Dermal Exposure Modeling

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With thanks to:

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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

Source: Marguart 2003, Ann. Occ. Hyg. Vol. 47, No. 8, pp. 599–607. See the publication for more details on dermal exposure determinants

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 m3/day is a typically assumed occupational value

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

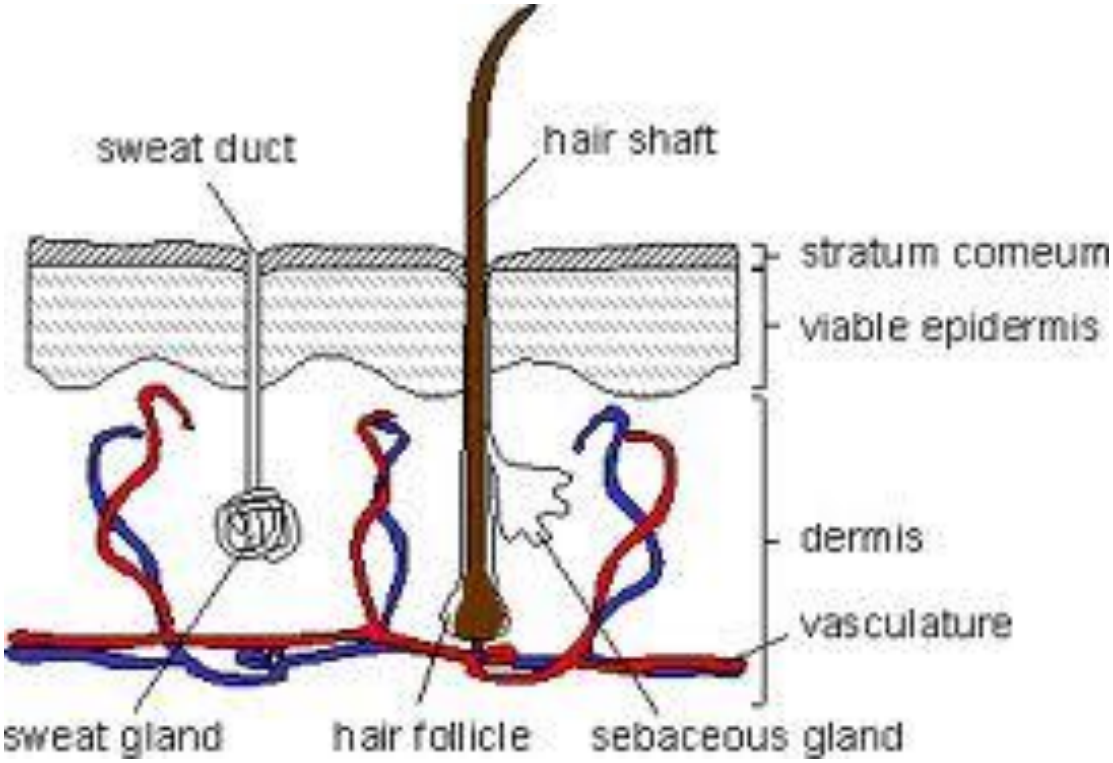
However, for some substances the retained inhaled

systemic dose < the total inhaled dose

Since it is USUALLY based on TLVs, it does not account for sensitive subpopulations and long tem 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

Intact Skin is a Complex Structure



Dermal permeation goes from surface deposition through the strateum 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 corrosio 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
Protecting Worker Health

IH SkinPerm

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

Ignacio and Bullock, eds. A Strategy for Assessing and Managing Occupational Exposures, 3rd ed. Fairfax, VA: AIHA Press, 2006. Appendix II: Dermal Exposure Assessments.

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, m^2, and 2009, Chapter 7: Dermal, Table 7-11, Surface Area of Adult Males (21 Years and Older) in Square Meters

Body Part	Mean (Men) 1997	Mean (Men) 2009
Head	1180 cm^2	1360 cm^2
Arms	2280 cm^2	2890 cm^2
Forearms	1140 cm^2	1460 cm^2
Hands	840 cm^2	1070 cm^2
Palms	150 cm^2	
Thumb	~24 cm^2	

WHOLE BODY about 20,000 cm^2

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 x Q x WF x FQ x ABS

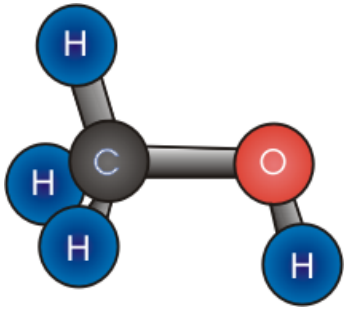
S = Surface area = 2 hands = 840 cm^2

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 cm^2*1.4mg/cm^2*0.30*1*100%

D= 354 mg

PEL/REL = 260 mg/m^3 x (10m^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 x Q x WF x FQ x 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%?**

$D = 300\ cm^2 \times 1.4\ mg/cm^2 \times 1 \times 0.01 \times 0.01 =$ 0.42 mg/day

PEL/REL = 1.6 mg/m^3 × 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
- Kp, or permeability rate

If concentration is constant, Kp = cm/hr

Based on Fick's Law of Diffusion and flux:

Kp = Flux ($mg/cm^2/hr$) / Conc. (mg/cm^3)

Estimating Kp Values

Some sources of Kp values:

SkinPerm tool computes estimated Kp values:

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

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):

$$Kp = \frac{1}{\frac{1}{Klip + Kpro} + \frac{1}{Kaq}} \quad (Cm / hour)$$

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

*Potts, R.O., and R.H. Guy: Predicting skin permeability. Pharm. Res. 9:663–669 (1992).

Use of Log Kow

- 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

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

Some Data Sources

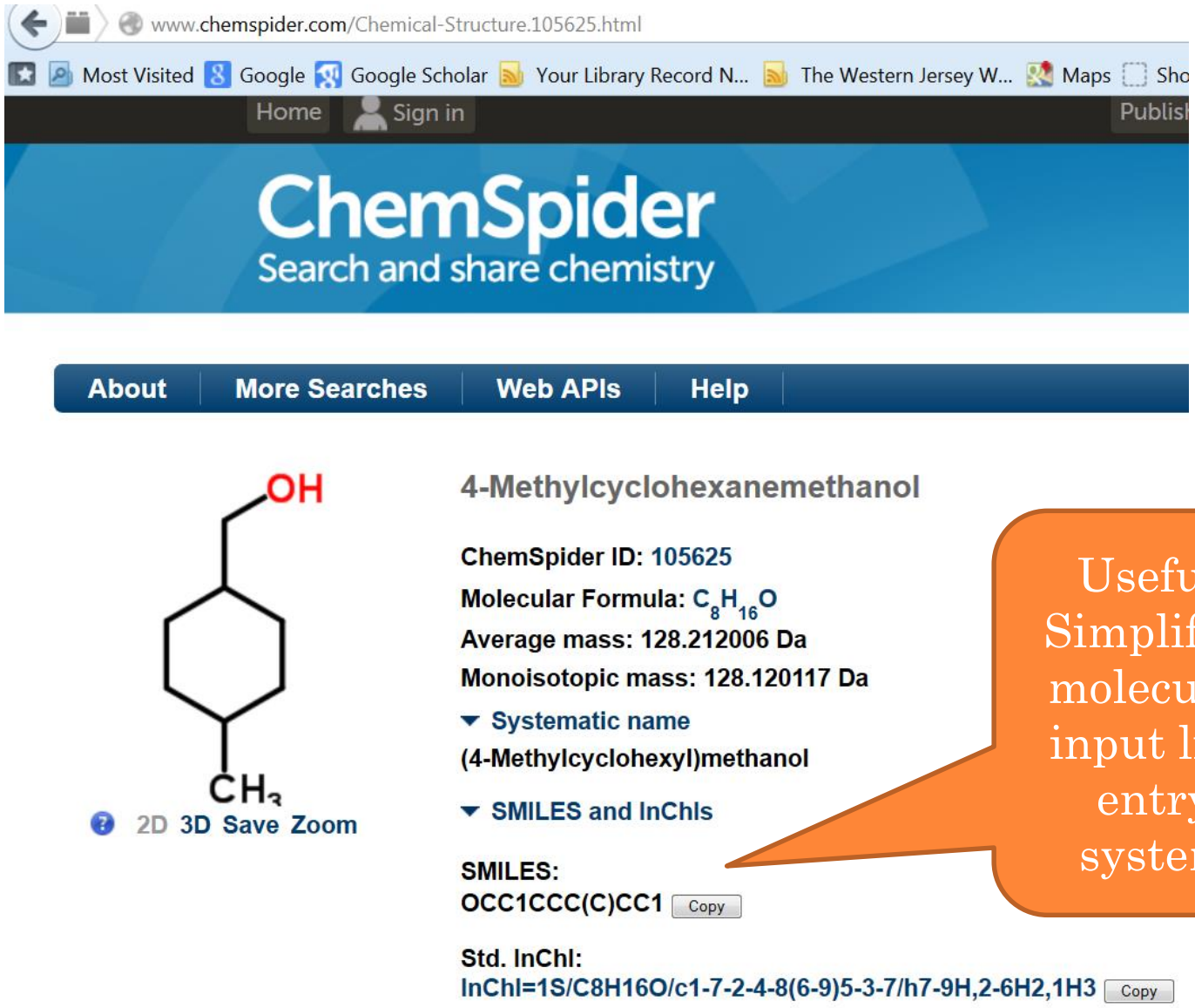
- Syracuse Research Corporation website, LogKow values
- Syracuse Research Corporation website, Kp Values
- U.S. Environmental Protection Agency, Dermal Exposure Assessment: Principles and Applications, Summary of Compound-Specific Kp Values, 1992, pp. 5-65 to 5-98: http://www.epa.gov/nceawww1/pdfs/derexp.pdf
- U.S. Environmental Protection Agency: http://www.epa.gov/oppt/exposure/pubs/episuitedl.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.

- **U.K. Royal Society of Chemistry: http://www.rsc.org/ChemSpider/index.asp**

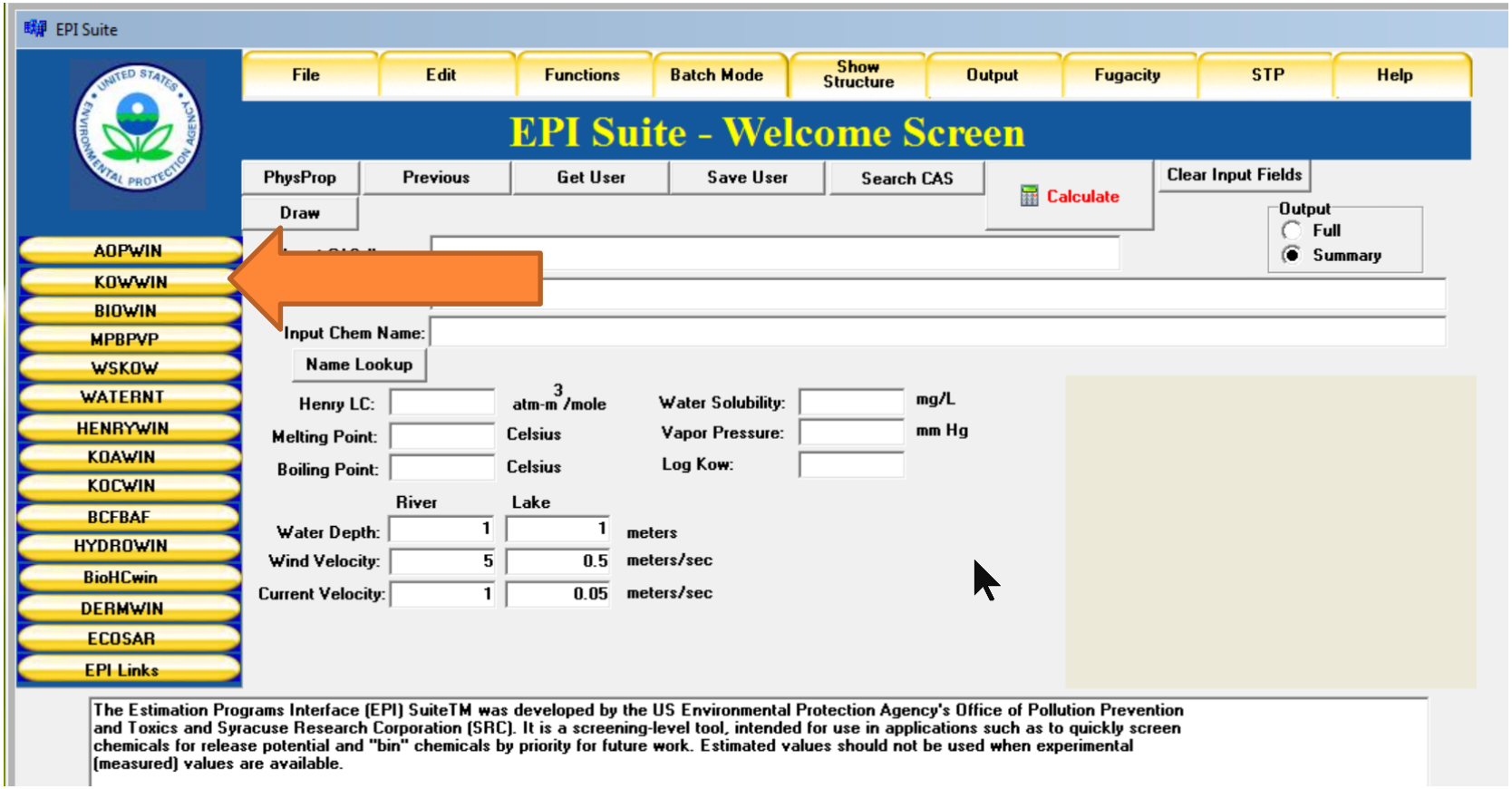
Note: The ChemSpider program reportedly has SOME LogKow Values at skin pH of 5.5

