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A quantitative property-property relationship for the internal diffusion coefficients of organic compounds in solid materials

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Abstract

Indoor releases of organic chemicals encapsulated in solid materials are major contributors to human exposures and are directly related to the internal diffusion coefficient in solid materials. Existing correlations to estimate the diffusion coefficient are only valid for a limited number of chemical-material combinations. This paper develops and evaluates a quantitative property-property relationship (QPPR) to predict diffusion coefficients for a wide range of organic chemicals and materials. We first compiled a training dataset of 1103 measured diffusion coefficients for 158 chemicals in 32 consolidated material types. Following a detailed analysis of the temperature influence, we developed a multiple linear regression model to predict diffusion coefficients as a function of chemical molecular weight (MW), temperature, and material type (adjusted R^2 of .93). The internal validations showed the model to be robust, stable and not a result of chance correlation. The external validation against two separate prediction datasets demonstrated the model has good predicting ability within its applicability domain ($R^2_{ext} > .8$), namely MW between 30 and 1178 g/mol and temperature between 4 and 180°C. By covering a much wider range of organic chemicals and materials, this QPPR facilitates high-throughput estimates of human exposures for chemicals encapsulated in solid materials.

KEYWORDS
consumer products, correlation, diffusion, indoor release, organic chemicals, solid materials

1 | INTRODUCTION

Chemicals encapsulated in solid materials have been identified as a major source of passive emissions to indoor air[1-3] and of transfers into food[4] and onto skin.[5] Typical examples include chemicals used as flame retardants in furniture and plasticizers in food contact materials (FCMs). To estimate the release of these chemicals from solid materials, and eventually consumer exposures, the diffusion coefficient, D (m²/s), for chemicals encapsulated in solid materials, is essential information. D describes the transport of a molecule through a material, which is specific for a chemical-material combination and is also influenced by ambient temperature. Experimental techniques such as chamber tests for building materials,[6,7] and sorption/desorption experiments for polymer

materials[8-10] have enabled measurement of a limited number of chemical diffusion coefficients for building materials such as vinyl flooring, gypsum board, particle board, plywood, carpet, and cement,[11-14] as well as polymer materials including polyethylene (PE), polystyrene (PS), polypropylene (PP), and polyvinyl chloride (PVC).[4,15,16] However, given the limited number of chemical-material combinations with measured Ds, and the costly and time-consuming nature of experiments, quantitative relationships are needed to complement existing measurements by predicting the diffusion coefficients from known physiochemical properties for chemicals without experimental data. This is especially important for high-throughput approaches where a large number of chemical-material combinations need to be evaluated and for which it is unrealistic to perform experiments on all relevant combinations.

Several correlation methods have been developed to estimate the diffusion coefficients from physicochemical properties of chemicals.[8,12,17-19] For example, Berens and Hopfenberg[8] correlated the D to the mean molecular diameter of the diffusing molecule, using data on more than 20 chemicals in three glassy materials including PVC, PS, and polymethyl methacrylate (PMMA). Zhao et al.[19] found a correlation between D and vapor pressure for water and eight aromatic hydrocarbons in polyurethane foam (PUF). Furthermore, both Bodalal et al.[12] and Cox et al.[18] estimated the D as a function of molecular weight. The former study considered measured D data on five aromatics and five aldehydes in several building materials,[12] while the latter study considered data on four alkanes in vinyl flooring.[18] For each of these aforementioned approaches, the main limitation is that the correlations are specific to certain chemical classes and materials, for example, aldehydes in plywood, which limits their application for other materials and chemical classes. Addressing this research gap to facilitate wider applicability, Guo[17] developed a method which estimates the diffusion coefficient as a function of the chemical's molar volume for mixed chemical classes. However, this approach is limited to six building materials and is developed based on a small dataset of limited chemical classes (≤3 chemical classes for five of the six building materials).

The aforementioned correlation methods consider experiments for building materials at room temperature, and therefore, temperature is not relevant and thus not considered in the correlation model. For other exposure scenarios, such as transfer of chemicals from FCMs into food, ambient temperature is highly relevant because FCMs can be heated, refrigerated, or frozen. Accordingly, Begley et al.[4] presented a correlation method to estimate the diffusion coefficient in nine polymer materials as a function of molecular weight and temperature, which is not applicable beyond the considered polymers.

In all, the currently available correlation methods to estimate D do not provide sufficient coverage of chemicals encapsulated in consumer products in different use scenarios (ie, ambient temperatures). Developing low-tier, high-throughput methods to estimate exposure to chemical in consumer products across a variety of chemical-material combinations is a recent focus in various science-policy fields such as computational exposure science and life cycle assessment (LCA).[20-25] Addressing the lack of methods to estimate D for a variety of chemical-product scenarios, this study aims to develop a more comprehensive correlation method to estimate D for wide range of organic compounds in multiple solid materials. More specifically, we aim to:

- carry out a comprehensive and extensive literature review to collect experimental diffusion coefficient data on a wide range of materials and chemicals.
- use multiple linear regression (MLR) techniques to establish the relationship between the diffusion coefficient and various predictor variables including physiochemical properties, material properties, and environmental characteristics.
- perform internal and external validations to characterize the validity and predictive power of the developed correlation.

Practical Implications

- The quantitative property-property relationship developed by this study provides a more comprehensive correlation method to estimate the diffusion coefficients, as it covers a wide range of organic chemicals and solid materials, and also considers the effect of temperature. This model provides the basis for facilitating high-throughput estimates of indoor human exposures for chemicals encapsulated in solid materials relevant for several science-policy fields, such as chemical alternatives assessment (CAA), risk assessment (RA), and life cycle assessment (LCA).

As the material type is a categorical property variable and is not related to the chemical's molecular structure, we call this correlation a quantitative property-property relationship (QPPR) instead of a quantitative structure-activity relationship (QSAR). This QPPR provides a more advanced correlation method to estimate the diffusion coefficients of organic compounds compared to previous studies, as it covers a wide range of solid materials and physiochemical properties, and also considers the effect of temperature. By providing reliable estimates of this key diffusion parameter for a large number of chemicals, this method will facilitate high-throughput assessments of chemical emissions and human exposures for chemicals encapsulated in solid materials relevant for chemical alternatives assessment (CAA), risk assessment, and LCA.

