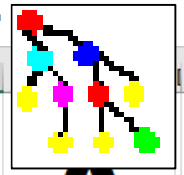
GERMAN FEDERAL INSTITUTE
FOR RISK ASSESSMENT

BfR
Bundesinstitut für Risikobewertung

User requirements and concepts I

Falko Frenzel

Much more design properties and user functions!



Metabol AS Tool

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6	Chemical structure notation	Downward compatible	0	?	1
7	Chemical structure notation	Support different notations	0	?	1
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10	Chemical structure notation	Search for structure similarities	1	1	1
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12	Chemical structure notation	The similarity search filter could be combined with additional filter clauses	0	0	1
16	Assesment process	Usable for "non-guideline experiments"	0	0	1
17	Assesment process	Manage "tentative results"	0	0	1
18	Assesment process	Usable for "freestyle" studies	0	0	?
19	Assesment process	Manage of textual summaries of the interpretation of the results	1	1	1
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25	Assesment process	Manage Q(SAR) responses in a user storable "List of similar substances"	0	0	1
26	Assesment process	Integrated start into Q(SAR) Tools with SMILES as the parameter	0	0	O
27	Assesment process	Manage response from the Q(SAR) tools according ECHA guide	0	0	O
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29	Assesment process	Prediction of metabolic pathways	0	?	?
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31	Assesment process	Mange substance groups by defined characteristics (e.g. according to functional groups, conjugates, …)	0	0	O
52	Vizualisation	Metabolic pathway	1	1	1
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Chemical Structure Notation

Currently used in Composer and MetaPath

- SMILES as a standard input for chemical structures
- depending on the chosen longest chain, different SMILES notations are possible
- therefore: SMILES are no good identifier