GETTING TO LOGKOW – SMILES FROM CHEMSPIDER

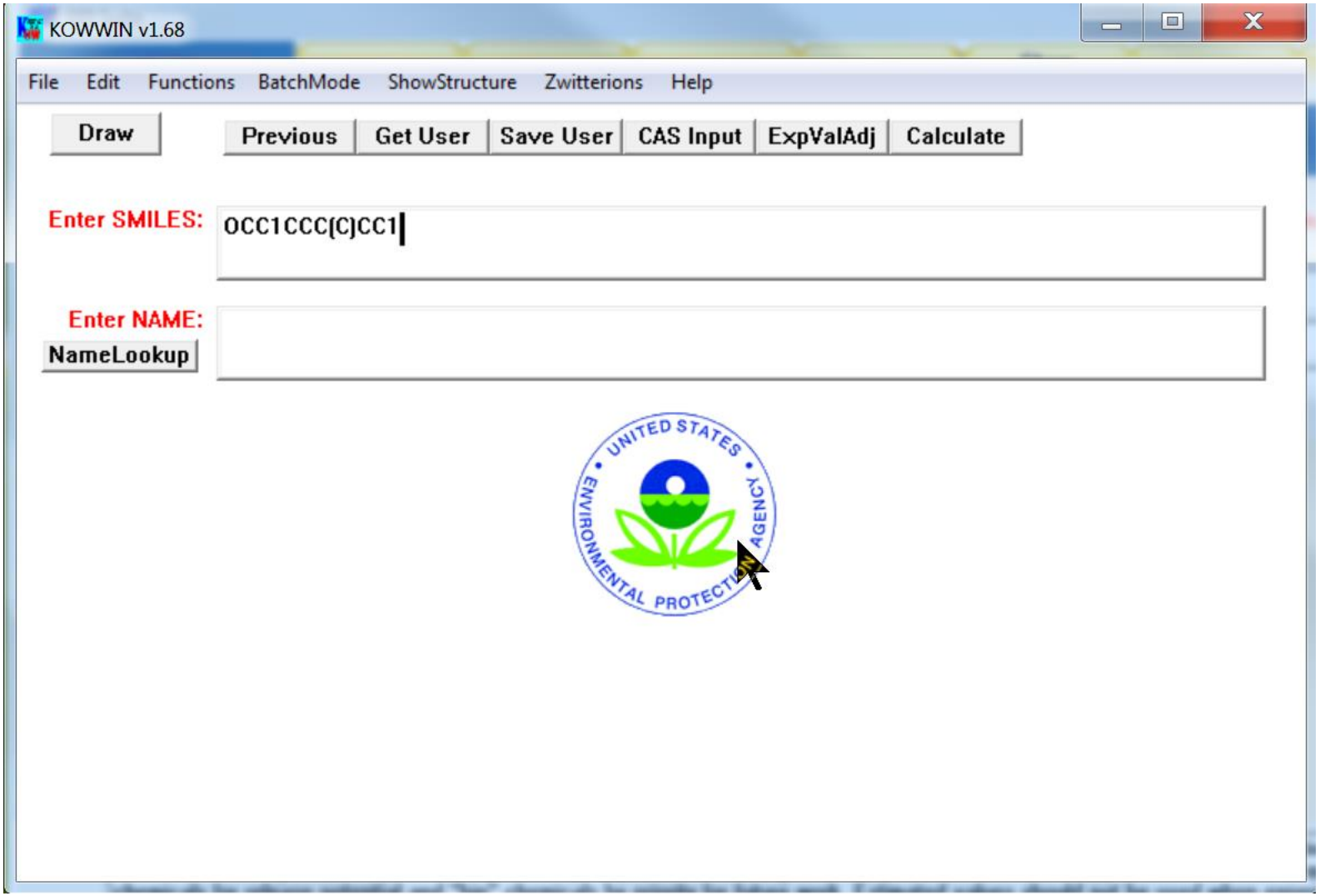


Useful. Simplified molecular input line entry system

EPIWIN, EPIWEB



KowWin Tab


KOWWIN v1.68
File
Edit
Functions
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Get User
Save User
CAS Input
ExpValAdj
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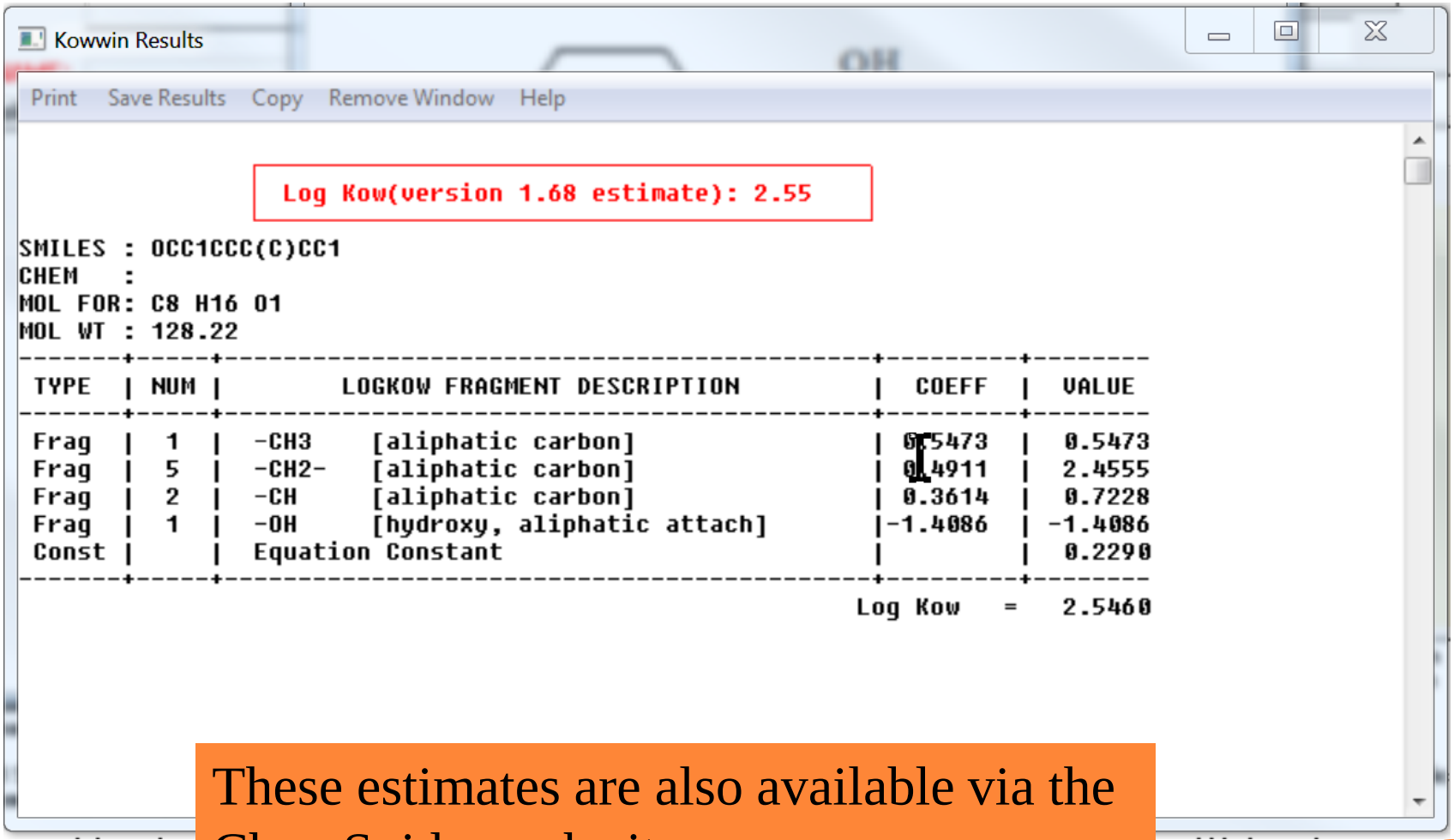
UNITED STATES
ENVIRONMENTAL PROTECTION AGENCY

Results Estimated Log Kow



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(CCCC)C
CHEM : Hexane
MOL FOR: C6 H14
MOL WT : 86.18

Useful. Simplified molecular input line entry system

TYPE	NUM	LOGKOW v1.66 FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	2	-CH3 [aliphatic carbon]	0.5473	1.0946
Frag	4	-CH2- [aliphatic carbon]	0.4911	1.9644
Cons t		Equation Constant		0.2290

Log Kow = 3.2880

Experimental Database Structure Match:
Name: n-Hexane
CAS Registry Number : 000110-54-3
Experimental Log Kow: 3.90
Experim. Reference : Hansch,C et al. (1995)

IDEALLY, KOW AT PH 5.5

From: Geochemical Journal, Vol. 46, pp. 517 to 520, 2012

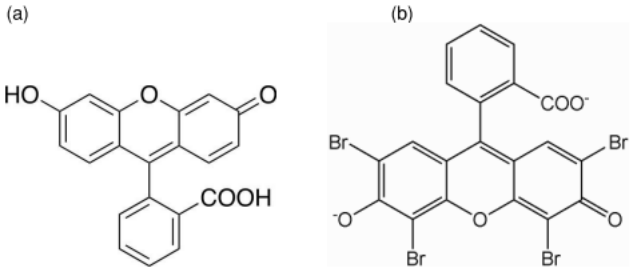


Fig. 1. Chemical structure of: (a) fluorescein, neutral form (H_2Fl^0); (b) eosin Y, deprotonated form.

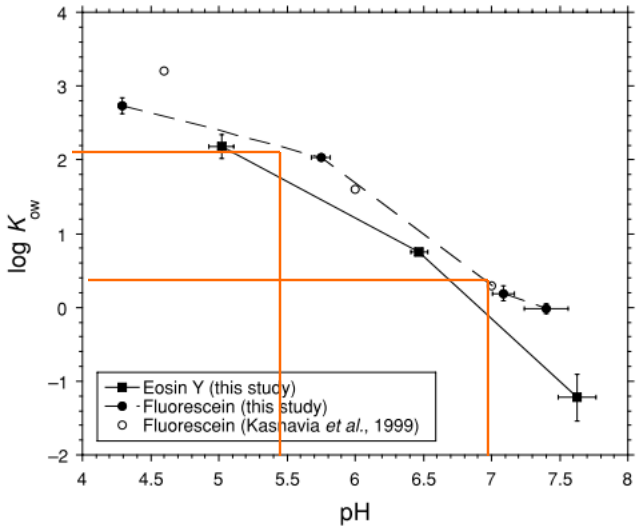


Fig. 2. Values of log K_{ow} vs. pH for fluorescein (this study; Kasnavia et al., 1999) and eosin Y (this study). Data points represent average of 3 to 5 experiments, and error bars represent 1 standard deviation. Some error bars are smaller than the data symbol.