2 | MATERIALS AND METHODS

2.1 | Dataset

Experimental diffusion coefficient data were compiled from 68 references from the peer-reviewed scientific literature. The initial dataset contained a total of 1124 records covering 161 unique chemicals and 88 distinct solid materials (provided in Appendix S2). Experimental data expressed in cm^2/s were converted to m^2/s. There are different types of diffusion coefficients reported in the literature, so harmonization of these data was performed to develop a consistent dataset. For diffusion coefficients measured in liquid sorption experiments, the "intrinsic" diffusion coefficients, corrected for the swelling of materials, were collected.[10] Sorption of the liquid molecules inside the solid material may cause swelling of the material, which would lead to decreased observed diffusion coefficients and thus need to be corrected.[10] For porous materials consisting of pore space and solid material, two types of models can be used to describe the chemical transport through these materials. The one-phase model considers the porous material as an assumed homogeneously mixed material, so an "apparent" diffusion coefficient is used to describe the chemical diffusion through such imaginary material.[7] In contrast, the multiphase model considers the material as a mixture of pores and solid parts, and the chemical diffuses mainly through the pores if the pores are

interconnected, or through the pores and solid parts alternately if the pores are isolated from each other. The gas-phase diffusion through the pores, which can be described by an "effective" diffusion coefficient, is assumed to be much faster than the diffusion through the solid parts.[7] Haghighat et al.,[7] has demonstrated that the "apparent" diffusion coefficient is equivalent to the "effective" diffusion coefficient (D_e) divided by the material phase-gas phase partition coefficient (K_{ma}). Thus, for porous materials the "apparent" diffusion coefficients reported in studies were collected.[26] For studies where only the D_e and K_{ma} were reported,[27-29] they were converted to "apparent" diffusion coefficients using the aforementioned method. Data were excluded for studies where only the "effective" diffusion coefficients were reported.

From the initial dataset, 21 records were excluded from further analyses because they involve chemicals that are inorganic, chemicals for which no CAS number could be identified, or chemicals that are polymer chains with varying molecular weights. The final considered dataset thus includes 1103 records for 158 unique chemicals and 87 materials.

2.2 | Modeling methods

2.2.1 | Multiple linear regression

An MLR analysis was performed to identify and quantify the effect of different parameters on the diffusion coefficient. The MLR model takes the following general form:

$$\log_{10} D = \alpha + \beta_1 \cdot X_1 + \cdots + \beta_n \cdot X_n + b_1 \cdot M_1 + \cdots + b_m \cdot M_m \quad (1)$$

where $\log_{10}D$ is the logarithm of the diffusion coefficient (m^2/s), α is the intercept; X_1 to X_n are independent variables related to physiochemical properties, such as molecular weight, molar volume, and vapor pressure, and/or environmental characteristics like temperature; β_1 to β_n are regression coefficients for the respective independent variables X_1 to X_n; and M_1 to M_m are dummy variables for the solid materials, with one dummy variable per type of material. A dummy variable equals 1 for the material type it represents, and equals 0 for all other materials; for example, M_1=1 for material type=1, M_1=0 for material types 2 to m. b_1 to b_m are regression coefficients for the respective dummy variables M_1 to M_m. The number of m is equal to the number of material types considered −1, as the material type with the highest number of measured D data is used as the reference material type and does not require a dummy available in the MLR. Note that the MLR model gives one coefficient for each material type, while a material type can represent a single pure substance such as calcium silicate, a composite material such as vinyl flooring and gypsum board, or a group of similar materials such as wooden boards. Details of the material types will be discussed later. This regression equation also implies that the material coefficients (b_1 to b_m) and the physiochemical property coefficients (β_1 to β_n) are independent of each other, which if corroborated by internal and external validations (Section 2.3), allow for the maximum prediction coverage in terms of chemical-material combinations. All regression coefficients were estimated by the least squares (LS) method. All regression analyses were performed using IBM SPSS Statistics version 23 (IBM corporation, Armonk, NY, USA).

2.2.2 | Grouping of materials and initial regressions

To reduce the number of dummy variables, to avoid over-fitting of the MLR model, and to have a minimum of 10 records and three different chemicals per material type to ensure enough variability, the 87 original materials were grouped into 32 consolidated material types, based on the similarity of the regression coefficients and the material types (see Appendix S1, Section S1). Thus m=31 in Equation (1), with polyethylene terephthalate (PET) as the 32nd and reference material, as it is the material with most reported diffusion coefficients.

In previous studies, either the chemical's molecular weight (MW), molar volume (MV) or vapor pressure (VP) has been used as predictor of the diffusion coefficient in a given material.[12,17-19] Begley et al.[4] also suggested that the logarithm of the diffusion coefficient varies linearly with the inverse of the absolute temperature (1/T). Thus, the initial regression was performed to identify which of the above variables (MW, MV, VP, and 1/T) are best predictors of the diffusion coefficients of compounds encapsulated in the 32 material types, that is, to identify X_1 to X_n in Equation (1). Details of the initial regression process are presented in Appendix S1, Section S2. Results of the initial regression model suggest that the log-molecular weight and the inverse of the absolute temperature are the most important predictors, and therefore the employed MLR model takes the following form:

$$\log_{10} D = \alpha + \beta_{\log_{10} MW} \cdot \log_{10} MW + \beta_{1/T} \cdot \frac{1}{T} + b_1 \cdot M_1 + \ldots + b_m \cdot M_m \quad (2)$$

where MW is the chemical's molecular weight (g/mol) and T is the absolute temperature (K).

The model performance of using log-molecular weight and molecular weight as predictors were very close when using the training dataset (1103 records, m=31), but the model using log-molecular weight as predictor was finally selected as it performs better for high-molecular-weight chemicals (Section 3.3.3).

2.2.3 | Temperature dependence

Studies have shown that the activation energy of diffusion is a contributor to the temperature dependence of the diffusion coefficient and varies as function of both the material and the chemical properties.[4,30,31] Thus, ideally a specific temperature correction coefficient should be used for each chemical-material combination. As data availability is not sufficient to determine chemical-specific temperature coefficients for each of the 32 materials, and as chemical properties seem to have limited influence on the activation energy,[4,30] we followed the strategy of Begley et al.,[4] differentiating temperature coefficients for a limited number of material groups, applying one generic temperature coefficient for all chemicals within each material group. Begley et al.[4] have introduced a variable τ to adjust the

temperature coefficient for two groups of materials, where τ equals 0 or 1577 for nine different polymers, which corresponds to activation energy of 86.9 kJ/mol for e.g. LDPE or 100 kJ/mol for e.g. HDPE. To analyze the temperature dependency of the diffusion coefficients in our dataset, we first plotted $\log_{10}D$ against $1/T$ for each of the 32 material types (Appendix S1, Section S3). The plots generally show as expected[4] an inverse relationship in which $\log_{10}D$ is decreasing with increasing $1/T$, different materials exhibiting different slopes. As variability in diffusion coefficient is higher between than within given studies, we first determined a temperature coefficient for each chemical-material type-study combination, and then calculated an average temperature coefficient for each material type by averaging all temperature coefficients belonging to the same material type. The analysis of the material-specific temperature coefficients showed that the material types can be grouped into three categories: (i) high-, (ii) medium-, and (iii) low-coefficient categories, with three corresponding values for the temperature coefficient adjustment factor τ, which are given later in Section 3.1. Details are presented in Appendix S1, Section S3.3. The adjusted MLR model takes the following form accordingly:

$$\log_{10} D = \alpha + \beta_{\log} MW \cdot \log_{10} MW + \frac{\beta_{1/T} + \tau}{T} + b_1 \cdot M_1 + \ldots + b_m \cdot M_m \quad (3)$$

