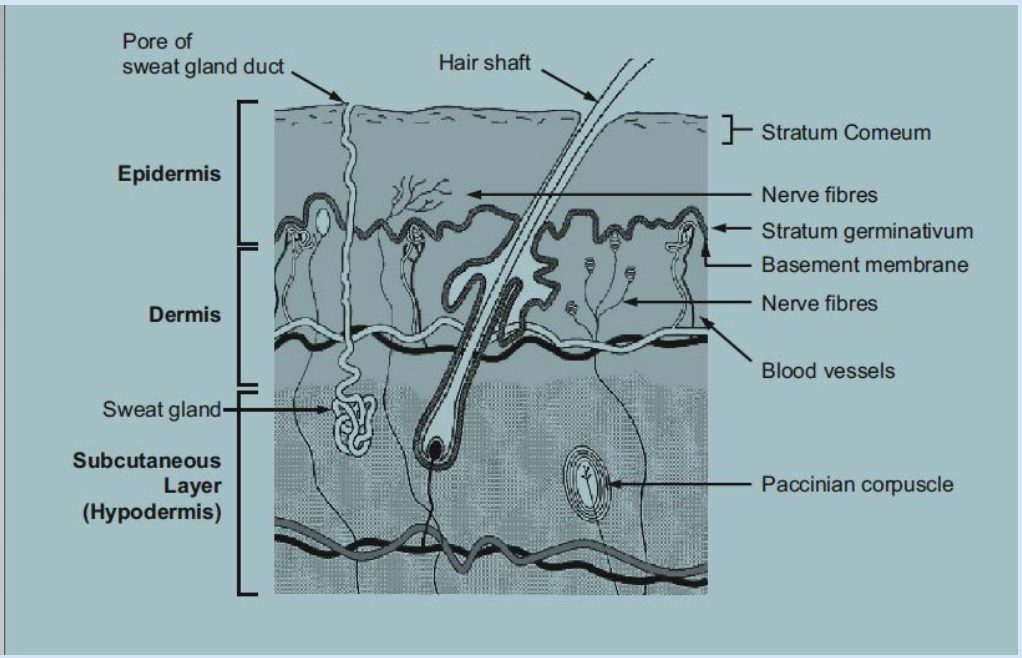
DERMAL EXPOSURE AND DERMAL ABSORPTION:

two interdependent steps in the risk assessment of chemicals



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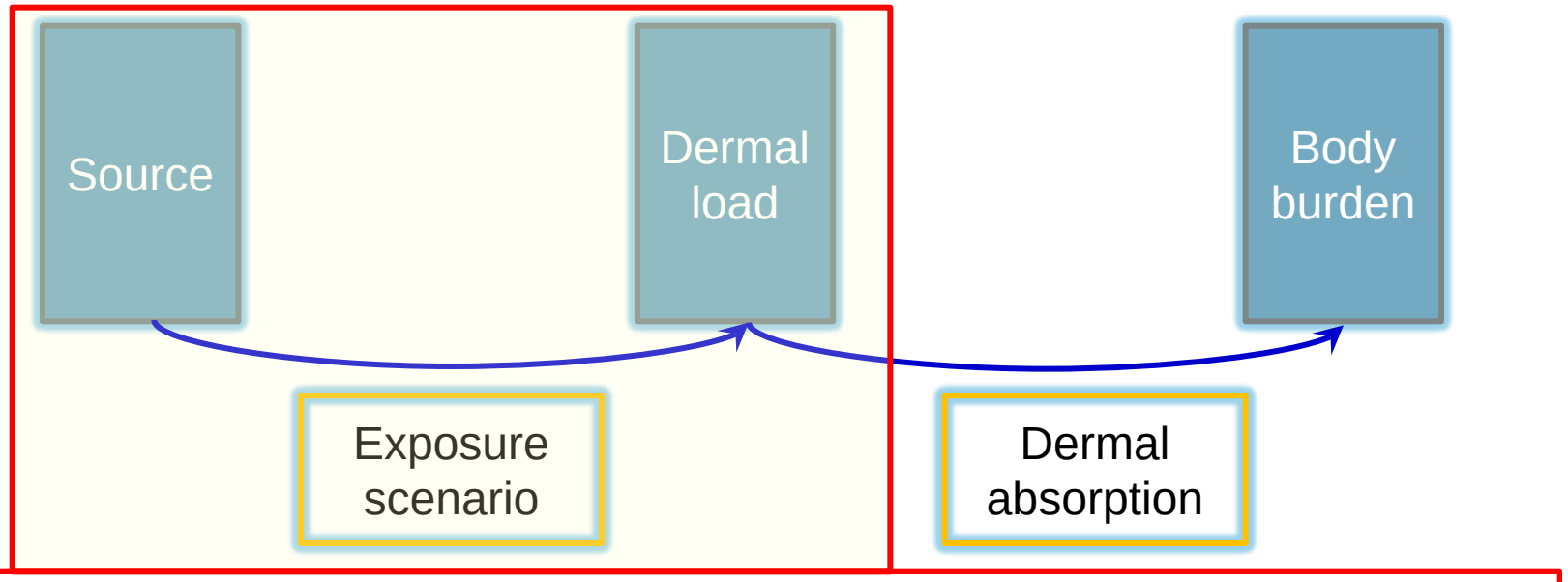
Dermal exposure assessment



