Predicting Repeated Dose Toxicity in OECD (Q)SAR Toolbox

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Abstract

The OECD (Q)SAR Toolbox and Japanese Hazard Evaluation Support System (HESS) for predicting repeated dose toxicity (RDT) have been developed as two compatible hazard evaluation platforms. As a result of this compatibility, the toxicological categories developed for HESS has been implemented for grouping purposes in Toolbox. This work represents the capabilities of Toolbox in predicting repeated dose toxicity of chemicals.

Workflow

<u>Input</u> - entering chemical into the system

3,5-Dimethylaniline (CAS # 108-69-0)



Introduction

The goal of this study is to demonstrate Toolbox capabilities in predicting repeated dose toxicity (RDT) of chemicals. The workflow consists of five stages: input of chemical, identification of toxicological profiler of the chemical, identification of the appropriate structural analogues based on toxicological similarity, gathering from the database the available experimental data for the analogues, and finally applying read-across for calculating RDT in terms of lowest-observed-effect level (LOEL) and no-observed-effect level (NOEL) associated with a specific organ and associated effect(s).

Materials and methods

Repeated dose profiler developed for HESS is implemented in Toolbox for grouping purposes. It is organized as a collection of 33 toxicological categories



Profiling - identifying toxicological profiler of chemical



<u>Category definition</u> – collecting analogues

1 [target]



The target chemical falls into chemical class "Anilines" associated with two different effects. The aim of this stage is to identify analogues which are similar to the target with respect to their chemical structure and toxicological effects associated with the target. The category Hemolytic anemia with methemoglobin anemia is further investigated

Effect on the Liver

Liver-wt î

Adducts

with DNA,

Tissue protein

Urine (Detoxification

GOT \uparrow , GPT \uparrow , γ -GTP \uparrow

Regeneration hepatocyte

Necrosis hepatocyte



Data Gap filling - applying **Read-across** for calculating RDT

The read-across prediction is performed mixing up all organs, effects, examination items and tissues



nalogues and target ve same Anemia RBC V HGB J HTC J Reticulocyte ' Methemoglobin 🔁 Select o 🖌 Remov

Refining the category is performed using subcategorization by RDT profiler

each chemical class



NOT Members of the commo fragments used for defining the structural boundaries o

Conclusions

•The HESS profiler for grouping chemicals according their Repeated dose toxicity is implemented in OECD Toolbox

•This profile allows adequate read-across for 33 classes of organic chemicals

The next two subsequent subcategorizations are performed: •Chemical element •Hindered anilines

Result of read-across related to **Anemia** is: 64.3 mg/kg/day Similarly, read-across analyses are performed for investigating: • LOEL related to decrease of red blood cell (RBC \downarrow) • LOEL related to effects associated with Liver toxicity

| | | | | | | | | | | | | | | Results from read-across are: |
|------|------|------|------------|--------------|-------|--------|-----|--------|------|------|------|------|------|--|
| | | | | | | | | | | | | | | LOEL (RBC \downarrow) = 75 mg/kg/day |
| | | | | | | | | | | | | | | LOEL (Anemia) = 64.3 mg/kg/day |
| 1.90 | 1.95 | 2.00 | 2.05 Io | 2.1 g Kow | 0 2.1 | 5 2.20 | 2.2 | 5 2.30 | 2.35 | 2.40 | 2.45 | 2.50 | 2.55 | LOEL (Liver) = 79.9 mg/kg/day |

Estimated LOEL for whole body is 64.3 mg/kg/day

<u>**Report**</u> – Results could be reported in any of the Toolbox reporting formats



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|-------|----------|----------|-----------|
| Paper | PDF file | RTF file | HTML file |

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