

ChemTunes-ToxGPS®

Mar 12, 2019

- ▶ Welcome
- ▶ ChemTunes·ToxGPS®
- ▶ Example: EFSA
Genotoxic Impurities
Assessment
- ▶ Product use case demo
- ▶ Open Discussion

Overview

- ▶ Combination of In Silico Outcomes
 - ▷ Different QSARs, Structural Rules
- ▶ Combination of Experimental Results
 - ▷ *In vivo* and *in vitro*
 - ▷ Resolve conflicts with quantitative uncertainty
- ▶ Read-across
 - ▷ Easily applicable to diverse endpoints
 - ▷ One Analog -> one Target
 - ▷ Many Analogs -> one Target
- ▶ Applicable to wide range of regulatory programs
 - ▷ ICH M7
 - ▷ EFSA, ECHA Weight of Evidence Rationales...

Evaluation of (Q)SAR and read-across to evaluate genotoxicity of pesticide active substances and their metabolites.

- ▶ **Read-across** on a metabolite (target) using experimental data on the parent pesticide active substance (analog).
- ▶ Apply **(Q)SAR** (models and structural alerts) to target to support read-across evaluation.
- ▶ Compare rigorous vs. simple **weight-of-evidence** approaches.

Analog quality

The quality of an analog for read-across on a specific target is assessed based on:

- ▶ Structure-based similarity
- ▶ Property-based similarity
 - ▷ Molecular properties
 - ▷ Physicochemical properties
- ▶ Biological similarity
 - ▷ Pesticidal mode of action (to group chemicals)
- ▶ Reactivity
 - ▷ Metabolic similarity between target and analog

Experimental study reliability

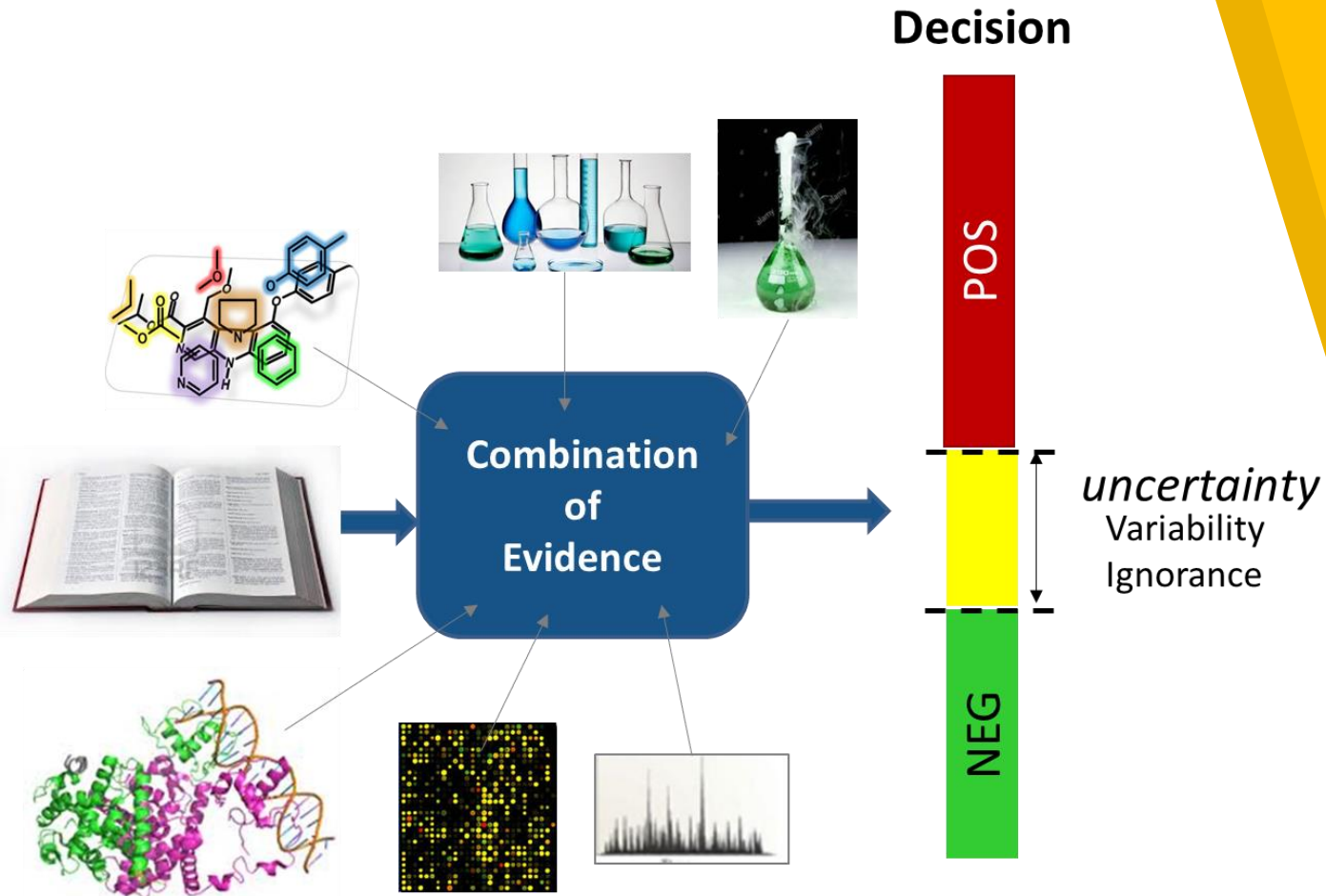
Five factors in rating study quality:

- 1) OECD guideline and deviation
- 2) GLP compliance
- 3) Study design with respect to species, strains, cell lines, metabolic activation
- 4) Study design with respect to concentration, dose levels and ranges, number of duplicates, repeated experiments
- 5) Control information

Study Reliability Scoring

Reliability Score	Description	Example
1.0	Meets all five on previous slide. Also the number of revertant counts at a given conc. level are available along with the precipitation and cytotoxicity information.	If we reviewed the conc. / dose level data from study records that satisfy all , then the study reliability would be 1.0.
0.95	Meets all five on previous slide, but no conc. level detailed reading.	
0.85	Studies either missing records or not conducted and at least one deficiency in the five aspects.	OECD equivalent guideline. The deviation included the highest concentration did not cover the full range recommended.
0.70	Studies either missing records or not conducted and at least two deficiencies in the five aspects.	If the OECD guideline deviation was the test system with strains lacking WP2 or TA102 and the outcome was negative.
0.50	Studies either missing records or not conducted and at least two deficiencies in the five aspects.	If the OECD guidelines had deviation of the test system, and there were only one test done with control data not providing details.

Lining up, Selecting, and Combining the Evidence



Quantitative weight-of-evidence approach used to combine diverse evidence and estimate uncertainty

- ▶ **Combined outcome and uncertainty**

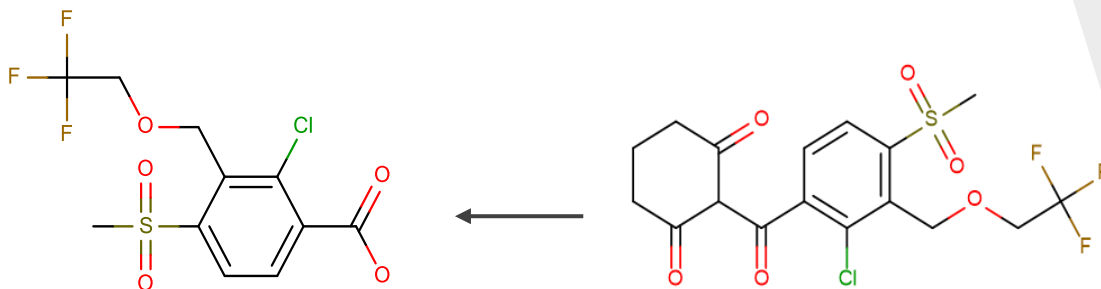
- ▶ **Sources of uncertainty**

- ▷ Analog quality
- ▷ Experimental study reliability
- ▷ (Q)SAR model reliability

- ▶ **Interactive workflow**

- ▷ Select evidence to be used
- ▷ Adjustable reliabilities

Case Study



Target impurity (metabolite)

Tembotrione (analogue)

Compound Detail	Description
Target	M6 of tembotrione (CMS-203791)
Parent	Tembotrione (CMS-11340)
CAS RN (target)	NONE
CAS RN (Parent)	335104-84-2
Pesticidal MOA	HPPD inhibitors

CS(=O)(=O)C1=CC=C(C(O)=O)C(Cl)=C1COCC(F)(F)F



The screenshot shows the ChemTunes ToxGPS web interface. At the top, there is a header with the ChemTunes logo (a blue hexagon with a white 'C' and a musical note) and the text 'ChemTunes'. Below this is a decorative wavy line in blue and orange, followed by the text 'ToxGPS' and an orange location pin icon inside a hexagon. The main content area is divided into two columns: 'Version 3' on the left and 'Version 1.2' on the right. The 'Version 3' column lists: 'Main Page', 'Start Generic or Read Across Workflow', and 'Data Manager'. The 'Version 1.2' column lists: 'Main Page', 'Database Search', 'Predict Toxicity', 'Export Structures and Data', 'Compare Compounds', 'TTC Export', and 'TTC Workflow'. At the bottom of the interface, it says 'designed and developed by MN/AM'.

Version 3	Version 1.2
Main Page	Main Page
Start Generic or Read Across Workflow	Database Search
Data Manager	Predict Toxicity
	Export Structures and Data
	Compare Compounds
	TTC Export
	TTC Workflow

designed and developed by  MN/AM

Product DEMO

WOE Process

Genetox, RDT

***Feedback
&
Discussion***

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Booth 2816

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