2.2.4 | Final regression

To avoid multicollinearity problems in the MLR model and to avoid the influence of the material type "Limited-data material group" on the temperature coefficients, we fixed the temperature coefficients determined using Equation (3) and thus the final regression takes the following form:

$$\log_{10} D - \frac{\beta_{1/T} + \tau}{T} = \alpha + \beta_{\log} MW \cdot \log_{10} MW + b_1 \cdot M_1 + \ldots + b_m \cdot M_m \quad (4)$$

where the dependent variable is $\log_{10}D - (\beta_{1/T+}\tau)/T$ instead of $\log_{10}D$, with the values of $\beta_{1/T}$ and τ obtained from Equation (3) and presented later in Section 3.1. In this final regression, all 1103 records of measured D data were utilized including the material type "Limited-data material group," leading to $m=31$ material types, plus one reference material type, PET, with $b_{PET}=0$.

2.3 | Model validation

Validation of the final MLR model (Equation 4) was performed using the QSARINS software, version 2.2.1 (www.qsar.it) which is developed by Gramatica et al.[32,33]

2.3.1 | Internal validation

The MLR model's capacity to predict portions of the training dataset was evaluated in an internal validation process, using two techniques for internal validation in QSARINS. The first one is the leave-more-out (LMO) cross-validation technique, which iteratively and randomly exclude a certain percentage of the measured diffusion coefficient data, and then computes the regression coefficients with the remaining data and uses those coefficients to make predictions for the excluded ones.[33] We used 1000 iterations and the percentage of the excluded elements was set as 20%.

The second technique for internal validation is the Y-scrambling procedure, which demonstrates that the model is not the result of chance correlation. In this procedure, the experimental responses (in our study, the temperature-adjusted diffusion coefficients) are shuffled at random and used with the original predictors to establish an MLR model. If the original MLR model is internally valid, the performances of the scrambled models should be much worse than the original model.[33] We used 1000 iterations for the Y-scrambling.

2.3.2 | External validation

We also evaluated the model ability to provide reliable predictions on new datasets in a so-called external validation process, using the following two approaches.

The first approach was to split the existing dataset (1103 records) into one training dataset and one prediction datasets. The training dataset was used to generate regression coefficients of the MLR model, and then, the MLR model was applied to the prediction set to examine the prediction performances of the model. Three kinds of splitting were performed using existing options in the QSARINS software (see Appendix S1, Section S5.1 for details) by random percentage (20% of the entire dataset randomly selected as the prediction set, 80% rest to the training set), by response and by structure (data first ordered by responses of the temperature-adjusted diffusion coefficient, or by the first axis of principal component analysis (PCA) of the descriptors, respectively). We introduced a fourth kind of splitting by studies, as variability across studies for a given material is in general larger than variability within a given study, yielding similar sample sizes of approximately 880 data for the training set and 220 data for the prediction set (Appendix S1, Table S3).

The second approach of external validation was to use the entire collected dataset (1103 records) as the training set and to use an entirely separate dataset as the prediction set. For the prediction set, two datasets were used. The first one is a database of diffusion coefficients from the United States Food and Drug Administration (FDA), which is a "database available upon request" for guidance for industry (http://www.fda.gov/Food/ucm081818.htm), and includes non-peer-reviewed diffusion coefficient data reported by industry. This dataset includes 191 records of experimental diffusion coefficients of 46 chemicals in 22 materials which are mainly polymers used for FCM (Appendix S1, Section S5.1). The quality and reliability of these data are not characterized by FDA. The second prediction dataset is constructed from several studies conducted before 1982,[34-36] referenced in an EPA report.[37] This dataset, designated as "Data by 1982," includes 281 records of measured diffusion coefficients of 92 chemicals in eight polymer materials, also including self-diffusion (Appendix S1, Section S5.1). Data for both prediction sets are provided in Appendix S2.

2.3.3 | Applicability domain

The analysis and definition of the applicability domain (AD) of models is a fundamental issue that must be addressed in QSAR and QPPR studies. The study of AD can provide information on the reliability of the model predictions, that is, if the chemicals are inside the AD, the predictions are interpolated and are more reliable; if the chemicals are outside the AD, the predictions are extrapolated and less reliable, because effects can occur outside the AD that do not exist within the AD.[38] Three complementary methods were applied to define the AD of the diffusion coefficient QPPR: the range of model predictors, the leverage approach, and the PCA of the model predictors.[39] More explanation of these methods is provided in Appendix S1, Section S6.1. In our analysis, chemicals are considered inside the AD if they are viewed inside AD by all three methods, whereas chemicals are considered outside AD if they are viewed outside AD by all three methods, and finally chemicals that fall inside the AD for only one or two methods are considered as "borderline".

3 | RESULTS AND DISCUSSION

3.1 | Temperature dependence of the diffusion coefficient

The compiled dataset of 1103 records including 158 chemicals and 32 material types shows that the diffusion coefficient in solid materials decreases with decreasing temperature, as demonstrated by the highly significant negative regression coefficient for the variable $1/T$, with $\beta_{1/T} = -4440\,(K)$ with a standard error (SE) of 164 (K) and $P<.001$ in Equation 2 (Appendix S1, Section S3.1). This is in agreement with previous studies.[4,30,31] This general tendency of decreasing diffusion with increasing $1/T$ is well illustrated by the example of PET, the material with the most data available (Figure 1A - see Appendix S1, Figure S1 for other materials). To further refine the coefficient for the temperature variable into specific materials groups, Figure 1B illustrates well for methyl methacrylate (MMA) homopolymer the importance of first determining a temperature coefficient for each separate study and material-chemical combination (Section 2.2.3) and then averaging the temperature coefficients across studies. The molecular weight-normalized diffusion coefficients show a negative linear relationship with $1/T$ within each of the three experimental studies of Figure 1B,[40-42] with similar regression coefficients of −4530 (K), −5704 (K), −3415 (K), averaging −4550 (K) with an SE of 305 (K). However, as the absolute $\log_{10}MW$-normalized diffusion coefficients reported by Hennebert et al.[42] are much higher than those reported by the other two studies, doing one regression with all data from the three studies would result in a non-significant temperature coefficient (P-value of .19), thus demonstrating the importance to first perform temperature regressions using data from the same study and for the same chemical.

