Food and Chemical Toxicology 166 (2022) 113118

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Modeling the migration of chemicals from food contact materials to food: The MERLIN-expo/VERMEER toolbox

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ARTICLE INFO

Handling Editor: Dr. Jose Luis Domingo

Keywords:
Food contact material
Migration model
Uncertainty analysis

ABSTRACT

Evaluating the migration of chemicals from food contact materials (FCM) into food is a key step in the safety assessment of such materials. In this paper, a simple mechanistic model describing the migration of chemicals from FCM to food was combined with quantitative property-property relationships (QPPRs) for the prediction of diffusion coefficients and FCM-Food partition coefficients. The aim of the present study was to evaluate the performance of these operational models in the prediction of a chemical's concentration in food in contact with a plastic monolayer FCM. A comparison to experimental migration values reported in literature was conducted. Deterministic simulations showed a good match between predicted and experimental values. The tested models can be used to provide insights in the amount and the type of toxicological data that are needed for the safety evaluation of the FCM substance. Uncertainty in QPPRs used for describing the processes of both diffusion in FCM and partition at the FCM-Food interface was included in the analysis. Combining uncertainty in QPPR predictions, it was shown that the third quartile (75th percentile) derived from probabilistic calculations can be used as a conservative value in the prediction of chemical concentration in food, with reasonable safety factors.

1. Introduction

Food contact materials (FCM) are omnipresent in everyday life. Despite their multiple benefits in food handling and processing, the safety of these FCM should be assessed as migration of compounds from FCM into the food has clearly been established (Muncke et al., 2020). Although migration generally occurs in relatively small amounts, life-long exposure to low levels of these food contaminants may lead to serious adverse human health effects (Van Bossuyt et al., 2019). In Europe, a specific regulation exists only for plastic FCM, including a positive list (Annex I) of substances authorized for use as starting product (EU, 2011). Migration of substances included in Annex I should be below the specific migration limit (SML), if available. These SML values have been derived based on toxicological data submitted by the applicant. The type and amount of toxicological data depends on the estimated exposure, which is driven by the level of migration of the chemical from the FCM into the food (EFSA, 2008). In case migration of a chemical is below 0.05 mg/kg food, exposure is considered to be low and only limited toxicological testing is required. However, if migration becomes higher, additional toxicological information needs to be provided by the applicant.

Consequently, evaluating the migration of chemicals from FCMs into food is a key step in the safety assessment of such materials. Migration of chemical substances within FCM and at the FCM-food interface is driven both by kinetic diffusion and thermodynamic partitioning between the FCM and the food. The kinetic dimension of migration determines how fast the migration process occurs, while the thermodynamic dimension has an impact on the magnitude of the transfer of chemicals at equilibrium. Various models have been developed to integrate such diffusion and partitioning processes, thereby taking into account the effect of the plastic FCM material, nature of food or beverage, temperature, media thicknesses and the initial amount of chemical in the FCM (Brandsch et al., 2002, 2015; Helmroth et al., 2002; Begley et al., 2005; Barnes et al., 2006; Oldring et al., 2014; Poças et al., 2008; Biryol et al., 2017;

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https://doi.org/10.1016/j.fct.2022.113118
Received 27 September 2021; Received in revised form 21 March 2022; Accepted 4 May 2022
Available online 20 May 2022

Ernstoff et al., 2017; Gavriil et al., 2018). Some of these models are used for regulatory purposes and are assumed to be based on conservative assumptions. However, some gaps can be identified. Firstly, some of the models are purely empirical and are not based on explicit mechanistic foundations, making their extrapolation to other conditions (i.e. other materials, time scales, etc.) difficult. For example, Biryol et al. (2017) developed an empirical linear regression model for migration at equilibrium by fitting available migration measurements. By construction, this model is unable to provide kinetic information since it is based on data at equilibrium only. Secondly, in the absence of adequate models for the prediction of partition coefficients at the FCM-food interface (which govern the thermodynamic dimension indicated above), most models are based on default partition coefficient values, not specific to the substances tested. For example, Begley et al. (2005) developed a model considering 'worst case' partition coefficients: in absence of specific data, partition coefficient is assumed to be equal to 1, which means that the substance is very soluble in food, leading to the highest migration predictions. Third, models for predicting diffusion coefficients (which govern the kinetic dimension indicated above) were generally only calibrated and applicable to a small number of FCMs, mainly plastic materials. For example, models proposed by Begley et al. (2005) are applicable for low-density and high-density polyethylene (LDPE, HDPE), polyethylene terephthalate and naphtalate (PET, PEN), polypropylenes (PP), general-purpose and high-impact polystyrene (PS, HIPS), and polyamide (PA). Finally, it remains difficult to estimate the confidence level associated with the results of models since many parameters used in migration modeling (in particular diffusion or partition coefficients) may show large uncertainty. Yet, available codes are not designed for conducting global multi-parametric uncertainty analysis since parameter values are set at 'best estimate' or 'default' values. Simulations performed with 'best estimates' or 'default' parameter values only do not provide a good indication of the confidence level associated with the model results. A model can indeed give good results 'on average', but the confidence interval can range over orders of magnitude. Uncertainty assessment is then essential for the performance evaluation of a model and for decision-making.

