The Final EUTOXRISK Symposium 18

Chemical-induced Mitochondrial Toxicity
Mode of action based biological read-across

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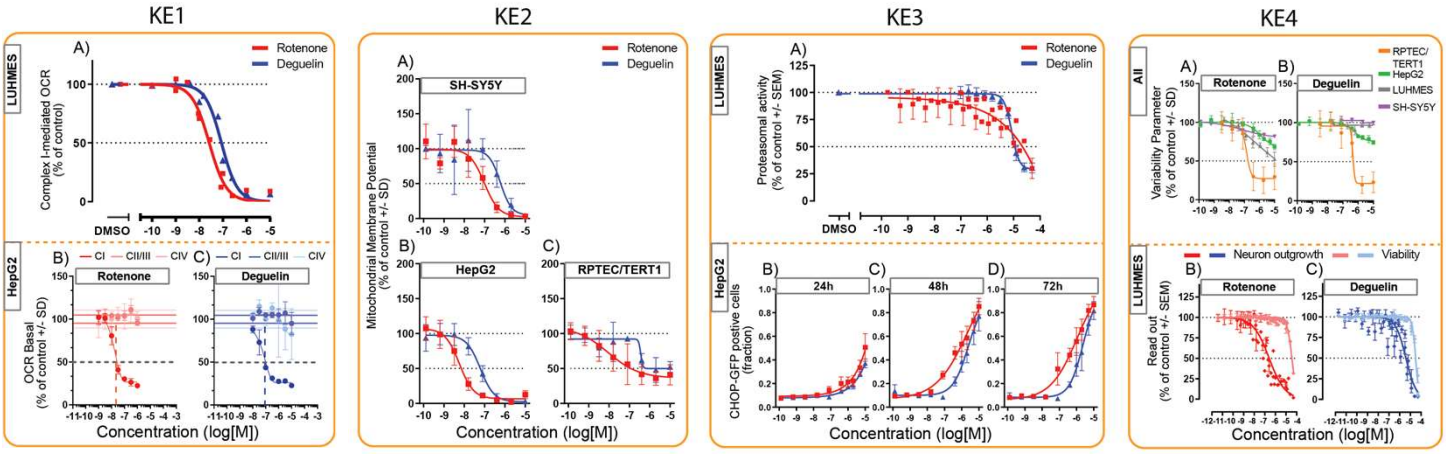
Case Study Testing Approach

Summary of all test system data generated for the rotenoids and the strobilurins case studies for data gap filling for read-across. The data indicate BMC values for individual test systems. The table represents an straightforward data summary to compare source and target compounds.

