FEDERAL INSTITUTE FOR RISK ASSESSMENT

BfR

Risiken erkennen – Gesundheit schützen

The BfR Decision Support System (DSS) for Local Lesions

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The BfR Decision Support System (DSS) is...

...a system to predict the presence or absence of a chemical's potential to cause skin and/or eye irritation/corrosion following acute topical exposure...

...in terms of EU classification criteria (Dir. 67/548/EEC)/OECD TG.

Right from the start the DSS was designed as an ITS building block

Component 1: Physico-Chemical Exclusion Rules

- To predict the ABSENCE of an irritant/corrosive potential
- Straight-forward, UNAMBIGUOUS IF...THEN NOT... logic:

Rules appropriate for all groups of chemicals

Basis
Evaluation of data for 1627 chemicals with purity ≥ 95%

If melting point > 200°C	Then not	(skin corrosion R34 or R35) (true for 245/252 chemicals tested)[a]
If log P_{ow} > 9	Then not	(lesions R34, R35, R36 or R41) (true for 32/32 chemicals tested)
If log P_{ow} < –3.1	Then not	(skin corrosion R34 or R35) (true for 53/53 chemicals tested)
If lipid solubility < 0.01g/kg	Then not	(skin corrosion R34 or R35) (true for 58/58 chemicals tested)
If aqueous solubility < 0.00002g/l	Then not	(eye irritation R41) (true for 109/109 chemicals tested)
If aqueous solubility < 0.000005g/l	Then not	(eye irritation R36) (true for 38/38 chemicals tested)
If molecular mass > 650g/Mol	Then not	(eye irritation R36) (true for 139/139 chemicals tested)[b]

[a]*The seven skin corrosive substances are organic salts which release strong inorganic acids or bases when in contact with aqueous substrates/organic media.*

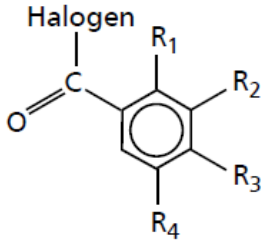
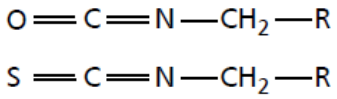
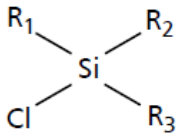
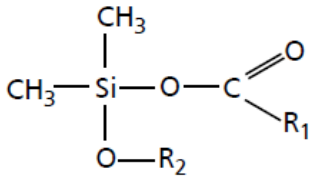
[b]*Chemicals with molecular mass > 650g/Mol may elicit severe tissue damage resulting in local corrosion (labelled R41).*

(Gerner et al. (2005), ATLA 33, 215–237

Component 2: Structural alerts

- To predict the PRESENCE of an irritant/corrosive potential
- Based on reactive substructures

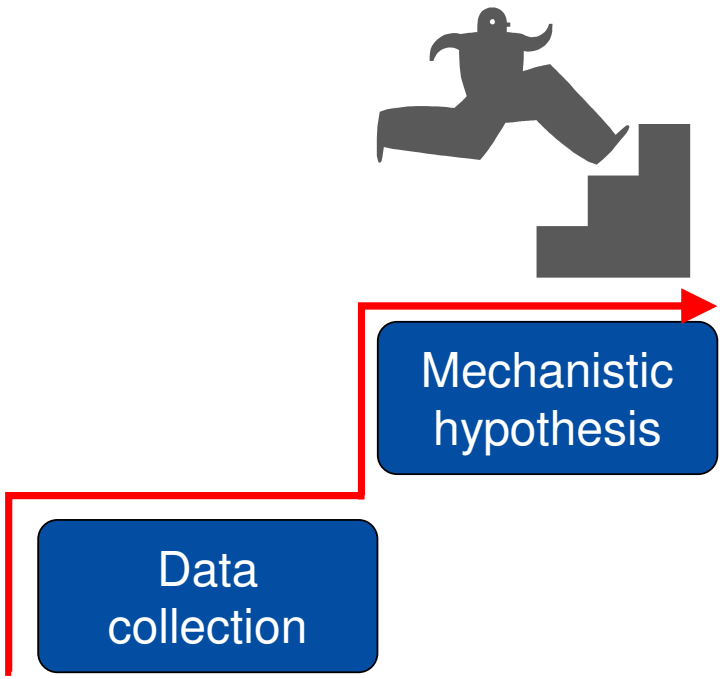
Chemical substructures indicative of skin corrosion:

1) Substituted benzoic acid halogenides[d] Halogen = Cl or F R_1–R_4 = any substituent	
2) Aliphatic iso(thio)cyanates[e] R = aliphatic chain	
3) Chlorosilanes R_1–R_3 = any (for example, further halogen)	
4) Mixed Oxy- Carboxy- silanes	

