CASE STUDY 5

L'OREAL APPROACH & DECISION STRATEGY

ALTERNATIVES FOR SKIN SENSITIZATION TESTING

Joint Cefic/Cosmetics Europe/EPAA Workshop

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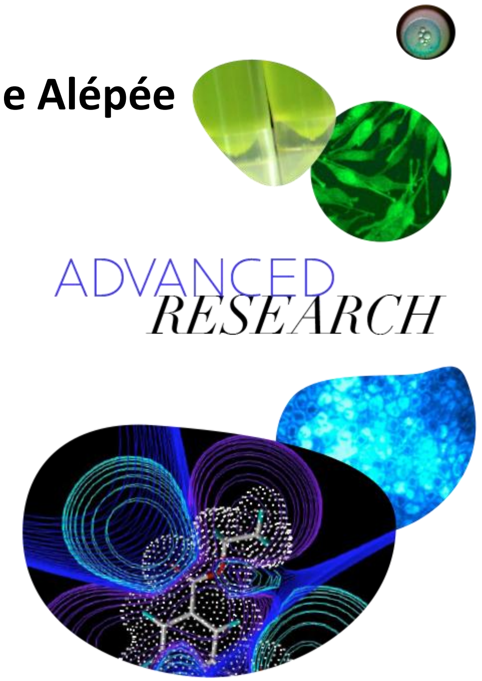
Silvia Teissier / Nathalie Alépée



CRITERIA AND NEEDS FOR AN IDEAL INDUSTRY-APPLICABLE ITS

- **Based on robust/reliable data → Validated assays (internally and/or formally evaluated)**
- **Mechanistic-based → Integrating data from different key events**
- **Well defined Predictive Models → Comprehensive and statistically validated**

  (learning sets ≠ validation sets / avoid statistical bias through unbalanced sets)
- **Prediction with confidence indication → Probability of S/NS**
- **Has to be « toxicologist-/ user friendly », not dependent on particular / subjective expertise or interpretations**
- **Applicable to the wide physicochem. diversity of cosmetic ingredients**
- **Accessible assay (Availability/Cost/Time…)**

DIFFERENT APPROCHES TO BUILD SUCH AN ITS

Selection of Input Methods / Parameters	Input Data	Approach to build Prediction models
A priori selection empiric, pragmatic, mechanism-based, only if validated	**Gold Standards References** LLNA, human only few cosmetic ingredients	**Choice for a particular approach** - Empiric (BASF) - Decision-Tree (RIVM/Kao) - Mechanism-based: Bayesian (P&G) - Blackbox : NeuronalNetworks (Shiseido)
Non *à priori* selection High Content parameters, statistical driven selection	**+ Real-Life** Substances from cosmetic industry (LLNA)	**Integration of several models** Score Method, Bayesian, Sparse PLS SVM, Boosting

THE STATISTICAL APPROACH

37 Input variables
on
165 substances
with LLNA conclusion (S NS)

Bayesian

Conditional probability

Score Method

Flexibility and expertise

Sparse PLS DA

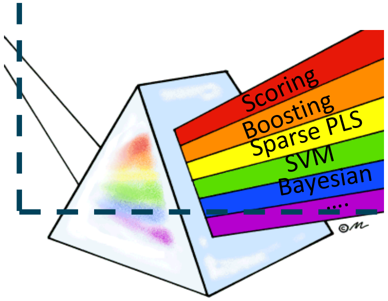
Accepting the colinearity between the explanatory parameters