Recent papers present the basis for improving these models and extending their applicability domain. Ozaki et al. (2010) and Ernstoff et al. (2017) combined food and chemical factors to derive predictive models for FCM/food partition coefficients. Huang and Jolliet (2019) refined the approach previously developed by Ernstoff et al. (2017) and developed a quantitative property-property relationship (QPPR) for predicting FCM/food partition coefficients, extending the number of materials of concern and introducing the temperature dependency. Instead of using default and/or 'worst case' partition coefficients, it is therefore possible to exploit this QPPR to determine values specific to the substances and conditions tested, thus improving the relevance of predictions. In addition, Huang et al. (2017) developed a QPPR for predicting diffusion coefficients in FCM as a function of material type. This model covers a wide range of substance-material combinations, i.e. 87 original materials grouped into 32 consolidated material types. It therefore opens up the perspective of simulating the migration of chemicals from a wider range of FCMs. Finally, each abovementioned QPPR integrates information about prediction uncertainty. Combining such uncertainties in a common tool can then provide a global overview of the confidence level in predictions of chemical concentrations in food.

To our knowledge, these recent developments have not been integrated into a global migration model including uncertainty assessment, nor have they been compared with 'old' models and experimental data. To bridge this gap, a migration model was implemented in the MERLIN-Expo/VERMEER platform. The MERLIN-Expo tool (https://merlin-expo.eu/) is presented in detail in Ciffroy et al. (2016) and has already been used for various applications dealing with environmental and human health exposure issues (Giubilato et al., 2016; Radomyski et al., 2016; Fierens et al., 2016; Van Holderbeke et al., 2016; Ciffroy and Benedetti, 2018). Briefly, the MERLIN-Expo tool is a library of models providing an integrated assessment tool for state-of-the-art exposure assessment for environment, biota and humans. In the frame of the European Life-VERMEER project, the MERLIN-Expo tool was merged with the VEGA tool, which is a library of QSAR models predicting physico-chemical, fate and (eco)toxicological parameters of chemicals (https://www.vegahub.eu/). The new integrated tool resulting from the merging of MERLIN-Expo and VEGA was called VERMEER FCM, allowing a comprehensive analysis of uncertainties occurring at the different steps of the assessment. In this context, a migration model predicting the transfer of chemicals from FCM to food was incorporated in the MERLIN-Expo library. Focus was put on widely used migration models that require a limited amount of input parameters and on QPPR models able to provide parameter estimations for a wide range of chemicals and FCMs. A comparison to experimental migration values was conducted using the database published by Begley et al. (2005). Considering this background, the main objective of this study was to evaluate global performance of this new integrated model, including uncertainty assessment.

2. Material and methods

2.1. The migration model

A one-dimensional (1D) diffusion model simulating the transfer of chemicals from a monolayer plastic FCM layer and food was considered here. The governing partial differential equation describing diffusion is the second Fick's Law:

$$\frac{\partial C_i}{\partial t} = D_i . \frac{\partial^2 C_i}{\partial x^2} \tag{1}$$

where C_i is the concentration of the chemical in compartment i (in mg.g^{-1}); D_i is the diffusion coefficient in compartment i (in m^2.s^{-1}).

When only one FCM layer is considered, the mass-balance equation based on Fick's second law (Equation (1)) satisfies an analytical solution, as described in Crank (1979) and adapted in Piringer (2007):

$$m_{Food}(t) = m_{FCM,0} . \left(\frac{\rho_{FCM} . \alpha}{\rho_{Food} + \rho_{FCM} . \alpha}\right) . \left[1 - \sum_{n=1}^{\infty} \frac{2\alpha . (1+\alpha)}{1 + \alpha + \alpha^2 q_n^2} exp\left(- D_{FCM} . t . \frac{q_n^2}{d_{FCM}^2}\right)\right] \tag{2}$$

where $m_{Food}(t)$ represents the amount of the migrating chemical after the contact time t in food (mg); $m_{FCM,0}$ is the initial amount of the chemical in FCM (mg); with the volumes V_{FCM} and V_{Food} of FCM and food (cm^3).

α (unitless) represents the ratio:

$$\alpha = \frac{V_{Food}}{V_{FCM} . K_{FCM,Food}} = \frac{d_{Food}}{d_{FCM} . K_{FCM,Food}} \tag{3}$$

with $K_{FCM,Food}$ representing the partition coefficient of the chemical between FCM and food; d_{Food} is the thickness of the food layer (cm); d_{FCM} is the thickness of the FCM layer (cm).

The parameters q_n involved in Equation (2) are the positive roots of the transcendent equation: $\tan(q_n) = -\alpha q_n$. Solutions of this latter trigonometric identity are tabulated for some values of α, but approximated solutions were used in the present model, i.e. (Equation (4)):

$$for\ \alpha \ll 1, \quad q_n \approx \frac{n\pi}{1+\alpha}$$

$$else, \quad q_n \approx \left[n - \frac{\alpha}{2(1+\alpha)}\right]\pi \tag{4}$$

According to Piringer (2007), solutions of Equation (2) converge rapidly for long diffusion times, while for short times, e.g., at the beginning of diffusion ($T = 0.001$), approximately 50 q_n terms are needed. Ernstoff et al. (2017) observed that few roots were needed (e.g.

5 to 50.000) when α is high ($\alpha > 10$). Instead, for very low α (<0.001), even 1 million roots resulted in several orders of magnitude overestimation during short time scales (i.e. in the first 24 h). Thus, the main obstacle for solving Equation (2) could be the computation time for some cases. Having highlighted this issue, Ernstoff et al. (2017) developed an alternative analytical solution based on empirical solutions of Equation (2) for predefined ranges of α values. However, we did not identify major gaps in computation times for our applications with the Ecolego® software (https://www.ecolego.se/) used for coding and running the model and the original solution (Equation (2)) was therefore maintained.