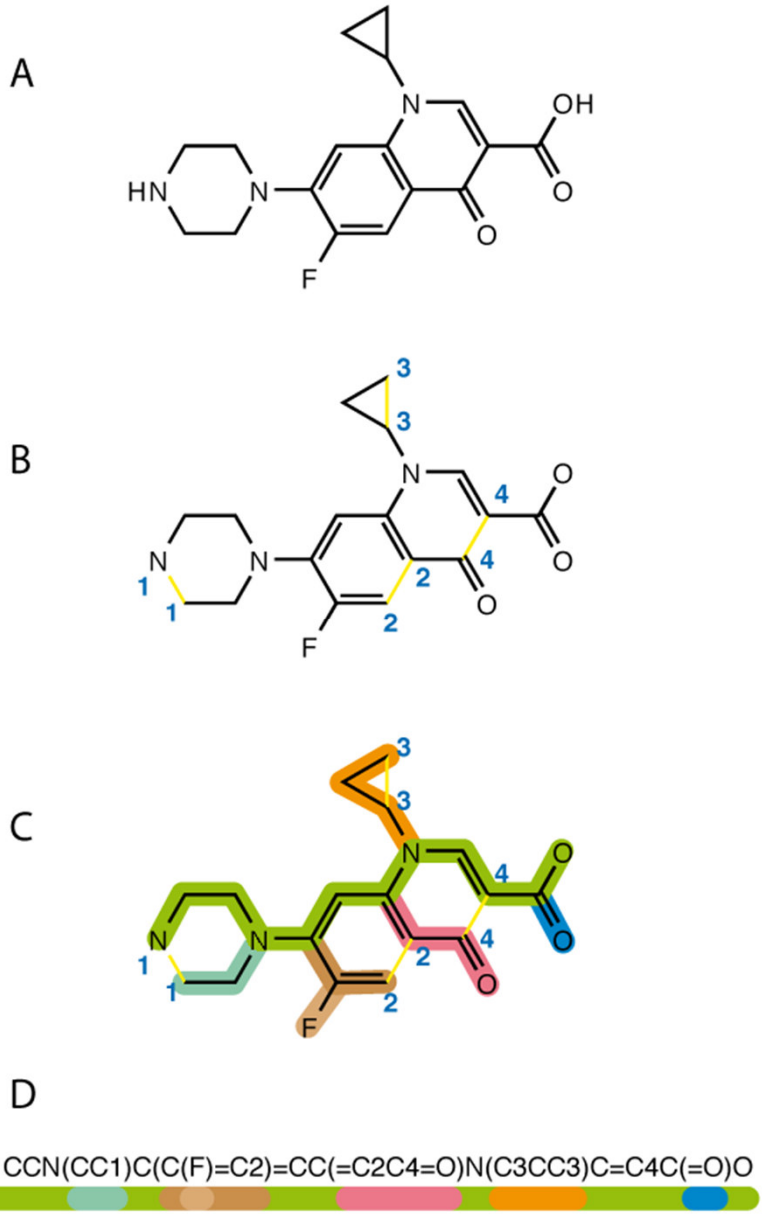
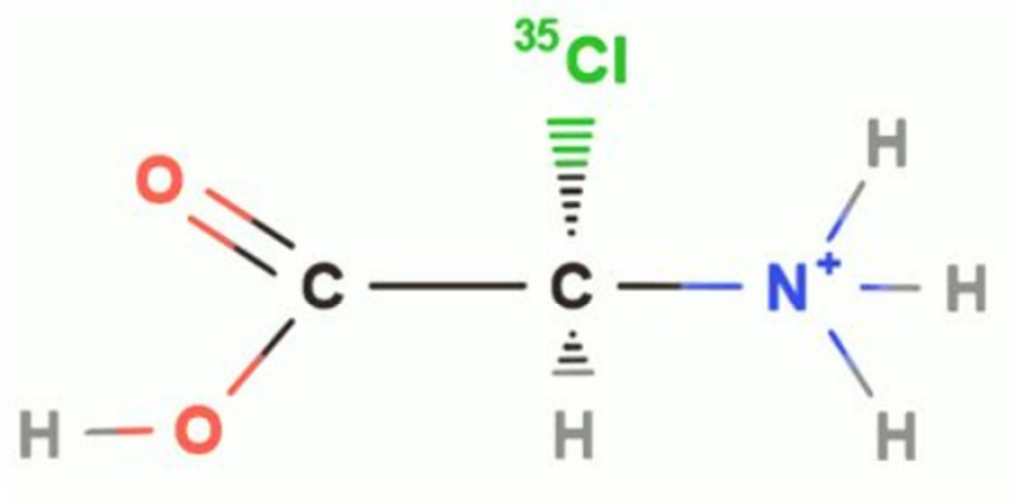


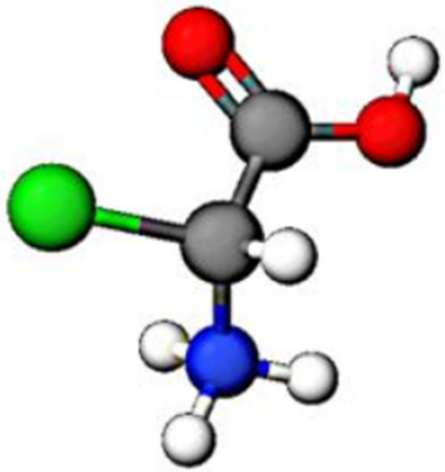
image source: https://upload.wikimedia.org/wikipedia/commons/0/00/SMILES.png

Chemical Structure Notation

Future use of InChI?

