

Validation of Testing Strategies (?)

3rd OSIRIS Stakeholder Workshop

(BCF and Skin Sensitisation)

1-2 March 2010

BfR Berlin

Manfred Liebsch

Federal Institute for Risk Assessment (BfR)

Centre for Alternative Methods to Animal Experiments - ZEBET

Contribution of BfR to ITS

	1996	TG 423 Acute Oral Toxicity : ATC Method
	2002	TG 404 Skin irritation / corrosion (BfR & U.S. EPA: <i>in vitro/in vivo</i> strategy)
	2002	TG 404 Eye irritation / corrosion (BfR & U.S. EPA: <i>in vitro/in vivo</i> strategy)
	2004	TG 427 Skin Absorption (<i>in vivo</i>)
	2004	TG 428 Skin Absorption (<i>in vitro</i>)
	2004	GD 28 on Skin Absorption Testing
	2004	TG 430 Skin Corrosion : TER
	2004	TG 431 Skin Corrosion : human 3D skin model
	2004	TG 432 In Vitro Phototoxicity : 3T3NRU-PT
	2005	GD 34 on Validation and Acceptance
	2008	TG 436 Acute Inhalation Toxicity : ATC Method
	2008	GD 39 on Acute Inhalation Testing

...currently ongoing

Implementation of BfR SAR Expert System DSS (skin and eye) into OECD QSAR toolbox

Skin: ITS developed by Competent Authorities

Evaluation of skin irritation of chemical using (Q)SAR models

BfR-rules




Integrated Testing Strategy



Structural alerts



Validation of Test Methods: OECD GD 34 (2005)



Organisation de Coopération et de Développement Economiques
Organisation for Economic Co-operation and Development

ENV/JM/MONO(2005)14

Unclassified


ENV/JM/MONO(2005)14
Unclassified

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

English - Or. English

OECD SERIES ON TESTING AND ASSESSMENT
Number 34

GUIDANCE DOCUMENT ON THE VALIDATION AND INTERNATIONAL ACCEPTANCE OF NEW
OR UPDATED TEST METHODS FOR HAZARD ASSESSMENT



10 Years to reach agreement on GD 34

- Hans Ahr, Bayer AG, Wuppertal, Germany
- Michael Balls, EC/ECVAM, Ispra, Italy
- Robert Boethling, US-EPA, Washington, DC, USA
- Dorothy Canter, US-EPA, Washington, DC, USA
- Mark Chamberlain (BIAC) Unilever, UK
- Alan Goldberg, CAAT, Baltimore, MD, USA
- Petra Greiner, UBA, Germany
- Kailash Gupta, CPSC, Bethesda, MD, USA
- Karen Hamernik, US-EPA, Washington, DC, USA
- David Hattan, FDA, Bethesda, MD, USA
- Abigail Jacobs, FDA, Rockville, MD, USA
- – Manfred Liebsch, ZEBET, Berlin, Germany
- Kimmo Louekari, Product Control Agency for Welfare and Health, Finland
- Yasuo Ohno, NIHS, Tokyo, Japan
- Willie Owens, (BIAC) Procter and Gamble, USA
- Richard Phillips, Exxon/Mobile, East Millstone, NJ, USA
- Amy Rispin, US-EPA, Washington, DC, USA
- Andrew Rowan, Humane Society of the US, Washington, DC, USA
- Len Schechtman, FDA, Rockville, MD, USA
- – Jerry Smrchek, US-EPA, Washington, DC, USA
- Horst Spielmann, ZEBET, Berlin, Germany
- Martin Stephens (ICAPO), USA
- William Stokes, NIEHS, Research Triangle Park, NC, USA
- Gary Timm, US-EPA, Washington, DC, USA
- Leslie Touart, US-EPA, Washington, DC, USA
- Neil Wilcox, formerly of FDA, Rockville, MD, USA
- Marilyn Wind, CPSC, Bethesda, MD, USA
- Andrew Worth, JRC-EC, Italy
- Errol Zeiger, formerly of NIEHS, Research Triangle Park, NC, USA

Final consensus on GD 34 Bethesda 2004




GD 34 is Guidance for Single Test Validation

Batteries only mentioned in § 48


“individual tests within a battery of tests or tiered testing strategy should be validated using the validation principles and **taking into consideration their restricted roles** in the test battery/testing strategy.