2.2. Models for estimating the diffusion coefficient

For running the diffusion transport equation (Equation (2)), diffusion coefficient in FCM D_{FCM} must be determined for the targeted chemical and for each type of FCM material. Two alternative approaches, the EU-approved (Oldring et al., 2014) and the recent Huang's approaches respectively, were considered for estimating the diffusion coefficient. The EU-approved approach is applicable for a restricted number of FCMs (i.e. those indicated in the introduction) while the Huang's model was calibrated for a wider range of FCMs, opening the perspective of extending the applicability domain of a migration model.

2.2.1. Piringer's model for estimating the diffusion coefficient

A simplified, empirical approach to obtain diffusion coefficients for the migration modelling was approved in the EU (Oldring et al., 2014), for the cases where only little or no data exist for the system of interest. The concerned model was the semi-empirical model proposed by Piringer (2007) for safe overestimation of diffusion coefficients. Safe overestimation means that the model is theoretically optimized to predict or overpredict most of the diffusion coefficient data used for the development of the model. The model correlates diffusion coefficient with the relative molecular mass, M, of the chemical migrating in FCM, with a matrix-specific parameter, noted A_{FCM}, and with the absolute temperature, T. An equation for D_{FCM} in a reference amorphous polyolefin material was developed by Brandsch et al. (2002) and extended to some other FCMs:

$$D_{FCM} = D_{ref}.exp\left(A_{FCM} - 0.1351.M^{2/3} + 0.003.M - \frac{10454 + \tau_{Piringer}}{T}\right) \quad (5)$$

with the unit reference diffusion coefficient, $D_{ref} = 1\ m^2.s^{-1}$ (or $D_{ref} = 10000\ cm^2.s^{-1}$ or $D_{ref} = 8.64.10^8\ cm^2.d^{-1}$); A_{FCM} is a standard polymer-specific diffusivity parameter (unitless); M is the relative molecular mass of the migrating chemical (Da); T is the temperature (in K); $\tau_{Piringer}$ is the specific contribution of the polymer matrix to the diffusion activation energy (K).

The diffusion coefficient then results from three contributions: the term $exp(A_{FCM})$ describes the contribution of the polymer matrix of the FCM; the term $exp(-0.1351.M^{2/3} + 0.003.M)$ describes the effect of the migrating chemical incorporated in the FCM; the term $exp\left(-\frac{10454+\tau_{Piringer}}{T}\right)$ describes the effect of temperature.

The parameter A_{FCM} is specific to the FCM material. It may be assimilated to a 'conductance' of the polymer matrix towards the diffusion of the migrating chemical.

The molecular mass is used as estimator for the molecular volume, which represents the real parameter determining the diffusion. For deriving the influence of molecular mass on diffusion coefficient through the term $exp(-0.1351.M^{2/3} + 0.003.M)$, the starting point was the development of an equation for n-alkanes with the elementary composition C_iH_{2i+2} (Piringer, 2007). Piringer (2007) correlated the diffusion coefficient to the cross-sectional area of the diffusing molecule, representing the relative resistance of the polymer matrix against the movement of the diffusing molecule. In the special situation of n-alkanes, this area can be represented by the term $0.1351.M^{2/3}$. A slower decrease of the diffusion coefficient D_{FCM} was however observed at high molecular masses. The correction factor $0.003.M$ was therefore introduced.

The effect of temperature was simulated according to the Arrhenius relationship: $D = D_0.\exp\left(-\frac{E_a}{RT}\right)$, where D_0 is the hypothetical diffusion coefficient at very high temperature, E_a is the activation energy of diffusion (J.mol^{-1}), R the gas constant (J.mol^{-1}.K) and T the temperature (K). A reference activation energy of $E_a = 86.9\ kJ.mol^{-1}$, corresponding to the diffusion process in the reference amorphous polyolefin matrix, divided by R leads to the reference value 10,454 K in Equation (5). The parameter $\tau_{Piringer}$ with the dimension *Kelvin* accounts for a specific contribution of the polymer matrix to the diffusion activation energy. Depending on the nature of the polymer, this contribution may lead to higher or respectively lower E_a than the reference activation energy of 86.9 kJ mol^{-1}.

2.2.2. Huang's model for estimating the diffusion coefficient

The Piringer's relationship (Equation (5)) is the most commonly used model for estimating the diffusion coefficient. It was calibrated however only for a limited set of FCM, i.e. only plastic materials. In order to extend the applicability of the VERMEER FCM tool described here, an alternative model was tested, i.e. the model proposed by Huang et al. (2017). Huang et al. (2017) developed a QPPR for predicting diffusion coefficients in FCM (plastics and others) as a function of molecular mass, M, of the chemical migrating in FCM, temperature and material type. Using the full dataset (1103 records), which has the advantage of covering a wide range of chemical-FCM combinations (158 chemicals and 87 original food contact materials grouped into 32 consolidated food contact material types), the final QPPR model for predicting the diffusion coefficient in solid materials is expressed as follows:

$$log_{10}(D_{FCM}) = 6.39 - 2.49.log_{10}(M) + \frac{\tau_{Huang} - 3486}{T} + b \quad (6)$$

where b is a material-specific coefficient. It may be observed that the approach selected for representing the temperature dependence is mathematically consistent with those initially proposed by Piringer (2007).