- layer based coding system
- with defined standards – oneunique structure encoding





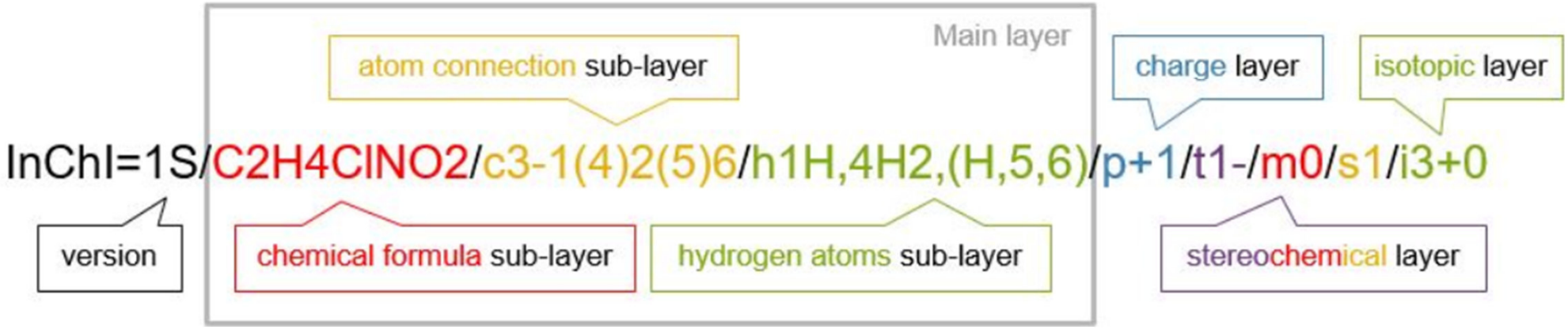
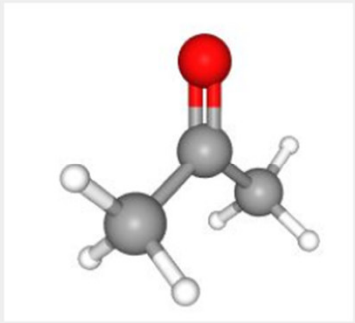


Image source: https://chem.libretexts.org/Courses/Fordham_University/Chem1102%3A_Drug_Discovery_-_From_the_Laboratory_to_the_Clinic/05%3A_Organic_Molecules/5.08%3A_Line_Notation_(SMILES_and_InChI)

Chemical Structure Notation

SMILES	InChI
CC(=O)C	InChI=1S/C3H6O/c1-3(2)4/h1-2H3



Acetone

image source: https://chem.libretexts.org/Courses/Fordham_University/Chem1102%3A_Drug_Discovery_-_From_the_Laboratory_to_the_Clinic/05%3A_Organic_Molecules/5.08%3A_Line_Notation_(SMILES_and_InChI)

Chemical Structure Notation

Currently used:

SMILES (since 1980s)

Pro:

- *better* human readability
- broadly supported

Contra:

- mediocre stereochemical representation
- inconsistent across multiple parser

➔ this makes it hard for interoperability

- non unique data base entry

InChI (since 2006)

Pro:

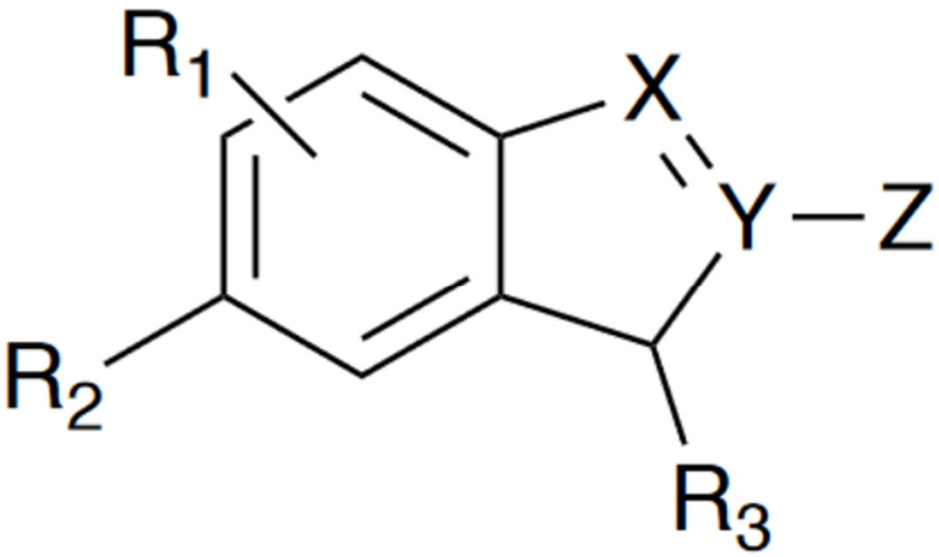
- unique string representation
- includes stereochemical properties
- standardised rules for interpretation
- broadly supported

