

DESIGNATHON - Evolutionary Regulatory Toxicology Approach

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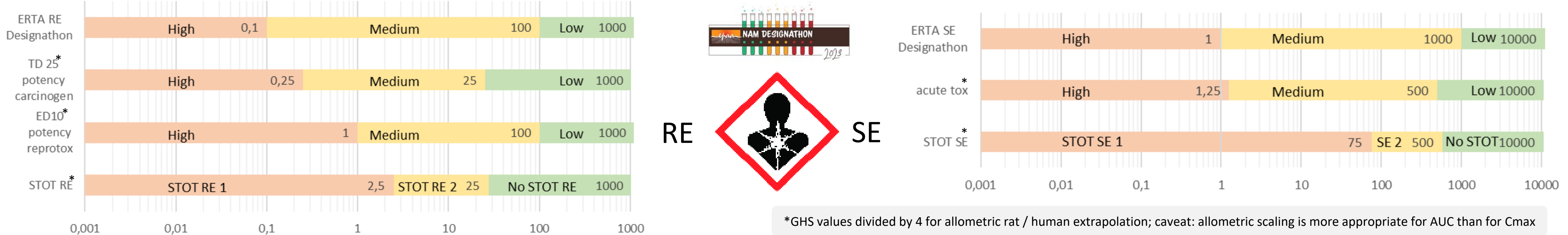
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Concept

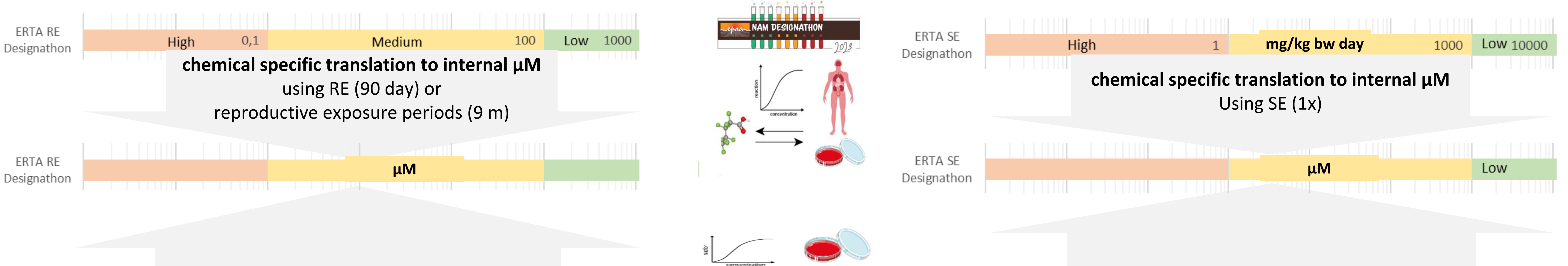
- science will ever continue to discover new mechanisms/MoAs/NAMs; use NAMs now & integrate new NAMs along scientific evolution
 - use potency (BMDs) from in vitro & in silico methods as sole criteria for categorization
 - demonstrate approach with DNT IVB, to be amended with further in vitro & in silico data streams

Approach

1) adapt/harmonize current Repeated Exposure (RE) & Single Exposure (SE) GHS category boundaries [mg/kg bw day] to 3 new categories



2) for each chemical translate the category boundaries (single and repeated exposure) to internal μM concentrations, using high-throughput PBK (PK-Sim) modeling. The internal dosimetries used are Cmax and time-weighted average (TWA) within maternal plasma and total fetal compartment



3) generate in vitro/in silico BMDs and match chemical specific in vitro - in silico BMDs with chemical specific new category boundaries

4) provide uncertainty for match with 3 new categories, using a) BMD / category border ratios & b) WHO APROBA human variability data

