IH SkinPerm v2.0
Reference Manual

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I. General Information

1. IH SkinPerm is a model for estimating dermal absorption. It is formatted in Microsoft® Excel and is compatible with Excel 2003, 2007, 2010 and 2013. Basic knowledge of Excel is all that is needed to operate IH SkinPerm.

2. Apple® computers running Excel may not handle the Visual Basic coding in IH SkinPerm. The project team has not verified this. Therefore be aware IH SkinPerm may not run correctly or at all on Apple® computers.

3. Embedded in IH SkinPerm are Visual Basic macros (Microsoft® Excel) and Quantitative Structural Activity Relationships (QSARs) which drive the application. More detailed explanations of the QSARs in IH SkinPerm are published elsewhere

4. Spreadsheet protection is provided to prevent inadvertent changes to the equations and other functions. As stated in the “disclaimer”, users unlocking and modifying the spreadsheet accept all responsibility for their modifications.

5. IH SkinPerm is a work product of the AIHA Exposure Assessment Strategies Committee (EASC) and the Dermal Project Team (DPT) in collaboration with Wil ten Berge, author of the original SkinPerm model.

6. Although various parameters and data outputs have been explained or defined in IH SkinPerm through comments tagged on individual fields, users are encouraged to read Tibaldi et al. 2014.

7. In the Appendix the mathematical basis of IH SkinPerm is worked out.

II. Key assumptions built in IH SkinPerm

The stratum corneum cannot absorb more than 20% of its volume. If it absorbs more, the structure of the stratum corneum is damaged and no longer mimics intact skin. If the evaporation rate plus the absorption rate are less than the deposition rate, a film of liquid may appear on the skin. The stratum corneum thickness is assumed as 20 micrometers (2 x 10^{-5} meters).

Maximum absorption from the stratum corneum into the blood can never exceed the absorption, observed from a saturated aqueous solution of the substance. If the solubility is increased by solvents, the solubility of the substance should be revised to the measured aqueous solubility of the substance in the mixture.

IH SkinPerm model assumes the epidermis provides no barrier against permeation due to the lipid content of the blood and interstitial fluids around ~0.4%.
III. Substance domain of IH SkinPerm

The dermal absorption behavior is predicted from physicochemical properties of the substance like:

- **Molecular weight.** The molecular weight controls the diffusivity and the lag time. The statistical non-linear regression equations used for prediction of the permeation coefficient were derived for substances with a molecular weight range between 18 and 584.

- **Octanol/water partition coefficient (Kow) at the skin pH of 5.5.** A substance may permeate the stratum corneum through the lipid layers and the protein layers. The log(Kow) controls, which pathway of the stratum corneum is preferred. The statistical non-linear regression equations used for prediction of the permeation and partition coefficient were derived for substances with a log(Kow) range between -3.70 through 5.49.
  
The pH affects the log(Kow) of ionizable substances like organic acids and amines. For salts of strong acids and strong bases it is recommended to enter - 3 as value for the log(Kow).

- **Vapor pressure.** Exposure of the skin to a splash of a volatile substance (high vapor pressure) results mostly in a short exposure duration due to fast evaporation. On the contrary, less volatile substances (low vapor pressure) results into a long exposure duration due to slow evaporation in the absence of skin cleaning.

- **Water solubility.** The maximum dermal absorption flux is controlled by the water solubility and the aqueous permeation coefficient. Mixtures, which enhance the water solubility of the substance of interest, increase the maximum dermal absorption flux. The use of solvents like ethanol and propanol may enhance the water solubility. In complex mixtures of petroleum distillates the water solubility of many solid constituents compared to the pure compounds is increased.

IV. Getting Started with the Data Entry Sheet (Step 1)

Substance selection is the first step in using the tool. There is a SkinPerm database containing a pre-populated list of substances which can be select from the drop down arrow. There is a User’s database option to retrieve new substances added by the user. To add new substances the user will need to have physicochemical properties of the substance.
V. Exposure scenarios in IH SkinPerm (Step 2)

The skin may be exposed in many ways. IH Skinperm will estimate systemic absorption from skin exposure under the following scenarios.

On the Data Entry Sheet select the exposure scenario for which the dermal absorption of a substance during and after exposure is to be predicted.

1. Instantaneous deposition onto the skin is like a splash exposure. This requires the mass deposited in mg and the affected skin surface in cm² as inputs.
2. Continuous deposition upon the skin for example may occur during occupational loading activities or painting. Requires the skin deposition rate be estimated and inputted as mg/cm²/hour.
3. Airborne exposure to vapor of volatile substances. Requires the air concentration as mg/m³ as an input.
4. Skin exposure from an aqueous solution. This may simulate the dermal exposure of in vitro tests with a Franz Cell, or skin exposure from a pool of water. Water concentration as mg/L is required.

The required parameters to be entered for a selected scenario are highlighted in black.