Contra:

- hard to read by the naked eye (*minor*)
- is meant to be purely machine readable

Chemical Structure Notation

- Markush notations are more complex notations
- often used in patent descriptions



R_1 = H, Me
R_2 = Me, Et, Pr, Bu
R_3 = Ph, tolyl
X = N, CH
Y = C, N+
Z = Cl, CH_2Cl

image source: http://www-jmg.ch.cam.ac.uk/inchi/Variable_InChI.pdf

Switch to the voting system now regarding the relevance of Markush structures

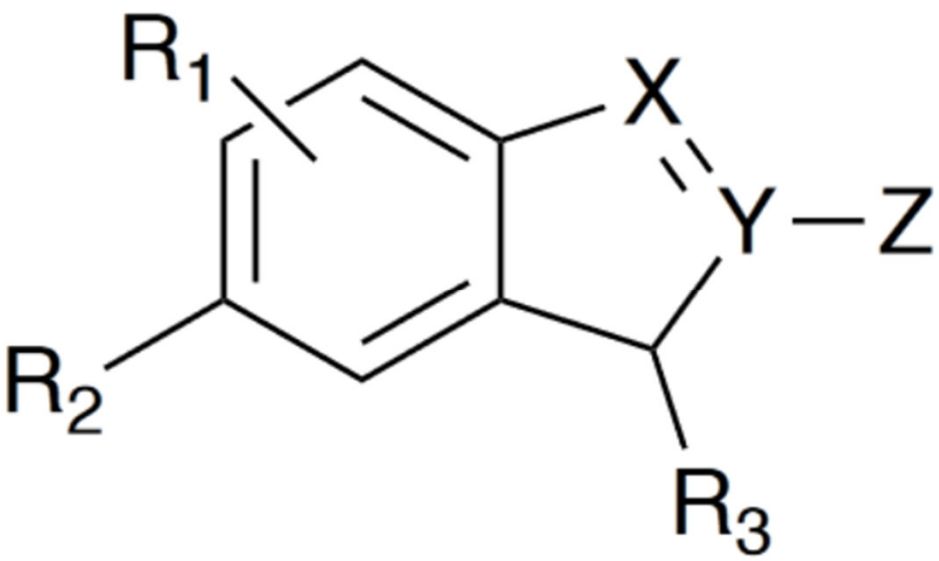
Are there any questions? Please use the hand raise in the TEAMS environment.
For statements you could use also the TEAMS chat. The chat will be recorded. **So no idea is lost.**

How often would you need a generic Markush Notation?

Would the "missing of Markush Notation" be a showstopper for the project?

Chemical Structure Notation

- Markush notations are more complex notations
- often used in patent descriptions
- hard to encode, but there are solutions on the way (MarkInChI by the InChI Trust)
- currently no open standard available, due to financing issues (InChI Trust Report 2016)



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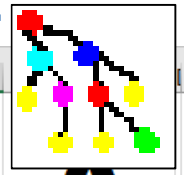
Much more design properties and user functions!



