



**Karolinska
Institutet**

Basis for skin notation. Dermal penetration data for substances on the Swedish OEL list.

Matias Rauma, PhD, MSc

Gunnar Johanson, Professor

Department of Work Environment Toxicology

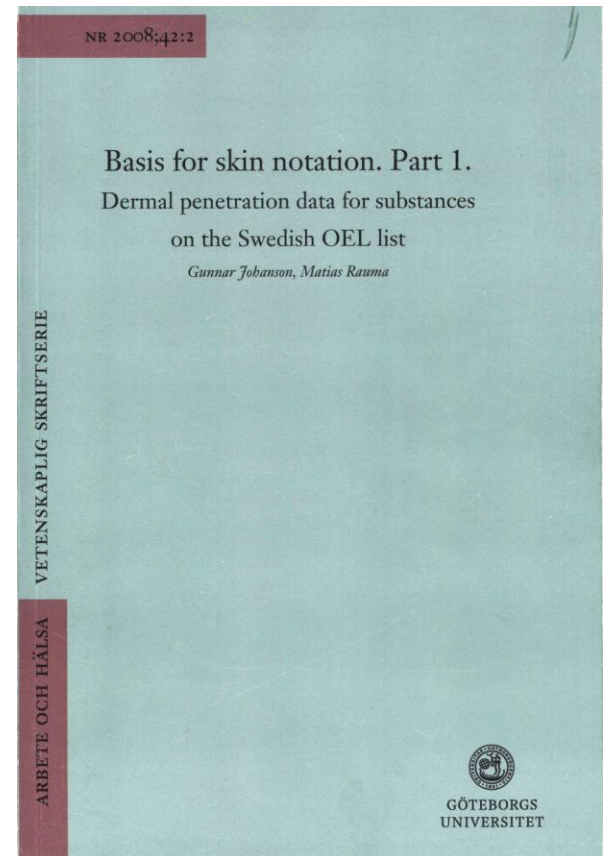
Institute of Environmental Medicine

Karolinska Institutet

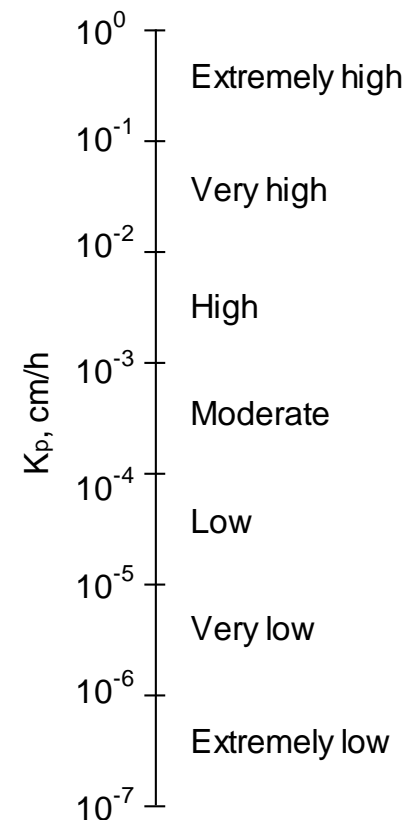
Introduction

- Commissioned by Swedish Work Environment Agency (SWEA)
- Swedish OEL list - AFS 2005:17*
 - Skin notation, “H”
 - Substances may easily be absorbed percutaneously
 - ~350 substances
 - ~115 skin notations (1/3)
- Aim of this study
 - Investigate the scientific basis for skin notations
- Published report (Arbete och Hälsa 2008;42:2)