Regulation	
Pesticides	UK model(POEM), Dutch model, German model, PHED, Europoem
Biocides	BEAT, ConsExpo, TNsG, HEEG Opinions , HEAdhoc
REACh	ECETOC TRA, Risk-of-Derm, …

Exposure scenarios for biocides

"*In regulatory applications of risk assessments, exposure estimates are often constructed using existing data or single point measurements to estimate the risk …. This approach can result in large errors in the exposure assessment and hence the risk assessment*" (WHO EHC 214 Human Exposure Assessment)

- Main group 1: Disinfectants and general biocidal products
  (e.g. products for surface disinfection)
- Main group 2: Preservatives
  (e.g. wood preservatives, in-can preservatives, MWF)
- Main group 3: Pest control
  (e.g. rodenticides, insecticides)
- Main group 4: other biocidal products
  (e.g. antifoulings)

⇒ high variety of different (dermal) exposure situations

- 18 HEEG opinions and 8 recommendations from the human exposure ad hoc working group

Example for exposure estimation: Metalworking (PT13)

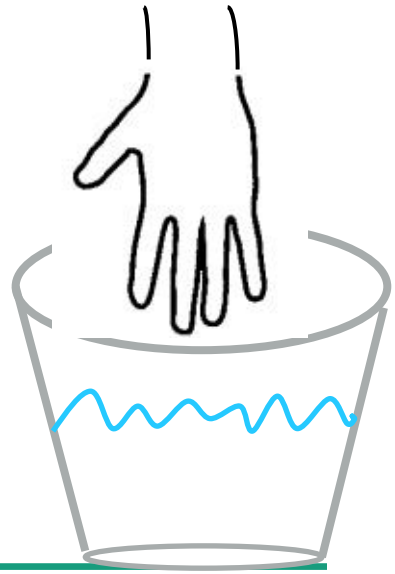
Reference	Amount of dermal load both hands		Method
HEEG (2008)	12 ml/h	200 mg/min	model - to be used if no better model for hands exposure can be found
Roff et al. (2004)	max. 1.4 ml/h	46 mg/min	patching method
van Wendel de Joode et al. (2005)	0.198 ml/h	3.3 mg/min	tracer chemical: detection of fluorescence on skin after adding tracer to MWF
Semple et al. (2007)	max. 1.3 ml/h	22 mg/min	wipe-off experiment
Henriks-Eckerman et al. (2007)	max. 2 ml/h	33 mg/min	rinse-off method

Extrapolation of exposure data for risk assessment

- In the reference scenarios for biocides a potential exposure is usually given as amount of biocide per unit time (mg/min) or task (mg/cycle)
  ⇒ influence of exposure time (flux or % absorbed)

