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Emerging investigator series: the role of chemical properties in human exposure to environmental chemicals

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One of the ultimate goals of environmental exposure science is to mechanistically understand how chemical properties and human behavior interactively determine human exposure to the wide spectrum of chemicals present in the environment. This comprehensive review assembles state-of-the-art knowledge of the role of partitioning, dissociation, mass transfer, and reactive properties in human contact with and absorption of organic chemicals *via* oral, dermal, and respiratory routes. Existing studies have revealed that chemicals with different properties vary greatly in mass distribution and occurrence among multiple exposure media, resulting in distinct patterns of human intake from the environment. On the other hand, these chemicals encounter different levels of resistance in the passage of intestinal, dermal, and pulmonary absorption barriers and demonstrate different levels of bioavailability, due to the selectivity of biochemical, anatomical and physiological structures of these absorption barriers. Moving forward, the research community needs to gain more in-depth mechanistic insights into the complex processes in human exposure, advance the technique to better characterize and predict chemical properties, generate and leverage experimental data for a more diverse range of chemicals, and describe better the interactions between chemical properties and human behavior.

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Environmental significance

During the past decades, enormous theoretical and empirical efforts have been devoted to revealing how chemical properties impact the susceptibility and disparity in human exposure to the myriad of environmental chemicals. Here we systematically compile and critically curate the up-to-date mechanistic understandings of how human external and internal exposures respond to the variability in chemical properties. Information presented in this comprehensive review aids the effective identification of the most relevant exposure pathways based on chemical properties, benefits cost-effective decision-making in risk management and reduction, guides future exposure-oriented biomonitoring efforts, and sheds light on "benign" molecular design and synthesis in green chemistry.

1. Introduction

Humans are exposed to a wide spectrum of chemicals present in the ambient environment, diet, and consumer products, *i.e.*, environmental chemicals. Presently, more than 200 environmental chemicals are routinely detected in the human body;[1] this number has even been expanded to nearly 1000 with the latest instrumental technique[2] and is anticipated to further increase with the advancement of "exposome" research.[3,4] Exposure to certain environmental chemicals has been linked to adverse health impacts such as endocrine disruption, cancer, metabolic syndrome, IQ loss, and infertility.[5–7] To protect human health and safeguard public benefits, it is imperative to understand the sources, mechanisms, and routes of human exposure to the myriad of chemicals present in the environment.[8] The large and ever-growing number of chemicals in the environment further warrants holistic, systematic understandings of these aspects, since assessing exposure to individual chemicals is challenging given the time and resource constraints.

Overall, environmental chemicals take three main courses to reach and enter the human body: (i) oral ingestion of chemicals followed by absorption in the gastrointestinal tract, (ii) nasal and oral inhalation of chemicals followed by absorption in the respiratory tract, and (iii) dermal contact and absorption.[9] Contact with and absorption of environmental chemicals are complex processes mediated by a wide array of physical, chemical, physiological, behavioral, and socioeconomic factors. Underlying these factors is the interaction between the intrinsic properties of chemicals and the behavior of receptors.[10] Chemical properties, *e.g.*, partitioning, dissociation, mass transfer, and reactive tendencies, are critical determinants of the multimedia distribution of chemicals in indoor and outdoor environments, which govern their presence in various exposure media (foods, drinking water, air, dust, *etc.*) and

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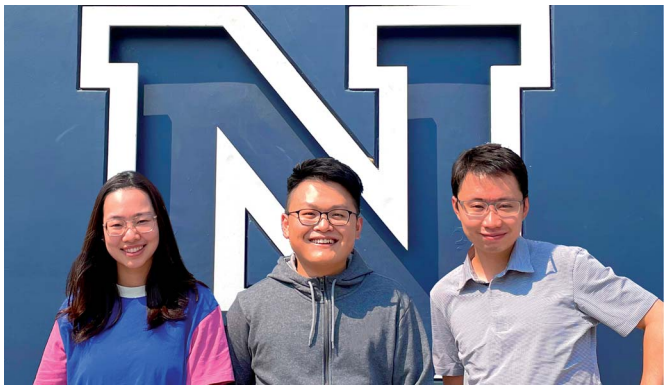
proximity to the human receptor. Chemical properties also govern a chemical's capability to reach the exterior boundary of the human body, penetrate absorption barriers, and enter the systemic circulation. In addition, the distribution, metabolism (biotransformation), and elimination of chemicals are also dependent on chemical properties. For these reasons, one can expect considerable variability in human exposure to distinct environmental chemicals, even if they are used at similar rates, in the same environment, and for similar functions. A well-recognized example is phthalates: Whereas they are commonly used as plasticizers in consumer articles, inhalation of the indoor air is often identified as the dominant mechanism for human exposure to dimethyl phthalate, but diet is the dominant route for other phthalates, notably the most common di(2-ethylhexyl)phthalate.[11,12] In some cases, even if a chemical is used exclusively indoors, consumption of foods originating in the outdoor environment may still contribute more to human exposure than indoor exposure pathways do.[13] As such, a lack of mechanistic insights into the paramount role of chemical properties may hinder a comprehensive and clear understanding of human exposure to environmental chemicals.

Such mechanistic insights are vital for the surveillance, simulation modeling, assessment, and management of chemical exposure and potential risks. For instance, based on information on chemical properties, decision-makers can make initial preliminary statements on the relative importance of different sources, routes, and pathways of exposure, which enables prioritizing resources for cost-effective management of the leading source.[13] Strategic use of such information, if partnered with human behavioral and socioeconomic information, further aids in interpreting interindividual variability and disparity in chemical exposure and protecting the most vulnerable subpopulations.[14,15] The efficient identification of relevant exposure pathways also facilitates high-throughput screening of tens of thousands of chemicals in commerce.[16] In addition, environmental monitoring and biomonitoring efforts also benefit from the identification of predominant sources and routes of exposure, as it advises the appropriate environmental or biological compartments where a high abundance of chemicals of interest is likely to be found. Furthermore, such understanding informs us of the attributes that can trigger adverse environmental and health outcomes of chemicals, *e.g.*, high susceptibility to human absorption and/or high resistance to biotransformation or elimination from the body, which facilitates decisions before the manufacturing and commercialization of new chemicals and sheds light on "benign" molecular design and synthesis in green chemistry.

Pioneering empirical and theoretical studies have provided extensive information on the role of chemical properties in human exposure to environmental chemicals, as reviewed in this paper. However, existing reviews and synthetic studies largely focus separately on either oral ingestion,[17,18] inhalation,[19] or dermal absorption,[20–22] and describe distinct facets of the complex exposure process. While preliminary efforts sought to aggregate multiple sources and routes of exposure, *e.g.*, by considering multi-pathway exposure to chemicals released from multiple lifecycle stages,[13,23–26] there generally lacks a comprehensive overview of the impact of chemical properties on the totality of human exposure. Therefore, the objective of this article is to systematically compile and critically curate up-to-date findings on the response of human exposure to variability in chemical properties. We seek to assess the current understanding of exposure sciences from an environmental chemistry perspective. This article is organized as follows. First, we introduce general principles on chemical properties of partitioning, dissociation, mass transfer, and reaction (Section 2), as well as important concepts in exposure science (Section 3). We then discuss the role of chemical properties in oral ingestion (Section 4), dermal absorption (Section 5), and inhalation (Section 6), by introducing the occurrence of chemicals in exposure media, biochemical, anatomical and physiological structures of the absorption surfaces, the link between these structures and the absorption of chemicals, as well as chemical properties controlling the absorption of chemicals. Finally, we assemble the information to form a complete picture of the relative importance of multiple exposure routes and discuss potential directions for future research (Section 7).



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2. Properties of environmental chemicals

Chemicals can be characterized and identified by their partitioning, dissociation, mass transfer, and reactive properties.

A chemical can be found in multiple environmental phases, such as air (*e.g.*, gas and vapor), polar liquids (*e.g.*, water, moisture, and mucus), and weakly polar or nonpolar condensed phases (*e.g.*, lipids, plant waxes, dust, soils and sediments, and polymeric materials). In the real world, these environmentally relevant phases are not pure, varying in composition and physical state, and characterizing chemical behavior in these phases is often expensive, uncertain, variable, and less reproducible than characterization in pure phases in the laboratory. To address these problems, environmental chemists instead use water as a simple, standard surrogate for various polar liquid phases and *n*-octanol for weakly polar or nonpolar condensed phases.[27] Therefore, the mass distribution in a ternary system comprising three immiscible phases of air, water, and *n*-octanol often serves as a convenient approximation to mass distribution among environmental media. In chemistry, the extent to which a chemical is mixed with a phase is quantified using solubility. For instance, water-soluble chemicals can be found abundant in the "water" phase, and vapor pressure can also be viewed as a pseudo solubility in the "air" phase. The ratio between solubilities in two immiscible phases, also the ratio between corresponding concentrations when phase distribution is in equilibrium, is known as "partition coefficient", or more recently referred to as "partition ratio".[27–29] In the ternary air–water–octanol system, one can define partition coefficients between air, water, and octanol (K_{OW}, K_{OA}, and K_{AW}). For neutral organic chemicals, a simple and effective conceptual and quantitative model for these three primary phases is the "three solubility approach".[29] The "three solubility approach" is founded on thermodynamic principles and can address inconsistencies (errors) in chemical properties used in exposure science.[30–32] The K_{OW}, also expressed using the symbol P_{OW} or P in toxicological and pharmaceutical studies, is an ideal measure for a chemical's preference for water. Chemicals with small K_{OW} prefer partitioning into water over octanol and are thus regarded as "hydrophilic", whereas a high K_{OW} favors chemicals partitioning into octanol over water and identifies them as "hydrophobic". Phospholipids are "amphiphilic" because they contain both hydrophobic (lipid tails) and hydrophilic (polar phosphate heads) domains in the same molecule.[33] On the other hand, K_{AW} (*i.e.*, the unitless Henry's law constant) and K_{OA} describe a chemical's tendency to volatilize from water and condensed phases.[34] The use of the air–water–octanol system is advantageous because partitioning between environmentally relevant phases can be conveniently correlated with these three partition coefficients; such empirical correlations are called single-parameter linear free energy relationships (sp-LFER).[35] For instance, a comprehensive investigation into 158 diverse chemicals derives statistically significant linear log–log dependence of partition coefficients between phospholipids and water (K_{PL-W}) on K_{OW},[36] and data summarized from 30 chemicals further indicates similar linear log–log dependence of partition coefficients between proteins and water (K_{P-W}) on K_{PL-W}.[37] Therefore, with a known K_{OW}, one can easily predict the sorption of chemicals to phospholipids and proteins, which makes K_{OW} reasonably applicable to chemicals favoring partitioning into not only storage lipids (*e.g.*, hydrophobic organochlorines) but also membranes and proteins (*e.g.*, perfluoroalkyl substances).[38] The sp-LFER enables chemically sound and computationally efficient predictions of chemical fate, transport, exposure, and effects in the multimedia environment.

For ionizable organic chemicals that can dissociate in the aqueous phase, the partitioning behavior differs between neutral and charged fractions (cations, anions, and/or zwitterions). Typically, compared to neutral fractions, charged fractions are minimally volatile and orders of magnitude more soluble in water, due to the formation of hydrogen bonds.[39,40] That is, the overall partition coefficient (often termed "distribution ratio", *e.g.*, D_{OW}, D_{OA}, and D_{AW}) of the composite of neutral and charged molecules depends closely on the pH of an environmental medium. A common practice is to calculate distribution ratios as the average of respective partition coefficients of neutral and charged fractions, weighted by their relative abundance in the environmental medium.[39] In general, the distribution ratios of ionizable organic chemicals function in the same way as the partition coefficients of neutral chemicals in terms of the control of chemical fate, transport, exposure, and effects. Hence, the empirical relationships summarized in this article are largely applicable to ionizable organic chemicals if the partition coefficients therein are substituted with distribution ratios.

Chemical molecules can diffuse within an environmental medium and permeate from one to another. The mass transfer obeys Fick's laws of diffusion. The rate of interphase diffusion is closely related to a chemical's relative solubilities between two phases. For instance, the "Overton Rule" a century ago stated that the rate of a chemical's penetration through a lipid-rich membrane is largely governed by its lipid solubility.[38] In most cases, a polar phase poses high resistance to the diffusion of hydrophobic chemicals, and diffusion across this polar phase is often the rate-limiting step in interphase diffusion. Likewise, the diffusion of hydrophilic chemicals is resisted by a weakly polar or nonpolar phase. Therefore, we can expect that a layer of water or water-like liquids (*e.g.*, mucus) forms a barrier to the passage of hydrophobic chemicals, whereas a layer of lipids (*e.g.*, cholesterol and long-chain fatty acid) forms a barrier to the passage of hydrophilic chemicals. Due to their amphiphilicity, phospholipids resist the passage of both hydrophobic and hydrophilic chemicals. In addition to the partitioning properties, the rate of diffusion is also governed by the molecular size (molar mass or volume). Large and bulky molecules often diffuse more slowly in any phase.[41]

Finally, environmental chemicals undergo various irreversible reactions to change into other forms in environmental compartments and organisms. For instance, chemicals in air react with hydroxyl radicals (hydroxylation) and ozone (ozonization) to break down into smaller molecules. Microorganisms degrade environmental chemicals in surface media (biodegradation). Exogenous chemicals can also be biotransformed at different rates in all higher-order organisms (plants, invertebrates, vertebrates, *etc.*). The nature that chemicals are highly durable in the environment or hardly degraded by organisms is termed persistence, which is often described using the half-life,

i.e., the time required for a chemical being reduced to half of its initial abundance.[27,42,43] A longer half-life is associated with a slower rate of irreversible reactions. Half-lives can be determined experimentally or calculated by quantitative structure–activity relationships (QSARs). For instance, earlier studies estimated biotransformation half-lives in fish from (i) direct *in vivo* measurements,[44] (ii) *in vivo* toxicokinetic measurements coupled with mass balance physiologically based toxicokinetic models,[45] (iii) *in vitro* assays coupled with *in vitro–in vivo* extrapolation models,[46] and (iv) QSARs.[47–50]

3. Intake and uptake of environmental chemicals

Exposure, or more specifically, external exposure takes place when there is a contact between environmental chemicals and the visible exterior surfaces of humans, *e.g.*, the skin surface, and conceptual surface over the open mouth and nose. The concept "intake" describes the process by which an environmental chemical crosses these exterior exposure surfaces.[51] Intake depends closely on the occurrence and status of chemicals in the environment and exposure media (foods, drinking water, air, dust, *etc.*), which reflects the composite effect of multiple chemical properties. It also depends on human behavior, *e.g.*, the frequency, duration, and media of exposure.

However, passage through these exterior exposure surfaces does not necessarily mean the absorption of environmental chemicals by humans, as chemicals can still be resisted by various membrane structures inside the body, *e.g.*, the intestinal lining in the digestive system, alveolar lining in the respiratory system, and epidermis of the skin. Only when chemicals cross these membrane structures, enter the blood capillaries and become available for systemic circulation, can they be viewed as being "absorbed". For this reason, these membrane structures are called absorption barriers.[51] Correspondingly, the concept "uptake" describes the crossing of chemicals through absorption barriers.[51] Uptake reflects the interaction between chemical properties and the biochemical structural composition of absorption barriers. Particularly, the ratio between the doses of uptake and intake is an important indicator gauging the "absorption efficiency" of an environmental chemical.

It is uptake that makes an exogenous chemical appear in internal biological fluids like blood. A high dose of intake is a necessary, but not sufficient, condition for a remarkable level of an exogenous chemical in the body because the latter is governed simultaneously by external exposure, portal specific absorption, and residence time in the body (often determined by rates of passive elimination and biotransformation).

4. Oral ingestion

4.1 Occurrence of environmental chemicals in ingested items

Humans ingest chemicals through the consumption of food (*e.g.*, beef, fish, pork, vegetables, *etc.*), drinking water, and non-food items (*e.g.*, settled dust and soil particles). Specifically, environmental chemicals appear in food due to either bioaccumulation through the food webs, leaching migration, or generation during food preparation and delivery. Chemical properties are an important determinant of the potential of human contact with these contaminated items.

4.1.1 Bioaccumulation of chemicals in food. Partition tendency is an important determinant of the relative distribution of environmental chemicals among different natural environmental media. For illustration, Fig. 1a illustrates the relative distribution of chemicals with different partitioning tendencies among multiple environmental media of an archetypal North American environment. It indicates that, for instance, a perfectly persistent chemical can be found predominantly (>50% of the total mass present in the environment) in water if it has a log K_{AW} lower than −2.5 and a log K_{OW} lower than 3, whereas it is predominantly in soil if log K_{OA} is greater than 5 and log K_{OW} is greater than 3. These "thresholds" also apply to ionizable organic chemicals if partition coefficients are replaced by corresponding distribution ratios. A chemical is distributed less in an environmental medium if it has a short degradation half-life in this medium.

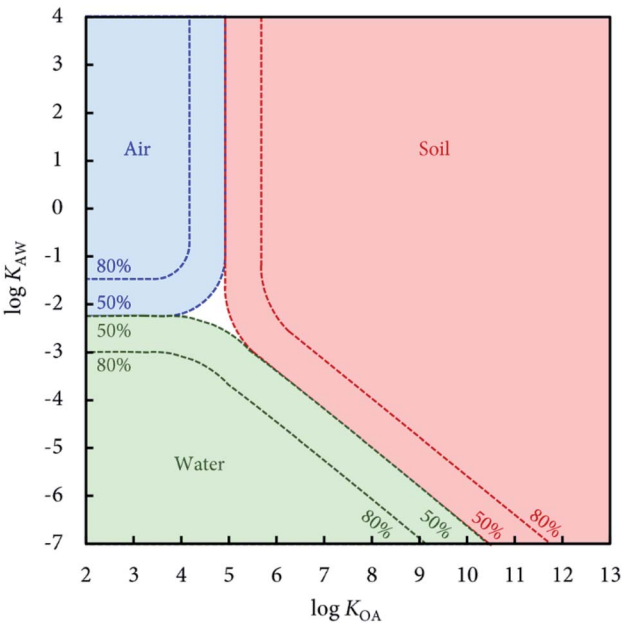

Fig. 1 Relative mass distribution of perfectly persistent chemicals between air, water, soil, and sediment in an archetypal rural region in North America, as a function of their octanol–air (K_{OA}) and air–water (K_{AW}) partition coefficients (or distribution ratios for ionizable organic chemicals). Diagonals from the top left to the bottom right of this partitioning space represent chemicals with the same log K_{OW}. The dashed contour lines represent K_{OA}–K_{AW} combinations leading 80% and 50% of the total mass to be distributed in an environmental medium. The diagram builds on predictions from a comprehensive fate and exposure model named RAIDAR.[53] As defined in the model, water and sediment account for 10% of the regional area, and soil accounts for 90% of the regional area. Chemicals (with a typical molar mass of 300 g mol^{-1}) are assumed to be released into the air. Default parameters of RAIDAR are used for modeling.

