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An *in silico* skin absorption model for fragrance materials

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ABSTRACT

Fragrance materials are widely used in cosmetics and other consumer products. The Research Institute for Fragrance Materials (RIFM) evaluates the safety of these ingredients and skin absorption is an important parameter in refining systemic exposure. Currently, RIFM's safety assessment process assumes 100% skin absorption when experimental data are lacking. This 100% absorption default is not supportable and alternate default values were proposed. This study aims to develop and validate a practical skin absorption model (SAM) specific for fragrance material. It estimates skin absorption based on the methodology proposed by Kroes et al. SAM uses three default absorption values based on the maximum flux (J_{max}) – namely, 10%, 40%, and 80%. J_{max} may be calculated by using QSAR models that determine octanol/water partition coefficient (K_{ow}), water solubility (S) and permeability coefficient (K_p). Each of these QSAR models was refined and a semi-quantitative mechanistic model workflow is presented. SAM was validated with a large fragrance-focused data set containing 131 materials. All resulted in predicted values fitting the three-tiered absorption scenario based on J_{max} ranges. This conservative SAM may be applied when fragrance material lack skin absorption data.

1. Introduction

Skin absorption is a very important parameter for safety assessment, especially for topically applied fragrance materials. Chemicals in contact with the skin have the potential to be absorbed into the skin and enter the systemic circulation. To enter the systemic circulation, the chemical must reach the underlying dermis replete with capillaries. Skin absorption occurs by passive diffusion through the epidermis and directly by sweat glands and hair follicles (Ngo et al., 2010). Chemicals that penetrate no further than the epidermis are destined to be eliminated by desquamation and thus not reach the systemic circulation (Sundberg et al., 2012). Therefore, determining the penetration of a substance is crucial for assessing systemic exposure.

Usually, skin absorption of a target material is obtained experimentally *in vitro* and/or *in vivo* based on different species, including pig, monkey and human subjects. In the absence of experimental skin absorption data, it is customary, by safety assessors, to extrapolate via read-across structural analogs or use default values. The European Commission (EC) guidance on dermal absorption, proposed two default values – 100% or 10% if the substance of interest is very lipophilic or very hydrophilic (i.e., **log** K_{ow} <–1 or >+4) with a MW >500 (European Commission, 2004). For pesticides, the European Food Safety Authority (EFSA) replaced these EC default values with 25% for liquid concentrates and 75% when diluting them for spraying (EFSA Panel on Plant Protection Products and their Residues, 2011, 2012). More recently however, Aggarwal et al. (2014) analyzed human skin absorption data on pesticides that were available until 2012 and proposed a 6% default value for liquid concentrates and 30% for spray dilutions.

Currently, in RIFM's (Research Institute for Fragrance Materials) safety assessment process, a 100% default absorption value is applied for materials without experimental data (Belsito et al., 2007, 2011, 2012a, 2012b, 2012c). However, as discussed by Kroes et al. (2007), "the assumption of 100% absorption is not scientifically supportable" and, based on their analysis of 15 cosmetic ingredients and 62 chemicals in the EDETOX database (Williams, 2004), they proposed three default skin absorption values for cosmetic ingredients. Based on their derivation and analysis, the three different default skin absorption values proposed were based on the maximum flux (J_{max}, in unit of μg/cm^2/h). J_{max} is the theoretically achieved dose, based on Fick's first law of diffusion (Fick, 1855), when a material

Abbreviations: RIFM, Research Institute for Fragrance Materials; SAM, skin absorption model; QSAR, Quantitative Structure–Activity Relationship; EC, European Commission; EFSA, European Food Safety Authority; EDETOX, Evaluations and Predictions of Dermal Absorption of Toxic Chemicals; USEPA, United States Environmental Protection Agency; ACTOR, Aggregated Computational Toxicology Resource; SE, standard error; OECD, Organisation for Economic Co-operation and Development; RMSE, root-mean-square deviation; TTC, Threshold of Toxicological Concern; MOE, margin of exposure; MOS, margin of safety; CAESAR, Computer Assisted Evaluation of industry chemical Substances According to Regulations.

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is maintained in a saturated solution or at steady state equilibrium whose flux describes the amount of permeant per unit time and area (i.e., μg/cm²/h) (Magnusson et al., 2004). J_{max} is independent of the formulation in which the material contacts the skin and is a constant value when the formulation does not change the skin barrier (Kroes et al., 2007). Based on J_{max}, the default absorption values proposed were as follows:

- Material with J_{max} ≤0.1 μg/cm²/h should be assigned a skin absorption default value of less than 10%.
- If the J_{max} value is >0.1 μg/cm²/h but ≤10 μg/cm²/h, the default skin absorption assigned did not exceed 40%.
- If a material had a J_{max} of >10 μg/cm²/h, the default skin absorption assigned was no more than 80%.