Table 1 presents the average temperature coefficients and their standard errors for each of the 32 consolidated material types. Based on the values of the temperature coefficients (unit in K), the 32 material types can be grouped into three categories: (i) high-coefficient
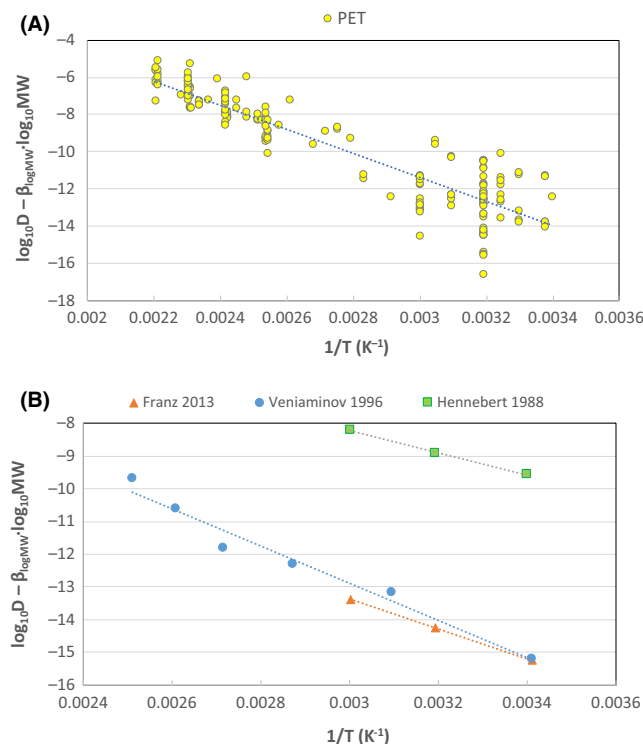

(A)

(B)

FIGURE 1 Relationship between the diffusion coefficient D (corrected for $\log_{10}MW$) and the inverse of temperature for (A) polyethylene terephthalate (PET), and (B) methyl methacrylate (MMA) homopolymer. The units of D and molecular weight (MW) are m^2/s and g/mol, respectively

category with relatively high (absolute value) temperature coefficients (<−5000), that is, materials in which diffusion coefficients are highly sensitive to the change in temperature, (ii) medium-coefficient category with temperature coefficients in between (−5000<($\beta_{1/T} + \tau$)<−3000), and (iii) low-coefficient category with relatively low (absolute value) temperature coefficients (>−3000), that is, materials in which diffusion coefficients are least sensitive to the change in temperature. Details for the grouping of temperature coefficients can be found in Appendix S1, Section S3.3.

The temperature coefficients $\beta_{1/T}$ and τ used in Equation (4) for each of the three temperature dependency material categories are obtained from the regression using the MLR model of Equation S3-2 (Appendix S1, Section S3.3), yielding values of $\beta_{1/T} = -3486 \pm 299\,(K)$ and $\tau_{high} = -2391 \pm 356\,(K)$, $\tau_{medium} = 0\,(K)$ and $\tau_{low} = +1676 \pm 510\,(K)$. Thus, for the high-, medium-, and low-coefficient categories, the final temperature coefficients ($\beta_{1/T+\tau}$) are −5877 (K), −3486 (K), and −1810 (K), corresponding to activation energy of 113, 66.7, and 34.7 (kJ/mol), respectively. Begley et al.[4] also aggregated nine types of polymer materials into two temperature categories, with activation energy of 100 and 86.9 (kJ/mol), which have similar values with the high- and medium-coefficient categories in the present paper, to which these nine polymer materials are assigned. These results indicate that the categorization of the temperature coefficient in the present paper is consistent with previous studies, while extending the QPPR to a wider range of materials.

TABLE 1 Temperature dependence of diffusion coefficient in the 32 consolidated material types (all numbers are in the unit of K)

Category	Consolidated material type	Mean coefficient of $1/T$	SD between studies	Coefficient value for Equation (5)		
				$\beta_{1/T}$	τ	$\beta_{1/T}+\tau$
High-coefficient category	PP homopolymer	−6665	2354			
	Polyethylene terephthalate (PET)	−6567	2399			
	General polystyrene (PS)	−5713	3560	−3486	−2391	−5877
	Polyethylene naphthalate (PEN)	−5449	1940			
	PP copolymer	−5384	1194			
	High-density polyethylene (HDPE)	−5294	1124			
Medium-coefficient category	MMA homopolymer	−4549	1145			
	ABS, EVOH	−4222	n/a			
	High-impact polystyrene (HIPS)	−4215	n/a			
	Polyamide (PA)	−4179	1854			
	MMA copolymer-medium or low density	−4056	1272			
	Polyethylene (PE, LDPE, LLDPE)	−3713	536	−3486	0	−3486
	Limited-data material group	n/a	n/a			
	Calcium silicate	n/a	n/a			
	Carpet	n/a	n/a			
	Glass, Stainless steel	n/a	n/a			
	Vinyl acetate-based polymers	n/a	n/a			
	Cement	n/a	n/a			
Low-coefficient category	Gypsum board	n/a	n/a			
	Plywood	n/a	n/a			
	Flexible PVC	−2917	2618			
	Other wooden boards	−2411	888			
	Polychloroprene (CR)	−2127	286			
	Vinyl flooring	−1951	n/a			
	Polystyrene foam (XPS, EPS)	−1806	n/a			
	Polyurethane foam-based materials[a]	−1705	699	−3486	1676	−1810
	Synthetic rubber	−1326	205			
	Ethylene-propylene rubbers	−1145	300			
	Natural rubber (NR)	−939	337			
	Rigid polymers	−510	1552			
	Paper	−312	n/a			
	Gypsum and cellulose ceiling tile	331	294			

[a]This material type refers to low-density polyurethane foams with a density of 0.005-0.03 g/cm^3.

3.2 | Final QPPR and model fitting

Using the full dataset (1103 records) and Equation (4), the final MLR model for predicting the diffusion coefficient in solid materials is as follows:

$$\log_{10} D - \frac{\tau - 3486}{T} = 6.39 - 2.49 \cdot \log_{10} MW + b \quad (5)$$

$$N = 1103, R^2 = .932, R^2_{adj} = .930, SE = 1.17, RMSE = 1.15$$

$$ANOVA: F = 457, df = 32, P < .0001$$

where D is the diffusion coefficient (m^2/s), MW is molecular weight (g/mol), T is absolute temperature (K), b and τ (K) are the material-specific coefficients presented in Table 2. This model is provided as an excel model in Appendix S3 to facilitate application. The standard errors for the intercept (6.39) and the coefficient of $\log_{10}$ MW (−2.49) are 0.29 and 0.13, respectively. An SE of 1.17 of the final model (Equation 5) indicates that the 95% confidence interval (CI) of the predicted response, $\log_{10}D\text{-}(\tau\text{−}3486)/T$, is the predicted value±2.30. The 95% CI of the $\log_{10}D$ cannot be directly calculated, but the average absolute difference between predicted and measured $\log_{10}D$ is 0.83 across the whole dataset (1103 records), and 95% of this absolute difference is below 2.54.

