

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 $\geq 95\%$

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

^aThe seven skin corrosive substances are organic salts which release strong inorganic acids or bases when in contact with aqueous substrates/organic media.

^bChemicals with molecular mass $> 650\text{g/Mol}$ may elicit severe tissue damage resulting in local corrosion (labelled R41).

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

Component 2: Structural alerts

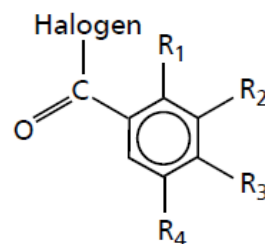
- To predict the **PRESENCE** of an irritant/corrosive potential
- Based on reactive substructures

Chemical substructures indicative of skin corrosion:

1) **Substituted benzoic acid halogenides^d**

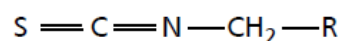
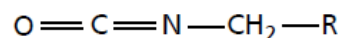
Halogen = Cl or F

R₁-R₄ = any substituent



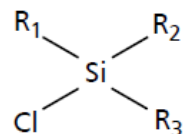
2) **Aliphatic iso(thio)cyanates^e**

R = aliphatic chain

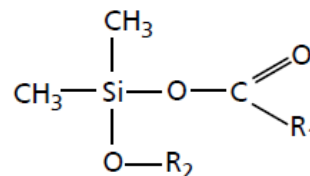


3) **Chlorosilanes**

R₁-R₃ = any (for example, further halogen)

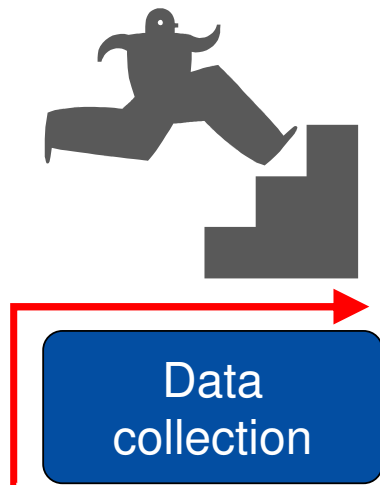


4) **Mixed Oxy- Carboxy- silanes**

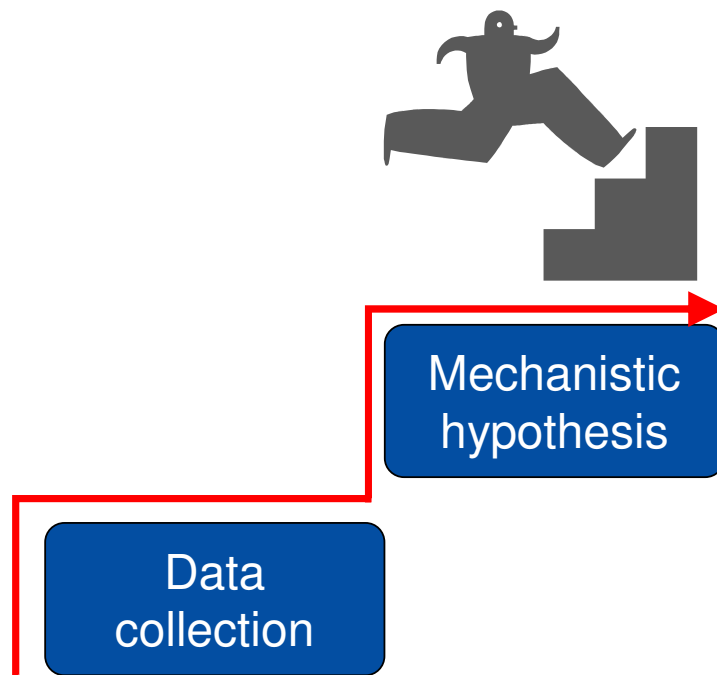


(Gerner et al. (2005), ATLA 33, 215–237

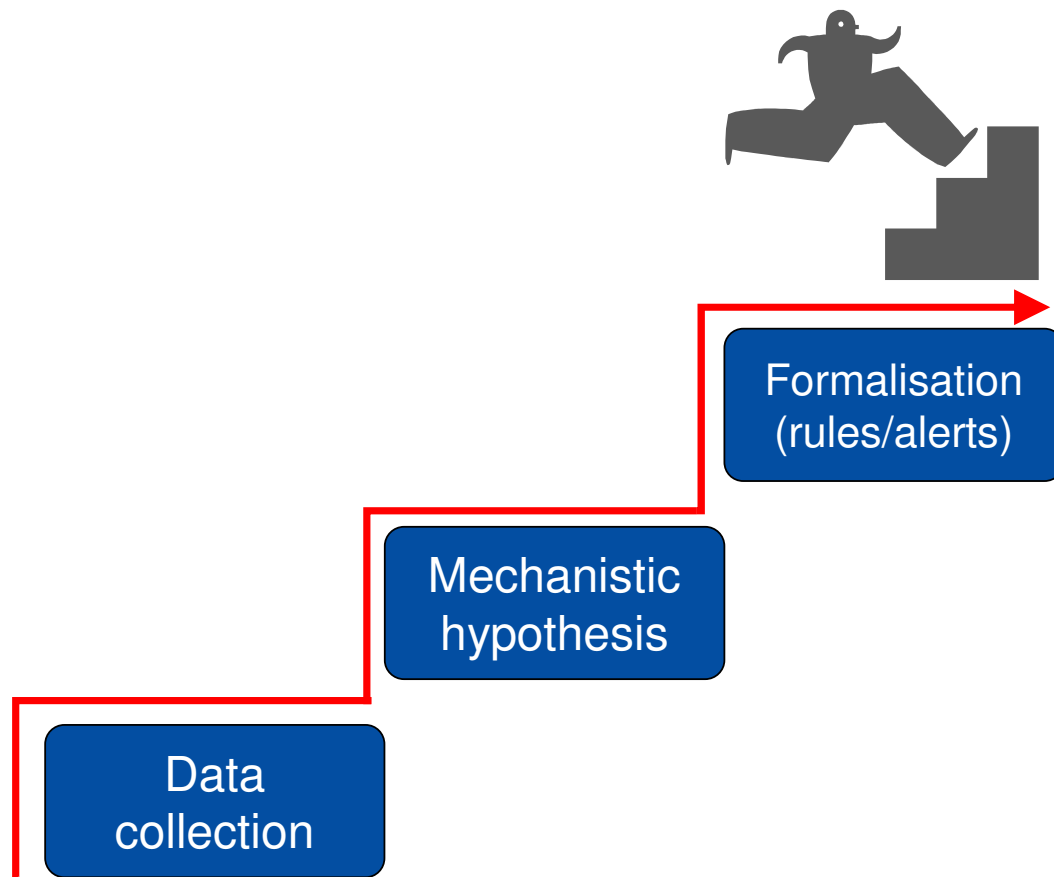
Mining existing knowledge – Step 1: Data collection



