Integrated Testing Strategy for Skin Sensitization potential assessment

from theory to practice

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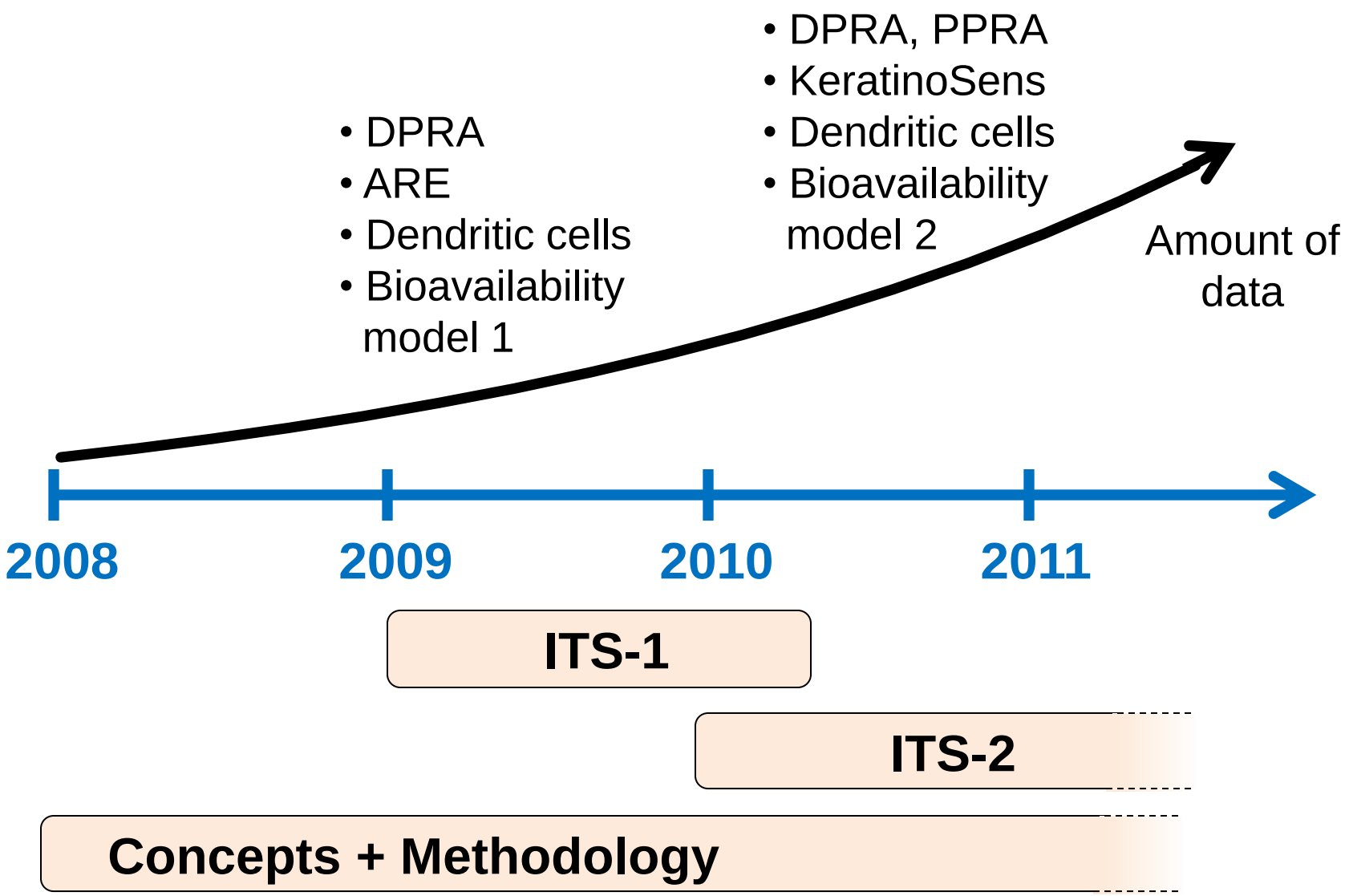
Timeline


• DPRA
• ARE
• Dendritic cells
• Bioavailability model 1
• DPRA, PPRA
• KeratinoSens
• Dendritic cells
• Bioavailability model 2
Amount of data
2008
2009
2010
2011
ITS-1
ITS-2
Concepts + Methodology