This pH effect is important for acids, bases. Skin pH = 5.5

Relationship of Log $K_{O/W}$ to Kp

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

Compound	Kp	Log Ko/w
Methanol	0.0005	-0.77
Ethanol	0.0008	-0.31
Propanol	0.0014	0.30
Butanol	0.0025	0.65
Pentanol	0.0060	1.56
Hexanol	0.0130	2.03

What trends do you see?

Kp tends to increase with increasing Log $K_{O/W}$ (up to saturation)

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

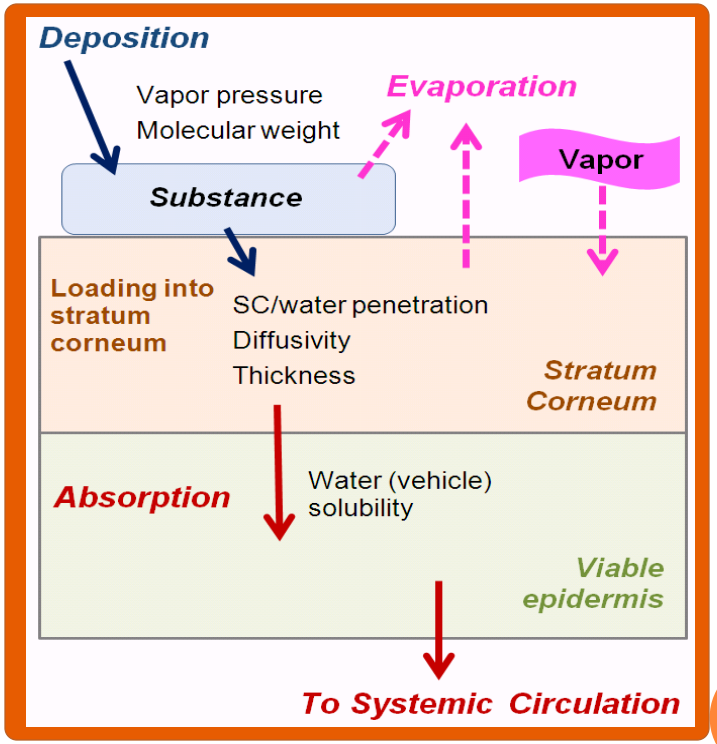


Illustration from IH SkinPerm

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).

Vecchia, B.E., Bunge, A.L., (2002a). Skin absorption databases and predictive equations. In: Guy, R.H., Hadgraft, J. (Eds.), Transdermal Drug Delivery. Publisher Marcel Dekker, pp. 57–141 (Chapter 3).

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

ten Berge WF. (2009). A simple dermal absorption model: Derivation and application. Chemosphere 75, 1440-1445

What is "Under the Hood" in IH SkinPerm?

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

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

$$Kpol = \frac{b4}{M4^{b5}} \qquad Kaq = \frac{b6}{Mw^{b7}}$$

$$Klip = permeation\ coefficient\ lipid\ medium$$

$$Kpol = permeation\ coefficient\ corneocytes\ [proteins]$$

$$Kaq = permeation\ coefficient\ epidemis\ [aqueous\ medium]$$

$$Kow = \frac{octanol}{water}\ partition\ coefficient$$

$$Mw = molecular\ weight$$

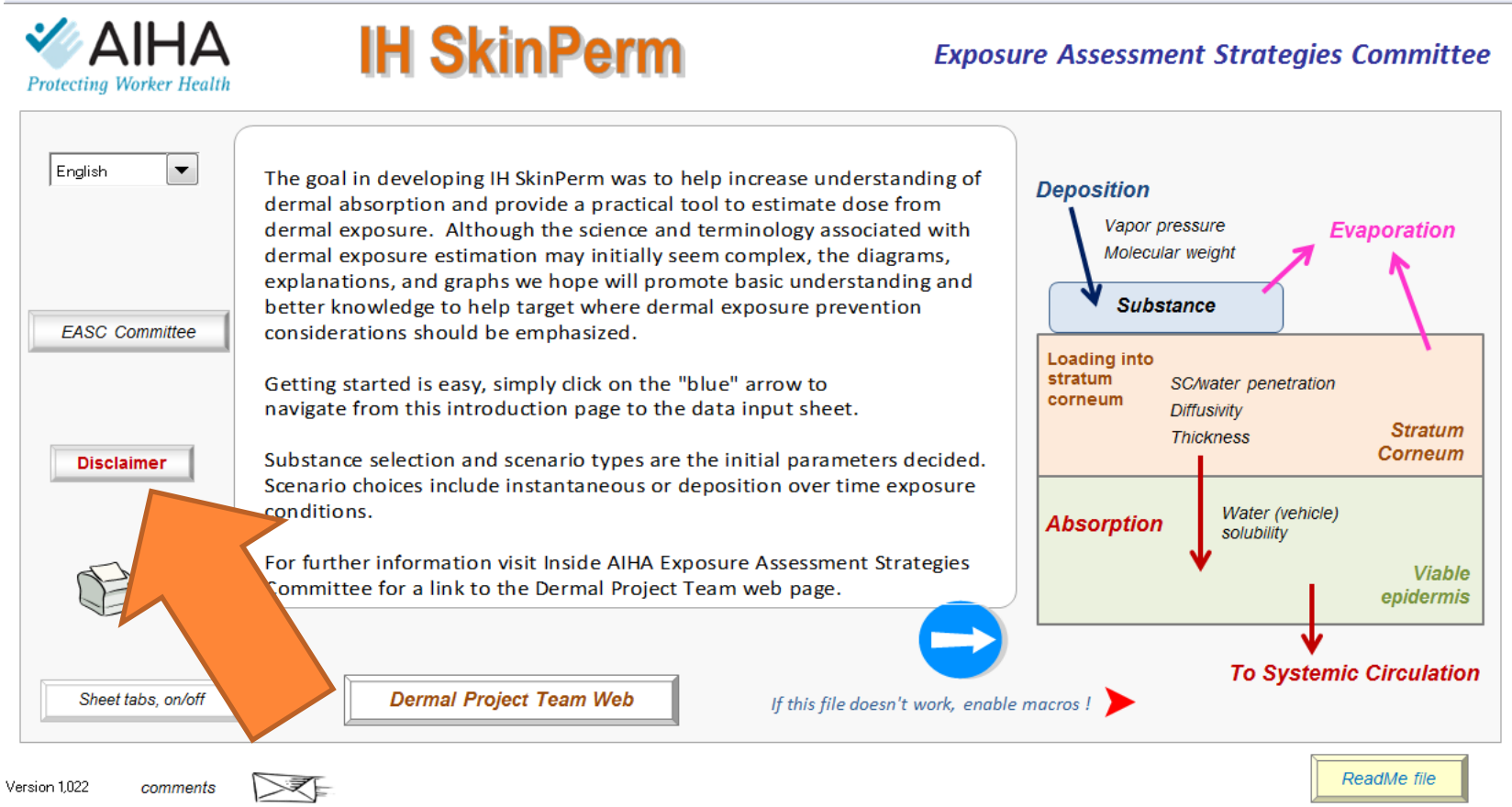
$$b1, b2, b3, b4, b5, b6, b7 = regression\ coefficients$$

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

Running IH SkinPerm Initial Screen



Disclaimer Screen

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IH SkinPerm

Disclaimer

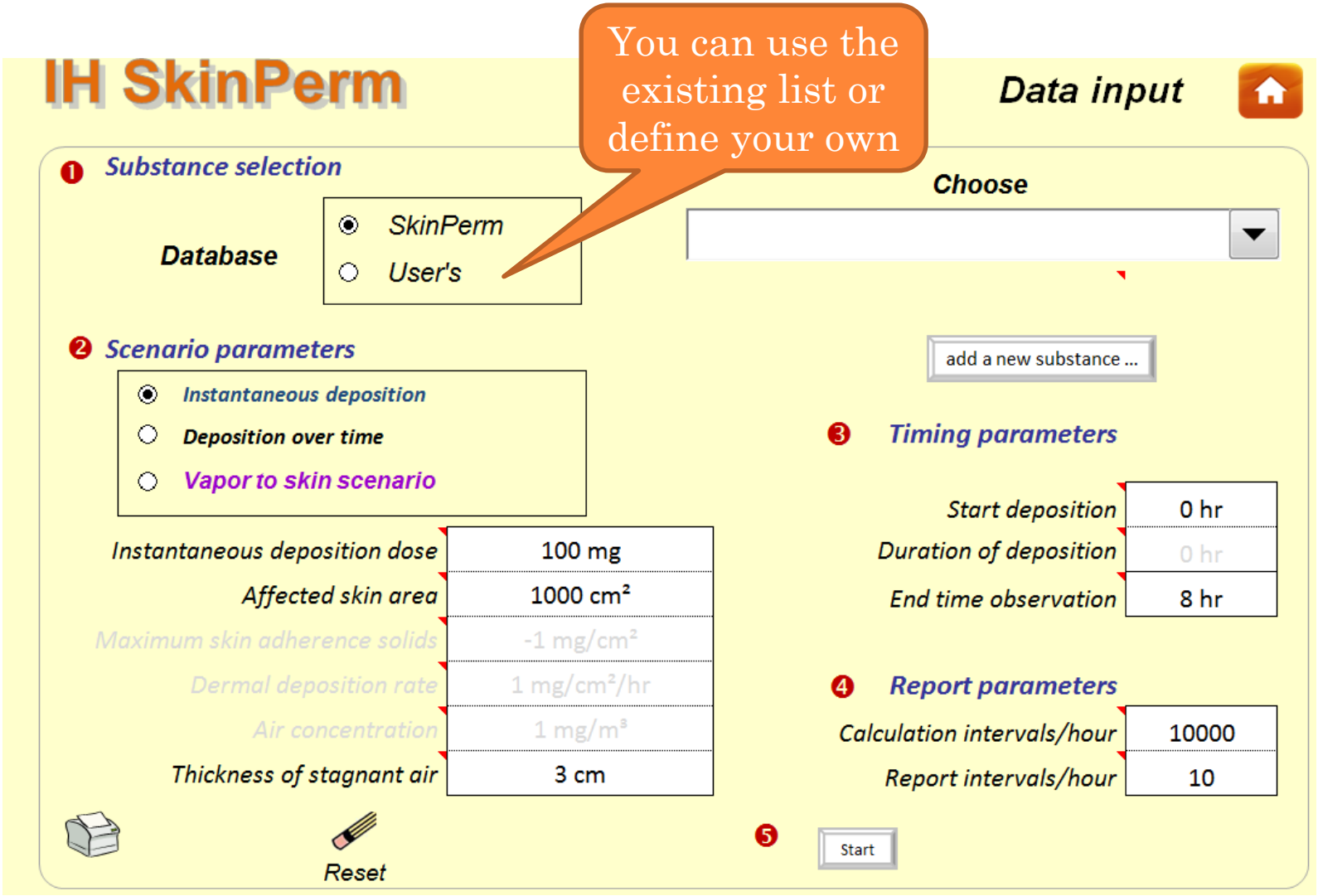
Developers and users of this and earlier versions of the Excel spreadsheet have found it to be useful in estimating skin permeation. Equations and concepts upon which this model is based are in the public domain through published literature. Equations embedded in this spreadsheet were verified upon released. 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 IHSTAT and IHMOD and enables multilingual capability. Additional collaborators deserving special mention include Thomas W. Armstrong, Jennifer Sahmel, and Michael Jayjock.