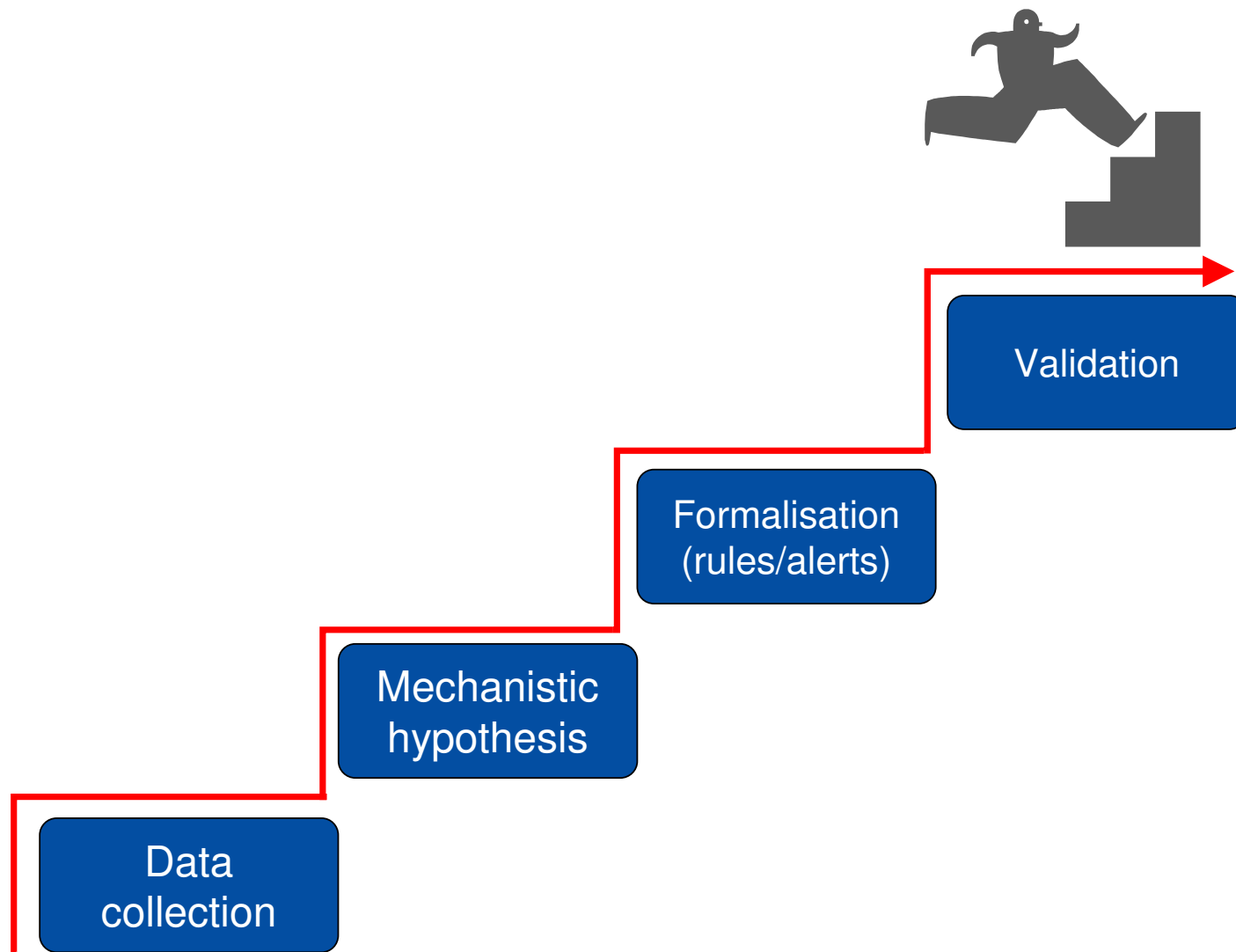
Mining existing knowledge – Step 2: Generating a Hypothesis