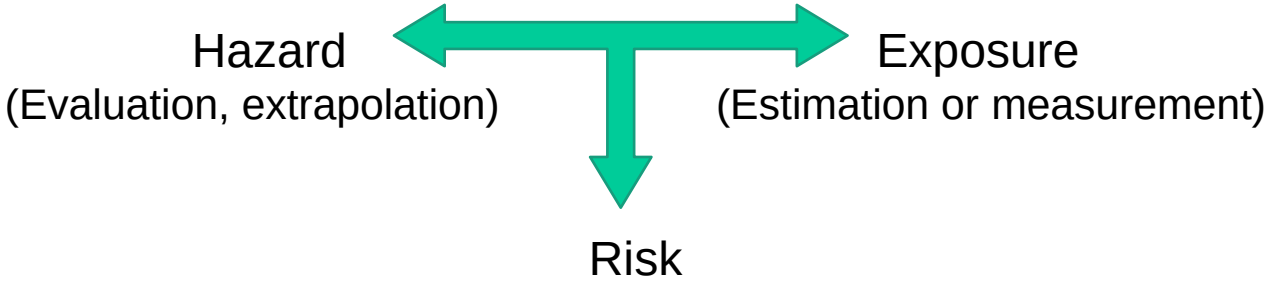
  - Extrapolation of by exposure time not always adequate
  - When is the surface on a hand “saturated” *
  - “wet work” is still not considered

What data are needed and useful from absorptions studies?



* Frasch et al 2013

Toxicity and exposure in risk assessment

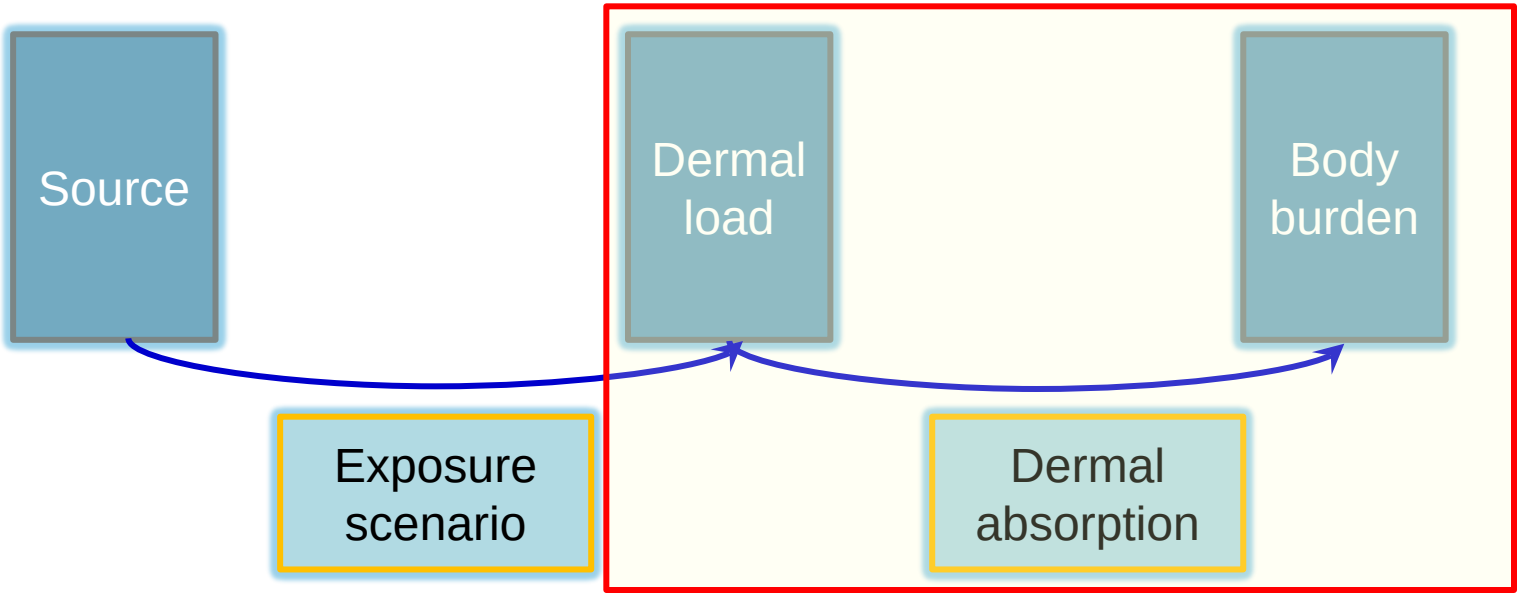


- **Local** toxicity
  - Skin, (mucuous membranes)
  - **AEC**
- **Systemic** toxicity
  - Liver, kidney, hematology, …
  - **AEL or DNEL…**