TABLE 2 Material-specific coefficients for Equation (5)

Consolidated material type	Coefficient b			τ (K)	$b+(\tau+2391.15)/T$ at 25°C
	Coefficient	SE[a]	P-value		
Calcium silicate	1.17	.29	<.0001	0	9.19
Carpet	−1.23	.28	<.0001	0	6.79
Cement	0.330	.226	.15	0	8.35
Ethylene-propylene rubbers	−6.32	.29	<.0001	1676	7.32
Flexible PVC	−8.51	.31	<.0001	1676	5.13
General polystyrene (PS)	2.04	.30	<.0001	−2391	2.04
Glass, Stainless steel	−8.57	.38	<.0001	0	−0.550
Gypsum and cellulose ceiling tile	−1.24	.31	<.0001	1676	12.4
Gypsum board	−5.77	.30	<.0001	1676	7.87
High density polyethylene (HDPE)	5.11	.20	<.0001	−2391	5.11
High-impact polystyrene (HIPS)	−7.11	.27	<.0001	0	0.907
Methyl methacrylate (MMA) copolymer-medium or low density	−7.73	.21	<.0001	0	0.294
Methyl methacrylate (MMA) homopolymer[b]	−7.84	.31	<.0001	0	0.175
Natural rubber (NR) [b]	−3.60	.27	<.0001	1676	10.0
Other wooden boards[c]	−6.72	.21	<.0001	1676	6.92
Paper	−8.53	.34	<.0001	1676	5.11
Plywood	−5.61	.34	<.0001	1676	8.03
Polyamide (PA)	−5.40	.16	<.0001	0	2.62
Polyacrylnitrile butadiene styrene (ABS), Ethylene vinyl alcohol (EVOH)	−4.97	.23	<.0001	0	3.05
Polychloroprene (CR)	−6.31	.35	<.0001	1676	7.33
Polyethylene (PE, LDPE, LLDPE)	−1.65	.16	<.0001	0	6.37
Polyethylene naphthalate (PEN)	−1.16	.28	<.0001	−2391	−1.16
Polyethylene terephthalate (PET)[d]	**0.00**	**.15**	**n/a**	**−2391**	**0.00**
Polystyrene foam (XPS, EPS)	−8.32	.29	<.0001	1676	5.32
Polyurethane foam-based materials[e]	−7.35	.25	<.0001	1676	6.30
PP copolymer	4.79	.28	<.0001	−2391	4.79
PP homopolymer	4.53	.15	<.0001	−2391	4.53
Rigid polymers[f, b]	−11.9	.25	<.0001	1676	1.70
Synthetic rubber	−5.93	.32	<.0001	1676	7.71
Vinyl acetate-based polymers[g]	−0.459	.326	.16	0	7.56
Vinyl flooring	−6.77	.21	<.0001	1676	6.87
Limited-data material group[h]				See footnotes	

[a]Standard error.
[b]Coefficients should be taken with care due to large variations between studies.
[c]Includes Particleboard, Oriented strand board (OSB), Medium-density fiberboard (MDF), High-density board, and Wood chamber wall.
[d]Reference material (in bold).
[e]This material type refers to low-density polyurethane foams with a density of 0.005 to 0.03 g/cm^3.
[f]Includes polyether ether ketone (PEEK), rigid PVC, polytetrafluoroethylene (PTFE), and polycarbonate.
[g]Includes ethyl vinyl acetate (EVA), polyvinyl acetate (PVA), and polyvinyl acetate polyacrylic acid copolymer.
[h]The coefficient b for this group is −2.26 with an SE of 0.18, and the coefficient τ is 0. "Limited-data material group" includes data from 20 different materials, so the accuracy of the coefficients is low and they are not recommended for use in predicting diffusion coefficients. This group includes alginate film, balance, decorative and overlay layers of wooden flooring, cellulose, epichlorhydrin-dimethylamine polymer (EDP), epoxy/acrylic copolymer, latex, MMA/Butyl methacrylic (BMA) copolymer-very low density, nanocomposite polyamide, paint, pectin film, pectin/alginate composite film, polydimethylsiloxane (PDMS) membrane, polyisoprene (PI) membrane, polyoctenamer (PO) membrane, polyoxymethyene, polytrimethylene terephthalate (PTT), polyvinylidene chloride (PVDC), and silicone.

This MLR model shows excellent fitting of the experimental data, with an adjusted R-square of 0.932 and a root mean square error (RMSE) of 1.15. The model fit is highly significant with an ANOVA P-value smaller than .0001. Figure 2A shows the scatter plot of experimental vs predicted responses, which aligns well with the 1:1 line. In this MLR model, the response (dependent variable) is the temperature-adjusted log diffusion coefficient, that is, $\log_{10}D\text{-}(\tau-3486)/T$, instead of $\log_{10}D$, in order to fix the temperature coefficients and to avoid multicollinearity problems, as mentioned in Section 2.2.4. The residual plot (Figure 2B) shows that the residuals are distributed evenly throughout the dataset, again indicating the good fit of the linear model for the data.

The key predictors other than temperature in the MLR model are the material type and the molecular weight of the diffusing chemical. The regression coefficient when considering log-molecular weight is equal to −2.49, indicating that the diffusion coefficient decreases with increasing molecular weight. This implies that larger molecules diffuse more slowly compared to smaller molecules in solid materials, which is intuitive and consistent with findings from previous studies.[4,12,17,18] However, although the molecular weight is a highly significant predictor ($P<.0001$), it explains <10% of the total variance of the diffusion coefficient (Appendix S1, Section S4).