2.3. Model for estimating the partition between FCM and food

In a two-phase food/FCM system, transfer of the migrating chemical from one phase to the other occurs to reach thermodynamic equilibrium. This thermodynamic equilibrium is described by a partition coefficient $K_{FCM,Food}$ defined as the ratio at equilibrium of the migrating chemical concentration in FCM, C_{FCM}, to its equilibrium concentration, in the food phase, C_{Food}, i.e.:

$$K_{FCM,Food} = \left(\frac{\rho_{FCM}.C_{FCM}}{\rho_{Food}.C_{Food}}\right)_{equ} \quad (7)$$

where C_{FCM} is the concentration of the chemical in FCM (mg.g^{-1}); C_{Food} is the concentration of the chemical in Food (mg.g^{-1}); ρ_{FCM} is the FCM density (g.cm^{-3}); ρ_{Food} is the Food density (g.cm^{-3}).

$K_{FCM,Food}$ is higher than one when more chemical is absorbed into the polymer than in the food. For food safety, a large $K_{FCM,Food}$ limits migration from FCM material to food; conversely, a lower $K_{FCM,Food}$ indicates that more chemical is associated to the food. Partition coefficients depend on the solubility coefficient of the chemical for both the FCM and food.

Seiler et al. (2014) showed that certain characteristics of foodstuffs such as fat, water or carbohydrate content dominate their solubility for organic chemicals. Solubility of migrating chemicals for foods may be correlated with ethanol–water mixtures. In the present model, the ethanol-equivalency ($EtOH_{equ}$) is therefore used as the food proxy.

Ozaki et al. (2010) and Ernstoff et al. (2017) combined food and chemical factors (i.e. food $EtOH_{equ}$ and migrant K_{ow}) to derive predictive models for FCM/food partition coefficients. Huang and Jolliet (2019) refined the approach previously developed by Ernstoff et al. (2017), extending the number of materials of concern and introducing the temperature dependency of $K_{FCM,Food}$. They finally built the following generic QPPR model:

$$\log_{10}(K_{FCM,Food}) = -1.96 + 1.16.\log(K_{ow}) - 0.0059.EtOH_{equ} - 0.0079.\log(K_{ow}).EtOH_{equ} + 805.\left(\frac{1}{T} - \frac{1}{298.15}\right) \quad (8)$$

This model was selected for the MERLIN-Expo FCM model because it is based on a large number of data, and statistical analysis of the QPPR is explicitly provided (see 2.5).

2.4. Parameter values

Parameters required for predicting diffusion coefficients by the Piringer's relationship (i.e. the standard polymer-specific diffusivity parameter A_{FCM} and the Specific contribution of the polymer matrix to the diffusion activation energy $\tau_{Piringer}$ - Equation (5)) or by the Huang's relationship (i.e. the material-specific coefficient b and the Specific contribution of the polymer matrix to the diffusion activation energy τ_{Huang} - Equation (6)) are taken from Begley et al. (2005) and Huang et al. (2017).

A statistical treatment was however necessary for deriving mean values for the A_{FCM} parameter. Indeed, Begley et al. (2005) fitted experimental release data (i.e. kinetic release of chemicals into food simulants from FCMs), and derived A_{FCM} values for each experiment separately (Ernstoff et al., 2017). However, a preliminary qualitative analysis of the data available in Begley et al. (2005) suggested the presence of one or several outliers for most of the investigated FCMs (for example, the A_{FCM} values estimated by Begley et al. (2005) from different experiments for PA were −7.7, −2.2, −3.7, −4.6, −3.9, −3.7, −3.9, showing a relative homogeneity, except for the '-7.7' value). Outliers are data that are extremely large or small relative to the rest of the data and are therefore suspected of misrepresenting the data population. Our purpose here was not to investigate the sources of the outliers or to decide whether they were true or false. For our testing exercise, we instead chose to remove them from the datasets because they could lead to a distortion of the estimates of population parameters, such as mean. The Grubb's test was used to identify the potential presence of outliers in Begley's datasets. The Grubb's test statistic is defined as $G = \frac{X_{max} - \overline{X}}{s}$ (or $G = \frac{\overline{X} - X_{min}}{s}$), where $\overline{X}$ and s refer to the sample mean and standard deviation, respectively. The hypothesis of no outliers is rejected at significance level α (here $\alpha = 0.05$ was chosen) if $G > \frac{N-1}{\sqrt{N}}\sqrt{\frac{t^2_{\alpha/N,N-2}}{N-2+t^2_{\alpha/N,N-2}}}$, where $t^2_{\alpha/N,N-2}$ is the upper critical value of the t-distribution with N-2 degrees of freedom and a significance level of α/N. Mean values for the A_{FCM} parameter were then calculated after removing outliers.

Parameter values are reported in the Supporting Information.