For risk assessment for systemic toxicity the external exposure data have to be turned into internal data and compared with information from toxicity studies

⇒ information about dermal absorption needed

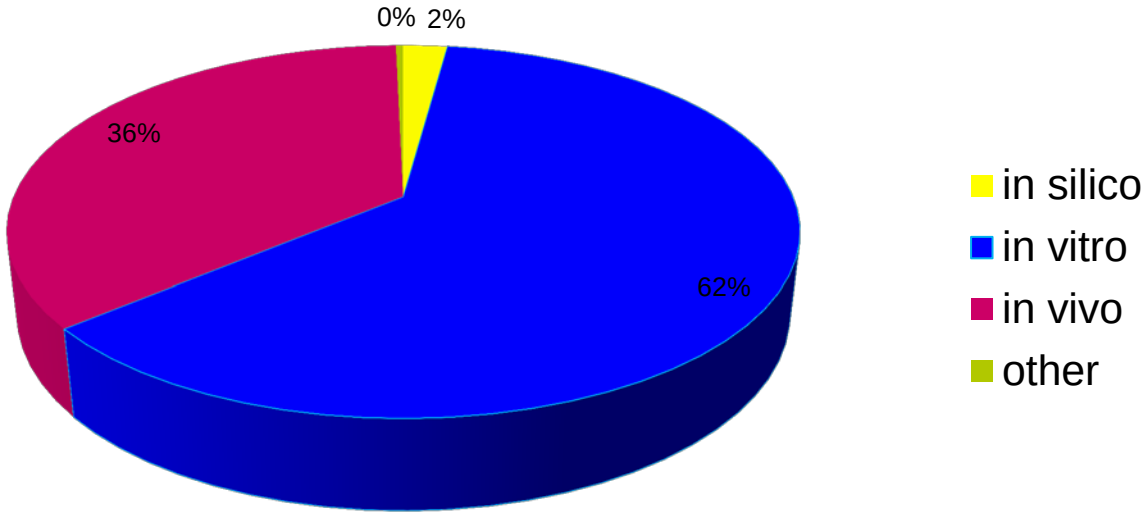
Dermal absorption assessment



Regulation	Defaults (no reliable study data available)
Pesticides	10% if MW >100 and log Pow < -1 or >4, 25% if a.s. > 5%, 75% if a.s. ≤ 5%
Biocides	100% reduced by PPE to 10% (gloves) and 25% (cotton coveralls)

Dermal absorption data as requirement in regulation

What kind of data have been submitted by applicants in different regulations (i.e. REACh and BPR)*