V.1 Instantaneous deposition

Substance mass and skin surface area in contact with the substance are required for this scenario. The maximum skin adherence refers to the substance mass per cm² that can physically stay on the skin. This may be referenced in the literature or estimated. The maximum for solids is 3 mg/cm² and for liquids 10 mg/cm². If the instantaneous deposition is larger than the maximum skin adherence, the surplus is assumed to get lost. In a splash exposure IH SkinPerm will consider up to the maximum skin adherence for the affected skin area for the dermal absorption prediction. If the instantaneous dose is 10
mg/cm² and the maximum skin adherence is 1 mg/cm², then IH SkinPerm corrects the instantaneous dose to the maximum skin adherence of 1 mg/cm².

Air in direct contact with the skin is not fully mixed with the ambient air. It may be considered as a layer of stagnant air. The suggested thickness of the stagnant air layer above the skin is 1 cm for bare skin and 3 cm for light clothing.

The weight fraction is an important parameter for mixtures and should be considered dependent on the composition of the mixture. Examples of simple mixtures are discussed below.

**Considerations on the weight fraction**

*If a specific substance with low volatility is dissolved in hexane, acetone, ethanol or even water, the result is a mixture. After this mixture is instantaneously applied to the skin by a splash the solvent evaporates fast and the low volatility solute remains on the skin. In this case the mass of the solute may be considered as if it were applied as pure substance. The evaporation rates of hexane, acetone, ethanol and water are respectively 10, 9, 2.3 and 0.4 mg/cm²/minute estimated by IH SkinPerm. If the evaporation of the solute is less than 0.01 mg/cm²/minute, it is a reasonable approach to consider only the deposition of the solute per cm².*

Another exposure scenario is the application of a cream on the skin as an oil in water emulsion. An oil in water emulsion may be prepared from 3% polyglyceryl distearate; 3% cetyl stearyl alcohol; 10% light mineral oil; 5% propylene glycol; 0.5% propyl-p-hydroxybenzoate; 0.5% methyl-p-hydroxybenzoate and 78% water. Using a dermal cream results mostly into an application of about 1 mg/cm². The majority of the water (78%) will disappear within a few minutes. The remaining 22% (= 0.22 mg) will be absorbed into the stratum corneum. If the cream contains a constituent of interest at a content of 5% (w/w), the stratum corneum contains 50 microgram per cm². The dermal flux of the constituent of interest is predicted, as if this constituent would be applied as a pure substance.

The constituents of a hydrocarbon distillate have fractions with more or less comparable vapor pressure, because the composition of hydrocarbon distillate fractions are based on boiling point separation. Evaporation of the constituents is assumed to occur equally. If the complete distillate enters the stratum corneum, the maximum volume in the stratum corneum is assumed as 0.4 microliter. If the fraction of each constituent is known, the mass of each constituent in the stratum corneum per cm² can be calculated based on its weight composition. Because the mass of each constituent in the stratum corneum controls the flux according to IH SkinPerm, the dermal flux can be predicted for each constituent. Especially in the case of hydrocarbon distillates it is necessary to enter a value for the weight fraction in order to avoid flux overestimation. This is explained using jet fuel as an example.
Jet fuel contains aliphatic and aromatic hydrocarbons. The weight fraction of naphthalene has been reported to be about 0.3 mg/ml in jet fuel. If the skin is saturated with jet fuel, the naphthalene constituent in the stratum corneum would be 0.3 * 0.4 = 0.12 microgram/cm². (0.4 microliter is maximum volume that can be absorbed in the stratum corneum) Absorption estimation from jet fuel would be based on 0.12 microgram naphthalene per cm² of the stratum corneum.

An alternative, but incorrect calculation would as be as follows. Assume a maximum 8 microliter/cm² jet fuel is on the skin. This volume contains 2.4 microgram naphthalene. If one inputted an instantaneous deposition of 2.4 microgram pure naphthalene per cm² to the model this neglects the major part of the hydrocarbon mixture that would also be present in the stratum corneum. This would result in an overestimation of the systemic dermal absorption.

V.2 Deposition over time

This scenario is applied during occupational activities, in which exposure occurs over a period of several hours. The deposition over time in typical industrial activities can be referenced in risk assessment reports as mg/cm²/day. One source for dermal exposure is ECETOC, 2012. These estimates might be easily converted into mg/cm²/hour.

In this scenario the same considerations apply as described in instantaneous deposition.

V.3 Vapor to skin scenario

This scenario is useful to assess dermal absorption from airborne vapor. This also enables relative risk by exposure routes to be compared. The rate of skin absorption is controlled by the total body surface in contact with vapor and the airborne concentration. Clothing is assumed to form a barrier of stagnant air for vapor transfer. The thickness of this stagnant air layer is estimated to be 1 cm in case of bare skin and 3 cm in case of light work clothes.
V.4 Absorption from Water Solution

This scenario may be relevant for estimating absorption of a substance in water. Following are two examples.

a) Skin exposure to an aqueous solution of a substance in an in vitro laboratory test to simulate the design of an in vitro test. The affected skin area may be a value of 0.64 cm² or 1 cm². Substance concentration as mg/L is entered. A water and air thickness layer of 1 cm may be used. The amount absorbed into and permeated through the stratum corneum disappears from the mass of solute in the aqueous volume. This disappearance is considered in the simulation.

b) Skin exposure by swimming or bathing in contaminated water. In this case skin surface area should be set between 15000 and 20000 cm² and the water thickness should be set to 1000 in order to prevent depletion of the solute in the aqueous volume. This is highly relevant for lipophilic chemicals, because their water solubility is low.