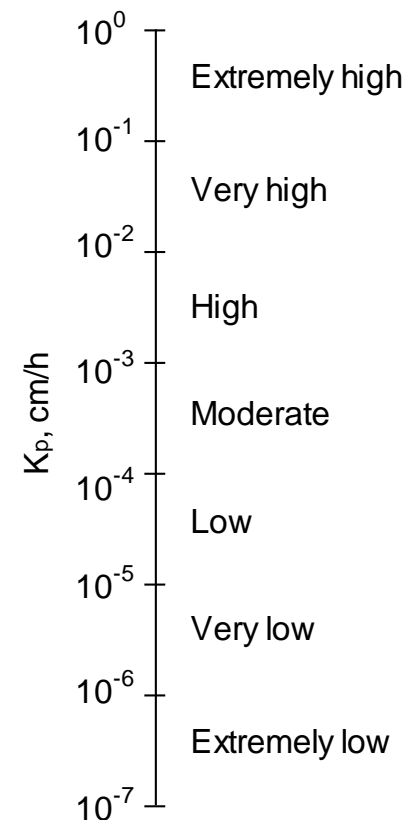
* Occupational exposure limit values and measures against air contaminants, Statute Book of the Swedish Work Environment Authority, AFS 2005:17



- **Materials**
 - All 115 substances having skin notation
 - 50 other substances on the OEL list
- **Methods**
 - Data search
 - EDETOX-database (<http://www.ncl.ac.uk/edetox/>)
 - Pubmed
 - Citing ~250 references (~1000 experiments)
 - Tabulate data
 - e.g. species, type of experiment (*in vitro/in vivo*), skin location, vehicle, concentration, exposure duration and percent absorbed chemical
 - Calculate values (if not presented)
 - Permeability coefficient – K_p (cm/h)
 - Flux – J_{ss} (mg/cm²/h)
 - Categorize permeability coefficient
 - Marzulli F., Callahan J. and Brown D. 1965
 - Barber E., Hill T. and Schum D. 1995
 - Calculate dermal/inhalation ratio
 - ECETOC criteria
 - 1 h dermal exposure, 2000 cm², to neat solvent
 - 8 h inhalation exposure, 10 m³ – 50% uptake, to OEL concentration
 - Skin notation if dermal/inhalation ratio > 0.1



- Large variations
 - Between substances
 - Fastest – Metal mercury vapor, ~ 1 cm/h
 - Slowest – Octanes, 10^{-9} cm/h
 - Within substances
 - Largest – Phenol, 10^8
 - In study designs
 - In vivo/in vitro
 - Species
 - Human, monkey, pig, dog, cat, rabbit, hamster, guinea pig, rat, mouse, snake
 - Receptor medium
 - Water, PEG-20, BSA, ethanol
 - Exposure duration
 - Minutes → Days
 - Vehicle
 - H₂O, saline, PBS, acetone, ethanol, soil, octanol, JP-8, oil, cream, toluene, methanol, chloroform, n-hexane, n-heptane, gasoline, propylene glycol
 - Skin preparation
 - Dermatome, trypsin, heat, ammoniac vapor
 - Chemical amount
 - 1 μ l → Infinite
 - Skin thickness
 - Stratum corneum → Full thickness
- Lack of published dermal penetration data (53 of 115 lack data)



Results – No data

Substance: Methyl morpholine, N-

CAS: 109-02-4

Scientific basis: Not available

Skin notation: Yes

Skin permeability: No data

Molecular weight: 101.1

Density: 0.92 g/cm³

Melting point: -66°C

Boiling point: 115°C

Vapour pressure: 2.3 kPa (at 20°C)

Evaporation rate: 1.8

Log Kow: -0.33

Reported data

Sp	Loc	Cell	L (µm)	A (cm ²)	V Vehicle (ml)	C (mg/ml)	n	T _{Exp} (h)	T _{Obs} (h)	T _{Lag} (h)	Abs (%)	K _p (10 ⁻⁴ cm/h)	Flux Reference (µg/cm ² /h)
----	-----	------	-----------	-------------------------	-------------------	--------------	---	-------------------------	-------------------------	-------------------------	------------	---	---

In vitro

No data available

In vivo

No data available

Assessment

No quantitative experimental data on dermal uptake were found in the literature.

No Swedish consensus or ACGIH report was found on n-methyl morpholin.

The Swedish skin notation is likely based on analogy with the closely related substance morpholine.

