DERMAL EXPOSURE MODELING

Tom Armstrong, CIH, PhD

With thanks to:
Rosalie Tibaldi, Daniel Drolet,
Wil Ten Berge and Jennifer Sahmel
PRINCIPLES TO COVER (BRIEFLY)

- Dermal deposition, liquids and solid particulates, for pure substances and mixtures
- General dermal exposure models
  - Deposition
  - Absorption
- Dermal permeation theory
- Octanol-water partitioning, its importance and methods of estimation
- Important tools and data sources

PRINCIPLES TO COVER --- IN MORE DETAIL

- IH SkinPerm development, theory and use
  - Neat compounds
  - Aqueous mixtures
  - Air to dermal absorption
ESTIMATES OF DEPOSITION MODELS – HOW MUCH GETS ONTO SKIN

RISKOFDERM: The RISKOFDERM model was developed for estimating potential dermal exposure, i.e., the total amount of a substance coming into contact with the protective clothing, work clothing and exposed skin … **it does not estimate absorption**. The model originally consists of a set of equations, which have been entered into a user friendly MS Excel® spreadsheet. This model is used to estimate potential dermal exposure to a product or substance used for, or handled in a separate process or task within a workday.

“… not targeted at experts in occupational hygiene, physicians, toxicologists or enterprises with the capability to carry out more detailed dermal risk assessments. However, these experts may find the toolkit useful as an initial rough estimate of dermal hazard, dermal exposure and dermal health risk before starting in-depth investigations.”

RiskofDerm was build with occupational task scenarios, but can be easily extrapolated to consumer task exposures in similar categories.

To find the link to download the tool from TNO, just Google search RiskofDerm
THE OLD UK HSE MODEL EASE INCLUDED ESTIMATES OF DEPOSITION

- EASE an expert system that used rules on a scenario description to search an evaluated exposures database
- For described scenario and substance properties, it delivered an estimated load in mg/cm$^2$ for the affected skin area
- It did not predict absorbed dose or evaporated fraction
- The principles of this seem to have been expanded and updated in RiskofDerm
ESTIMATING DEPOSITION VIA FIELD STUDIES
How Can Contact leading to Dermal Deposition Occur?

- Direct contact with the chemical, or matrix containing the chemical
- Contact with contaminated surfaces (e.g. tools, tables, walls, clothing, even other persons)
- Contact with an aerosol after deposition
DETERMINANT CATEGORIES FOR DERMAL CONTACT

- substance and product characteristics
- task done by the user
- task process techniques and equipment
- exposure control measures
- user characteristics and habits
- environmental conditions

**Calculating a Dermal OEL Equivalent**

- In some cases, an existing airborne OEL can be used to evaluate semi-quantitative data for dermal exposures
- Inhalation rates: 11-19 m$^3$ air inhaled/day (moderate activity - EPA Exposure Factors Handbook); 10 m$^3$/day is a typically assumed occupational value

OEL (mg/m$^3$) x m$^3$ air inhaled/work day = mg/day

However, for some substances the retained inhaled systemic dose < the total inhaled dose

Since it is USUALLY based on TLVs, it does not account for sensitive subpopulations and long term continuous exposures, but some organizations apply a series of safety factors to OELs

Various sources of general population target doses may be useful for comparison to dermal doses such as RfDs
Dermal permeation goes from surface deposition through the stratum corneum and viable epidermis to the vasculated layer where aqueous solubility drives systemic uptake.
Here is a Description of Intact Skin

- The strateum corneum is the outermost layer, of flattened dead ketatinized corneocytes in a lipid matrix.
  Corneocytes are polyhedral, anucleated cells without cytoplasmic organelles, interlocked with each other and organized as vertical columns of 10–30 cells and embedded within a highly hydrophobic lipid matrix to form the stratum corneum.
- This layer can absorb up to three times its weight in water.
- The viable epidermis is the next layer down – living cells in an aqueous matrix.
- Keratinocytes in the viable epidermis will multiply through cell division and migrate toward the skin surface.
- From the viable epidermis, the permeating material is available for dissolution and uptake via the capillary bed.
- The interstitial fluid is largely water, but with some blood lipids.
How thick is the epidermis?

- In humans it is thinnest on the eyelids at 0.05 mm (0.0020 in) and thickest on the palms and soles at 1.5 mm (0.059 in)
- This different thickness affects the lag time of permeation and the loading in the epidermis.
- This thickness also affects the time it takes for the loading in the skin to be absorbed
Some Examples of Dermal Exposure Models

The models presented can be used only for systemic toxics – *they do not address sensitization or irritation or corrosion of the skin*.

Three basic “models” presented here:

- Calculation of a dermal OEL equivalent
- AIHA dermal exposure model (conservative, uses a 100% absorption value by default, but that is easily modified)
- IH SkinPerm Tool - Revised Robinson model (estimates skin absorption based on exposure concentration and chemical-specific skin permeation rate)
AIHA’S EXPOSURE ASSESSMENT STRATEGIES COMMITTEE MODEL: DERMAL EXPOSURE MODEL

\[ D = (S)(Q)(WF)(FQ)(ABS) \]

D = potential dose (mg/day)
S = surface area of contact (cm\(^2\))
Q = amount retained on the skin (mg/cm\(^2\))
WF = C = concentration of chemical (percent by weight)
FQ = number of contact events per day
ABS = absorption (default 100% absorption into skin; or empirically derived data may be appropriate)

Variations on this model are widely used

# Skin Surface Areas

Taken from the U.S. EPA’s Exposure Factors Handbook, 1997, Volume I, Chapter 6: Dermal, Table 6-4, Surface Area by Body Part for Adults, m², and 2009, Chapter 7: Dermal, Table 7-11, Surface Area of Adult Males (21 Years and Older) in Square Meters

<table>
<thead>
<tr>
<th>Body Part</th>
<th>Mean (Men) 1997</th>
<th>Mean (Men) 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head</td>
<td>1180 cm²</td>
<td>1360 cm²</td>
</tr>
<tr>
<td>Arms</td>
<td>2280 cm²</td>
<td>2890 cm²</td>
</tr>
<tr>
<td>Forearms</td>
<td>1140 cm²</td>
<td>1460 cm²</td>
</tr>
<tr>
<td>Hands</td>
<td>840 cm²</td>
<td>1070 cm²</td>
</tr>
<tr>
<td>Palms</td>
<td>150 cm²</td>
<td></td>
</tr>
<tr>
<td>Thumb</td>
<td>~24 cm²</td>
<td></td>
</tr>
</tbody>
</table>

WHOLE BODY about 20,000 cm²
AMOUNT OF CHEMICAL RETAINED ON SKIN

- The amount retained on skin, or Q values, have been experimentally estimated.
- These are given as mass per surface area of skin (surface density) rather than mass per volume (concentration).
- The US EPA table of suggested Q values for common industrial tasks (and similar consumer tasks) is available in the course handouts: routine or incidental contact in the range of 0.7 – 2.1 mg/cm².
  (consider lower values for thin watery fluids, and higher values for thicker oily compositions)
- Values from updated EPA Exposure Factors Handbook (2009) for solids are in the range of 0.13 – 0.27 mg/cm² for adults.
- These are for the whole matrix. A constituent would be proportionally less.
**Thick Viscous Films on Skin Have Several Aspects to Consider**

- The total quantity of the substance of concern may not be available if it remains in the film.
- There will be a concentration gradients, possibly at the skin-film and air-film interfaces.
- The kinetics of molecular diffusivity may limit the quantities delivered to the skin interface or to the air interface.