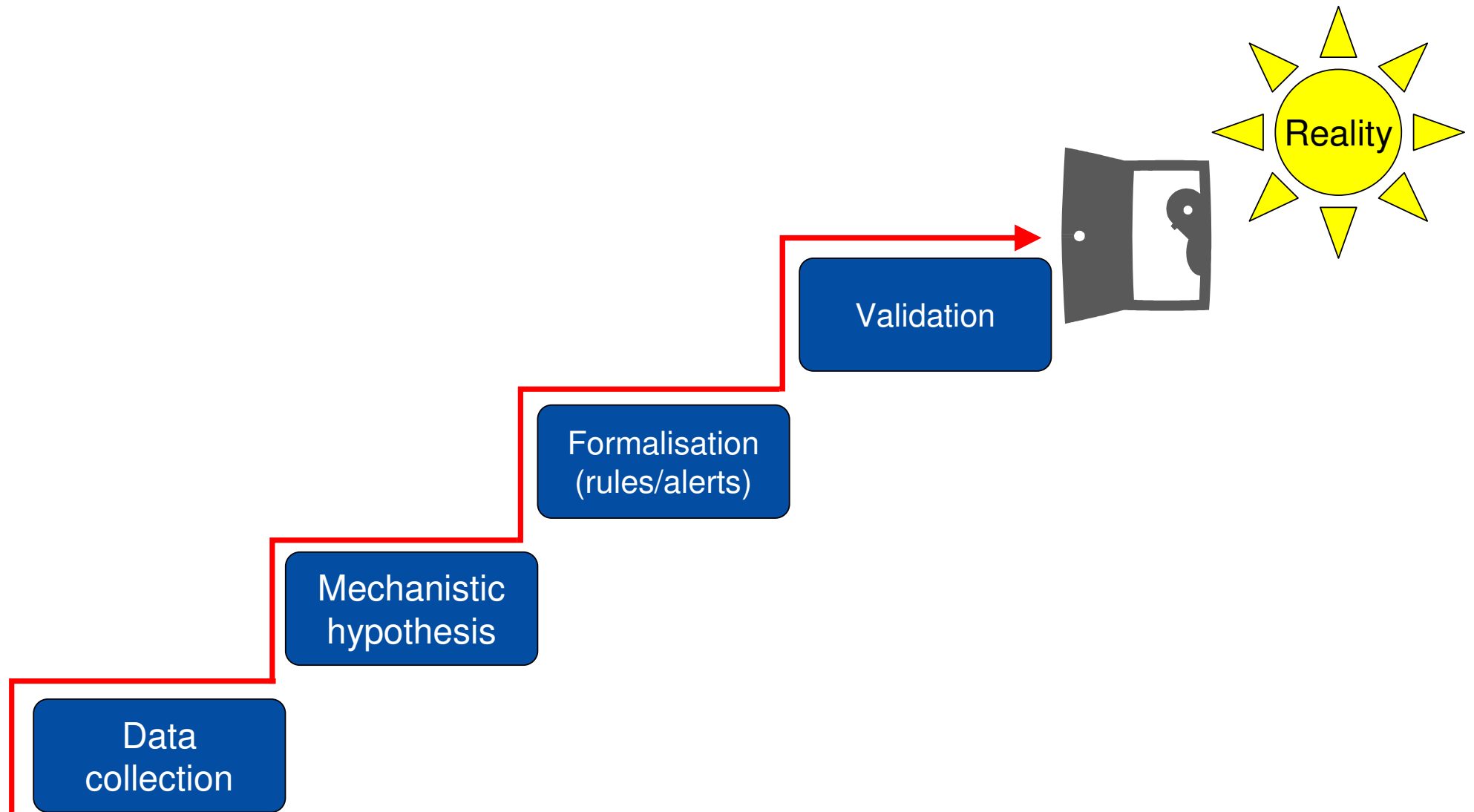
Mining existing knowledge – Step 3: Formalisation



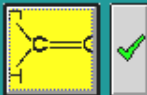
Mining existing knowledge – Step 4: Validation



Mining existing knowledge – Step 5: The Reality Test



Data collection – The BfR ESTOFF Database

Identity	Stoff-ID: 1234	Stoffnummer: 12-34-5678	Referenzstoff: C11H1005NCI
	C Hauptgruppe: CNH	Summenformel: 271 g/mol	
	H Gruppe: Halogenbenzole mit N-Funktionen am Ker	Molekulgewicht: 271 g/mol	
	E Untergruppe: Halogenbenzole mit Nitro-Gruppen	Anion: 0 g/mol	
Phys.-chem.	Unter-Untergruppe: 	Kation: 0 g/mol	
	P Wasserlöslichkeit: 0.176 g/l	Fettlöslichkeit: 0 g/kg	og POW: 1.5
	HY pH-Wert: 4.1	Oberfl.-Spannung: 71.3 mN/m	Dampfdruck: 0.0241 Pa
	Schmelzpunkt: 114 - 115 °C	Siedepunkt: 185 - 0 °C	Hydrolyse:
Acute Toxicity	LD50 [mq/kg]	dermale: 2000 - 0	LC50 [mq/l in 4h]
	orale: > 2000 - 0	dermale weibl.: ? 0 - 0	inhalativ: ? 0 - 0
	orale weibl.: ? 0 - 0	dermale männl.: ? 0 - 0	inhalativ weibl.: ? 0 - 0
	orale männl.: ? 0 - 0	inhalativ männl.: ? 0 - 0	
Irritation/corrosion	R-Satz oral: nicht eingestu	R-Satz dermal: nicht eingestu	R-Satz inhalativ: nicht bekannt
	R-Satz: nicht eingestuft	R-Satz: 41	
	Ödeme: ö Eryth. e	Ödeme: ö Eryth. I Cornea: I Iris: S	
	Beobachtungsdauer: o.B. nac 7 Tage	Beobachtungsdauer: o.B. nac irreversibel	
Sensitisation	Ätzung/Reizung wegen 		
	liegt Haut-Sensibilisierung vor: J Test: 100 % im MKT		
Add. Information	liegt Atemwegs-Sensibilisierung vor: ?		
	Bemerkungen: > 185°C Zersetzung		