After discontinuation of the aqueous exposure, the substance is still present in the stratum corneum. The substance is absorbed into the viable epidermis but evaporates also from the stratum corneum of bare skin. The thickness of stagnant air layer should be entered for correct simulation of the evaporation of the substance from the stratum corneum after exposure.
VI. Timing Parameters of the dermal exposure (Step 3)

The start of exposure should always be equal to or later than 0 hours but is typically set at 0 hours. This option is only made in order to modify the graphical presentation of an exposure and to start exposure at a later time than 0. The start of the observation is always implicitly set at 0 hours.

The duration of exposure cannot be set in case of instantaneous deposition. The duration of exposure in case of instantaneous deposition is dependent on the deposited mass and on the physicochemical properties of the substance.

A duration of exposure is required for deposition over time, vapor and water scenarios to simulate dermal exposure. The duration of exposure can never be larger than the end time of observation. So entering a duration value larger than the end time of observation will prompt a message for correction.

One should consider, that at the end time of observation, the substance might be still present in the stratum corneum. This means, that the selected end time of observation (mostly 8 hours for a working day) is not equivalent with discontinuation of dermal exposure. So it is recommended to select an end time of observation, where the dermal flux of the substance is close to zero.
VII. Reporting parameters (the 4th step).

Two parameters are of interest in the final prediction:
1) The calculation interval per hour. A value of 10000 means that for each subsequent 0.36 seconds the following quantities per cm² are calculated:
   a) upon the skin
   b) in the stratum corneum
   c) evaporated
   d) absorbed in the blood
   e) dermal flux

2) Report intervals per hour. A value of 100 means, that 100 time points are used for drawing the graph of the quantities mentioned above (a through e). The report interval per hour controls the speed of the calculations. The report interval can never exceed the calculation intervals. Entering a value for reporting intervals/hour higher than the calculation intervals/hour will prompt immediately a message for correction of the input value.

VIII. The start of the calculation

The final last step 5 is clicking on the green button for starting the calculation.
IX. Report Sheet

The report sheet of IH SkinPerm shows many results and graphical pictures. The meaning of all these data in relation to dermal absorption are explained below.

IX.1 Absolute and relative absorption in the blood

The most relevant information is presented in the upper left corner of the report sheet. The absolute mass absorbed is stated and also the percentage of the total applied dose. One should realize, that this is the absorbed mass at the end of the observation period. The observation period in this example was 3 hours and the absorption amount was determined on the basis of the fate of the substance against the time of observation.

IX.2 Standard data on kinetics of the dermal permeation

These data are presented on the middle left side of the report sheet. The most relevant data are the lag time and the maximum dermal flux.
In addition, the predicted dermal permeation coefficient from water or from air as vehicle are presented with the corresponding confidence limits, considering the variances of the statistical regression analysis.

In the benzylalcohol example above it should be noted, the permeation coefficient from air was predicted taking into account a stagnant air layer of 3 cm, ie skin covered with light clothing. If the benzylalcohol scenario involved bare skin a stagnant air layer of 1 cm would be used. One would then observe the permeation coefficient from air to be about a factor 2 larger. So the dermal absorption flux is generally larger for someone dressed in shorts (major part bare skin) than wearing light work clothes.

**IX.3 Use of estimated results for hazard labelling and risk assessment**

This graph is presented in the lower left corner of the report sheet and is meant to provide some perspective on the dermal absorbed mass in comparison with absorbed mass by inhalation.

The maximum dermal absorption through a skin area of 2000 cm² per hour can be compared with the absorption by inhalation exposure over 8 hours at the level of the occupational exposure limit (OEL). If the maximum dermal absorption is higher than one tenth of the inhaled absorbed dose over 8 hours, the substance will get a Skin notation in Europe.

Exposure to vapor can result in an absorption by inhalation and skin. IH SkinPerm estimates the dermal absorption dose for full body exposure wearing light work clothes (stagnant air layer of 3 cm) for a period of 8 hours. This dermal absorbed dose over 8 hours is compared with an inhaled dose over 8 hours. The ratio between the dermal dose and the inhaled dose is presented. From this ratio the level of protection by full respiratory protection is estimated. This is not so important for benzyl alcohol, but for substances with a low OEL like aniline, phenol and nitrobenzene this is highly relevant.
**IX.4 Fate of the substance in the dermal compartments**

The graph in the right upper part of the report sheet presents the fate of the substance. The simulated scenario is the instantaneous application of 250 mg of benzyl alcohol on a skin surface of 1000 cm².