Is the thick layer wiped off or washed off before the applied dose can be absorbed?
**Example: AIHA Model Dermal Calculation for Methanol**

A person is filling an automobile windshield washer solvent reservoir. The solvent is water with 30% methanol by weight. Both hands may be slashed with the solvent.

\[ D = S \times Q \times WF \times FQ \times ABS \]

- **S** = Surface area = 2 hands = 840 cm\(^2\)
- **Q** = Amount retained on skin = 1.4 mg/cm\(^2\)
- **WF** = Concentration by weight = 30% or 0.30
- **FQ** = Number of contacts = 1
- **ABS** = 100% or 1.0 (default assumption)

\[ D = 840 \text{ cm}^2 \times 1.4 \text{ mg/cm}^2 \times 0.30 \times 1 \times 100\% \]

\[ D = 354 \text{ mg} \]

**PEL/REL** = 260 mg/m\(^3\) x (10 m\(^3\)/day) = 2600 mg/day

**US EPA IRIS CHRONIC RfD** 2 mg/kg/day for 50 Kg = 100 mg/day

*What “errors” … and in what direction … might we identify in this estimate of D?*
**Example: Dermal Contact Calculation for Benzene**

A home mechanic is replacing a fuel line filter on a lawn mower. Contact of one hand with gasoline containing 1% benzene by weight occurs.

\[
D = S \times Q \times WF \times FQ \times ABS
\]

- **S** = Surface area = portion of hands = 300 cm\(^2\)
- **Q** = Amount retained on skin = 1.4 mg/cm\(^2\)
- **WF** = Concentration by weight = 1% or 0.01
- **FQ** = Number of contacts = 1
- **ABS** = 1% (derived empirically) **WHY JUST 1%?**

\[
D = 300 \text{ cm}^2 \times 1.4 \text{ mg/cm}^2 \times 1 \times 0.01 \times 0.01 = 0.42 \text{ mg/day}
\]

- PEL/REL = 1.6 mg/m\(^3\) \times 11 m\(^3\)/day = 17.6 mg/day
- US EPA IRIS RfD 4 x 10-3 mg/Kg/Day for 70 KG = 0.28 mg/day

What “errors” … and in what direction … might we identify in this estimate of D?
LIMITATIONS OF ESTIMATES THAT USE A PERCENT ABSORPTION FACTOR

- The absorption rate in the real world is typically variable, not constant.
- The absorption rate is linked closely to the mass loading of the contaminant on the skin, and absorption rate increases as the topical exposure mass increases.
- Time is a key aspect of absorption (most absorption occurs within 24 hours) – time must be the same when comparing values.
- EVAPORATION is not considered in a rigorous way – just via the estimate of the ABS fraction.
ESTIMATING SKIN ABSORPTION

Two important variables in dermal absorption estimation are:

- Mass of the contaminant on the skin and
- \( K_p \), or permeability rate

If concentration is constant, \( K_p = \text{cm/hr} \)

Based on Fick’s Law of Diffusion and flux:

\[ K_p = \frac{\text{Flux (mg/cm}^2\text{/hr)}}{\text{Conc. (mg/cm}^3\text{)}} \]
**ESTIMATING KP VALUES**

Some sources of Kp values:

SkinPerm tool computes estimated Kp values:  
[http://home.planet.nl/~wtberge/home.html](http://home.planet.nl/~wtberge/home.html)

IH SkinPerm calculates estimated Kps too, using a few physical chemical properties and algorithms

EPA’s Dermal Exposure Assessment: Principles and Applications (1992), Summary of Compound-Specific Kp values, pp. 5-65 to 5-98.  
[http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=12188](http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=12188)

Some are available in published literature.
SKIN ABSORPTION

A model that attempts to refine Potts & Guy* is the revised Robinson Equation (this model is in the IH SkinPerm Tool):

\[ K_p = \frac{1}{1 + \frac{1}{K_{lip}} + \frac{1}{K_{aq}}} \quad (Cm / hour) \]

The terms \( K_{lip}, K_{pro} \) and \( K_{aq} \) have further mathematical components.

The model requires the octanol-water partition coefficient (log \( K_{o/w} \)) and molecular weight.

The log$K_{ow}$ value provides an estimate of a chemical’s relative oil (lipid) and water solubility, which can be a predictor of dermal absorption.

In general, a log$K_{ow}$ value between 1 and 3 indicates significant dermal absorption potential.

SRC Website estimates LogKow values: [http://www.syrres.com/esc/kowdemo.htm](http://www.syrres.com/esc/kowdemo.htm)

The US EPA EPIWIN suite (that uses the SRC method) also gives methods to estimate LogKow values.
SOME DATA SOURCES

- Syracuse Research Corporation website, LogKow values
- Syracuse Research Corporation website, Kp Values
- U.S. Environmental Protection Agency: http://www.epa.gov/oppt/exposure/pubs/episuiteldl.htm
- Note: The DermWin module in EPI Suite has LogKow and chemical physical properties for substances
- Merck Index of chemicals: https://www.rsc.org/Merck-Index/
  Note: Limited access without access rights. This index contains information on chemicals including common and generic names, trademarks and associated companies, CAS Registry Numbers, chemical structures, molecular formulae, weights and percentage composition, physical and toxicity data, and caution and hazard information.