The acceptance of a test battery should be primarily based on its overall performance for the intended purpose. When tests are used in a tiered approach, the overall results will depend on the strength of the individual tests in the tier, unless certain tests in the tier are used in a confirmatory manner.”

Validation of QSAR's: OECD GD 65 (2007)

 ENV/JM/MONO(2007) For Official Use	For Official Use	ENV/JM/MONO(2007)2
	Organisation de Coopération et de Développement Economiques Organisation for Economic Co-operation and Development	15-Feb-2007
	English, French	
	ENVIRONMENT DIRECTORATE JOINT MEETING OF THE CHEMICALS COMMITTEE AND THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY	
Many principles identical to GD34. More strict and conservative with regard to precise definition of Applicability Domain!		
	GUIDANCE DOCUMENT ON THE VALIDATION OF (QUANTITATIVE)STRUCTURE-ACTIVITY RELATIONSHIPS [(Q)SAR] MODELS	

Non Testing: Grouping: OECD GD 80 (2007)

 ENV/JM/MONO(2007)28 Unclassified	Unclassified	ENV/JM/MONO(2007)28
	Organisation de Coopération et de Développement Economiques Organisation for Economic Co-operation and Development	26-Sep-2007
	English - Or. English	
	ENVIRONMENT DIRECTORATE JOINT MEETING OF THE CHEMICALS COMMITTEE AND THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY	
...often not used embedded in ITS, but stand-alone		
SERIES ON TESTING AND ASSESSMENT Number 80		
GUIDANCE ON GROUPING OF CHEMICALS		

EPAA-ECVAM: Validation of ITS necessary ?

ATLA 37, 1–8, 2009

1

Overcoming Barriers to Validation of Non-animal Partial Replacement Methods/Integrated Testing Strategies: The Report of an EPAA–ECVAM Workshop

Agnieszka Kinsner-Ovaskainen,¹ Zerrin Akkan,² Silvia Casati,¹ Sandra Coecke,¹ Raffaella Corvi,¹ Gianni Dal Negro,³ Jack De Bruijn,⁴ Odile De Silva,⁵ Laura Gribaldo,¹ Claudius Griesinger,¹ Joanna Jaworska,⁶ Joachim Kreysa,¹ Gavin Maxwell,⁷ Pauline McNamee,⁶ Anna Price,¹ Pilar Prieto,¹ Roland Schubert,⁸ Luca Tosti,¹ Andrew Worth¹ and Valerie Zuang¹

¹Institute for Health and Consumer Protection, European Commission Joint Research Centre, Ispra, Italy;

²Ciba Inc., Basel, Switzerland; ³GlaxoSmithKline, Verona, Italy; ⁴European Chemical Agency, Helsinki, Finland; ⁵L'Oréal, Paris, France; ⁶Procter and Gamble, Strombeek Bever, Belgium, ⁷Unilever, Sharnbrook, Beds., UK; ⁸DG Enterprise, European Commission, Brussels, Belgium

WS Conclusion:

In principle, yes, however, not feasible & too expensive

EPAA-ECVAM WS

Table 2: Requirements for formal validation of ITS

	Formal validation of ITS component	Formal validation of ITS
Screening	Not required	Not required
Hazard classification & labelling	Not required ???	Not required ???
Replacement of Test Guideline used for regulatory purposes	Required (<i>data requirements are different than in validation of 1-to-1 replacement methods</i>)	Required (<i>the principles of ITS validation need to be established</i>)
Risk assessment	Not required	Not required

How many of you do agree with this table ?

CASE 1: Skin Irritation/Corrosion

OECD/OCDE

404

Adopted:
24th April 2002

OECD GUIDELINE FOR THE TESTING OF CHEMICALS

Acute Dermal Irritation/Corrosion

INTRODUCTION

1. OECD Guidelines for Testing of Chemicals are periodically reviewed to ensure that they reflect the best available science. In the review of this Guideline, special attention was given to possible improvements in relation to animal welfare concerns and to the evaluation of all existing information on the test substance in order to avoid unnecessary testing in laboratory animals. This updated version of Guideline 404 (adopted in 1981 and first revised in 1997) includes the recommendation that prior to