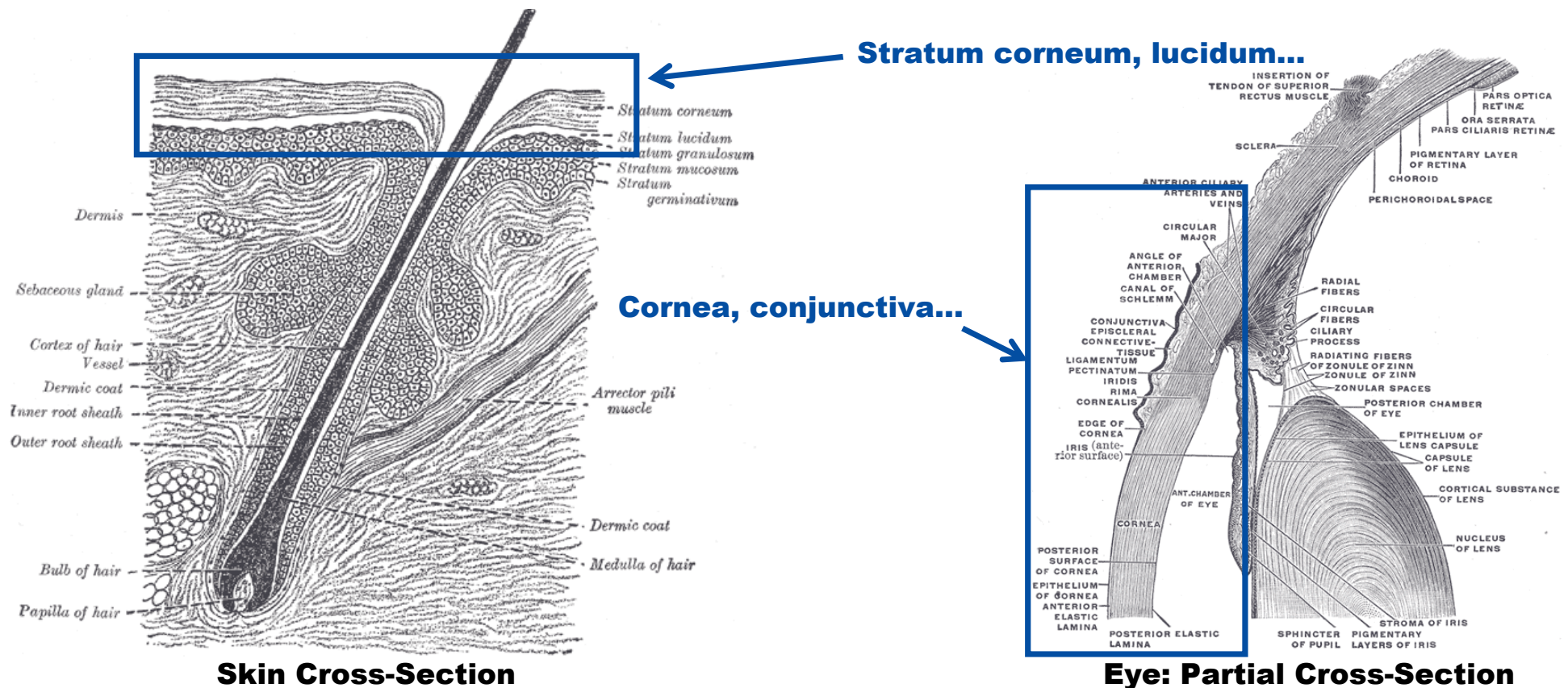
- 1992 entries, ca. 1400 for DSS training set, 200 for validation test set