  Note: The ChemSpider program reportedly has SOME LogKow Values at skin pH of 5.5
**Getting to LogKow – SMILES from ChemSpider**

[Image of the ChemSpider website showing molecular structure and SMILES representation]

4-Methylcyclohexanemethanol

ChemSpider ID: 105625
Molecular Formula: C_{8}H_{16}O
Average mass: 128.212006 Da
Monoisotopic mass: 128.120117 Da

- **Systematic name**
  (4-Methylcyclohexyl)methanol

- **SMILES and InChls**

  **SMILES:**
  OCC1CCC(C)CC1

  **Std. InChl:**
  InChI=1S/C8H16O/c1-7-2-4-8(6-9)5-3-7/h7-9H,2-6H2,1H3

**Useful. Simplified molecular input line entry system**
EpiWin, EpiWeb

The Estimation Programs Interface (EPI) Suite™ was developed by the US Environmental Protection Agency's Office of Pollution Prevention and Toxics and Syracuse Research Corporation (SRC). It is a screening-level tool, intended for use in applications such as to quickly screen chemicals for release potential and "bin" chemicals by priority for future work. Estimated values should not be used when experimental (measured) values are available.
KowWin Tab

Enter SMILES: OCC1CCC[C]CC1

Enter NAME: NameLookup
These estimates are also available via the ChemSpider web site.
**EXAMPLE OF SRC’S LOG K_{OW} CALCULATOR: HEXANE**

KowWin(LogKow) Log P Calculation:
SMILES : C(C(C(C(C(C))C
CHEM : Hexane
MOL FOR: C6 H14
MOL WT : 86.18

<table>
<thead>
<tr>
<th>TYPE</th>
<th>NUM</th>
<th>LOGKOW v1.66 FRAGMENT DESCRIPTION</th>
<th>COEFF</th>
<th>VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frag</td>
<td>2</td>
<td>-CH3 [aliphatic carbon]</td>
<td>0.5473</td>
<td>1.0946</td>
</tr>
<tr>
<td>Frag</td>
<td>4</td>
<td>-CH2- [aliphatic carbon]</td>
<td>0.4911</td>
<td>1.9644</td>
</tr>
<tr>
<td>Cons t</td>
<td></td>
<td>Equation Constant</td>
<td></td>
<td>0.2290</td>
</tr>
</tbody>
</table>

Log Kow = 3.2880

**Experimental Database Structure Match:**
Name: n-Hexane
CAS Registry Number : 000110-54-3
Experimental Log Kow: 3.90
Ideally, Kow at pH 5.5


Fig. 1. Chemical structure of: (a) fluorescein, neutral form ($H_2Fl^+$); (b) eosin Y, deprotonated form.

Fig. 2. Values of log $K_{ow}$ vs. pH for fluorescein (this study; Kasnavia et al., 1999) and eosin Y (this study). Data points represent average of 3 to 5 experiments, and error bars represent 1 standard deviation. Some error bars are smaller than the data symbol.

This pH effect is important for acids, bases. Skin pH = 5.5
# Relationship of Log KO/w to KP

Permeability of Human Skin (In Vitro) to Alcohols (Aqueous Solutions)

<table>
<thead>
<tr>
<th>Compound</th>
<th>KP</th>
<th>Log KO/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>0.0005</td>
<td>-0.77</td>
</tr>
<tr>
<td>Ethanol</td>
<td>0.0008</td>
<td>-0.31</td>
</tr>
<tr>
<td>Propanol</td>
<td>0.0014</td>
<td>0.30</td>
</tr>
<tr>
<td>Butanol</td>
<td>0.0025</td>
<td>0.65</td>
</tr>
<tr>
<td>Pentanol</td>
<td>0.0060</td>
<td>1.56</td>
</tr>
<tr>
<td>Hexanol</td>
<td>0.0130</td>
<td>2.03</td>
</tr>
</tbody>
</table>

KP tends to increase with increasing Log KO/w (up to saturation)

What trends do you see?

Taken from: Dermal Exposure Assessment: Principles and Applications, U.S. EPA, 1992
**IH Skin Perm Can Estimate the Loss to Evaporation, Skin Absorption and Systemic Dose**

- Penetration is complex; models can assist in estimating the dose which may be systemically available.
- For volatiles, the program estimates evaporation along with absorption.
- It is important to understand the principles and limitations behind any model.

Illustration from IH SkinPerm
IH SkinPerm: Part of the AIHA EASC Toolbox

Thoughts from Wil ten Berge, a primary developer of IH SkinPerm theory and QSARs:

1. Published permeation coefficients of organic substances from aqueous solutions through human skin in vitro appeared to support a theoretical model \{Note: SkinPerm\} for simulation of permeation of organic substances through the skin.

2. Modeling of skin permeation requires not only substance properties like the octanol/water partition coefficient and the molecular weight or the molar volume, but should also include diffusion kinetics.

3. Diffusion kinetics may provide additional understanding for the rate of permeation of gases, of liquids and of solid substances dissolved in water.

4. The model applies to non-ionized substances that do not irritate, do not remove lipids from the skin and permeate faster than the substance is metabolized in the epidermis.

5. Model predictions are accurate within one order of magnitude. This is accurate enough to get some feeling for the contribution of dermal absorption in comparison to absorption by inhalation or ingestion.
IH SkinPerm: Basis for the Theoretical Model

IH SkinPerm is based on 2 critical QSARs for:

- Human aqueous permeability coefficient of the stratum corneum, predicted from the log(Ko/w) and the molecular weight. This QSAR was derived from 182 measured and validated human aqueous skin permeation coefficients in vitro (ten Berge 2009, Vecchia and Bunge 2002a).

- Stratum corneum/water partition coefficient, predicted from the log(Kow). This QSAR was derived from 97 measured and validated human stratum corneum/water partition coefficients in vitro (ten Berge 2009 and Vecchia and Bunge 2002b).


**What is “Under the Hood” in IH SkinPerm?**

\[
10 \log[Kp_{sk-water}] = 10 \log \left[ \frac{1}{Klip + Kpol + 1/Kaq} \right] \text{cm/hr}
\]

\[
Klip = 10^{[b1+b2*10 \log(Kow)+b3*Mw]}
\]

\[
Kpol = \frac{b4}{M4^{b5}} \quad Kaq = \frac{b6}{Mw^{b7}}
\]

\[
Klip = \text{permeation coefficient lipid medium}
\]

\[
Kpol = \text{permeation coefficient corneocytes [proteins]}
\]

\[
Kaq = \text{permeation coefficient epidemis [aqueous medium]}
\]

\[
Kow = \frac{\text{octanol}}{\text{water}} \text{partition coefficient}
\]

\[
Mw = \text{molecular weight}
\]

\[
b1, b2, b3, b4, b5, b6, b7 = \text{regression coefficients}
\]
USES of IH SkinPerm

- Neat liquids
  - Instantaneous deposition (e.g., one splash)
  - Deposition over time
  - Portions absorbed, evaporated, remaining in or on skin

- Aqueous mixtures
  - Instantaneous deposition (e.g., one splash)
  - Deposition over time
  - Portions absorbed, evaporated, remaining in or on skin

- Uptake via skin of vapor from air

It is not ready for use with non-aqueous mixtures – but this is a development goal
The goal in developing IH SkinPerm was to help increase understanding of dermal absorption and provide a practical tool to estimate dose from dermal exposure. Although the science and terminology associated with dermal exposure estimation may initially seem complex, the diagrams, explanations, and graphs we hope will promote basic understanding and better knowledge to help target where dermal exposure prevention considerations should be emphasized.

Getting started is easy, simply click on the "blue" arrow to navigate from this introduction page to the data input sheet.