Summary of data gap filling				RX complex I inhibition: rotenoids		RX complex III inhibition: strobilurins					
Type of chemical				Target	Source1	Target	Source1	Source2	Source3	Source4	Reference
Chemical				Deguelin	Rotenone	Azoxystrobin	Pyraclostrobin	Picoxystrobin	Trifloxystrobin	Kresoxim-methyl	Antimycin A
	Event	Assay									
in silico	Chemical specific	Similarity 3D		structural modeling complex I	structural modeling complex I	1.00	0.76	0.65	0.70	0.61	NT
		Permeability (*in humans*)		not in report	not in report	High	High	High	High	High	High
		Absorption (*in humans*)		not in report	not in report	High	High	High	Low	Moderate	Low
		Distribution (*in humans*)		not in report	not in report	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
		Metabolism (*in humans*)		not in report	not in report	Extensive	Extensive	Extensive	Extensive	Extensive	Extensive
		Excretion (*in humans*)		not in report	not in report	Moderate	Low	Low	Moderate	High	Low
	Key event	Tissue	Assay	Value		Value					
in vivo	AO	Brain	*in vivo* indication	# = data gap	Degeneration nigrostriatal dopaminergic neurons	# = data gap	Not detected in acute and repeat-dose neurotox. studies	Not detected in standard repeat-dose studies. No neurotox studies available	Not detected in acute neurotox study and neurotox (evaluation of 90 day repeat study)	Not detected in acute and repeat-dose neurotox. studies	No data
in vitro	KE1	LUHMES	OCR intact (*)	1.00E+02	2.50E+01	≤ 5.00E+4	≤ 5.00E+4	≤ 5.00E+4	≤ 5.00E+4	≤ 5.00E+4	5.00E+02
		LUHMES	OCR perm. (*)	8.61E+01	2.64E+01	≤ 5.00E+4	≤ 5.00E+4	≤ 5.00E+4	NT	NT	NT
		Liver	OCR perm. (*)	1.05E+02	3.31E+01	> 1.00E+4	3.92E+02	4.02E+03	5.33E+03	6.16E+03	1.85E+01
		Liver	OCR intact (b)	1.58E+02	5.01E+01	4.79E+03	4.90E+02	8.32E+02	2.40E+03	5.13E+03	6.70E+00
		Liver	OCR intact (m)	2.57E+01	1.05E+01	9.33E+03	7.24E+02	1.12E+03	4.88E+03	2.69E+03	3.39E+00
		Kidney	OCR intact (b)	1.35E+02	1.35E+02	3.47E+03	4.17E+02	2.00E+03	1.17E+03	> 1.00E+4	2.34E+01
		Kidney	OCR intact (m)	3.72E+01	2.89E+01	1.82E+03	1.10E+02	1.91E+02	1.91E+03	5.50E+03	4.37E+00
	KE2	Liver	MMP	2.40E+01	3.00E+00	1.12E+03	2.88E+02	3.89E+02	> 1.00E+4	> 1.00E+4	3.00E+00
		Kidney	MMP	7.50E+01	1.70E+00	> 1.00E+4	7.90E+01	> 1.00E+4	2.57E+03	> 1.00E+4	8.00E-01
		SH-SY5Y	MMP	3.35E+02	3.45E+01	3.25E+03	2.96E+02	8.32E+03	3.83E+02	1.35E+03	6.60E+01
		Liver	Lactate	1.02E+02	7.50E+01	2.44E+03	1.79E+02	4.75E+02	9.22E+03	1.19E+02	7.20E+01
		Kidney	Lactate	1.91E+02	1.82E+02	9.71E+02	2.49E+02	3.31E+02	1.57E+03	> 1.00E+4	1.74E+02
		SH-SY5Y	Lactate	<8.00E+01	2.30E-01	4.89E+03	3.91E+03	7.78E+02	3.16E+03	> 1.00E+4	<8.00E+01
	KE3	LUHMES	Protease assay	6.17E+03	6.61E+03	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable
		Liver	Proteasome (**)	4.00E+02	8.00E+01	not applicable	not applicable	not applicable	not applicable	not applicable	not applicable
	KE4	Liver	Viability	> 1.00E+4	> 1.00E+4	> 1.00E+4	> 1.00E+4	> 1.00E+4	> 1.00E+4	> 1.00E+4	> 1.00E+4
		Kidney	Viability	3.98E+02	1.02E+02	5.01E+03	4.37E+02	8.71E+02	6.03E+03	7.76E+02	3.60E+01
		SH-SY5Y	Viability	> 1.00E+4	> 1.00E+4	> 1.00E+4	> 1.00E+4	> 1.00E+4	> 1.00E+4	> 1.00E+4	> 1.00E+4
		LUHMES	Viability	9.12E+03	3.16E+02	> 5.00E+4	> 5.00E+4	> 5.00E+4	> 5.00E+4	> 5.00E+4	2.57E+04
		LUHMES	NO	1.15E+03	3.80E+01	3.16E+04	1.74E+04	4.90E+04	1.82E+04	4.17E+04	1.74E+04
		LUHMES	NV	2.00E+04	2.00E+04	> 150000	5.25E+04	> 5.00E+4	> 5.00E+4	> 5.00E+4	>12500
		LUHMES	N ATP	4.37E+03	4.37E+03	1.95E+04	1.51E+04	NT	NT	NT	9.55E+03
		SH-SY5Y	ND (24h)	> 1.00E+4	3.20E+01	> 1.00E+4	> 1.00E+4	> 1.00E+4	> 1.00E+4	> 1.00E+4	1.99E+03
		SH-SY5Y	N tox (24h)	> 1.00E+4	> 1.00E+4	> 1.00E+4	> 1.00E+4	> 1.00E+4	> 1.00E+4	> 1.00E+4	> 1.00E+4
	Repeat	LUHMES	ND (2x in 10d)	3.98E+02	3.98E+01	2.51E+04	3.98E+03	1.58E+04	NT	NT	1.00E+04
		LUHMES	N tox (2x in 10d)	1.28E+03	3.16E+02	3.16E+04	7.94E+03	2.00E+04	NT	NT	1.02E+04
		SH-SY5Y	ND (2x in 120h)	3.87E+03	2.65E+01	> 1.00E+4	3.06E+03	> 1.00E+4	2.07E+03	7.89E+03	4.23E+03
		SH-SY5Y	N tox (2x in 120h)	3.14E+03	1.22E+02	> 1.00E+4	5.02E+03	9.04E+03	> 1.00E+4	> 1.00E+4	3.34E+03

