USING (Q)SAR AND READ ACROSS TO EVALUATE THE TOXICOLOGICAL RISKS OF DATA-POOR DRUG IMPURITIES AND EXTRACTABLES/ LEACHABLES

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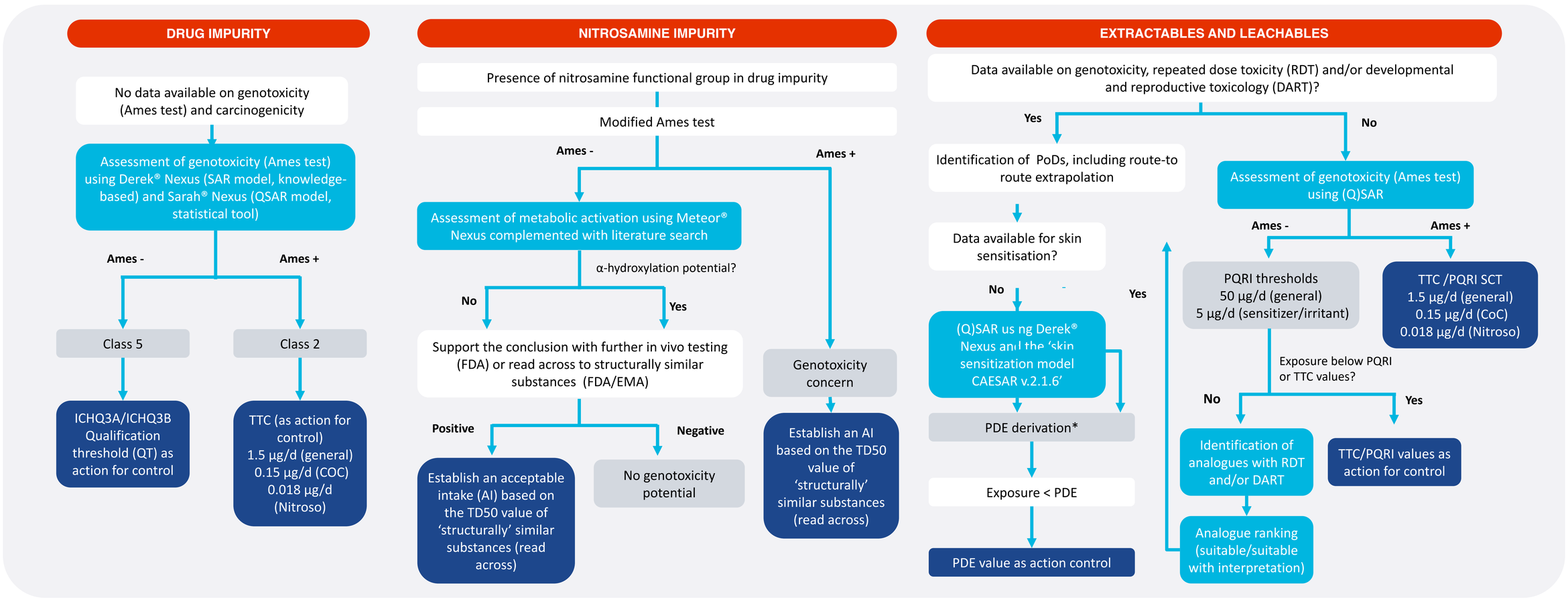
ToxMinds
THINKING AHEAD IN TOXICOLOGY

Introduction

Regulatory authorities such as the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have increased their scrutiny of drug products coming into direct or indirect contact with humans. Drug manufacturers are expected to identify and characterize impurities as well as major extractables/leachables, in order to evaluate the toxicological risks posed by these compounds. Only very recently, read across, as proposed by the Organisation for Economic Co-operation and Development (OECD) and the European Chemical Agency (ECHA), has been accepted as an additional approach for risk assessment by EMA and FDA.

At ToxMinds, we have established a process to perform read across to analogues which are identified using ECHA-recommended tools such as the OECD QSAR Toolbox v.4.5 and the US EPA AIM model. Analogues with relevant toxicological data are further evaluated for their suitability in accordance with OECD guidelines and the ECHA read across assessment framework (RAAF). Based on case studies, this poster presents toxicological assessment approaches showing how to address safety concerns and establish permissible daily exposure (PDE) or acceptable intake (AI) levels for data-poor impurities and extractables/leachables from drug products. These assessments are based on (Q)SAR analyses and or/read across approach.

Workflow for the assessment of data-poor drug impurities and extractables/leachables

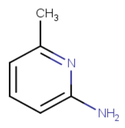


* For non-threshold carcinogens, PDE derivation is based on TD50 approach. For sensitisers/irritants the PQRI threshold (5 µg/d) has to be used.

Case study I: Use of (Q)SAR for qualification of an impurity according to ICH Q3A/ICH Q3B

OBJECTIVE

Determine if qualification threshold of 0.15% can be applied to **2-Amino-6-methylpyridine** (CAS No. 1824-81-3), impurity of drug A.