2.5. Uncertainty in QPPR models

2.5.1. Uncertainty in QPPR for diffusion and partition coefficients

Models developed by Huang et al. (2017, 2019) for predicting diffusion coefficients (Equation (6)) and partition coefficients (Equation (8)) are based on QPPRs. The above-mentioned QPPR models are based on linear regressions fitted by ordinary least squares. Huang et al. (2017, 2019) provided the statistical summaries of their regression models, in particular the number of data in the training set (n = 1103 and n = 1847) and the standard error (SE = 1.17 and SE = 0.9 respectively). Taking into account the theory on regression, the uncertainty in the prediction can be estimated. Assuming identical, independent and normally distributed errors, the uncertainty in the prediction of the variable $log_{10}(D_{FCM})$ (respectively $log_{10}(K_{FCM,Food})$) can be defined from the predictive mean $\overline{log_{10}(D_{FCM})}$ (respectively $\overline{log_{10}(K_{FCM,Food})}$) and standard error of predictions $SE[\overline{log_{10}(D_{FCM})}]$ (respectively $SE[\overline{log_{10}(K_{FCM,Food})}]$), i.e.

$$log_{10}(D_{FCM}) = \overline{log_{10}(D_{FCM})} + t_{n-k-1}.SE[\overline{log_{10}(D_{FCM})}] \quad (9)$$

$$log_{10}(K_{FCM,Food}) = \overline{log_{10}(K_{FCM,Food})} + t_{n'-k'-1}.SE[\overline{log_{10}(K_{FCM,Food})}] \quad (10)$$

where t_{n-k-1} is the student t-distribution with n-k-1 degrees of freedom, n is the number of data in the training set, k is the number of descriptors in the model (and k+1 is the intercept plus the number of descriptors). Here $n = 1103$; $k = 3$; $SE = 1.17$ for the QPPR for diffusion coefficient, and $n' = 1847$; $k' = 3$; $SE = 0.9$ for the QPPR for partition coefficient.

Uncertainty variables noted $\varepsilon_{\log(D_{FCM})}$ and $\varepsilon_{\log(K_{FCM,Food})}$ are then defined as:

$$\varepsilon_{\log(D_{FCM})} = SE.t_{1099} = 1.17.t_{1099} \quad (11)$$

$$\varepsilon_{\log(K_{FCM,Food})} = SE.t_{1843} = 0.9.t_{1843} \quad (12)$$

and the predicted $log_{10}(D_{FCM})$ and $\log(K_{FCM,Food})$ can be calculated as follows, with the random variables $\varepsilon_{\log(D_{FCM})}$ and $\varepsilon_{\log(K_{FCM,Food})}$ reflecting the uncertainty in the prediction:

$$log_{10}(D_{FCM}) = 6.39 - 2.49.log_{10}(M) + \frac{\tau_{Huang} - 3486}{T} + b + \varepsilon_{\log(D_{FCM})} \quad (13)$$

$$\log(K_{FCM,Food}) = -1.96 + 1.16.\log(K_{ow}) - 0.059.EtOH_{equ} - 0.0079.\log(K_{ow}).EtOH_{equ} + 805.\left(\frac{1}{T} - \frac{1}{298.15}\right) + \varepsilon_{\log(K_{FCM,Food})} \quad (14)$$

2.5.2. Uncertainty in QPPR for octanol-water partition coefficient

Equation (14) requires the previous determination of the octanol-water partition coefficient. In our work, the Moriguchi et al.'s QSAR model (Moriguchi et al., 1992, 1994) available in the VEGA toolbox (Benfenati et al., 2019) was used. This QSAR model is based on a multiple regression considering 13 molecular descriptors. The version implemented in the VEGA toolbox is based on 9961 compounds in the training set, with a RMSE of 0.96. As described above, the uncertainty in the prediction of $\log(K_{ow})$ can be defined as the predictive distribution by the predictive mean $\overline{\log(K_{ow})}$ (given by the VEGA toolbox) and standard error of predictions $SE[\overline{\log(K_{ow})}]$, i.e.

$$\begin{aligned}\log(K_{ow}) &= \overline{\log(K_{ow})} + t_{n-k-1}.SE[\overline{\log(K_{ow})}] \\ &= \overline{\log(K_{ow})} + \varepsilon_{\log(K_{ow})} \\ &= \overline{\log(K_{ow})} + 0.96.t_{9947}\end{aligned} \quad (15)$$

Besides, the VEGA toolbox also provides an 'applicability domain' index (ADI) for each prediction. This score results from several criteria: (i) the presence of similar molecules with experimental data in the training set. The index takes into account the level of similarity of the first two most similar compounds found; (ii) the accuracy (average error) prediction of similar compounds; (iii) the concordance with similar molecules (average difference between target compound prediction and experimental values of similar compounds); (iv) the maximum error of prediction among similar compounds. All these criteria are integrated to provide a global ADI ranging from 0 to 1. Beyond the purely predictability of the regression model (represented by the random term $\varepsilon_{\log(K_{ow})}$), the inclusion in the applicability domain must also be taken up in the parameter uncertainty. An additional uncertainty

term is then incorporated as:

$$\log(K_{ow}) = \overline{\log(K_{ow})} + \frac{\varepsilon_{\log(K_{ow})}}{ADI}$$

That means that if the targeted compound is integrally within the applicability domain (ADI = 1), no additional uncertainty is considered, while if it is at the borders or outside of the applicability domain (ADI<1), an additional uncertainty factor is applied.

2.6. Global uncertainty analysis

10,000 random parameter samples were generated by a Monte Carlo generator, using $\varepsilon_{\log(D_{FCM})}$, $\varepsilon_{\log(K_{FCM,Food})}$ and $\varepsilon_{\log(K_{ow})}$ as random variables reflecting the uncertainty in QPPR predictions. The model then runs simulations with all the parameter samples that were previously generated and provides summary statistics for describing the uncertainty of the selected endpoint; i.e. the concentration in food of the chemical having migrated from FCM to food after a given contact time.