Aquatic and terrestrial organisms can enrich environmental chemicals from the surrounding environment of air, water, soil, and sediment and/or from their diet. Environmental chemicals differ in their ability to be enriched in different organisms. Also, to achieve a considerable level in organisms, a chemical needs to resist elimination, *e.g.*, biotransformation, fecal egestion, exhalation, urine excretion (for terrestrial animals), and/or gill ventilation (for aquatic animals), from organism bodies.[52]

Water-respiring organisms (*e.g.*, fish and crustaceans) can absorb and eliminate environmental chemicals through water ventilation with gills, in addition to dietary ingestion and fecal egestion. As such, K_{OW} is the most important determinant of chemical bioaccumulation in these organisms. Chemicals with moderate to high hydrophobicity (with a log K_{OW} ranging from 5 to 9.5) demonstrate the highest bioaccumulation potential (Fig. 2). More hydrophilic chemicals (with a log K_{OW} lower than 5) are less bioaccumulative in water-respiring organisms because these chemicals are often subject to less efficient absorption but more efficient loss through respiratory water exchange, *e.g.*, through gill.[54] Meanwhile, more hydrophobic chemicals are to a greater extent enriched in lipid tissues, which sequesters them from high blood concentrations and subsequent biotransformation, primarily in the liver.[55] These two reasons lead the bioaccumulation potential to increase with increased K_{OW}. In fact, the ball-park estimate of log K_{OW} greater than 5 is used as a bright-line cut-off in regulatory policies.[56] For instance, while a bioconcentration or bioaccumulation factor (BCF or BAF) greater than 5000 L kg^{-1} is used as a "rule of thumb" for "very bioaccumulative" chemicals in bioaccumulation screening, the Stockholm Convention also prioritizes chemicals with a log K_{ow} greater than 5 as candidates for persistent organic pollutants when bioconcentration or bioaccumulation data are absent or inadequate.[57] Table 1 outlines empirical equations correlating BCF or BAF with K_{OW}, which all show that BCF or BAF achieves 5000 when log K_{OW} is close to 5. Nevertheless, the dependence of bioaccumulation on K_{OW} is not always monotonic. While organisms do absorb super hydrophobic chemicals, *i.e.*, those with a log K_{OW} greater than 9.5,[58] the absorption rates are so slow due to slow mass transfer through the hydrophilic structures in absorption barriers, that the time required for a chemical to reach an equilibrium between water and organism tissue may exceed the lifetime of an organism.[52,54] In this situation, the lifetime of an organism plays a more important role than partition tendency in determining the level of chemical accumulation in organisms. European Union's Guidance on Information Requirements and Chemical Safety Assessment[59] proposes that chemicals with a log K_{OW} greater than 10 are "unlikely" to be bioaccumulative in aquatic organisms; however, reliable quality measurements are still scarce to support this assertion.[60,61] Furthermore, D_{OW} should be used for assessments of ionizable organic chemicals, as the organism absorption of charged ions is rather limited compared to neutral molecules.[62,63]

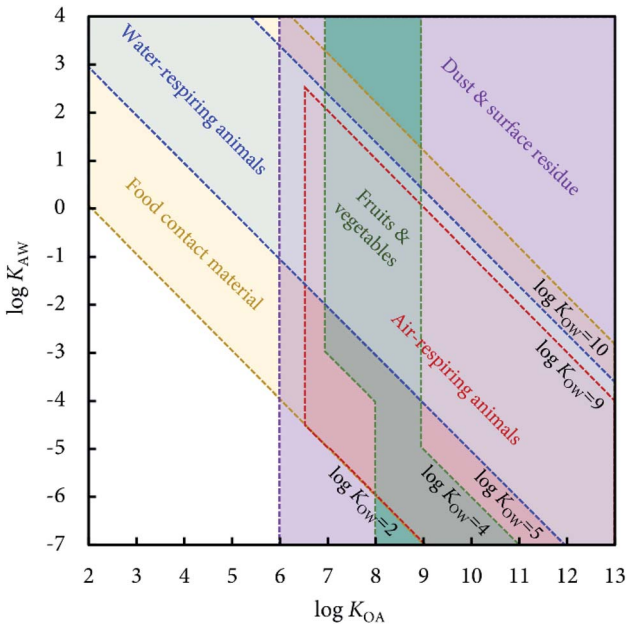

Fig. 2 Combinations of octanol–air and air–water partition coefficients (K_{OA} and K_{AW}; or distribution ratios for ionizable organic chemicals) leading to pronounced bioaccumulation in air-respiring animals (in red), water-respiring animals (in blue), fruits and vegetables (in green), high leaching migration from food contact materials (in yellow), as well as a high presence on dust and as surface residues (in aqua). Diagonals from the top left to the bottom right of this partitioning space represent chemicals with the same log K_{OW}. For references for the threshold of each colored region, please see the main text.

Both K_{OA} and K_{OW} are useful to indicate chemical bioaccumulation in air-respiring organisms (*e.g.*, terrestrial reptiles and mammals, including humans) (Fig. 2).[64,65] Since chemical elimination through air respiration is correlated with the K_{OA}, volatile chemicals with log K_{OA} smaller than 6.5 become less bioaccumulative because of relatively efficient exhalation.[65,66] On the other hand, chemicals with log K_{OW} smaller than 2 are also less bioaccumulative because they are eliminated relatively quickly due to excretion in urine.[65,66] Similar to the case of water-respiring organisms, air-respiring organisms also have reduced absorption of highly hydrophobic chemicals (log K_{OW} > 9) within their lifetime.[64,66] Therefore, we can expect the highest bioaccumulation potential for environmental chemicals with a moderate log K_{OW} (ranging from 2 to 9) but a high K_{OA} (greater than 6.5).[64]

Furthermore, partitioning tendency also controls chemical bioaccumulation in plants. When contaminated soil is the dominant source for contamination in plants, chemicals with a log K_{OW} smaller than 4 and a log K_{OA} greater than 8 are most bioaccumulative (Fig. 2).[67,68] This is because these chemicals are most efficiently taken up *via* the roots,[69,70] compared to more hydrophobic chemicals, but not rapidly eliminated from plants *via* volatilization, compared to more volatile chemicals. By contrast, when the atmosphere is the dominant source for contamination in plants, moderately volatile chemicals with a log K_{OA} between 7 to 9 and a log K_{OW} greater than 4 are the most bioaccumulative.[68,71] These chemicals are abundant in the gas phase of air and efficiently taken up by foliar gaseous absorption, and once absorbed, they are minimally eliminated from plants *via* volatilization.

Table 1 Correlations of bioconcentration or bioaccumulation factor (BCF or BAF; in L kg^{-1}) in fish with the octanol–water partition coefficient (K_{OW}) for non-ionizable organic chemicals. Here, bioconcentration results from the absorption of chemicals from the ambient environment *via* non-dietary routes of exposure (*i.e.*, respiratory and dermal exchanges), while bioaccumulation results from the absorption of chemicals from all routes of exposure[61a]

	Correlation	$\log K_{OW}$ for BCF or BAF = 5000 L kg^{-1}
EU Technical Guidance Documents and the EUSES model[86]	$\log \mathrm{BCF} = 0.85 \times \log K_{OW} - 0.70$ (for $K_{OW} \leq 6$) ($n = 55$, $R^2 = 0.90$) $\log \mathrm{BCF} = -0.20 \times (\log K_{OW})^2 + 2.74 \times \log K_{OW} - 4.72$ (for $K_{OW} > 6$) ($n = 43$, $R^2 = 0.78$)	5.18
BCFBAF model implemented in EPI Suite[87,88]	$\log \mathrm{BCF} = 0.5$ (for $K_{OW} \leq 1$) $\log \mathrm{BCF} = 0.6598 \times \log K_{OW} - 0.333 + \Sigma\mathrm{CFs}$ (for $1 < K_{OW} \leq 7$) ($n = 396$; $R^2 = 0.792$) (1) $\log \mathrm{BCF} = -0.49 \times \log K_{OW} + 7.554 + \Sigma\mathrm{CFs}$ (for $K_{OW} > 7$) ($n = 35$; $R^2 = 0.634$) (1)	6.11 (2)
The Arnot-Gobas BAF-BCF model[89]	$\mathrm{BCF} = 0.8 + \dfrac{(1/(0.01 + 1/K_{ow})) \times (1/(1 + 1.75 \times 10^{-8} K_{ow}))}{0.0005 + \left(\dfrac{K_{ow}}{0.002 + \dfrac{0.2}{K_{ow}}}\right)^{0.6} + 2.5 \times 10^{-3}\, e^{5.1 \times 10^{-8} K_{ow} + 2}}$ ($n = 483$, $\log K_{OW}$ from 0 to 10)	4.49
Arnot and Gobas (2006)[61]	$\log \mathrm{BCF} = 0.6 \times \log K_{OW} - 0.23$ (3) ($n = 2393$, $\log K_{OW}$ from −6 to 12, $R^2 = 0.52$) $\log \mathrm{BAF} = 0.86 \times \log K_{OW} + 0.12$ (4) ($n = 912$, $\log K_{OW}$ from −6 to 12, $R^2 = 0.55$)	6.55 (for BCF) 4.16 (for BAF)

[a] (1) For chemicals containing certain structural features (*e.g.*, phenanthrene ring, long-chain alkyl chains, *etc.*), structural feature-specific correction factors (CFs) are linearly combined to adjust the BCF or BAF calculated by the generic correlations. (2) The number is calculated based on the correction factors of 0. (3) The equation is the "acceptable fish BCF model" reported in the reference. (4) The equation is the "acceptable fish BAF model" reported in the reference.

The ranges of partition coefficients favorable for bioaccumulation are necessary, but not sufficient, for chemical bioaccumulation because rapid biotransformation elimination can substantially diminish a chemical's capability of bioaccumulation.[55,72,73] McLachlan *et al.*[55] found that chemical bioaccumulation in humans is more responsive to the change in biotransformation compared to partition coefficients: realistic variability in biotransformation half-life results in chemical bioaccumulation varying by 6 to 9 orders of magnitude, whereas realistic variability in partition coefficients results in around one order of magnitude variation in chemical bioaccumulation. Notably, when a chemical has a biotransformation half-life shorter than 700 hours (*i.e.*, a rate constant faster than 0.001 h^{-1}) in terrestrial mammals, it is unlikely to be bioaccumulative in humans regardless of the combination of partition coefficients.[55]

It should be noted that the empirical relationships outlined in Table 1 were developed a few decades ago. These empirical relationships estimate only the central tendency of BAF and BCF among chemicals sharing the same K_{OW}, without considering variability resulting from chemical-specific biotransformation rates. In fact, the above analysis by McLachlan *et al.*[55] brings into question the relevance of current bright-line criteria for partitioning tendency for bioaccumulation assessment aiming to protect human health, which underscores the need for explicitly considering chemical-specific biotransformation rates in bioaccumulation assessment.[45,74] The recent development of mechanistic physiologically based bioaccumulation models[35,45,46,74–80] for animals consumed by humans provides significant advancements for estimating bioaccumulation and exposure concentrations in food items. There is also a strong rationale to continue advancing methods to address uncertainty in estimating rates of biotransformation in various biota, including those that form the basis of human food chains.

In summary, chemicals with a high bioaccumulation potential in food items share the following features: resistance to biotransformation in organisms (with a biotransformation half-life longer than 700 hours), moderate hydrophobicity ($\log K_{OW}$ ranging from 5 to 8), and minimal volatility ($\log K_{OA}$ greater than 6). Compared to terrestrial animal-based foods, consumption of aquatic animals additionally contributes to human exposure to volatile chemicals ($\log K_{OA}$ smaller than 6); on the other hand, compared to aquatic animal-based foods, consumption of terrestrial animals additionally contributes to human exposure to relatively hydrophilic chemicals ($\log K_{OW}$ between 2 and 5).[52,64,66] Note that the thresholds of partitioning and reaction properties may vary between species or organisms living in different habitats because of differences in age, growth rate, prey behavior and diet composition, physiology, trophic levels, reproductive status, the temperature of the environment, and other features.[65,81–85]

4.1.2 Chemicals present in drinking water. Chemicals appear in drinking water when (i) they are readily transported in the aqueous environment from the sites of emission, and (ii) they are not efficiently resisted by natural barriers (*e.g.*, soils, riverbanks, and aquifers) or removed during regular water treatment procedures. Many polar and ionizable organic

chemicals share these features and cause environmental and health concerns for their high "mobility" in the aqueous environment.[90] Presently, the criteria for "mobility" are still under discussion. The most recent criterion is given by the German Federal Environment Agency,[91] which considers a chemical to be "mobile" if it has a low sorption potential to sediments and soils, *i.e.*, with an organic carbon normalized sorption coefficient log K_{OC} or log D_{OC} smaller than 4.0 over the pH range of 4–9. Since K_{OC} is linked to K_{OW} based on the Karickhoff sp-LFER, this cut-off can correspond roughly to a log K_{OW} or log D_{OW} smaller than 4.5 for screening or indication purposes alone.[92] One may be cautious about the use of log K_{OW} or log D_{OW} in assessments of polar and ionizable chemicals because the Karickhoff sp-LFER does not include polar chemicals in the training set and largely disregards ionic interactions with counterions in water or natural sorbents.[90,92,93] In addition, monitoring evidence has demonstrated that chemicals selected based on this cut-off may not necessarily appear in drinking water, and chemicals failing to meet this criterion can also reach the aqueous environment.[94,95]

4.1.3 Leaching or generation during food preparation. Chemicals of health concern can be generated during cooking. For instance, dioxins and polycyclic aromatic hydrocarbons are unintentional byproducts of combustion and thus can be detected in grilled, smoked, or roasted foods.[96,97] With the presence of chlorine from inorganic (*e.g.*, table salt) and organic sources (*e.g.*, chlorine-containing artificial sweeteners), dioxin-like polychlorinated biphenyls can be formed,[98] and polybrominated diphenyl ethers (PBDEs) in foods can be converted into mixed polychlorinated/brominated diphenyl ethers[99] and polybrominated dibenzofurans.[100] While the unintended formation of chemicals has been well documented in the literature, little has been done to link the occurrence of these compounds with their properties.

In addition, food preparation processes can also alter the level of chemicals existing in foods.[101] Several mechanisms may be responsible for such alteration: (i) chemicals with small molecular sizes (*e.g.*, a molar mass of ~300 g mol^{-1}) can be lost to volatilization due to the high temperature during cooking;[102] (ii) chemicals with low thermal stability, *e.g.*, BDE-209 and algae toxins, undergo thermal degradation during heating;[102,103] (iii) hydrophobic chemicals are extracted by cooking oil, which can be viewed as an "extraction solvent";[104] and (iv) hydrophobic chemicals can be removed along with the removal of lipid-rich skin because the skin is the main depository of these chemicals.[104,105]

Synthetic chemicals, such as phthalates and perfluoroalkyl substances, are often added to polymeric food contact materials (FCM) to improve the performance of FCMs. These chemicals may leach from FCMs during food storage, preparation, and delivery. Highly hydrophilic chemicals (with log K_{OW} < 2) are rarely used as additives because the incompatibility with polymers prevents their stable binding with polymeric matrices.[106] If found in FCMs, these hydrophilic chemicals are primarily residual unreacted monomers or degradation products of the polymeric matrices. In general, leaching migration is a diffusion process, governed largely by the molecule size (molar mass or molar volume) of the chemical of interest, the nature of the polymeric matrix, and the composition of food.[107–111] For instance, smaller molecules (with a molar mass smaller than 1000 g mol^{-1}) are more likely to migrate from FCMs to food due to their faster diffusion within polymeric matrices.[112] Compared to stiff-chain polymers like polyesters and polystyrene, flexible polymers like polyethylene provide higher "conductance" towards the diffusion of chemicals and favor the migration of chemicals.[113] In addition, the partition coefficient between polymeric FCMs and different types of food ($K_{P,F}$), which depends closely on the types of the polymer and food, also governs this migration.[114] Large $K_{P,F}$ values are desired for FCMs because leaching migration becomes negligible for chemicals with log $K_{P,F}$ greater than 3.[115] Empirical evidence has shown that $K_{P,F}$ is correlated well with K_{OW} (Fig. 3).[107,116] As such, this log $K_{P,F}$ threshold corresponds to a log K_{OW} between 6 to 10 (Fig. 2). Compared with lean or water-rich foods (*e.g.*, fruits and vegetables), fatty foods have a stronger sorption capacity for chemicals and favor the leaching migration of a wider range of chemicals, notably more hydrophobic ones, from FCMs (Fig. 3).[106]

4.1.4 Dust and surface residues. Residential and working environments are comprised of various surfaces, *e.g.*, painted walls and ceilings, vinyl flooring, carpet, polyurethane foams (PUFs), and impermeable or hard surfaces. On impermeable indoor surfaces, there usually exists a layer of greasy organic films, made up mainly of lowly volatile organic matters (log K_{OA}

