

Application of the QAF check list – WoE evaluation for Ames mutagenicity of 2-heptenal

Australian case study

The views expressed in this presentation are those of the speakers and not an official position of the Australian Industrial Chemicals Introduction Scheme (AICIS)



Australian Government

Department of Health and Aged Care

Australian Industrial Chemicals Introduction Scheme

industrialchemicals.gov.au



Agenda

- Introduction of the chemical used in the case study
- Experimental data availability
- Model checklist for OASIS TIMES and DEREK NEXUS (Focus on unfulfilled elements)
- Prediction checklist and result checklist for OASIS TIMES and DEREK NEXUS (Focus on elements with moderate or high uncertainty)
- Conclusions



Australian Government

Department of Health and Aged Care

Australian Industrial Chemicals Introduction Scheme

industrialchemicals.gov.au



2-heptenal (CAS No. 2463-63-0)



- 2-heptenal was assessed by AICIS as part of a group C7–C12 linear alpha-beta unsaturated aldehydes. Limited point mutation data with or without metabolic activation were available for the chemicals in the C7–C12 group.
- The data available for 2-heptenal indicated it was negative for point mutations in *Salmonella typhimurium* strain TA104 without metabolic activation.
- Dose-dependent increases in mutation frequency were observed in *S. typhimurium* strain TA100, however, these increases were never two-fold higher than the spontaneous mutation frequency.



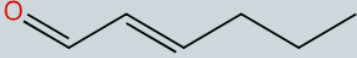
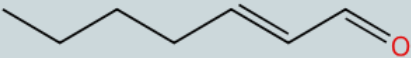
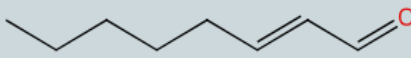
Australian Government

Department of Health and Aged Care

Australian Industrial Chemicals Introduction Scheme

industrialchemicals.gov.au

Data availability for 2-heptenal and its closest analogues (without S9)

<i>S. typhimurium</i> strain	2-hexenal	2-heptenal	2-octenal
			
TA100	Equivocal	Equivocal	-
TA104	Positive	Negative	Negative
TA98	Negative	-	-
TA102	Negative	-	-
TA1535	Negative	-	-
TA1537	Negative	-	-



The QAF checklists

Model checklist

- Enables systematic assessment of a (Q)SAR model
- Consists of a list of assessment elements to evaluate a model according to the OECD (Q)SAR Model Principles (OECD, 2007)
- Contains instructions how to map QMRF information to the checklist

Result checklist

- Used when assessing a result derived from multiple predictions for the same or related properties.
- Contains multiple prediction checklists that establishes whether:
 - the model input(s) is correct;
 - the substance(s) is within the applicability domain;
 - the prediction(s) are reliable;
 - the outcome is fit for a regulatory purpose.
- Establishes uncertainty of the prediction



OASIS TIMES (v2.28.1.6)

Model check list

- All assessment elements were fulfilled apart from
 - 4.1 Goodness-of-fit, robustness
 - 4.2 Predictivity
- Reasons for not fulfilling AEs
 - Statistics cross-validation not performed.
 - Full training set was not available
 - No external validation available

In this example, predictions were used in combination with other in silico predictions and experimental data in a weight of evidence (WoE) approach. The mechanistic basis of the model allows us to assess reliability of its individual predictions even in the absence of comprehensive information on the global performance of the model. Therefore, we considered the model valid for its purpose



Australian Government

Department of Health and Aged Care

Australian Industrial Chemicals Introduction Scheme

industrialchemicals.gov.au

DEREK NEXUS (v2.2)

Model check list

- All assessment elements were fulfilled apart from
 - 1.2 Transparency of the underlying experimental data
 - 4.1 Goodness-of-fit, robustness (not applicable/not assessed)
 - 4.2 Predictivity (not applicable/not assessed)
- Reasons for not fulfilling AEs
 - Data for each descriptor variable or dependent variable for the training set were not available.
 - The training set was not available. (Expert and ruled-based model.)
 - External validation is carried out on each knowledge base release: however, the curated data-sets used at Lhasa are proprietary.



Australian Government

Department of Health and Aged Care

Australian Industrial Chemicals Introduction Scheme

industrialchemicals.gov.au



DEREK NEXUS (v2.2)

Model check list

- In this example, DEREK predictions were used in combination with other in silico predictions and experimental data in a weight of evidence approach. Therefore, the model documentation is considered sufficient for assessing the validity of individual predictions with the prediction checklist.
- While the curated training set is not available, the mechanistic basis of the model allows us to assess reliability of its individual predictions even in the absence of comprehensive information on the data set used to create this expert rule-based model.
- Each prediction is supported by publicly available references.