Substance selection and scenario types are the initial parameters decided. Scenario choices include instantaneous or deposition over time exposure conditions.

For further information visit Inside AIHA Exposure Assessment Strategies Committee for a link to the Dermal Project Team web page.

If this file doesn’t work, enable macros!
Developers and users of this and earlier versions of the Excel spreadsheet have found it to be useful in estimating skin permeation. Equations and concepts upon which this model is based are in the public domain through published literature. Equations embedded in this spreadsheet were verified upon release. However, no certainty is assigned to the results for any given situation as the results are based on a limited set of data collected under laboratory conditions. The user of this spreadsheet assumes all responsibility for selection of the model, understanding its limitations, selection of values for input variables, and interpretation of its results and calculations. Additional guidance on skin permeation is contained in "Mathematical Models for Estimating Occupational Exposure to Chemicals", 2nd Edition, C. Keil, Editor, AIHA Press 2009. Any user "unlocking" a worksheet and modifying the equations contained within assumes all responsibility for any modifications' adequacy and DISCLAIMER: The material embodied on this software is provided "as-is" and without warranty of any kind, expressed, implied or otherwise, including without limitation any warranty of merchantability or fitness for a particular purpose.

In no event shall the authors: Wil ten Berge, Daniel Drolet, Rosalie Tibaldi or the American Industrial Hygiene Association (AIHA) be liable for any direct, indirect, special, incidental, or consequential damages of any kind, or any damages whatsoever, including without limitation loss of profit, loss of use, savings or revenue, or the claims of third parties, whether or not Wil ten Berge, Daniel Drolet, Rosalie Tibaldi or the AIHA has been advised of the possibility of such loss, however caused, and on any theory of liability, arising out of or in connection with the possession, use or performance of this free software.

Acknowledgements

Wil ten Berge created the original SkinPerm model. In collaboration with Wil ten Berge, Daniel Drolet and Rosalie Tibaldi as members of the AIHA Exposure Assessment Strategies Committee (EASC) and Dermal Project Team (DPT) worked to create an upgraded, more user-friendly Excel based model now called IH SkinPerm. The EASC and DPT value practical modeling tools to help estimate skin exposures in occupational settings. IH SkinPerm is formatted similarly to other EASC tools such as IHESTAT and IHMOD and enables multilingual capability. Additional collaborators deserving special mention include Thomas W. Armstrong, Jennifer Sahmel, and Michael Jayjock.
You can use the existing list or define your own.
**Maximum Skin Adherence**

The skin adherence field is greyed out and a default of -1 is indicated if the substance is a liquid at 25°C. Smart logic is built into IH SkinPerm; the program recognizes whether a substance is a solid or liquid at standard temperature (25°C) based on the physicochemical properties. For substances that are solids at 25°C a maximum adherence value up to 2 mg/cm² is allowed based on studies of soil-on-skin adherence. If the deposition rate results in an increase above the input figure (0.2-2 mg/cm²), it is assumed that the surplus disappears just by removal from the skin.
Evaporation rate is calculated based on REACh technical guidance and uses the following equations and assumptions:

\[
Evaporation\ rate(LF) = \frac{\beta \cdot Mw \cdot Vp}{R \cdot T \cdot 10} \quad \text{eq. 8}
\]

\[
\beta = \frac{0.0111 \cdot V^{0.96} \cdot D_g^{0.19}}{\nu^{0.15} \cdot X^{0.04}} \quad \text{eq. 9}
\]

- **Mw**  Molecular weight
- **Vp**  Vapor pressure of the liquid at skin temperature in Pascal
- **R**  Gas constant in J/Mol/°K
- **T**  Skin temperature in °K (normal range 28-32°C) (assume 303°K)
- **β**  Coefficient of mass transfer in the vapour phase in meter/hour
- **V**  Velocity of air (at workplaces ranges 0.3 to 0.6 m/s) (assume or 0.3 m/s ie. 1080 meter/hour)
- **D_g**  Diffusivity of the liquid in the gas phase (range 0.03 to 0.06 m2/hr) (assume 0.05 m2/hr)
- **ν**  Kinematic viscosity of air (Literature value 0.054 m2/hour)
- **X**  Length of the area of evaporation in the direction of the air stream (assume 0.1 meter)
IH SkinPerm Estimates the Maximum Dermal Absorption for 2000 cm² in One Hour (mg) (From Liquid)

A surface area of 2000 cm² is the approximate skin surface area of the hands and forearms. If the dermally absorbed amount (mg) in one hour is greater than a tenth of the OEL inhalation dose equivalent (mg) then the substances meets the EU Skin Notation criteria.
THIS IS THE IH SKINPERM REPORT PAGE

Example Comparative Analysis

Max. derm. abs. for 2000 sqm in 1 hour (mg) (from liquid): 0.0000 + 0 mg

Dermal/Respiratory uptake ratio (from airborne vapor): 0

A surface area of 2000 sqm is the approximate skin surface of the hands and forearms. This dermally absorbed amount (reg. 1 hour) is higher than one third of the OIT value, therefore equivalent (mg), the substance meets the EU skin notation criteria.

This means that full respiratory protection will provide 7 percent protection against overexposure to the substance in the form of vapour due to dermal vapour absorption over whole body surface.
### Chemical Properties Database Tables

#### The SkinPerm Table and User Defined Table

<table>
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<tr>
<th>Substance</th>
<th>CAS</th>
<th>Mol</th>
<th>Temp °C</th>
<th>Vapour Pressure Pa</th>
<th>Water Solubility mL</th>
<th>LogKow (pH 5.5)</th>
<th>Density</th>
<th>Measured Perm Coeff</th>
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<td>1 HBr</td>
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</tr>
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<td></td>
</tr>
<tr>
<td>8 CH₃CNH₂</td>
<td>73-37-3</td>
<td>0.4</td>
<td>25</td>
<td>17 000</td>
<td>15.00</td>
<td>1.43</td>
<td>1265</td>
<td></td>
</tr>
<tr>
<td>9 CH₃COOH</td>
<td>64-19-7</td>
<td>0.4</td>
<td>25</td>
<td>17 000</td>
<td>66.00</td>
<td>2.77</td>
<td>1469</td>
<td></td>
</tr>
<tr>
<td>10 CH₃CO₂H</td>
<td>64-12-2</td>
<td>0.7</td>
<td>25</td>
<td>17 000</td>
<td>17.00</td>
<td>2.19</td>
<td>1778</td>
<td></td>
</tr>
<tr>
<td>11 CH₃CNH₂</td>
<td>73-37-3</td>
<td>0.7</td>
<td>25</td>
<td>17 000</td>
<td>15.00</td>
<td>1.43</td>
<td>1265</td>
<td></td>
</tr>
<tr>
<td>12 CH₃CO₂H</td>
<td>64-12-2</td>
<td>0.7</td>
<td>25</td>
<td>17 000</td>
<td>17.00</td>
<td>2.19</td>
<td>1778</td>
<td></td>
</tr>
<tr>
<td>13 CH₃CNH₂</td>
<td>73-37-3</td>
<td>0.7</td>
<td>25</td>
<td>17 000</td>
<td>15.00</td>
<td>1.43</td>
<td>1265</td>
<td></td>
</tr>
<tr>
<td>14 CH₃CO₂H</td>
<td>64-12-2</td>
<td>0.7</td>
<td>25</td>
<td>17 000</td>
<td>17.00</td>
<td>2.19</td>
<td>1778</td>
<td></td>
</tr>
<tr>
<td>15 CH₃CNH₂</td>
<td>73-37-3</td>
<td>0.7</td>
<td>25</td>
<td>17 000</td>
<td>15.00</td>
<td>1.43</td>
<td>1265</td>
<td></td>
</tr>
<tr>
<td>16 CH₃CO₂H</td>
<td>64-12-2</td>
<td>0.7</td>
<td>25</td>
<td>17 000</td>
<td>17.00</td>
<td>2.19</td>
<td>1778</td>
<td></td>
</tr>
</tbody>
</table>