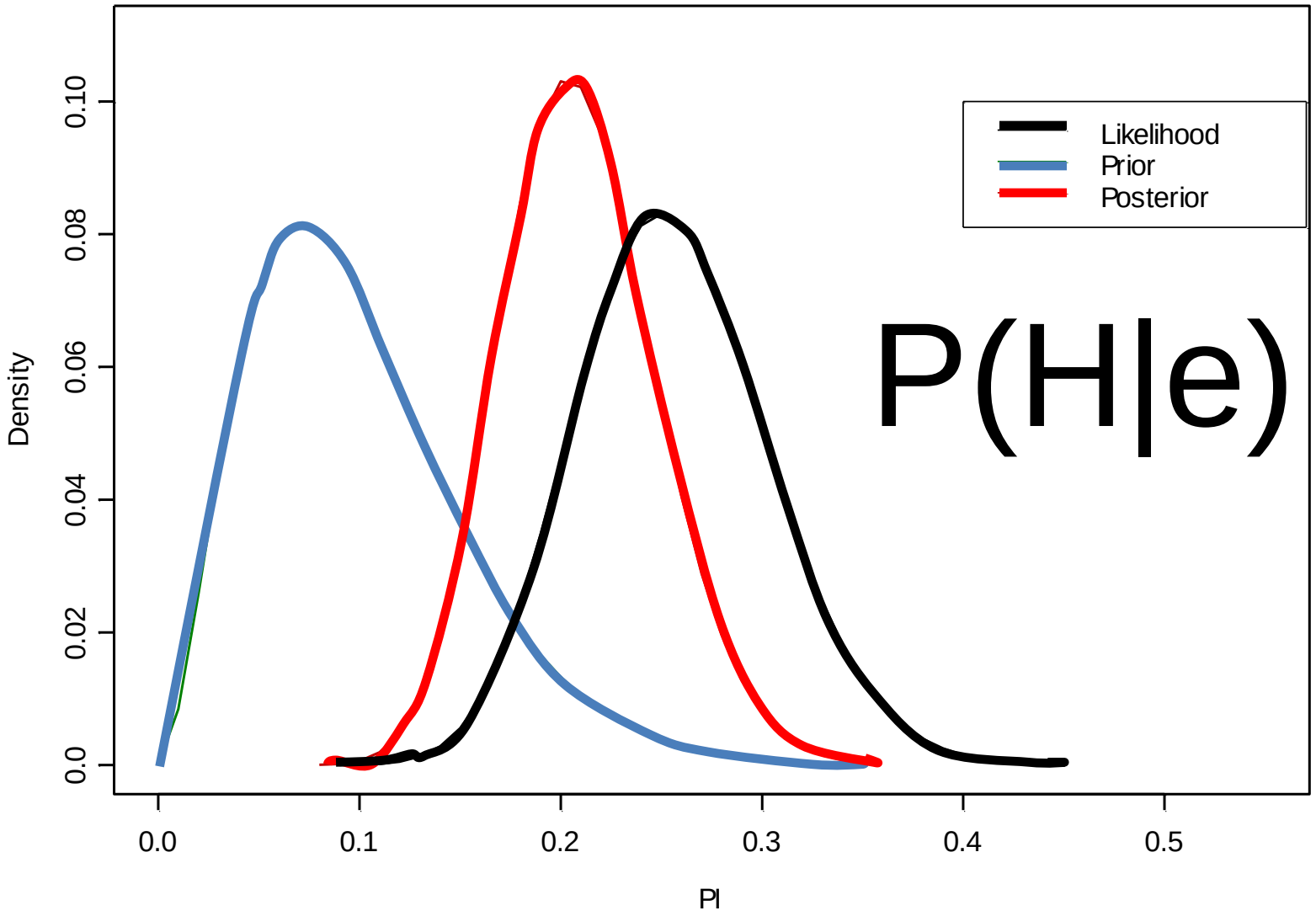
Multi-test qWoE and ITS framework

- From structured narrative and flow charts to decision theory based
  - Quantitative, transparent, consistent, objective

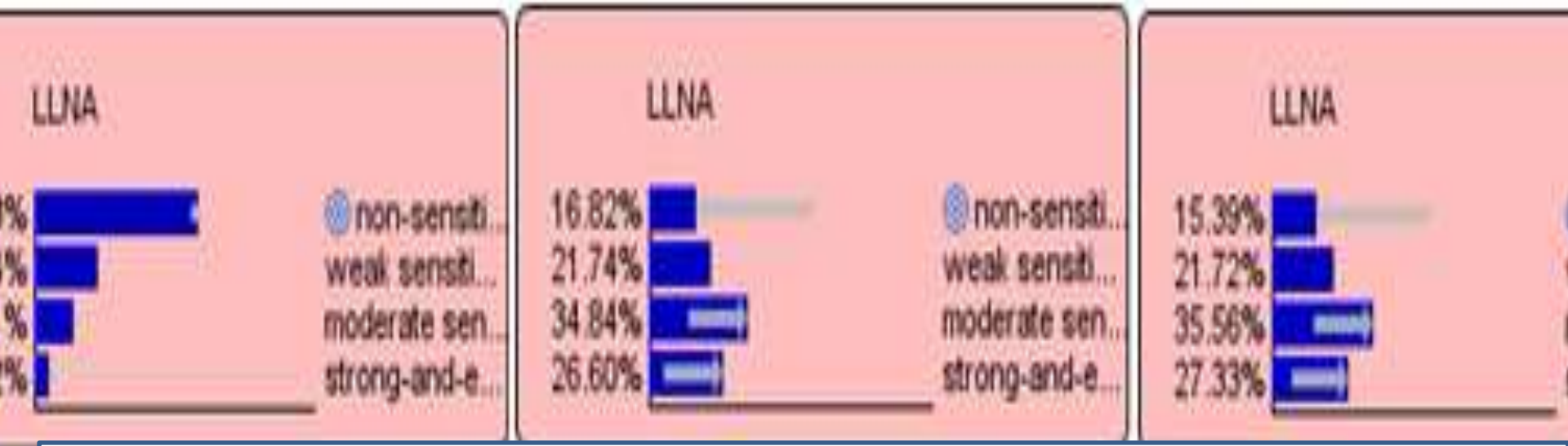
- Bayesian Network ITS as the probabilistic operational framework
  - Uncertainties,
  - dependencies between pieces of information,
  - heterogeneous information,
  - hypotheses can be updated when new data arrive.

