Predicting genotoxicity and carcinogenicity of drugs and chemicals using OECD QSAR toolbox, Derek® Nexus and TEST

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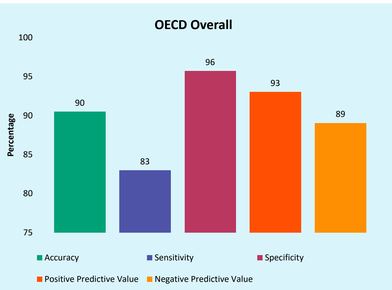
Introduction

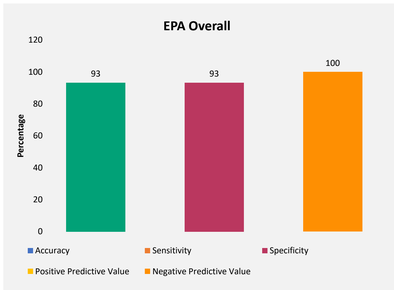
- The assessment of genotoxicity and carcinogenicity is an essential component of the safety assessment of chemical substances for regulatory approval. However, a battery of experimental tests are required to cover the different endpoints, these experimental tests come with time demands, ethical concerns, and huge costs.
- We have performed *in silico* evaluation of several substances including industrial substances, pharmaceutical products, pesticides, food additives, biocides, flavoring agents, natural products and cosmetic ingredients using three software's viz. QSAR Toolbox (v4.5) by OECD, Derek Nexus by Lhasa Limited (UK) and TEST (v5.1.1.0) by US EPA, thus aiming for a quicker and cost-effective screening.
- We compared the *in silico* prediction with the results obtained by the curated collection of data from published literature.

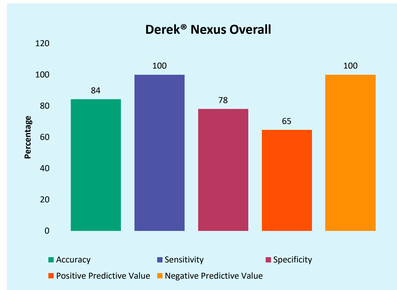
Methods

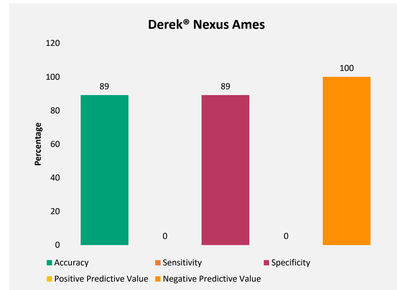
- Approximately 110 substances (majority being industrial substances, pharmaceutical products and pesticides, but also included food additives, biocides, flavouring agents, natural products and cosmetic ingredients) were analyzed.
- *In silico* analysis conducted for various endpoints viz. (i) Ames, (ii) *in vitro* mammalian cell gene mutation, (iii) *in vitro* micronucleus, (iv) *in vitro* chromosomal aberration, (v) *in vivo* micronucleus, (vi) *in vivo* chromosomal aberration, (vii) *in vivo* transgenic rodent gene mutation assay, (viii) *in vivo* unscheduled DNA synthesis, (ix) *in vivo* DNA damage and (x) rodent carcinogenicity.
- All the available endpoints data were compiled and compared with *in silico* predictions. Results were obtained in four categories: True positive, true negative, false positive and false negative.
- Only positive and negative results were considered; hence, inadequate/inconclusive results were not used in current scenario.