Case Study Toxicodynamics NAM Toolbox

Rotenoids case study: AOP-driven assessment of the relationship between complex I inhibition and neurotoxicity in a battery of *in vitro* models



Case Study Toxicokinetics NAM Toolbox

Rotenoids case study: Assessment of chemical behavior *in vitro, in vivo* for rat, and *in vivo* for human

In vitro kinetics

Predicted distribution of rotenone and deguelin

* Nominal concentration of 1E-06 M

Cell Line	Rotenone (M)		Deguelin (M)	
	Media	Cell	Media	Cell
RPTEC/TERT1	2.88E-07	5.01E-05	2.03E-07	5.64E-05
HepG2	9.88E-08	2.71E-05	6.31E-08	2.76E-05
LUHMES	6.46E-07	3.75E-04	5.38E-07	4.98E-04
SHSY5Y	3.18E-07	1.85E-04	2.27E-07	2.10E-04

Ratio cell to nominal concentration

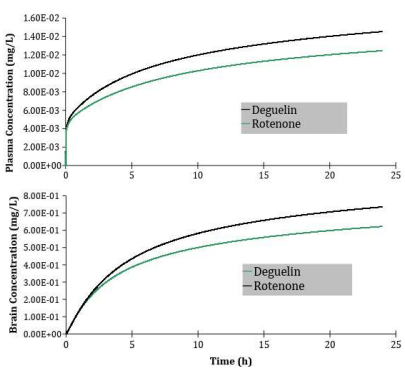
* Static model

Cell Line	Rotenone	Deguelin
RPTEC	50.1	56.4
HepG2	27.1	27.6
LUHMES	375	498
SHSY5Y	185	210

PBPK modeling (rat)

Simulated concentrations for rat

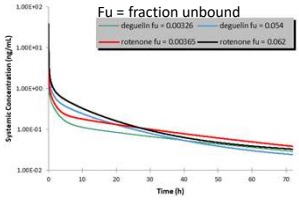
* following 1mg/ml dose administrated as a 24-h infusion.



PBPK modeling (human)

Simulated mean plasma exposure for human

* iv 10 mg to a population of 100 individuals aged 20-50 (50% female)



Publications:

1. van der Stel W, et al. Arch Toxicol. 2021 Oct 13. Epub ahead of print. PMID: 34642769.
2. van der Stel W et al. ALTEX 2021 Jun;38(4):615-635
3. Delp J et al. Arch Toxicol. 2021 Feb;95(2):591-615.
4. van der Stel W et al. Arch Toxicol. 2020 Aug;94(8):2707-2729.
5. Delp J et al. Arch Toxicol. 2019 Jun;93(6):1585-1608.

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www.eu-toxrisk.eu/