Results – LD-50 data

Substance: Hydroxyethylacrylate, 2-; propenoic acid, 2-
CAS: 818-61-1
Scientific basis: Not available

Skin notation: Yes
Skin permeability: No data

Molecular weight: 116.1
Density: 1.101 g/cm³
Melting point: -60.2°C
Boiling point: 210°C
Vapour pressure: 7 Pa (at 25°C)
Evaporation rate: Not available
Log Kow: -0.21

Reported data

Sp	Loc	Cell	L (μm)	A (cm^2)	V Vehicle (ml)	C (mg/ml)	n	T _{Exp} (h)	T _{Obs} (h)	T _{Lag} (h)	Abs (%)	K _p (10 ⁻⁴ cm/h)	Flux ($\mu\text{g}/\text{cm}^2/\text{h}$)	Reference
In vitro <i>No data available</i>														
In vivo <i>No data available</i>														

Assessment

No quantitative experimental data on dermal uptake were found in the literature.

No documentation was found from the Swedish criteria group or the ACGIH-TLV committee.

OECD (2005) reports the following LD50 values (mg/kg bw):

oral rat/mouse	601, 1070, 1040, 810, 540, 650, 548
dermal rabbit	250, 298, 154, >63, 1100, 3000
dermal rat	>1000

The dermal and oral LD50 values are in the same range, suggesting that skin absorption may be significant.

Also a study cited in OECD (2005) showed that two thirds (66%) of dermally applied radiolabelled 2-hydroxyethylacrylate (4 male rats, clipped fur, 12.5 mg/kg bw, exposed area not given) was recovered within 48h. This suggests extensive skin penetration.

Results – Dermal penetration data

Substance: Ethylene glycol
CAS: 107-21-1
Scientific basis: AoH 1982:24

Skin notation: Yes
Skin permeability: Moderate

Molecular weight: 62.1
Density: 1.116 g/cm³
Melting point: -13°C
Boiling point: 195°C
Vapour pressure: 13 Pa (at 25°C)
Evaporation rate: 0.01
Log Kow: -1.36

Reported data

Sp	Loc	Cell	L (µm)	A (cm ²)	V (ml)	Vehicle	C (mg/ml)	n	T _{Exp} (h)	T _{Obs} (h)	T _{Lag} (h)	Abs (%)	K _p (10 ⁻⁴ cm/h)	Flux Reference (µg/cm ² /h)
In vitro														
Hum	Br	Fl	Full				Neat	8	16.5	16.5	-0.5		1.1	120 Loden (1986b)
Hum	Leg	Fl	500	1		Ac	1.6	3	24	24		18	0.56	0.09 Driver et al. (1993)
Hum		St	900	0.64	0.13	H2O	10%		8	8	2	9 µg	0.21	2.3 Korinth et al. (2003)
Hum		St	900	0.64	0.13	H2O	50%		8	8	2	30 µg	0.14	7.8 Korinth et al. (2003)
In vivo														
Mou	Ba						Neat (10 mg/kg bw)	4	96	96		77	0.014	1.6 Frantz et al. (1996a)
Mou	Ba						Neat (1000 mg/kg bw)	4	96	96		84	1.6	180 Frantz et al. (1996a)
Mou	Ba					H2O	50% (1000 mg/kg bw)	4	96	96		60	2.2	130 Frantz et al. (1996a)
Rat	Ba						Neat (10 mg/kg bw)	4	96	96		32	0.059	6.6 Frantz et al. (1996a)
Rat	Ba						Neat (1000 mg/kg bw)	4	96	96		29	5.5	610 Frantz et al. (1996a)
Rat	Ba					H2O	50% (1000 mg/kg bw)	4	96	96		26	9.7	540 Frantz et al. (1996a)
Rat	Ba						Neat (10 mg/kg bw)	4	96	96		32	0.059	6.6 Frantz et al. (1996b)
Rat	Ba						Neat (1000 mg/kg bw)	4	96	96		36	6.6	740 Frantz et al. (1996b)
Rat	Ba					H2O	50% (1000 mg/kg bw)	4	96	96		22	8.3	460 Frantz et al. (1996b)