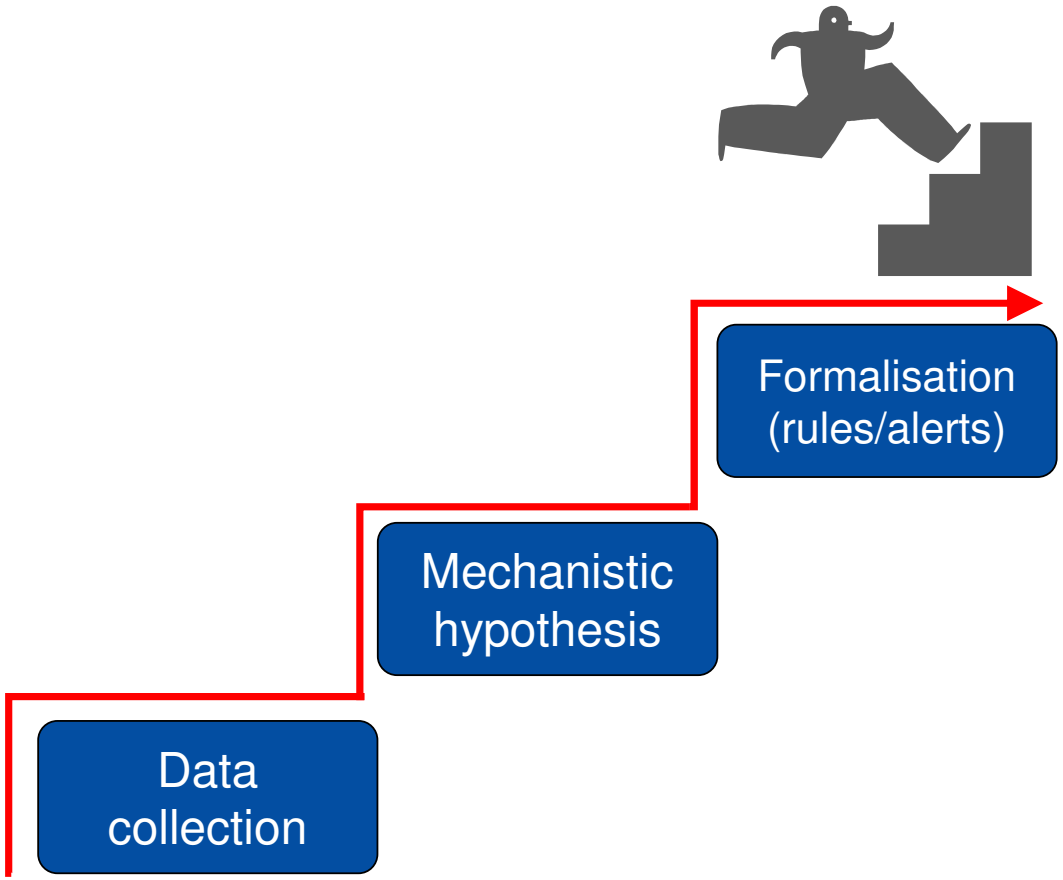
(Gerner et al. (2005), ATLA 33, 215–237

Mining existing knowledge – Step 1: Data collection

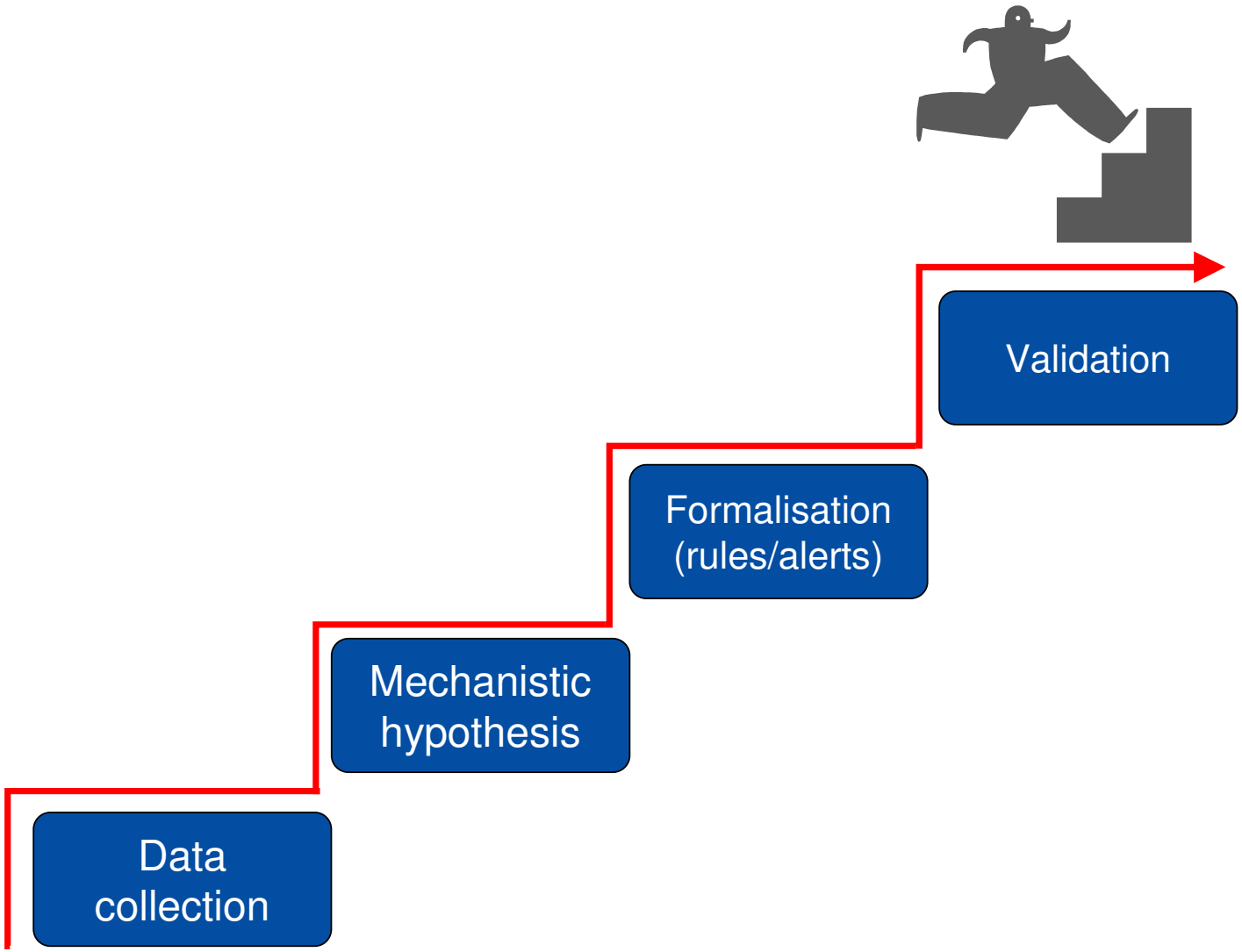
Mining existing knowledge – Step 2: Generating a Hypothesis



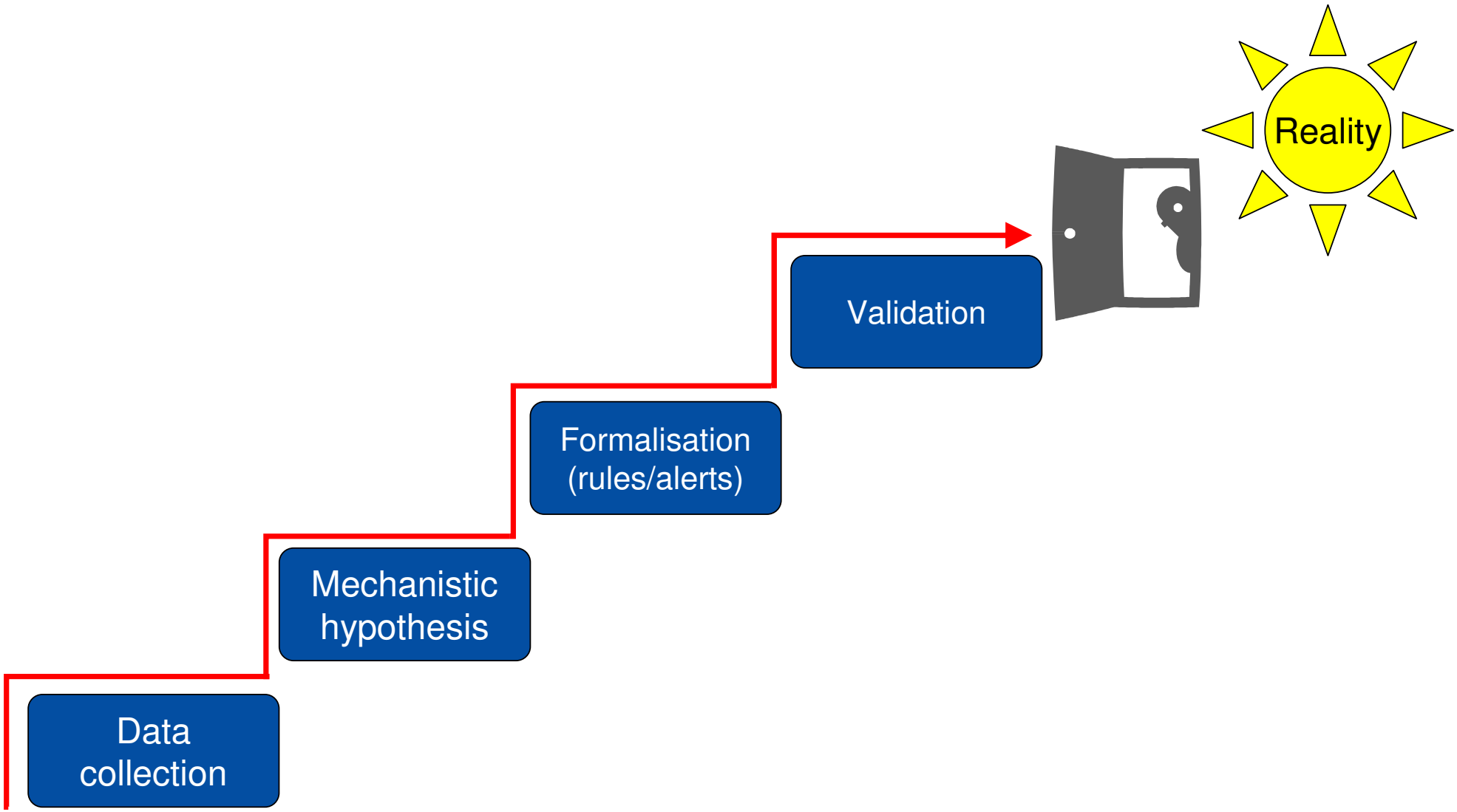
Mining existing knowledge – Step 3: Formalisation