Boosting

Combination of several decision trees

SVM

Transformation of the data to avoid problems of non linearity



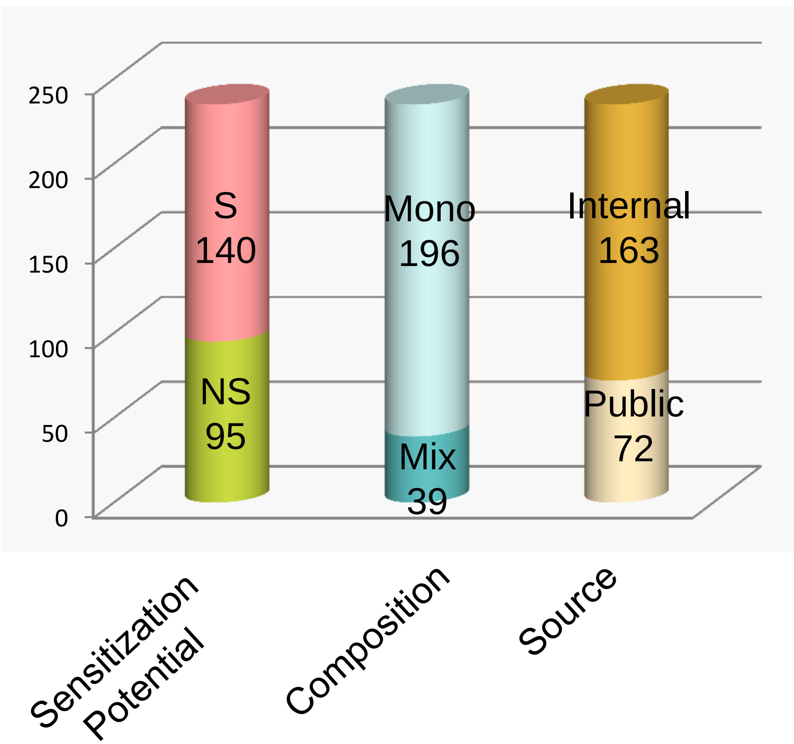
Meta Model

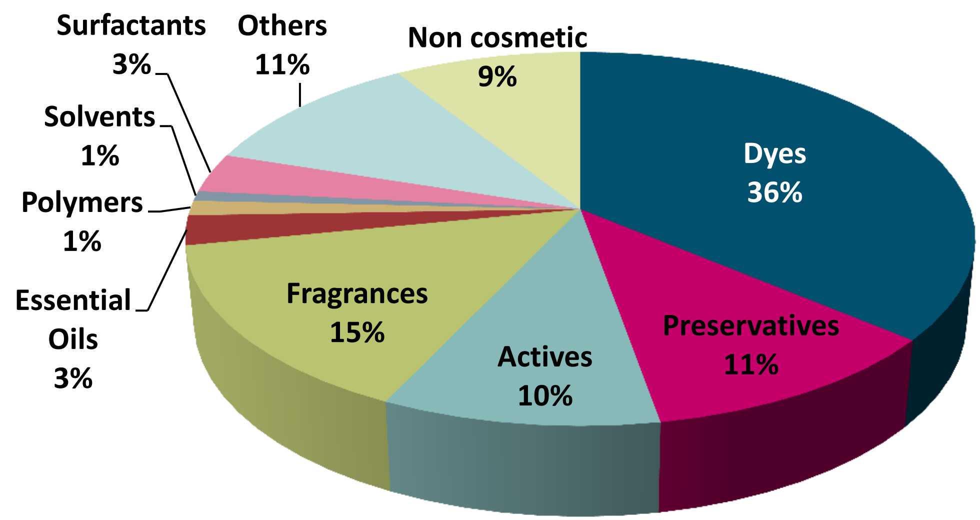
Optimal Final Prediction on 10 variables
2 classes : S / NS