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30	Assesment process	Pooling of identical substances of different names across the studies	?	?	1
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Grouping and Calculation

- raw data will collect all necessary information
- grouping and calculation are “pivot” tables

Column Group name / Row group name	Column group	Column group	…	Optional Mean	Optional SD
Row group 1					
Row group 2					
Row group 3					
Sum of all rows					

Dose group / and or ID for animal	DG1	DG2	…
Excretion product 1 Excretion product 2 Excretion product … Organ 1 Organ 2 Organ … Sum of all TRR	TRR per excretion product or organ		

Grouping and Calculation
Grouping

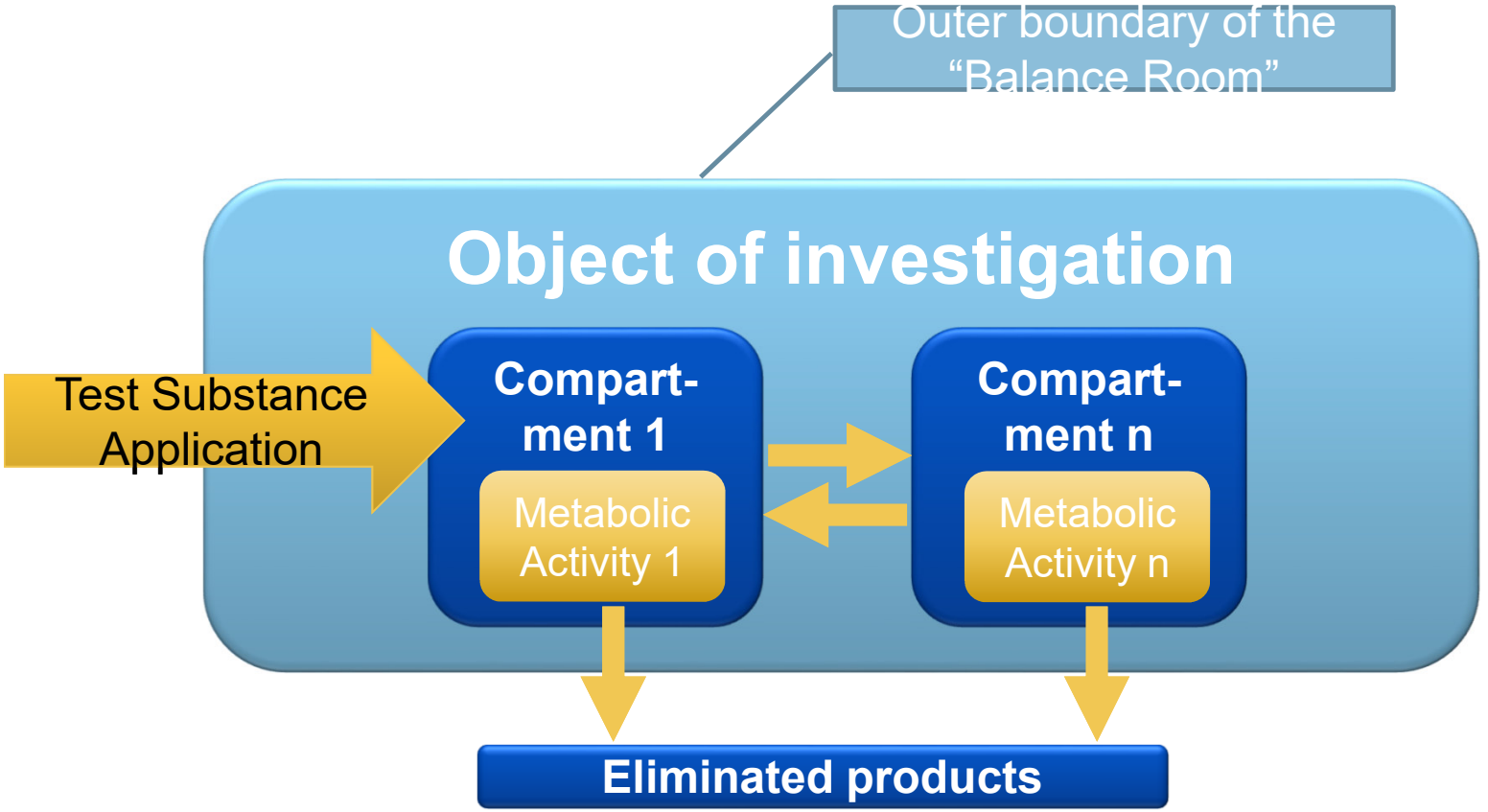
- grouping based on substances (e.g. similarity based), dose groups, sample groups, matrices and studies should be available by default