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

Mechanistic Hypothesis – Two-step process

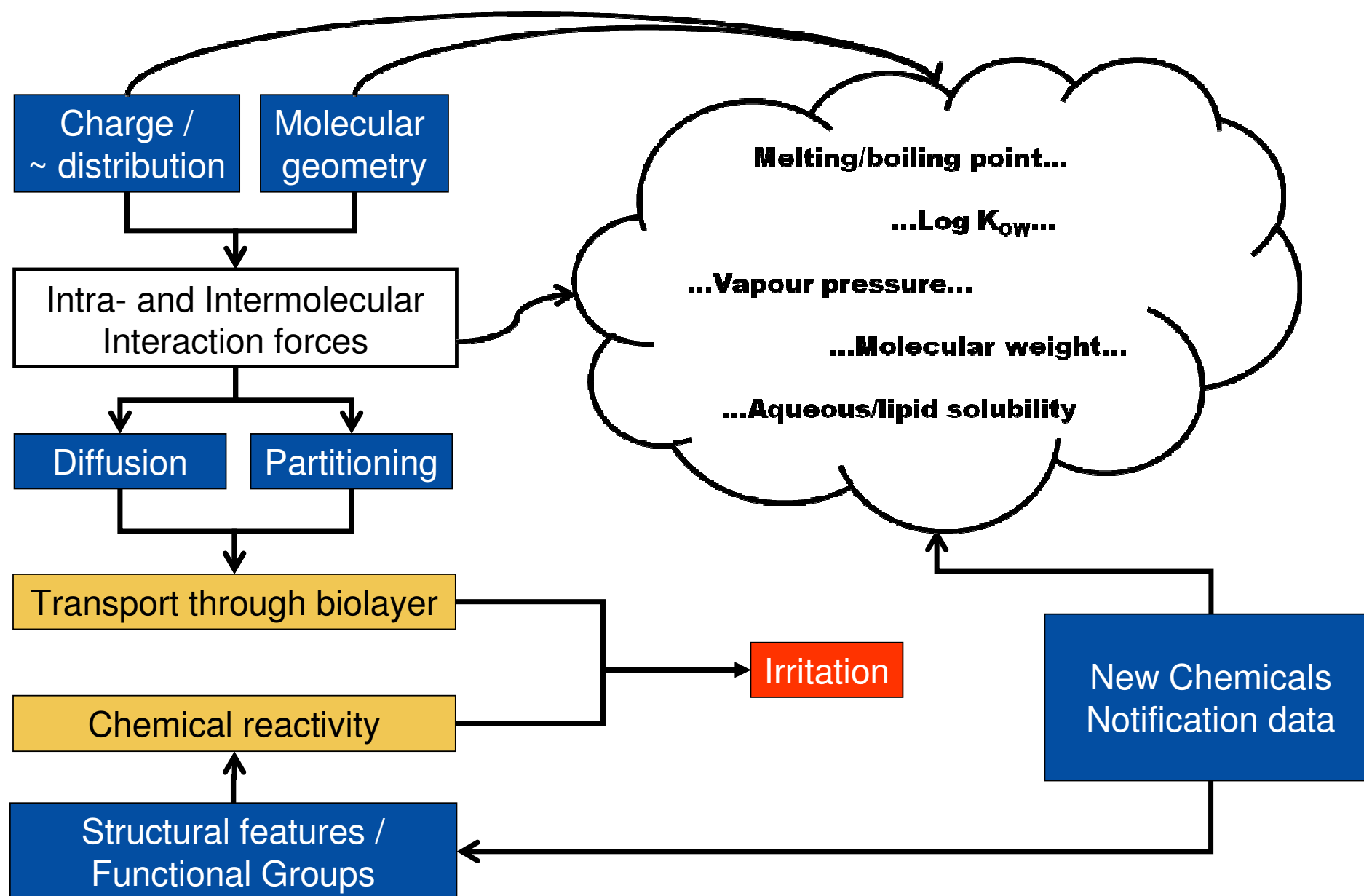
Step 1: Active **destruction** (corrosion) or passive **transport** through protective biolayers

Step 2: **Reaction**/interference with biological structures/processes



(Source: Wikipedia/Gray's Anatomy 1918)

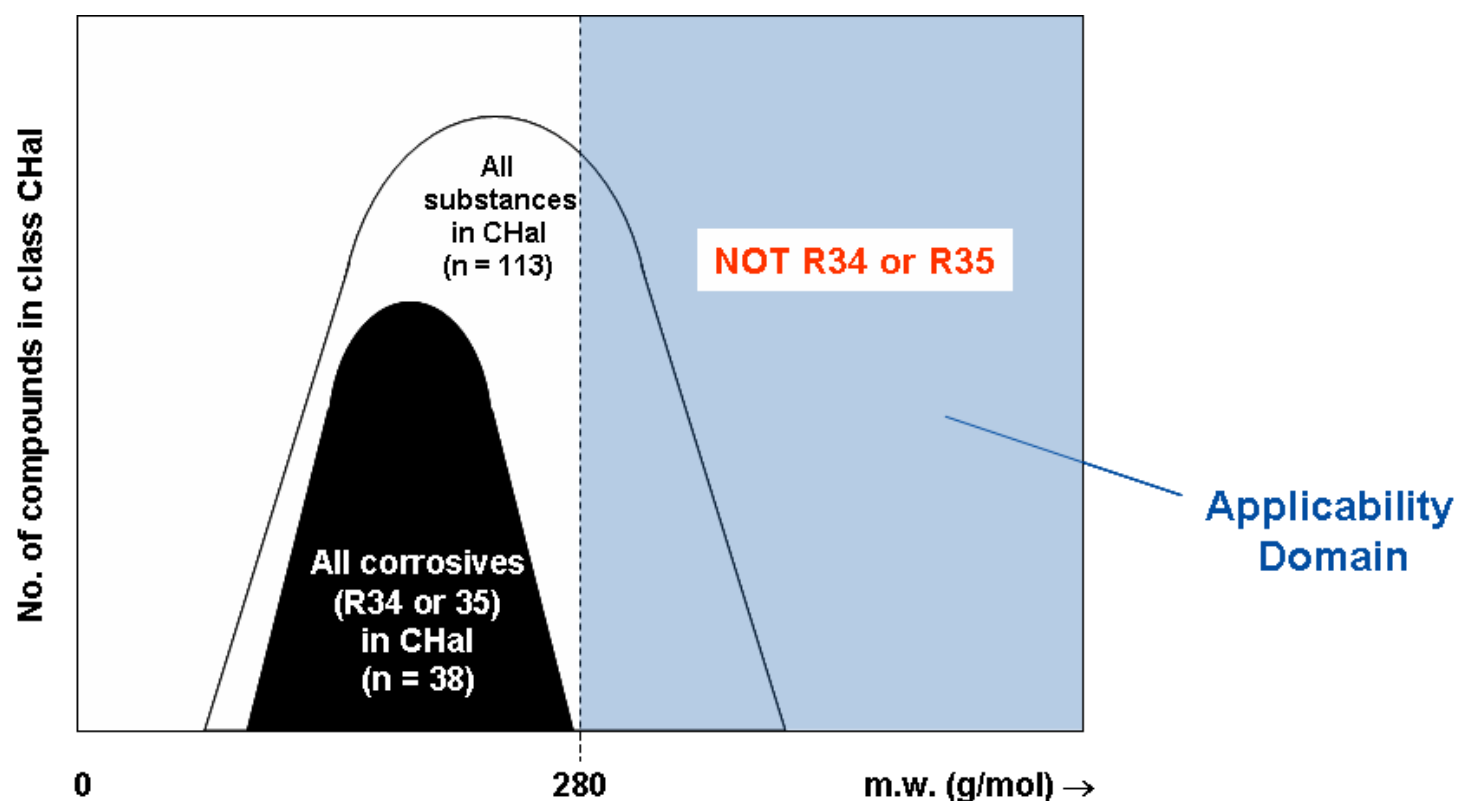
Mechanistic Hypothesis – Factors Influencing Irritation Potential