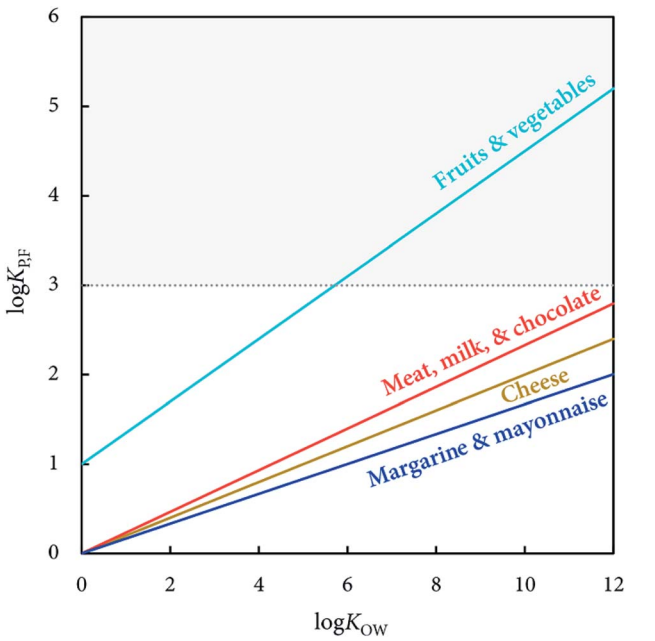

Fig. 3 Correlations of partition coefficients between polymeric food contact materials and different types of food ($K_{P,F}$) with the octanol–water partition coefficient (K_{OW}) (based on data provided in ref. 116). The gray area indicates chemicals (log $K_{P,F}$ > 3) with a negligible potential of leaching migration from food contact materials. When food-specific data are unavailable in food safety assessments, a conservative condition of log $K_{P,F}$ = 0 is recommended for all chemicals, meaning that the chemicals are very soluble in food.[107]

between 10 and 13) generated from human activities such as cooking (see Weschler and Nazaroff[117] and citations therein). Environmental chemicals are found on indoor surfaces, either bound to settled dust, *i.e.*, "particles in building interiors that have settled onto objects, surfaces, floors, and carpeting",[118] or as surface residues, *i.e.*, chemical molecules sorbed to an impervious surface (*e.g.*, glass and stainless steel), dissolving in the organic film, or penetrating shallowly into materials (*e.g.*, polymers making up the carpet and flooring).[119] Unintended hand-to-mouth and object-to-mouth contact mediates oral ingestion of dust and surface residues, *i.e.*, mouthing-mediated ingestion.[18,119]

Earlier studies have revealed that K_{OA} is a reasonable surrogate for describing the partitioning between indoor surfaces or dust and air (Table 2). In other words, indoor surfaces or dust can be approximated as consisting of a certain proportion of octanol, which plays a central role in governing the interphase distribution of chemicals.[120,121] Typically, indoor surfaces and dust have a considerable affinity for chemicals with high K_{OA} values. However, it should be emphasized that the empirical equations compiled in Table 2 may not apply to chemicals with extremely high K_{OA} values.[122,123] This is because when K_{OA} increases, the time required for the equilibrium partitioning of gaseous chemicals into these surface or dust phases also increases, which may exceed the residence of these phases in the indoor environment.[34,122,124] This phenomenon is prominent for dust because dust usually has a short residence in homes due to frequent cleanup. Kinetically speaking, the fraction of chemical mass in dust may not have sufficient time to equilibrate with its gas phase or *vice versa*. Such a "kinetic delay to achievement of equilibrium"[125] results in an asymptote limit for the dust–air partition coefficient, departing from the linear correlation with log K_{OA}, when log K_{OA} approaches 11 (corresponding to a vapor pressure lower than 10^5 Pa) and above.[122]

Fig. 4 shows that for chemicals with a log K_{OA} greater than ~6, over 80% of the chemical mass indoors is present in surface compartments. By contrast, chemicals with log K_{OA} smaller than 4 are too volatile to be abundant in surface compartments. Likewise, an earlier ballpark estimate also indicates that >99% of the indoor mass of chemicals with log K_{OA} greater than 8 can be found in surface compartments.[34] Therefore, poorly volatile chemicals are more likely to be found in dust or as surface residues.

A close inspection of the compiled empirical relationships in Table 2 indicates that dust generally has a higher affinity for chemicals, compared to indoor surface compartments, given that the dust–air partition coefficient (K_{DA}) is higher than other surface–air partition coefficients for most of the K_{OA} range. As such, compared to surface residues, dust is a more efficient vehicle for transferring chemicals from indoor surfaces to hands. For instance, for chemicals with a log K_{OA} between 6 and 10, >80% of the mass transferred from the surface to hands is dust bound.[119] After transfer to hands, chemicals can repartition between the skin (*e.g.*, lipids in the stratum corneum) and the dust thereon. Since the skin has a larger sorption capacity than dust, the majority mass fraction of chemicals would migrate to the skin. Meanwhile, chemicals bound to dust on hands are easily lost *via* abrasion with indoor surfaces. The abrasion loss is more pronounced for poorly volatile chemicals because they are more prone to be distributed in dust relative to volatile chemicals. Therefore, the majority (>50%) of chemicals transferred from hands to mouths are not dust bound. Dust-bound transfer contributes most to the hand-to-mouth transfer of moderately volatile chemicals with log K_{OA} from 5 to 9.[119]

Overall, mouthing-mediated ingestion, *i.e.*, the ingestion of dust-bound chemicals and/or surface residues through hand-to-mouth contact, is an important mechanism responsible for human exposure to poorly volatile chemicals. Existing studies indicate that mouthing-mediated ingestion matters most for

Table 2 Empirical relationships between octanol–air partition coefficient (K_{OA}) and partition coefficients between indoor phases and air[a]

Indoor phase	Correlation between partition coefficient and K_{OA}	Reference
Polymeric materials (M)	$K_{MA} = 0.06 \times K_{OA}$ ($n = 1273$, log K_{OA} from 2.0 to 18.7, $R^2 = 0.86$, RMSE = 1.21)	Reppas-Chrysovitsinos *et al.* (2016)[121]
Dust (D)	$\log K_{DA} = 0.860 \times \log K_{OA} - 0.086$ (1) ($n = 66$, $\log K_{OA}$ from 7.5 to 13.1, $R^2 = 0.78$)	Weschler and Nazaroff (2010)[123]
Carpet (C)	$\log K_{CA} = 0.931 \times \log K_{OA} - 2.408$ (2) ($n = 8$, $\log K_{OA}$ from 1.98 to 4.28)	Bennett and Furtaw (2004)[129]
Vinyl flooring (V)	$\log K_{VA} = 0.688 \times \log K_{OA} - 0.693$ (2) ($n = 13$, $\log K_{OA}$ from 2.74 to 8.67, $R^2 = 0.80$)	Bennett and Furtaw (2004)[129]
Cotton (C)	$\log K_{CA} = 0.248 \times \log K_{OA} + 4.447$ ($n = 13$, $\log K_{OA}$ from 7.97 to 12.2, $R^2 = 0.545$)	Saini *et al.* (2016)[130]
Steel (S)	$\log K_{SA} = 0.216 \times \log K_{OA} + 1.420$ (3) ($n = 7$, $\log K_{OA}$ from 10.7 to 14.5, $R^2 = 0.62$)	Saini *et al.* (2016)[131]
Organic film (F)	$\log K_{FA} = 1.100 \times \log K_{OA} - 0.540$ ($n = 62$, $\log K_{OA}$ from 6.8 to 10.6, $R^2 = 0.84$–0.98)	Csiszar *et al.* (2012)[132]

[a] (1) For a comprehensive review of empirical relationships between K_{DA} and K_{OA} (or vapor pressure), see Wei *et al.*[133] (2) Converted from empirical relationships expressed as functions of vapor pressure, based on an empirical relationship between K_{OA} and vapor pressure ($n = 222$, log K_{OA} from −0.95 to 11.89, $R^2 = 0.99$).[134] (3) K_{SA} is the ratio of area-specific chemical concentration on steel to volume-based concentration in the air. K_{SA} has a unit of *m*.

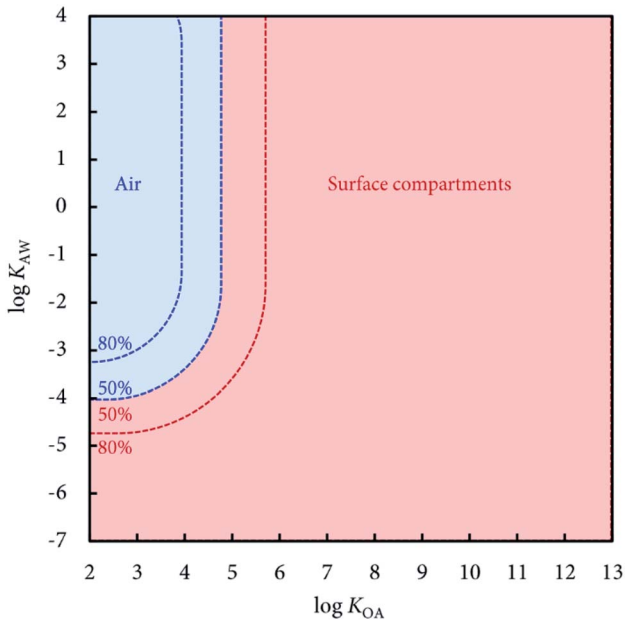

Fig. 4 Relative mass distribution of perfectly persistent chemicals between air and surface compartments (carpet, vinyl flooring, hard surfaces, walls, and the organic film) in an archetypal North American home, as a function of their octanol–air (K_{OA}) and air–water (K_{AW}) partition coefficients (or distribution ratios for ionizable organic chemicals). Diagonals from the top left to the bottom right of this partitioning space represent chemicals with the same log K_{OW}. The dashed contour lines represent K_{OA}–K_{AW} combinations leading 80% and 50% of the total mass to be distributed in the indoor air or surface compartments. The diagram builds on predictions from a comprehensive fate and exposure model named PROTEX.[24,126] As defined in the model, the carpet and vinyl flooring account for 60% and 40% of the indoor area, respectively, and the carpet contains 3% of water moisture. Chemicals (with a typical molar mass of 300 g mol^{-1}) are assumed to be released into the indoor air. Default parameters of PROTEX are used for modeling.

chemicals with log K_{OA} greater than 6 to 9.[119,127] Note that this K_{OA} threshold can differ between indoor environments containing different surface settings. For example, since PUF furniture has a higher sorptive capacity than other surface compartments, the K_{OA} threshold can be lower in rooms with a large surface covered by PUF furniture (log K_{OA} of ~6 for rooms with PUF[127] and of ~9 for rooms without PUF furniture[119]). This K_{OA} threshold also depends on the mode of chemical emission, *e.g.*, the initial release to the indoor air *versus* direct application to surfaces.[128] In addition, children tend to have a lower K_{OA} threshold than adults do because of the more frequent mouthing behavior.[13]

4.2 Absorption of environmental chemicals in the gastrointestinal tract

The absorption of ingested chemicals requires their migration from the lumen of the gastrointestinal tract (GIT) to the blood capillaries, passing through the epithelium of GIT, mainly the small intestine. GIT comprises a series of hollow organs (*e.g.*, esophagus, stomach, small and large intestines) that hold, transport, and digest food and/or other ingested items. When foods move in the GIT, the lipid and water contents keep declining due to digestion and absorption, which lowers the capability of the foods holding chemicals (*i.e.*, fugacity capacity) and thus increases the chemical contamination in food (*i.e.*, fugacity) relative to the human body.[135] This forms a gradient of fugacity between the digested food in the GIT lumen and blood capillaries, which drives the diffusion of chemicals through the lining of GIT.[17,135,136]

The lining facing the lumen (termed apical side) is a mucous membrane, or mucosa, which wrinkles and folds to form millions of 1 mm finger-like intestinal villi. Such a villus

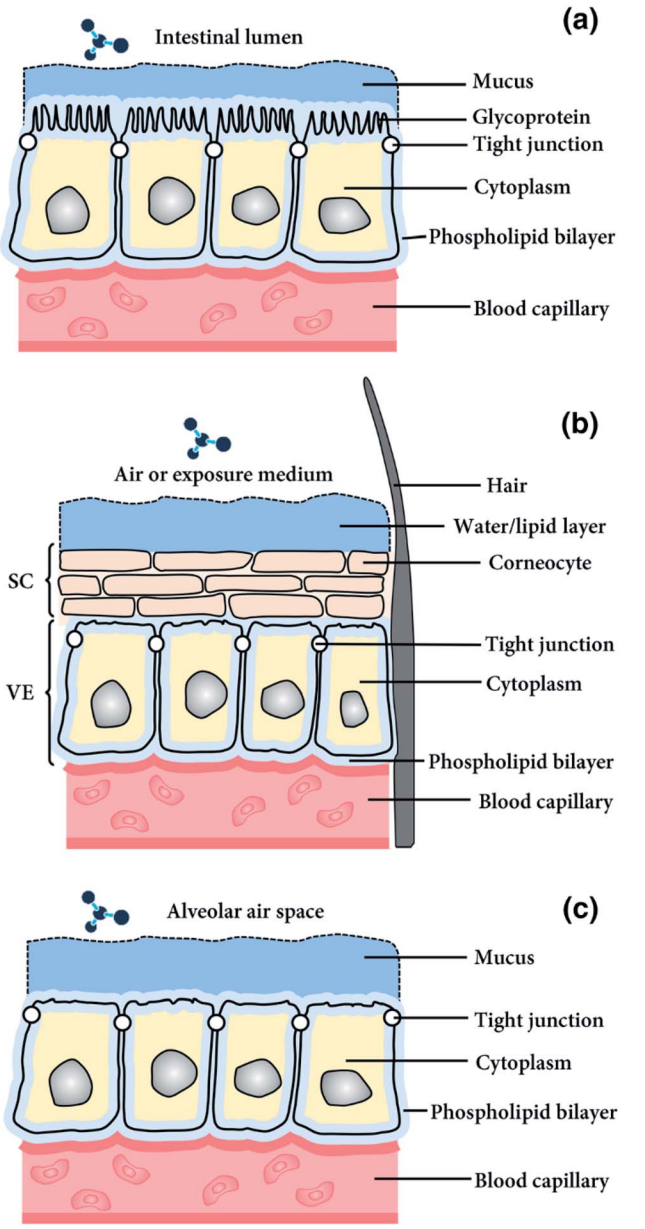

Fig. 5 The anatomical and physiological structure of absorption barriers: (Panel a) intestinal lining in the digestive system, (Panel b) epidermis (stratum corneum = SC; viable epidermis = VE) of the skin, and (Panel c) alveolar lining in the respiratory system. The size of each structure is illustrative and does not represent the actual size.

structure substantially increases the total internal surface area of the intestinal lining and facilitates the absorption of nutrients and environmental chemicals. Each villus comprises a layer of epithelial cells (epithelium) on the apical side, as well as numerous capillaries on the basal side that eventually merge into blood vessels (Fig. 5a). The epithelium comprises a cell membrane composed of two layers of amphiphilic phospholipid molecules (*i.e.*, phospholipid bilayer) and aqueous cytoplasm (Fig. 5a). The space between epithelial cells, *i.e.*, the intercellular space, is abundant in the water-rich interstitial fluid and has a low content of collagen fibers.[137] Adjacent epithelial cells are joined by a set of multiprotein structures called "tight junctions" (Fig. 5a), which have minimal porosity and resist the passage of large molecules through the intercellular space of epithelial cells.[138,139] In most cases, digested food is separated from the epithelium by a layer of mucus (Fig. 5a), which typically comprises water, electrolytes, lipids, and enzymes and is more acidic than the aqueous phase of the intestinal contents. While it is not entirely stationary, part of this layer of mucous flows in a slow, laminar manner parallel to the epithelium, which is often treated as a layer of stagnant water, named "unstirred water layer (UWL)" in the literature.[140] The thickness of UWL, which is not actual but operational, has been determined to be from 30–100 μm.[141] Immersed in the mucous are glycoproteins, which are mainly hydrophobic oligosaccharides bound to and protruding from the surface of the epithelium, similar to a brush border.[142] Therefore, to reach blood capillaries, environmental chemicals in the intestinal lumen need to traverse the UWL and epithelial cells (a "transcellular" route), while environmental chemicals with a small molecular size can additionally pass through the UWL and the intercellular space (a "paracellular" route).[139]

The absorption of exogenous chemicals is largely a diffusion process.[17,136] Both hydrophilic (UWL, the hydrophilic tail of phospholipids, and cytoplasm) and hydrophobic (glycoproteins, and the hydrophobic head of phospholipids) components in the GIT pose resistance to diffusion. Therefore, chemicals that are either highly hydrophobic (log K_{OW} greater than 7 to 9) or hydrophilic (log K_{OW} smaller than −1 to 0) are anticipated to have a reduced absorption efficiency.[143] In general, highly hydrophobic chemicals have low aqueous concentrations in the hydrophilic components, notably in the UWL, which makes the diffusion through the UWL very slow and the rate-limiting step.[17,144,145] Highly hydrophobic chemicals thus require a rather long time (from days to years) to cross the UWL,[144] which limits the absorption efficiency when the required time exceeds the residence of digested food in the GIT.[58] Therefore, absorption efficiency declines when log K_{OW} exceeds 7.[58,136] Here, we need to note that the lowered absorption of highly hydrophobic chemicals does not mean that a cut-off exists for K_{OW}, beyond which the GIT absorption would become impossible. In fact, the absorption of super hydrophobic chemicals is still possible, but the absorption efficiency is too low to be reliably measured. That is, the observed absence of absorption of super hydrophobic chemicals is simply an experimental artifact.[58] On the other hand, highly hydrophilic chemicals are also poorly absorbed because diffusion through the hydrophobic components in the GIT is the rate-limiting step.[143,146]