Australian Government

Department of Health and Aged Care

Australian Industrial Chemicals Introduction Scheme

industrialchemicals.gov.au



OASIS TIMES – Negative, in domain

Prediction check list

- 1.3 Reliable input (parameters): Uncertainty = medium
 - Smiles was the only input
- 3.1 Reproducibility: Uncertainty = medium
 - We have not tried prediction with another version of OASIS TIMES
- 3.2 Overall performance of the model: Uncertainty = medium
 - Sensitivity (predicted positive/observed positive) = 84% (internal training set only)
- 3.4 Performance of the model for similar substances: Uncertainty = medium
 - same prediction for 2-hexenal and 2-octenal, however experimental data are limited
- 4.1–4.3 Outcome is fit for the regulatory purpose
 - Not applicable/assessed selected because we were not using the prediction as a standalone result



Australian Government

Department of Health and Aged Care

Australian Industrial Chemicals Introduction Scheme

industrialchemicals.gov.au

OASIS TIMES – Negative, in domain

Prediction checklist

- Acceptable for the intended purpose
- Uncertainty = medium

QSAR was used as weight of evidence. We compared test data for the chemical and its analogues, with QSAR predictions. Therefore, although 4.1, 4.2 and 4.3 are not fulfilled, the prediction was considered acceptable to use in WoE determination.



Australian Government

Department of Health and Aged Care

Australian Industrial Chemicals Introduction Scheme

industrialchemicals.gov.au



DEREK NEXUS – positive, reasoning level plausible

Prediction checklist

- 2.1 Substance within the applicability domain: Uncertainty = medium
 - The SARs describing the mutagenicity are defined by the developer to be the applicability domain for the model. Therefore, if a chemical activates an alert describing a SA for mutagenicity it can be considered as within the applicability domain.
- 3.1 Reproducibility: Uncertainty = medium
 - We have not tried prediction with another version of DEREK NEXUS
- 3.2 Overall performance of the model
 - Not assessed since it is an expert model
- 3.3 Fit within the physicochemical, structural and response spaces of the training set of the model
 - Not assessed since training set is not available



Australian Government

Department of Health and Aged Care

Australian Industrial Chemicals Introduction Scheme

industrialchemicals.gov.au



DEREK NEXUS – positive, reasoning level plausible

Prediction checklist

- 4.1–4.3 Outcome is fit for the regulatory purpose
 - Not applicable/assessed selected because we were not using the prediction as a standalone result
- Acceptable for the intended purpose
- Uncertainty = medium

(Q)SAR was used as weight of evidence. We compared test data for the chemical and its analogues, with (Q)SAR predictions. Therefore, although 4.1, 4.2 and 4.3 were not fulfilled, the prediction was considered acceptable.



Australian Government

Department of Health and Aged Care

Australian Industrial Chemicals Introduction Scheme

industrialchemicals.gov.au

Conclusion on the final results

Result checklist

- Outcome of the assessment (final result)
 - Acceptable for the intended purpose
- As a freestanding outcome (without experimental data to compare), this (Q)SAR result may not be acceptable for a hazard conclusion. As the (Q)SAR predictions were conducted to compare it with test data (in weight of evidence assessment), this (Q)SAR result is considered acceptable for the intended purpose (expert judgement used).
- The reason for the conflicting prediction results (without metabolism) may be due to strain dependent mutagenicity in *Salmonella typhimurium*.



Australian Government

Department of Health and Aged Care

Australian Industrial Chemicals Introduction Scheme

industrialchemicals.gov.au



Comment on the final results

Result checklist

- Both Derek Nexus and TIMES models identified the same alerting group 'alpha,beta-unsaturated aldehydes'. The two models gave contradictory predictions for the Ames assay (without metabolic activation) in *S. typhimurium* strains.
- The in vitro mutagenicity test data available for the chemical and other alpha,beta-unsaturated aldehydes also reported contradictory results



Australian Government

Department of Health and Aged Care

Australian Industrial Chemicals Introduction Scheme

industrialchemicals.gov.au



Conclusion on Ames mutagenicity

- The reason for the conflicting prediction results (without metabolism) is likely due to *S. typhimurium* strain-dependent mutagenicity of 2-heptenal. This is supported by evidence of strain dependency in other alpha,beta-unsaturated aldehydes.

<i>S. typhimurium</i> strain	2-butenal	2-pentenal	2-hexenal	2-heptenal	2-octenal	2-nonenal
TA100	Positive	Equivocal	Equivocal	Equivocal	-	-
TA104	-	-	Positive	Negative	Negative	Negative
TA98	Negative	Negative	Negative	-	-	-
TA102	Negative	-	Negative	-	-	-
TA1535	Negative	Negative	Negative	-	-	-
TA1537	Negative	Negative	Negative	-	-	-
OASIS TIMES	-	-	Negative	Negative	Negative	-
DEREK NEXUS	-	-	Positive	Positive	Negative	-



Thank you for listening!

Mia Akerfeldt & Nobheetha Jayasekara

Please see QAF excel spreadsheet for further details



Australian Government

Department of Health

Australian Industrial Chemicals Introduction Scheme

industrialchemicals.gov.au

