DECO2: Moving from DECO towards OECD

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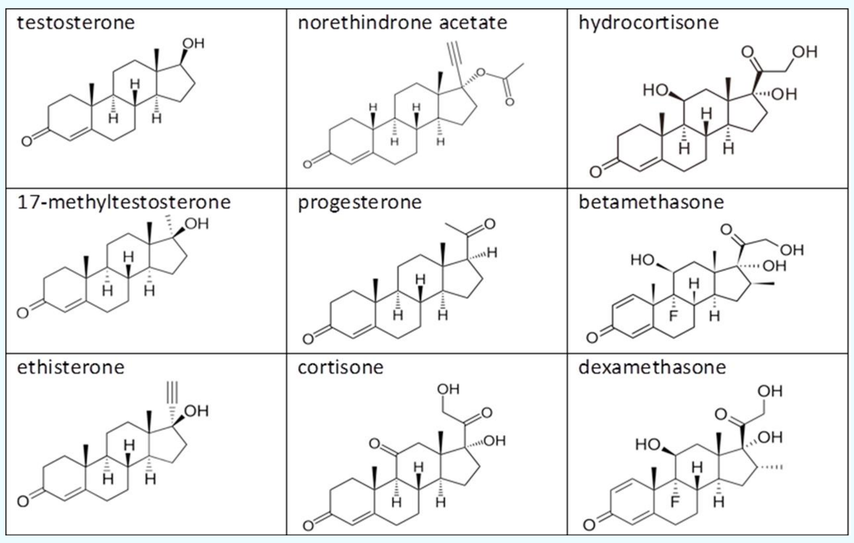
DECO

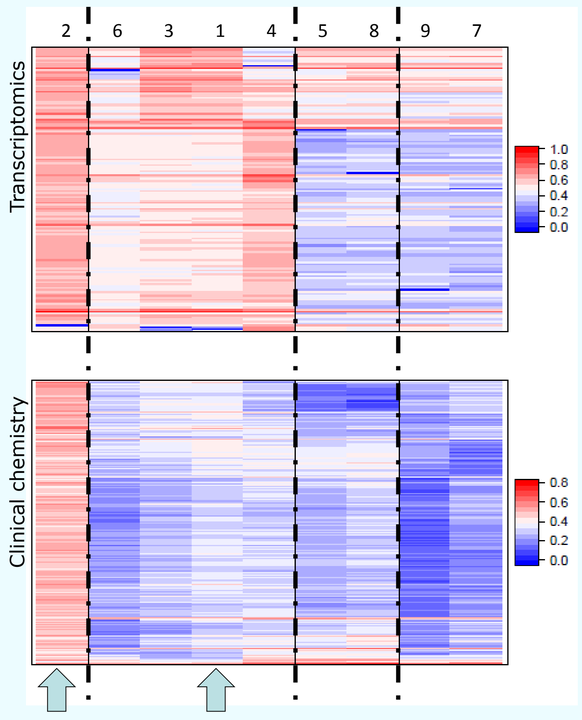
Lessons from DECO

Integrating different data types improves the clustering of structural analogues, thus improving read-across.

Example: structural similar (Tanimato score > 0.8) steroid hormones from DrugMatrix.



iClusterPlus on DrugMatrix data, Transcriptomics (144 features) & Clinical chemistry (613 features)



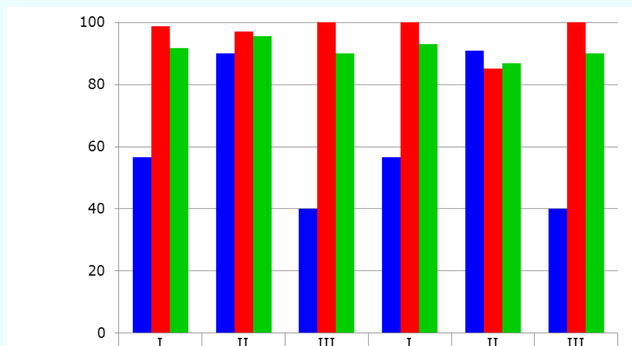
1=betamethasone
2=dexamethasone
3=hydrocortisone
4=17-methyltestosterone
5=ethisterone
6=norethindrone acetate
7=progesterone
8=cortisone
9=testosterone

The use of omics data has an added value to the prediction of liver toxicity induced by chemical compounds

Example: PAM classification using combination of TG-GATEs and DrugMatrix data.