- More than 50% in-vitro studies
- Approximately 2% QSAR approaches

* information extracted from e-Chem portal

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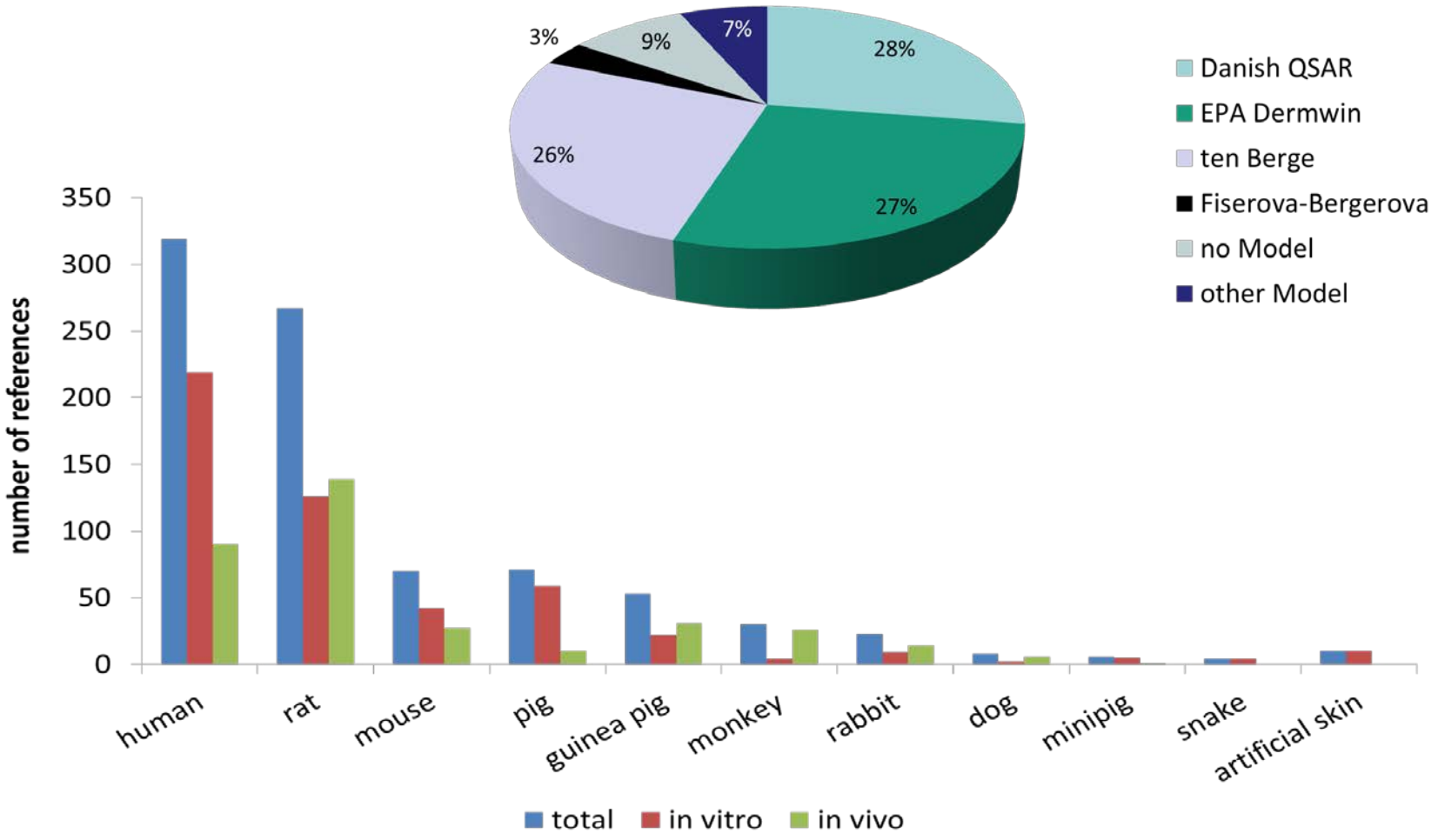
Some further analysis of data submitted for regulatory purposes



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Data quality for dermal absorption

- All in all there is a high heterogeneity of absorption data

  ⇒ Problems for risk assessment and data comparison

  ⇒ Problems for model generation and derivation of rules

- Heterogeneity and guideline studies

In-vivo OECD 427

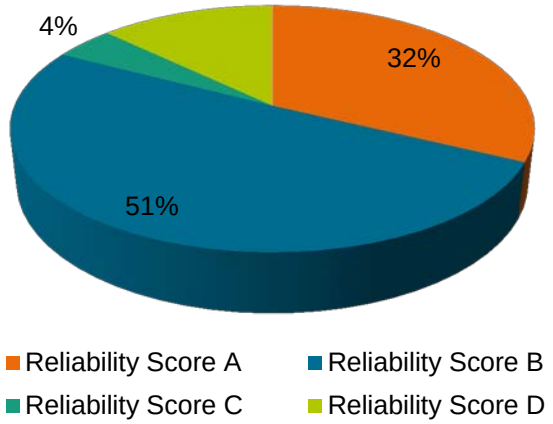
- Very general description
- Predominantly finite dose
- Criteria for the choice of species
- Recovery 100±10%
- Read out: typically % absorbed dose

In-vitro OECD 428

- Very general description
- differentiation finite / infinite dose
- No criteria for the choice of species
- recovery 100±10%
- Read out: % absorbed, flux, permeability coefficient , „lag time“

Data base for dermal absorption data

- Database on industrial chemicals
- Data from regulatory data (eChem portal) and publicly available data sources (publications)
- Data curation needed
- Reliability scores adapted to Klimisch score