Mining existing knowledge – Step 4: Validation



Mining existing knowledge – Step 5: The Reality Test



Data collection – The BfR ESTOFF Database

Identity

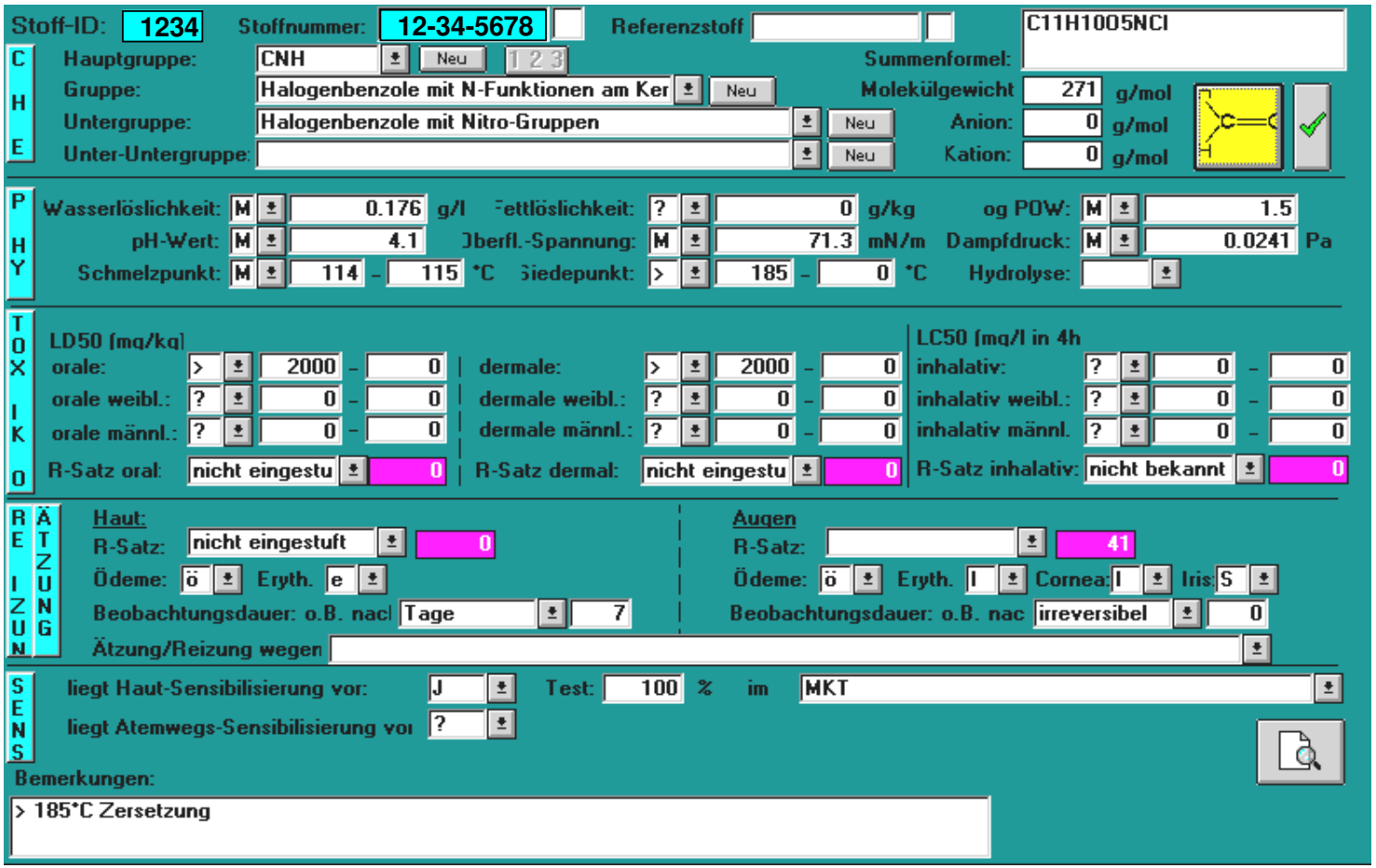
Phys.-chem.