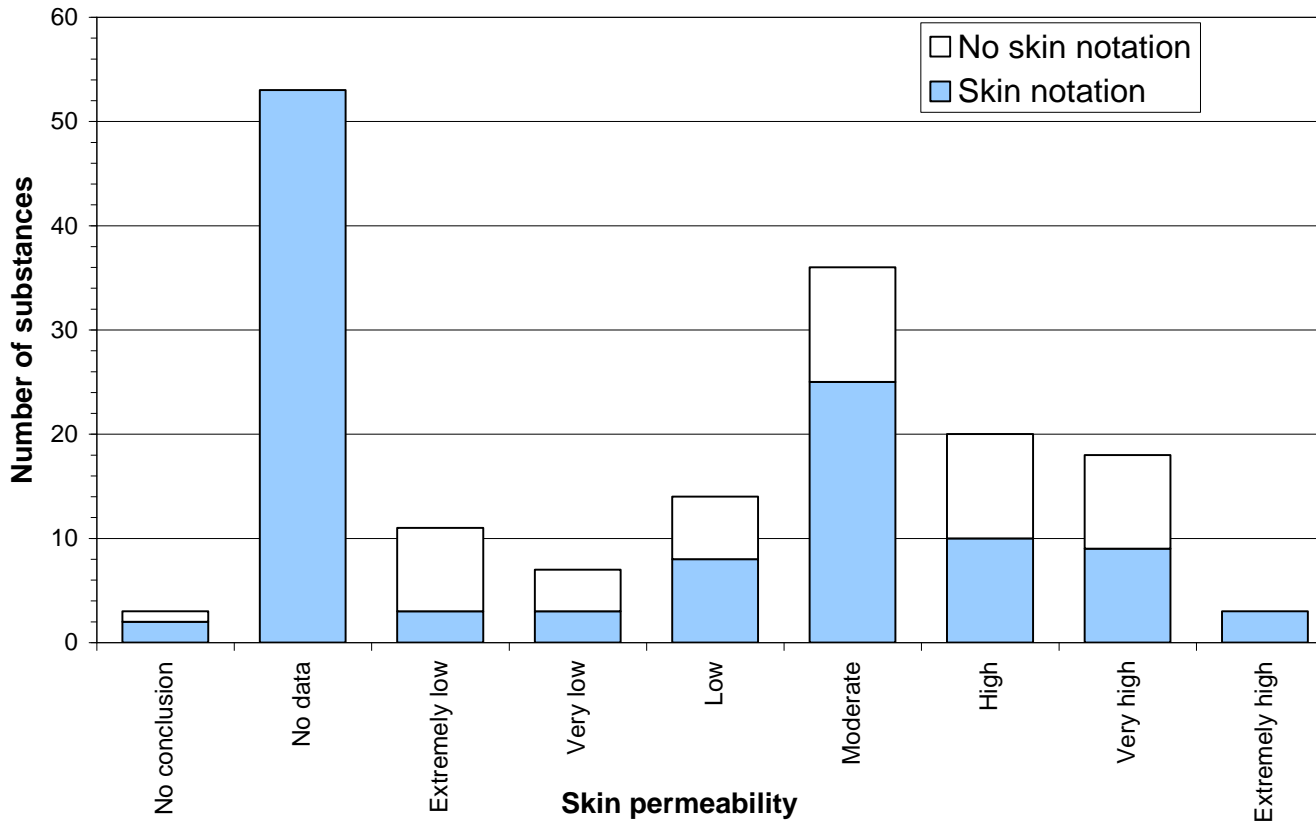
Assessment

The experiment using acetone as vehicle is disregarded, as skin permeability may be affected.