#### USER database

<table>
<thead>
<tr>
<th>Substance</th>
<th>CAS</th>
<th>Mol</th>
<th>Temp °C</th>
<th>Vapour Pressure Pa</th>
<th>Water Solubility mL</th>
<th>LogKow (pH 5.5)</th>
<th>Density</th>
<th>Measured Perm Coeff</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Testone</td>
<td>111-81-3</td>
<td>0.4</td>
<td>25</td>
<td>17 000</td>
<td>18.00</td>
<td>1.30</td>
<td>1200</td>
<td></td>
</tr>
<tr>
<td>2 Ironformic acid</td>
<td>67-86-5</td>
<td>0.4</td>
<td>25</td>
<td>17 000</td>
<td>100.00</td>
<td>1.86</td>
<td>1778</td>
<td></td>
</tr>
<tr>
<td>3 Nitroformic acid</td>
<td>104-23-2</td>
<td>0.4</td>
<td>25</td>
<td>17 000</td>
<td>20.00</td>
<td>2.42</td>
<td>1608</td>
<td></td>
</tr>
</tbody>
</table>

**You CAN (with care!) UNPROTECT the sheet, add Rows to the USER database And copy, modify data from The SKINPERM database portion.**

NEEDED: name, Temp, VP, Water solubility. LogKow, Density
IH SkinPerm Tool: Data for n-Hexane

Substance selection

- SkinPerm
- User’s

Scenario parameters

- Instantaneous deposition
- Deposition over time

Instantaneous deposition dose: 100 mg
Affected skin area: 1070 cm²
Maximum skin adherence solids: 1 mg/cm²
Dermal deposition rate: 1 mg/cm²/hr

Timing parameters

- Start deposition: 0 hr
- Duration of deposition: 0 hr
- End time observation: 1 hr

Report parameters

- Calculation intervals/hour: 1000
- Report intervals/hour: 100

LogKow at skin pH 5.5: 3.5

Add a new substance...
# SkinPerm Tool: Results for n-Hexane

## Substance
<table>
<thead>
<tr>
<th>N-hexane</th>
</tr>
</thead>
</table>

## Deposition Duration
<table>
<thead>
<tr>
<th>Total Deposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg</td>
</tr>
</tbody>
</table>

## Fraction absorbed
<table>
<thead>
<tr>
<th>Amount absorbed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1%</td>
</tr>
</tbody>
</table>

## Water
<table>
<thead>
<tr>
<th>Substance</th>
<th>Partition Coefficient (cm/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kp-lipids (vehicle water)</td>
<td>2.41E-01</td>
</tr>
<tr>
<td>Kp-keratins (vehicle water)</td>
<td>9.98E-05</td>
</tr>
<tr>
<td>Lag time stratum corneum</td>
<td>1.909 min</td>
</tr>
<tr>
<td>Diffusivity of Stratum corneum</td>
<td>2.10E-05</td>
</tr>
<tr>
<td>Skin/Water partition ratio</td>
<td>23.032</td>
</tr>
</tbody>
</table>

## Air
<table>
<thead>
<tr>
<th>Substance</th>
<th>Partition Coefficient (cm/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kp-lipids (vehicle air)</td>
<td>3.47E-03</td>
</tr>
<tr>
<td>Kp-keratins (vehicle air)</td>
<td>1.40E-06</td>
</tr>
<tr>
<td>Kp-stagnant air layer</td>
<td>1.13E+02</td>
</tr>
<tr>
<td>Skin/Air partition ratio</td>
<td>0.331</td>
</tr>
</tbody>
</table>

## Permeation Coefficient
<table>
<thead>
<tr>
<th>Water</th>
<th>Air</th>
</tr>
</thead>
<tbody>
<tr>
<td>5th percentile</td>
<td>1.47E-01</td>
</tr>
<tr>
<td>95th percentile</td>
<td>3.95E-01</td>
</tr>
</tbody>
</table>

## Max. derm. abs.
<table>
<thead>
<tr>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.41E-03 mg/cm²/hour</td>
</tr>
</tbody>
</table>
SKINPERM TOOL: DATA FOR N-HEXANE

IH SkinPerm

<table>
<thead>
<tr>
<th>Substance</th>
<th>N-hexane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure</td>
<td>Instantaneous</td>
</tr>
<tr>
<td>Duration</td>
<td>700 mg</td>
</tr>
<tr>
<td>Total Exposure</td>
<td>1,115 mg</td>
</tr>
<tr>
<td>Fraction absorbed</td>
<td>1.14</td>
</tr>
<tr>
<td>Amount absorbed</td>
<td>100 mg</td>
</tr>
</tbody>
</table>

**AIR**

- Ko-lipids (vehicle oil): 2.4E-1 cm/hr
- Ko-keratin (vehicle oil): 3.6E-2 cm/hr
- Ko-lipids (vehicle air): 1.0E-1 cm/hr
- Ko-keratin (vehicle air): 1.2E-2 cm/hr
- Ko-striated air layer: 0.13 cm/hr
- SkinAir partition ratio: 0.79

**WATER**

- Permeation coefficient water: 2.4E-1 cm/hr
- 5th percentile water: 1.6E-1 cm/hr
- 50th percentile water: 2.0E-1 cm/hr
- 55th percentile water: 2.5E-1 cm/hr
- Max. derm. abs.: 2.4E-3 mg/cm²/hr

Example Comparative Analysis

Max. derm. abs. for 2000 cm² in 1 hour (mg) (from liquid): 4.8E-6 mg

Dermal/Respiratory uptake Ratio (from airborne vapor): 0.0000666

A surface area of 2000 cm² is the approximate skin surface of the hands and forearms. If the dermally absorbed amount (mg) in 1 hour is higher than one tenth of the OEL inhalation dose equivalent (mg), the substance meets the EU skin notation criteria.