The 31 dummy variables for the material types reflect the material dependency and account for most of the total variance of the diffusion
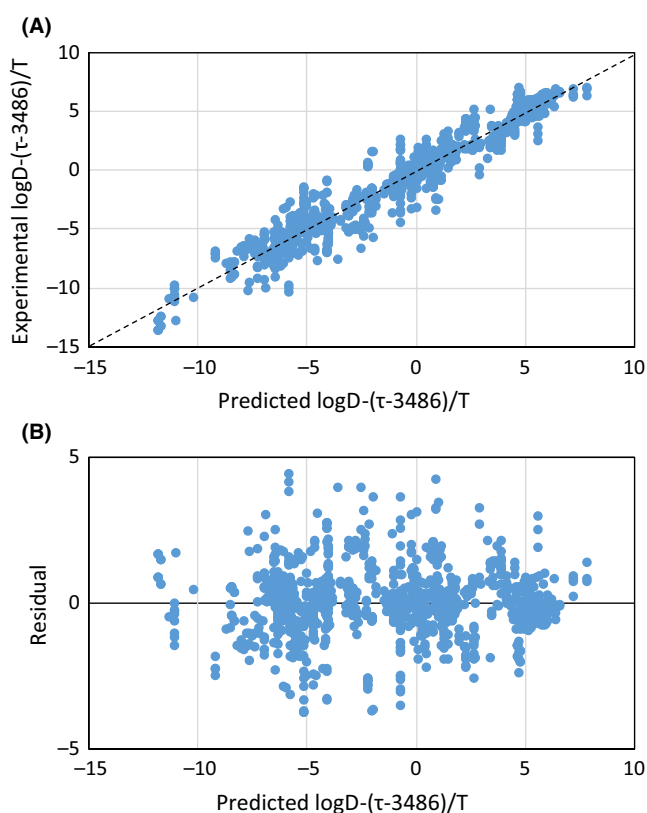

FIGURE 2 Values of $\log_{10}D\text{-}(\tau-3486)/T$ predicted by the final QPPR (Equation 5) vs (A) experimental values, and (B) residuals. The dotted line in (A) indicates the 1:1 line. The units of D and T are m^2/s and K, respectively
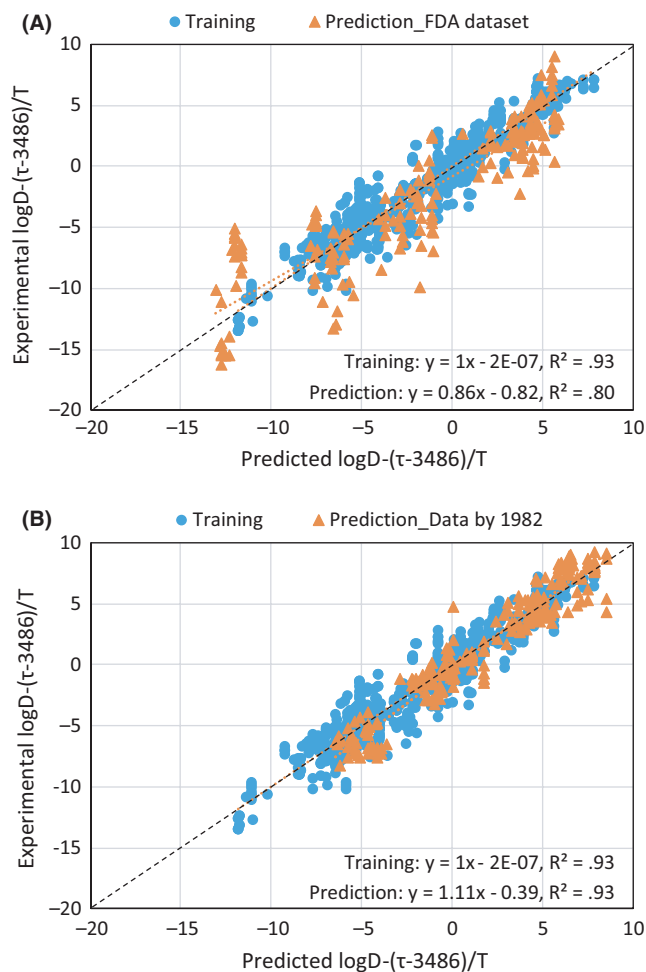

FIGURE 3 Values of $\log_{10}D\text{-}(\tau-3486)/T$ predicted by the final QPPR (Equation 5) vs experimental values when using (A) FDA dataset and (B) Data by 1982 as the prediction sets. The black dotted line indicates the 1:1 line. The units of D and T are m^2/s and K, respectively

coefficient, indicating that the diffusion coefficient in solid materials is strongly dependent on the material type. As "PET" was used as the reference material in the regression, the value of its coefficient b is zero (Table 2). For each of the other material types, the coefficient b, combined with the temperature coefficient τ, that is, $b+(\tau+2391)/T$, determines the difference in log diffusion coefficient between that material type and PET, as PET has a temperature coefficient τ of −2391 (K) (Table 2, last column). Chemicals in material types with high values of $b+(\tau+2391)/T$ diffuse quicker than in material types with low values. Therefore, under room temperature (T=298.15 K), the values of $b+(\tau+2391)/T$ and the corresponding diffusion coefficients tend to be lower in dense, rigid materials such as glass, stainless steel, methyl methacrylate (MMA) polymers, polyethylene naphthalate (PEN), and rigid polymers including polyether ether ketone (PEEK), rigid PVC, polytetrafluoroethylene (PTFE), and polycarbonate (Table 2). In contrast, the values of $b+(\tau+2391)/T$ and the corresponding diffusion coefficients can be up to 13 orders of magnitude higher in flexible or porous materials, such as gypsum, wood, rubber, and polyurethane

foam-based materials (Table 2). It should be noted that the composition and properties of a given material type may vary considerably depending on the intended use, as well as over time as material substitutions are made and production procedures differ. Thus, the material type coefficients in Table 2 actually represent an average composition and diffusion behavior for the specific material types.

The significance of the material type coefficient only indicates that the coefficient bs of these material types are significantly different from the reference material type, PET, but if another material type was selected as the reference material, the regression coefficients and statistical significance of all materials would change. Thus, the insignificance of the regression coefficients for material type variables does not indicate that those material types do not have a relevant influence on the diffusion coefficient. As a result, we keep all 31 material type dummy variables in the final regression to retain as much information as possible.

The MLR model given in Equation (5) contains material-specific variables, so it is only valid for the 32 material types presented in Table 2. For materials that do not belong to those 32 types, we built another generic QPPR to predict the diffusion coefficients, which is presented in Appendix S1, Section S4, which should be used with caution because of higher uncertainties.

3.3 | Model validation results

3.3.1 | Internal validation

For the 20% LMO cross-validation, the correlation coefficient, Q^2_{LMO} for the 1000 iterations ranges from 0.89 to 0.95, with an average of 0.93, and a root mean square error for cross-validation (RMSE$_{cv}$) average of 1.19. Both the Q^2_{LMO} and RMSE$_{cv}$ are similar to the R^2 and RMSE computed using the full dataset, which is 0.93 and 1.15, respectively. These results indicate that when fitted to a random 80% of

the dataset the model is still able to predict the remaining 20% of the dataset, meaning that the model is internally stable.

For the Y-scrambling, the average R^2_{Yscr} and Q^2_{Yscr} for the 1000 iterations are 0.029 and −0.033, respectively, which are much smaller than the R^2 and Q^2_{LMO} of the original model. The RMSE for Y-scrambling, RMSE$_{Yscr}$, is 4.36 which is much higher than the RMSE and RMSE$_{cv}$ of the original model. These results demonstrate that no correlation exists between the scrambled responses and the predictors. Thus, chance correlation for the original model can be ruled out.