Data Entry Screen



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

Evaporation rate is calculated based on REACh technical guidance and uses the following equations and assumptions:

$$Evaporation\ rate(LF) = \frac{\beta * Mw * Vp}{R * T * 10} \qquad eq.\ 8$$

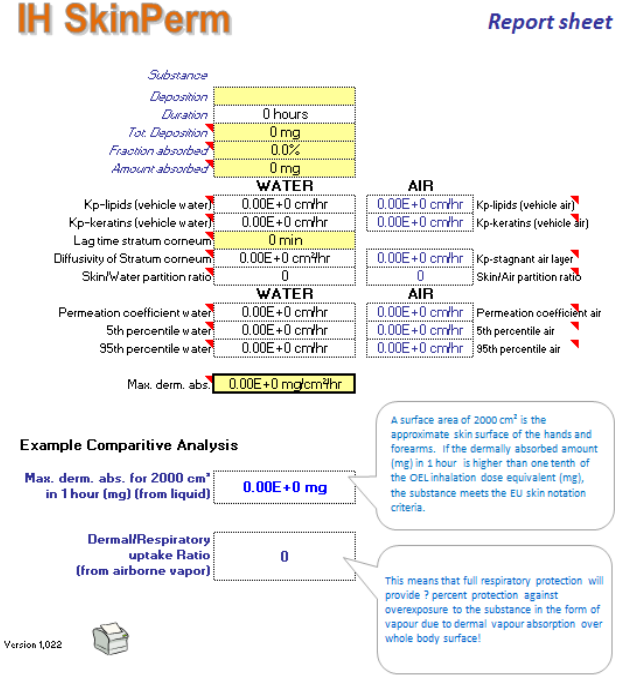
$$\beta = \frac{0.0111 * V^{0.96} * D_g^{\ 0.19}}{\nu^{0.15} * X^{0.04}} \qquad eq.\ 9$$

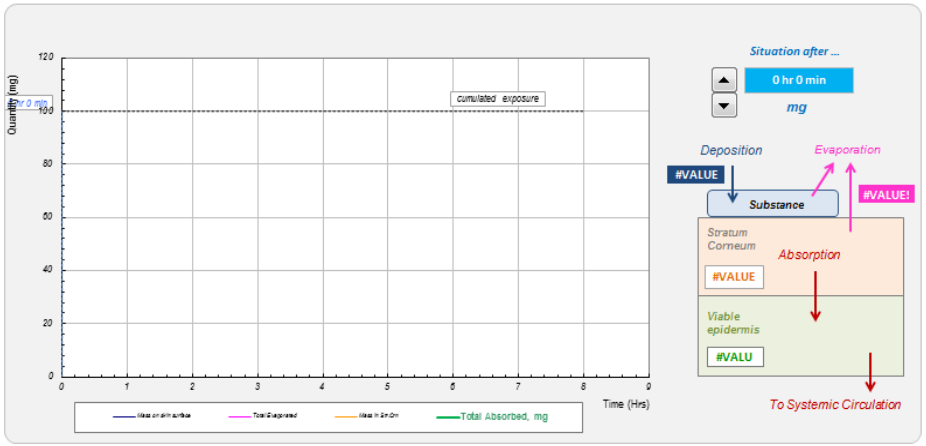
Mw	*Molecular weight*
Vp	*Vapor pressure of the liquid at skin temperature in Pascal*
R	*Gas constant in J/Mol/°K*
T	*Skin temperature in°K (normal range 28-32°C) (assume 303°K)*
β	*Coefficient of mass transfer in the vapour phase in meter/hour*
V	*Velocity of air (at workplaces ranges 0.3 to 0.6 m/s) (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)*
v	*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)*

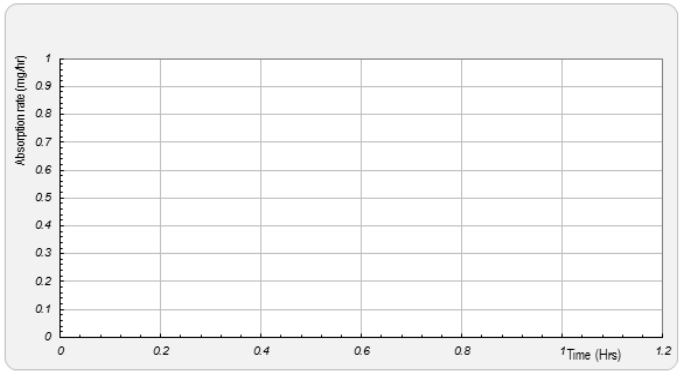
IH SkinPerm Estimates the Maximum Dermal Absorption for 2000 cm^2 in one hour (mg) (from liquid)

A surface area of 2000 cm^2 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







Chemical Properties Database Tables The SkinPerm Table and User Defined Table

SkinPerm database

Num	Substance	CAS	MW	Temp °C	Vapour Pressure Pa	Water Solubility mg/L	LogKow bij skin pH 5.5	Density mg/cm³	Measured Perm. Coeff. cm/hr
1	111-trichloroethane	71-55-6	133.4	25	13300	4400	2.49	1320	
2	12-Dichloroethane	107-06-2	98.96	25	10500	8600	1.48	1230	
3	13-dinitrobenzene	99-65-6	168	25	0.027	530	1.52	1575	
4	1-methylnaphthalene	90-12-0	142.2	25	8.9	25.8	3.87	1145	
5	24-dichlorophenoxy acetic acid	94-75-7	221	25	0.01	677	0.09	1420	
6	26ditertbutylphenol	128-39-2	206.4	25	0.35	0.4	5.43	910	
7	2-chloronitrobenzene	88-73-3	157.6	25	3.8	590	2.42	1368	
8	2-methylnaphthalene	91-57-6	142.2	25	7.3	24.6	3.86	1000	
9	2-nitrophenol	88-75-5	139.1	25	6.9	1300	1.9	1490	
10	3-xylene	108-38-3	106.17	25	1110	161	3.2	870	
11	4-hydroxy-benzonitril	767-00-0	119.2	25	0.24	10000	1.6	1000	
12	4tertbutylphenol	98-54-4	150.2	25	0.64	26	3.31	908	
13	Acetochlor	34256-82-1	269.77	25	0.0037	223	3.03	1136	
14	Acetone	67-64-1	58.1	25	24000	800000	-0.24	790	
15	Acrylamide	79-06-1	71.1	25	0.9	2155	-0.67	1130	
16	Ahtn(musk)	1506-02-1	258.41	25	0.0682	1.25	5.7	919	
17	Allylglycidylether	106-92-3	114.06	25	627	140000	0.45	962	
18	Aniline	62-53-3	93	25	40	34000	0.9	1022	
19	Anthracene	120-12-7	178.24	25	0.066	0.0434	4.45	1250	
20	Arildone	56219-57-9	368.9	25	0.0002	2	5.87	1078	
21	B-chloropreen	126-99-8	88.5	25	25000	256	1.73	958.3	
22	Benzene	71-43-2	78	25	12673	1780	2.13	878.6	
23	Benzo(a)pyrene	50-32-8	252	25	0.00000073	0.00162	6.13	1286	
24	Benzylalcohol	100-51-6	108.14	25	12.4	42900	1.1	1042	
25	Betamethason	378-44-9	392.47	25	1.3E-09	89	1.9	1240	
26	Biphenyl	92-52-4	154.21	25	1.19	6.94	3.98	992	
27	Butoxyethanol	111-76-2	118.2	25	117	900000	0.83	897	
28	Caffeine	58-08-2	194.2	25	2000	21600	-0.07	1230	
29	Caprolactam	105-60-2	113.2	25	0.3	820000	-0.19	1010	

USER database

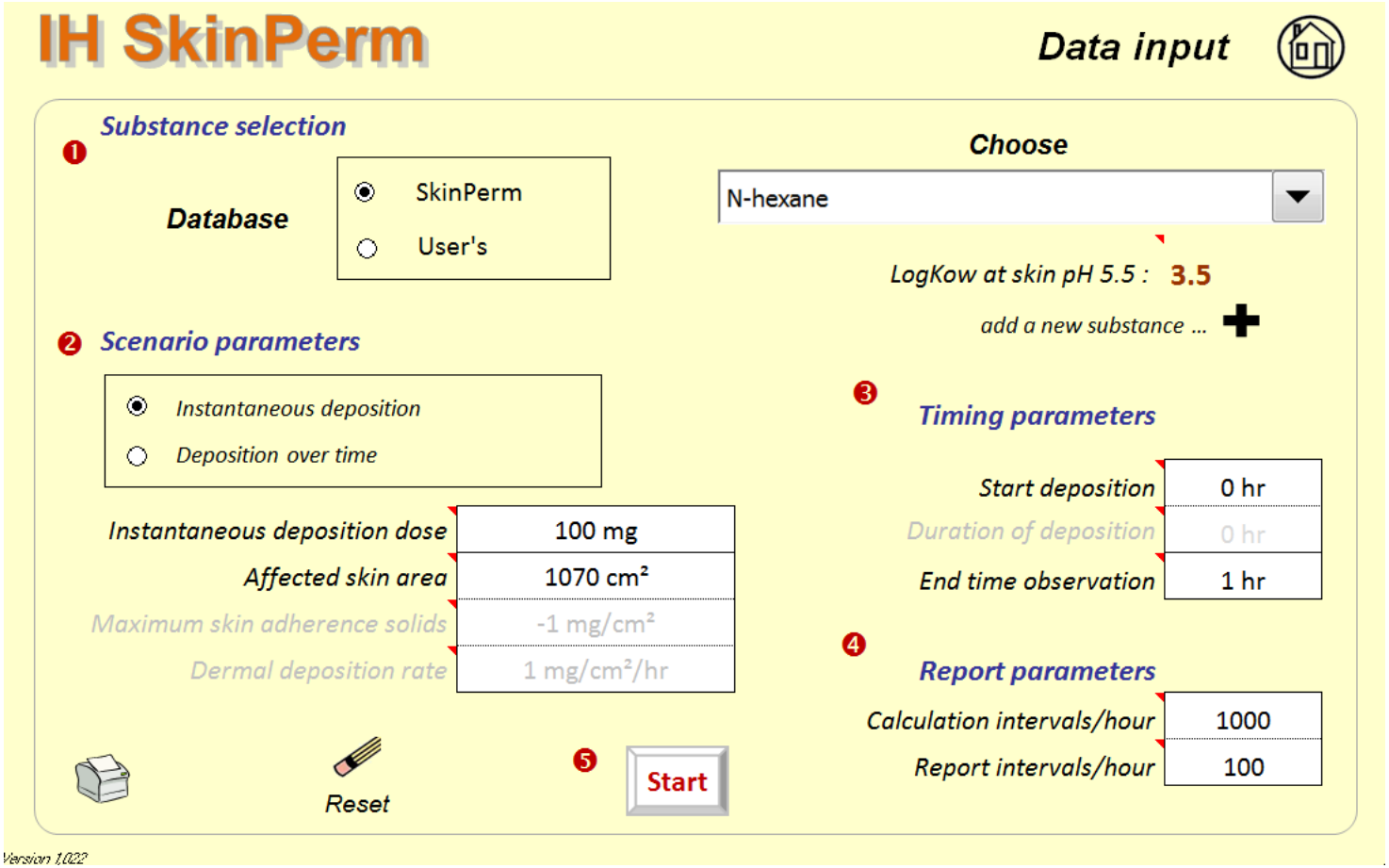
Number : 3

Num	Substance	CAS	MW	Temp °C	Vapour Pressure Pa	Water Solubility mg/L	LogKow bij skin pH 5.5	Density mg/cm³	Measured Perm. Coeff. cm/hr
1	test twa	1111	18	30	15	8	1.7	1	
2	chloroform in water	67-66-3-1	118	35	5066	9300	1.97	1180	
3	NN-diethyltoluamide	134-62-3	191.28	25	0.267	420	2.18	984	

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



SkinPerm Tool: Results for n-Hexane

AIHA
Protecting Worker Health

IH SkinPerm — **Report sheet**

Substance	**N-hexane**		
Deposition	**Instantaneous**		
Duration			
Tot. Deposition	100 mg		
Fraction absorbed	1.1%		
Amount absorbed	1.0813 mg		
	Water	**AIR**	
Kp-lipids (vehicle water)	2.41E-01 cm/hr	3.47E-03 cm/hr	Kp-lipids (vehicle air)
Kp-keratins (vehicle water)	9.98E-05 cm/hr	1.40E-06 cm/hr	Kp-keratins (vehicle air)
Lag time stratum corneum	1.909 min		
Diffusivity of Stratum corneum	2.10E-05 cm^2/hr	1.13E+02 cm/hr	Kp-stagnant air layer
Skin/Water partition ratio	23.032	0.331	Skin/Air partition ratio
	WATER	**AIR**	
Permeation coefficient water	2.41E-01 cm/hr	3.47E-03 cm/hr	Permeation coefficient air
5^{th} percentile water	1.47E-01 cm/hr	2.12E-03 cm/hr	5^{th} percentile air
95^{th} percentile water	3.95E-01 cm/hr	5.68E-03 cm/hr	95^{th} percentile air
Max. derm. abs.	2.41E-03 mg/cm^2/hour		