Acute Toxicity

Irritation/corrosion

Sensitisation

Add. Information



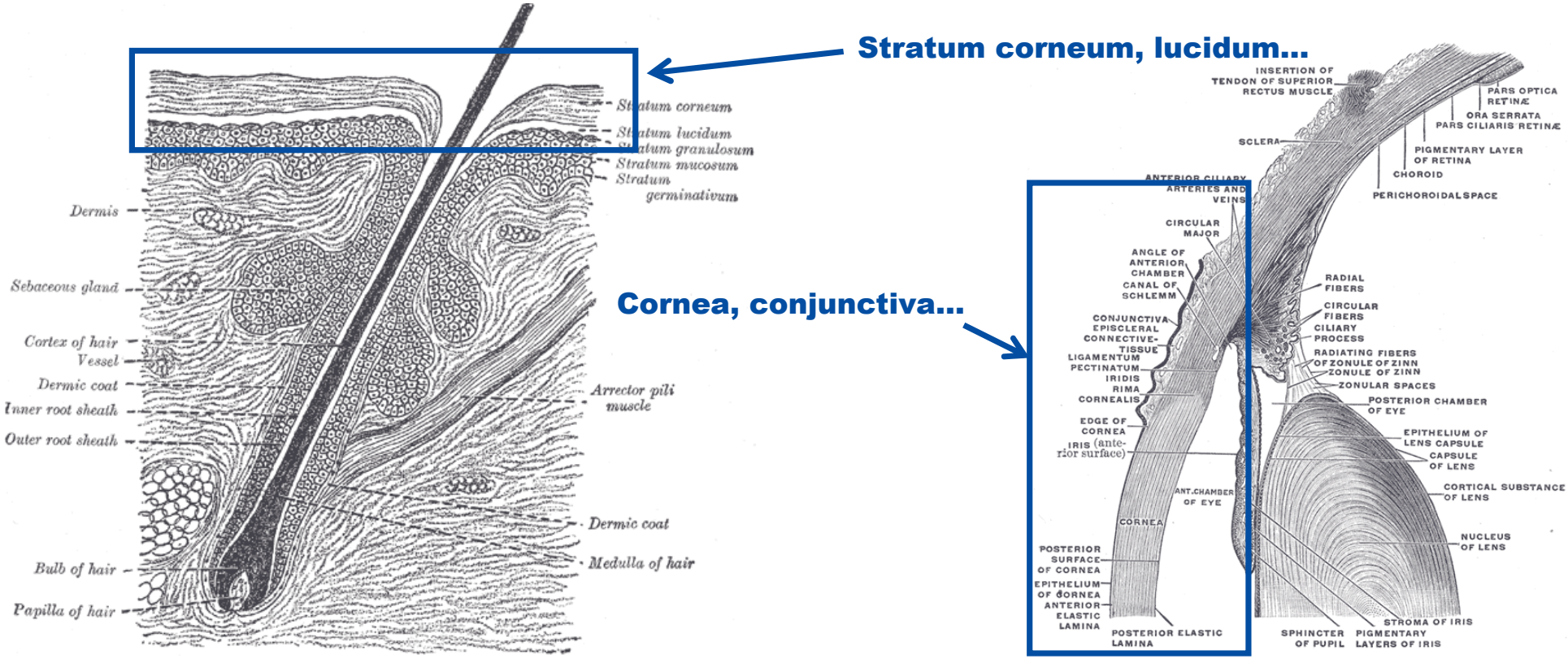
- 1992 entries, ca. 1400 for DSS training set, 200 for validation test set

Quality-controlled, peer-reviewed data; uniform evaluation criteria

Mechanistic Hypothesis – Two-step process

Step 1: Active destruction (corrosion) or passive transport through protective biolayers

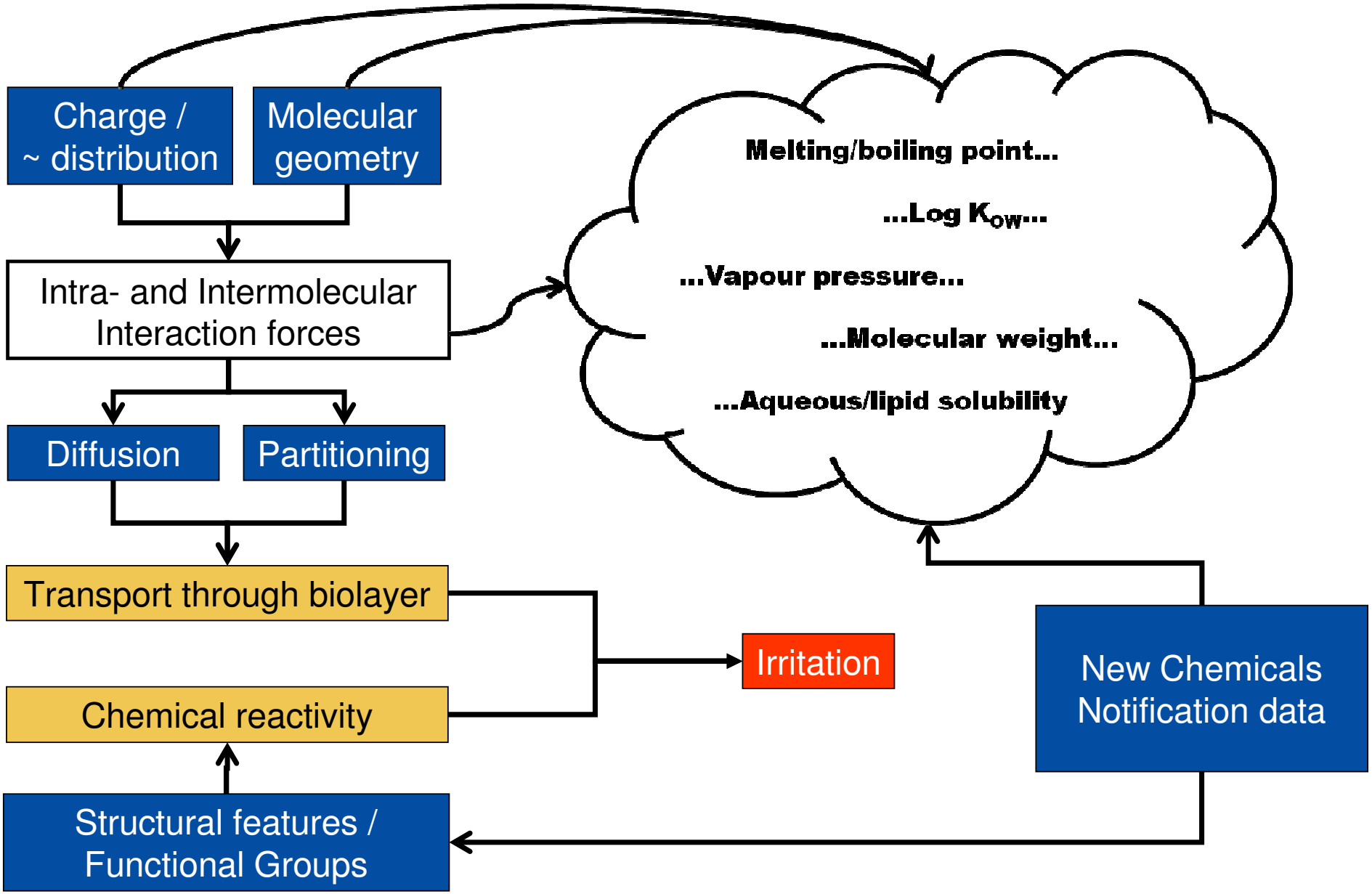
Step 2: Reaction/interference with biological structures/processes



Skin Cross-Section **Eye: Partial Cross-Section**

(Source: Wikipedia/Gray's Anatomy 1918)