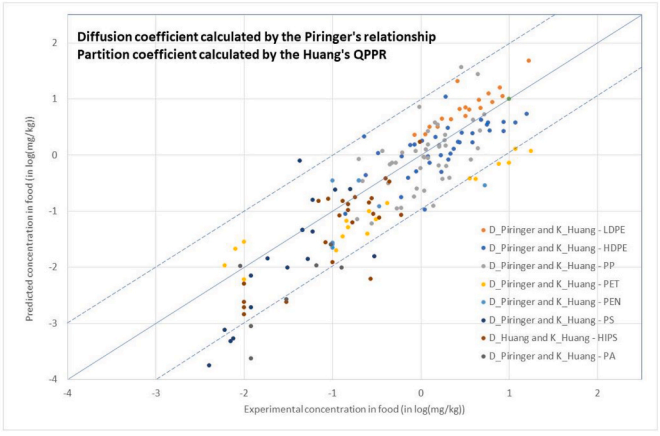
3. Results and discussion

3.1. Deterministic simulations

The modelled concentrations of chemicals in food are plotted against the corresponding measured experimental data. Two alternative models were tested, based on the Piringer's relationship (equation (5)) and the Huang's relationship (equation (6)) respectively for the prediction of the diffusion coefficient; these models are combined to the Huang's QPPR for the prediction of the partition coefficient (equation (8)). All the models are used with best estimate values of the parameters (i.e. with null values of the error variables $\varepsilon_{\log(D_{FCM})}$, $\varepsilon_{\log(K_{FCM,Food})}$ and $\varepsilon_{\log(K_{ow})}$). Results are presented in Fig. 1 (where the unity-slope line through the origin shows the ideal unbiased model, and the dotted lines show the one-order of magnitude interval around the ideal model).

A visual analysis of the results thus obtained showed a good match between predicted and experimental values, with a majority of predicted values not differing from experimental values by more than one order of magnitude.

In this case, however, the analysis of the regression curves presented in Fig. 1 are not sufficient to assess the performance of the models. Firstly, from a regulatory perspective, one cannot consider as equivalent underestimation and overestimation of actual concentrations respectively; indeed, the model is expected to be globally conservative, i.e. it is expected to predict chemical concentrations in food at least equal to or higher than the actual experimental values. Secondly, in a regulatory approach, estimating the migration of chemicals from FCMs to food is only a first step, driving the amount and type of toxicological data needed for the safety assessment. In particular, EFSA recommends a tiered approach: in case of low migration of the substance into food (<0.05 mg kg^{-1} food), only absence of genotoxicity has to be proven. For migration values between 0.05 and 5 mg kg^{-1}, *in vivo* subchronic toxicity data and data on accumulation in humans have to be provided in addition to the results of genotoxicity tests, while for high migration values (>5 mg kg^{-1}) a full toxicological data set (including information on absorption, distribution, metabolism and excretion (ADME), and data on reproductive toxicity, teratogenicity, chronic toxicity/carcinogenicity) is needed. In this context, the concentrations of chemicals in food must therefore be compared with a specified threshold (referred to an 'alarm' or 'trigger' value). For these reasons, the performance of the two models tested was evaluated on the basis of contingency tables: a contingency table reports the number of occurrences in which real data and predicted values were both above the threshold (*hits*), the number in which they were both below (*correct negatives*), the number of alarms missed by the model (*missed*) and that of *false alarms*. For illustrating the construction of contingency tables, two examples of subdivision of the data into these four categories (corresponding to two different threshold values) are shown in Fig. 2. Several metrics can be used for evaluating the performance of the model (Bennett et al., 2013). The purpose of these metrics is to summarize the model results in terms of critical thresholds. Several metrics were calculated for the two models tested and for different threshold values (0.05, 0.1, 0.5 and 1 mg kg^{-1} (the latter were selected as tests even if they have no direct link with the regulatory thresholds; 5 mg kg^{-1} was not selected despite its regulatory relevance since too few experimental values exceed this value in our dataset). The purpose of each metric, as well as range and ideal value, are presented in Table 1.



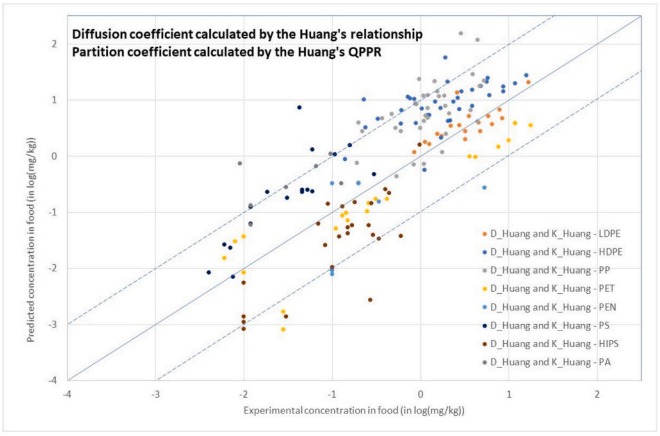


Fig. 1. Predicted vs Measured $\log_{10}(C_{food})$ for two alternative models (where Cfood is the concentration of the chemical in food after a given contact time, expressed in mg.kg-^{1}) (data from Begley et al., 2006).