The graph plots the start of exposure in mass over time in hours. The mass is related to:
- mass on the skin surface
- mass evaporated from the stratum corneum
- mass in the stratum corneum
- mass permeated through the stratum corneum and absorbed in the systemic circulation

The vertical dotted line indicates the time point 36 minutes after the start of exposure. This vertical line is moved forward and backward with the so-called Drolet spinner.
**IX.5 The Drolet spinner**

The spinner enables one to view exposure and permeation by compartment at various time settings.

As in this figure the time after exposure has been set to 0 hr 36 min. At this point in time the mass:
- upon the skin is 0 percent.
- evaporated is 35.1 percent.
- in the stratum corneum is 30.5 %.
- permeated into in the body 34.5 %.

Please, consider that the dermal absorption has been finished only, when the mass in the stratum corneum is zero. As long as the substance is present in the stratum corneum, the absorption into the body may continue.
**IX.6 Plot of the systemic absorption rate against time after start of exposure**

The systemic dermal absorption rate has toxicological significance. The dermal dose rate may be compared for instance with an intravenous infusion rate or the absorbed dose rate from inhalation exposure in mg/hour.

Comparison of this graph in IX.6 with the graph shown in IX.4 reveals, that the absorption continues as long as the mass of the substance in the stratum corneum is larger than zero.

There are substances which have a long residence time in the stratum corneum. If the maximum dermal absorption rate is about 0.001 mg/cm² per hour and the stratum corneum contains 0.04 mg/cm², dermal absorption may continue for more than 40 hours in the absence of any skin metabolism.
X. Dermal assessment examples

The following examples further elaborate on technical aspects around dermal absorption and assessment of results for pure substances and mixtures.

X.1 Water furfural mixture

The evaporation rate of water and furfural from a liquid surface is in the same order of magnitude. The final maximum concentration in the stratum corneum is linearly related to the concentration of the substance of interest, if the substances in the mixture have vapor pressures within one order of magnitude. This means that the evaporation of the total mixture should be taken into account. The absorption will be simulated for a splash of 20 ml of the mixture or less over the hands in a laboratory. The extent of absorption will be simulated for different furfural levels in the mixture but the total deposited dose of furfural is similar in all scenarios.

Because this example deals with exposure to bare skin, the thickness of the stagnant air layer is set to 1 cm.

A splash of 20 ml over the hands (1000 cm² area) results in a deposited dose of 20 mg/cm². Maximum skin adherence of this mixture however is estimated as 7 mg/cm².

The absolute mass is estimated, that is absorbed into the blood dependent on the furfural content of the mixture (12.5%, 25%, 50% and 100%). In the table below the instantaneously deposited mixture mass is decreasing, furfural mass remains the same, and its weight fraction in the mixture increases. The table below shows the differences in systemic absorbed mass (mg) after 6 hours exposure.

<table>
<thead>
<tr>
<th>Deposited mass Mixture (mg)</th>
<th>Deposited mass Furfural (mg)</th>
<th>Weight fraction (w/w)</th>
<th>Systemic Absorption furfural (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20000</td>
<td>2500</td>
<td>0.125</td>
<td>51</td>
</tr>
<tr>
<td>10000</td>
<td>2500</td>
<td>0.250</td>
<td>102</td>
</tr>
<tr>
<td>5000</td>
<td>2500</td>
<td>0.500</td>
<td>158</td>
</tr>
<tr>
<td>2500</td>
<td>2500</td>
<td>1.000</td>
<td>187</td>
</tr>
</tbody>
</table>

A large part of the difference is caused by the loss of the mass, because the mass on the skin is limited to 7 mg/cm² as maximum adherence. In the first row of the table a mass of 20000 mg has been applied to 1000 cm² skin, that is 20 mg/cm². Only 7 mg/cm² sticks to the skin, so a mass of 13 mg/cm² of the mixture get lost or a total mass of 13000 mg. This can be an important exposure factor to consider.

It is recommended the deposited mass of the mixture and the weight fraction of the substance of interest be entered, if the constituents have vapor pressures within one order of magnitude.
### X.2 Oil in water emulsion (cream)

A dermal absorption study of dibutylphthalate, farnesol and geraniol in the hairless guinea pig was published by Doan et al (2010). These compounds may be present in skin cream. These compounds were applied as constituents of an oil in water emulsion at 1 mg per cm² skin. The cream contained 78% water. After application on the skin the water evaporates in a few minutes and the oil fraction (0.22 mg per cm²) is fully absorbed into the stratum corneum.

In this mixture, the lipophilic fraction is fully absorbed in the stratum corneum. The behavior of the applied constituents are as if they were applied as a tiny dose of the pure constituent. In the study, 70 microgram dibutylphthalate, 50 microgram farnesol and 20 microgram geraniol were in the mixture dose of 1 mg/cm². These amounts are entered as an instantaneous dose per cm² in IH SkinPerm. Bare skin is assumed, so the thickness of the stagnant air layer is set to 1.