Data base on dermal absorption

Present status of the data base:

- > 650 chemicals
- > 4000 studies
- 165 chemicals investigated in comparable test systems
- 79 chemicals have a low very dermal absorption (< 1%)

	A	B	C	D	E	F	G	R	S	T	U	V	W	X	Y	Z	AA	AB
1	No.	Intern. Nc	Substance	Source Su	IUPAC-Be	CAS No.	EINECS/E(	expo	Density /	Dose	dose dimension	Amount A	Amount A	Concentra	concentra	n	Test Site/	Membran
23	5177	B-0693	314	formaldehyc	formaldehyc	"50-00-0"	"200-001-8"	270		0,0002 mg		0,005 mL		0,04 mg/mL		2		
24	5182	B-0698	314	formaldehyc	formaldehyc	"50-00-0"	"200-001-8"	60		0,0002 mg		0,005 mL		0,04 mg/mL		2		
25	5179	B-0695	314	formaldehyc	formaldehyc	"50-00-0"	"200-001-8"	210		0,0002 mg		0,005 mL		0,04 mg/mL		2		
26	3068	A-2294	427	nitrilotrimet	[nitrilotris(n	"6419-19-8"	"229-146-5"	1440		0,0002 mL/cm²	mL/cm²	0,2 mL		1%		2		
27	3069	A-2295	427	nitrilotrimet	[nitrilotris(n	"6419-19-8"	"229-146-5"	1440		0,0002 mL/cm²	mL/cm²	0,2 mL		1%		2		
28	5607	A-3936	491	zinc chloride	zinc dichlori	"7646-85-7"	"231-592-0"	120		0,0002-0,0004 mg/kg bw		0,025 mL		0,0013 mg/mL		6	both flanks	

Table 1
Chemical properties

Table 2
Study information

Table 3
Results

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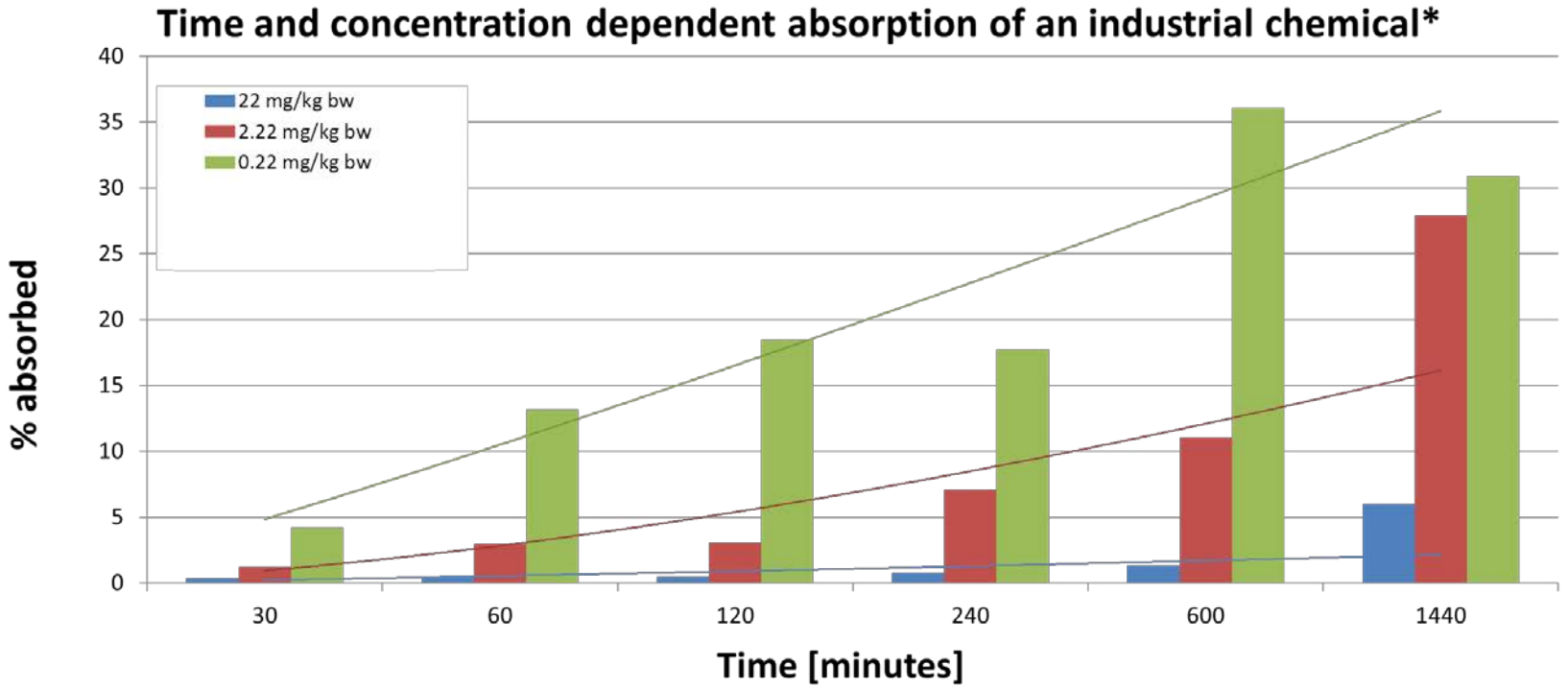
Preliminary analyses of the data base: time and concentration effects