Crop	**Soybean**			
Study reference	**6.2.1/03, Desai 2016; 2013MET-IFP0730, ASB2019-7510**			
No and Rate	**3 x 125 g as/ha**			
N rate	**3N rate**			
Application method	**Foliar spray, ~BBCH 15/16+60+79**			
Label	**Phenyl (ph) and pyrazole (py) label**			
DALA	21 DAA 1	7 DAA 2	7 DAA 2	7 DAA 2
Sample	**Forage**	**Forage**	**Hay**	**Hay**
TRR mg/kg (combustion)	0,301	0,514	1,794	1,598
	% TRR (ph)	**% TRR (py)**	**% TRR (ph)**	**% TRR (py)**
TRR (extraction+comb. of PES)	103,0	100,7	101,9	98,0
M351 Fluindapyr (IR9792/F9990)	14,80	11,40	6,64	10,2
M367/3 3-OH-fluindapyr	4,04	2,40	4,44	4,40
M353 3-OH-methyl-N-desmethyl fluindapyr				
M381 1-COOH fluindapyr				
M162 N-desmethyl pyrazole COOH				
M176 Pyrazole-COOH		3,27		4,17
M175 Pyrazole-carboxamide		3,49		4,37
M337 N-desmethyl fluindapyr (free and N-conj.)	16,53	19,36	18,17	16,09
M337 N-desmethyl-fluindapyr	*[4.60]*	*[4.16]*	*[0.97]*	*[1.59]*
M499 N-desmethyl-fluindapyr-N-glu	*[11.1]*	*[15.2]*	*[17.2]*	*[14.5]*
M585 N-desmethyl-fluindapyr-N-glu-mal	*[0.83]*	*[0]*	*[0]*	*[0]*
M424 N-desmethyl-fluindapyr-N-serine				

Example for user defined substance groups where results should be aggregated.

Grouping and Calculation
Calculation

- the raw data are delivered with the study
- data might be delivered in concentration per compartment



- distribution coefficient across the test system might be of interest
- BfR has experience in designing and implementing such calculations (e.g. RUEDIS)

Switch to the voting system now regarding the grouping/calculation functionalities

Are there any questions? Please use the hand raise in the TEAMS environment.
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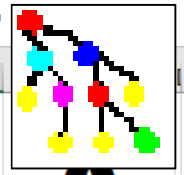
Is there a real need for the evaluators to create flexible reports for substance grouping to calculate concentration factors etc.?

Much more design properties and user functions!