The experimental and IH SkinPerm predicted results are summarized in the table below. The study by Doan et al (2010) was an in vivo study and a single result on systemic absorption and evaporation was made after 24 hours.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Measured systemic absorption %</th>
<th>Simulated systemic absorption %</th>
<th>Measured evaporation %</th>
<th>Simulated evaporation %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dibutylphthalate</td>
<td>65.4</td>
<td>48.6</td>
<td>7.4</td>
<td>3.6</td>
</tr>
<tr>
<td>Farnesol</td>
<td>44.1</td>
<td>94.6</td>
<td>5.0</td>
<td>5.3</td>
</tr>
<tr>
<td>Geraniol</td>
<td>21.3</td>
<td>51.3</td>
<td>49.9</td>
<td>48.7</td>
</tr>
</tbody>
</table>

In the case of geraniol the evaporative loss occurred in the first hour after application, both in the experiment and the simulation. This example provides some validation on predictions by IH SkinPerm. It also demonstrates how the tool might aid the design dermal absorption studies with a simple model simulation.
X.3 Simulation of dermal permeation by occupational exposure to vapor.

Dermal absorption of vapor from air should consider the body surface area exposed. Total body surface area is between 15000 and 20000 cm² and a large part of the body is often covered by light clothing. In this case the thickness of stagnant air layer around the body should be set to 3 cm. The total systemic absorption by exposure to 1 mg/m³ for 8 hours is presented in the figure below.

In this specific example of aniline the systemic body flux via the skin is 1 mg/hour. The systemic flux by inhalation is found to also be about 1 mg per hour. This means that full respiratory protection is only 50% effective in the case of aniline.

This finding does not apply to all substances. However, IH SkinPerm provides the tool to recognize the relevance of the dermal route.
X.4  *In vitro exposure of human skin to an aqueous solution*

This example shows the limitations on measuring the flux of an aqueous solution of a lipophilic substance over a period of 24 hours. A milliliter solution of triclosan in water (10 mg/liter) is in contact with 1 cm2 human skin in vitro. In this case the thickness of the water layer is set to 1 cm.

IH SkinPerm plots the triclosan mass in the stratum corneum (orange line) and absorbed mass reaching the receptor fluid (green line) with exposure time. In a separate graph below the dermal flux in mg/cm2/hr is plotted.

In this example no steady state is achieved (The green line does not level off). Triclosan enters the stratum corneum and the receptor fluid. The aqueous solution gets depleted of triclosan as triclosan mass is absorbed into stratum corneum and in the receptor fluid. After 24 hours the aqueous solution contains only 1.5 mg/liter, quite different from the starting level of 10 mg/liter.

Absorption rate at steady state is linearly related to the solute concentration. If the triclosan concentration decreases, the absorption rate does too. The lower graph is used to show this.

For triclosan the maximum absorption rate is 0.823 ug/cm2/hour calculated by IH SkinPerm. In this scenario the absorption rate of 0.7 ug/cm2/hr was reached in the first 2 hours (nearly achieving the max rate).

At 24 hours only 8.43 ug was absorbed in the receptor fluid as noted in first graph. This is an average absorption rate of 0.352 microgram/cm2/hour. This is quite different from the maximum rate of 0.823 microgram/cm2/hour. This shows that averaging absorption from an aqueous solution over 24 hours for estimation of the flux per hour can underestimate the max flux rate as shown in the triclosan case and more generally for substances with a log(Kow) of larger than 5.
IX. References


Vecchia BE and Bunge AL, 2002b. Partitioning of chemicals into skin: Results and Predictions. Chapter 4 in Transdermal Drug Delivery, edited by Guy RH and Hadgraft J, Publisher Marcel Dekker


Appendix

QSARs and differential equations incorporated in IH SkinPerm are discussed below. Explanation of parameters and units are provided below in the annex.

**QSARs**

Each chemical has its own aqueous skin permeation coefficient and partition coefficient. Vecchi and Bunge compiled a database of validated permeation and partition coefficients of many substances for human skin, in vitro, exposed to aqueous solutions. Ten Berge (2009) used the database of the validated aqueous permeation coefficients to derive a QSAR for the aqueous permeation coefficient, related to the molecular weight and the octanol/water partition coefficient. In addition, he used the validated partition coefficients to derive a QSAR for the stratum corneum/water partition coefficient, related to the octanol/water partition coefficient.