Jaworska, Aldenberg, Gabbert 2010, *Reg Tox Pharm;*
Jaworska & Hoffmann 2010; *Altex;*
Aldenberg &Jaworska 2010 qWoE *Predictive Toxicology* Ch 17

Hypothesis (prior) X evidence (likelihood) = Revised hypothesis (posterior)



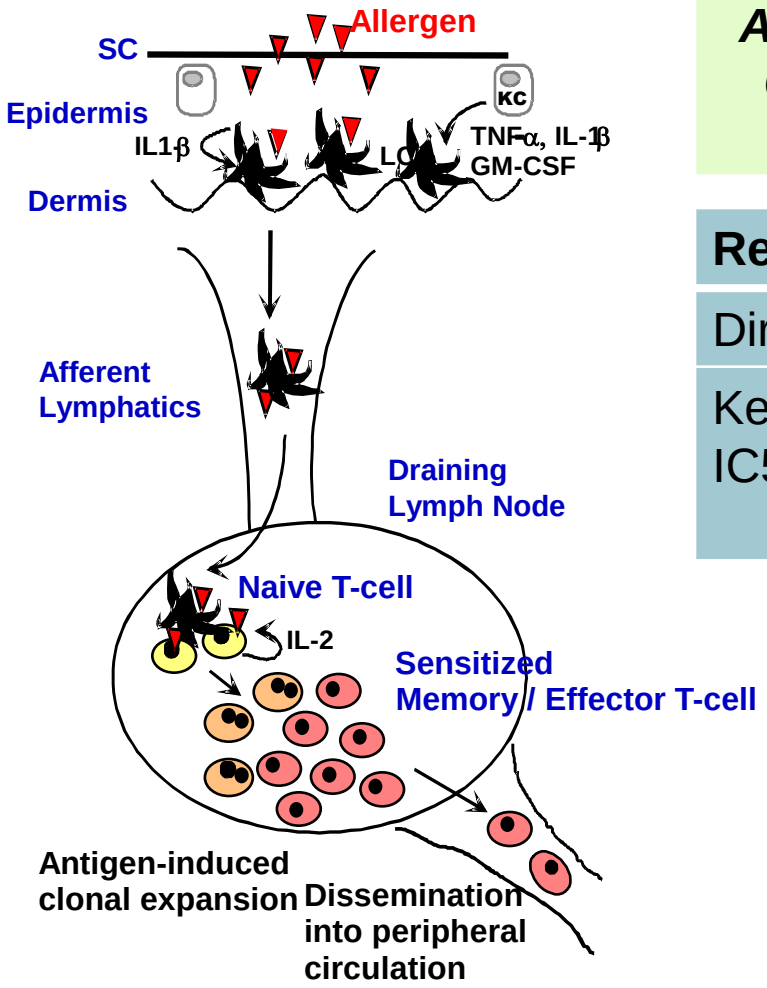
How does the final answer look like ?



P(LLNA=NS, W, M, S| evidence)

Mechanism of Contact Sensitization

Sensitization Phase



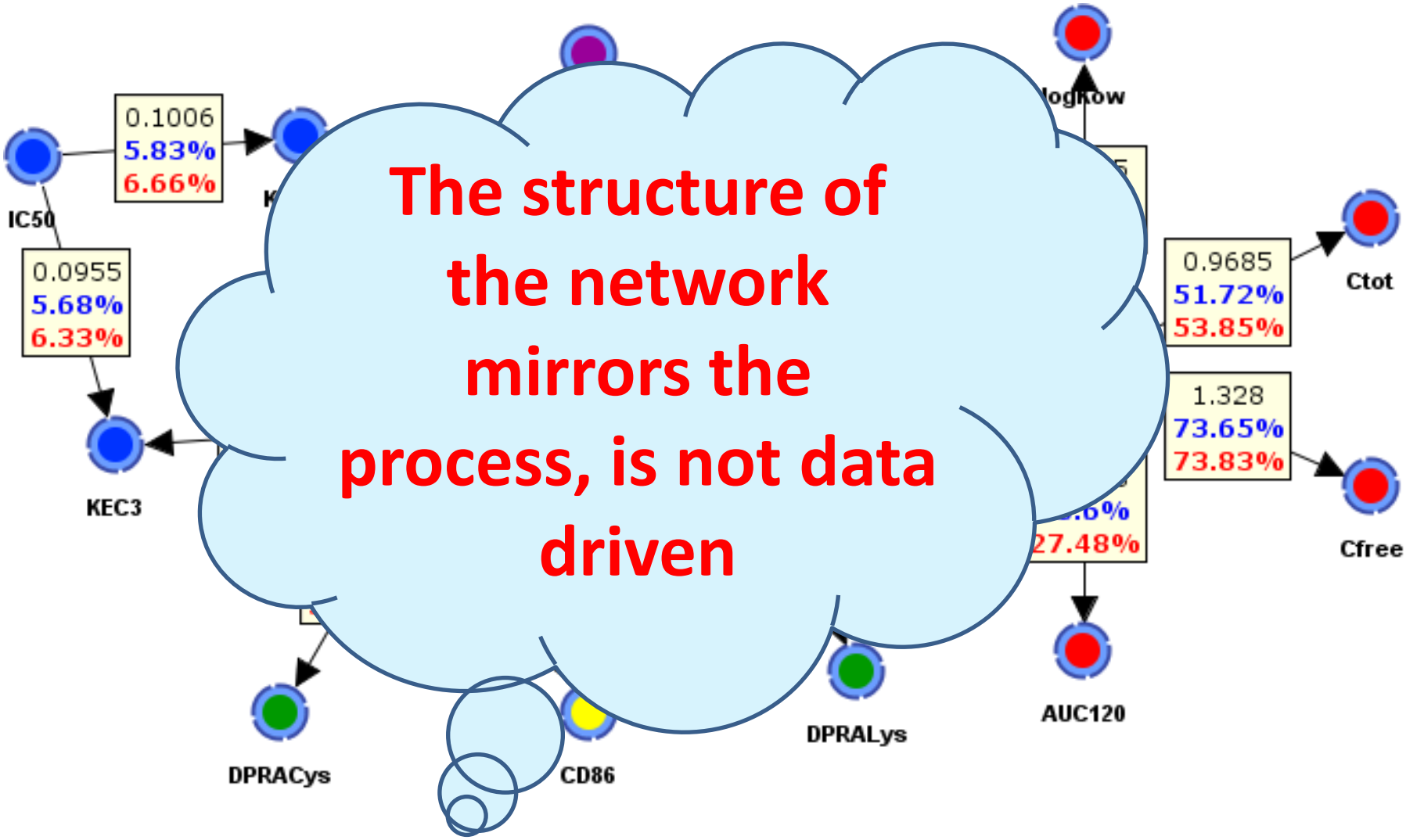
Log K_{ow}, *AUC*120, $C_{tot,free}$	**Bioavailability data:** lipophilicity and kinetic parameters in epidermis from a simulation of exposure in a LLNA test