C. Gomes et al, Compstat 2012

LEARNING AND VALIDATION SET

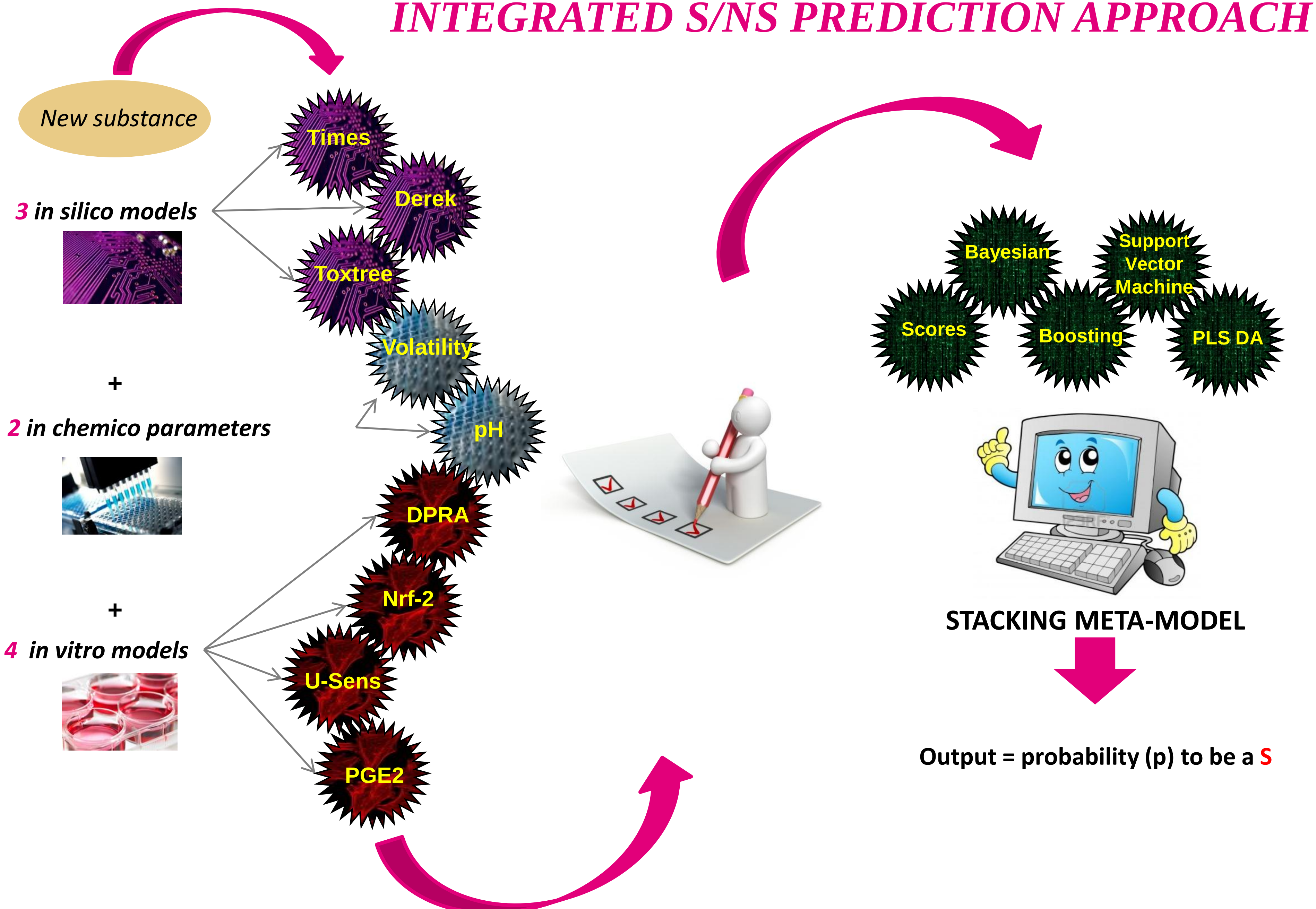
DISTRIBUTION & CHARACTERIZATION OF 165 +70 SUBSTANCES





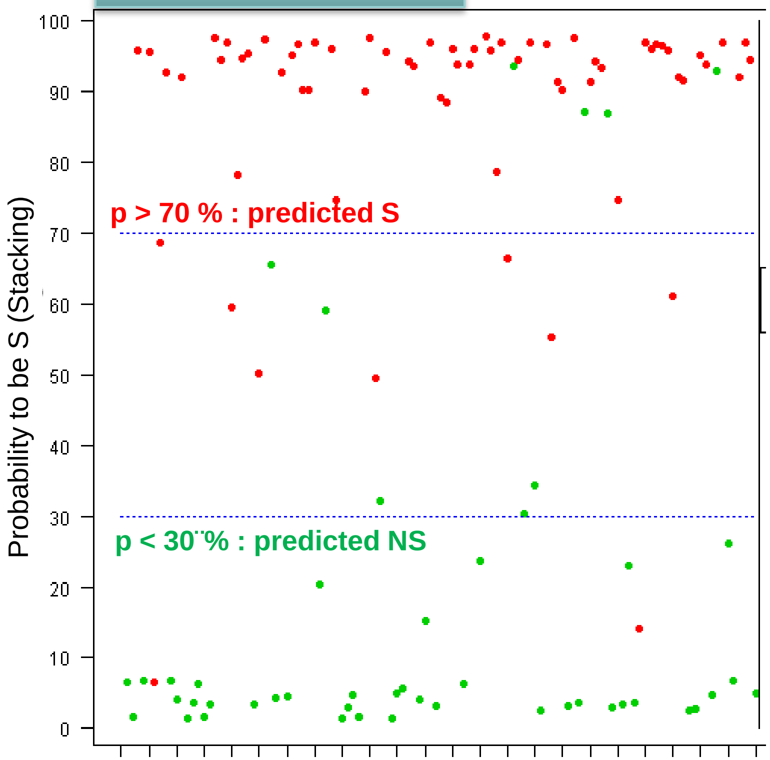