Back to Data imput

SkinPerm Tool: Data for n-Hexane

IH SkinPerm — *Report sheet*

Substance	**N-hexane**		
Deposition	**Instantaneous**		
Duration			
Tot. Deposition	100 mg		
Fraction absorbed	1.1%		
Amount absorbed	1.0829 mg		
	WATER	**AIR**	
Kp-lipids (vehicle water)	2.41E-1 cm/hr	3.47E-3 cm/hr	Kp-lipids (vehicle air)
Kp-keratins (vehicle water)	9.98E-5 cm/hr	1.40E-6 cm/hr	Kp-keratins (vehicle air)
Lag time stratum corneum	1.909 min		
Diffusivity of Stratum corneum	2.10E-5 cm²/hr	1.13E+2 cm/hr	Kp-stagnant air layer
Skin/Water partition ratio	23.032	0.331	Skin/Air partition ratio
	WATER	**AIR**	
Permeation coefficient water	2.41E-1 cm/hr	3.47E-3 cm/hr	Permeation coefficient air
5th percentile water	1.47E-1 cm/hr	2.12E-3 cm/hr	5th percentile air
95th percentile water	3.95E-1 cm/hr	5.68E-3 cm/hr	95th percentile air
Max. derm. abs.	2.41E-3 mg/cm²/hr		

Example Comparitive Analysis

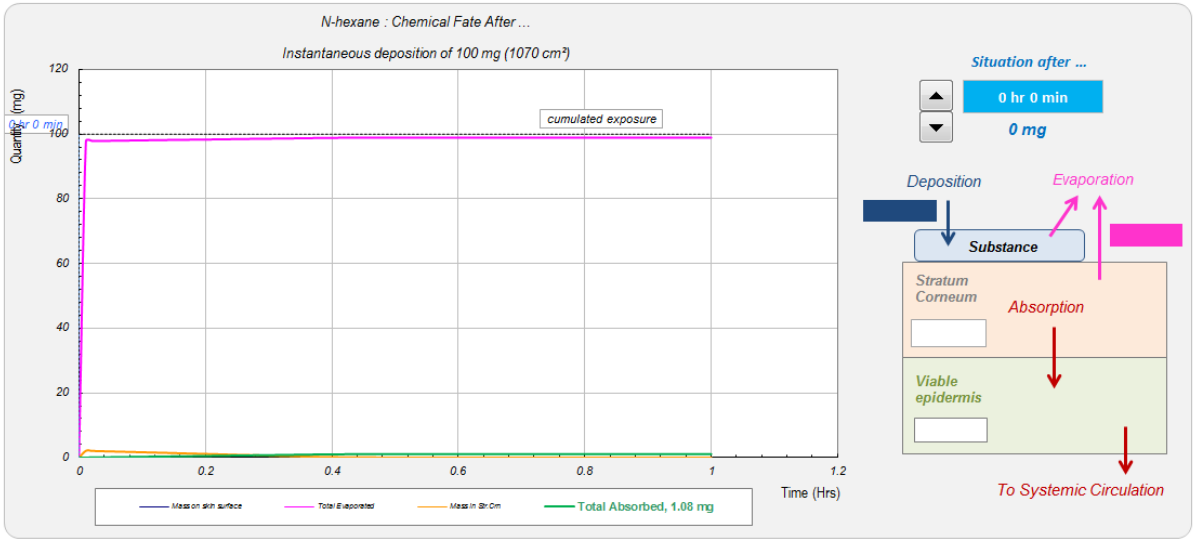
Max. derm. abs. for 2000 cm² in 1 hour (mg) (from liquid)	4.83E+0 mg
Dermal/Respiratory uptake Ratio (from airborne vapor)	0.0000666

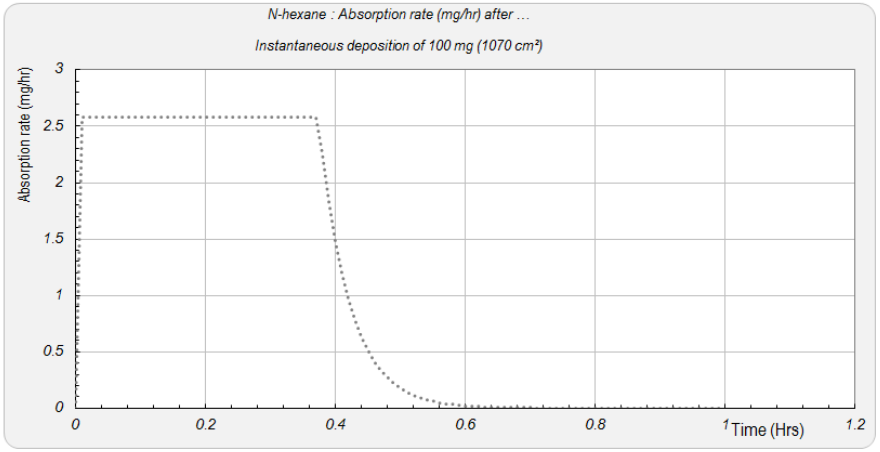
A surface area of 2000 cm² is the approximate skin surface of the hands and forearms. If the dermally absorbed amount (mg) in 1 hour is higher than one tenth of the OEL inhalation dose equivalent (mg), the substance meets the EU skin notation criteria.

This means that full respiratory protection will provide 100 percent protection against overexposure to the substance in the form of vapour due to dermal vapour absorption over whole body surface!

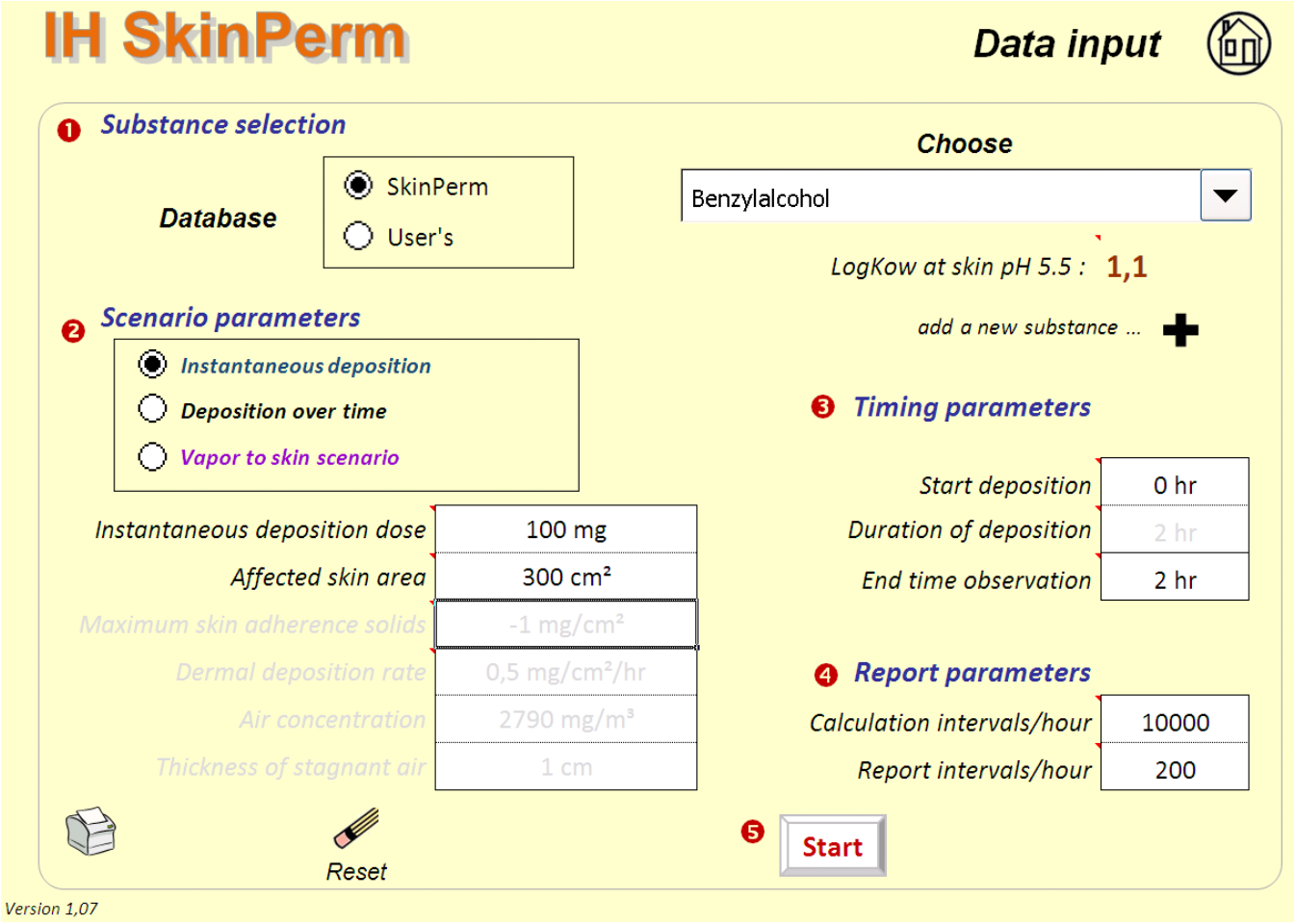
Version 1.022

Results Graphs for N-Hexane – different durations, etc. will autoscale





IH SkinPerm Tool: Data for benzylalcohol



RESULTS FOR BENZYL ALCOHOL

IH SkinPerm

Report sheet

Substance	**Benzylalcohol**		
Deposition	**Instantaneous**		
Duration			
Tot. Deposition	100 mg		
Fraction absorbed	59.4%		
Amount absorbed	59.39 mg		
	WATER	**AIR**	
Kp-lipids (vehicle water)	2.99E-3 cm/hr	2.37E+2 cm/hr	Kp-lipids (vehicle air)
Kp-keratins (vehicle water)	7.33E-5 cm/hr	5.81E+0 cm/hr	Kp-keratins (vehicle air)
Lag time stratum corneum	13.954 min		
Diffusivity of Stratum corneum	2.90E-6 cm²/hr	1.01E+2 cm/hr	Kp-stagnant air layer
Skin/Water partition ratio	2.1396	169593	Skin/Air partition ratio
	WATER	**AIR**	
Permeation coefficient water	3.07E-3 cm/hr	7.12E+1 cm/hr	Permeation coefficient air
5th percentile water	2.26E-3 cm/hr	6.44E+1 cm/hr	5th percentile air
95th percentile water	4.16E-3 cm/hr	7.71E+1 cm/hr	95th percentile air
Max. derm. abs.	1.32E-1 mg/cm²/hr		