New since 2002: Tiered Testing Strategy

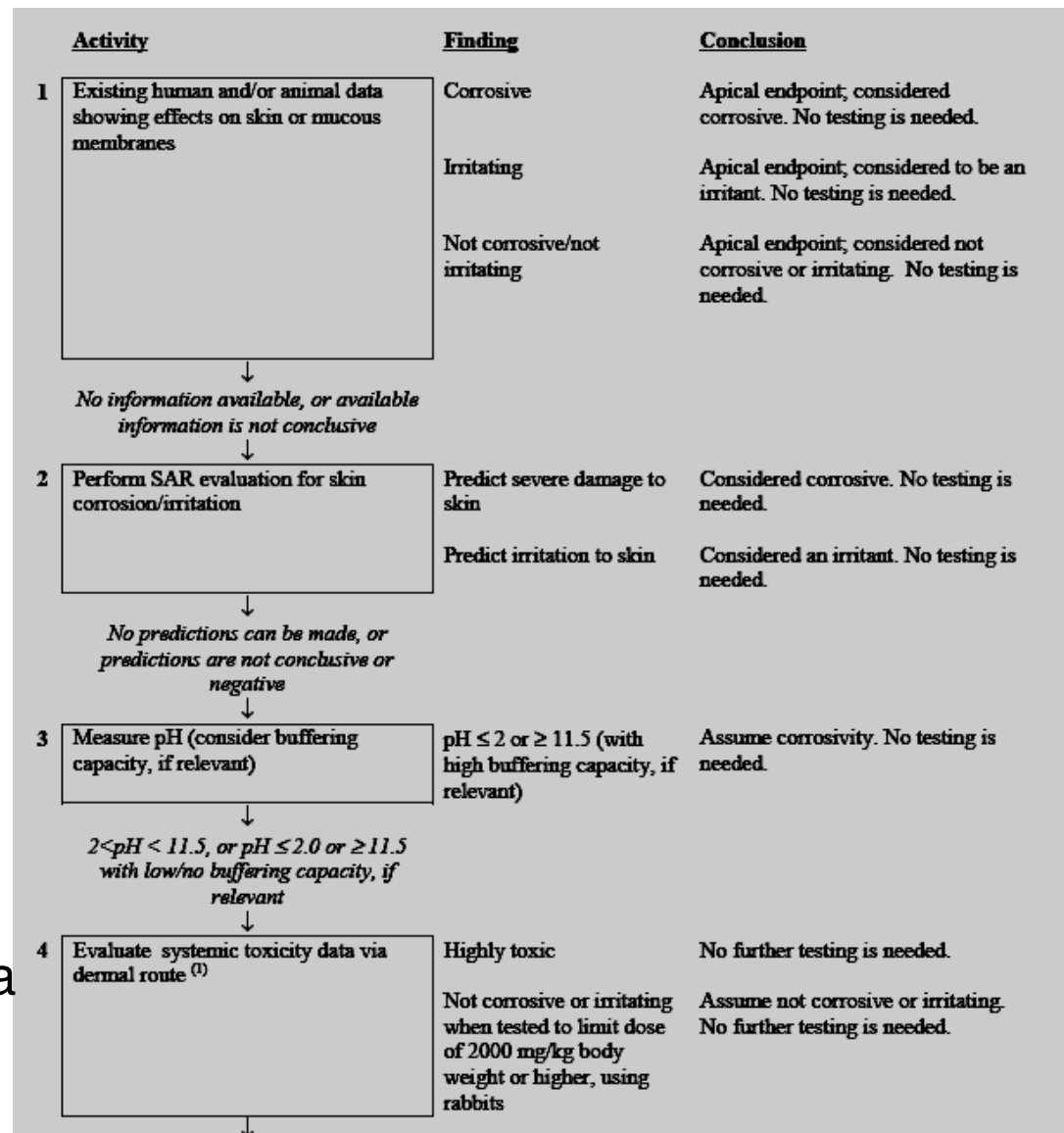
Case 1: Skin Irritation/Corrosion

Use of **existing** human and animal data

Use of SAR

Use of pH
(& acid / alkaline reserve)