This means that full respiratory protection will provide 100 percent protection against overexposure to the substance in the form of vapor due to dermal vapor absorption over whole body surface.
RESULTS GRAPHS FOR N-Hexane – Different Durations, etc. Will Autoscale
IH SkinPerm Tool: Data for Benzylalcohol

1. **Substance selection**
   - Database:
     - SkinPerm
     - User’s

2. **Scenario parameters**
   - Instantaneous deposition
   - Deposition over time
   - Vapor to skin scenario

   - Instantaneous deposition dose: 100 mg
   - Affected skin area: 300 cm²

3. **Timing parameters**
   - Start deposition: 0 hr
   - Duration of deposition: 2 hr
   - End time observation: 2 hr

4. **Report parameters**
   - Calculation intervals/hour: 10000
   - Report intervals/hour: 200

5. **Reset**

LogKow at skin pH 5.5: 1,1

Add a new substance...
## RESULTS FOR BENZYL ALCOHOL

### IH SkinPerm

#### Report Sheet

**Substance:** Benzyl Alcohol  
**Deposition:** Instantaneous

<table>
<thead>
<tr>
<th>Total Deposition</th>
<th>Amount absorbed</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg</td>
<td>59.39 mg</td>
</tr>
</tbody>
</table>

#### WATER

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kp-lipids (vehicle w/ater)</td>
<td>2.99E-3 cm/hr</td>
</tr>
<tr>
<td>Kp-keratins (vehicle w/ater)</td>
<td>7.33E-5 cm/hr</td>
</tr>
<tr>
<td>Lag time stratum corneum</td>
<td>13.954 min</td>
</tr>
<tr>
<td>Diffusivity of Stratum corneum</td>
<td>2.90E-6 cm²/hr</td>
</tr>
<tr>
<td>Skin/Water partition ratio</td>
<td>2.1396</td>
</tr>
</tbody>
</table>

#### AIR

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kp-lipids (vehicle air)</td>
<td>2.37E+2 cm/hr</td>
</tr>
<tr>
<td>Kp-keratins (vehicle air)</td>
<td>5.81E+0 cm/hr</td>
</tr>
<tr>
<td>Kp-stagnant air layer</td>
<td>1.01E+2 cm/hr</td>
</tr>
<tr>
<td>Skin/Air partition ratio</td>
<td>169593</td>
</tr>
</tbody>
</table>

#### Permeation coefficient w/ater

<table>
<thead>
<tr>
<th>Percentile</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5th percentile</td>
<td>3.07E-3 cm/hr</td>
</tr>
<tr>
<td>95th percentile</td>
<td>4.16E-3 cm/hr</td>
</tr>
</tbody>
</table>

Max. derm. abs.: 1.32E-1 mg/cm²/hr

**Example Comparative Analysis**

Max. derm. abs. for 2000 cm² in 1 hour (mg) (from liquid): 2.63E+2 mg

Dermal/Respiratory uptake Ratio (from airborne vapor): 1.3661

A surface area of 2000 cm² is the approximate skin surface of the hands and forearms. If the dermally absorbed amount (mg) in 1 hour is higher than one tenth of the OEL inhalation dose equivalent (mg), the substance meets the EU skin notation criteria.

This means that full respiratory protection will provide 42.3 percent protection against overexposure to the substance in the form of vapour due to dermal vapour absorption over whole body surface!
IH SkinPerm Tool: Data for Benzyl Alcohol

Benzyl alcohol: Chemical Fate After...

Instantaneous deposition of 100 mg (300 cm²)

Situation after...

- 0 hr 34 min
- 100 mg

Deposition → Evaporation → Vapor

Substance:
- Stratum Corneum: 50% Absorption
- Viable epidermis: 21.2%
- To Systemic Circulation

Graph showing the quantity (mg) over time (hrs) with different deposition and exposure levels.

Legend:
- Mass on skin surface mg
- Total Evaporated mg
- Mass in Str Corneum
- Total Absorbed, 51.8 mg
The model has published validation data against which it was tested. (e.g., 1. ten Berge 2009 2. Jongeneelen and ten Berge 2011)

1. is for aqueous permeation coefficients (human skin \textit{in vitro})
2. is for the blood/air partition coefficient (human PBPK)

The model has been used and “validated” against chemical hazards in addition to those in the original validation set and beyond these two graphic analyses
IH SkinPerm Parameter Guidance

- Thickness of stagnant air layer
  - 3 cm if clothing involved
  - 1 cm if bare skin involved
- Adherence of solids
  - Max 2 mg/cm²
- Range of liquid film loading 0.7 to 2.5 mg/cm²
- Range of Log Kow -3 to 6
- MW < 600
**Adding a Compound to the Database in IH SkinPerm**

We can also use this to define characteristics of an aqueous mixture.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Values</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS number</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecular weight</td>
<td></td>
<td>g/mole</td>
</tr>
<tr>
<td>Temperature</td>
<td></td>
<td>°C</td>
</tr>
<tr>
<td>Vapour Pressure</td>
<td></td>
<td>Pa</td>
</tr>
<tr>
<td>Water Solubility</td>
<td></td>
<td>mg/L</td>
</tr>
<tr>
<td>LogKow at skin, pH 5.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Density</td>
<td></td>
<td>mg/cm³</td>
</tr>
<tr>
<td>Measured Perm. Coeff.</td>
<td></td>
<td>cm/hr</td>
</tr>
</tbody>
</table>

(Optional)
CASE STUDY: DERMAL EXPOSURE TO A CHEMICAL IN WATER DURING SHOWERING

4-Methylcyclohexanemethanol in water at 100mg/liter = 0.1 gr/L = 0.1gr/Kg = 0.0001 wt%
- LogKow 2.546
- MW 128, CAS # 34885-03-5
- VP 0.133 Torr at 25 C at
- The Raoult’s Law Partial VP = 5.8 E-9 at 0.0001wt%
- Water solubility estimated about 2 grams per liter
- Whole body skin exposure 20000 cm²
- Activity coefficient (UNIFAC estimate) shows major departure from ideality (Activity coeff. about 2000) so PVpa = 1.15E-5 Torr so we might expect very little lost to air. What actually happens?
A spreadsheet may be useful in calculating and documenting some of these input parameters