The *Accuracy* metric, which measures the fraction of correct predictions, is close to the ideal unity value (>0.80) for the two models and all tested thresholds. This shows that at least 80% of predictions successfully detects hits and correct negatives. The *Success index* metric provides similar kind of information and similar results: it measures the ability to exceed or not exceed the threshold value, weighting equally hits and correct negatives. Calculated *Success index* metric showed that both models result in values close to the ideal unity value (with slightly better results for the Piringer's model at low thresholds). The *Bias score* metric, which indicates the tendency of underestimation or overestimation, is different for the Piringer's and the Huang's models respectively. It is below unity for the Piringer's model (between 0.85 and 0.9), indicating a slight tendency to underestimation. It is close to ideal unity value for the Huang's model at low thresholds (0.99 and 1.01 at 0.05 and 0.1 mg kg^{-1} thresholds) and increases with the thresholds; at higher thresholds (0.5 and 1 mg kg^{-1}), the bias scores are 1.16 and 1.32, indicating a tendency to overestimation (in agreement with what expected in a regulatory point of view). These tendencies are also confirmed by the *Hit rate* metric, which specifically measures the

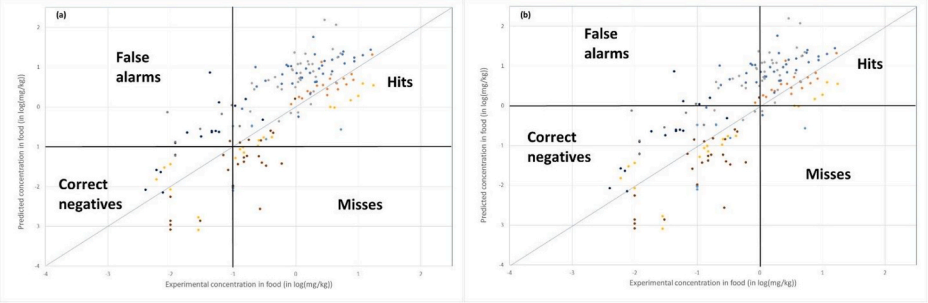


Fig. 2. Subdivision of dataset in four categories (*hits, correct negatives, misses, false alarms*) according to Predicted vs Experimental results – Examples presented in the figure: (a) Huang's models for diffusion coefficient and partition coefficient; Threshold = 0.1 mg kg^{-1} (i.e. −1 in log units) – (b) Huang's models for diffusion coefficient and partition coefficient; Threshold = 1 mg kg^{-1} (i.e. 0 in log units).

Table 1
Metrics for evaluating the performance of the two models for different thresholds.

Criteria	Formula	Range	Ideal value	Notes	Piringer's relationship for diffusion coefficient - Huang's QPPR for partition coefficient				Huang's relationship for diffusion coefficient - Huang's QPPR for partition coefficient			
					Selected threshold (in mg.kg^{-1})				Selected threshold (in mg. kg^{-1})			
					0.05	0.1	0.5	1	0.05	0.1	0.5	1
Accuracy	$\frac{hits + correctnegatives}{total}$	(0; 1)	1	Measures the fraction of correct predictions.	0.90	0.87	0.87	0.82	0.87	0.84	0.88	0.80
Success index	$\frac{\left(\frac{hits}{hits + misses} + \frac{correctnegatives}{correct\ negatives + false\ alarms}\right)}{2}$	(0; 1)	1	Weights equally the ability of the model to detect correctly occurrences and no-occurrences of events	0.93	0.88	0.87	0.81	0.75	0.76	0.87	0.82
Bias score	$\frac{hits + falsealarms}{hits + misses}$	(0; ∞)	1	Indicates whether the model has a tendency to underestimate (Bias<1) or overestimate (Bias>1).	0.90	0.89	0.90	0.85	0.99	1.01	1.16	1.32
Hit rate	$\frac{hits}{hits + misses}$	(0; 1)	1	Sensitive to hits, but ignore false alarms.	0.89	0.87	0.83	0.72	0.92	0.90	0.97	0.93
False alarm ratio	$\frac{false\ alarms}{hits + false\ alarms}$	(0; 1)	0	Sensitive to false alarms, but ignore misses	0.008	0.03	0.08	0.16	0.08	0.11	0.17	0.29

ability to detect hits: the Piringer's model is less performant at high thresholds (0.72 against 0.93 for the Huang's model at 1 mg kg^{-1}), indicating less tendency to overestimation. The *false alarm ratio* measures the risk of wrongly predicting an exceedance of the threshold value. It results close to the zero ideal value for both models at low thresholds; it is significantly higher at the 1 mg kg^{-1} threshold, indicating a tendency to overestimation in such case.

Globally, all these metrics give an overview of the performance of the models to be used in a regulatory context, i.e. for detecting alarms in the frame of a tiered approach for driving the amount and type of toxicological data needed. Calculated metrics values are generally close to the ideal values and then demonstrated the good performance of both models in this context.