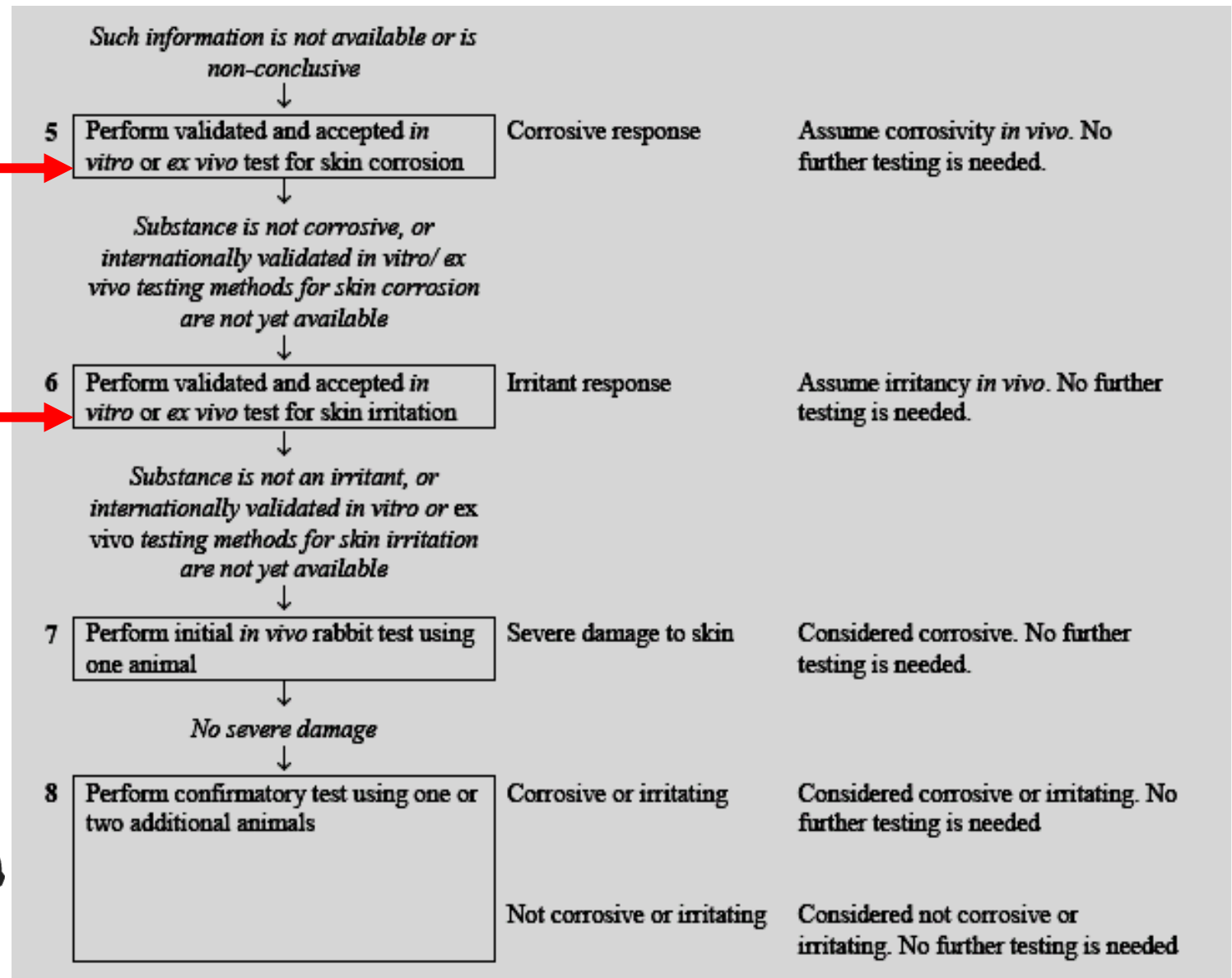
Use of acute dermal tox data



Case 1: Skin Irritation/Corrosion

Accepted
EU B.40
OECD 430
OECD 431
(OECD 435)

Accepted
in EU only
EU B.46
...not yet
by OECD



“Top-down” and “Bottom-up” Strategy

TOP-DOWN (corrosion → irritation)

positive result: no further testing (classify cat. 1)*

negative result: further irritation test as tier 2

BOTTOM-UP (irritation → corrosion)

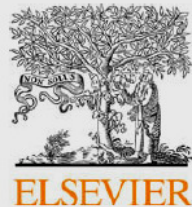
positive result: classify cat. 2, further corrosion test as tier 2 required

negative result: stop testing, chemical has no skin irritating potential

*Unless subcategories I, II, III for corrosives are needed. Then, TG 435 should be used