Example Comparitive Analysis

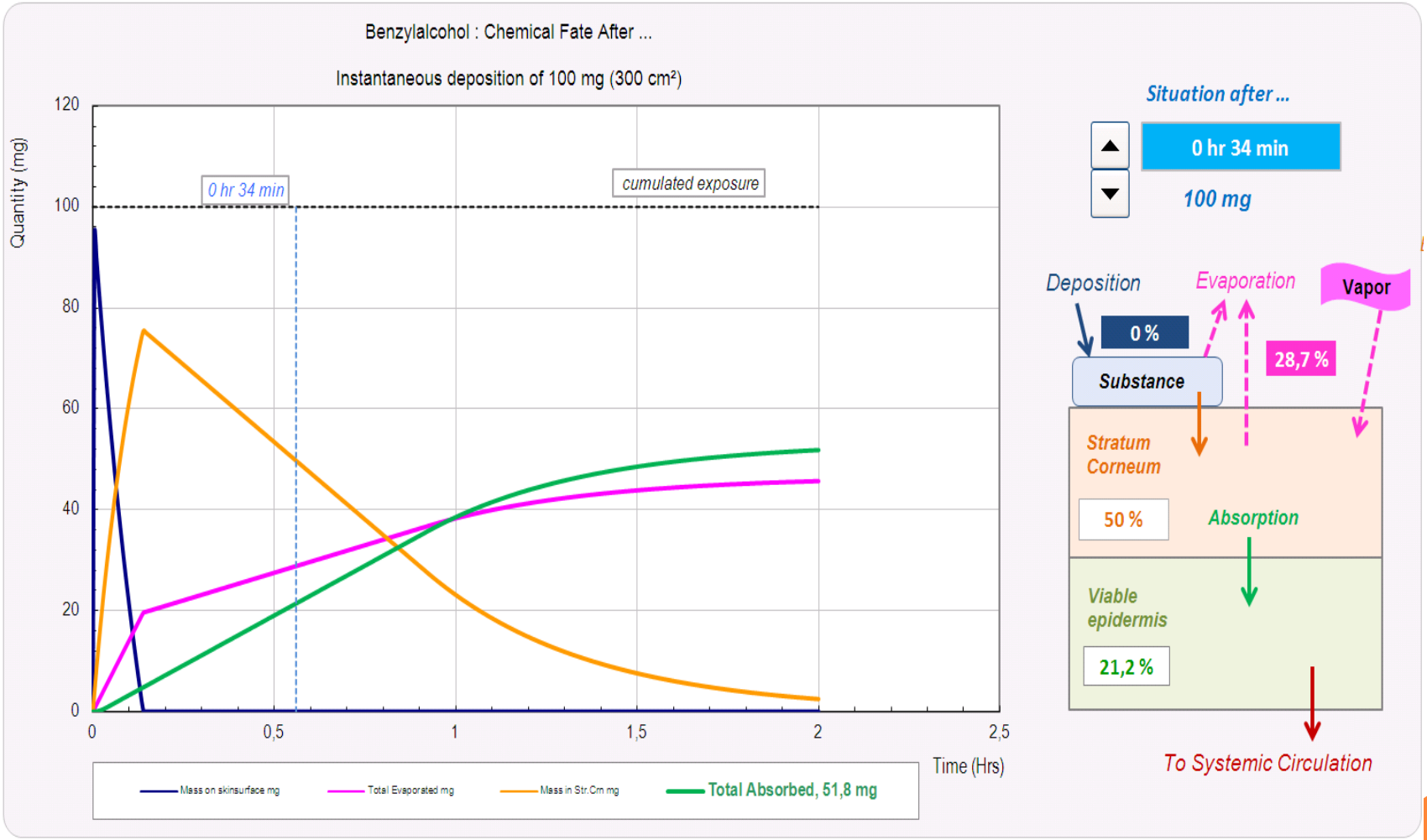
Max. derm. abs. for 2000 cm² in 1 hour (mg) (from liquid)	**2.63E+2 mg**
Dermal/Respiratory uptake Ratio (from airborne vapor)	**1.3661**

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!

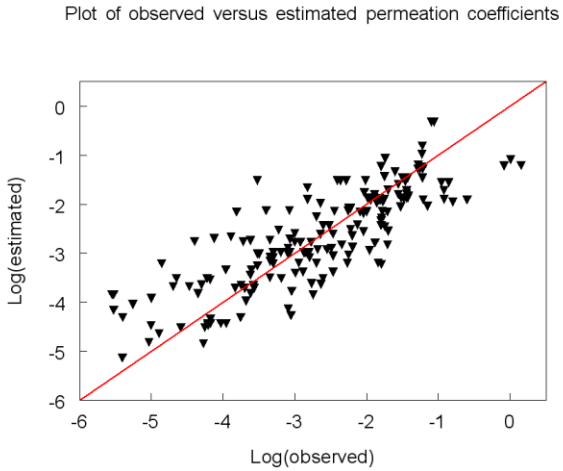
Version 1,022

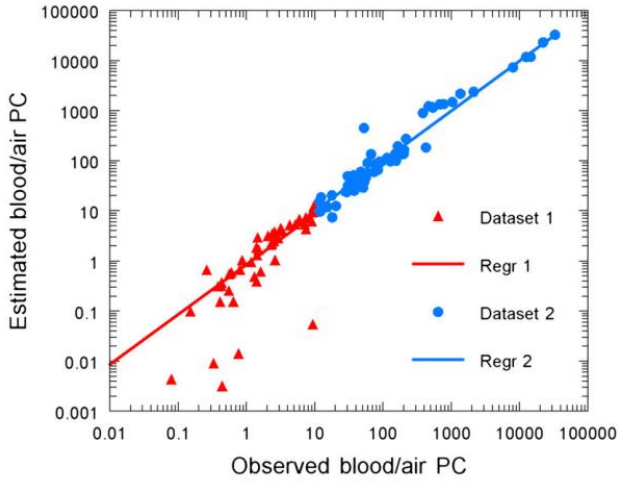
IH SkinPerm Tool: Data for benzylalcohol



IH SkinPerm: Validation Studies of the Theoretical Model

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 *in vitro*)
- 2. is for the blood/air partition coefficient (human PBPK)

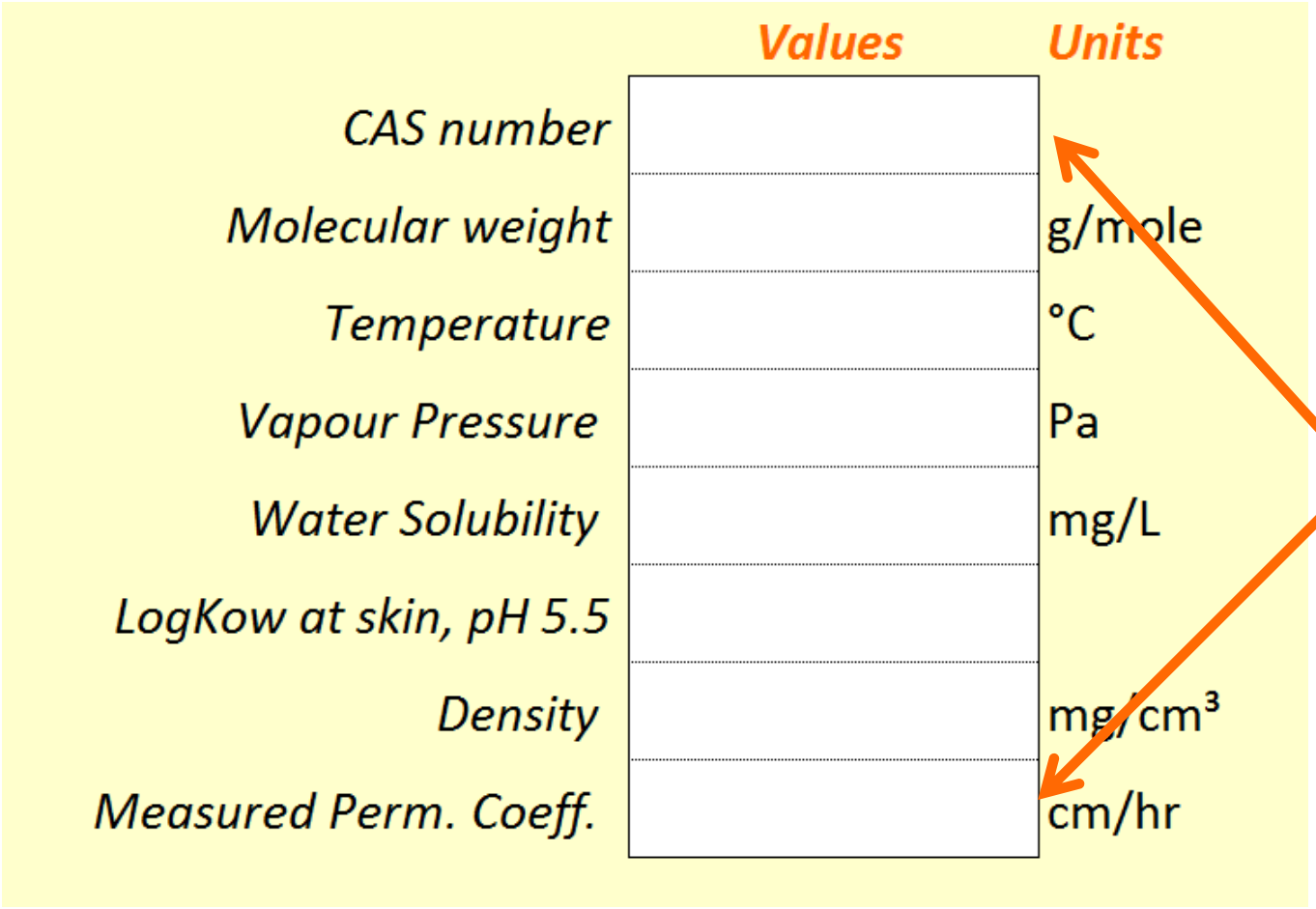
The model has been used and "validated" against chemical hazards in addition to those in the original validation set and beyond these two graphic analyses

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/cm^2
- Range of liquid film loading 0.7 to 2.5 mg/cm^2
- 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



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?

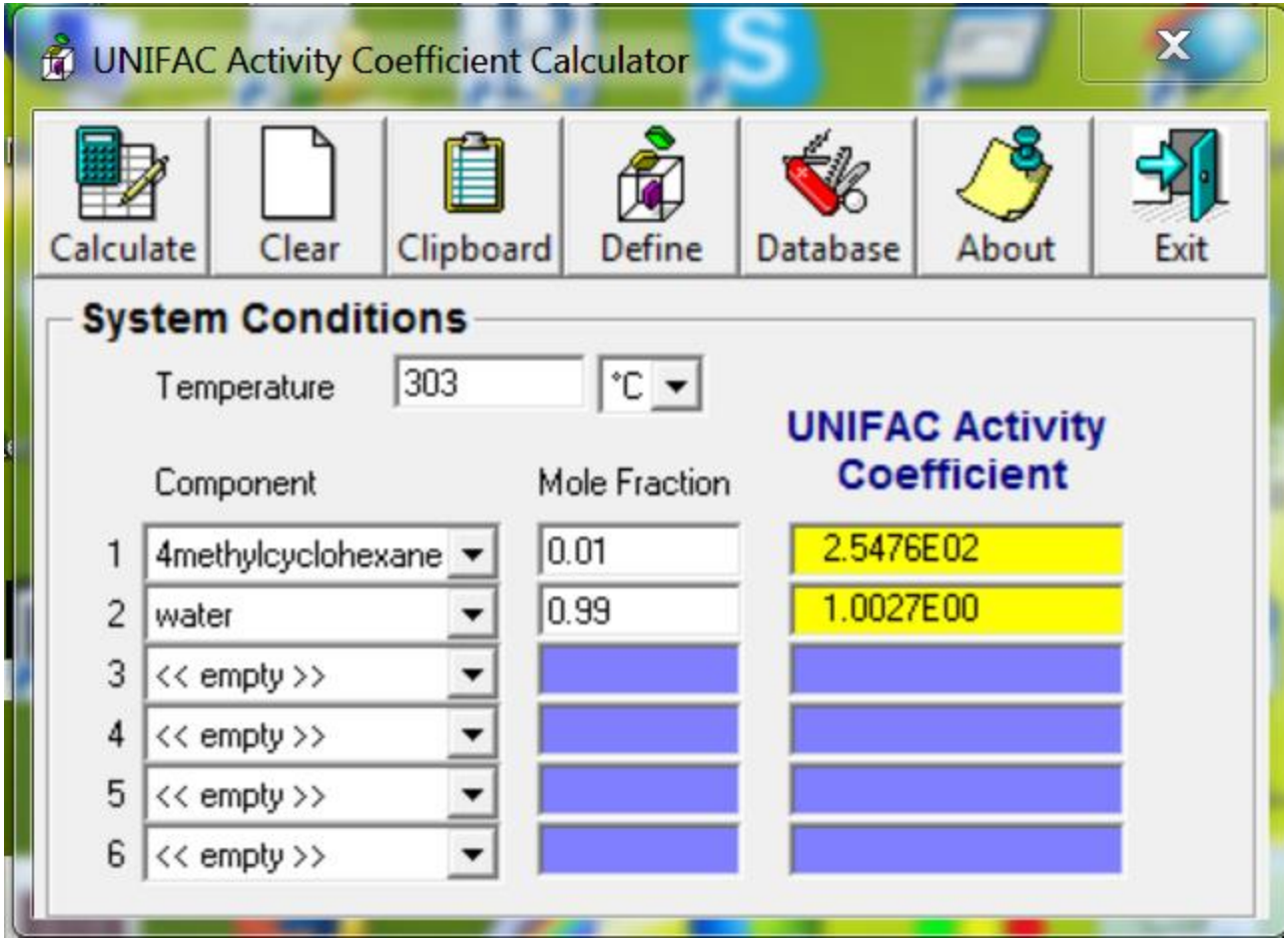
A SPREADSHEET MAY BE USEFUL IN CALCULATING AND DOCUMENTING SOME OF THESE INPUT PARAMETERS