- Higher absorption rate for lower concentration
- Absorption rate constantly increasing over time

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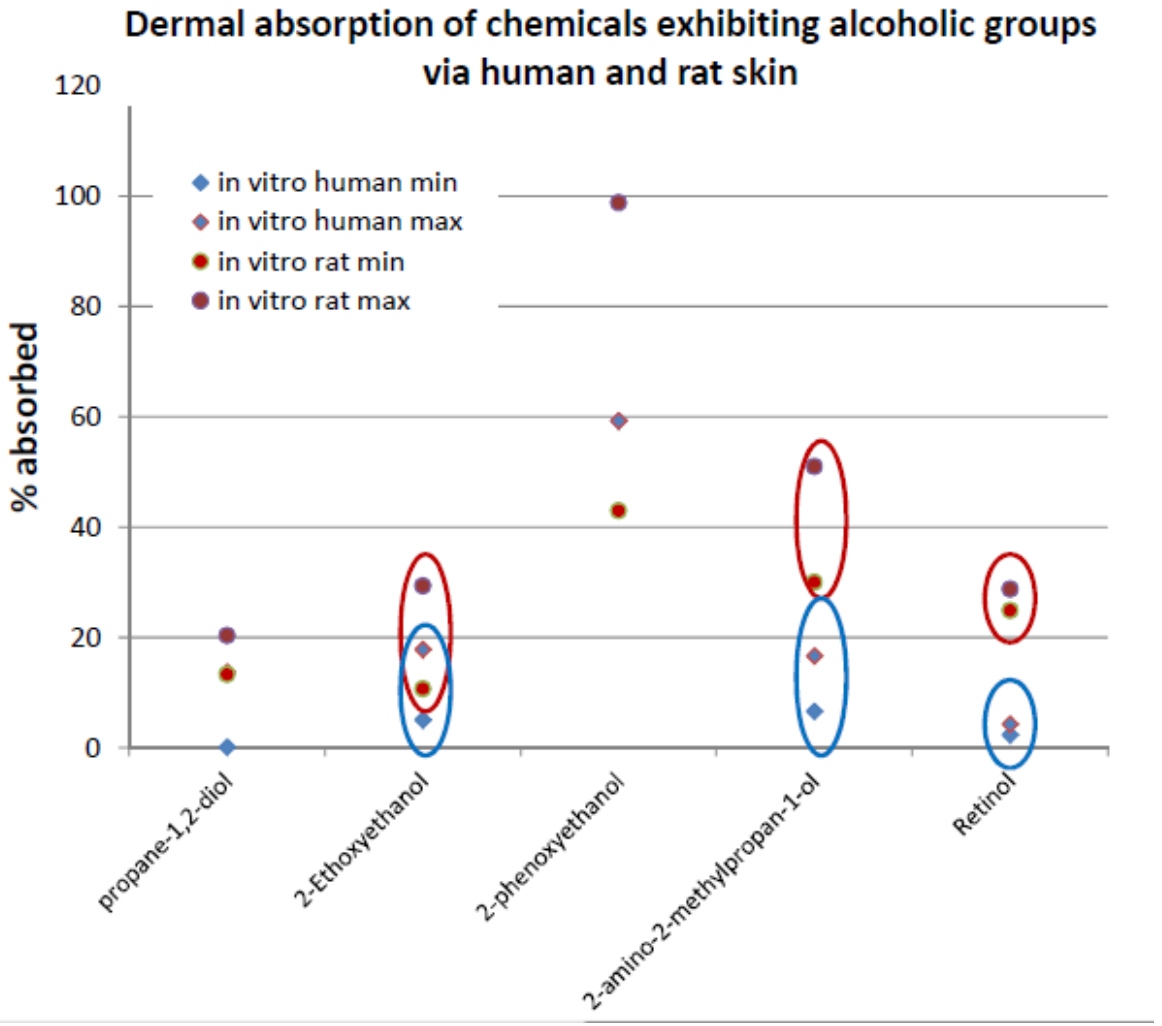
Preliminary analysis: dermal absorption in two species