abbrevi- ation	summary category	Exposure Boundary/BMC Ratios												Categories						Quantiles for (Exposure Boundary/BMC uncertainty*human variability)																																
		Repeated Exposure: daily for 9 months				Single Exposure				Repeated Exposure: daily for 9 months				Single Exposure		Repeated Exposure: daily for 9 months			Single Exposure																																	
		0.1 mg/kg bw d		100 mg/kg bw d		1 mg/kg bw d		1000 mg/kg bw d		0.1 mg/kg bw d		100 mg/kg bw d		1 mg/kg bw d		1000 mg/kg bw d																																				
		Cmax	fetal	maternal	TWA	Cmax	fetal	maternal	TWA	Cmax	fetal	maternal	TWA	Cmax	fetal	maternal	TWA	Cmax	fetal	maternal	TWA	Cmax	fetal	maternal	TWA	Cmax	fetal	maternal	TWA	Cmax	fetal	maternal	TWA																			
		ratio_re_0	ratio_re_0	ratio_re_0	ratio_re_0	ratio_re_10	ratio_re_10	ratio_re_10	ratio_re_10	ratio_se_1	ratio_se_1	ratio_se_10	ratio_se_10	category_re	category_re	category_re	category_re	category_se	category_se	quantiles_re_0	quantiles_re_0	quantiles_re_0	quantiles_re_0	quantiles_re_10	quantiles_re_10	quantiles_re_10	quantiles_re_10	quantiles_se	quantiles_se	quantiles_se	quantiles_se																					
		1mg_mater	1mg_fetal	1mg_materna	1mg_fetal	0mg_mater	0mg_fetal	0mg_materna	0mg_fetal	1mg_mater	1mg_fetal	1mg_materna	1mg_fetal	maternal	fetal	maternal	fetal	maternal	fetal	maternal	fetal	maternal	fetal	maternal	fetal	maternal	fetal	maternal	fetal	maternal	fetal	maternal	fetal	maternal	fetal																	
EDP	specific hit	0.35	0.57	0.24	0.43	100.16	161.06	67.69	121.43	1.18	0.44	51.61	29.74	RE_MEDIUM	RE_MEDIUM	RE_MEDIUM	RE_MEDIUM	SE_HIGH	SE_MEDIUM	P05 = 0.00316;	P50 = 0.0188;	P95 = 1;	P05 = 1;	P50 = 0.133;	P95 = 0.00759;	P05 = 1;	P50 = 0.999;	P95 = 1;	P05 = 0.00316;	P50 = 0.0188;	P95 = 1;	P05 = 1;	P50 = 0.133;	P95 = 0.00759;	P05 = 1;	P50 = 0.999;	P95 = 1;															
MAB	unspecific hit	0.24	0.22	0.05	0.12	243.31	224.21	50.33	122.39	2.32	1.24	2317.65	1238.37	RE_MEDIUM	RE_MEDIUM	RE_MEDIUM	RE_MEDIUM	SE_HIGH	SE_HIGH	P05 = 5.9e-05;	P50 = 0.0241;	P95 = 0.457	P05 = 3.75e-05;	P50 = 0.0185;	P95 = 0.414	P05 = 1;	P50 = 0.852;	P95 = 0.998	P05 = 1;	P50 = 0.381;	P95 = 0.981	P05 = 1;	P50 = 0.0475;	P95 = 0.981	P05 = 1;	P50 = 0.0475;	P95 = 0.981	P05 = 1;	P50 = 0.0475;	P95 = 0.981	P05 = 1;	P50 = 0.0475;	P95 = 0.981									
TDCPP	specific hit	0.02	0.01	0.01	0.01	13.26	4.36	6.62	3.40	0.17	0.04	14.08	3.97	RE_MEDIUM	RE_MEDIUM	RE_MEDIUM	RE_MEDIUM	SE_MEDIUM	SE_MEDIUM	P05 = 1.34e-13;	P50 = 1.77e-07;	P95 = 0.00203	P05 = 6.87e-19;	P50 = 2.32e-11;	P95 = 6.38e-06	P05 = 0.886;	P50 = 0.973;	P95 = 1	P05 = 1.78e-06;	P50 = 1.74e-11;	P95 = 0.421	P05 = 1.74e-11;	P50 = 0.9;	P95 = 0.0143	P05 = 1.78e-06;	P50 = 1.74e-11;	P95 = 0.421	P05 = 1.74e-11;	P50 = 0.9;	P95 = 0.0143	P05 = 1.78e-06;	P50 = 1.74e-11;	P95 = 0.421	P05 = 1.74e-11;	P50 = 0.9;	P95 = 0.0143						
SDF	no hit	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	RE_LOW	RE_LOW	RE_LOW	RE_LOW	SE_LOW	SE_LOW	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.									
TBT	no hit	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	RE_LOW	RE_LOW	RE_LOW	RE_LOW	SE_LOW	SE_LOW	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.									
PFOA	no hit	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	RE_LOW	RE_LOW	RE_LOW	RE_LOW	SE_LOW	SE_LOW	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.									
SBZ	no hit	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	RE_LOW	RE_LOW	RE_LOW	RE_LOW	SE_LOW	SE_LOW	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.									
CBR	specific hit	0.04	0.02	0.00	0.00	35.52	17.28	3.86	2.51	0.35	0.17	297.69	144.39	RE_MEDIUM	RE_MEDIUM	RE_MEDIUM	RE_MEDIUM	SE_MEDIUM	SE_MEDIUM	P05 = 6.28e-12;	P50 = 5.31e-15;	P95 = 0.994;	P05 = 0.937;	P50 = 0.00011;	P95 = 1.46e-06;	P05 = 1.46e-06;	P50 = 1.74e-11;	P95 = 0.9;	P05 = 1.46e-06;	P50 = 1.74e-11;	P95 = 0.9;	P05 = 6.28e-12;	P50 = 5.31e-15;	P95 = 0.994;	P05 = 0.937;	P50 = 0.00011;	P95 = 1.46e-06;	P05 = 1.46e-06;	P50 = 1.74e-11;	P95 = 0.9;	P05 = 1.46e-06;	P50 = 1.74e-11;	P95 = 0.9;	P05 = 6.28e-12;	P50 = 5.31e-15;	P95 = 0.994;	P05 = 0.937;	P50 = 0.00011;	P95 = 1.46e-06;			
GFA	no hit	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	RE_LOW	RE_LOW	RE_LOW	RE_LOW	SE_LOW	SE_LOW	P05 = 2.71e-06;	P50 = 1.84e-08;	P95 = 0.000527	P05 = 1.84e-08;	P50 = 1;	P95 = 0.777	P05 = 0.777;	P50 = 0.413;	P95 = 1	P05 = 2.71e-06;	P50 = 1.84e-08;	P95 = 0.000527	P05 = 1.84e-08;	P50 = 1;	P95 = 0.777	P05 = 0.777;	P50 = 0.413;	P95 = 1	P05 = 2.71e-06;	P50 = 1.84e-08;	P95 = 0.000527	P05 = 1.84e-08;	P50 = 1;	P95 = 0.777	P05 = 0.777;	P50 = 0.413;	P95 = 1						
MNZ	unspecific hit	0.01	0.00	0.00	0.00	5.64	2.70	1.16	2.34	0.05	0.00	53.18	3.56	RE_MEDIUM	RE_MEDIUM	RE_MEDIUM	RE_MEDIUM	SE_MEDIUM	SE_MEDIUM	P05 = 3.79e-20;	P50 = 2.45e-12;	P95 = 1.3e-06	P05 = 2.56e-24;	P50 = 1.43e-15;	P95 = 0.991;	P05 = 0.198;	P50 = 4.93e-10;	P95 = 1.06e-22;	P05 = 4.93e-10;	P50 = 2.63e-14;	P95 = 1;	P05 = 3.79e-20;	P50 = 2.45e-12;	P95 = 1.3e-06	P05 = 2.56e-24;	P50 = 1.43e-15;	P95 = 0.991;	P05 = 0.198;	P50 = 4.93e-10;	P95 = 1.06e-22;	P05 = 4.93e-10;	P50 = 2.63e-14;	P95 = 1;	P05 = 3.79e-20;	P50 = 2.45e-12;	P95 = 1.3e-06	P05 = 2.56e-24;	P50 = 1.43e-15;	P95 = 0.991;	P05 = 0.198;	P50 = 4.93e-10;	P95 = 1.06e-22;

