MATRIX CASE STUDY SUMMARY IDEA WORKSHOP 16-17 MAY 2018, BRUSSELS

Case Study	Read Across Applied?	Information sources: In silico	Information sources: In chemico	Information sources: In vitro	Information sources: Other	Data Interpretation Procedure (DIP) Applied	Basis of dose selection	Benchmark data used for DIP (e.g. LLNA/Human)	Proprietary Element	Sources of uncertainty	Limitations/Areas of further study
1 Natsch	Yes, for uncertainty analysis	TIMES, for domain attribution, not for prediction	LC-MS assay, fluorescent kinetic peptide assay, DPRA, amine binding assay	KeratinoSen®, metabolism assays	No	Regression models (domain specific and global)	According to SOP or Test Guidelines.	LLNA	No	Unknown, but uncertainty assessed by specific workflow	For typical chemical classes of fragrance ingredients probably reliable, how to assess new chemistry with little benchmark data needs further work
2 Kern	Not required, but can be used, to increase confidence in prediction.	TIMES input, Phys chem properties calculations	DPRA	KeratinoSens®, h-CLAT	Analogue data can be incorporated if wanted.	BN-ITS3 (Bayesian network)	According to SOP or Test Guidelines.	LLNA	No, but software requires licence. Will be adapted. There is a public version.	As usual: variability of assays, knowledge around AOP and BN construction.	Applicability domain (water solubility, cytotoxicity, fully ionized compounds). Define rules for pEC3 to EC3 conversions and cut off values for BF confidence estimation. Define rules on how to input analogue data to reduce uncertainty.
3 Hirota	Yes	TIMES-M/ Toxtree (for ANN) DEREK, original in silico skin absorption model and OECD tool box (for read across)	DPRA	h-CLAT, KeratinoSens®	No	ANN (artificial neural network)	Dose setting of in vitro tests was determined by each of OECD Guidelines (DPRA, KeratinoSens® and h-CLAT)	LLNA	ANN: No patent; TIMES, DEREK need licence fee; KeratinoSens® available in CROs	ANN prediction includes uncertainty (but covered by read across)	Mixtures, and very new chemicals without human exposure history

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5 Carsten	Yes, for interpretation purposes	OECD toolbox	DPRA; PPRA	CoCAT; KeratinoSens®; h-CLAT	Metabolism and reactivity prediction	Linear interpolation and DC-ITS (Bayesian network)	According to SOP or Test Guidelines.	LLNA	No	Bayesian net and weighing approach; danger signals	Applicability domain; activation patterns and human conditions
6 Gilmour	Yes, within IATA Within DA – under evaluation	Yes, within IATA Within DA – under evaluation	Within DA – DPRA	Within DA – h-CLAT; KeratinoSens®; USENS	Within DA – HRIPT; LLNA	SARA	According to SOP or Test Guidelines.	Human: probability of inducing sensitisation in population under conditions of HRIPT	No, but software required; Publication in preparation	SARA model - Human variability; Concordance in data; relationships between data; other areas of uncertainty addressed by SAFs	Small number of chemicals in HRIPT dose response predictions. Addition of new input data (in silico / in chemico in vitro). Applicability domain. How to address other areas of uncertainty in RA. Clinical benchmarking
7 Groux	Yes	No	No	SENS-IS data	No	Direct dose measurement or ranking in comparison to other chemicals	According to SOP 50, 10, 1 and 0.1%	Public LLNA and Human	Yes	For the ranking ongoing process	Include more chemicals in the ranking process, analysis of Chemical reactivity based on chemical group could help