(Q)SAR PREDICTIONS

Derek Nexus[1] v.6.1

◆ **Mutagenicity in vitro in bacterium is INACTIVE**
• No misclassified or unclassified features

Sarah Nexus[2] v.3.1

Positive
with 9% confidence in the prediction

- Low level of accuracy.
- Analysis of the compounds of the training set with an acceptable similarity index:
  - 2,6-diaminopyridine (CAS No. 141-86-6), positive in Ames test, presents an additional amine functional group
  - 2-Amino-4,6-dimethylpyridine (CAS No. 5407-87-4), negative in Ames test, presents only one amine functional group similar to the query substance.

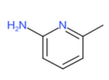
T.E.S.T (REF) v.5.1.1

Prediction results

Endpoint	Experimental value	Predicted value
Mutagenicity value	N/A	0,45
Mutagenicity result	N/A	Mutagenicity Negative

Individual Predictions

Method	Predicted value
Hierarchical clustering	0,56
Nearest neighbor	0,33



The consensus method predicted 2-Amino-6-methylpyridine to be non-mutagenic, with the prediction being within the applicability domain.

CONCLUSION

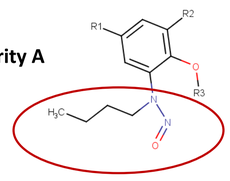
Based on this analysis, 2-Amino-6-methylpyridine can be considered as a class 5 impurity according to ICHM7.

Case study II: Use of (Q)SAR and read across for nitrosamines genotoxicity assessment

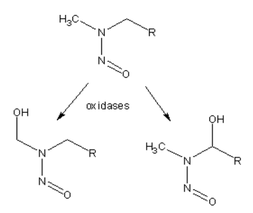
OBJECTIVE

Perform a Meteor-based metabolism assessment (as requested by authorities) of a nitrosamine impurity to support the negative *in vitro* genotoxicity results.

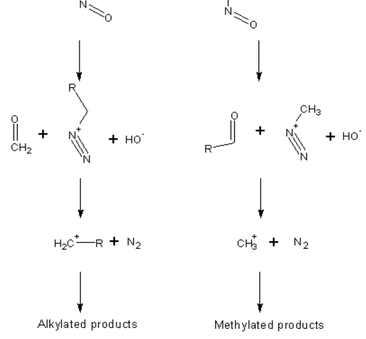
Impurity A



Metabolic activation of nitrosamines



Mode of action: Metabolic activation of via cytochrome P450-mediated α-hydroxylation, with formation of alkyldiazonium ions



Metabolism prediction for impurity A using Meteor® Nexus[3] v.3.1

- Meteor predicted glucuronidation as the major pathway and hydroxylation of the terminal methyl group as the minor pathway.
- The hydroxylation of terminal methyl in the minor pathway, may be followed by oxidation leading to the formation of nitroso methylamine via stepwise elimination of C2-units in the β-oxidation pathway[4, 5].

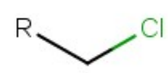
CONCLUSION

The metabolism path including 2 cycles of β-oxidation seems subordinated and of little relevance. This would explain the fact that the nitrosamine impurity is negative in *in vitro* genotoxicity assays.

Case study III: PDE derivation using toxicological data on read across substance

OBJECTIVE

Determine the PDE value of a leachable compound using a read across approach.

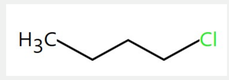


Leachable A

Analogue Identification and ranking

- Similarity searches based on structure and/or structural alerts in publicly available sources (e.g., OECD QSAR Toolbox, AMBIT, US EPA AIM and ChemMine) or proprietary databases
- Chemical structure and reactivity
- Physico-chemical properties
- Predicted or known toxicokinetic behaviour
- Metabolic pathway

- High similarity index: 0.8
- Same functional group (alkyl halide)
- Similar structural alerts (systemic toxicity, genotoxicity, sensitization and skin irritation), with the analogue presenting an additional alert for genotoxicity
- Physico-chemical properties in the same range
- Aliphatic hydroxylation as first metabolic reaction



Analogue

PDE calculation

A NOAEL of 43 mg/kg bw/day from the GLP-compliant 2-year oral carcinogenicity study in rats with the structural analogue was considered as the Point of Departure for the PDE calculation. Factor 10 was used for route-to-route extrapolation from oral to IV route.

$$PDE = \frac{43 \times 50}{5 \times 10 \times 1 \times 1 \times 1 \times 10}$$

CONCLUSION

Using a read across approach, the PDE for the leachable A was established at 4.3 mg/day.

References

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5 Grislain L, Gele P, Bertrand M, Luijten W, Bromet N, Salvadori C, Kamoun A. 1990. Drug Metab. Dispos., 18: 804-808.