Result

- the presented categorization relates to the protection level of the current GHS classification systems
 - all chemicals with DNT hits are categorized in the MEDIUM or HIGH category
 - only for 2 chemicals the category is different between RE and SE
- similar categorization, if internal exposure is assessed for maternal plasma or for the total fetal compartment, except for one chemical in SE category (HIGH vs MEDIUM); but considering Exposure Boundary/BMC ratios, this chemical appears as a borderline chemical between HIGH and MEDIUM for SE classification
 - for all the tested chemicals using Cmax or TWA, results in the same categorization
- for DNT the Cmax may be most relevant for SE and RE, since an exposure in a short developmental time window may lead to a long lasting effect on the organism; in contrast for other toxicities (not yet covered in our demonstration) both, Cmax and TWA, may be relevant metrics; e.g. for carcinogenicity, TWA may be relevant due to the chronic stress important for tumor development
 - approach shall be augmented by data streams from other chemicals and other mature in vitro & in silico methods results

Uncertainty

- uncertainty for categorization can be expressed as Exposure Boundary/BMC ratios for each chemical (see blue cells)
 - uncertainty for categorization can be expressed as the fraction of the population below the exposure boundary (P50) with a 90% CI ranging from P05 to P95 (see turquoise cells)
 - Alternatively or in addition to the WHO 2017 approach used here, PBK models could be used to calculate kinetic variability between humans
 - PBK models can be parameterized with a multitude of inputs parameters and QSARs. The uncertainty in the simulations resulting from different parameterization strategies can also be propagated into the internal dosimetries