Bile salt micelles facilitate the diffusion of hydrophobic chemicals through the UWL.[147] Biles salts are amphiphilic molecules, with a hydrophobic four-ring-structure head and a hydrophilic carboxyl tail. Their neutral forms (protonated) are less soluble in water. Humans secrete bile salts to facilitate the absorption of lipids. Bile salt micelles enclose hydrophobic substances, such as monoglycerides, free fatty acids, fat-soluble vitamins, and hydrophobic organic chemicals, and their hydrophilic surfaces make them efficient at moving across the UWL.[17] For this reason, bile salt micelles act as a transport agent to ferry hydrophobic organic contaminants through the UWL. Since the UWL is more acidic than the aqueous phase of the GIT, bile salt micelles become more protonated and less stable when approaching the brush border of the epithelium.[17] This leads to their dissociation and the release of enclosed hydrophobic substances, including environmental chemicals, from the micelles.[148] The collision between micelles and epithelial cell membranes is also a possible reason for the release of hydrophobic substances.[149] After the release, these hydrophobic substances permeate through the epithelium as monomers.[148]

Since phospholipid bilayers are negatively charged, cationic chemicals are anticipated to have an elevated absorption efficiency compared to their neutral counterparts due to electrostatic interactions with the phospholipid bilayers.[150,151] Such cation-facilitated increase in absorption efficiency is more remarkable for highly hydrophobic chemicals.[150]

Other factors also impact absorption efficiency. For instance, absorption efficiency can be lowered due to luminal biotransformation, *i.e.*, degradation of chemicals in the GIT.[146,152–154] Notably, luminal biotransformation leads to a more pronounced reduction in absorption efficiency for hydrophobic chemicals relative to hydrophilic chemicals.[146] For this reason, the absorption efficiencies of highly persistent pollutants can be viewed as the upper bounds of absorption efficiencies for chemicals with similar hydrophobicity. Furthermore, an excessive number of hydrogen bond donors (mainly OH and NH groups) and/or hydrogen bond acceptors (mainly O and N), and a small polar surface area in chemicals also impair the GIT absorption.[155–157] For instance, a simple, empirical mnemonic in drug design called "the rule of five", which specifies cut-offs of indicators for poorly absorbed chemicals that are multiples of five, generalizes that a chemical with more than 5 hydrogen bond donors or 10 hydrogen bond acceptors tends to be poorly absorbed.[155] Finally, for hydrophobic chemicals, lean food has generally higher digestibility than fatty food, which creates a sharper fugacity gradient between the GIT lumen and blood capillaries and, hence, increases absorption efficiency.[135]

5. Dermal exposure

5.1 Contact of environmental chemicals with the skin

Environmental chemicals may take three main courses to reach the skin surface. The first is direct dermal contact with chemicals due to intentional application of consumer products (*e.g.*, cosmetics, pharmaceuticals, and personal care products),

accidental splashes, or contact with contaminated objects or articles.[23] A more recent research focus is the role of clothing in mediating dermal exposure:[158–161] freshly laundered, uncontaminated clothing materials sorb gaseous chemicals from the indoor air, protecting a person from dermal exposure, whereas previously exposed clothing materials can release slowly the sorbed chemicals for amplified, prolonged dermal exposure. Overall, this course is less relevant for highly volatile chemicals because they can either readily evaporate from the skin surface if applied on the skin,[162] or partition minimally into the clothing if present in the indoor air.[130] The second is the diffusion of gaseous chemicals to the proximity to the skin surface followed by dermal absorption.[20,21] The third is the absorption of chemicals in dust or surface residues adhered to the skin on the hand as a result of hand contact with contaminated surfaces or objects.[163–165] Here, the second course is relevant for volatile chemicals (with low K_{OA} smaller than 5, see Fig. 4) that are abundant in the gas phase, whereas the third course is the main mechanism for minimally volatile chemicals (with K_{OA} higher than 7 to 8 or low K_{AW}) because they have a strong affinity for dust and indoor surfaces.

After reaching the skin surface, environmental chemicals first cross a very thin (~1 μm) stagnant boundary layer adjoining the skin surface, which can be either a layer of water[22](in the cases of application of aqueous chemical solutions and/or with sweat) or lipids (*e.g.*, sebum secreted from sebaceous glands),[21,158] or their combination (Fig. 5b). There is a gradient in chemical abundance (*i.e.*, fugacity) between the stagnant boundary layer and the skin, which drives the transdermal permeation of the chemicals. Therefore, chemical solubility in this boundary layer is a critical factor controlling transdermal permeation, especially when crossing this boundary layer is the rate-limiting step for dermal absorption. For example, sweaty skin often demonstrates a low efficiency of sorbing gaseous hydrophobic chemicals from the indoor air because of their considerably low solubilities in water. In this situation, we can expect reduced transdermal permeation fluxes of hydrophobic chemicals, compared to their hydrophilic counterparts.[22] The presence of salts or grease may reduce chemical solubility in sweat (*i.e.*, the "salting out" effect) and thus reduce dermal absorption of gaseous chemicals.[166,167]

5.2 Absorption of environmental chemicals through transdermal permeation

The human skin has a laminar structure, with the two most important layers being the outermost epidermis (5% of the skin thickness) and the inner dermis (95% of the skin thickness). The epidermis contains no blood vessels, and its growth, development, and recovery largely depend on the nutritional support from the dermis, where blood capillaries and lymphatics are localized.[5] Dermal absorption means the transdermal permeation of chemicals and the penetration into the blood capillaries. The extent to which the chemical flux reaching the skin surface ends up in blood capillaries is quantified by a "permeability", typically with a unit of mass transfer coefficient (mass per time). From an anatomic perspective, the permeability of the epidermis governs the absorption efficiency of dermal exposure.

The epidermis contains two sublayers: the stratum corneum (25% of the epidermis thickness[22]) and viable epidermis (75% of the epidermis thickness) (Fig. 5b). The stratum corneum is composed of 15 to 20 layers of corneocytes (Fig. 5b), which are flattened cells (with aqueous cytoplasm) covered with a highly cornified envelope, filled with keratin (protein) filaments, and embedded in a lipid-like intercellular matrix that contains typically 45–50% ceramides, 25% cholesterol, 15% long-chain free fatty acids, and 5% other lipids.[168] The corneocytes are tightly interlocked with each other. By contrast, the viable epidermis consists of living cells, with the cell membrane composed of the phospholipid bilayer and water-rich cytoplasm (Fig. 5b). The intercellular space is filled with the water-rich interstitial fluid enmeshed in a network made by high contents of collagen fibers.[137]

Environmental chemicals take two main routes in transdermal permeation. First, with a "transcellular" route, environmental chemicals diffuse through corneocytes in the stratum corneum or living cells in the viable epidermis. Second, with a "paracellular" route, environmental chemicals diffuse through the hydrophobic intercellular space in the stratum corneum or the more hydrophilic interstitial fluids in the viable epidermis.[22] Other minor routes may also be responsible for transdermal permeation. For instance, chemicals can also permeate through appendageal structures such as hair follicles (Fig. 5b), sweat ducts, and sebaceous glands, even with orders of magnitude higher nominal permeabilities than penetration through stratum corneum at the beginning of absorption.[169] However, since the total area of these appendages accounts for less than 1% of the total skin area, such an appendageal route may not play a significant role in dermal absorption in most parts of the body. Lateral diffusion in the cell membranes of the viable epidermis is also hypothesized to be important.[170]

Within the stratum corneum, the lipid-like intercellular matrix poses resistance to the permeation of hydrophilic chemicals, while the protein-based corneocytes are more amphiphilic, allowing for the passage of both hydrophilic and hydrophobic chemicals.[171] Chemicals with larger molecular sizes may encounter higher resistance in diffusion within the corneocytes.[171] Therefore, if considering permeation resistance posed by the stratum corneum alone, we can expect a positive dependence of the permeability on hydrophobicity and a negative dependence on molecular weight or radius (Table 3; all Group I equations, as well as P_{SC} and P_{lip} for the lipid-like intercellular matrix and P_{OL} for protein-based corneocytes in Group II equations). However, the dependence of permeability on hydrophobicity can be limited by the resistance posed by the water-abundant viable epidermis, notably the aqueous cytoplasm, if a chemical becomes highly hydrophobic ($\log K_{OW} > 6$). Therefore, for highly hydrophobic chemicals, diffusion through the water-rich viable epidermis becomes the rate-limiting step (P_{AQ} in Group II equations in Table 3), and the permeability becomes no longer dependent on hydrophobicity. On the other hand, the transcellular route in both the stratum corneum (mainly the aqueous and protein components of corneocytes) and viable epidermis provides highly hydrophilic chemicals ($\log K_{OW} < -2$) with the possibility of

Table 3 Empirical relationships between skin permeability (P) and chemical properties. The collected empirical relationships are categorized into two groups. Group (I) considers the permeation resistance posed by the stratum corneum alone. Group (II) considers the permeation resistance posed by both the stratum corneum and viable epidermis. Parameters used in the equations: K_{OW}: octanol–water partition coefficient; MW: molar mass (in g mol^{-1}); r: molecular radius (in Angstrom); ABSQon: the sum of absolute charges on oxygen and nitrogen atoms; SsssCH: the sum of E-state indices for all methyl groups

Group	Empirical equation	Reference
I	$\log P$ (cm s^{-1}) = 0.71 $\log K_{OW}$ – 0.0061 MW–6.3 (n = 93, $\log K_{OW}$ from −3 to 6, MW from 18 to 750, R^2 = 0.67)	Potts and Guy (1992)[173]
I	$\log P$ (cm h^{-1}) = 0.77 $\log K_{OW}$ – 0.0103 MW–2.33 (n = 114, $\log K_{OW}$ from −4.82 to −1.52, R^2 = 0.67)	Cronin *et al.* (1999)[183]
I	P(cm s^{-1}) = 5.6 × 10^{-6} ($K_{OW}^{0.7}$) × exp (−0.46 r^2) (n = 23, $\log K_{OW}$ from 2 to 12, r^2 from 3 to 24 Angstrom^2; R^2 = 0.71)	Mitragotri (2002)[184]
I	$\log P$ (cm h^{-1}) = 0.74 $\log K_{OW}$ – 0.0091 MW–2.39 (n = 107, $\log K_{OW}$ from −3 to 6, R^2 = 0.86)	Moss and Cronin (2002)[185]
I	$\log P$ (cm h^{-1}) = 0.6646 $\log K_{OW}$ – 0.0056 MW–2.805 (ranges of $\log K_{OW}$ and MW should meet: −0.06831 ≤ 0.05616 $\log K_{OW}$ + 0.0005103 MW ≤ 0.5577, and −0.3010 ≤ 0.05616 $\log K_{OW}$ – 0.0005103MW ≤ 0.1758, R^2 = 0.66)	DERMWIN model implemented in EPI Suite[186,187]
I	$\log P$ (cm h^{-1}) = 0.652 $\log K_{OW}$ – 0.00603 MW–0.623 ABSQon – 0.313 SsssCH – 2.30 (n = 158, $\log K_{OW}$ from −1.43 to 4.78, R^2 = 0.83)	Patel *et al.* (2002)[176]
II	P (cm s^{-1}) = P_{CW}/(1 + B); where $\log P_{CW}$ (cm s^{-1}) = 0.71 $\log K_{OW}$ – 0.0061 MW–6.3, and B = (P_{CW} × 3600 × MW$^{0.5}$)/2.6 ($\log K_{OW}$ from −1.43 to 4, MW from 18 to 750, R^2 = 0.72)	Bunge and Cleek (1995)[188]
II	P (cm s^{-1}) = P_{CW}/(1 + B); where $\log P_{CW}$ (cm s^{-1}) = 0.7 $\log K_{OW}$ – 0.0722 MW$^{2/3}$–5.252, and B = (P_{CW} × 3600 × MW$^{0.5}$)/2.6 (n = 31, $\log K_{OW}$ from 1.4 to 12.1)	Weschler and Nazaroff (2012)[21]
II	P (cm h^{-1}) = 1/(1/P_{SC} + P_{OL}) +1/P_{AQ}); where $\log P_{SC}$ = 0.6097 $\log K_{OW}$ – 0.1786 MW$^{0.5}$–1.326, P_{OL} = 0.0001519/MW$^{0.5}$, and P_{AQ} = 2.5/MW$^{0.5}$ (n = 123, $\log K_{OW}$ from −3.58 to 5.58; MW from 18 to 764.9)	Wilschut *et al.* (1995)[189]
II	P (cm h^{-1}) = 1/(1/(P_{lip} + P_{OL}) +1/P_{AQ}), where $\log P_{lip}$ = 0.981 $\log K_{OW}$ – 0.0079 MW–2.69, P_{OL} = 0.0552/MW$^{1.38}$, and P_{AQ} = 1121/MW$^{1.96}$, (n = 182, $\log K_{OW}$ from −3.7 to 5.5; MW from 18 to 584)	ten Berge (2010)[190]
I	P (cm h^{-1}) = P_{lip} + P_{OL}, where $\log P_{lip}$ = 0.732 $\log K_{OW}$ – 0.00683 MW–2.59 P_{OL} = 0.043/MW$^{1.36}$ ($\log K_{OW}$ from −3.7 to 5.5; MW from 18 to 584)	IH SkinPerm model[191]

transdermal permeation. For these highly hydrophilic chemicals, molecular size, instead of K_{OW}, is the main determinant of permeability (see Group II equations in Table 3).

Like the case of GIT absorption efficiency, the hydrogen bonding character of a chemical can also add variability to permeability. For instance, empirical analyses have revealed that the strong ability of hydrogen bond donor and/or acceptor (*e.g.*, reflected by the charges of oxygen- and nitrogen-containing parts of a molecule) impairs the chemical's ability to permeate the skin, mostly the stratum corneum.[172–176]

The above empirical relationships are largely based on our understanding of the transdermal permeation of neutral compounds. More recent work shows that the dissociation of ionizable organic chemicals decreases transdermal permeation because charged molecules do not penetrate, as efficiently as neutral molecules, through the hydrophobic components in the epidermis, mostly the lipid layer in the stratum corneum.[177] For ionizable organic chemicals, one can simply assume that transdermal permeation is attributed to the fraction of neutral species alone[177] in the application of these empirical relationships.

It should also be noted that a chemical's permeability varies between skin conditions. For instance, the permeability is anticipated to increase if the skin temperature increases and blood flows faster.[178] The skin temperature may also affect the structural composition of the stratum corneum, especially the lipid content,[179,180] and thus alter the permeability. In addition, an increase in water content in the stratum corneum, *e.g.*, from a typical level of less than 20% to a high level of 50% due to the coverage of the skin by impermeable films like diapers and gloves (termed "occlusion"), can increase transdermal permeation of hydrophilic chemicals,[178,181] whereas dehydration lowers the transdermal permeation of hydrophilic chemicals.[182]

6. Respiratory exposure

6.1 Occurrence of environmental chemicals in the inhaled air

Airborne environmental chemicals are present simultaneously in gas (vapor) and particulate phases (aerosols, suspended dust,

liquid droplets, or powders). Both gas and particles are inhaled when humans breathe.

Chemicals enter the air mostly due to intentional or unintentional releases of gas and particles from various industrial, consumer, and waste disposal processes. Highly volatile chemicals (log K_{OA} smaller than 5, see Fig. 1 and 4) readily vaporize into the air from condensed indoor and outdoor compartments, with air to be the predominant compartment of occurrence. Particles containing chemicals may also enter the air because of physical processes, *e.g.*, abrasing the matrix of consumer articles, resuspending from surface media.

Particles consist of moisture and water-insoluble organic matter. Since the latter can be reasonably approximated by octanol, the sorption of chemicals onto particles can be well characterized by K_{OA} and K_{AW}:[192] Chemicals with high K_{OA} and low K_{AW} tend to be distributed in the particulate phase.[193,194] For instance, monitoring evidence has demonstrated excellent linear log–log dependence of the particle-gas partition coefficient (K_P in m^3 μg^{-1}) on K_{OA} for a broad range of chemicals.[193] However, for low-volatility chemicals (log K_{OA} greater than 11), log K_P becomes independent of log K_{OA} and approaches a constant between −2 and 0 when emissions occur in the gas phase.[195,196] This phenomenon is another example of the "kinetic delay":[125] compared with more volatile counterparts, minimally volatile chemicals require a much longer time to reach the equilibrium between the gas and particulate phases if initially released to the gas phase. Such an equilibrium status becomes impossible when this time exceeds the time scale of deposition removal of particle-sorbed chemicals. It should be noted that the "kinetic delay" is more pronounced for coarse particles than fine particles and is absent when emissions occur exclusively in the particulate phase.[34,196,197]

6.2 Absorption of environmental chemicals in the respiratory tract

Inhaled chemicals are deemed to be "absorbed" by humans when diffusing through the lining of the respiratory tract and entering the blood capillaries. The respiratory system can be segmented into two parts: the alveolar region contains a lining of thin epithelium that allows the diffusive exchange of gases with bloodstreams, such as oxygen, carbon dioxide, and volatile organic chemicals (the "respiratory" part), whereas the head (nasal-pharyngeal) and tracheobronchial regions conduct airflows without air exchange (the "conducting" part).[198] Specifically, the alveolar region contains a huge amount of pulmonary alveoli, which are tiny sacs with enormous surface areas for air exchange. Such surface-intensive structures make the alveolar region the main location for the absorption of environmental chemicals. Therefore, a chemical's ability to reach and leave within the alveolar region (*i.e.*, deposition efficiency) determines its overall absorption efficiency. Overall, gaseous chemicals can move freely through the airway, and it is safe to assume a deposition efficiency of 100% (ref. 23) in exposure assessments. By contrast, the deposition efficiency of particle-bound chemicals depends more on the size of the particle. Smaller particles penetrate more deeply into the respiratory system and thus have a higher deposition efficiency: for instance, spherical particles with a diameter smaller than 10 μm can readily reach the alveolar region, whereas the larger ones may be impeded and stuck in the head and tracheobronchial regions without being deposited.[199] In addition, not all particles reaching the alveolar region can be equally efficiently retained within this area: particles with an aerodynamic diameter smaller than 0.1 μm are most efficiently accumulated in the alveolar region, whereas those between 0.1 to 1 μm are poorly deposited.[199] Therefore, the deposition efficiency of particles also governs the absorption efficiency of chemicals on particles. Also, it is worth mentioning that particle-bound chemicals may desorb from particles on their way towards the alveolar region, and such desorption is more pronounced for highly volatile chemicals and for smaller particles (notably ultrafine particles).[200] The desorbed chemicals may be deposited in the head and tracheobronchial regions without absorption, or be exhaled immediately, which reduces their absorption efficiency.[201]

Four mechanisms are responsible for the absorption of inhaled chemicals in the alveolar region: (i) direct gaseous deposition, (ii) evaporative gas deposition, *i.e.*, the evaporation of chemicals initially present in particles before reaching the alveolar region, followed by gaseous transport and absorption in the alveolar region, (iii) particle deposition with evaporation, *i.e.*, evaporation of chemicals initially present in particles deposited in the alveolar region, followed by gaseous absorption, and (iv) particle deposition with direct diffusion into the alveolar tissue.[202] Specifically, mechanisms (i) and (ii) are pronounced for volatile chemicals. For example, assuming a typical particle mass fraction of 150 μg m^{-3}, we can roughly estimate that more than 75% of the inhaled mass of neutral chemicals with log K_{OA} smaller than 10 is present in the gas phase, based on the K_P–K_{OA} relationship as described above. Therefore, no matter whether they are inhaled as vapor or particles, these chemicals can readily find their way to the gas phase and become available for mechanisms (i) and (ii). These two mechanisms are less efficient for ionized chemicals, *e.g.*, protonated pronicotine,[202,203] because they are minimally volatile and strongly sorbed onto particles. On the other hand, since mechanisms (iii) and (iv) are mediated by particle deposition, they depend more on the size-dependent efficiency of particle deposition, as described above.