The aqueous permeation coefficient considers two dermal pathways, one through the lipid layer and the other through the corneocytes. The permeation coefficient through the lipid layer is nearly similar to that of Potts and Guy (1992). The permeation coefficient through the corneocytes has been added. This second pathway is needed to describe the permeation of very water soluble compounds. The dermal permeation of ions might be simulated by setting the log(Kow) of ions to -3. For many substances like organic acids and bases the log(Kow) is dependent on the pH. The pH of the skin is about 5.5. So the log(Kow) at pH 5.5 should be used for the estimation of the aqueous permeation coefficient and for the estimation of the stratum corneum/water partition coefficient.

\[
K_{p_{sk-water}} = \frac{P_{sc/w}*D_{f_{sc}}}{h_{sc}}
\]

\[
t_{lag} = \frac{h_{sc}^2}{6D_{f_{sc}}} = \frac{h_{sc}*P_{sc/w}}{6K_{p_{sk-water}}}
\]

\[
D_{f_{sc}} = \frac{h_{sc}^2}{6t_{lag}} = \frac{P_{sc/w}}{P_{sc/w}}
\]

\[
P_{sc/w} = 0.72*K_{ow}^{0.43} \quad \text{if} \quad P_{sc/w} < 0.2 \quad \text{then} \quad P_{sc/w} = 0.2
\]

\[
K_{p_{sk-water}} = K_{p_{lipids}} + K_{p_{corneocytes}}
\]

\[
K_{p_{lipids}} = 10^{(-2.59+0.732*10\log(Kow)-0.00683*Mw)}
\]

\[
K_{p_{corneocytes}} = \frac{0.043}{Mw^{1.36}}
\]

**Differential Equations**

\[
\frac{dM_{surf}}{dt} = Deposition \ rate \ [mg/cm^2/h] - Uptake \ (SC) \ rate \ [mg/cm^2/h]
\]
\[
- \ Evaporation(\text{subst}) \ rate \ [mg/cm^2/h]
\]

\[
(8)
\]
**Evaporation of the Liquid Film on the Skin**

When deposition occurs on the surface of the skin, a film of liquid may form. The liquid evaporates. The method incorporated into IH SkinPerm for estimating the rate of evaporation has been reported by Gmehling et al (1989) and by Weidlich et al (1986). This method is referenced in the REACH guidance for occupational exposure assessment. The mathematical description of the evaporation from a liquid film on the skin is presented in equation 9 through 11.

\[
Evaporation(\text{neat liquid})\text{rate} = \frac{\beta \cdot M_w \cdot V_p}{R \cdot T \cdot 10} \quad [\text{mg/cm}^2/\text{h}] \tag{9}
\]

\[
\beta = \frac{0.0111 \cdot V^{0.96} \cdot D_g^{0.19}}{v^{0.15} \cdot x^{0.04}} \tag{10}
\]

\[
D_g = 0.06 \cdot \sqrt{76/M_w} \tag{11}
\]

**Absorption of Neat Liquid on the Skin into the Stratum Corneum**

The uptake of neat liquid into the stratum corneum is described in equation 12:

\[
\text{Uptake (into SC from neat liquid) rate} = 2 \cdot \left[\frac{\text{Den} + \text{Dif} \cdot \text{fsc}}{h_{sc}}\right] \cdot \left[\frac{M_{\max} - M_{sc}}{M_{\max}}\right] \quad [\text{mg/cm}^2/\text{h}] \tag{12}
\]

A critical assumption in the model is that the SC cannot absorb more than 20% of its volume because otherwise the physical chemical structure of the stratum corneum and permeation characteristics deviates from intact skin. This assumption requires the introduction of a parameter into the model to account for the maximum load of a substance per cm\(^2\) stratum corneum (M\(_{\max}\)). Dermal absorption into the stratum corneum is assumed to be controlled by the diffusivity of the chemical in the stratum corneum and the thickness of the stratum corneum. This means that the permeation coefficient for neat liquid into the stratum corneum may be described by the diffusivity divided by the thickness of the stratum corneum. In equation 12, the permeation coefficient of the neat liquid is multiplied by the density of the neat liquid, which results in an initial flux in mg/cm\(^2\)/hour. In order to be consistent with steady state, a factor of 2 is applied for mass balance. At steady state M\(_{sc}\) is assumed to be half M\(_{\max}\) in case of maximum flux of water soluble compounds.

**Absorption from Vapor in Air into the Stratum Corneum**

The mathematical description of dermal uptake into the stratum corneum from air is similar to that of the stratum corneum/water partition coefficient. Diffusivity does not change, it is a property specific to the substance. The partition coefficient SC/air is different from the partition coefficient SC/water with a factor K\(_{wa}\), the reciprocal dimensionless Henry coefficient (see equation 13).

\[
K_{wa} = \frac{R \cdot T \cdot W_{solub}}{M_w \cdot V_p} \tag{13}
\]
The gaseous dermal permeation coefficient $K_{p_0}$ of human stratum corneum in contact with the vapour of a chemical in air is the product of $K_{wa}$ and the aqueous skin permeation coefficient:

$$K_{p_0} = K_{wa} \times K_{p_{sk-water}} \quad [cm/h] \quad (14)$$

The permeation coefficient of the stratum corneum from a substance in the vehicle air $K_{p_0}$ is valid only if the air concentration in contact with the skin is similar to the ambient air concentration. In most cases this is true. In the case where substances permeate the stratum corneum very fast (e.g., butyloxyethanol), the air concentration in direct contact with the skin can be lower than in the workroom air. The resistance to mass transfer in air is higher than in the stratum corneum.