Creating Physico-Chemical Exclusion Rules

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

Example: Exclusion rule for corrosion for group CHal ($C_xH_yO_z\text{Halogen}_d$) 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 (Met)acrylic acids		R < C8 R1 = aliphatic chain no other subgroups	n = 8	28
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 R1 - R4 = any	Attention: some benzoic acid halogenides hydrolyse immediately when getting in contact with water, the resulting acid may cause only mild skin irritation e.g. cationic surfactants	15
Quaternary organic ammonium compounds		N as centre of attraction and weak chelation R1-R4, however one R group should be small e.g. < C3		27, 42
Primary and secondary aliphatic amines		Primary, secondary R and R1 = H and/or aliphatic	n = 16 [28] primary: n = 15 [34]	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: Xn, 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*	

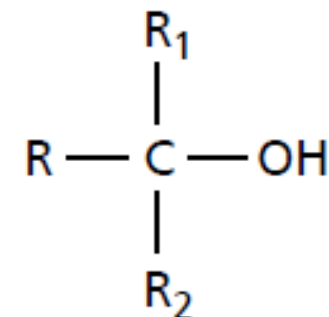
R₁-R₄ = H, aliphatic chain or halogen

1) Aliphatic monoalcohols

C₃-C₁₁: eye damage
C₁₂-C₁₄: eye irritation

R = aliphatic chain

R₁/R₂ = 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

Validation (2005-today)

Evaluation of (Q)SARs for the Prediction of Skin Irritation/Corrosion Potential
Physico-chemical exclusion rules

Sponsor: European Commission
 Directorate General
 Joint Research Centre
 Institute for Health and Consumer Protection

Authors: Emiel R. de Boer, Etje H. de Boer, Nat. Bur. of Standards, NIST

Evaluation of (Q)SARs for the Prediction of Eye Irritation/Corrosion Potential
Physicochemical exclusion rules

Ivanka Tsakovska, Tatjana Gallegos Saliner

2005

EUROPEAN COMMISSION
 DIRECTORATE-GENERAL
 Joint Research Centre

Evaluation of (Q)SARs for the Prediction of Skin Irritation/Corrosion Potential in the BfR decision support system

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 Joint Research Centre, European Commission, 21020 Ispra (VA), Italy

(Received 11 May 2006; in final form 22 September 2006)

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		
Acetamidrid	insecticide	CN-Hal											
Acibenzolar-S-methyl	fungicide	CNS											
Amidosulfuron	herbicide	CN											
Amitrole	herbicide	CNS											
Azimsulfuron	fungicide	CN											
Azoxystrobin	herbicide	CN-Hal											
Beflubutamid	fungicide	CN											
Benalaxyl	herbicide	CNS											
Bentazone	fungicide	Other											
Benthiavalicarb	disinfectant	C											
Benzoic acid	acaricide	CN											
Bifenazate	fungicide	CN-Hal											
Boscalid	herbicide	CN-Hal											
Bromoxynil	fungicide	Other											
Captan	fungicide	CN											
Carbendazim	herbicide	CN-Hal											
Carfentrazone-ethyl	fungicide	C											
Carvone	herbicide	CN-Hal											
Chloridazon	herbicide	CN-Hal											
Chlorpropham	herbicide	Other											
Glufosinate-ammonium	herbicide	Other											