The inner lining of a pulmonary alveolus is a layer of epithelial cells, with their cell membrane composed of the amphiphilic phospholipid bilayer (Fig. 5c). Like the GIT epithelium, the intercellular space between pulmonary epithelial cells is filled with the water-rich interstitial fluid and rather low contents of collagen fibers.[137] Neighboring epithelial cells are also locked by tight junctions, which have minimal porosity and resist the passage of large molecules.[138,139] Blood capillaries are distributed on the basal side of the epithelium. On the apical side, there is a lining of water-rich mucus, consisting of 97% water with 3% of salts, lipids, proteins, and cellular debris.[204] This layer of mucus can also be seen as the stagnant UWL. Relatively hydrophilic chemicals (with log K_{AW} smaller than −1) tend to dissolve efficiently into the mucus.[201] Specifically, super hydrophilic chemicals (log K_{AW} smaller than −4) are

readily captured by mucus in the head and tracheobronchial regions, which prevents them from approaching the deeper alveolar region and reduces their absorption. By contrast, moderately hydrophilic chemicals (with log K_{AW} between −4 and −1) have a higher absorption efficiency because they can reach the alveolar region and then dissolve in alveolar mucus.[201] Relatively hydrophobic chemicals (log K_{AW} > −1) are poorly absorbed because they are less efficient at diffusing through alveolar mucus.

Furthermore, the physical state of environmental chemicals impacts their dissolution in the mucus layer: compared to their gaseous counterparts, chemicals bound to dust or aerosols are less dissoluble because desorption from dust or aerosols is the rate-limiting step.[205] Therefore, compared to volatile chemicals with the same hydrophilicity, minimally volatile chemicals (log K_{OA} > 9) demonstrate a reduced absorption efficiency if they are present predominantly in the particulate phase of inhaled air.[201] By contrast, for volatile chemicals, the absorption efficiency differs little regardless of whether it is inhaled as the gaseous or particulate phase.[201] In addition, chemicals that can hardly desorb from dust or aerosols may be engulfed by alveolar macrophages without absorption.[205] The dissolution of chemicals in mucus creates a gradient of chemical concentration from alveolar ducts to capillaries, which drives the movement of chemicals through the pulmonary epithelium.

Similar to the cases of GIT and transdermal permeation, environmental chemicals may take two routes to permeate the epithelium: A "transcellular" route describes the traverse of chemicals across the entire epithelial cells, and a "paracellular" route describes the traverse of chemicals through the intercellular space. Hydrophobic components in the epithelium (*e.g.*, the hydrophobic head of phospholipids) resist the permeation of highly hydrophilic chemicals, whereas hydrophilic components (*e.g.*, UWL, the hydrophilic tail of phospholipids, and cytoplasm) resist the permeation of highly hydrophobic chemicals. For these reasons, chemicals with a moderate log K_{OW} value (between 0 and 4) are most efficiently absorbed in the respiratory tract.[205]

In summary, volatile and moderately hydrophilic chemicals tend to be readily absorbed, since volatility leads to efficient migration to alveolar mucus and moderate hydrophilicity leads to efficient diffusion across the mucus. Chemicals that are either minimally volatile or hydrophobic would have a reduced absorption efficiency in the lung.[201]

7. Summary and future directions

This article compiles the state-of-the-art understandings of the impacts of chemical properties on human exposure to chemicals through oral ingestion, inhalation, and dermal contact and absorption. A synthesis of these discrete understandings provides us with an integrative overview of the relative importance of different exposure routes as a function of chemical properties. For instance, Fig. 6 visualizes the dependence of ingestion of foods contaminated through bioaccumulation (dietary ingestion), ingestion of settled dust and surface residues (mouthing-mediated ingestion), dermal absorption, and inhalation of indoor air to an adult's uptake of chemicals released indoors on their partitioning coefficients K_{OA} and K_{AW}, estimated by a comprehensive human exposure model called PROTEX (using the similar approach as used in ref. 13). As Fig. 6 displays, inhalation of indoor air is the predominant mechanism for human exposure to volatile chemicals; mouthing-mediated ingestion is the most relevant contributor to human exposure to minimally volatile chemicals; dermal absorption is important for human exposure to highly hydrophilic chemicals. Notably, when chemicals are assumed to be perfectly persistent in the environment, dietary exposure through the outdoor environment matters for chemicals with intermediate hydrophobicity and low volatility, even if emissions occur exclusively indoors. In future exposure assessments, new chemicals can be placed as dots in this diagram, based on their partition properties, which provides us with quick, convenient insights into the dominant exposure pathways of specific chemicals. One can also compare such visualized results between chemicals with different extents of environmental persistence, between neutral and dissociable chemicals, and between human receptors differing in age, race/ethnicity, and gender.

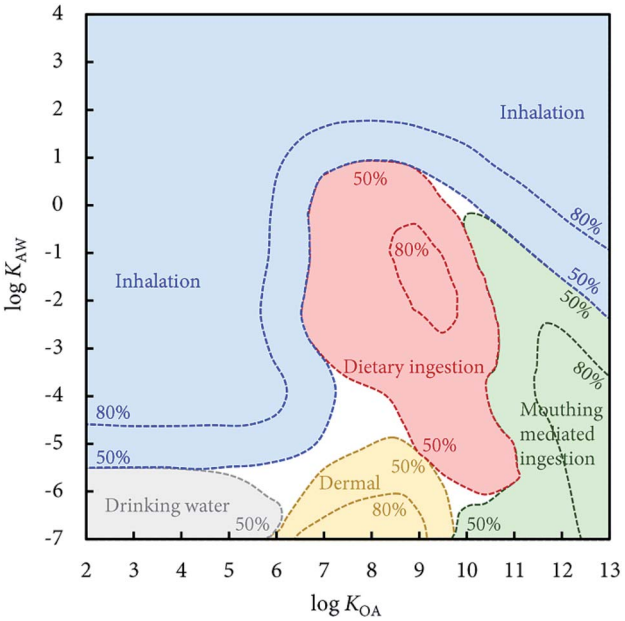

Fig. 6 Relative importance of ingestion of foods contaminated through bioaccumulation (dietary ingestion), ingestion of settled dust and surface residues (mouthing-mediated ingestion), dermal absorption, drinking water, and inhalation of indoor air in an archetypal adult American's uptake of chemicals released indoors, as a function of their octanol–air (K_{OA}) and air–water (K_{AW}) partition coefficients (or distribution ratios for ionizable organic chemicals). Diagonals from the top left to the bottom right of this partitioning space represent chemicals with the same log K_{OW}. The dashed contour lines represent K_{OA}–K_{AW} combinations leading 80% and 50% of the total mass to be taken up through an exposure route. The diagram builds on predictions from a comprehensive fate and exposure model named PROTEX.[24,126] Chemicals (with a typical molar mass of 300 g mol^{-1}) are assumed to be released into the indoor air and then diffuse to the outdoor environment to contaminate the food webs and drinking water. Default parameters of PROTEX are used for modeling.

Nevertheless, current understandings of human exposure are still limited, which warrants the following future efforts.

First, there is a continuous demand for more detailed information to further elucidate the complex processes governing external and internal exposures to environmental chemicals. Although the use of properties related to partitioning, dissociation, transport, and reaction, discussed in this article, enables us to capture and interpret the general trend in human exposure observations, they may not suffice to explain all variabilities in human exposure to chemicals. For instance, it may be overly simplistic to attribute variability in absorption efficiency to variations in partition coefficients and biotransformation, given that the size, configuration, polarity, and electrostatic status of molecules may also be important determinants of their permeability.[150,206] It is valuable to introduce a broader range of chemical properties and finer segmentation of the entire production-to-exposure continuum to maximize the coverage of variability in human exposure to chemicals.

Second, while the use of sp-LFER based on the ternary air–water–octanol system is straightforward, these empirical relationships are often limited to certain specific chemical categories with quite narrow domains of applicability. Extrapolating these empirical relationships to the huge universe of chemicals is problematic and inappropriate. Instead, well-calibrated polyparameter linear free energy relationships (pp-LFER) often outperform equally well-calibrated sp-LFER, since pp-LFERs account for a diversity of molecular interactions and have more degrees of freedom for characterizing variability.[207–209] Future efforts in expanding the use of pp-LFER in characterizing partition tendency will be commendable. We also encourage measuring and using partition coefficients for specific phase combinations, rather than correlations with K_{OA}, K_{AW}, and K_{OW}, in chemical exposure studies. For instance, information is currently insufficient regarding the extent to which many chemicals (*e.g.*, perfluoroalkyl acids[210]) are bound to phospholipids and proteins and their relative importance in governing the absorption, distribution, metabolism, and excretion of chemicals.

Third, it is still challenging to predict the partition, reaction, dissociation properties for many chemicals present in the environment, limiting our ability to predict their behavior in the environment and human body. For instance, for commercial chemicals, while their behaviors in the gas phase, *e.g.*, hydroxylation and ozonization, are relatively well predicted, their multiphase chemistry is currently poorly characterized.[211] Presently, QSAR models can reasonably predict only the biodegradation half-lives of hydrocarbons in water.[50,212] Computational tools are still lacking for the biodegradation of the rest of the tens of thousands of chemicals in the aqueous environment. It also remains unknown the relationship between the biodegradation rate in water and in other environmental media, as the current inter-medium extrapolation factors (*e.g.*, degradation half-lives are assumed to be 1 : 1 : 4 (ref. 213), 1 : 2 : 9 (ref. 214) or 1 : 2 : 10 (ref. 215) in water, soil, and sediment, respectively) are derived from a very small group of chemicals, mostly persistent organic pollutants. Also, model predictions of pK_a remain highly uncertain; a prominent example is the large variability in predicted pK_a values for perfluoroalkyl carboxylic acids.[216] In addition, there is a lack of modeling tools to quantify the permeability of chemicals through various absorption barriers, *e.g.*, intestinal and pulmonary epithelia. For these reasons, we also encourage the efforts to develop, evaluate, and apply new approach methodologies (NAMs),[217] *e.g.*, QSARs, high-throughput *in vitro* assays, and machine learning techniques, for quantifying chemical properties and characterize the uncertainty associated with the quantifications.

Fourth, there is a paucity of experimental data for chemicals with extreme properties for generalizing meaningful, solid conclusions. An example is the scarcity of measurements of absorption efficiency,[146] bioaccumulation potential,[89] and toxicokinetics[58] of super hydrophobic chemicals with $\log K_{OW}$ greater than 8. For these chemicals, current understandings build largely on limited numbers of measurements, which are uncertain and insufficient. As well, we should recognize challenges in observing or measuring the fate and behavior of chemicals with extreme properties. Environmental monitoring, biomonitoring, and instrumental analysis expertise are in urgent need in this regard.

Lastly, little is known about how the interaction between chemical properties, mode of emissions, and human behavior shapes human exposure to various chemicals. For instance, the prevalence of colored areas in Fig. 6 indicates that chemical properties play the sole leading role in determining the most predominant exposure pathway for most combinations of partition coefficients. That is, the identified most relevant exposure pathway is almost fixed regardless of variability in human behavior, as long as a chemical is released indoors. However, for chemicals located close to the edge of a colored area, the relative importance of exposure pathways may be reversed if a change occurs to human behavior and the mode of emissions, *e.g.*, a switch from indoor to outdoor emissions. A case is PCB-28, which is located near the border between areas of inhalation and dietary ingestion: Inhalation dominated aggregate exposure of adults for years with indoor PCB use, but dietary ingestion took the lead immediately after the ban of indoor use.[24] By contrast, the diet has always been the largest source of exposure of adults to PCB-153, which is located far from the border, throughout the time regardless of its indoor use.[24] Therefore, a holistic method is warranted to characterize comprehensively and reasonably the impact of mode of emissions and human behavior on exposure to these variable chemicals, which thus necessitates tools that mechanistically integrate emissions, fate, exposure, and risks, *e.g.*, the recent PROTEX[24,126] and PROTEX-HT[218] models. In addition, recognizing the fact that many commercial chemicals are "multimedia and multi-route" in nature largely because of their diverse chemical properties, regulatory agencies would be well-served to transition from the management of medium-specific contamination to a more integrated chemical management framework.

Conflicts of interest

There are no conflicts to declare.

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References

1 Centers for Disease Control and Prevention, *National Health and Nutrition Examination Survey Data*, available at: https://www.cdc.gov/nchs/nhanes/index.htm, accessed on May 1, 2021.

2 M. M. Plassmann, S. Fischer and J. P. Benskin, Nontarget Time Trend Screening in Human Blood, *Environ. Sci. Technol. Lett.*, 2018, **5**, 335–340, DOI: 10.1021/acs.estlett.8b00196.

3 R. Vermeulen, E. L. Schymanski, A.-L. Barabási and G. W. Miller, The Exposome and Health: Where Chemistry Meets Biology, *Science*, 2020, **396**(6476), 392–396.

4 K. K. Dennis, E. Marder, D. M. Balshaw, Y. Cui, M. A. Lynes, G. J. Patti, S. M. Rappaport, D. T. Shaughnessy, M. Vrijheid and D. B. Barr, Biomonitoring in the Era of the Exposome, *Environ. Health Perspect.*, 2017, **502**(4), 502–510.

5 T. M. Attina, R. Hauser, S. Sathyanarayana, P. A. Hunt, J. Bourguignon, J. P. Myers, J. Digangi, R. T. Zoeller and L. Trasande, Exposure to Endocrine-Disrupting Chemicals in the USA: A Population-Based Disease Burden and Cost Analysis, *LANCET Diabetes Endocrinol*, 2016, **4**(12), 996–1003.

6 L. Trasande, R. T. Zoeller, U. Hass, A. Kortenkamp, P. Grandjean, J. P. Myers, J. Digangi, M. Bellanger, R. Hauser, J. Legler, N. E. Skakkebaek and J. J. Heindel, Estimating Burden and Disease Costs of Exposure to Endocrine-Disrupting Chemicals in the European Union, *J. Clin. Endocrinol. Metab.*, 2015, **100**(4), 1245–1255.

7 P. J. Landrigan, R. Fuller, N. J. R. Acosta, O. Adeyi, R. Arnold, N. N. Basu, A. B. Baldé, R. Bertollini, V. Fuster, M. Greenstone and A. Haines, The *Lancet* Commissions The Lancet Commission on Pollution and Health, *Lancet Comm.*, 2017, **6736**(17), 462–512.

8 UN Environment Programme, *The Second Edition of the Global Chemicals Outlook*, available at: https://www.unep.org/explore-topics/chemicals-waste/what-we-do/policy-and-governance/global-chemicals-outlook, accessed on May 1, 2021.

9 U.S. Environmental Protection Agency, *Guidelines for Human Exposure Assessment*, available at: https://doi.org/https://www.epa.gov/risk/guidelines-human-exposure-assessment, accessed on May 1, 2021.

10 P. P. Egeghy, L. S. Sheldon, K. K. Isaacs, H. Özkaynak, M. Goldsmith, J. F. Wambaugh, R. S. Judson and T. J. Buckley, Computational Exposure Science: An Emerging Discipline to Support, *Environ. Health Perspect.*, 2016, **124**(6), 697–702.

11 G. Giovanoulis, T. Bui, F. Xu, E. Papadopoulou, J. A. Padilla-sanchez, A. Covaci, L. S. Haug, A. P. Cousins, J. Magnér, I. T. Cousins and C. A. D. de Wit, Multi-Pathway Human Exposure Assessment of Phthalate Esters and DINCH, *Environ. Int.*, 2018, **112**, 115–126.

12 M. Wormuth, M. Scheringer, M. Vollenweider and K. Hungerbühler, What Are the Sources of Exposure to Eight Frequently Used Phthalic Acid Esters in Europeans?, *Risk Analysis*, 2006, **26**(3), 803–824.

13 L. Li, J. A. Arnot and F. Wania, How Are Humans Exposed to Organic Chemicals Released to Indoor Air, *Enivronmental Sci. Technol.*, 2019, **53**(19), 11276–11284.