A layer of stagnant air is assumed to be present as an interface between workroom air and the skin. The thickness of the stagnant air layer can vary. IH SkinPerm uses a 3 cm default value based on observations made in diffusion and ventilation studies involving two layer clothing.\(^{(14,15)}\) For bare skin the stagnant air layer and resistance to vapor transfer is expected to be smaller, for example 1 cm.

The permeation coefficient through the stagnant air layer is estimated from the diffusivity of the chemical in air and the thickness assumed for the stagnant air layer (equation 15 and 16).

$$K_{p_{air}} = \frac{Diff_{air}}{Len_{air}} \quad [cm/h] \quad (15)$$

$$Diff_{air} = 360 \times \sqrt{76/Mw} \quad [cm^2/h] \quad (16)$$

In order to account for the resistance in the stagnant air layer and in the stratum corneum, the correct gaseous dermal permeation coefficient ($K_{p_{sk-air}}$) for vapor in workroom air is formulated in equation 17

$$K_{p_{sk-air}} = \frac{1}{1/K_{p_{0}} + 1/K_{p_{air}}} \quad [cm/h] \quad (17)$$

The increase of the mass in the stratum corneum is related to the concentration in air and the mass already in the stratum corneum. The mass in the stratum corneum may not be larger than the smaller value of $M_{max}$ or $Maq$. This is reflected in equations 18 and 19.

$$Uptake(\text{into SC from air}) \ rate = 2 \times K_{p_{sk-air}} \times (Conc_{Air} - Fr_{Maq} \times C_{max_{air}}) \quad [mg/cm^2/h] \quad (18)$$

$$C_{max_{air}} = \frac{V_{p+Mw}}{101.325 \times 24.45} \quad [mg/cm^3] \quad (19)$$

Transfer from the Stratum Corneum into the Blood

Transfer from the stratum corneum to the blood is assumed to be fully controlled by aqueous diffusion. Water solubility cannot be exceeded in an aqueous diffusion process. This means that the permeation rate of the substance into the skin will not exceed the dermal flux at the
maximum solubility of a substance in the aqueous medium. The stratum corneum may be loaded with more substance than the amount at equilibrium with a saturated aqueous solution (= Maq), however, it is assumed that the dermal flux will not increase. Maq is the maximum mass (mg/cm²), that can be absorbed into the stratum corneum from a saturated aqueous solution and at which the absorption rate in the blood is maximum. The absorption rate in the blood is assumed to be directly related to the mass of the chemical in the stratum corneum (= Msc) as a fraction of Maq. Because water solubility cannot be exceeded in aqueous diffusion, this fraction can never exceed the value of 1. The equations presented support experimental observations that find the maximum dermal flux is more or less similar for a neat chemical or saturated aqueous solution. The equation 20 covers the transfer from the stratum corneum into the dermis and finally the blood capillary bed.

\[
\text{Absorption from SC} = -2 \times K_{p_{sk-water}} \times Fr_{Maq} \times W_{solub}/1000 \quad [mg/cm^2/h] \quad (20)
\]

**Transfer from the Stratum Corneum into the Air.**

After evaporation of the substance as a liquid film on the surface of the skin, the stratum corneum may still contain the substance. The substance in the stratum corneum disappears via 2 pathways. The toxicological relevant pathway is absorption into the blood. The other pathway is transfer from the stratum corneum into the air.

The rate of transfer from the stratum corneum into the air is assumed to be related to the mass of the chemical in the stratum corneum in the same way as the transfer of the substance from of the stratum corneum to the blood. In addition, the mass transfer from the stratum corneum to the air also considers the stagnant air layer through which the vapor of the chemical is transferred to the ambient air. The transfer from the stratum corneum to air is described by equations 21 and 22.

\[
\text{Evaporation from SC} = -2 \times K_{p_{evap}} \times Fr_{Maq} \times W_{solub}/1000 \quad [mg/cm^2/h] \quad (21)
\]

\[
K_{p_{evap}} = \frac{1}{K_{p_{sk-water}} + \frac{K_{wa}}{K_{p_{air}}}} \quad cm/h \quad (22)
\]

The transfer coefficient from the SC into ambient air $K_{p_{evap}}$ decreases with an increasing $K_{wa}$. The $K_{wa}$ increases with low vapor pressure and/or large water solubility. Where $K_{wa}$ (reciprocal dimensionless Henry coefficient) is large, the $K_{p_{evap}}$ becomes very small and the evaporation rate from the stratum corneum becomes much smaller than the absorption rate into the viable epidermis.

**Transfer from aqueous solution into the stratum corneum**

The concentration of the aqueous solution is assumed to be constant in case of steady state calculations. In case of real time simulation, the concentration of the aqueous solution will decrease due to transfer of the substance from the aqueous solution into the Stratum corneum of the skin. If the concentration is high, the concentration will hardly decrease over the duration of
dermal exposure. In this case the dermal dose is called infinite. With decreasing water solubility the concentration may change during the duration of exposure. The dermal dose is considered to be finite. In the simulation of dermal absorption from the aqueous solutions the change of concentration is taken into account.