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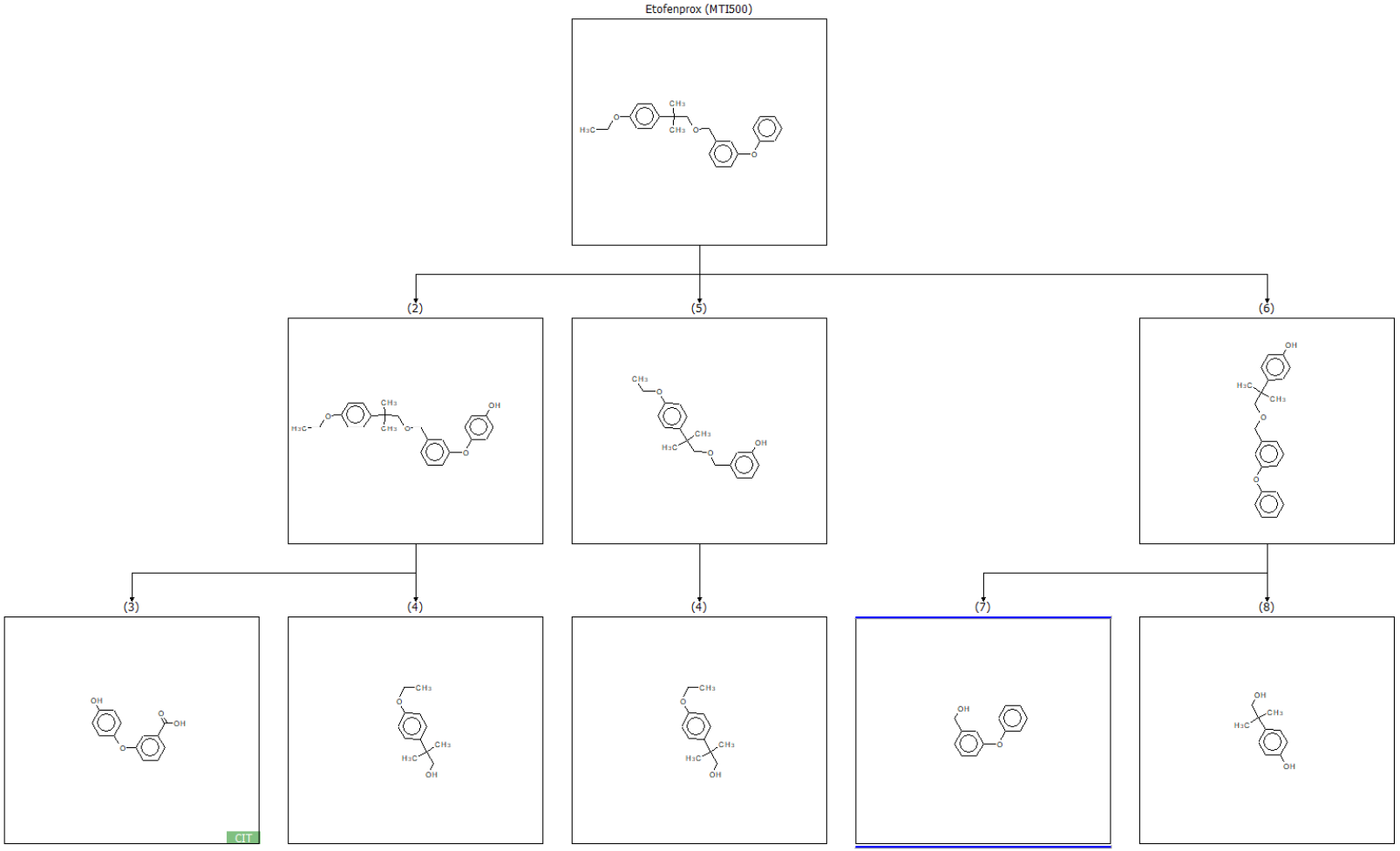
Visualisation

- implementation of PathVisio (OpenSource) which is used in WikiPathways
- in general the currently used visualisation tools in MetaPath are quite good



Visualisation

- implementation of PathVisio (OpenSource) which is used in WikiPathways
- in general the currently used visualisation tools in MetaPath are quite good
- the visualisation is capable of showing the „degradation“ process of a test substance and can merge multiple networks
- network data are always structured similarly:
  - **source**
  - **target**
  - **connection (type)**
  - additional data / meta data
- given this information in text format any modern visualisation tool can create networks/pathways (even webbased ones such as D3.js)