14 L. Li and D. Li, Inter-Individual Variability and Relationship in Assessing Human Health Impact From Chemicals in LCA: Addressing Uncertainties in Exposure and Toxicological Susceptibility, *Frontiers in Sustainability*, 2021, **2**, 648138.

15 E. Underman, T. N. Brown, M. S. McLachlan and F. Wania, Who in the World Is Most Exposed to Polychlorinated Biphenyls? Using Models to Identify Highly Exposed Populations, *Environ. Res. Lett.*, 2018, **13**(6), 064036.

16 C. L. Ring, J. A. Arnot, D. H. Bennett, P. P. Egeghy, P. Fantke, L. Huang, K. K. Isaacs, O. Jolliet, K. A. Phillips, P. S. Price, H. -M. Shin, J. N. Westgate, W. Setzer and J. F. Wambaugh, Consensus Modeling of Median Chemical Intake for the U.S. Population Based on Predictions of Exposure Pathways, *Environ. Sci. Technol.*, 2019, **53**, 719–732.

17 B. C. Kelly, F. A. P. C. Gobas and M. S. McLachlan, Intestinal Absorption and Biomagnification of Organic Contaminants in Fish, Wildlife, and Human, *Environ. Toxicol. Chem.*, 2004, **23**(10), 2324–2336.

18 J. Moya and L. Phillips, A Review of Soil and Dust Ingestion Studies for Children, *J. Exposure Sci. Environ. Epidemiol.*, 2014, **24**(6), 545–554.

19 W. Wei, N. Bonvallot, Å. Gustafsson, G. Ra, P. Glorennec, A. Krais, O. Ramalho, B. Le and C. Mandin, Bioaccessibility and Bioavailability of Environmental Semi-Volatile Organic Compounds *via* Inhalation: A Review of Methods and Models, *Environ. Int.*, 2018, **113**, 202–213.

20 C. J. Weschler and W. W. Nazaroff, Dermal Uptake of Organic Vapors Commonly Found in Indoor Air, *Environ. Sci. Technol.*, 2014, **48**(2), 1230–1237.

21 C. J. Weschler and W. W. Nazaroff, SVOC Exposure Indoors: Fresh Look at Dermal Pathways, *Indoor Air*, 2012, **22**(5), 356–377.

22 T. N. Brown, J. M. Armitage, P. Egeghy, I. Kircanski and J. A. Arnot, Dermal Permeation Data and Models for the Prioritization and Screening-Level Exposure Assessment of Organic Chemicals, *Environ. Int.*, 2016, **94**, 424–435.

23 L. Huang, A. Ernstoff, P. Fantke, S. A. Csiszar and O. Jolliet, A Review of Models for Near- Field Exposure Pathways of Chemicals in Consumer Products, *Sci. Total Environ.*, 2017, **574**, 1182–1208.
24 L. Li, J. Arnot and F. Wania, Revisiting the Contributions of Far- and Near-Field Routes to Aggregate Human Exposure to Polychlorinated Biphenyls (PCBs), *Environ. Sci. Technol.*, 2018, **52**(12), 6974–6984.
25 H.-M. Shin, T. E. McKone and D. H. Bennett, Model Framework for Integrating Multiple Exposure Pathways to Chemicals in Household Cleaning Products, *Indoor Air*, 2016, **27**(4), 829–839.
26 P. Fantke, A. S. Ernstoff, L. Huang, S. A. Csiszar and O. Jolliet, Coupled Near-Field and Far-Field Exposure Assessment Framework for Chemicals in Consumer Products, *Environ. Int.*, 2016, **94**, 508–518.
27 I. Cousins and D. Mackay, Correlating the Physical-Chemical Properties of Phthalate Esters Using the "Three Solubility" Approach, *Chemosphere*, 2000, **41**(9), 1389–1399.
28 D. Mackay, A. K. D. Celsie and J. M. Parnis, The Evolution and Future of Environmental Partition Coefficients, *Environ. Rev.*, 2016, **113**, 101–113.
29 J. G. Cole and D. Mackay, Correlating Environmental Partitioning Properties of Organic Compounds: The Three Solubility Approach, *Environ. Toxicol. Chem.*, 2000, **19**(2), 265–270.
30 A. Beyer, F. Wania, T. Gouin, D. Mackay and M. Matthies, Selecting Internally Consistent Physicochemical Properties of Organic Compounds, *Environ. Toxicol. Chem.*, 2002, **21**(5), 941–953.
31 T. F. M. Rodgers, J. O. Okeme, J. M. Parnis, K. Girdhari, T. F. Bidleman, Y. Wan, L. M. Jantunen and M. L. Diamond, Novel Bayesian Method to Derive Final Adjusted Values of Physicochemical Properties: Application to 74 Compounds, *Environ. Sci. Technol.*, 2021, DOI: 10.1021/acs.est.1c01418.
32 U. Schenker, M. Macleod, M. Scheringer and K. Hungerbühler, Improving Data Quality for Environmental Fate Models: A Least-Squares Adjustment Procedure for Harmonizing Physicochemical Properties of Organic Compounds, *Environ. Sci. Technol.*, 2005, **39**(21), 8434–8441.
33 J. L. Tymoczko, J. M. Berg and L. Stryer, *Biochemistry: A Short Course*, ed. W. H. Freeman, New York, NY, 3rd edn, 2013.
34 C. J. Weschler and W. W. Nazaroff, Semivolatile Organic Compounds in Indoor Environments, *Atmos. Environ.*, 2008, **42**(40), 9018–9040.
35 J. M. Armitage, J. A. Arnot, F. Wania and D. Mackay, Development and Evaluation of Mechanistic Bioconcentration Model for Ionogenic Organic Chemicals in Fish, *Environ. Toxicol. Chem.*, 2013, **32**(1), 115–128.
36 S. Endo, B. I. Escher and K. Goss, Capacities of Membrane Lipids to Accumulate Neutral Organic Chemicals, *Environ. Sci. Technol.*, 2011, **45**(14), 5912–5921.
37 W. Schmitt, General Approach for the Calculation of Tissue to Plasma Partition Coefficients, *Toxicol. In Vitro*, 2008, **22**(2), 457–467.
38 Q. Al-Awqati, One Hundred Years of Membrane Permeability: Does Overton Still Rule?, *Nat. Cell Biol.*, 1999, **1**, E201–E202.
39 R. P. Schwarzenbach, P. M. Gschwend and D. M. Imboden, *Environmental Organic Chemistry*, John Wiley & Sons, Hoboken, NJ, 2nd edn, 2003.
40 S. Trapp, A. Franco and D. Mackay, Activity-Based Concept for Transport and Partitioning of Ionizing Organics, *Environ. Sci. Technol.*, 2010, **44**(16), 6123–6129.
41 J. E. Birdwell and T. R. Marrero, Estimating Molecular Diffusivities in Environmental Media, in *Handbook of Chemical Mass Transport in the Environment*, ed. L. Thibodeaux and D. Mackay, CRC Press, Boca Raton, FL, 2011, pp. 71–101.
42 R. Boethling, K. Fenner, P. Howard, G. Klecka, T. Madsen, J. R. Snape and M. J. Whelan, Environmental Persistence of Organic Pollutants: Guidance for Development and Review of POP Risk Profiles, *Integr. Environ. Assess. Manage.*, 2009, **5**(4), 539–556.
43 I. T. Cousins, C. A. Ng, Z. Wang and M. Scheringer, Why Is High Persistence Alone a Major Cause of Concern?, *Environ. Sci.: Processes Impacts*, 2019, **21**, 781–792.
44 D. T. H. Sijm, G. Schaap and A. Opperhuizen, The Effect of the Biotransformation Inhibitor Piperonylbutoxide on the Bioconcentration of 2,8-Dichlorodibenzo-*p*-Dioxin and Pentachlorobenzene in Goldfish, *Aquat. Toxicol.*, 1993, **27**(3–4), 345–359.
45 J. A. Arnot, D. Mackay and M. Bonnell, Estimate Metabolic Biotransformation Rates in Fish from Laboratory Data, *Environ. Toxicol. Chem.*, 2008, **27**(2), 341–351.
46 J. W. Nichols, D. B. Huggett, J. A. Arnot, P. Fitzsimmons and C. E. Cowan-Ellsberry, Toward Improved Models for Predicting Bioconcentration of Well-Metabolized Compounds by Rainbow Trout Using Measured Rates of *In Vitro* Intrinsic Clearance, *Environ. Toxicol. Chem.*, 2013, **32**(7), 1611–1622.
47 J. A. Arnot, W. Meylan, J. Tunkel, P. H. Howard, D. Mackay, M. Bonnell and R. S. Boethling, A Quantitative Structure-Activity Relationship for Predicting Metabolic Biotransformation Rates for Organic Chemicals in Fish, *Environ. Toxicol. Chem.*, 2009, **28**(6), 1168–1177.
48 T. N. Brown, J. A. Arnot and F. Wania, Iterative Fragment Selection: A Group Contribution Approach to Predicting Fish Biotransformation Half-Lives, *Environ. Sci. Technol.*, 2012, **46**(15), 8253–8260.
49 E. Papa, L. van de Wal, J. A. Arnot and P. Gramatica, Metabolic Biotransformation Half-Lives in Fish: QSAR Modeling and Consensus Analysis, *Sci. Total Environ.*, 2014, **470–471**, 1040–1046.
50 K. Mansouri, C. M. Grulke, R. S. Judson and A. J. Williams, OPERA Models for Predicting Physicochemical Properties and Environmental Fate Endpoints, *J. Cheminform.*, 2018, **10**, 10.
51 V. Zartarian, T. Bahadori and T. O. M. Mckone, Adoption of an Official ISEA Glossary, *J. Exposure Sci. Environ. Epidemiol.*, 2005, **15**(1), 1–5.

52 B. C. Kelly, M. G. Ikonomou, J. D. Blair, A. E. Morin and F. A. P. C. Gobas, Food Web-Specific Biomagnification of Persistent Organic Pollutants, *Science*, 2007, **236**, 236–239.
53 J. A. Arnot and D. Mackay, Policies for Chemical Hazard and Risk Priority Setting: Can Toxicity , and Quantity Information Be Combined?, *Environ. Sci. Technol.*, 2008, **42**(13), 4648–4654.
54 J. A. Arnot and F. A. P. C. Gobas, A Food Web Bioaccumulation Model for Organic Chemicals in Aquatic Ecosystems, *Environ. Toxicol. Chem.*, 2004, **23**(10), 2343–2355.
55 M. S. McLachlan, G. Czub, M. MacLeod and J. A. Arnot, Bioaccumulation of Organic Contaminants in Humans: A Multimedia Perspective and the Importance of Biotransformation, *Environ. Sci. Technol.*, 2011, **45**(1), 197–202.
56 F. A. P. C. Gobas, W. D. Wolf, L. P. Burkhard, E. Verbruggen and K. Plotzke, Revisiting Bioaccumulation Criteria for POPs and PBT Assessments, *Integr. Environ. Assess. Manage.*, 2009, **5**(4), 624–637.
57 UN Environment Programme, *Stockholm Convention on Persistent Organic Pollutants*, available athttp://www.pops.intaccessed on Jun 2, 2021.
58 W. Larisch and K.-U. Goss, Modeling Oral Uptake of Hydrophobic and Super-Hydrophobic Chemicals in Fish, *Environ. Sci.: Processes Impacts*, 2017, **20**(1), 98–104.
59 European Chemicals Agency, *Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11, PBT/VPvB Assessment (Version 3.0)*, 2017.
60 J. A. Arnot, M. I. Arnot, D. Mackay, Y. Couillard, D. Macdonald, M. Bonnell and P. Doyle, Molecular Size Cutoff Criteria for Screening Bioaccumulation Potential: Fact or Fiction?, *Integr. Environ. Assess. Manage.*, 2009, **6**(2), 210–224.
61 J. A. Arnot and F. A. P. C. Gobas, A Review of Bioconcentration Factor (BCF) and Bioaccumulation Factor (BAF) Assessments for Organic Chemicals in Aquatic Organisms, *Environ. Rev.*, 2006, **14**, 257–297.
62 A. Ebert, C. Hannesschlaeger, K. Goss and P. Pohl, Passive Permeability of Planar Lipid Bilayers to Organic Anions, *Biophys. J.*, 2018, **115**(10), 1931–1941.
63 A. Kierkegaard, M. Sundbom, B. Yuan, J. M. Armitage, J. A. Arnot, S. T. J. Droge and M. S. Mclachlan, Bioconcentration of Several Series of Cationic Surfactants in Rainbow Trout, *Environ. Sci. Technol.*, 2021, **55**(13), 8888–8897.
64 F. A. P. C. Gobas, B. C. Kelly and J. A. Arnot, Quantitative Structure Activity Relationships for Predicting the Bioaccumulation of POPs in Terrestrial Food-Webs, *QSR Comb. Sci.*, 2003, **22**(3), 329–336.
65 B. C. Kelly and F. A. P. C. Gobas, An Arctic Terrestrial Food-Chain Bioaccumulation Model for Persistent Organic Pollutants, *Environ. Sci. Technol.*, 2003, **37**(13), 2966–2974.
66 J. M. Armitage and F. A. P. C. Gobas, A Terrestrial Food-Chain Bioaccumulation Model for POPs, *Environ. Sci. Technol.*, 2007, **41**(11), 4019–4025.
67 G. Czub and M. S. McLachlan, Bioaccumulation Potential of Persistent Organic Chemicals in Humans, *Environ. Sci. Technol.*, 2004, **38**(8), 2406–2412.
68 E. Undeman, G. Czub and M. S. Mclachlan, Addressing Temporal Variability When Modeling Bioaccumulation in Plants, *Environ. Sci. Technol.*, 2009, **43**(10), 3751–3756.
69 F. C. Hsu, R. L. Marxmiller and A. Y. S. Yang, Study of Root Uptake and Xylem Translocation of Cinmethylin and Related Compounds in Detopped Soybean Roots Using a Pressure Chamber Technique, *Plant Physiol.*, 1990, **93**(4), 1573–1578.
70 G. G. Briggs, R. H. Bromilow and A. A. Evans, Relationships Between Lipophilicity and Root Uptake and Translocation of Non-Ionised Chemicals by Barley, *Pestic. Sci.*, 1982, **13**(5), 495–504.
71 G. Czub and M. S. McLachlan, Bioaccumulation Potential of Persistent Organic Chemicals in Humans, *Environ. Sci. Technol.*, 2004, **38**(8), 2406–2412.
72 K. Goss, L. Linden, N. Ulrich and C. Schlechtriem, Revisiting Elimination Half Live as an Indicator for Bioaccumulation in Fish and Terrestrial Mammals, *Chemosphere*, 2018, **210**, 341–346.
73 K. Veltman, T. E. Mckone, M. A. J. Huijbregts and A. J. Hendriks, Bioaccumulation Potential of Air Contaminants: Combining Biological Allometry, Chemical Equilibrium and Mass-Balances to Predict Accumulation of Air Pollutants in Various Mammals, *Toxicol. Appl. Pharmacol.*, 2009, **238**(1), 47–55.
74 J. W. Nichols, P. Fitzsimmons and L. P. Burkhard, *In Vitro–in Vivo* Extrapolation of Quantitative Hepatic Biotransformation Data for Fish. II. Modeled Effects on Chemical Bioaccumulation, *Environ. Toxicol. Chem.*, 2007, **26**(6), 1304–1319.
75 M. C. Barber, Dietary Uptake Models Used for Modelling the Bioaccumulation of Organic Contaminated in Fish, *Environ. Toxicol. Chem.*, 2008, **27**(4), 755–777.
76 M. C. Barber, A Review and Comparison of Models for Predicting Dynamic Chemical Bioconcentration in Fish, *Environ. Toxicol. Chem.*, 2003, **22**(9), 1963–1992.
77 J. Nichols, S. Erhardt, S. Dyer, M. James, M. Moore, K. Plotzke, H. Segner, I. Schultz, K. Thomas, L. Vasiluk and A. Weisbrod, Use of *In Vitro* Absorption, Distribution, Metabolism, and Excretion (ADME) Data in Bioaccumulation Assessments for Fish, *Hum. Ecol. Risk Assess.*, 2007, **13**, 1164–1191.
78 J. A. Arnot, D. Mackay, T. F. Parkerton and M. Bonnell, A Database of Fish Biotransformation Rates for Organic Chemicals, *Environ. Toxicol. Chem.*, 2008, **27**(11), 2263–2270.
79 J. A. Arnot and C. L. Quinn, Development and Evaluation of a Database of Dietary Bioaccumulation Test Data for Organic Chemicals in Fish, *Environ. Sci. Technol.*, 2015, **49**(8), 4783–4796.
80 J. Costanza, D. G. Lynch, R. S. Boethling and J. A. Arnot, Use of the Bioaccumulation Factor to Screen Chemicals for Bioaccumulation Potential, *Environ. Toxicol. Chem.*, 2012, **31**(10), 2261–2268.

81 S. Baskaran, J. M. Armitage and F. Wania, Model-Based Exploration of the Variability in Lake Trout (*Salvelinus Namaycush*) Bioaccumulation Factors: The Influence of Physiology and Trophic Relationships, *Environ. Toxicol. Chem.*, 2019, **38**(4), 831–840.

82 P. Fantke, P. Wieland, R. Juraske, G. Shaddick, E. S. Itoiz, R. Friedrich and O. Jolliet, Parameterization Models for Pesticide Exposure *via* Crop Consumption, *Environ. Sci. Technol.*, 2012, **46**, 12864–12872.

83 A. M. H. DeBruyn and F. A. P. C. Gobas, A Bioenergetic Biomagnification Model for the Animal Kingdom, *Environ. Sci. Technol.*, 2006, **40**(5), 1581–1587.

84 C. L. Quinn, J. M. Armitage, F. Wania and J. A. Arnot, Development and Evaluation of a Combined Bioenergetics and Organic Chemical Mass-Balance Bioaccumulation Model for Fish, *Environ. Sci. Technol.*, 2018, **53**(2), 752–759.