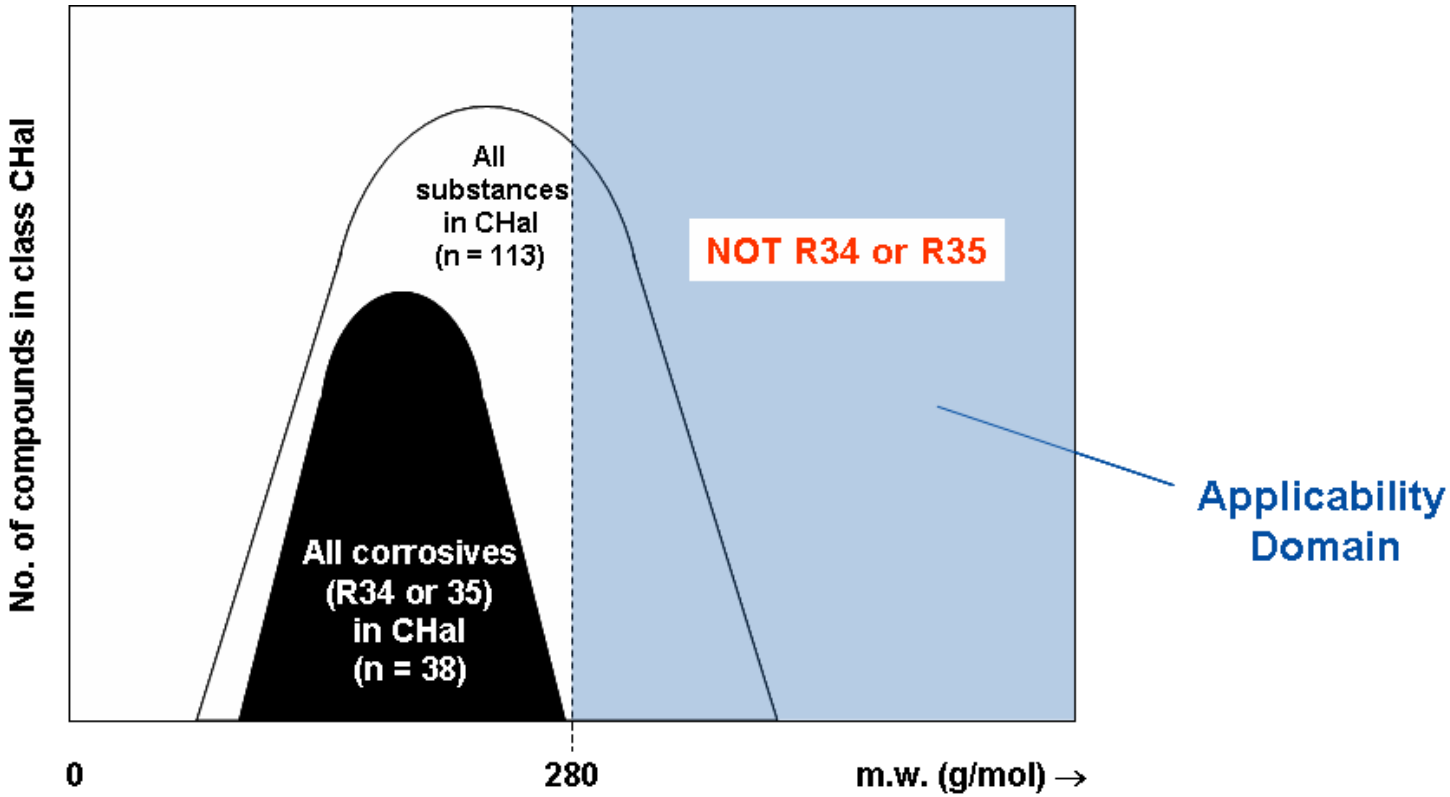
Mechanistic Hypothesis – Factors Influencing Irritation Potential



Creating Physico-Chemical Exclusion Rules

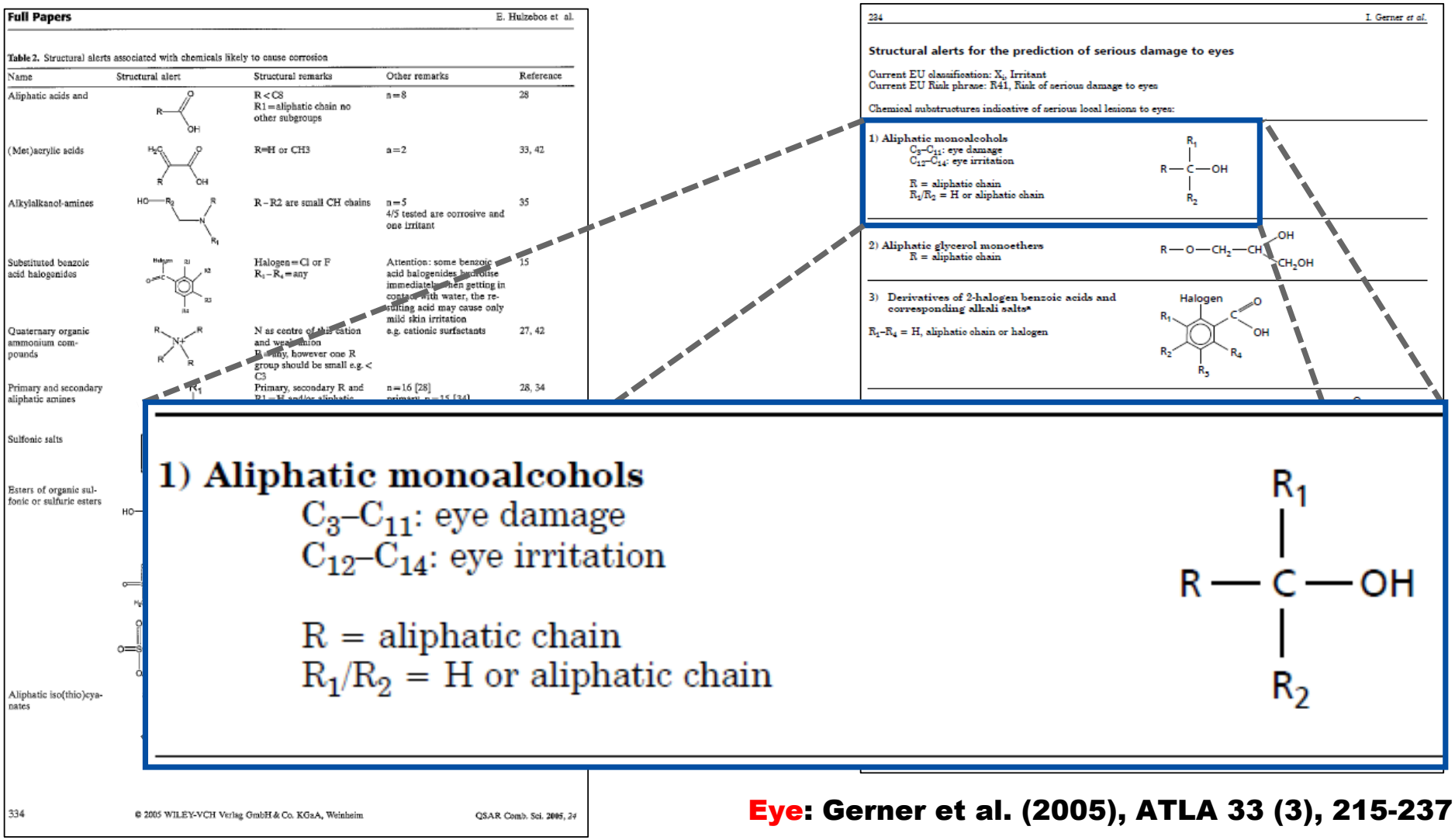
Extreme p.-c. properties → low penetration rate → low irritation potential

Example: Exclusion rule for corrosion for group CHal ($C_xH_yO_zHalogen_d$) based on m.w.