**Example**

<table>
<thead>
<tr>
<th>Compound</th>
<th>MW</th>
<th>Density (g/ml)</th>
<th>gr/L</th>
<th>VP Torr</th>
<th>Weight%</th>
<th>Moles</th>
<th>Mole Fr</th>
<th>PVP</th>
<th>Activity C</th>
<th>PVpa Torr</th>
<th>Pvp Pa</th>
<th>Contact Mass Load</th>
<th>Skin Area</th>
<th>Total Mass mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCHM</td>
<td>128</td>
<td>0.884</td>
<td>8</td>
<td>0.133</td>
<td>0.0001</td>
<td>7.8125E-07</td>
<td>4.33984E-08</td>
<td>5.77199E-09</td>
<td>2000</td>
<td>1.1544E-05</td>
<td></td>
<td></td>
<td>0.00015</td>
<td>20000</td>
</tr>
<tr>
<td>Water</td>
<td>18</td>
<td>1</td>
<td></td>
<td></td>
<td>0.9999</td>
<td>0.999999957</td>
<td>18.0018002</td>
<td>18.001801</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.5</td>
<td>20000</td>
</tr>
</tbody>
</table>
ACTIVITY

- Discussed in IH Mod webinar
Not much evaporated. Not all absorbed. Some remaining in SC at this time course.
### MCHM as Dilute Aqueous Solution with Partial Vapor Pressure – Raoult’s Law

#### IH SkinPerm

<table>
<thead>
<tr>
<th>Substance</th>
<th>4MCHMinWater0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure Duration</td>
<td>Instantaneous</td>
</tr>
<tr>
<td>TWA Duration</td>
<td>8.0003 mg</td>
</tr>
<tr>
<td>Fraction absorbed</td>
<td>85.4%</td>
</tr>
<tr>
<td>Amount absorbed</td>
<td>13007 mg</td>
</tr>
</tbody>
</table>

- **To-toe vehicle water**
  - Diffusivity of Stratum corneum: 2.88E-4 cm²/yr
  - Permeation coefficient: 2.59E-2 cm/hr
- **In-air**
  - Diffusivity of Stratum corneum: 9.26E-4 cm²/yr
  - Permeation coefficient: 0.91E-1 cm/hr

#### Example Comparative Analysis

- Max. dose, also for 2000 cm² in 1 hour (mg) (from liquid): 4.04E-1 mg
- Dermal/Respiratory uptake ratio (from airborne vapor): 1.7146

A surface area of 2000 cm² is the approximate skin surface of the hands and forearms. If the dermally absorbed amount (mg) in 1 hour is higher than one tenth of the OEL inhalation dose equivalent (mg), the substance meets the EU skin notation criteria.

This means that full respiratory protection will provide 36.8 percent protection against overexposure to the substance in the form of vapour due to dermal vapour absorption over whole body surface.

#### Report sheet

- **Cumulative exposure**: Instantaneous deposition of 3 mg (20000 cm²)

- **Absorption rate (mg/hr)**: Instantaneous deposition of 3 mg (20000 cm²)
**MCHM as Neat Liquid — Same Mass Loading**

**IH SkinPerm**

<table>
<thead>
<tr>
<th>Substance</th>
<th>MCHM/Neat</th>
<th>Instantaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deposition</td>
<td>3.0001 mg</td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>500%</td>
<td></td>
</tr>
<tr>
<td>% Deposition</td>
<td>405%</td>
<td></td>
</tr>
<tr>
<td>Absorbed</td>
<td>1.20 mg</td>
<td></td>
</tr>
<tr>
<td>WATER</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kp-lipids (vehicle water)</td>
<td>2.5E-2 cm/hr</td>
<td>2.2E-1 cm/hr</td>
</tr>
<tr>
<td>Kp-keratins (vehicle water)</td>
<td>5.1E-5 cm/hr</td>
<td>5.1E-4 cm/hr</td>
</tr>
<tr>
<td>Log time α-strain conomum</td>
<td>7.118 cm/hr</td>
<td></td>
</tr>
<tr>
<td>Diffusion of Σɑ-strain conomum</td>
<td>5.602 cm/hr</td>
<td>5.25E-1 cm/hr</td>
</tr>
<tr>
<td>Skin/Water partition ratio</td>
<td>5.895</td>
<td>2.2E-1 cm/hr</td>
</tr>
<tr>
<td>WATER</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permeation coefficient water</td>
<td>2.5E-2 cm/hr</td>
<td>2.2E-1 cm/hr</td>
</tr>
<tr>
<td>5th percentile water</td>
<td>1.7E-2 cm/hr</td>
<td>1.7E-1 cm/hr</td>
</tr>
<tr>
<td>95th percentile water</td>
<td>3.8E-2 cm/hr</td>
<td>3.8E-1 cm/hr</td>
</tr>
<tr>
<td>Max. derm. abs.</td>
<td>2.02E-4 mg/cm²/hr</td>
<td></td>
</tr>
</tbody>
</table>

**Example Comparative Analysis**

Max. derm. abs. for 2000 cm² in 1 hour (mg) (from liquid): 4.04E-1 mg

Dermal/Respiratory uptake ratio: 0.0004344

A surface area of 2000 cm² is the approximate skin surface of the hands and forearms. If the dermally absorbed amount (mg) in 1 hour is greater than one-tenth of the OEL inhalation dose equivalent (mg), the substance meets the EU skin notation criteria.

More evaporated. Less absorbed. Some remains in the SC at this time course.

A surface area of 2000 cm² is the approximate skin surface of the hands and forearms. If the dermally absorbed amount (mg) in 1 hour is greater than one-tenth of the OEL inhalation dose equivalent (mg), the substance meets the EU skin notation criteria.

This means that full respiratory protection will provide 99.6 percent protection against overexposure to the substance in the form of vapour due to dermal vapour absorption over whole body surface.

**Report sheet**

**MCHM/Neat: Chemical Fate After…**

Instantaneous deposition of 3 mg (20000 cm²)

**MCHM/Neat: Absorption rate (mg/hr) after…**

Instantaneous deposition of 3 mg (20000 cm²)
**Which Estimate is “Right?”**

- Who can say without experimental evidence?
- Even with experimental evidence, these are close enough that the experimental scatter would hide a difference
- Which is the more conservative?
- What “accuracy” is needed for the risk assessment decision?
VAPOR TO SKIN WHOLE BODY N-METHYL PYRROLIDONE

IH SkinPerm

1. Substance selection
   - SkinPerm
   - User's

2. Scenario parameters
   - Instantaneous deposition
   - Deposition over time
   - Vapor to skin scenario

   Instantaneous deposition dose: 100 mg
   Affected skin area: 20,000 cm²
   Maximum skin adherence solids: -1 mg/cm²
   Dermal deposition rate: 1 mg/cm²/hr
   Air concentration: 250 mg/m³
   Thickness of stagnant air: 3 cm