EXAMPLE

Compound	MW	Density (g/ml)	gr/L	VP Torr	Weight%	Moles	Mole Fr	PVp	Activity C	PVpa Torr	Pvpa Pa	Contact Mass Load mg/CM2	Skin Area CM2	Total Mass mg Compound
MCHM	128	0.884	8	0.133	0.0001	7.8125E-07	4.33984E-08	5.77199E-09	2000	1.1544E-05		0.00015	20000	3
Water	18	1			0.9999	18.0018002	0.999999957					1.5	20000	29997
						18.001801								

Activity

- Discussed in IH Mod webinar



Activity Coefficient applied to Raoult's Law Partial VP

IH SkinPerm

Report sheet

Substance **4MCHMinWater0.0001**

Deposition	Instantaneous
Duration	
Tot. Deposition	3.0003 mg
Fraction absorbed	63.4%
Amount absorbed	1.9027 mg

	WATER	AIR	
Kp-lipids (vehicle water)	2.52E-2 cm/hr	2.60E+3 cm/hr	Kp-lipids (vehicle air)
Kp-keratins (vehicle water)	5.83E-5 cm/hr	6.02E+0 cm/hr	Kp-keratins (vehicle air)
Lag time stratum corneum	7.1165 min		
Diffusivity of Stratum corneum	5.60E-6 cm²/hr	9.25E+1 cm/hr	Kp-stagnant air layer
Skin/Water partition ratio	8.9915	928213	Skin/Air partition ratio
	WATER	**AIR**	
Permeation coefficient water	2.53E-2 cm/hr	8.93E+1 cm/hr	Permeation coefficient air
5th percentile water	1.87E-2 cm/hr	8.82E+1 cm/hr	5th percentile air
95th percentile water	3.42E-2 cm/hr	9.01E+1 cm/hr	95th percentile air

Max. derm. abs. 2.02E-4 mg/cm²/hr

Example Comparitive Analysis

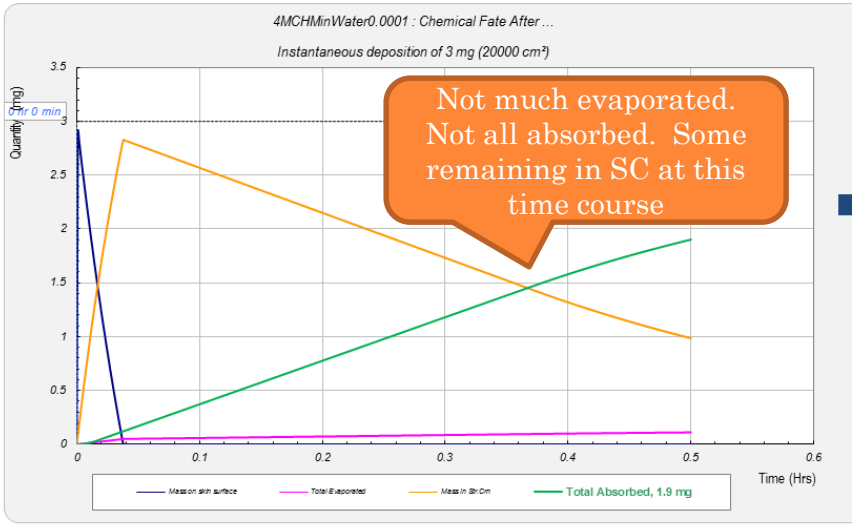
Max. derm. abs. for 2000 cm² in 1 hour (mg) (from liquid): **4.04E-1 mg**

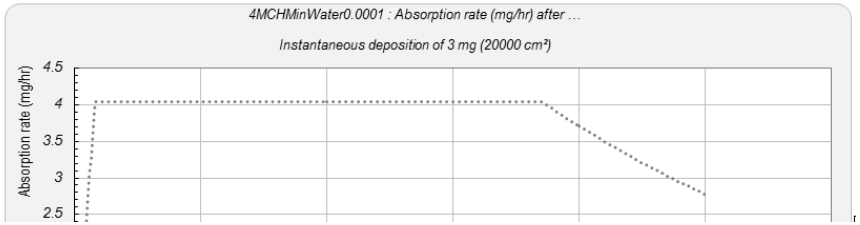
A surface area of 2000 cm² is the approximate skin surface of the hands and forearms. If the dermally absorbed amount (mg) in 1 hour is higher than one tenth of the OEL inhalation dose equivalent (mg), the substance meets the EU skin notation criteria.

Dermal/Respiratory uptake Ratio (from airborne vapor): **1.7146**

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!

Version 1.022





TWA8HR Occupational Hygiene Consulting, LLC

MCHM as Dilute Aqueous Solution with Partial vapor pressure – Raoult's Law

IH SkinPerm

Report sheet

Substance	**4MCHMinWater0.0001**		
Deposition	**Instantaneous**		
Duration			
Tot. Deposition	3.0003 mg		
Fraction absorbed	63.4%		
Amount absorbed	1.9027 mg		
	WATER	**AIR**	
Kp-lipids (vehicle water)	2.52E-2 cm/hr	2.60E+3 cm/hr	Kp-lipids (vehicle air)
Kp-keratins (vehicle water)	5.83E-5 cm/hr	6.02E+0 cm/hr	Kp-keratins (vehicle air)
Lag time stratum corneum	7.1165 min		
Diffusivity of Stratum corneum	5.60E-6 cm²/hr	9.25E+1 cm/hr	Kp-stagnant air layer
Skin/Water partition ratio	8.9915	928213	Skin/Air partition ratio
	WATER	**AIR**	
Permeation coefficient water	2.53E-2 cm/hr	8.93E+1 cm/hr	Permeation coefficient air
5th percentile water	1.87E-2 cm/hr	8.82E+1 cm/hr	5th percentile air
95th percentile water	3.42E-2 cm/hr	9.01E+1 cm/hr	95th percentile air
Max. derm. abs.	2.02E-4 mg/cm²/hr		

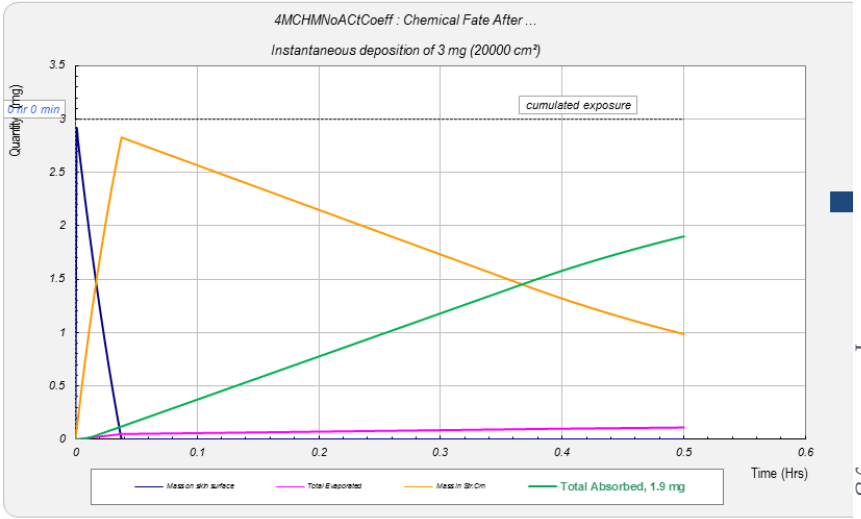
Example Comparitive Analysis

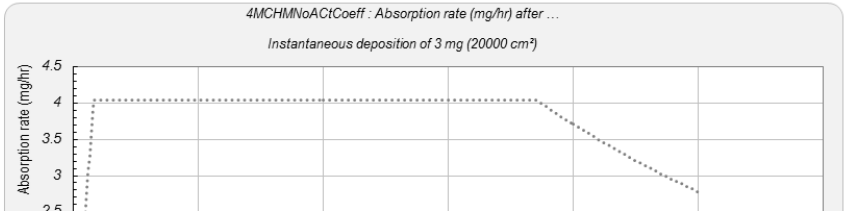
Max. derm. abs. for 2000 cm² in 1 hour (mg) (from liquid)	**4.04E-1 mg**
Dermal/Respiratory uptake Ratio (from airborne vapor)	**1.7146**

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!

Version 1.022





MCHM as Neat Liquid – same mass loading

IH SkinPerm

Report sheet

Substance	**MCHMNeat**		
Deposition	**Instantaneous**		
Duration			
Tot. Deposition	3.0001 mg		
Fraction absorbed	40.0%		
Amount absorbed	1.2011 mg		
	WATER	**AIR**	
Kp-lipids (vehicle water)	2.52E-2 cm/hr	2.21E-1 cm/hr	Kp-lipids (vehicle air)
Kp-keratins (vehicle water)	5.83E-5 cm/hr	5.10E-4 cm/hr	Kp-keratins (vehicle air)
Lag time stratum corneum	7.1165 min		
Diffusivity of Stratum corneum	5.60E-6 cm²/hr	9.25E+1 cm/hr	Kp-stagnant air layer
Skin\Water partition ratio	8.9915	78.662	Skin\Air partition ratio
	WATER	**AIR**	
Permeation coefficient water	2.53E-2 cm/hr	2.21E-1 cm/hr	Permeation coefficient air
5th percentile water	1.87E-2 cm/hr	1.63E-1 cm/hr	5th percentile air
95th percentile water	3.42E-2 cm/hr	2.98E-1 cm/hr	95th percentile air
Max. derm. abs.	2.02E-4 mg/cm²/hr		

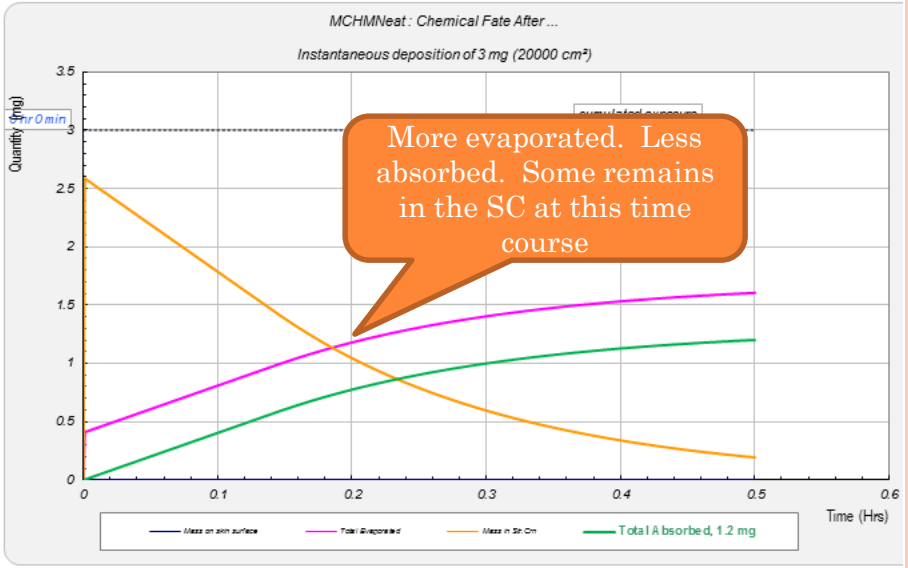
Example Comparitive Analysis

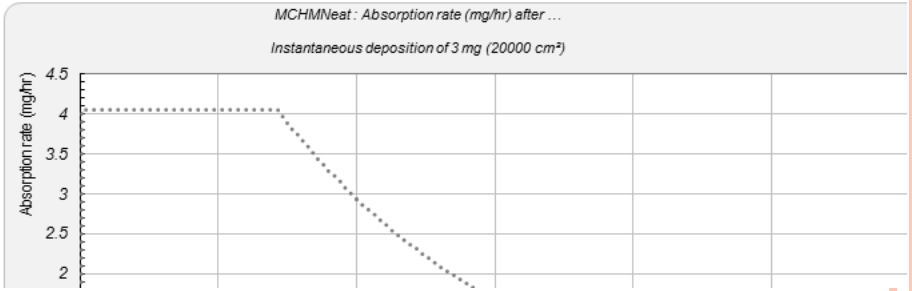
Max. derm. abs. for 2000 cm² in 1 hour (mg) (from liquid)	**4.04E-1 mg**
Dermal/Respiratory uptake Ratio (from airborne vapor)	**0.0042344**

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 99.6 percent protection against overexposure to the substance in the form of vapour due to dermal vapour absorption over whole body surface!