Overall, the internal validation demonstrates that the MLR model represented by Equation (5) is robust and stable, and is not a result of chance correlation.

3.3.2 | External validation

As described in Section 2.3.2, the first method of external validation was to split the full dataset (1103 records) into training set and prediction set, and four types of splitting were performed, including splitting by a random 20%, by ordered response, by ordered structure, and by studies. Six criteria for external validation were computed and are presented in Table 3. The R^2_{ext} is the determination coefficient of the prediction set data using the model calculated using the training set data. The other five criteria, Q^2_{F1},[43] Q^2_{F2},[44] Q^2_{F3},[45] γ^2_m,[46] and CCC,[47] are external validation criteria proposed by different studies, which evaluate various aspects of the model's external prediction ability. These criteria are usually in accordance with each other but can sometimes give contradictory results,[47] so they need to be evaluated together. Chirico and Gramatica[48] have proposed threshold values for these different criteria, which are presented in Table 3. For the first three types of splitting (by random 20%, by ordered response, and by ordered structure), the R^2_{ext} are higher than 0.9, and all of the other five criteria pass the threshold values and are also higher than 0.9, indicating good prediction ability of the model calculated using only the training set data.

TABLE 3 External validation results

External validation criteria	R^2_{ext}	Q^2_{F1}	Q^2_{F2}	Q^2_{F3}	$\overline{r^2_m}$	CCC
Threshold		>.70	>.70	>.70	>.65	>.85
Splitting by random percentage	.92	.92	.92	.92	.90	.96
Splitting by ordered response	.94	.94	.94	.95	.93	.97
Splitting by ordered structure	.94	.94	.94	.94	.91	.97
Splitting by studies	.85	.85	.84	.85	.78	.92
FDA dataset as prediction set	.80	.77	.77	.60	.71	.89
Data by 1982 as prediction set	.93	.93	.92	.90	.85	.95

R^2_{ext}, determination coefficient of the prediction set external data; Q^2_{F1}, correlation coefficient proposed by Shi et al.; Q^2_{F2}, correlation coefficient proposed by Schuurmann et al.; Q^2_{F3}, correlation coefficient proposed by Consonni et al.; $\overline{r^2_m}$, determination coefficient proposed by Ojha et al.; CCC, concordance correlation coefficient proposed by Chirico and Gramatica.

In these three types of splitting, the data were assigned to the training and prediction data sets either randomly or alternately (by ordered response or structure), so it is likely that a portion of the data from each study was assigned to the training set, while the remaining portion of the data was assigned to the prediction set. As a result, the prediction set is well within the AD defined by the training set (Appendix S1, Figures S2-S7), so it is expected that the model calculated using the training set can well predict the prediction set.

For the fourth type of splitting, splitting by studies, data from 30 studies were selected as the prediction set, while data from the remaining 48 studies constituted the training set. Thus, all data from one study and for one particular material will be either in the training or in the prediction set, so the validation using this splitting is close to a truly "external" validation. Most of the prediction set is inside the AD defined by the training set except for two data points (Appendix S1, Figures S8-S9). As a result, the R^2_{ext} dropped to 0.85, and the values of the other five validation criteria are apparently lower than those for the above three types of splitting, reflecting that variability is higher between than within studies. The five validation criteria nevertheless all pass the threshold values (Table 3), indicating that the model calculated using the training set has good prediction ability.

As a second method of external validation, the 1103 data points from the 68 studies were used as the training set, and additional data from an FDA database and from studies before 1982 were used as two separate prediction sets. As presented in Table 3, when using FDA dataset as the prediction set, the R^2_{ext} is reduced to 0.80 which is lower than the R^2_{ext} for the above four types of splitting. Four of the five validation criteria pass the threshold values, while Q^2_{F3} does not pass the threshold. In contrast, when using data by 1982 as the prediction set, the R^2_{ext} is 0.93, which is very close to the R^2 of the training dataset (Section 3.2). The absolute difference between predicted and measured $\log_{10}D$ averages 2.20 (95th percentile of 5.53) for the FDA dataset, and averages 1.08 (95th percentile of 2.68) for the data by 1982. Figure 3 presents the comparison between model predicted and experimental responses for these two prediction sets. Data from both prediction sets are generally distributed close to the 1:1 line, but the FDA data are more dispersed compared to the training set data, while the data by 1982 are almost as compact as the training set data. The FDA data lack documentation of experimental details, so their quality may not be as good as the data reported in peer-reviewed literature. Also, when the FDA polymer types were linked to our consolidated material types, mismatches may have occurred due to lack of description of the polymers in the FDA dataset, which may lead to inaccuracies in model predictions. Overall, however, our QPPR performs reasonably well on these two fully external datasets, demonstrating its good predictive ability.

3.3.3 | Applicability domain

We performed the analysis of the model's AD using the three approaches explained in Section 2.3.3. The model being evaluated is the final MLR model presented in Equation (5), which was calculated using the training set of 1103 data points collected from 68 studies

obtained from the peer-reviewed literature. For the analysis of AD, we focus on the two external prediction datasets: the FDA dataset (189 data points) and the data by 1982 (239 data points). Detailed results of the AD analysis are presented in Appendix S1, Section S6.1.

Combining the three methods, none of the data points in both prediction sets fell out of the AD. For the FDA dataset, the majority of the data points were inside the AD, while 15 data points were on borderline of AD. Similarly, only 35 data points from the data by 1982 were on borderline of AD. Thus, it is valid to use the present QPPR to make reliable estimates of diffusion coefficients for all data points in the two prediction sets. The physiochemical property space covered by the QPPR is mainly determined by the chemical's molecular weight, which ranges from 30 to 1178 g/mol. The vapor pressure at 25°C may also be a relevant property, which ranges from $9.8 \cdot 10^{-29}$ to $5.2 \cdot 10^5$ Pa. The range of $\log_{10}D$ covered by the QPPR is from −22.1 to −5.2 where D is measured in m^2/s.

As mentioned in Section 2.2.2, the model performances of using log-molecular weight and molecular weight as predictors were very close to each other when using the training dataset. However, residual analysis and external validation showed that $\log_{10}$ MW is a more stable predictor than MW when handling high-molecular-weight chemicals, which becomes prominent for the FDA dataset, which includes certain chemicals with molecular weight higher than 1500 g/mol. While none of the data points in the FDA dataset fell out of the AD using the $\log_{10}$ MW model, 11 data points would be outside AD using the MW model. Details are presented in Appendix S1, Section S6.2. Thus, $\log_{10}$ MW instead of MW was selected as a predictor in the final QPPR (Equation 5).