Validation – Summary of Results

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

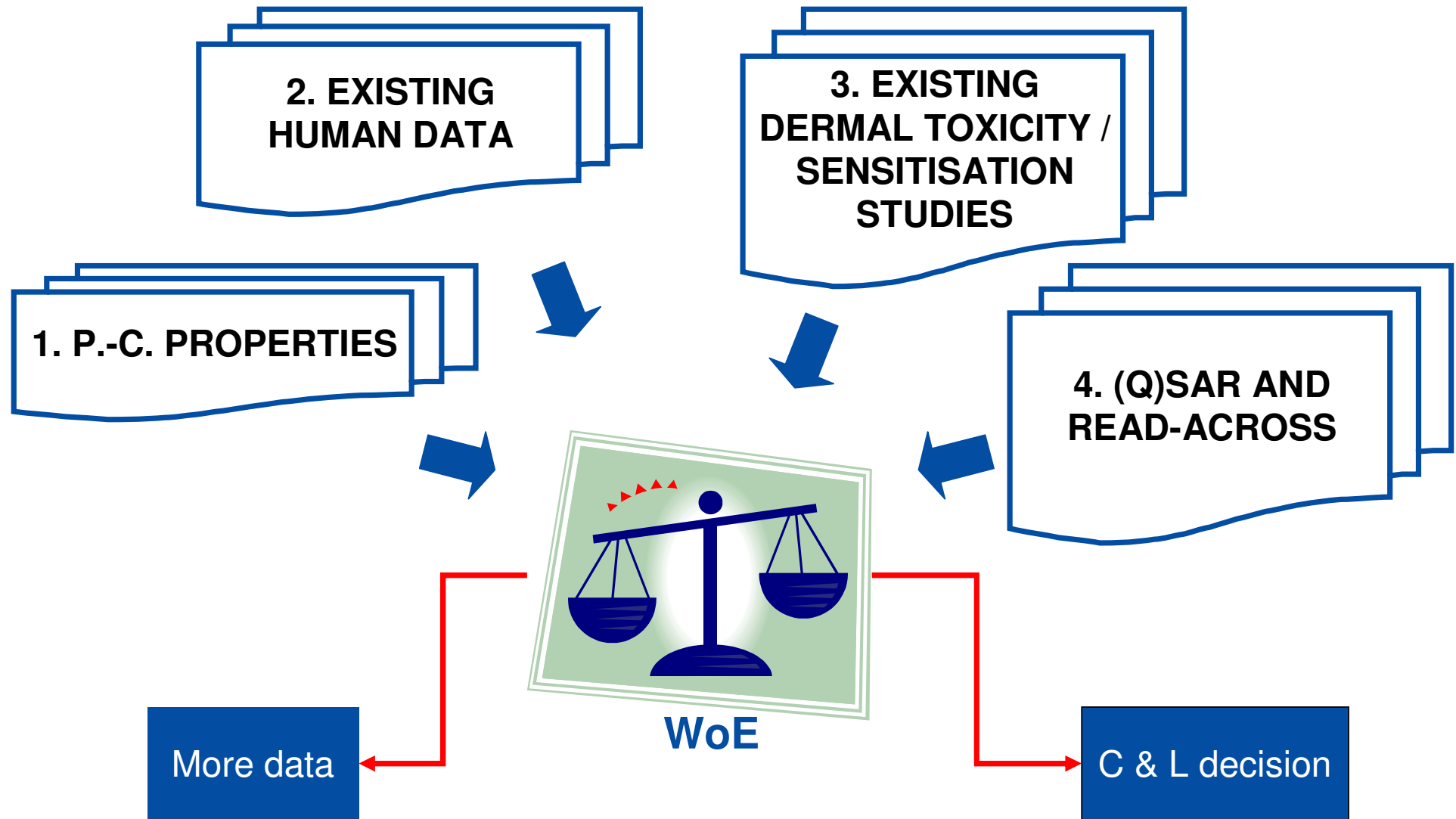
- predictivity (NPV) > 87 % (eye) and > 95 % (skin) upon external validation
- exclude > 40 % EU NONS from skin and ca. 10 % for eye irritation testing

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 **reliability** required
- the **costs** of a negative vs. a positive prediction
- **WoE** of other available data: supportive/equivocal/contradictory?

Availability of the DSS

TOXTREE



The screenshot shows the European Commission Joint Research Centre website. The main heading is "Toxtree". Below it, a paragraph describes Toxtree as a flexible and user-friendly open-source application that places chemicals into categories and predicts various kinds of toxic effect by applying decision tree approaches. A list of implemented decision trees is provided:

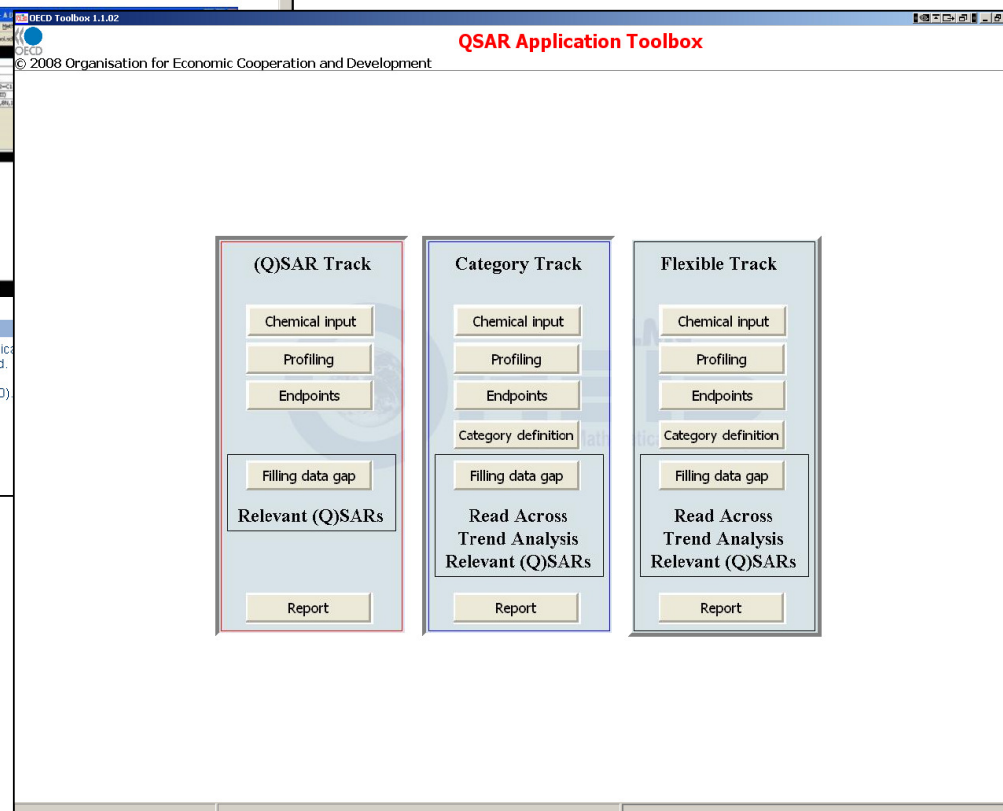
- the Cramer classification scheme
- an Extended Cramer scheme
- the Verhaar scheme for aquatic modes of action
- rulebases for skin and eye irritation and corrosion
- the Benigni-Bossa rulebase for mutagenicity and carcinogenicity
- the ToxMic rulebase for the in vivo micronucleus assay
- structural alerts for identification of Michael Acceptors
- the START rulebase for persistence / biodegradation potential

Below the list, a paragraph states: "Toxtree was developed by Ideaconsult Ltd (Sofia, Bulgaria) under the terms of a JRC contract. The software is made freely available as a service to scientific researchers and anyone with an interest in the application of computer-based estimation methods in the assessment of chemical toxicity."