Reactivity data
Direct Peptide Reactivity Assay (DPRA)
KeratinoSens Assay (Ksens) (KEC 1.5, KEC3, IC50)

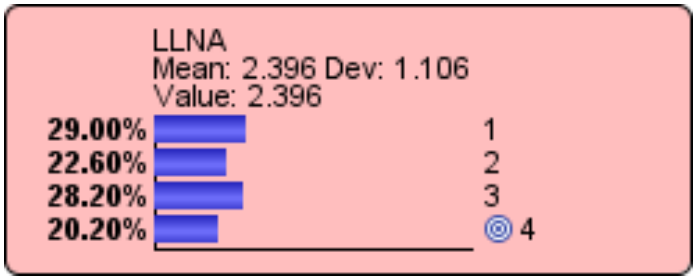
Dendritic cells activation: CD86

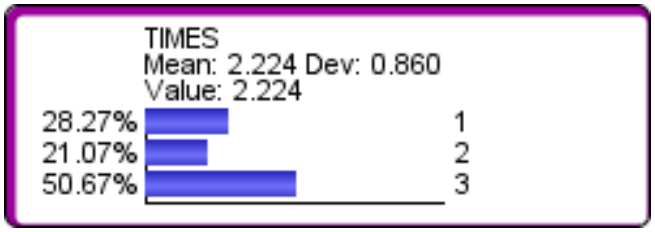
TIMES-M

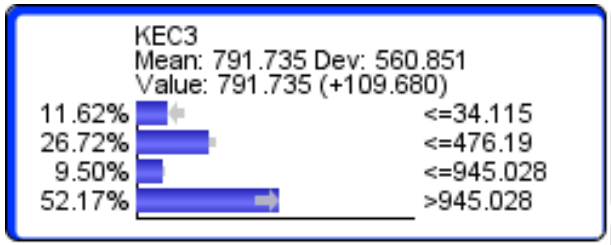
BN ITS abstracted skin sensitization process embedded into a decision analytic tool

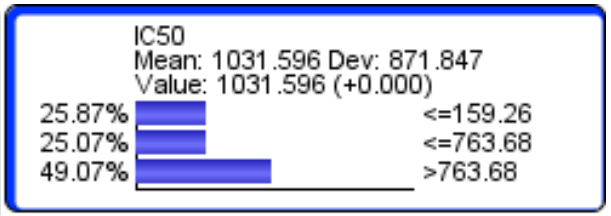


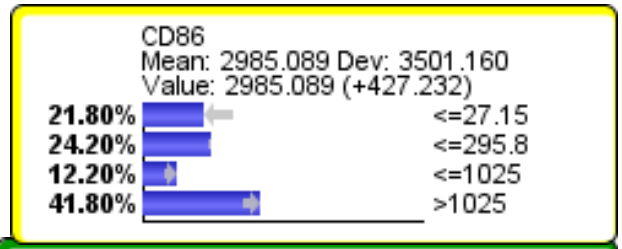
Data set of n=142 (124, 18)

