Workflow for collecting WoE

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Outlook

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Workflow for collecting WoE

General scheme

- Proposed scheme for collecting WoE is generally applicable for any QSAR study
- The application of scheme is critical in case of predictions which are:
  - Negative
  - Out of domain
  - Conflicting
Example 1

**Workflow for collecting WoE**

**Target chemical:** 3,3-Dimethylbutyne (CAS# 917-92-0)

![Chemical structure of 3,3-Dimethylbutyne](image)

**Target endpoint:** AMES Mutagenicity
The chemical is predicted **Negative** by TIMES AMES +S9 model. The prediction is out of the applicability domain of the model due to presence of “Unknown” atom-centered fragments extracted from the target structure.
By applying the category approach, four analogues of the target chemical were found all with **Negative** AMES experimental data (with and/or without S9). The read across prediction is **Negative**.
Propyne could be also regarded as analogue of the target chemical. The only difference is that it does not contain the branched alkyl group. Negative experimental data were found for Propyne when tested under gas exposure conditions in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 both with and without metabolic activation [1]. The compound was positive when tested in *E.coli* strain WP2 uvrA both in the presence and absence of metabolic activation. These equivocal results for propyne obtained with different bacterial strains cannot be explained by simple DNA reactivity factors, concerning the parent chemical. After microsomal/S9 metabolic activation, however, propyne may be converted into propargyl aldehyde which is strong bacterial mutagen [2]:

Unlike Propyne with compact molecular structure, the target chemical contains large, branched alkyl radical bound to the Csp atom. The electron-donating capacity of the alkyl radical and steric hindrance factors probably contribute to the negative *Ames* test result by making the target chemical less electrophilic and, hence, less reactive.

References:
Workflow for collecting WoE

Final decision

Expert conclusions:

• The reported experimental bacterial mutagenicity data for 3,3-Dimethylbutyne are negative;
• Negative data has also been found for other branched-chain structural analogues by read-across analysis;
• 3,3-Dimethylbutyne can be regarded as non-mutagenic in the Ames test.

Ultimate conclusion:

3,3-Dimethylbutyne is Non-mutagenic in the AMES test.
Example 2

Workflow for collecting WoE

**Target chemical:** N,N-diisopropylbenzothiazole-2-sulphenamide (CAS# 95-29-4)

![Chemical structure](image)

smiles: CC(C)N(Sc1nc2cccccc2s1)C(C)C

**Target endpoint:** Skin sensitization
The chemical is predicted **Positive** by TIMES SS model and the prediction is out of the applicability domain of the model due to presence of “Unknown” atom centered fragments (~67%).
Example 2

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The target chemical has been predicted by applying the category approach in the Toolbox. The primary group was defined by the endpoint specific profiler “Protein binding alerts for skin sensitization by OASIS”. The read across prediction is Positive based on two analogues.
Example 2

**Workflow for collecting WoE**

**Experts**

- In this case, there is **no conflict** between the prediction from **TIMES SS** model and the read across from **Toolbox**.
- Expert involvement is not necessary.
Example 2

Workflow for collecting WoE

Final decision

- In this case, there is no conflict between the prediction from TIMES SS model and the read across from Toolbox.
- Expert involvement is not necessary.

Ultimate conclusion:

The target chemical could be considered as Positive skin sensitizer.
Example 3

Workflow for collecting WoE

**Target chemical**: 3-Phenyl-1-propanol (CAS # 122-97-4)

![Chemical Structure]

smiles: OCCCc1ccccc1

**Target endpoint**: Reproductive toxicity
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TIMES ER binding + S9 model

The target chemical is predicted as Non ER binder. As a result of in vitro S9 metabolism and the target is hydroxylated at $p$-position to alkylphenol for which alert exist in the model. However, due to parametric boundaries (not falling into the range of logKow defined for Alkylphenols) the metabolite is predicted as Non binder. The prediction is in the model domain.
Example 3

Workflow for collecting WoE

Toolbox

Read across for ERBA

By applying the category approach in Toolbox, the read across prediction for ERBA is 0% based on three analogues.
Example 3

Workflow for collecting WoE

Toolbox

- QSAR + Read across → Conflict or Negative prediction → External knowledge → Conclusion

Read across for Relative Gene Activation

The read across prediction is **Non active** based on five analogues.
Example 3

Workflow for collecting WoE

Toolbox

Analysis of metabolites

The *in vivo* rat metabolic simulator was applied on the target chemical. 14 metabolites are generated.
Example 3

Workflow for collecting WoE

Toolbox

Analysis of metabolites

It was found that for one of the generated metabolites there is experimental data showing slightly Positive effect – ERBA = 0.00826%.
Example 3

Workflow for collecting WoE

Experts

- Parent chemical has Negative reproductive toxicity.
- However, after simulating *in vivo* metabolism the chemical is hydroxylated at para position and experimental data collected for this metabolite shows that it has slightly positive result (ERBA is 0.00826%).
- The target chemical could be considered as possible ER binder after metabolic activation.
• Parent chemical has **Negative** reproductive toxicity.
• However, after simulating *in vivo* metabolism the chemical is hydroxylated at para position and experimental data collected for this metabolite shows that it has slightly positive result (ERBA is 0.00826%).
• The target chemical could be considered as **possible ER binder** after metabolic activation.

**Ultimate conclusion:**

*3-Phenyl-1-propanol* is **possible ER binder** after metabolic activation.