Ingredient category

INTEGRATED S/NS PREDICTION APPROACH

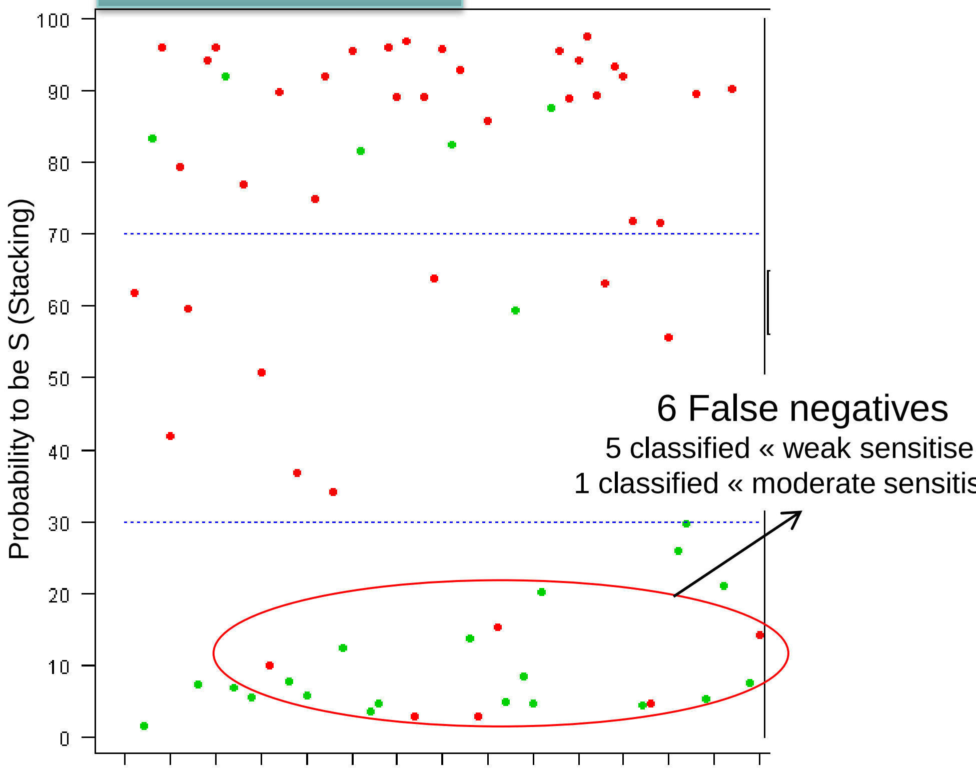


PERFORMANCES: NUMBERS AND FACTS

Learning Set (n=165)



Validation Set (n=70)