- Absorption in rat higher than in human
- Data show a certain variability but are in a comparable order of magnitude for the single chemical
- Grouping of chemicals not possible
- Database for specific queries is often small even with many studies



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Read-Across for quaternary ammonium compounds

	Cetrimonium chloride	DTAB	DTAB	DTAB
Study type	*In vitro*	*In vivo*	*In vivo*	*In vivo*
species	pig	rat	rat	rat
vehicle	hair care	hair care	water	water
expsoure time	30 min	8 min	18 min	48 h
dose	25 mg/cm²	0.12 mg/cm²	0.2 mg/cm²	0.9 mg/cm²
Total dose	?	2 mg	2 mg	7.2 mg
% absorbed	**0.27**	**0.093**	**0.59**	**3.15**
	presumably rinse off	rinse off	rinse off simulation	leave on

- Are these data comparable?
- Which use scenarios can be covered by these data

Preliminary analysis: a data rich compound

Diethanolamine						
method	**species**	**vehicle**	**exposure [min]**	**dose**	**Dimension**	**Absorption [%]**
in vitro	Human	water	360	7,4	mg/cm²	0.23
in vitro	Human	neat		20	mg/cm²	0.08
in vitro	Rat	water	360	7,4	mg/cm²	0.56
in vitro	Rat	neat		20	mg/cm²	0.04
in vivo	Rat	95% Ethanol	2880	2,1	mg/kg bw	2.9
in vivo	Rat	95% Ethanol		7,6	mg/kg bw	10.5
in vivo	Rat	95% Ethanol		27,5	mg/kg bw	16.2
in vivo	Mouse	95% Ethanol	2880	8	mg/kg bw	26.8
in vivo	Mouse	95% Ethanol		23	mg/kg bw	33.8
in vivo	Mouse	95% Ethanol		81	mg/kg bw	51.8
in vivo	Mouse	Ethanol	2880	8	mg/kg bw	26.8
in vivo	Mouse	Ethanol		23	mg/kg bw	33.8
in vivo	Mouse	Ethanol	2880	81	mg/kg bw	58.1

Preliminary analysis: absorption data versus in vivo toxicity

Diethanolamine Absorption				Diethanolamine In-vivo toxicity		
species	**Dose [mg/kgw]**	**Absorption [%]**	**Excretions [%]**	**Exposure time [d]**	**LOAEL dermal [mg/kgw]**	**LOAEL oral [mg/kgw]**
mouse	8	26.8	0,096	16	160	271
mouse	23	33.8	0,118	91	80	132
mouse	81	58.1	0,19			
rat	2,1	2.9	0,0063	16	125	86
rat	7,6	10.5	0,019	91	32	20
rat	27,5	16.2	0,044			

Conclusions

- External and internal exposure are not independent
- Problems with time extrapolation for exposure scenarios
- Large variety in absorption data for industrial chemicals ⇒ difficulties for risk assessment and comparative assessments
- Species differences for absorption
- Influences of dilution
- Requirement for very study detailed information
- Influence of vehicles
- Time course

- Large data sets needed for reliable analyses