Deduced rule : 'IF m.w. > 280 g/mol THEN NOT corrosion R34 or R35' (CHal)

Creating Structural Alerts



Full Papers — E. Hulzebos et al.

Table 2. Structural alerts associated with chemicals likely to cause corrosion

Name	Structural alert	Structural remarks	Other remarks	Reference
Aliphatic acids and		R < C8 R1 = aliphatic chain no other subgroups	n = 8	28
(Met)acrylic acids		R=H or CH3	n = 2	33, 42
Alkylalkanol-amines		R – R2 are small CH chains	n = 5 4/5 tested are corrosive and one irritant	35
Substituted benzoic acid halogenides		Halogen = Cl or F R_1 – R_4 = any	Attention: some benzoic acid halogenides hydrolise immediately when getting in contact with water, the resulting acid may cause only mild skin irritation	15
Quaternary organic ammonium compounds		N as centre of the cation and weak anion R – any, however one R group should be small e.g. < C3	e.g. cationic surfactants	27, 42
Primary and secondary aliphatic amines		Primary, secondary R and	n = 16 [28]	28, 34
Sulfonic salts				
Esters of organic sulfonic or sulfuric esters				
Aliphatic iso(thio)cyanates				

334 © 2005 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim QSAR Comb. Sci. 2005, 24

224 — I. Gerner et al.

Structural alerts for the prediction of serious damage to eyes

Current EU classification: X_i, Irritant
Current EU Risk phrase: R41, Risk of serious damage to eyes

Chemical substructures indicative of serious local lesions to eyes:

1) **Aliphatic monoalcohols**
C_3–C_{11}: eye damage
C_{12}–C_{14}: eye irritation
R = aliphatic chain
R_1/R_2 = H or aliphatic chain

2) **Aliphatic glycerol monoethers**
R = aliphatic chain

3) **Derivatives of 2-halogen benzoic acids and corresponding alkali salts**[a]
R_1–R_4 = H, aliphatic chain or halogen

1) Aliphatic monoalcohols

C_3–C_{11}: eye damage
C_{12}–C_{14}: eye irritation

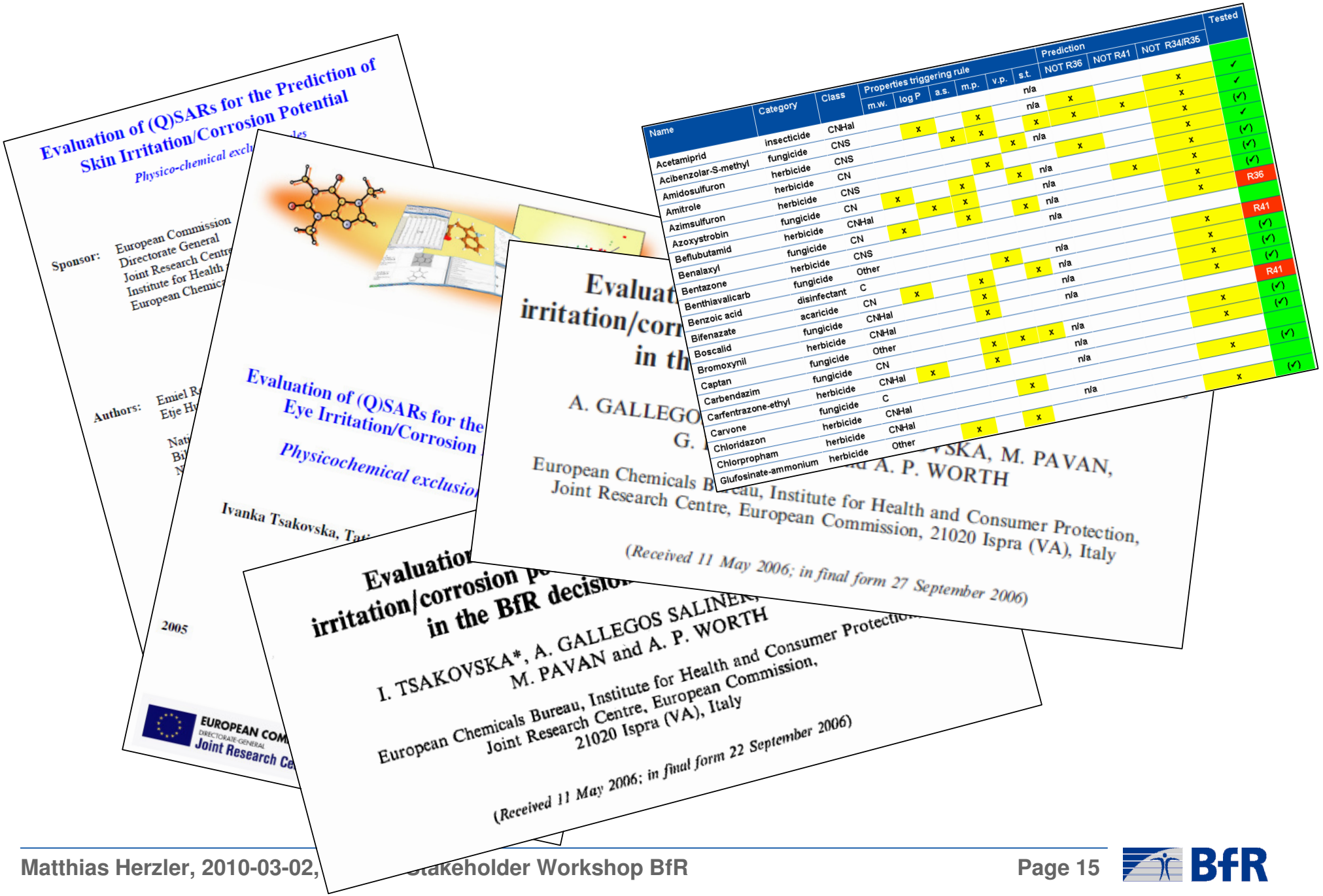
R = aliphatic chain
R_1/R_2 = H or aliphatic chain