Version 1.022

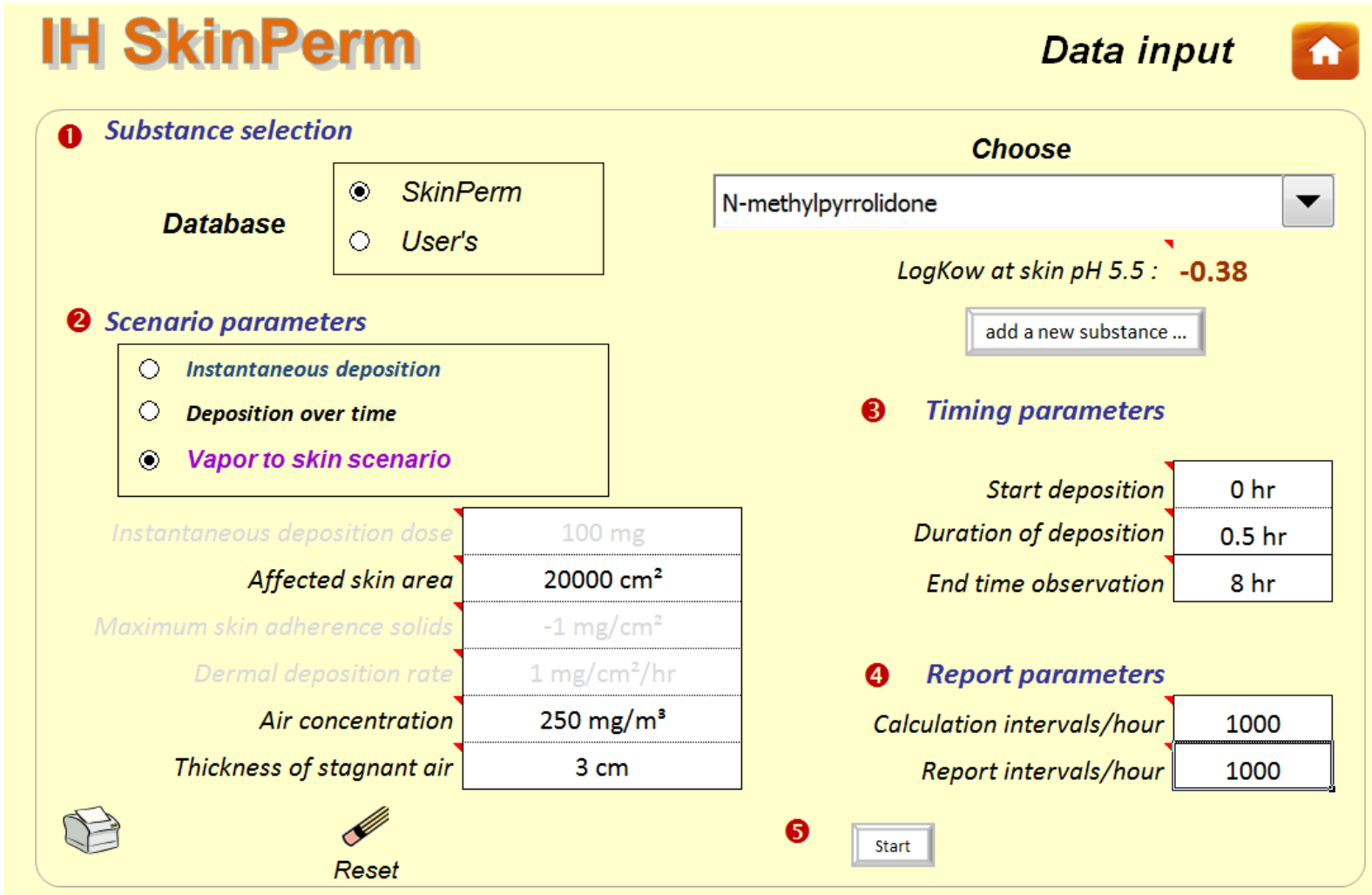




Which Estimate is "right?"

- 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-METHYLPYRROLIDONE



NMP Air to Dermal Results

IH SkinPerm — *Report sheet*

Substance	**N-methylpyrrolidone**		
Deposition	0 mg/hour		
Duration	0 hours		
Tot. Deposition	319.33 mg		
Fraction absorbed	78.6%		
Amount absorbed	250.95 mg		
	WATER	**AIR**	
Kp-lipids (vehicle water)	2.84E-4 cm/hr	1.54E+2 cm/hr	Kp-lipids (vehicle air)
Kp-keratins (vehicle water)	8.23E-5 cm/hr	4.47E+1 cm/hr	Kp-keratins (vehicle air)
Lag time stratum corneum	26.978 min		
Diffusivity of Stratum corneum	1.50E-6 cm²/hr	1.05E+2 cm/hr	Kp-stagnant air layer
Skin/Water partition ratio	0.49423	268045	Skin/Air partition ratio
	WATER	**AIR**	
Permeation coefficient water	3.66E-4 cm/hr	6.87E+1 cm/hr	Permeation coefficient air
5th percentile water	2.50E-4 cm/hr	5.92E+1 cm/hr	5th percentile air
95th percentile water	5.37E-4 cm/hr	7.71E+1 cm/hr	95th percentile air
Max. derm. abs.	3.66E-1 mg/cm²/hr		

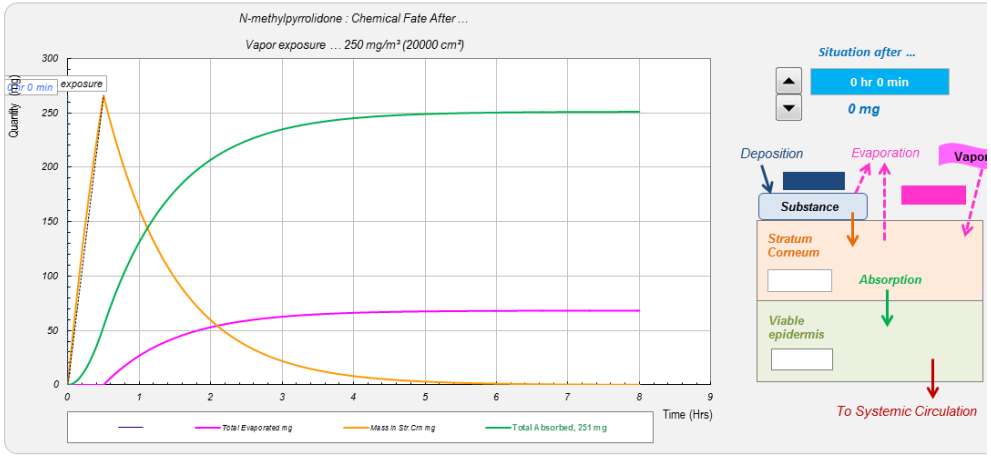
Example Comparitive Analysis

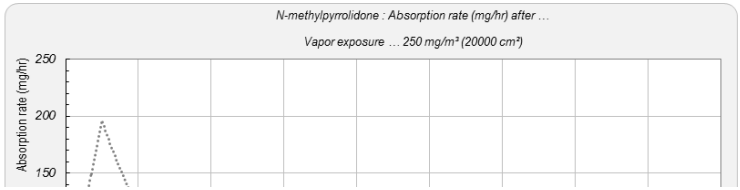
Max. derm. abs. for 2000 cm² in 1 hour (mg) (from liquid)	7.33E+2 mg
Dermal/Respiratory uptake Ratio (from airborne vapor)	1.3188

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 EU skin notation criteria.

This means that full respiratory protection will provide 43.1 percent protection against overexposure to the substance in the form of vapour due to dermal vapour absorption over whole body surface!

Version 1.15





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

- Warne, M. A., et al. "A QSAR investigation of dermal and respiratory chemical sensitizers based on computational chemistry properties." SAR and QSAR in Environmental Research 20.5-6 (2009): 429-451.
- Fedorowicz, Adam, et al. "Structure-activity models for contact sensitization." Chemical research in toxicology 18.6 (2005): 954-969.
- Miller, Matthew D., et al. "Quantum mechanical structure-activity relationship analyses for skin sensitization." Journal of chemical information and modeling 45.4 (2005): 924-929.
- Estrada, Ernesto, et al. "Computer-aided knowledge generation for understanding skin sensitization mechanisms: the TOPS-MODE approach." Chemical research in toxicology 16.10 (2003): 1226-1235.
- 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

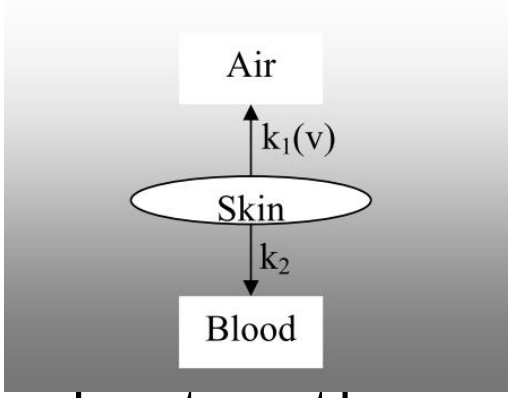
BACK UP MATERIALS

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.

- $\frac{dA}{dt} = -(k_1 + k_2)A$



- In eq. 3.1, A is the amount of ingredient on the skin surface, k 1 is the evaporation rate constant, $J_{\max} = const. \times S_{lip} \times MW^{-b}$

and k 2 is the absorption rate constant.

- The absorption rate is proportional to the product of maximum flux,

and the fractional saturation of the surface layer, A/A max . B approx = 2.7

$$k_2 A = const. \times (A / A_{\max}) \times S_{lip} MW^{-b}$$

$$k_2 = k_2^T \times MW_r^{-b}$$

- In eq. 3.3, molecular weight has been expressed in dimensionless or "reduced" form, MW r = MW/100 Da, for computational convenience. The parameter, T k 2 , is as yet undetermined. The superscript indicates that its value is a function of skin temperature, T (see Discussion). The value of T k 2 for a room temperature exposure (T ≈ 30°C) will be determined later by calibration with experimental data.

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

where the superscript on k_1^v indicates this parameter is dependent on airflow over the skin. The properties $P_{vpr} = P_{vp}/1$ torr and $(K_{oct}S_w)_r = (K_{oct}S_w)/1000$ gL^{-1} are dimensionless values chosen again for computational convenience. Like k_2^T, the value of k_1^v must be determined from experiment. The functional dependence of k_1^v on airflow will be discussed later.

The theory can now be completed. Integration of eq. 3.1 with initial dose A_0 yields

$$A(t) = A_0 \exp[-(k_1 + k_2)t] \qquad (3.6)$$

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

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

and

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

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

$$\%\text{evap} = 100 \times \frac{x_r}{k + x_r} \qquad (3.9)$$

$$\%\text{abs} = 100 - \%\text{evap} \qquad (3.10)$$

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_2^T / k_1^v, must be determined experimentally. The parameter x_r is the following dimensionless ratio of physicochemical properties of the PRM:

$$x_r = \frac{P_{vpr} MW_r^{2.7}}{(K_{oct} S_w)_r} \qquad (3.11)$$