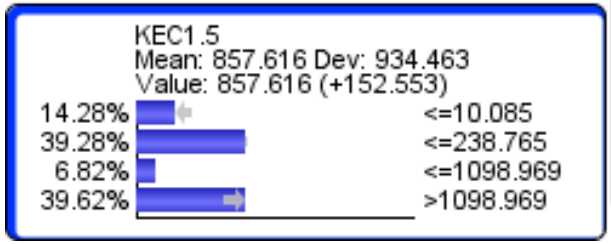


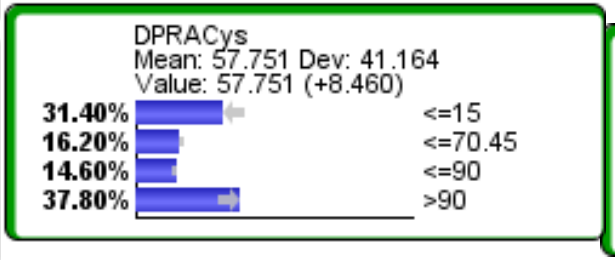


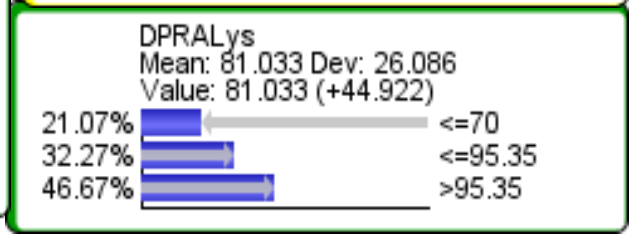


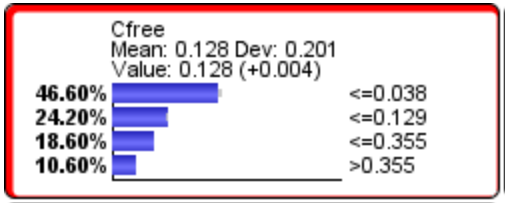


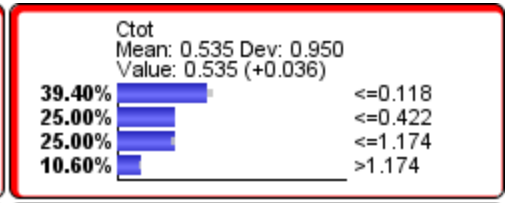


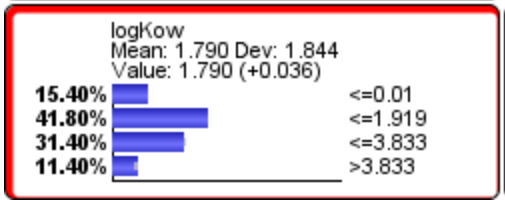


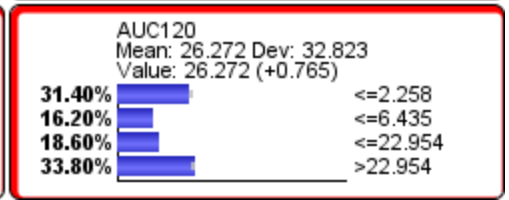




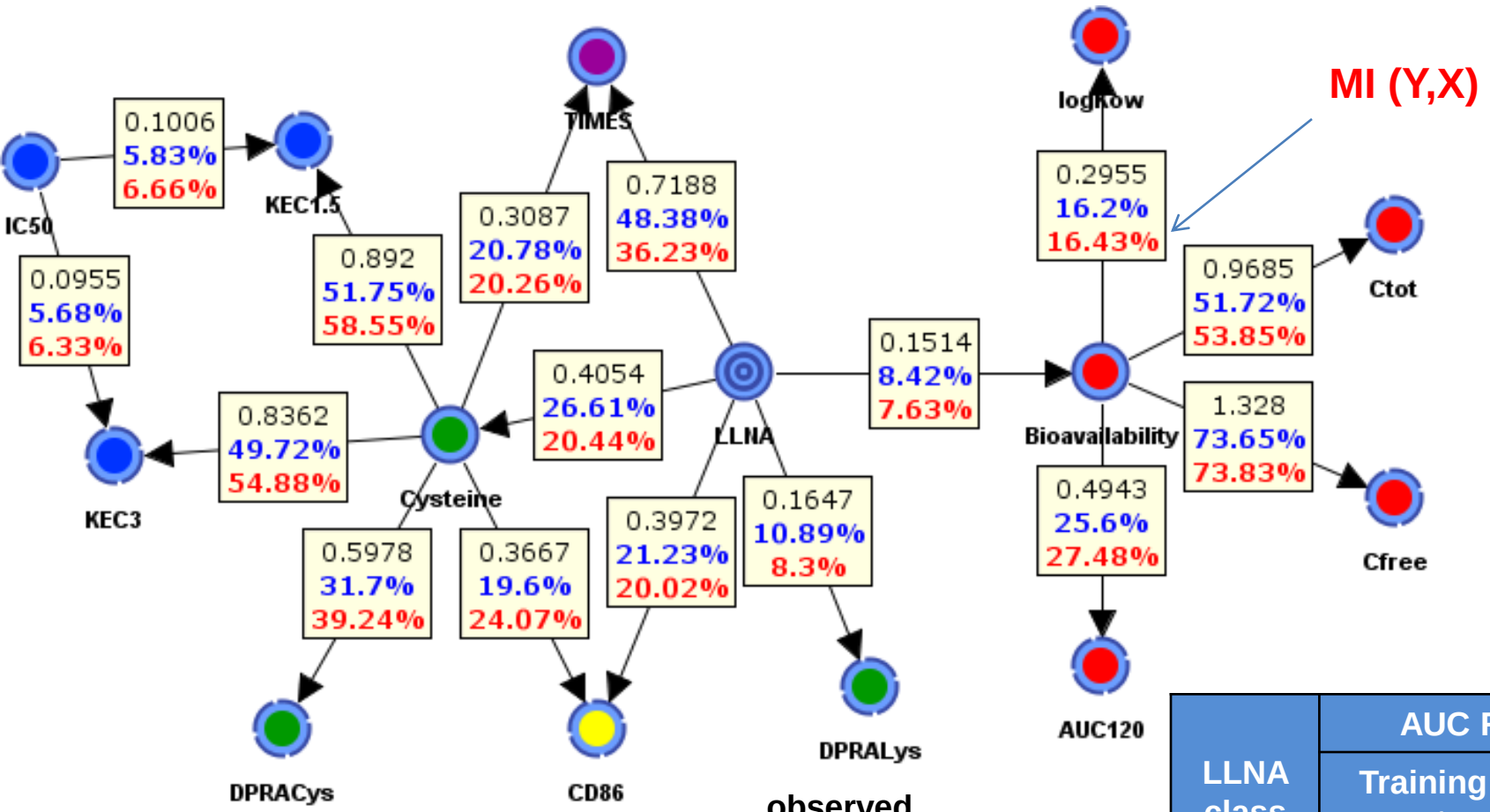








BN ITS test set

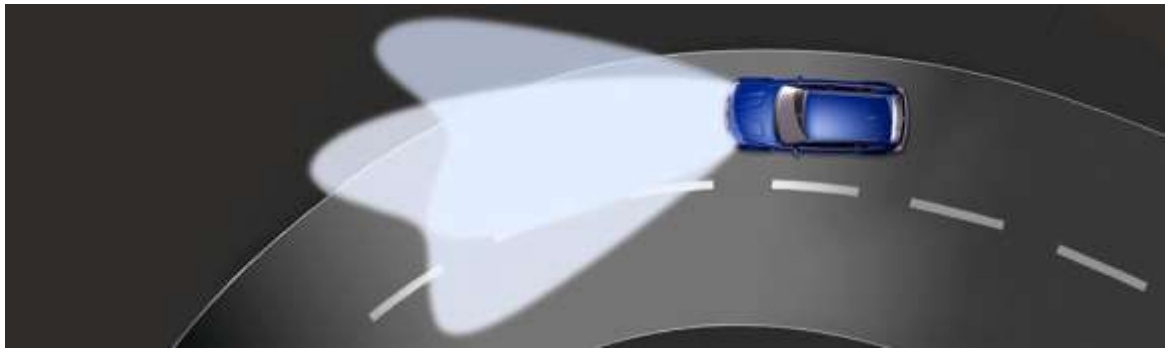


observed

predicted	NS (6)	W (6)	M (4)	S(3)
NS (7)	6	1	0	0
W (4)	0	4	0	0
M (5)	0	1	3	1
S (3)	0	0	1	2