As long as the aqueous solution is in contact, the following equations are to be applied:

\[
\frac{dM_{\text{wat}}}{dt} = \frac{2 \times Kp_{sk-water} \times (C_{\text{wat}} - Fr_{\text{Maq}} \times W_{\text{solub}})}{1000} \quad [\text{mg/cm}^2/\text{h}] \quad (23)
\]

\[
C_{\text{wat}} = \frac{1000 \times M_{\text{wat}}}{L_{\text{en,wat}}} \quad [\text{mg/litre}] \quad (24)
\]

\[
\frac{dM_{\text{sc,abs}}}{dt} = -2 \times Kp_{sk-water} \times Fr_{\text{Maq}} \times W_{\text{solub}} / 1000 \quad [\text{mg/cm}^2/\text{h}] \quad (25)
\]

\[
\frac{dM_{\text{sc}}}{dt} = \frac{dM_{\text{wat}}}{dt} + \frac{dM_{\text{sc,abs}}}{dt} \quad \text{change of mass in SC} \quad [\text{mg/cm}^2/\text{h}] \quad (26)
\]

Absorption rate in blood = \[
\frac{dM_{\text{sc,abs}}}{dt} \quad (27)
\]

Calculations by means of differential equations

The mass on the skin surface and in the stratum corneum and the mass permeated and evaporated are calculated by means of the differential equations with a time step of 0.0001 hour.

Annex

Explanation of parameters and units

\( \beta \) = coefficient of mass transfer (m/h)
\( C_{\text{max,air}} \) = maximum concentration in air at 25 °C \( [\text{mg/cm}^3] \)
\( \text{ConcAir} \) = concentration in the workroom air \( [\text{mg/cm}^3] \)
\( C_{\text{wat}} \) = concentration in the water layer
\( D_{\text{g}} \) = molecular diffusivity in air \( [\text{m}^2/\text{h}] \)
\( D_{\text{diff,air}} \) = molecular diffusivity in air \( [\text{cm}^2/\text{h}] \)
\( D_{\text{diff,sc}} \) = diffusivity stratum corneum \( [\text{cm}^2/\text{h}] \)
\( Fr_{\text{Maq}} \) = \( \frac{M_{\text{sc}}}{M_{\text{aq}}} \) : if \( Fr_{\text{Maq}} > 1 \) then \( Fr_{\text{Maq}} = 1 \)
\( K_{\text{ow}} \) = octanol/water partition coefficient of substance
\( h_{\text{sc}} \) = thickness stratum corneum \( [0.002 \text{ cm}] \)
\( Kp_{a0} \) = permeation coefficient of SC from air in contact with SC \( [\text{cm/h}] \)
\( Kp_{\text{air}} \) = permeation coefficient stagnant air layer \( [\text{cm/h}] \)
\( Kp_{\text{corneocytes}} \) = permeation coefficient corneocytes of SC \( [\text{cm/h}] \)
\( Kp_{\text{evap}} \) = mass transfer coeff. from SC to air \( [\text{cm/h}] \)
\( Kp_{\text{lipids}} \) = permeation coefficient lipid matrix of SC \( [\text{cm/h}] \)
\( Kp_{sk-air} \) = permeation coeff of SC from ambient air \( [\text{cm/h}] \)
\( Kp_{sk-water} \) = aqueous permeation coefficient of human skin \( [\text{cm/h}] \)
\( K_{\text{wa}} \) = ratio between conc in water and air
\( \text{Len}_{\text{air}} = \) stagnant skin air layer [1 to 10 cm]
\( \text{Len}_{\text{wat}} = \) thickness of water layer [cm]
\( \text{Maq} = h_{sc} \times P_{sc/w} \times W_{\text{solub}}/1000 \) [mg/cm\(^2\)]
\( \text{Maq} = \) mass in stratum corneum in equilibrium with saturated aqueous solution [mg/cm\(^2\)]
\( M_{\text{max}} = \) maximum mass in stratum corneum (0.0004 * Dens) [mg/cm\(^2\)]
\( M_{\text{sc}} = \) actual mass in stratum corneum [mg/cm\(^2\)]
\( M_{\text{surf}} = \) actual mass of neat liquid on skin surface
\( M_{\text{wat}} = \) actual mass of substance in aqueous volume [mg/cm\(^2\)]
\( M_w = \) molecular weight of substance [g/mol]
\( \nu = \) kinematic viscosity of air 0.054 [m\(^2\)/h]
\( P_{sc/w} = \) partition coefficient stratum corneum/water
\( R = \) gas constant 8.314 [Pa m\(^3\)/Mol/\(^o\)K]
\( SC = \) suffix, referring to stratum corneum of the skin
\( T = \) temperature \(^o\)K
\( t_{\text{lag}} = \) lag time [h]
\( V = \) velocity of air 1080 [m/h]
\( V_p = \) vapour pressure of the chemical at skin temperature [Pa]
\( W_{\text{solub}} = \) water solubility [mg/l]
\( X = \) length of area of evaporation 0.1 [m]