The three default skin absorption percentages were proposed to represent low absorbed, medium absorbed, and high absorbed material. These default values were derived from a broad range of 15 cosmetic ingredients and considered several worst-case assumptions such as, (i) cosmetic ingredients are present at saturation levels, (ii) no depletion of the ingredient occurs during the exposure period, (iii) the formulation does not affect the skin barrier, and (iv) by using the maximal flux over the entire exposure time, the lower flux during the lag time is ignored (Kroes et al., 2007). In another study, Guy proved that the skin absorption of chemicals may be classified by their calculated J_{max} (Guy, 2010). Using the same model, the J_{max} of 20 fragrance materials were calculated and 16 of them were taken one step further to calculate their absorption percentage by including the applied dose, area and time. Over-prediction was observed in 14 materials and therefore, this approach could also be considered an extreme estimation of absorption.

Based on the abovementioned studies, it is apparent that the key to determining a substance's default absorption value is to get an accurate J_{max}. Centered on this reasoning, we propose an *in silico* semi-quantitative mechanistic model for assigning the same default skin absorption values as proposed by Kroes et al. (2007), but specifically constructed around the fragrance material (Fig. 1). As we will show, their overall methodology can be applied to derive similar absorption values for RIFM's fragrance materials that lack experimental skin absorption data, provided we tailor the model to specifically fit a defined set of fragrance material physicochemical parameters. Our mechanistic model was validated with a fragrance-focused data set containing 131 materials. All resulted in predicted values fitting the proposed three-tiered SAM based on J_{max} ranges.

2. Methodology development and data sets

2.1. Defining the chemical space of fragrance materials

Getting insight into the chemical space of fragrance materials and where this space is located in the chemical universe was instructive for us to get the big picture and develop a fragrance-focused SAM. Herein, 2120 fragrance materials with known chemical structure in RIFM database were reviewed. The fragrance chemical space was profiled using three physicochemical properties that significantly influence the overall absorption of a topically applied substance, namely, molecular weight (MW), **log** K_{ow} (octanol/water partition coefficient) and water solubility (S). For perspective, these were compared to more than half a million industry chemicals from the United States Environmental Protection Agency (USEPA) ACTOR database (Judson et al., 2012).

As shown in Fig. 2, the *MW*, **log** K_{ow} and **log** S values of ~500,000 industry chemicals from USEPA ACTOR database are calculated using EPI Suite (USEPA) and plotted to represent the chemical universe (Fig. 2A, blue dots). The same parameters of 2120 fragrance materials are also calculated and plotted in the same chart (Fig. 2A, red dots). Clearly, not only the number of fragrance material is significantly small, but the fragrance space is limited. Further analysis indicates that more than 99% of fragrance materials gave a *MW* ranging from 30 to 330 (Fig. 2B), a **log** K_{ow} from –1 to 9 (Fig. 2C), and **log** S from –9 to 1 (Fig. 2D). As such, we consider any materials falling within these ranges as "fragrance-like" materials.

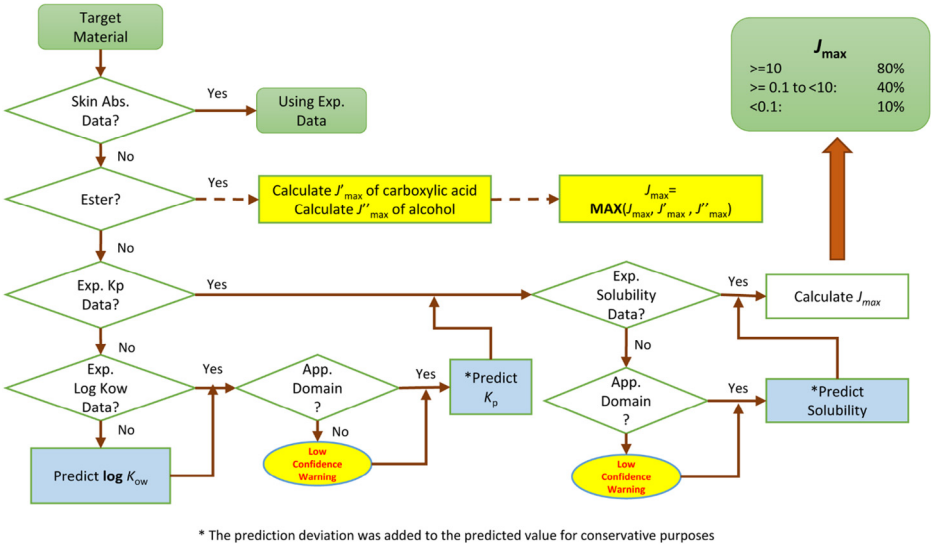

Fig. 1. Workflow for applying the skin absorption model (SAM) in safety assessment. For a target material, first, look for available skin absorption data. If an experimental value is not available, look for experimentally derived K_p and water solubility values to calculate J_{max}. If an experimentally derived K_p is not available, look for an experimentally derived **log** K_{ow}, or use consensus value to estimate the **log** K_{ow}, to determine a predicted K_p using Eq. (4). This predicted K_p may be used with experimentally derived or predicted solubility values to calculate J_{max}. Then the percent skin absorption is estimated based on Eq. (8). If the fragrance material is an ester, one needs to calculate the J_{max} of the parent and breakdown products (i.e., carboxylic acid and alcohol moieties). For conservative purposes accept the value that gives the highest skin absorption.