Visualisation

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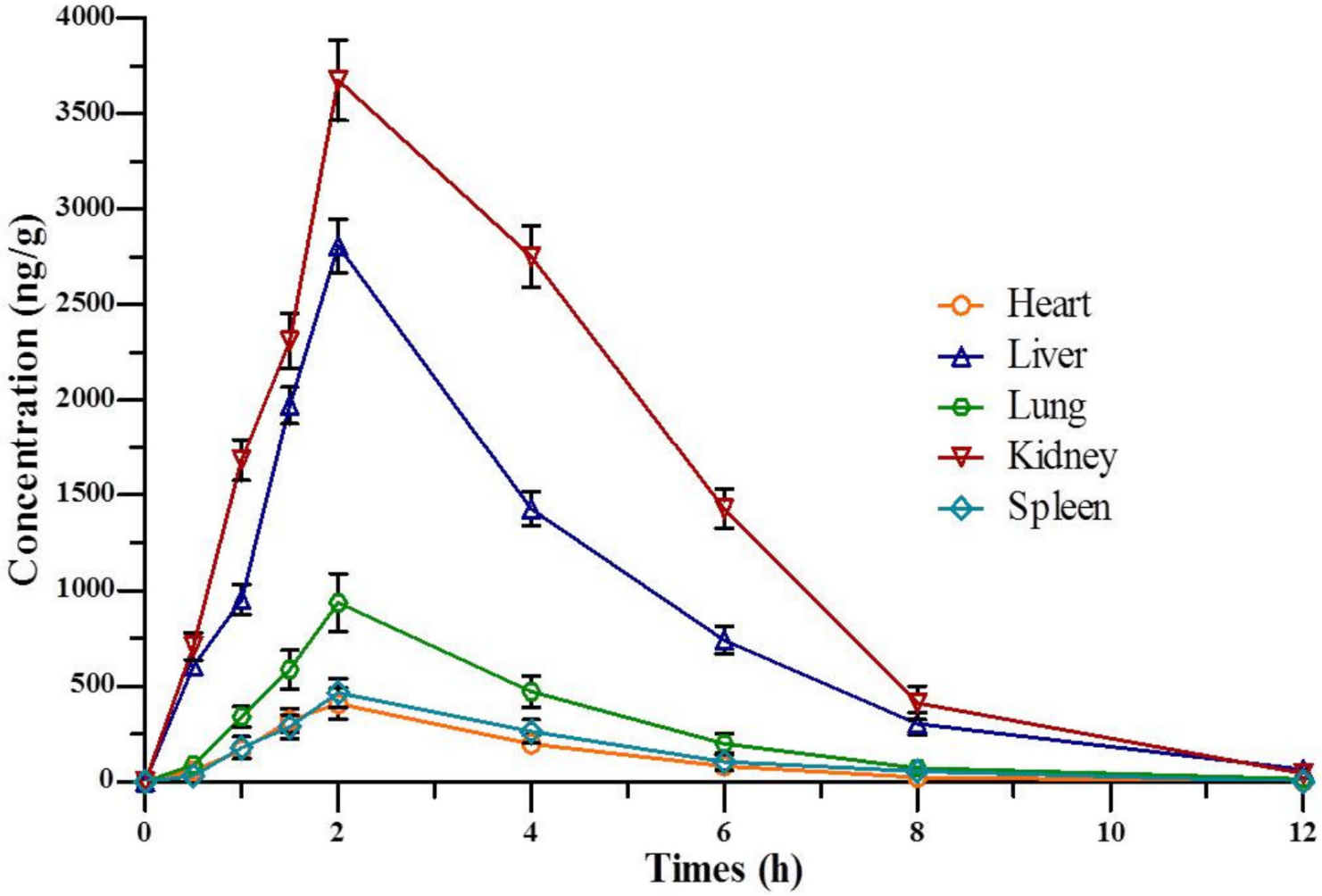

image source: Ambhore et al., 2020 (10.5530/jyp.2020.12.11)

Switch to the voting system now regarding the visualization functionalities

Are there any questions? Please use the hand raise in the TEAMS environment.
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Do you have ideas for additional visualisations which you would recommend to include in the project?

GERMAN FEDERAL INSTITUTE FOR RISK ASSESSMENT

BfR
Bundesinstitut für Risikobewertung

Thank you for your attention

Falko Frenzel

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