At the bottom, there is a section titled "Toxtree (Version 1.60) - Download area (July 2009)" with links to download the software and manuals.

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

OECD (Q)SAR TOOLBOX



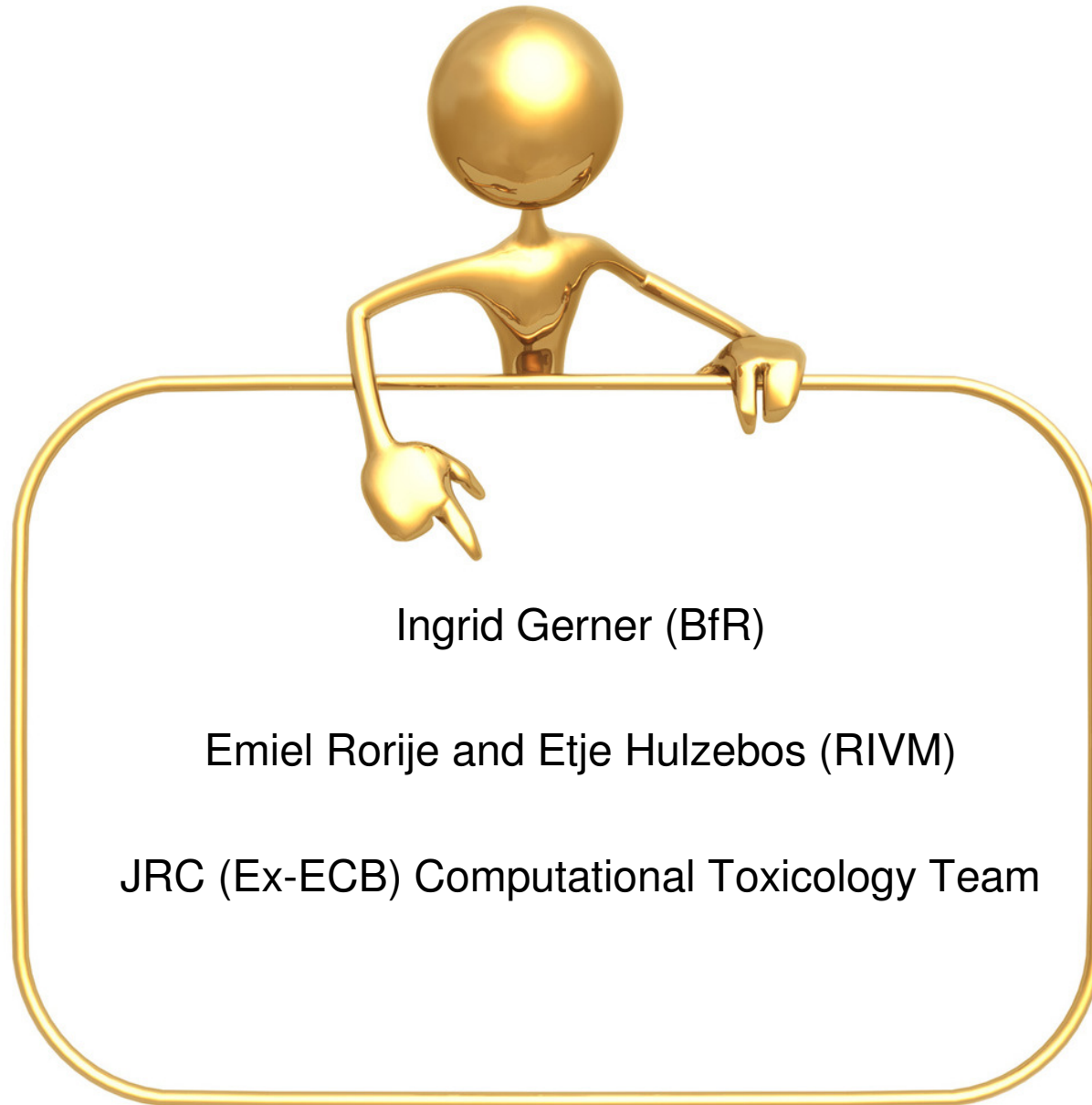
The screenshot shows the OECD (Q)SAR Toolbox application interface. The title bar reads "OECD Toolbox 1.1.02". The main heading is "QSAR Application Toolbox". Below this, there are three main tracks: (Q)SAR Track, Category Track, and Flexible Track. Each track has a series of buttons for different functions:

- (Q)SAR Track:** Chemical input, Profiling, Endpoints, Filling data gap, Relevant (Q)SARs, Report.
- Category Track:** Chemical input, Profiling, Endpoints, Category definition, Filling data gap, Read Across Trend Analysis Relevant (Q)SARs, Report.
- Flexible Track:** Chemical input, Profiling, Endpoints, Category definition, Filling data gap, Read Across Trend Analysis Relevant (Q)SARs, Report.

<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



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JRC (Ex-ECB) Computational Toxicology Team

Thank you for your attention

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