3. Timing parameters
   - Start deposition: 0 hr
   - Duration of deposition: 0.5 hr
   - End time observation: 8 hr

4. Report parameters
   - Calculation intervals/hour: 1000
   - Report intervals/hour: 1000

5. Data input

LogKow at skin pH 5.5: -0.38

TWA8HR Occupational Hygiene Consulting, LLC
NMP AIR TO DERMAL RESULTS

IH SkinPerm

N-methylpyrrolidone

<table>
<thead>
<tr>
<th>Substance</th>
<th>N-methylpyrrolidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deposition</td>
<td>0 mg/hour</td>
</tr>
<tr>
<td>Duration</td>
<td>8 hours</td>
</tr>
<tr>
<td>Tot. Deposition</td>
<td>24 mg</td>
</tr>
<tr>
<td>Fraction absorbed</td>
<td>70%</td>
</tr>
<tr>
<td>Amount absorbed</td>
<td>264 mg</td>
</tr>
<tr>
<td>AIR</td>
<td>2.94E-4 mg/h</td>
</tr>
<tr>
<td>Kp-lipid (vehicle/water)</td>
<td>1.54E+2 mg/h</td>
</tr>
<tr>
<td>Kp-lipid (vehicle/air)</td>
<td>1.95E+2 mg/h</td>
</tr>
<tr>
<td>Lag time (Stratum corneum)</td>
<td>20.8hrs</td>
</tr>
<tr>
<td>Diffusion of Stratum corneum</td>
<td>2.05E+7 mg/h</td>
</tr>
<tr>
<td>Skin/liver partition ratio</td>
<td>0.043</td>
</tr>
<tr>
<td>WATER</td>
<td>1.95E+2 mg/h</td>
</tr>
<tr>
<td>AIR</td>
<td>1.95E+2 mg/h</td>
</tr>
<tr>
<td>Permeation coefficient water</td>
<td>3.05E-4 cm/hr</td>
</tr>
<tr>
<td>50th percentile water</td>
<td>5.32E-4 cm/hr</td>
</tr>
<tr>
<td>90th percentile water</td>
<td>7.79E-4 cm/hr</td>
</tr>
<tr>
<td>Max. derm. abs.</td>
<td>1.19E+1 mg/kg/h</td>
</tr>
</tbody>
</table>

Example Comparative Analysis

Max. derm. abs. for 2000 cm² in 1 hour (mg/kg) (from liquid) | 7.33E+2 mg

Dermal/Respiratory uptake ratio (from airborne vapor) | 1.3188

A surface area of 2000 cm² is the approximate skin surface of the hands and forearms. If the dermally absorbed amount (mg) in 1 hour is higher than one tenth of the OEL inhalation dose equivalent (mg), the substance meets the 50 skin notation criteria.

This means that full respiratory protection will provide 50.1 percent protection against overexposure to the substance in the form of vapor due to dermal vapor absorption over whole body surface!

US EPA “Point of Departure” 56 mg/kg-day for 70 Kg male = 3900 mg
HERE ARE A FEW THOUGHTS ABOUT NON-AQUEOUS SOLUTIONS

- Chemical activity likely has a role in the various “fates” of evaporation, penetration, retention in SC
- Competing processes evaporation and dermal penetration remain as with aqueous mixtures
- The applied dose, application site, degree of hydration can be important as with aqueous solutions
- For volatiles, airflow velocity across the deposition layer can impact the evaporation fraction – velocity changes the thickness of the boundary layer as with aqueous mixtures
- Differential concentration effects may occur – is the vehicle more or less volatile than the compound of concern (CoC)
- Emulsion effect of enhanced absorption may in part be due to surfactants – enhanced penetration
What sorts of stuff does our skin encounter? As consumers, women arguably get the most.
What About Sensitizers?

There has been work in computational toxicology and QSARS

- Kupczewska-Dobecka, Jakubowski, Czerczak, Environmental Toxicology and Pharmacology 30 (2010) 95–102
Dermal Exposure Modeling: Summary

- Models can be a useful tool for IHs to estimate dermal exposures because of the complexities involved in dermal absorption and penetration.
- Some practical tools are available to assist in conducting these calculations.
- Modeling can be faster and easier than sampling, but may not be as “accurate” – appropriate model inputs are critical.
BACK UP MATERIALS
**Underlying Hypotheses**

1. The skin disposition of small topical doses of most materials follows nearly first-order kinetics and can be predicted from physico-chemical properties and environmental factors.

2. Ingredient interactions can affect the thermodynamic activity of fragrance components, thus having a significant impact on the rate of both the absorption and evaporation processes.
In eq. 3.1, $A$ is the amount of ingredient on the skin surface, $k_1$ is the evaporation rate constant, and $k_2$ is the absorption rate constant. The absorption rate is proportional to the product of maximum flux, $J_{\text{max}} = \text{const.} \times S_{\text{lip}} \times MW^{-b}$, and the fractional saturation of the surface layer, $A/A_{\text{max}}$. $B$ approx = 2.7

$$k_2A = \text{const.} \times (A/A_{\text{max}}) \times S_{\text{lip}} MW^{-b}$$
In eq. 3.3, molecular weight has been expressed in dimensionless or “reduced” form, \( MW_r = MW/100 \text{ Da} \), for computational convenience. The parameter, \( T \cdot k \), is as yet undetermined. The superscript indicates that its value is a function of skin temperature, \( T \) (see Discussion). The value of \( T \cdot k \) for a room temperature exposure (\( T \approx 30^\circ \text{C} \)) will be determined later by calibration with experimental data.

\[
k_2 = k_2^T \times MW_r^{-b}
\]

\[k_1 = k_1^v \times P_{vpr} / (K_{oct} S_w)_r\]

where the superscript on \( k_i^v \) indicates this parameter is dependent on airflow over the skin. The properties \( P_{vpr} = P_{vpr}^\prime \) torr and \( (K_{oct} S_w) = (K_{oct} S_w)^\prime \) 1000 gL\(^{-1}\) are dimensionless values chosen again for computational convenience. Like \( k_1^v \), the value of \( k_i^v \) must be determined from experiment. The functional dependence of \( k_i^v \) on airflow will be discussed later.
The theory can now be completed. Integration of eq. 3.1 with initial dose $A_0$ yields

$$A(t) = A_0 \exp[-(k_1 + k_2)t]$$

(3.6)

the fractions of the dose evaporated and absorbed after a long time are, respectively,

$$f_{\text{evap}} = \frac{k_1}{k_1 + k_2}$$

Substituting the results from eqs. 3.3 and 3.5 into eqs. 3.7 and 3.8, and expressing the results as a percentage, yields

$$\%\text{evap} = 100 \times \frac{x_r}{k + x_r}$$

(3.9)

and

$$f_{\text{abs}} = \frac{k_2}{k_1 + k_2}$$

$$\%\text{abs} = 100 - \%\text{evap}$$

(3.10)

In eq. 3.9, $k$ is a parameter depending on $v$ and $T$, but having the same value for all fragrance ingredients. Its value, equal to the ratio $k_f^1/k_1^f$, must be determined experimentally. The parameter $x_r$ is the following dimensionless ratio of physicochemical properties of the PRM:

$$x_r = \frac{P_{\omega, MW}^{1/f}}{(K_{\omega, S_r})}$$

(3.11)