85 G. Paterson, M. Ryder, K. G. Drouillard and G. D. Haffner, Contrasting PCB Bioaccumulation Patterns among Lake Huron Lake Trout Reflect Basin-Specific Ecology, *Environ. Toxicol. Chem.*, 2016, **35**(1), 65–73.

86 European Chemicals Agency, EUSES – European Union System for the Evaluation of Substances, European Chemicals Agency, available at: https://doi.org/https://echa.europa.eu/support/dossier-submission-tools/euses, accessed on May 1, 2021.

87 U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, *Exposure Assessment Tools and Models, Estimation Program Interface (EPI) Suite, version 4.11*, available at: http://www.epa.gov/opptintr/exposure/pubs/episuite.htm, accessed on May 1, 2021.

88 W. M. Meylan, P. H. Howard, R. S. Boethling, D. Aronson, H. Printup and S. Gouchie, Improved Method for Estimating Bioconcentration/Bioaccumulation Factors from Octanol/Water Partition Coefficient, *Environ. Toxicol. Chem.*, 1999, **18**(4), 664–672.

89 J. A. Arnot and F. A. P. C. Gobas, A Generic QSAR for Assessing the Bioaccumulation Potential of Organic Chemicals in Aquatic Food Webs, *QSAR Comb. Sci.*, 2003, **22**, 337–345.

90 T. Reemtsma, U. Berger, H. P. H. Arp, H. Gallard, T. P. Knepper, M. Neumann, J. B. Quintana and P. de Voogt, Mind the Gap: Persistent and Mobile Organic Compounds - Water Contaminants That Slip Through, *Environ. Sci. Technol.*, 2016, **50**(19), 10308–10315.

91 M. Neumann and I. Schliebner, *Protecting the Sources of Our Drinking Water: the Criteria for Identifying Persistent, Mobile and Toxic (PMT) Substances and Very Persistent and Very Mobile (vPvM) Substances under EU Regulation REACH (EC) No 1907/2006 (Report TEXTE127/2019)*, German Environment Agency (UBA), Dessau-Roßlau, Germany, 2019.

92 H. P. H. Arp, T. N. Brown, U. Berger and S. E. Hale, Ranking REACH Registered Neutral , Ionizable and Ionic Organic Chemicals Based on Their Aquatic Persistency and Mobility, *Environ. Sci.: Processes Impacts*, 2017, **19**, 939–955.

93 H. P. H. Arp and S. E. Hale, *REACH: Improvement of Guidance and Methods for the Identification and Assessment of PMT/VPvM Substances (Report TEXTE126/2019)*, German Environment Agency (UBA), Dessau-Roßlau, Germany, 2019.

94 S. Pawlowski, L. Aicher, A. Berends, P. Curtis-Jackson, K. Doornebosch, J. Franklin, M. Greener, J. Hollender, B. Jene, K. Jenner, A. Kowalczyk, D. Lewis, S. Marsden-Jones, A. Redman, N. Vallotton, N. Wang, J. Wheeler, G. Sanders and A. Häner, Persistent Chemicals and Water Resources Protection: Conclusions from the ECETOC Task Force, Presentation at the Virtual SETAC Europe Meeting, *SETAC SciCon*, 2020.

95 A. Redman, N. Wang, P. Curtis-Jackson and J. Hollender, Review of Monitoring Data and Critical Evaluation of Proposed P/vP and M/vM Criteria, Presentation at the Virtual SETAC Europe Meeting, *SETAC SciCon*, 2020.

96 A. Stołyhwo and Z. E. Sikorski, Food Chemistry Polycyclic Aromatic Hydrocarbons in Smoked Fish – A Critical Review, *Food Chem.*, 2005, **91**(2), 303–311.

97 A. Farhadian, S. Jinap, F. Abas and Z. I. Sakar, Determination of Polycyclic Aromatic Hydrocarbons in Grilled Meat, *Food Control*, 2010, **21**(5), 606–610.

98 S. Dong, J. Wu, G. Liu, B. Zhang and M. Zheng, Unintentionally Produced Dioxin-like Polychlorinated Biphenyls during Cooking, *Food Control*, 2011, **22**(11), 1797–1802.

99 M. Roszko, K. Szymczyk and R. Jędrzejczak, Fate of PBDEs during Food Processing: Assessment of Formation of Mixed Chlorinated/Brominated Diphenyl Ethers and Brominated Dioxins/Furans, *J. Environ. Sci. Health, Part B*, 2015, **50**(12), 884–895.

100 W. Vetter, P. Bendig, M. Blumenstein, F. Hägele, P. A. Behnisch and A. Brouwer, Formation of Polybrominated Dibenzofurans (PBDFs) after Heating of a Salmon Sample Spiked with Decabromodiphenyl Ether (BDE-209), *Environ. Sci. Pollut. Res.*, 2014, **22**(19), 14530–14536.

101 J. L. Domingo, Influence of Cooking Processes on the Concentrations of Toxic Metals and Various Organic Environmental Pollutants in Food: A Review of the Published Literature, *Crit. Rev. Food Sci. Nutr.*, 2011, **51**(1), 37–41.

102 P. Bendig, F. Ha, M. Blumenstein, J. Schmidt and W. Vetter, Fate of Polybrominated Diphenyl Ethers during Cooking of Fish in a New Model Cooking Apparatus and a Household Microwave, *Agric. Food Chem.*, 2013, **61**(27), 6728–6733.

103 A. I. Prieto, R. Guzm and Á. Jos, Influence of Cooking (Microwaving and Broiling) on Cylindrospermopsin Concentration in Muscle of Nile Tilapia (*Oreochromis Niloticus*) and Characterization of Decomposition Products, *Toxins*, 2017, **9**(6), 177.

104 S. Bayen, P. Barlow, H. K. Lee and J. P. Obbard, Effect of Cooking on the Loss of Persistent Organic Pollutants from Salmon, *J. Toxicol. Environ. Health, Part A*, 2007, **68**(4), 253–265.

105 X. Zhang, N. Gandhi, S. P. Bhavsar and L. S. W. Ho, Effects of Skin Removal on Contaminant Levels in Salmon and Trout Filets, *Sci. Total Environ.*, 2013, **443**, 218–225.

106 A. Seiler, A. Bach, M. Driffield, P. P. Losada, P. Mercea, V. Tosa and R. Franz, Correlation of Foodstuffs with Ethanol-Water Mixtures with Regard to the Solubility of Migrants from Food Contact Materials, *Food Addit. Contam., Part A*, 2014, **31**(3), 498–511.

107 M. F. Poças, J. C. Oliveira, F. A. R. Oliveira and T. Hogg, A Critical Survey of Predictive Mathematical Models for Migration from Packaging A Critical Survey of Predictive Mathematical Models for Migration, *Crit. Rev. Food Sci. Nutr.*, 2008, **48**(10), 913–928.

108 A. Baner, J. Brandsch, R. Franz and O. Piringer, The Application of a Predictive Migration Model for Evaluating the Compliance of Plastic Materials with European Food Regulations, *Food Addit. Contam.*, 2013, **13**(5), 587–601.

109 T. H. Begley, Migration from Food Packaging: Regulatory Considerations for Estimating Exposure, in *Plastic Packaging Materials for Food: Barrier Function, Mass Transport, Quality Assurance and Legislation*, ed. O. G. Piringer and A. L. Baner, Wiley-VCH Verlag GmbH, Weinheim, Germany, 2000, pp. 359–392.

110 T. Begley, L. Castle, A. Feigenbaum, R. Franz, K. Hinrichs, T. Lickly, P. Mercea, M. Milana, A. O. Brien, S. Rebre, R. Rijk and O. Piringer, Evaluation of Migration Models That Might Be Used in Support of Regulations for Food-Contact Plastics, *Food Addit. Contam.*, 2007, **22**(1), 73–90.

111 P. Mercea and O. Piringer, Possibilities and Limitations of Migration Modeling, in *Plastic Packaging: Interactions with Food and Pharmaceuticals*, ed. O. G. Piringer and A. L. Baner, Wiley-VCH Verlag GmbH, Weinheim, 2nd edn, 2008, pp. 499–522.

112 A. E. Feigenbaum, J. Bouquant, V. J. Ducruet, J. Ehret-Henry, D. L. Marque, A. M. Riquet, D. Scholler and J. C. Wittmann, Guidelines of the Commission of the European Communities: A Challenge for the Control of Packaging, *Food Addit. Contam.*, 1994, **11**(2), 141–154.

113 O. Piringer and F. Gmbh, Mathematical Modelling of Chemical Migration from Food Contact Materials, in *Chemical Migration and Food Contact Materials*, ed. K. A. Barnes, C. R. Sinclair and D. H. Watson, Woodhead Publishing Limited, Cambridge, UK, 2007, pp. 180–202.

114 E. A. Tehrany and S. Desobry, Partition Coefficients in Food/Packaging Systems: A Review, *Food Addit. Contam.*, 2004, **21**(12), 1186–1202.

115 J. Brandsch, P. Mercea, M. Rüter, V. Tosa and O. Piringer, Migration Modelling as a Tool for Quality Assurance of Food Packaging, *Food Addit. Contam.*, 2010, **19**, 29–41.

116 R. Franz and C. Simoneau, Modelling Migration from Plastics into Foodstuffs as a Novel and Cost Efficient Tool for Estimation of Consumer Exposure from Food Contact Materials, *Final Report for EU Project QLK1-CT2002-2390 "Foodmigrosure"*, 2008.

117 C. J. Weschler and W. W. Nazaroff, Growth of Organic Films on Indoor Surfaces, *Indoor Air*, 2017, **27**, 1101–1112.

118 US Environmental Protection Agency, (Update): Soil and Dust Ingestion, in *Exposure Factors Handbook*, National Center for Environmental Assessment, Office of Research and Development, Washington, DC, USA, EPA/600/R-17/384F, 2017, Chapter 5.

119 L. Li, L. Hughes and J. A. Arnot, Addressing Uncertainty in Mouthing-Mediated Ingestion of Chemicals on Indoor Surfaces, Objects, and Dust, *Environ. Int.*, 2021, **146**, 106266.

120 I. Liagkouridis, I. T. Cousins and A. P. Cousins, Emissions and Fate of Brominated Flame Retardants in the Indoor Environment: A Critical Review of Modelling Approaches, *Sci. Total Environ.*, 2014, **491–492**, 87–99.

121 E. Reppas-chrysovitsinos, A. Sobek and M. Macleod, Screening-Level Models to Estimate Partition Ratios of Organic Chemicals between Polymeric Materials, Air and Water, *Environ. Sci. Process. Impacts*, 2016, **18**(6), 667–676.

122 J. M. Parnis, T. Taskovic, A. K. D. Celsie and D. Mackay, Indoor Dust/Air Partitioning: Evidence for Kinetic Delay in Equilibration for Low-Volatility SVOCs, *Environ. Sci. Technol.*, 2020, **54**, 6723–6729.

123 C. J. Weschler and W. W. Nazaroff, SVOC Partitioning between the Gas Phase and Settled Dust Indoors, *Atmos. Environ.*, 2010, **44**(30), 3609–3620.

124 J. Cao, J. Mo, Z. Sun and Y. Zhang, Indoor Particle Age, a New Concept for Improving the Accuracy of Estimating Indoor Airborne SVOC Concentrations, and Applications, *Build. Environ.*, 2018, **136**, 88–97.

125 D. Mackay, A. K. D. Celsie and J. M. Parnis, Kinetic Delay in Partitioning and Parallel Particle Pathways: Underappreciated Aspects of Environmental Transport, *Environ. Sci. Technol.*, 2019, **53**, 234–241.

126 L. Li, J. A. Arnot and F. Wania, Towards a Systematic Understanding of the Dynamic Fate of Polychlorinated Biphenyls in Indoor , Urban and Rural Environments, *Environ. Int.*, 2018, **117**, 57–68.

127 X. Zhang, J. A. Arnot and F. Wania, Model for Screening-Level Assessment of Near-Field Human Exposure to Neutral Organic Chemicals Released Indoors, *Environ. Sci. Technol.*, 2014, **48**, 12312–12319.

128 H. Shin, T. E. Mckone and D. H. Bennett, Intake Fraction for the Indoor Environment: A Tool for Prioritizing Indoor Chemical Sources, *Environ. Sci. Technol.*, 2012, **46**, 10063–10072.

129 D. H. Bennett and E. J. J. Furtaw, Fugacity-Based Indoor Residential Pesticide Fate Model, *Environ. Sci. Technol.*, 2004, **38**(7), 2142–2152.

130 A. Saini, J. O. Okeme, J. M. Parnis, R. H. Mcqueen and M. L. Diamond, From Air to Clothing: Characterizing the Accumulation of Semi-Volatile Organic Compounds to Fabrics in Indoor Environments, *Indoor Air*, 2016, **27**(3), 631–641.

131 A. Saini, C. Rauert, M. J. Simpson, S. Harrad and M. L. Diamond, Characterizing the Sorption of Polybrominated Diphenyl Ethers (PBDEs) to Cotton and Polyester Fabrics under Controlled Conditions, *Sci. Total Environ.*, 2016, **563–564**, 99–107.

132 S. A. Csiszar, M. L. Diamond and L. J. Thibodeaux, Modeling Urban Films Using a Dynamic Multimedia Fugacity Model, *Chemosphere*, 2012, **87**(9), 1024–1031.
133 W. Wei, C. Mandin, O. Blanchard, F. Mercier, M. Pelletier, B. B. Le, P. Glorennec and O. Ramalho, Distributions of the Particle/Gas and Dust/Gas Partition Coefficients for Seventy-Two Semi-Volatile Organic Compounds in Indoor Environment, *Chemosphere*, 2016, **153**, 212–219.
134 H. Xiao and F. Wania, Is Vapor Pressure or the Octanol-Air Partition Coefficient a Better Descriptor of the Partitioning between Gas Phase and Organic Matter?, *Atmos. Environ.*, 2003, **37**(20), 2867–2878.
135 F. A. P. C. Gobas, X. Zhang and R. Wells, Gastrointestinal Magnification: The Mechanism of Biomagnification and Food Chain Accumulation of Organic Chemicals, *Environ. Sci. Technol.*, 1993, **27**(13), 2855–2863.
136 G. A. Moser and M. S. McLachlan, Modeling Digestive Tract Absorption and Desorption of Lipophilic Organic Contaminants in Humans, *Environ. Sci. Technol.*, 2002, **36**(15), 3318–3325.
137 K. Aukland and G. Nicolaysen, Interstitial Fluid Volume: Local Regulatory Mechanisms, *Physiol. Rev.*, 1981, **61**(3), 556–643.
138 M. G. Farquhar and G. E. Palade, Junctional Complexes in Various Epithelia, *J. Cell Biol.*, 1963, **17**(2), 375–412.
139 K. L. Lutz and T. J. Siahaan, Molecular Structure of the Apical Junction Complex and Its Contribution to the Paracellular Barrier, *J. Pharm. Sci.*, 1997, **86**(9), 977–984.
140 A. B. R. Thomson and J. M. Dietschy, The Role of the Unstirred Water Layer in Intestinal Permeation, in *Pharmacology of Intestinal Permeation II. Handbook of Experimental Pharmacology (Continuation of Handbuch der experimentellen Pharmakologie)*, ed. T. Z. Csáky, Springer, Berlin, Heidelberg, 1984, pp. 165–269.
141 H. Lennernas, Human Intestinal Permeability, *J. Pharm. Sci.*, 1998, **87**(4), 403–410.
142 J. L. Madara, Functional Morphology of Epithelium of the Small Intestine, in *Comprehensive Physiology, Supplement 19. Handbook of Physiology, The Gastrointestinal System, Intestinal Absorption and Secretion*, ed. R. Terjung, 1991, pp. 83–120.
143 I. A. O. Connor, M. A. J. Huijbregts, A. M. J. Ragas and A. J. Hendriks, Predicting the Oral Uptake Efficiency of Chemicals in Mammals: Combining the Hydrophilic and Lipophilic Range Membrane, *Toxicol. Appl. Pharmacol.*, 2013, **266**(1), 150–156.
144 F. A. P. C. Gobas, D. C. G. Muir and D. Mackay, Dynamics of Dietary Bioaccumulation and Faecal Elimination of Hydrophobic Organic Chemicals in Fish, *Chemosphere*, 1988, **17**(5), 943–962.
145 G. Raffy, F. Mercier, P. Glorennec, C. Mandin and B. Le Bot, Oral Bioaccessibility of Semi-Volatile Organic Compounds (SVOCs) in Settled Dust: A Review of Measurement Methods, Data and Influencing Factors, *J. Hazard. Mater.*, 2018, **352**, 215–227.
146 J. A. Arnot and D. Mackay, The Influence of Chemical Degradation during Dietary Exposures to Fish on Biomagnification Factors and Bioaccumulation Factors, *Environ. Sci.: Processes Impacts*, 2018, **20**(1), 86–97.
147 W. J. Dulfer, J. P. Groten and H. A. J. Govers, Effect of Fatty Acids and the Aqueous Diffusion Barrier on the Uptake and Transport of Polychlorinated Biphenyls in Caco-2 Cells, *J. Lipid Res.*, 1996, **37**(5), 950–961.
148 A. B. R. Thomson, C. Schoeller, M. Keelan, L. Smith and M. T. Clandinin, Lipid Absorption: Passing through the Unstirred Layers, Brush-Border Membrane, and Beyond, *Can. J. Physiol. Pharmacol.*, 1993, **71**(8), 531–555.
149 B. Mutsch, N. Gains and H. Hauser, Interaction of Intestinal Brush Border Membrane Vesicles with Small Unilamellar Phospholipid Vesicles. Exchange of Lipids between Membranes Is Mediated by Collisional Contact, *Biochemistry*, 1986, **25**(8), 2134–2140.
150 K. Obata, K. Sugano, R. Saitoh, A. Higashida, Y. Nabuchi, M. Machida and Y. Aso, Prediction of Oral Drug Absorption in Humans by Theoretical Passive Absorption Model, *Int. J. Pharm.*, 2005, **293**, 183–192.
151 K. Sugano, Y. Nabuchi, M. Machida and Y. Asoh, Permeation Characteristics of a Hydrophilic Basic Compound across a Bio-Mimetic Artificial Membrane, *Int. J. Pharm.*, 2004, **275**, 271–278.
152 J. C. Lo, D. A. Campbell, C. J. Kennedy and F. A. P. C. Gobas, Somatic and Gastrointestinal *In Vivo* Biotransformation Rates of Hydrophobic Chemicals in Fish, *Environ. Toxicol. Chem.*, 2015, **34**(10), 2282–2294.
153 J. C. Lo, D. J. Letinski, T. F. Parkerton, D. A. Campbell and F. A. P. C. Gobas, In-Vivo Biotransformation Rates of Organic Chemicals in Fish: Relationship with Bioconcentration and Biomagnification Factors, *Environ. Sci. Technol.*, 2016, **50**(24), 13299–13308.
154 R. Xiao, J. A. Arnot and M. Macleod, Towards an Improved Understanding of Processes Controlling Absorption Efficiency and Biomagnification of Organic Chemicals by Fish, *Chemosphere*, 2015, **138**, 89–95.
155 C. A. Lipinski, F. Lombardo, B. W. Dominy and P. J. Feeney, Experimental and Computational Approaches to Estimate Solubility and Permeability in Drug Discovery and Development Settings, *Adv. Drug Delivery Rev.*, 1997, **23**, 3–25.
156 A. D. Paterson, R. A. Conradi, A. R. Hilgers, T. J. Vidmar and P. S. Burton, A Non-Aqueous Partitioning System for Predicting the Oral Absorption Potential of Peptides, *QSAR Comb. Sci.*, 1994, **13**(1), 4–10.
157 T. Österberg and U. Norinder, Prediction of Polar Surface Area and Drug Transport Processes Using Simple Parameters and PLS Statistics, *J. Chem. Inf. Comput. Sci.*, 2000, **40**(6), 1408–1411.
158 G. Beko, G. Morrison, C. J. Weschler, H. M. Koch, T. Salthammer, T. Schripp, A. Eftekhari and G. Clausen, Dermal Uptake of Nicotine from Air and Clothing: Experimental Verification, *Indoor Air*, 2017, **28**(2), 247–257.
159 M. Gong, C. J. Weschler and Y. Zhang, Impact of Clothing on Dermal Exposure to Phthalates: Observations and Insights from Sampling Both Skin and Clothing, *Environ. Sci. Technol.*, 2016, **50**(8), 4350–4357.

