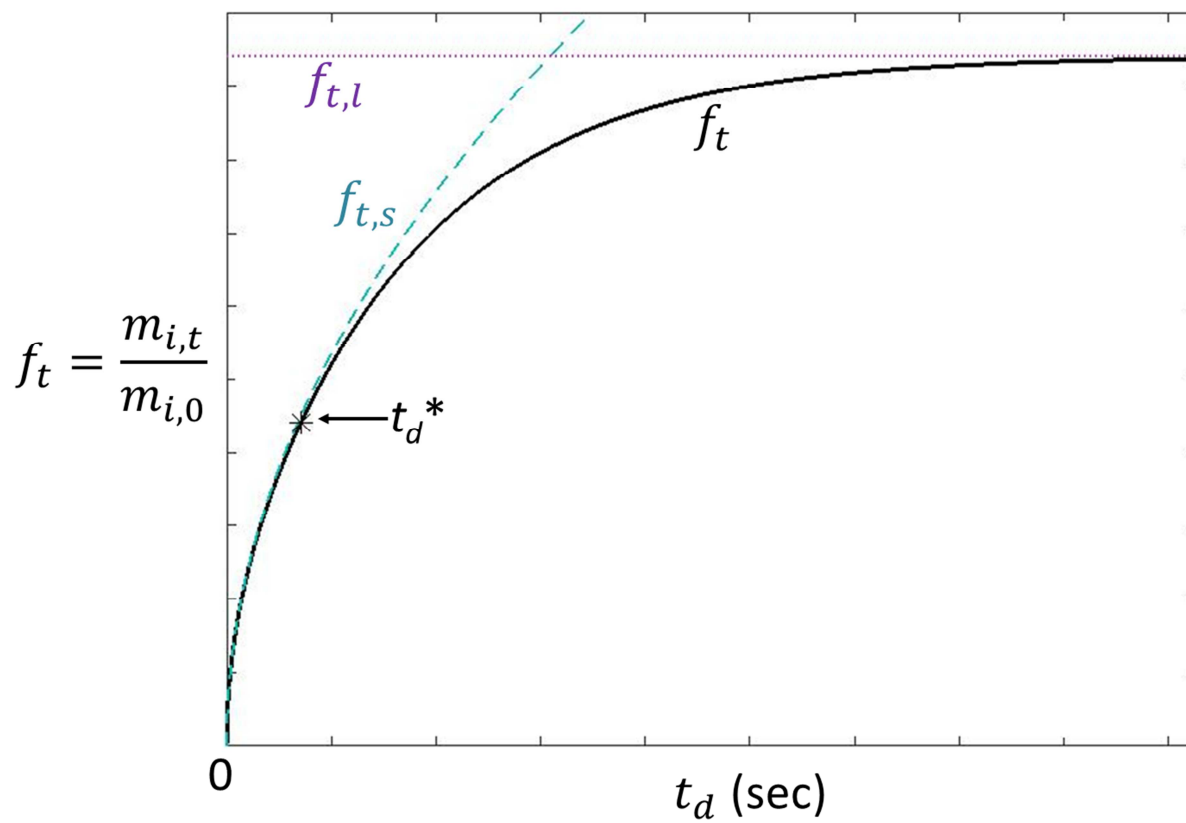
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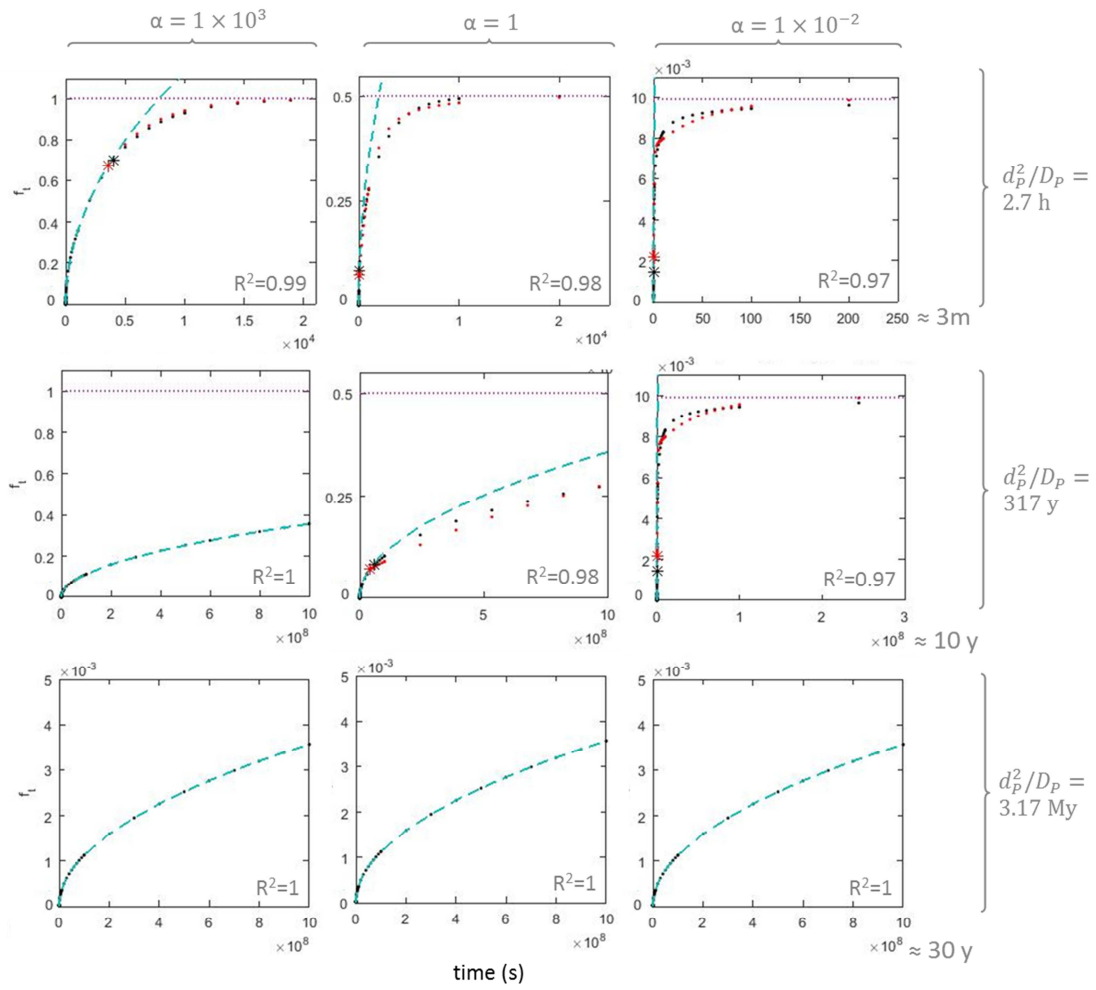
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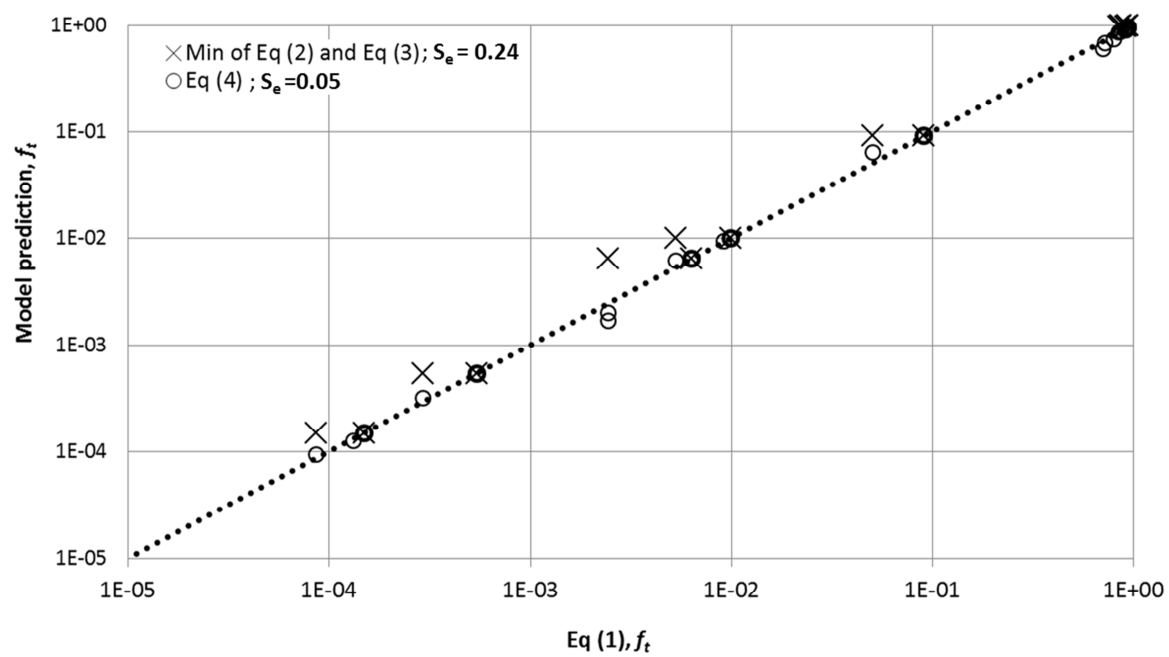


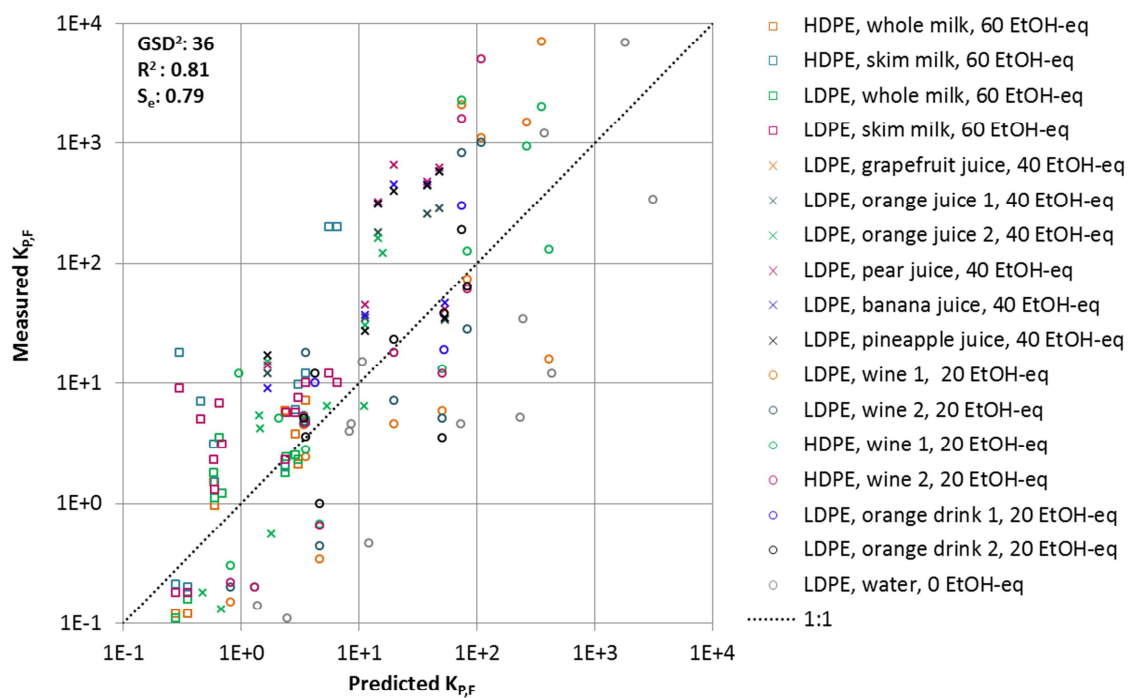


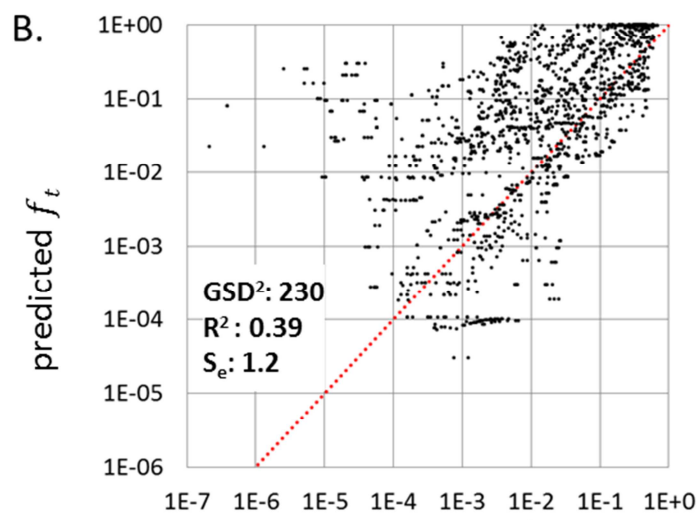
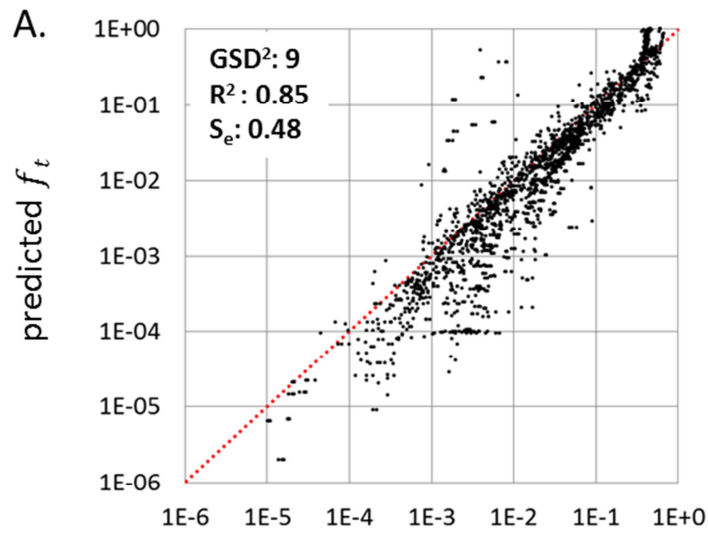
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**Highlights**

- A rapid and accurate migration model for chemicals in food packaging was developed for exposure screening and assessment.
- The model estimates the product intake fraction due to transfer of organic chemicals in polymeric packaging to food.
- The model is a function of packaging, food, and chemical aspects, as well as time and temperature.
- The model performs well when compared to empirical data, but the diffusion coefficient estimation leads to uncertainty.
- The model is available for dissemination in a spreadsheet to facilitate application in prioritization and screening tools.