Eye: Gerner et al. (2005), ATLA 33 (3), 215-237

Skin: Hulzebos et al. (2005), QSAR Comb. Sci. 24, 332-342

(Source: Gerner et al. 2005)

Validation (2005-today)



Name	Category	Class	Properties triggering rule						Prediction			Tested
			m.w.	log P	a.s.	m.p.	v.p.	s.t.	NOT R36	NOT R41	NOT R34/R35	
Acetamiprid	insecticide	CNHal		x		x		n/a	x		x	✓
Acibenzolar-S-methyl	fungicide	CNS			x	x		n/a	x		x	✓
Amidosulfuron	herbicide	CNS						x	x	x	x	(✓)
Amitrole	herbicide	CN				x		x	x		x	✓
Azimsulfuron	fungicide	CNS						x	n/a		x	(✓)
Azoxystrobin	herbicide	CN	x		x						x	(✓)
Beflubutamid	fungicide	CNHal		x		x		x	n/a	x	x	(✓)
Benalaxyl	herbicide	CN	x						n/a		x	R36
Bentazone	fungicide	CNS						x	n/a			
Benthiavalicarb	herbicide	Other						x	n/a		x	R41
Benzoic acid	disinfectant	C							n/a		x	(✓)
Bifenazate	acaricide	CN	x			x		x	n/a		x	(✓)
Boscalid	fungicide	CNHal				x			n/a		x	(✓)
Bromoxynil	herbicide	CNHal				x			n/a		x	R41
Captan	fungicide	Other					x	x	n/a			(✓)
Carbendazim	fungicide	CN				x	x	x	n/a		x	(✓)
Carfentrazone-ethyl	herbicide	CNHal	x			x			n/a		x	(✓)
Carvone	fungicide	C						x	n/a			
Chloridazon	herbicide	CNHal							n/a		x	(✓)
Chlorpropham	herbicide	CNHal				x			n/a		x	(✓)
Glufosinate-ammonium	herbicide	Other						x	n/a			

Validation – Summary of Results

P.-C. rules: good agreement with OECD (Q)SAR validation principles

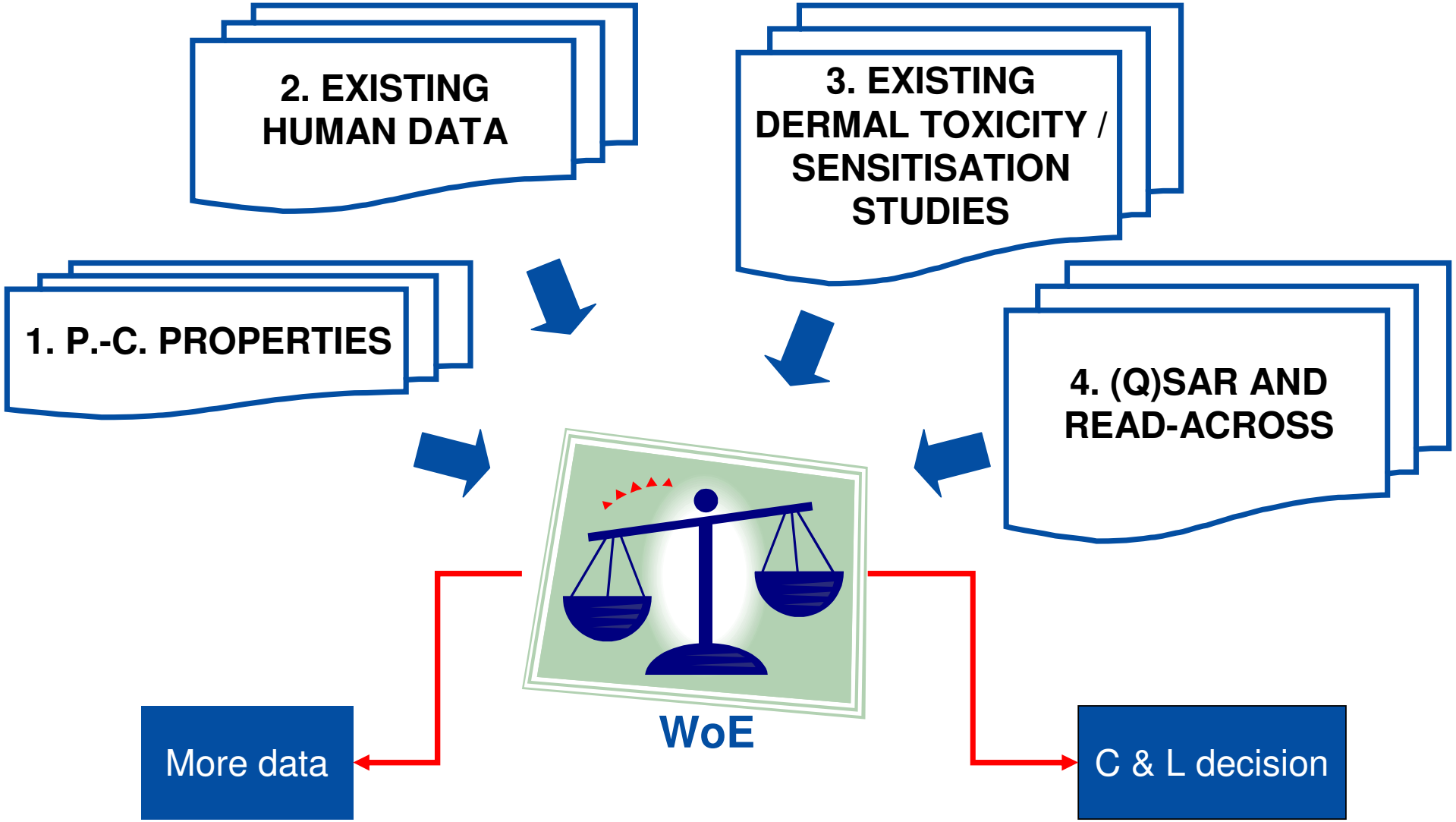
- predictivity (NPV) > 87 % (eye) and > 95 % (skin) upon external validation
- exclude > 40 % EU NONS from skin and ca. 10 % for eye irritation testing

Structural Alerts:

- predictivity (PPV) between 80-100 % upon internal validation (training set)
- low to no coverage of the test set chemical space

Considerable relevance for pesticide active ingredients

Use of the DSS: REACH ITS for irritation/corrosion



How to interpret the outcome of a DSS prediction

There can be no general recommendation.