160 G. C. Morrison, C. J. Weschler, G. Bekö, H. M. Koch, T. Salthammer, T. Schripp, J. Toftum and G. Clausen, Role of Clothing in Both Accelerating and Impeding Dermal Absorption of Airborne SVOCs, *J. Exposure Sci. Environ. Epidemiol.*, 2015, **26**(1), 113–118.

161 D. Licina, G. C. Morrison, G. Beko, C. J. Weschler and W. W. Nazaroff, Clothing-Mediated Exposures to Chemicals and Particles, *Environ. Sci. Technol.*, 2019, **53**, 5559–5575.

162 H. F. Frasch, G. S. Dotson, A. L. Bunge, C. Chen, J. W. Cherrie, G. B. Kasting, J. C. Kissel, J. Sahmel, S. Semple and S. Wilkinson, Analysis of Finite Dose Dermal Absorption Data: Implications for Dermal Exposure Assessment, *J. Exposure Sci. Environ. Epidemiol.*, 2013, **24**(1), 65–73.

163 G. Bekö, C. J. Weschler, S. Langer, M. Callesen, J. Toftum and G. Clausen, Children's Phthalate Intakes and Resultant Cumulative Exposures Estimated from Urine Compared with Estimates from Dust Ingestion, Inhalation and Dermal Absorption in Their Homes and Daycare Centers, *PLoS One*, 2013, **8**(4), e62442.

164 C. Christia, G. Poma, S. Harrad, C. A. de Wit, Y. Sjostrom, P. Leonards, M. Lamoree and A. Covaci, Occurrence of Legacy and Alternative Plasticizers in Indoor Dust from Various EU Countries and Implications for Human Exposure *via* Dust Ingestion and Dermal Absorption, *Environ. Res.*, 2019, **171**, 204–212.

165 E. A. C. Hubal, P. P. Egeghy, K. W. Leovic and G. G. Akland, Measuring Potential Dermal Transfer of a Pesticide to Children in a Child Care Center, *Environ. Health Perspect.*, 2006, **114**(2), 264–269.

166 W. Cheng, Dissolved VOC Concentrations and Salt Contents Affecting Air-Sweat Equilibrium Partition of Hydrophilic and Hydrophobic VOCs, *J. Environ. Sci. Health, Part A: Environ. Sci. Eng.*, 2007, **43**(1), 98–104.

167 W. Cheng, P. Lin and P. Su, The Effects of Salts and Grease on BTEXs Gas/Sweat Equilibrium Partition: The Effects on Human BTEX Dermal Exposures, *Hum. Ecol. Risk Assess.*, 2010, **16**(1), 199–209.

168 J. Kielhorn, S. Melching-Kollmub and I. Mangelsdorf, *Environmental Health Criteria 235, Dermal Absorption*, World Health Organization, Geneva, 2006.

169 R. Scheuplein, Transient Diffusion and the Relative Importance of Various Routes of Skin Penetration, *J. Invest. Dermatol.*, 1967, **48**(1), 79–88.

170 M. E. Johnson, D. Blankschtein and R. Langer, Evaluation of Solute Permeation through the Stratum Corneum: Lateral Bilayer Diffusion as the Primary Transport Mechanism, *J. Pharm. Sci.*, 1997, **86**(10), 1162–1172.

171 R. Tibaldi, W. ten Berge and D. Drolet, Dermal Absorption of Chemicals: Estimation by IH SkinPerm, *J. Occup. Environ. Hyg.*, 2014, **11**(1), 19–31.

172 R. O. Potts and R. H. Guy, A Predictive Algorithm for Skin Permeability: The Effects of Molecular Size and Hydrogen Bond Activity, *Pharm. Res.*, 1995, **12**(11), 1628–1633.

173 R. O. Potts and R. H. Guy, Predicting Skin Permeability, *Pharm. Res.*, 1992, **9**(5), 663–669.

174 M. H. Abraham, H. S. Chadha and R. C. Mitchell, The Factors That Influence Skin Penetration of Solutes, *J. Pharm. Pharmacol.*, 1995, **47**(1), 8–16.

175 W. J. Pugh, M. S. Roberts and J. Hadgraft, The Effect of Hydrogen Bonding Interactions and Molecular Size on Diffusion across the Stratum Corneum, *Int. J. Pharm.*, 1996, **138**(2), 149–165.

176 H. Patel, W. ten Berge and M. T. D. Cronin, Quantitative Structure – Activity Relationships (QSARs) for the Prediction of Skin Permeation of Exogenous Chemicals, *Chemosphere*, 2002, **48**(6), 603–613.

177 B. E. Vecchia and A. L. Bunge, Skin Absorption Databases and Predictive Equations, in *Transdermal Drug Delivery*, ed. R. H. Guy and J. Hadgradt, Marcel Dekker, Inc., New York, NY, 2003, pp. 57–133.

178 R. J. Scheuplein and I. H. Blank, Permeability of the Skin, *Physiol. Rev.*, 1971, **51**(4).

179 M. W. de Jager, G. S. Gooris, I. P. Dolbnya, W. Bras, M. Ponec and J. A. Bouwstra, Novel Lipid Mixtures Based on Synthetic Ceramides Reproduce the Unique Stratum Corneum Lipid Organization, *J. Lipid Res.*, 2004, **45**(5), 923–932.

180 G. S. K. Pilgram, A. M. E. Pelt, H. K. Koerten and J. A. Bouwstra, Electron Diffraction Provides New Information on Human Stratum Corneum Lipid Organization Studied in Relation to Depth and Temperature, *J. Invest. Dermatol.*, 1999, **113**(3), 403–409.

181 H. Zhai and H. I. Maibach, Occlusion *vs.* Skin Barrier Function, *Ski. Res. Technol.*, 2002, **8**(1), 1–6.

182 D. Bucks and R. Guy, Effects of Occlusion, in *In Vitro Percutaneous Absorption: Principles, Fundamentals, and Applications*, ed. R. L. Bronaugh and H. I. Maibach , CRC Press, Boca Raton, 1991, pp. 85–114.

183 M. T. D. Cronin, J. C. Dearden, G. P. Moss and G. Murry-Dickson, Investigation of the Mechanism of Flux across Human Skin *in Vitro* by Quantitative Structure – Permeability Relationships, *Eur. J. Pharm. Sci.*, 1999, **7**, 325–330.

184 S. A. Mitragotri, Theoretical Analysis of Permeation of Small Hydrophobic Solutes across the Stratum Corneum Based on Scaled Particle Theory, *J. Pharm. Sci.*, 2002, **91**(3), 744–752.

185 G. P. Moss and M. T. D. Cronin, Quantitative Structure – Permeability Relationships for Percutaneous Absorption: Re-Analysis of Steroid Data, *Int. J. Pharm.*, 2002, **238**, 105–109.

186 U.S. Environmental Protection Agency, *The Dermal Permeability Coefficient Program, DERMWIN v2.01, Estimation Programs Interface (EPI) Suite for Microsoft® Windows, ver. 4.1*, U. S. Environmental Protection Agency, Washington, D.C., 2011.

187 U.S. Environmental Protection Agency, *Risk Assessment Guidance for Superfund Volume I: Human Health Evaluation Manual (Part E, Supplemental Guidance for Dermal Risk Assessment), Final, (EPA/540/R/99/005)*, Office of Superfund Remediation and Technology Innovation, Washington, D.C., 2004.

188 A. L. Bunge and R. L. Cleek, A New Method for Estimating Dermal Absorption from Chemical Exposure: Effect for Molecular Weight and Octanol-Water Partitioning, *Pharm. Res.*, 1995, **12**(1), 88–95.
189 A. Wilschut, W. F. ten Berge, P. J. Robinson and T. E. McKone, Estimating Skin Permeation. The Validation of Five Mathematical Skin Permeation Models, *Chemosphere*, 1995, **30**(7), 1275–1296.
190 W. ten Berge, *QSARs for Skin Permeation of Chemicals*, available at http://home.wxs.nl/~wtberge/qsarperm.Html.
191 R. Tibaldi, W. ten Berge and D. Drolet, *IH SkinPerm v2.0. Reference Manual*, 2017, available at https://aiha-assets.sfo2.digitaloceanspaces.com/AIHA/resources/IH_SkinPerm_Manual_May_2017.pdf, accessed on May 1, 2021.
192 C. Wang, D. B. Collins, C. Arata, A. H. Goldstein, J. M. Mattila, D. K. Farmer, L. Ampollini, P. F. Decarlo, A. Novoselac, M. E. Vance, W. Nazaroff and J. P. D. Abbatt, Surface Reservoirs Dominate Dynamic Gas-Surface Partitioning of Many Indoor Air Constituents, *Sci. Adv.*, 2020, **6**, eaay8973.
193 I. T. Cousins and D. Mackay, Gas-Particle Partitioning of Organic Compounds and Its Interpretation Using Relative Solubilities, *Environ. Rev.*, 2001, **35**(4), 643–647.
194 F. Wania, Y. D. Lei, C. Wang, J. P. D. Abbatt and K. Goss, Using the Chemical Equilibrium Partitioning Space to Explore Factors Influencing the Phase Distribution of Compounds Involved in Secondary Organic Aerosol Formation, *Atmos. Chem. Phys.*, 2015, **15**, 3395–3412.
195 Y. F. Li, W. L. Ma and M. Yang, Prediction of Gas/Particle Partitioning of Polybrominated Diphenyl Ethers (PBDEs) in Global Air: A Theoretical Study, *Atmos. Chem. Phys.*, 2015, **15**, 1669–1681.
196 F. Zhao, I. Riipinen and M. Macleod, Steady-State Mass Balance Model for Predicting Particle−Gas Concentration Ratios of PBDEs, *Environ. Sci. Technol.*, 2021, **55**(14), 9425–9433.
197 C. Liu, S. Shi, C. Weschler, B. Zhao and Y. Zhang, Analysis of the Dynamic Interaction Between SVOCs and Airborne Particles, *Aerosol Sci. Technol.*, 2013, **47**, 125–136.
198 G. W. Wright, Respiratory System and Airborne Infection in Relation to Infection, *Microbiol. Mol. Biol. Rev.*, 1961, **25**(3), 219–227.
199 W. Stahlhofen, G. Rudolf and A. C. James, Intercomparison of Experimental Regional Aerosol Deposition Data, *J. Aerosol Med.*, 1989, **2**(3), 285–308.
200 C. Liu, Y. Zhang and C. J. Weschler, Exposure to SVOCs from Inhaled Particles: The Impact of Desorption, *Environ. Sci. Technol.*, 2017, **51**, 6220–6228.
201 W. Wei, O. Ramalho and C. Mandin, Modeling the Bioaccessibility of Inhaled Semivolatile Organic Compounds in the Human Respiratory Tract, *Int. J. Hyg. Environ. Health*, 2020, **224**, 113436.
202 J. F. A. Pankow, Consideration of the Role of Gas/Particle Partitioning in the Deposition of Nicotine and Other Tobacco Smoke Compounds in the Respiratory Tract, *Chem. Res. Toxicol.*, 2001, **14**(11), 1465–1481.
203 N. Gowadia and D. Dunn-rankin, A Transport Model for Nicotine in the Tracheobronchial and Pulmonary Region of the Lung, *Inhalation Toxicol.*, 2010, **22**(1), 42–48.
204 J. V. Fahy and B. F. Dickey, Airway Mucus Function and Dysfunction, *N. Engl. J. Med.*, 2010, **363**, 2233–2247.
205 E. Nielsen, G. Østergaard and J. C. Larsen, *Toxicological Risk Assessment of Chemicals: A Practical Guide*, CRC Press, Boca Raton, FL, 2008.
206 M. R. Sebastiano, B. C. Doak, M. Backlund, V. Poongavanam, B. Over, G. Ermondi, G. Caron and J. Kihlberg, Impact of Dynamically Exposed Polarity on Permeability and Solubility of Chameleonic Drugs Beyond the Rule of 5, *J. Med. Chem.*, 2018, **61**, 4189–4202.
207 K. Goss and Ä. P. Schwarzenbach, Linear Free Energy Relationships Used To Evaluate Equilibrium Partitioning of Organic Compounds, *Environ. Sci. Technol.*, 2001, **35**(1), 1–9.
208 S. Endo and K. Goss, Applications of Polyparameter Linear Free Energy Relationships in Environmental Chemistry, *Environ. Sci. Technol.*, 2014, **48**(21), 12477–12491.
209 K. Breivik and F. Wania, Expanding the Applicability of Multimedia Fate Models to Polar Organic Chemicals, *Environ. Sci. Technol.*, 2003, **37**, 4934–4943.
210 C. A. Ng and K. Hungerbühler, Bioaccumulation of Perfluorinated Alkyl Acids: Observations and Models, *Environ. Sci. Technol.*, 2014, **48**, 4637–4648.
211 Q. Liu, J. Liggio, D. Wu, A. Saini, S. Halappanavar, J. J. B. Wentzell, T. Harner, K. Li, P. Lee and S. Li, Experimental Study of OH-Initiated Heterogeneous Oxidation of Organophosphate Flame Retardants: Kinetics, Mechanism, and Toxicity, *Environ. Sci. Technol.*, 2019, **53**(24), 14398–14408.
212 P. Howard, W. Meylan, D. Aronson, W. Stiteler, J. Tunkel, M. Comber and T. F. Parkerton, A New Biodegradation Prediction Model Specific to Petroleum Hydrocarbons, *Environ. Toxicol. Chem.*, 2005, **24**(8), 1847–1860.
213 R. S. Boethling, P. H. Howard, J. A. Beauman and M. E. Larosch, Factor for Intermedia Extrapolation in Biodegradability Assessment, *Chemosphere*, 1995, **30**(4), 741–752.
214 D. Aronson, R. Boethling, P. Howard and W. Stiteler, Estimating Biodegradation Half-Lives for Use in Chemical Screening, *Chemosphere*, 2006, **63**(11), 1953–1960.
215 K. Fenner, M. Scheringer, M. Macleod, M. Matthies, T. Mckone, M. Stroebe, A. Beyer, M. Bonnell, A. C. Le Gall, J. Klasmeier, D. Mackay, D. van de Meent, D. Pennington, N. Scharenberg, N. Suzuki and F. Wania, Comparing Estimates of Persistence and Long-Range Transport Potential among Multimedia Models, *Environ. Sci. Technol.*, 2005, **39**(7), 1932–1942.
216 L. Vierke, U. Berger and I. T. Cousins, Estimation of the Acid Dissociation Constant of Perfluoroalkyl Carboxylic Acids through an Experimental Investigation of Their Water-to-Air Transport, *Environ. Sci. Technol.*, 2013, **47**(19), 11032–11039.
217 J. F. Wambaugh, J. C. Bare, C. C. Carignan, K. L. Dionisio, R. E. Dodson, O. Jolliet, X. Liu, D. E. Meyer, S. R. Newton,

K. A. Phillips, P. Price, C. L. Ring, H. -M. Shin, J. R. Sobus, T. Tal, E. M. Ulrich, D. A. Vallero, B. A. Wetmore and K. Issacs, New Approach Methodologies for Exposure Science, *Curr. Opin. Toxicol.*, 2019, **15**, 76–92.

218 L. Li, A. Sangion, F. Wania, J. M. Armitage, L. Toose, L. Hughes and J. A. Arnot, Development and Evaluation of a Holistic and Mechanistic Modeling Framework for Chemical Emissions, Fate, Exposure, and Risk, *Environ. Health Perspect.*, 2021, in press.