LLNA class	AUC ROC (%)	
	Training set N=124	Test set N=18
NS	92	100
W	92	82
M	76	73
S	81	58

Value of Information (VoI) driven Testing Strategy



- To identify **optimal testing strategy BN ITS uses** “**One step look – ahead hypothesis**”. It amounts to computing the mutual information MI(X, Y) for all possible observations X and choosing the one that has the highest MI with the hypothesis variable Y.

- Mutual Information MI (X, Y)- "the amount of uncertainty in *Y* which is removed by knowing *X*". MI(Y,X) = H(Y)-H(Y|X) where H (Y) is entropy of Y. Relative MI (MI(X,Y)/H(Y)) informs about % of uncertainty in Y removed by X.

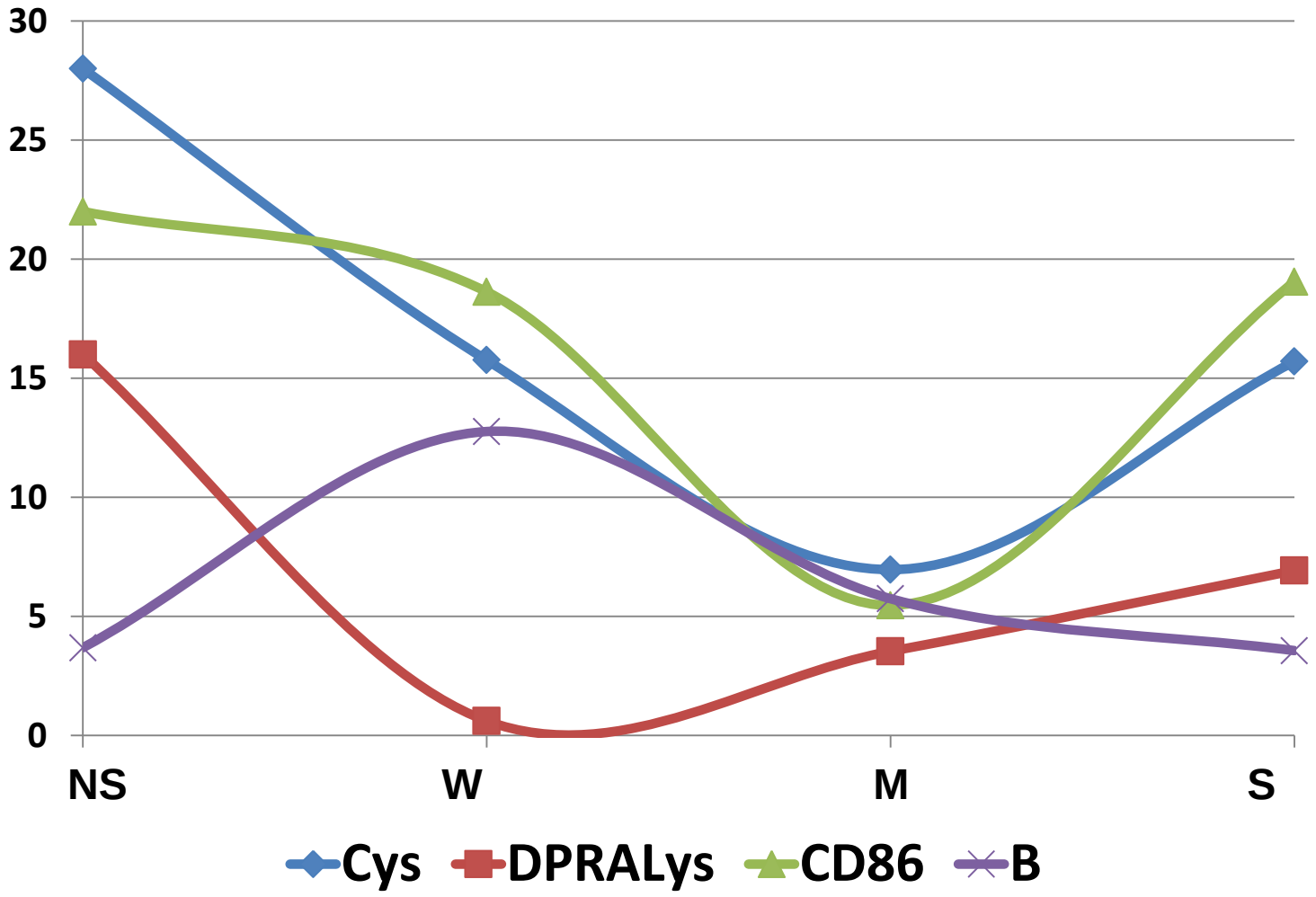
Learnings from BN ITS-1

- A single generic set of tests as in vivo replacement strategy is unlikely to be the most effective.