Schwope et al.[37] suggested that the linear relationship between $\log_{10}D$ and $\log_{10}$ MW may only be valid for a certain range of molecular weight, and there may be a saturation of diffusion coefficients for small molecular weights, that is, for a given material and a given temperature, the diffusion coefficient does not continue to increase for chemicals with molecular weight lower than a certain value, which is likely determined by the material type. To further examine the effect of molecular weight on model applicability, we analyzed the model residuals vs the log of molecular weight for the training dataset and the two prediction sets (Figure 4). For the three datasets, the residuals are distributed evenly on both sides of zero in the MW range of the training dataset of 30 to 1178 g/mol ($\log_{10}$ MW of 1.48-3.07). For methane (MW=16 g/mol), most of the predictions overestimate diffusivity, suggesting that diffusivity may indeed not further decrease below MW of 30 g/mol. As methane was the only chemical with data available for MW lower than 30 g/mol, data for additional chemicals and materials are therefore needed to further test this hypothesis of saturation at low MW. Similarly, additional data are needed to provide more accurate estimates for chemicals with very high molecular weights.

Overall, the performance of the final model (Equation 5) in this external validation indicates that it has the ability to provide reliable predictions, as long as the considered chemicals are within the model's AD. With the log-molecular weight as a predictor, our model is able to make reliable extrapolations on chemicals with molecular weights up to about 2500 g/mol, but caution still needs to be taken when applying
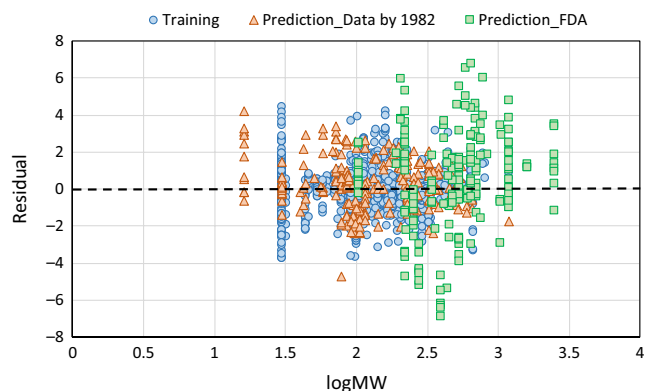
FIGURE 4 Residual between the present QPPR and observed data as a function of $\log_{10}$MW for the training dataset, the FDA dataset, and the data by 1982 set. The unit of MW is g/mol

the model on extremely high-molecular-weight chemicals. Ideally, the model should be applied to predict diffusion coefficients for chemicals with molecular weights lower than 1178 g/mol which is the maximum within the training dataset. Caution also needs to be taken when applying the model on very-low-molecular-weight chemicals due to the possible saturation effect. Both the FDA dataset and the data by 1982 were used for the external validation but not combined with the original training dataset to calculate a more comprehensive MLR model, because these data are somewhat outdated; the FDA data are not published in literature, so there is a lack of experimental details, making these undocumented data less reliable than the data collected from peer-reviewed literature.

3.4 | Limitations and future work

While the extension to 32 different consolidated material types is a major progress, the present model is still not fully comprehensive. First, the model may not be valid for very high or very low molecular weight (MW) chemicals. It may not be valid for ionizing organic chemicals either, as ionizing chemicals such as acids, alcohols/phenols, and amines are not well represented in the training dataset, as they only account for <10% of the data points, and the model does not consider chemical ionization or interaction within a material, which may make the chemical's diffusivity lower than that predicted by the model. Second, the present model is not applicable for materials types other than the 32 types in the training set, for example, for material such as resin and textiles, due to the lack of experimental data. Although a more general MLR model (Appendix S1, Section S4) was developed which does not require material type as the predictor, it gives much less accurate predictions of the diffusion coefficient. Third, the present model does not consider any interaction between MW and material type, that is, it assumes the effect of MW is the same across different materials. Although model validations show that this assumption may be reasonable for the existing data, ideally it needs to be further verified using data spanning the whole MW range (30-1178 g/mol) for each material. Therefore, more experimental diffusion coefficient data need to be obtained, or more advanced experimental methods

to measure diffusion coefficients need to be developed, for other material types and chemical sizes and classes to make the model more comprehensive.

There are also large variations in the experimental diffusion coefficients between some of different studies for three material types, namely "MMA homopolymer," "Natural rubber," and "Rigid polymers," even after correcting for molecular weight and temperature, as shown in Figure 1 and Appendix S1, Figure S1. This means that the regression coefficients b and τ for these material types should be taken with care. The variations could be due to three causes. First, experimental variation, for example, Franz et al.[40] used desorption experiments to measure the diffusion coefficients in MMA homopolymer, while Hennebert et al.[42] used sorption experiments. Second, the swelling of polymers during liquid sorption experiments, which generally occurs for cross-linked polymers in low-molecular weight solvents,[49] may not always be accounted for, and can lower the diffusion coefficients by orders of magnitude.[10] Third, the properties of the same material can vary between studies depending on how it was made and which additives were used. This may also be the case for some other materials such as vinyl flooring, carpet, and synthetic rubber for which the material type coefficients in Equation (5) can only represent some sort of average composition and diffusion behavior for the specific materials. Ideally, quantitative, continuous properties of the solid materials, such as density, porosity, and crystalline state of the material as well as other descriptors of the material's composition and molecular structure, instead of qualitative material types could be measured and entered into the model as predictors, so that the model can be more accurate and can be extrapolated to various material types outside the training dataset.

4 | CONCLUSIONS

A MLR model has been developed to predict the internal diffusion coefficients of organic compounds in various solid materials (excel model provided in Appendix S3). Experimental diffusion coefficient data collected from 68 studies of the peer-reviewed literature were used as the training set for the regression. The model uses two continuous variables, molecular weight and inversed absolute temperature, and one categorical variable, material type, as predictors. The model has been internally validated to be robust, stable and not a result of chance correlation. External validation using two prediction sets demonstrates that the model predictions are most reliable within the model's AD, namely molecular weight between 30 and 1178 g/mol, temperature between 4 and 180°C, and material type belonging to the 32 consolidated types.

The main advantage of the present model is that it is applicable for chemicals with a wide range of molecular weights (but only up to about 16-2500 g/mol, with special treatment for molecular weight lower than 30 g/mol) in various materials. This is advantageous compared to the correlation methods developed in previous studies often specific for certain chemical classes or materials. The present model is able to provide reliable estimates of diffusion coefficients for a large

number of chemical-material combinations, making it suitable for high-throughput assessments of the releases and human exposures to chemicals encapsulated in solid materials, particularly building materials and FCMs. To make the model comprehensive, more experimental diffusion coefficient data need to be obtained for other material types, or quantitative and continuous parametrization of various solid materials needs to be further developed.

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