Case 2: Tiered Testing for Eye Irritation

Regulatory Toxicology and Pharmacology 54 (2009) 197–209



Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph



A tiered approach to the use of alternatives to animal testing for the safety assessment of cosmetics: Eye irritation

Pauline McNamee^a, Jalila Hibatallah^b, Margit Costabel-Farkas^c, Carsten Goebel^d, Daisuke Araki^e, Eric Dufour^f, Nicola J. Hewitt^g, Penny Jones^h, Annette Kirstⁱ, Béatrice Le Varlet^j, Martin Macfarlane^h, Monique Marrec-Fairley^k, Joanna Rowland^l, Florian Schellauf^k, Julia Scheel^{m,*}

^aProcter & Gamble, Rusham Park Technical Centre, Whitehall Lane, Egham, Surrey TW20 9NW, UK

^bChanel Parfums Beauté 135, Avenue Charles de Gaulle, 92525 Neuilly sur Seine, France

^cJohnson & Johnson GmbH, Kaiserswerther Straße 270, 40474 Düsseldorf, Germany

^dProcter & Gamble, Darmstadt Innovation Center, Berliner Allee 65, 64274 Darmstadt, Germany

^eKanebo Cosmetics, 89/91 Rue du Faubourg St Honoré, 75008 Paris, France

^fL'Oréal, River Plaza 25-29, quai Aulagnier 92600 Asnières-sur-Seine, France

^gScientific Writing Services, Wingertstrasse 25, 64390 Erzhausen, Germany

^hUnilever, Colworth Science Park, Sharnbrook, Bedford MK44 1LQ, UK

ⁱKPSS – Kao Professional Salon Services GmbH, Pfungstaedter Strasse 92-100, 64297 Darmstadt, Germany

^jLinks Ingénierie, Paris, France

^kColipa, Avenue Herrmann Debroux 15A, B-1160 Auderghem, Brussels, Belgium

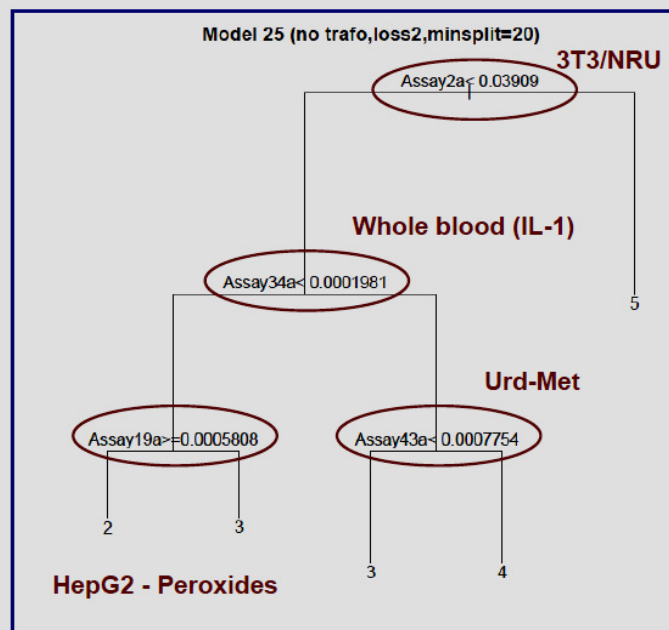
^lGlaxoSmithKline Consumer HealthCare R&D, Weybridge, Surrey KT13 ODE, UK