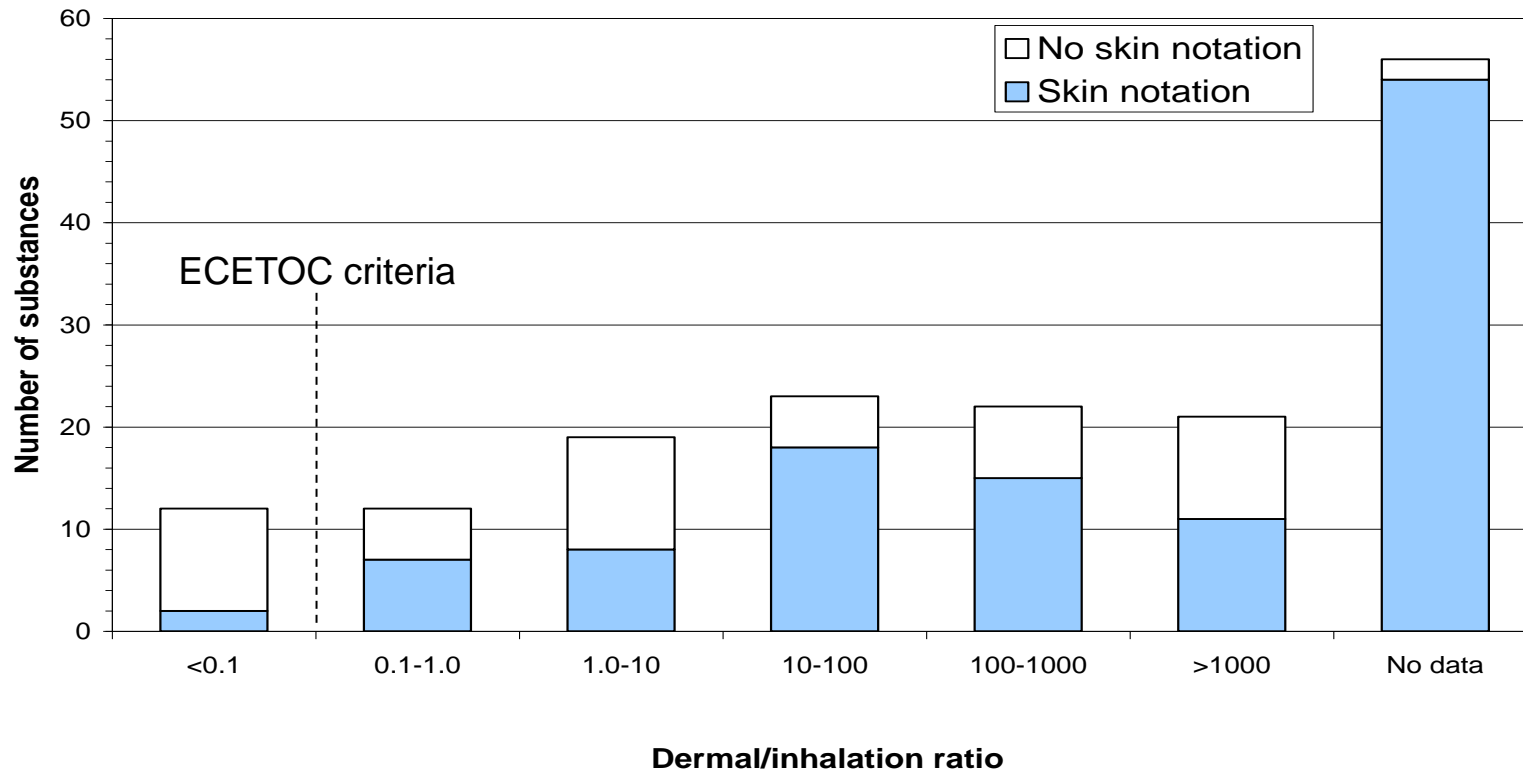
The preferred study is that of Loden (1986b) using neat ethylene glycol and human skin.

The K_p value of 1·10⁻⁴ cm/h, corresponds to "moderate" permeability.

Results – Skin permeability



Results – dermal/inhalation ratio



Conclusions

- **Large variations**
 - Between substances
 - Within substances
 - In study designs
- **Lack of data**
 - No data for 45% of substances having skin notation (in Sweden)
- **Lack of skin notations**
 - Unassigned substances were found in all permeability categories
 - 1/3 of the chemicals with dermal contribution of >100% lack skin notation
- **The scientific basis is weak for many of the skin notations in the Swedish OEL list**
- **The report can be downloaded for free at AoH-website**
 - http://gupea.ub.gu.se/dspace/bitstream/2077/9876/1/ah2008_2.pdf