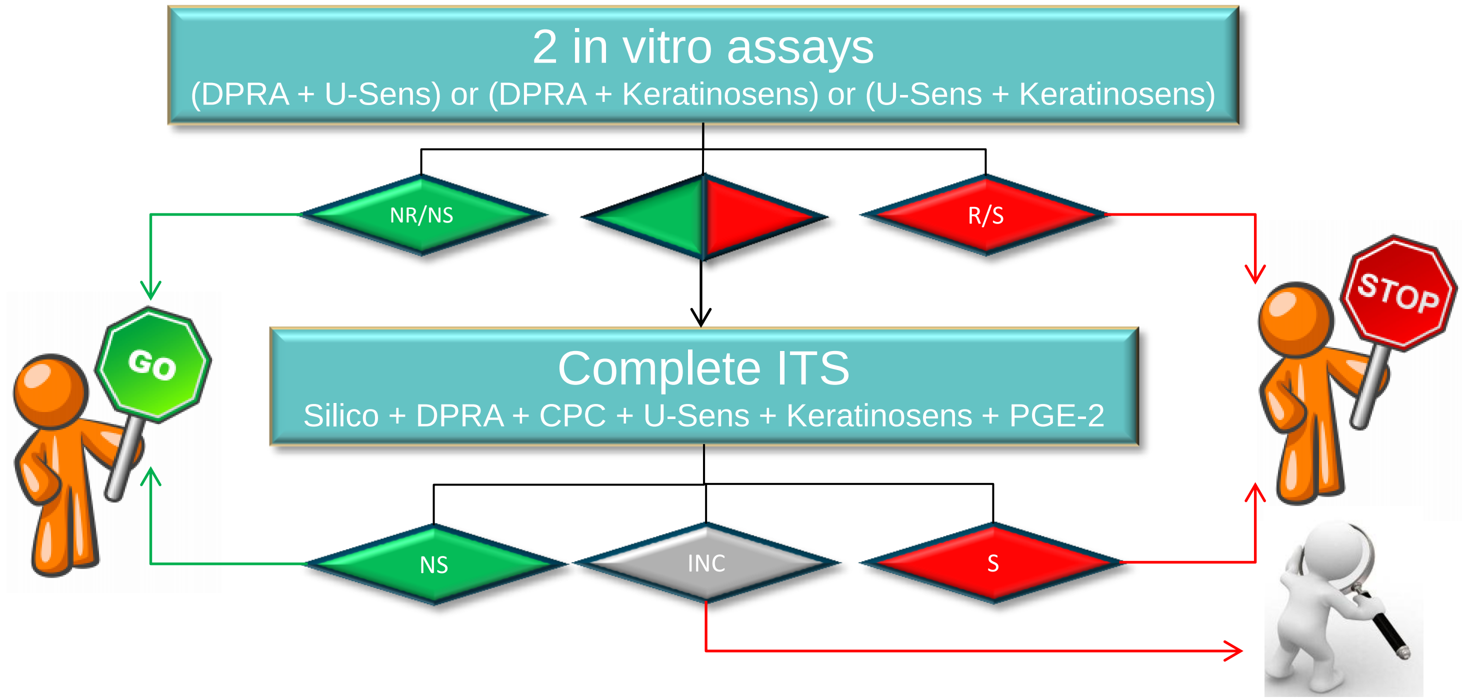


PREDICTIVITY on Learning Set
Concordance = 94 %
Sensitivity = 97 %
Specificity = 91 %

ACCURACY on Validation Set
Concordance = 81%
Sensitivity = 82 %
Specificity = 80 %

FROM A COMPLETE/CUMBERSOME ITS TO A MORE PRAGMATIC ITS

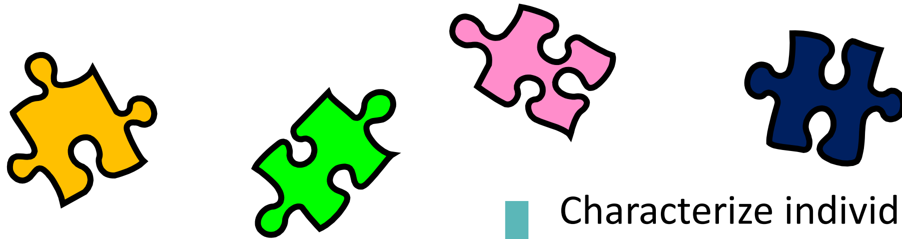
Aims / Needs : → reduce de number of assays to be done → time / cost
→ Focus on assays undergoing ‘ VAM validation → external recognition
→ Preserve the high confidence in the prediction → performance



Comparison between the one-step ITS and the 2-steps ITS		
Accuracy: = or -2 %	**Sensitivity : = or -1 %**	**Specificity : = or -4 %**
INC : -4% to -9% increase of clear-cut conclusions		**Number of in vitro-assays: till- 25%**

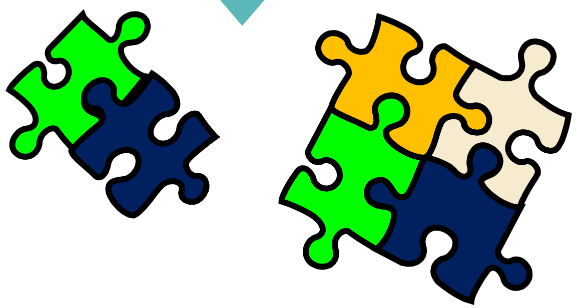
L'ORÉAL
Recherche & Innovation

DECISION STRATEGY



Characterize individual tools
Combining tools

Building an integrated model



✓ Prediction of hazard
with a high degree of confidence

NS

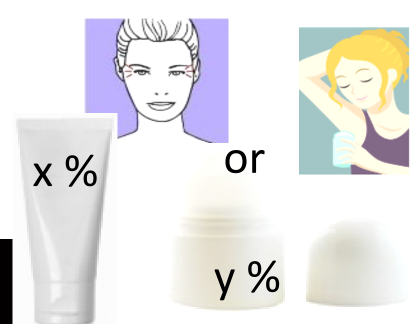
Quantitative parameters

S

Additional parameters
e.g. SensIS, KineticDPRA,
T cells…

Bioavailibility based on
exposure conditions

Potency Information
for Risk Assessment



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Thank you for your attention !!