The decision depends on

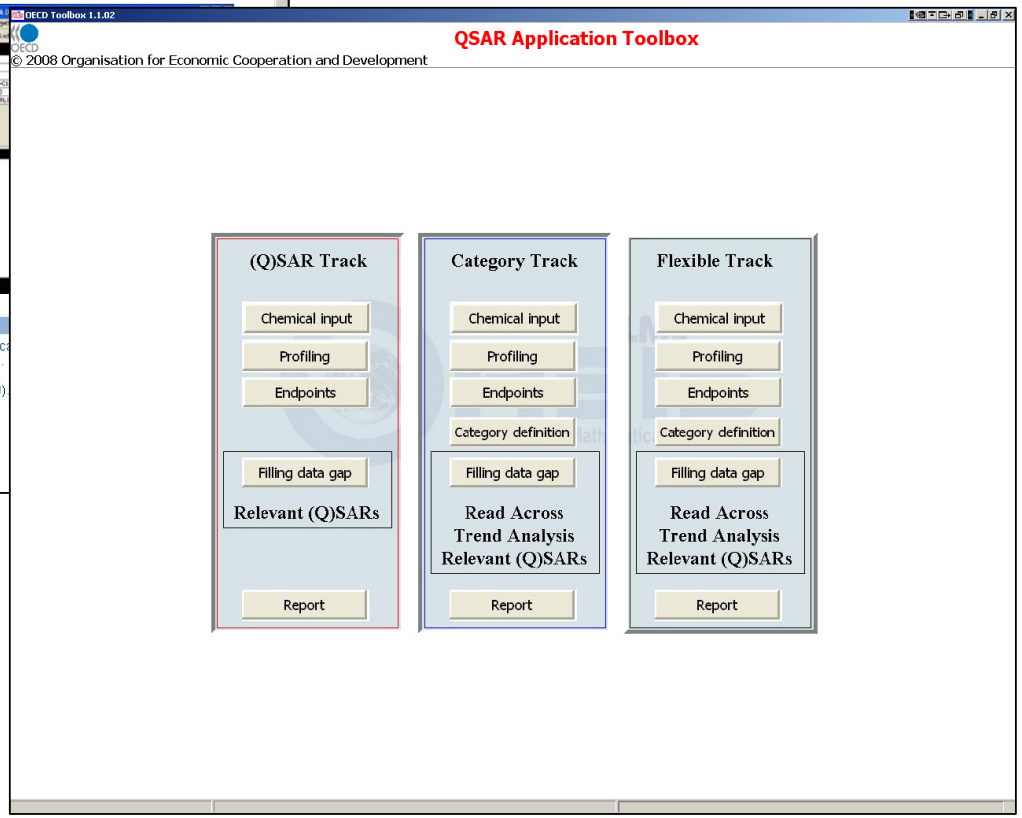
- the purpose of the prediction
- the degree of reliabililty required
- the costs of a negative vs. a positive prediction
- WoE of other avaible data: supportive/equivocal/contradictory?

Availability of the DSS

TOXTREE

http://ecb.jrc.ec.europa.eu/qsar/qsar-tools

OECD (Q)SAR TOOLBOX

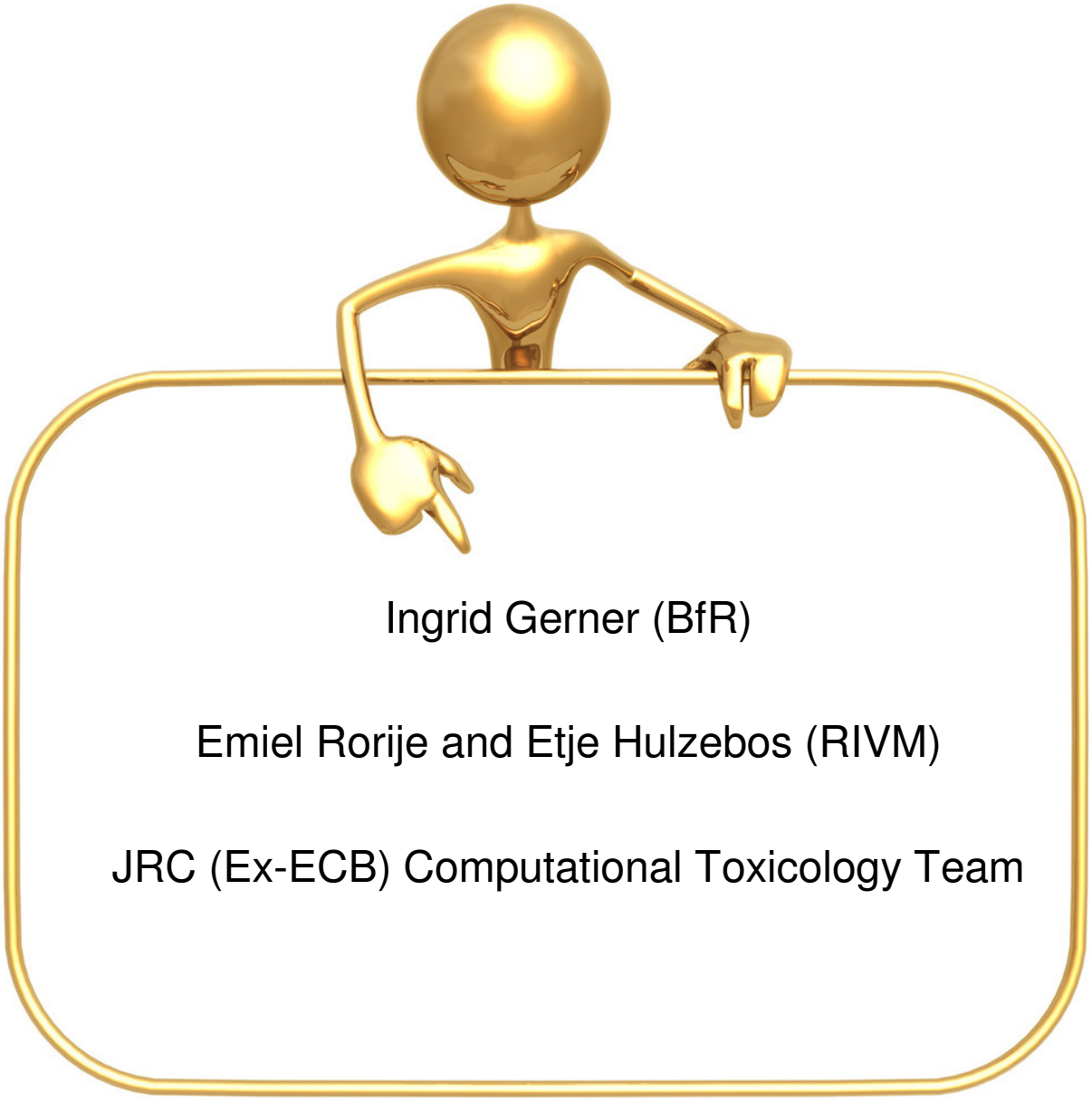


http://www.oecd.org

Outlook

- Combined validation (rules+alerts, ITS)
- RIVM work: - Distributions and error probability
  - Using DSS with calculated phys.-chem. properties
- Multivariate analysis of descriptors/p.c. properties
- Work on p.-c. properties and dermal absorption
- Skin sensitisation
  - ➢ alerts have been derived
  - ➢ similar mechanistic concept
  - ➢ combining LLNA database with alerts/p.c. rules

Credits



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Thank you for your attention

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