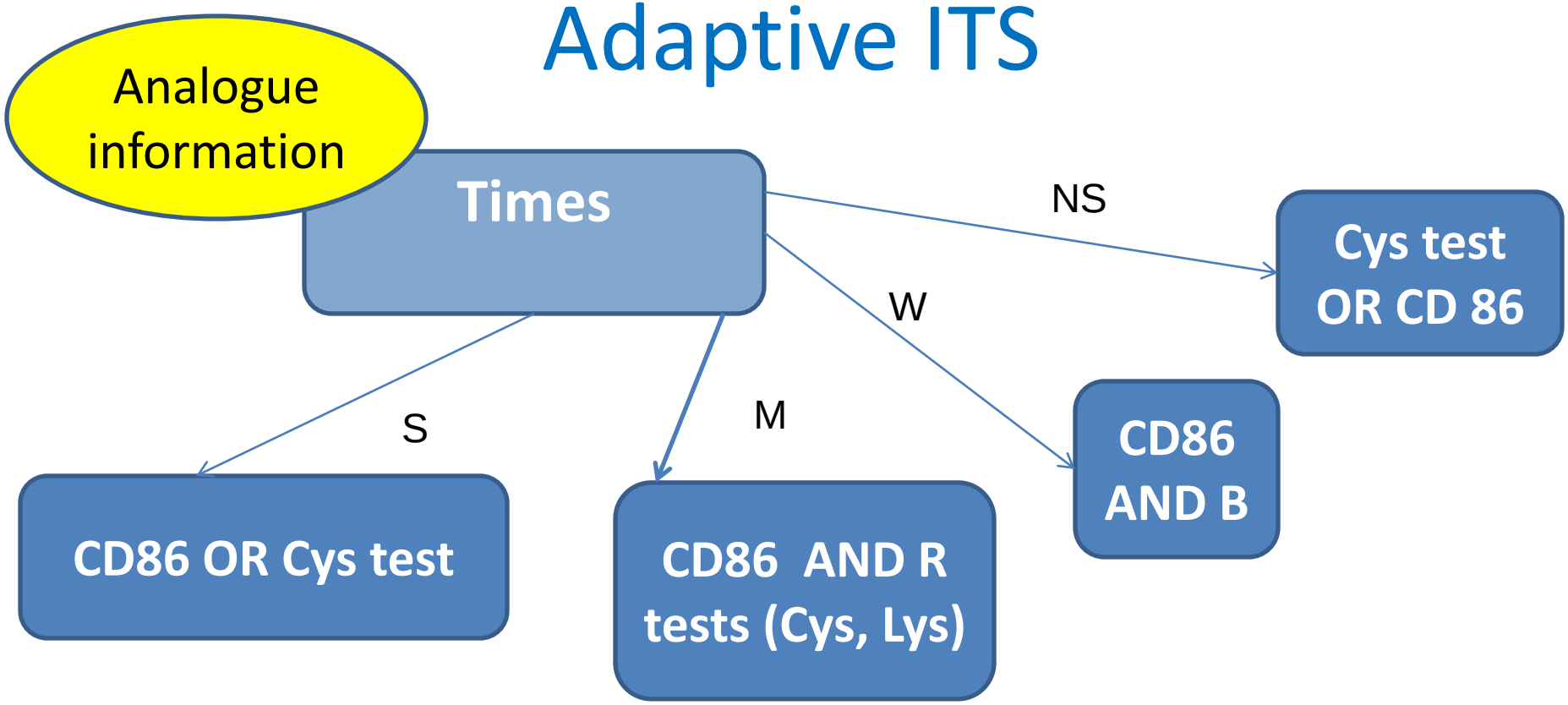
- **Effective strategy** depends on the initial information, and changes based on additional information. Thus it should be **adaptive, flexible, and Value of Information (VoI) driven.**

Jaworska, Harol, Kern, Gerberick, Altex 2011 Integrating Non-Animal Test Information into an Adaptive Testing Strategy – Skin Sensitization Proof of Concept Case

Mutual information (LLNA, …)



Adaptive ITS



•BN ITS adapts to a generated *in silico/* analogue hypothesis about LLNA potency.