^mHenkel AG & Co. KGaA, Henkelstraße 67, 40191 Düsseldorf, Germany

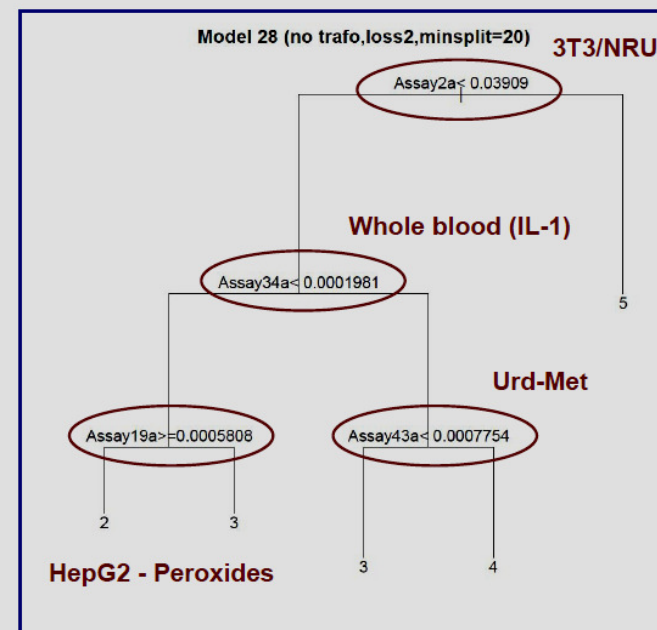
Case 3: ACuteTox: CART Analysis

Best multivariate models identified :

Model 1 – Loss matrix 2 – no transformation



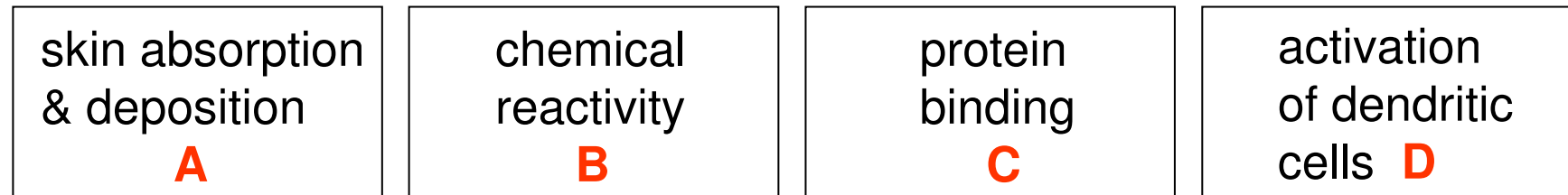
Model 2 – Loss matrix 2 – no transformation



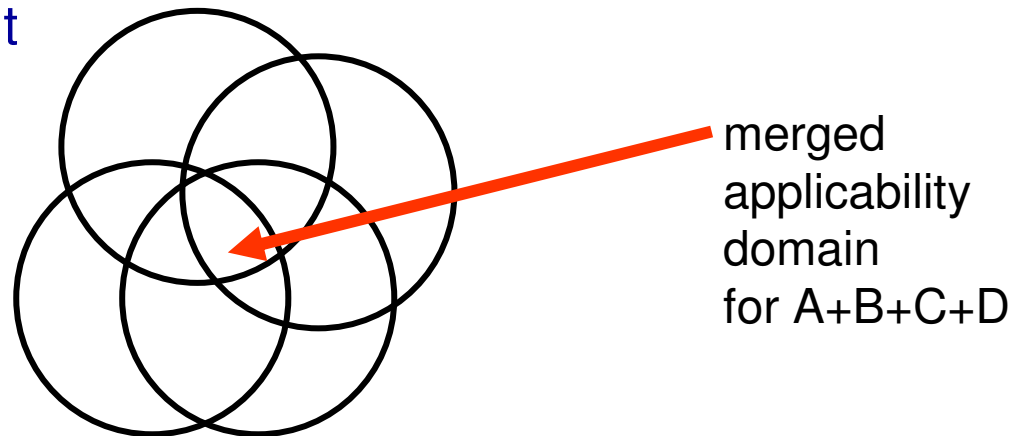
Source: Anette Kopp-Schneider (DKFZ, Heidelberg)

Strategy biostatistically developed at DKFZ with ACuteTox data in 2009 is now **validated experimentally** with a different set of test chemicals

Case 4 (hypothetic) “*In vitro* Sensitisation”



- Each of the four tests has its own threshold to predict **+ or –** sensitisation potential (or potency). **However, the four thresholds may influence each other.**
- The applicability domains of each of the four tests may be different



Conclusions

- The Data Integration and Weight of Evidence processes (ITS) in the REACh System are **expert judgement** driven, and therefore not easily defined.
- To increase robustness of these ITS systems, (retrospective) **validation is needed**.
- Given the different applicability domains of individual components of a strategy, **the data sets** (training set to develop the strategy and validation set for verification / falsification) **should preferably be larger** than for single stand alone tests.