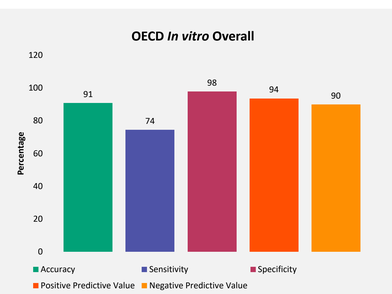
Results

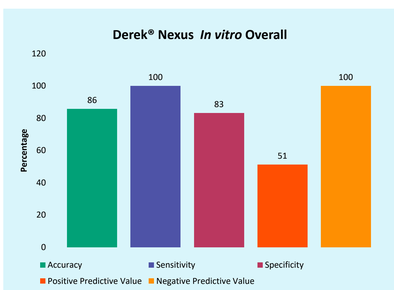


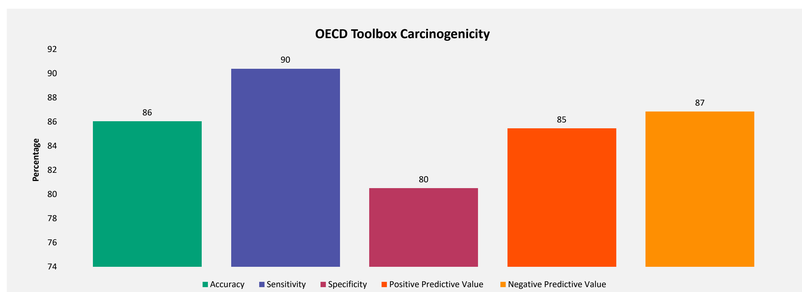


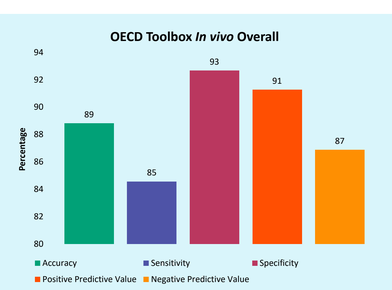


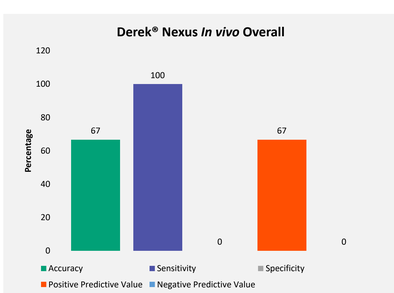


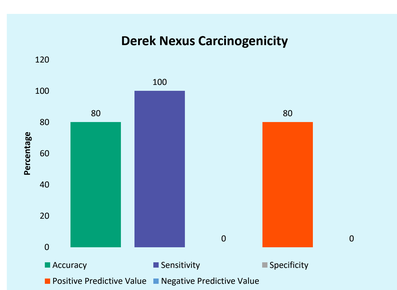


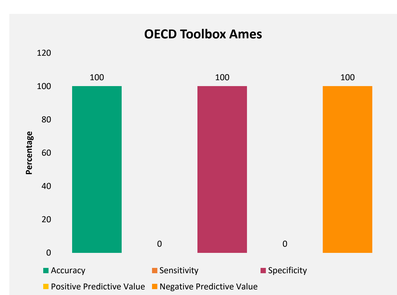












Formula used:

Accuracy = Percentage of correct predictions [TP+TN/Total] x 100;

Sensitivity = Ability of a test to detect true positive [TP/TP+FN] x 100

Specificity = Ability of a test to detect true negative [TN/TN+FP] x 100

Positive Predictive Value = Number of true positives, out of all positives [TP/TP+FP] x 100

Negative Predictive Value = Number of true negatives - out of all negatives [TN/TN+FN] x 100

Conclusion

- For mutagenicity (Ames only) QSAR Toolbox, Derek and TEST showed an accuracy of 100%, 89% and 93%, respectively.
- QSAR Toolbox and Derek had an accuracy of 91% and 86% for overall *in vitro* genotoxicity (Ames assay, Mammalian cell gene mutation assay, Chromosomal Aberration assay).
- QSAR Toolbox and Derek had accuracy of 86% and 80% for carcinogenicity endpoints.
- QSAR Toolbox and Derek had an accuracy of 89% and 67% for overall *in vivo* genotoxicity (*in vivo* micronucleus, *in vivo* chromosomal aberration, *in vivo* transgenic rodent gene mutation assay, *in vivo* unscheduled DNA synthesis, *in vivo* DNA damage.

References

1. Madia F, Kirkland D, Morita T, White P, Asturiol D, Corvi R (2020). EURL ECVAM genotoxicity and carcinogenicity database of substances eliciting negative results in the Ames test: construction of the database. *Mutat Res Gen Tox En*, 854-855: 503199.