Results for peroxisome proliferation at day 3 & 7

I. Training: 35 comp from TG-GATEs
Test: 17 comp from TG-GATEs
II. Training: 60 comp from TG-GATEs
Test: 44 comp from DrugMatrix
III. Training: 44 comp DrugMatrix
Test: 60 comp from TG-GATEs



	day 3			day 7		
	I	II	III	I	II	III
sensitivity	56.7	90	40	56.7	90.9	40
specificity	98.7	97.1	100	100	85.2	100
accuracy	91.8	95.5	90	92.9	86.8	90

Background

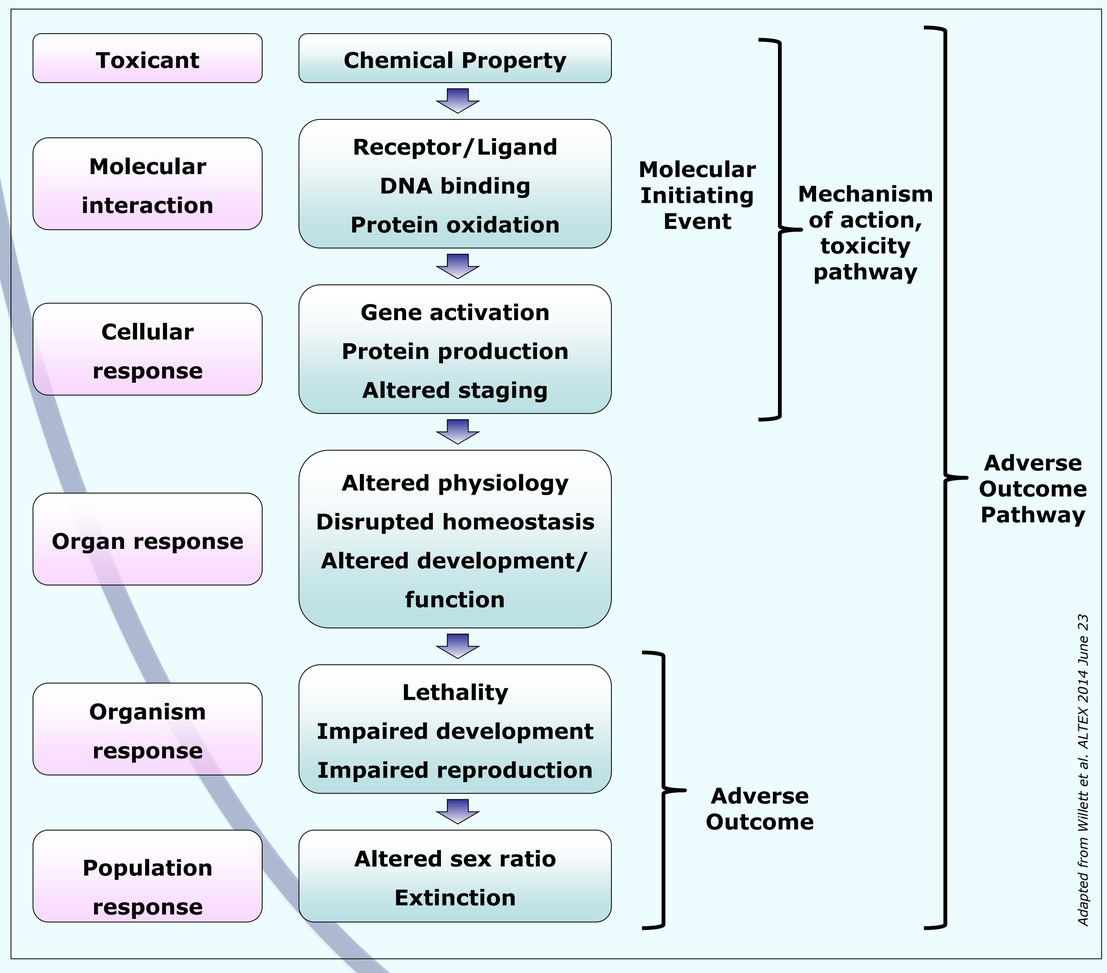
Read-across is a viable approach to fill data gaps in regulatory programmes within the EU and in other regions. Whilst much has been described to characterise how to undertake read-across in a systematic manner in both regulatory and industry guidance, regulatory acceptance continues to be a challenge. One of the reasons of this is related to the manner in which uncertainty in the read-across is identified and addressed. It is recognised that Tox21 approaches could play an important role in addressing these uncertainties but how they might be practically applied is an area yet to be properly investigated.
This project will explore the extent to which HT/HC methods may be used in an integrated, weight of evidence approach, together with traditional toxicity read-outs to justify read-across assessments to meet regulatory expectations. The aim of this project is to establish a framework for tools usable in integrated approaches.

Objectives

- To collect publically available and relevant data on liver toxicity, kidney toxicity, (non-genotoxic) carcinogenicity and developmental toxicity as well as on non-toxic compounds;
- To further develop integrated approaches based on chemoinformatics, 'omics' and HTS data, that address the similarity (or lack thereof) between structural analogues or chemicals within a presumptive category;
- To generate proof-of-principle studies for these approaches supporting read-across;
- To deliver visualisation and summarization tools facilitating end users in their understanding and acceptance.

Final outcome

To establish a framework of scientific confidence considerations that address both the development of read-across and its evaluation.
Insights from our proof of principle studies will be shared with OECD's AOP workgroup and task-force hazard assessment to stimulate further AOP development, and for practical use within the revised OECD grouping guidance.



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