3.2. Probabilistic simulations

Although the metrics presented above show a good overall performance of the models, the *hit rates* show that these models are not systematically conservative, which is expected in a regulatory framework. One strategy to improve the conservatism of the prediction is to use an uncertainty analysis, as presented in 2.6. This approach was tested with the model combining the Huang's QPPRs for the prediction of diffusion and partition coefficients (Equations (6) and (8)). Uncertain variables are then $\varepsilon_{\log(D_{FCM})}$, $\varepsilon_{\log(K_{FCM,Food})}$ and $\varepsilon_{\log(K_{ow})}$. Results are presented in Fig. 3, with the 5th, 25th, 75th and 95th percentiles extracted from the 10,000 simulations (see 2.6). They were compared to the ideal unbiased model (i.e. the unity-slope line through the origin). On average, the 90th confidence interval (difference between the 95th and 5th percentiles respectively) covers about 2.2 orders of magnitude, while the interquartile (difference between the 75th and 25th percentiles respectively) covers about 0.9 order of magnitude. From a regulatory point of view, what is expected is to overestimate concentrations of chemicals in food. It was observed that using the 75th percentile respects this *conservatism* rule in most cases since almost all points are close to or above the unbiased line. If the 75th percentile is used, the level of conservatism (difference between the predicted and the experimental concentration in food) is about 0.4 order of magnitude. Using the 75th percentile seems then a good strategy for guaranteeing conservatism without applying too important safety factors.

4. Availability of the VERMEER FCM tool

The models that are presented in the present paper are freely available on http://www.life-vermeer.eu/download-software/, https://www.vegahub.eu/portfolio-item/vermeer-fcm/ and on https://merlin-expo.eu/ with the associated user manual.

5. Conclusions

The aim of the present study was to evaluate the performance of

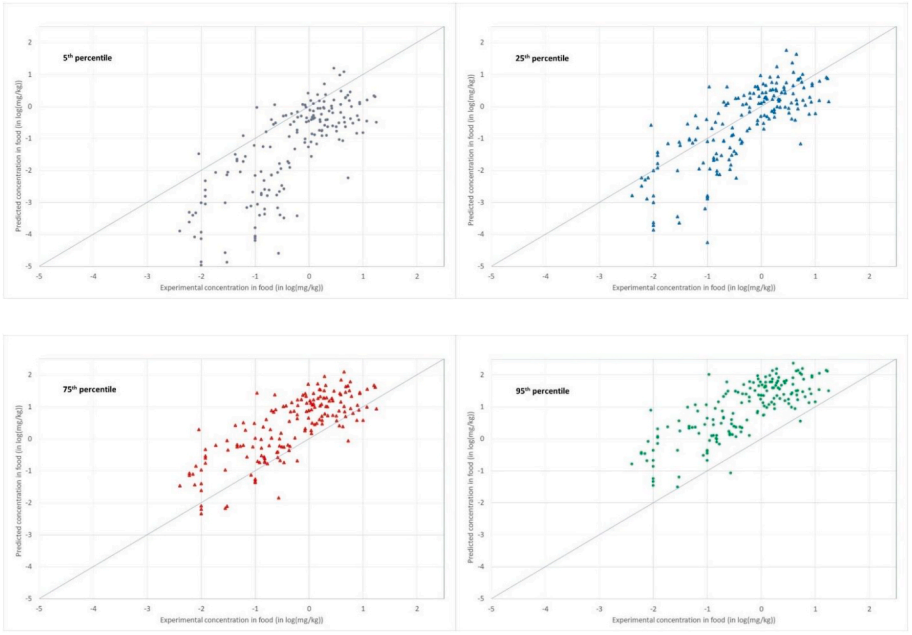


Fig. 3. Percentiles of the probabilistic simulations – Uncertainty variables are the error functions $\varepsilon_{\log(D_{FCM})}$, $\varepsilon_{\log(K_{FCM,Food})}$, $\varepsilon_{\log(K_{ow})}$ of the QPPRs for the prediction of Diffusion coefficients, FCM-Food Partition coefficients and Octanol-Water partition coefficients.

operational models in the prediction of a chemical's concentration in food in contact with plastic monolayer FCM. The tested migration models can be used for regulatory purposes and results described in the present paper can provide new insights on such regulatory applications. Uncertainty in QPPR used for describing the processes of both diffusion in FCM and partition at the FCM-Food interface was included in the analysis. A simple mechanistic model was combined with QPPRs for the prediction of diffusion coefficients and FCM-Food partition coefficients. Deterministic simulations showed that a good match between predicted and experimental values was obtained. The tested models can be used in particular as alarms for triggering or not toxicological investigations. Combining uncertainty in QPPR predictions, it was shown that the third quartile (75th percentile) derived from probabilistic calculations can be used as a conservative value in the prediction of chemical concentration in food, with reasonable safety factors.

CRediT authorship contribution statement

P. Ciffroy: was in charge of all the modelling work presented in this paper, calibration, coding, Validation, uncertainty, Formal analysis, interpretation. **B. Mertens:** (Sciensano) were in charge of the specifications of the software tool with regard to the regulations. **E. Van Hoeck:** (Sciensano) were in charge of the specifications of the software tool with regard to the regulations. **I. Van Overmeire:** (Sciensano) were in charge of the specifications of the software tool with regard to the regulations. **E. Johansson:** (Afry) provided technical assistance in coding the model in the Ecolego® software environment. **B. Alfonso:** (Afry) provided technical assistance in coding the model in the Ecolego® software environment. **D. Baderna:** (IRFMN) provided technical support on QSAR/QPPR models. **G. Selvestrel:** (IRFMN) provided technical support on QSAR/QPPR models. **E. Benfenati:** (IRFMN) coordinated the work in the Life-Vermeer project.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was founded by the LIFE + Projects VERMEER (LIFE16/ENV/IT/000167). Authors would like to thank Chemaxon (http://www.chemaxon.com) for the academic license of Marvin suite used to displaying and characterizing chemical structures.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.113118.

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