- •Refinement by adding chemistry based rules ongoing

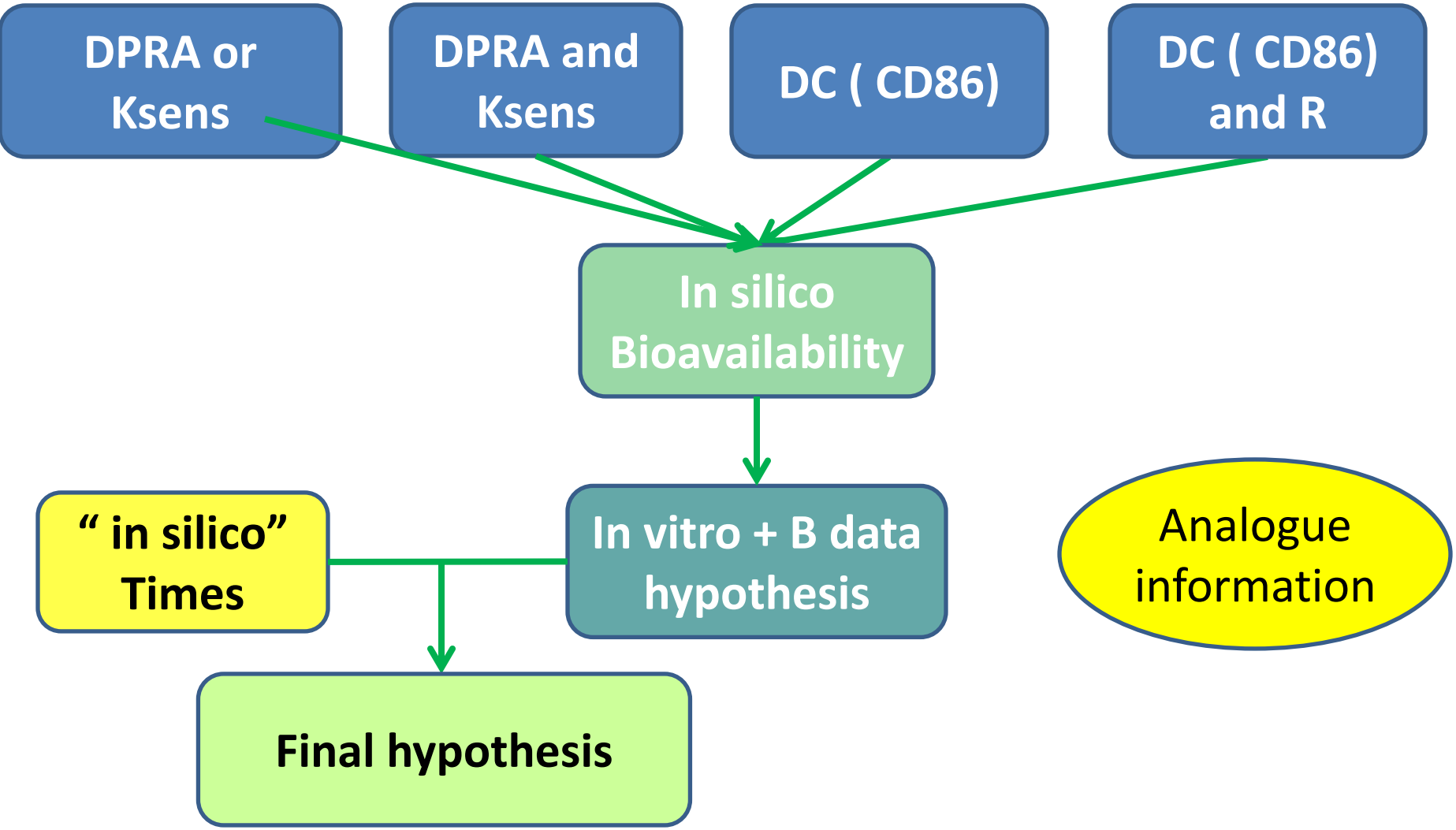
•Depending on the hypothesis, different in vitro tests are recommended as confirmatory tests.

• Current data suggests use of R and CD86 simultaneously to test NS and S hypothesis is not effective.

Flexible ITS

Many ways to get to the final decision

Many strategies with equivalent outcome BUT different cost



Flexible ITS

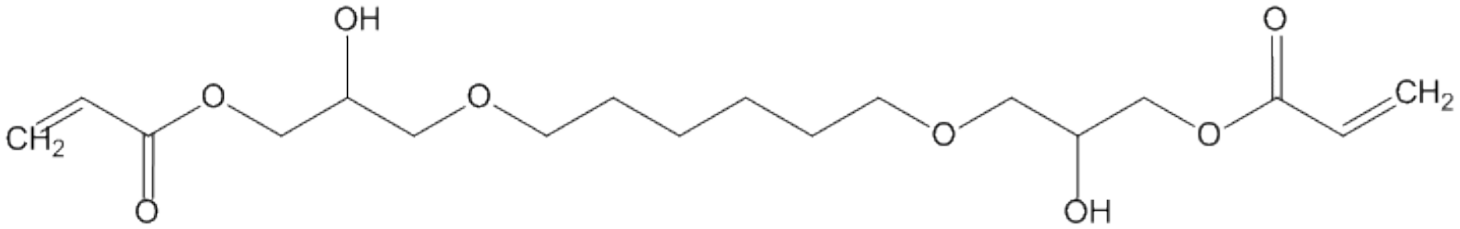
performance with partial evidence on test set (n=18)

Case	TIMES	B	CD86	Cys	Lys	Precision NS/W/M/S %	Precision NS/S %
1	X	X	√	√	√	58	100
2	X	√	X	√	√	63	100
3	X	√	√	X	√	63	100
4	X	√	√	√	X	69	100
5	X	X	√	X	X	63	100
6	X	X	X	√	√	69	100
7	x	√	√	√	√	69	100
8	√	√	√	√	√	84	100

How can we use the ITS tool in practice?

- Setting success criteria
  - Performance related
  - Features related (like ability to explain)
- How does the BN prediction compare with our “classical” SAR approach?
- 1 case study

Case study: 2-Propenoic acid bis-ester



Available Data	
DEREK	Unsaturated Ester
TIMES	(non sensitizer)
Toxtree	Michael acceptor (MA) alert
Analogues	Weak to moderate potencies
DPRA	**High reactivity**

- SAR:
  - DPRA suggests hypothesis of Skin sensitizer
  - Due to high reactivity but MA alert, conservative estimation of moderate sensitizer was made.

Case study: BN ITS

Evidence	NS	Weak	Moderate	Strong
DPRA (Cys/Lys)	2	11	27	**59**
Cys/Lys/B	1	13	24	**62**
Cys/Lys/B/ MA	1	13	**54**	32
Times - M	**80**	7	9	4
All w/o MA	29	21	38	12
All/MA	29	**51**	8	12

BN ITS with all the same evidence allows to develop a hypothesis that the chemical is a weak sensitizer. If we want to continue based on VoI CD86 will be most useful:

CD86 <= 30 mM	6	32	**41**	20
CD86 <= 300 mM	5	**68**	25	1
CD86 > 300 mM	**70**	33	1	1

Summary

We formalized process of WoE into a qWoE and developed a tool to run qWoE and ITS. Practical evaluation/deployment are ongoing.

- Conflicting evidence
- Different set of evidence
- Bioavailability
- Can guide testing

We are developing chemistry based rules for a refined interpretation of both individual assays and in vivo potency

Thank you for your attention