Using MechoA scheme to support cross-species extrapolations between species used in human health and environmental hazard assessment: a case study

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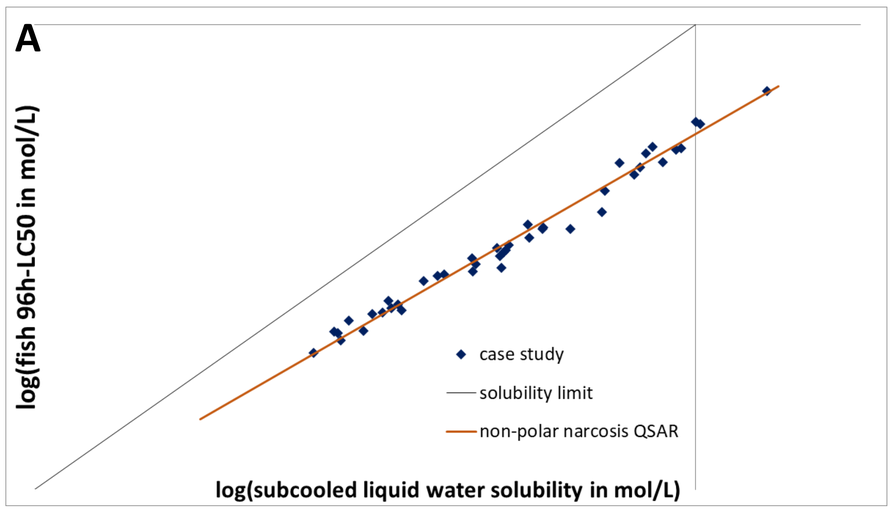
INTRODUCTION

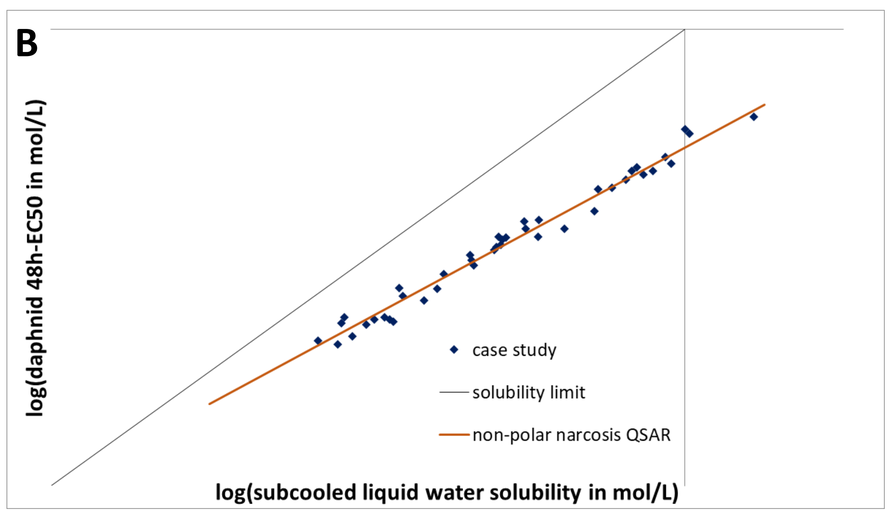
Mechanisms of toxic Action (MechoAs) classification model is a structural alerts scheme that identifies Molecular Initiating Events (MIE) in various species including mammals and aquatic organisms among others. Recently, we significantly updated the MechoA scheme now named MechoA Premium[1,2]. Notably, the use of protein orthology databases has enabled better characterisation of species applicability of structural alerts. Used correctly, it can participate in reduction of animal testing together with the identification of potential hazards for species for which experimental data are lacking, constituting a precious addition to cross-species extrapolations in weight-of-evidence approaches.

Among MechoA classes, narcosis is considered the so called, "baseline toxicity" mechanism which is the theoretically minimum toxicity that can be exerted by virtually any substance. Narcosis is transient and reversible, with symptoms such as ataxia and lethargy[3], but can lead to cytotoxicity with disruption of cell membrane integrity at high doses/concentrations, and subsequently to fish mortality, daphnid immobilization and narcosis syndrome in rodents. This poster highlights a case study examining the correlation between narcotic effects observed in rodents and toxicity in aquatic animals.

Narcosis as a universal mechanism of toxic action, a proof of MechoA usefulness for cross-species extrapolation

Figure 1. Correlation of the 42 substances with baseline toxicity for (A) fish acute toxicity studies and (B) daphnid acute toxicity studies.





METHODS

First, a list of 42 substances was gathered, which were predicted MechoA 1.1 i.e., non-polar narcotics for aquatic species[4]. Those had validated experimental ecotoxicity values for both acute fish and daphnid toxicity that perfectly fit with the predictions of iSafeRat® high accuracy QSAR models for baseline toxicity, corresponding to non-polar narcosis.

Next, we searched whether these substances were officially classified STOT-SE3 for narcotic effects (*i.e.* H336 phrase) in ECHA dossiers, based on rodent acute toxicity studies. In the absence of classification, we proceeded to an in-house classification based on clinical signs related to narcotic effects reported in studies according to the following criteria:

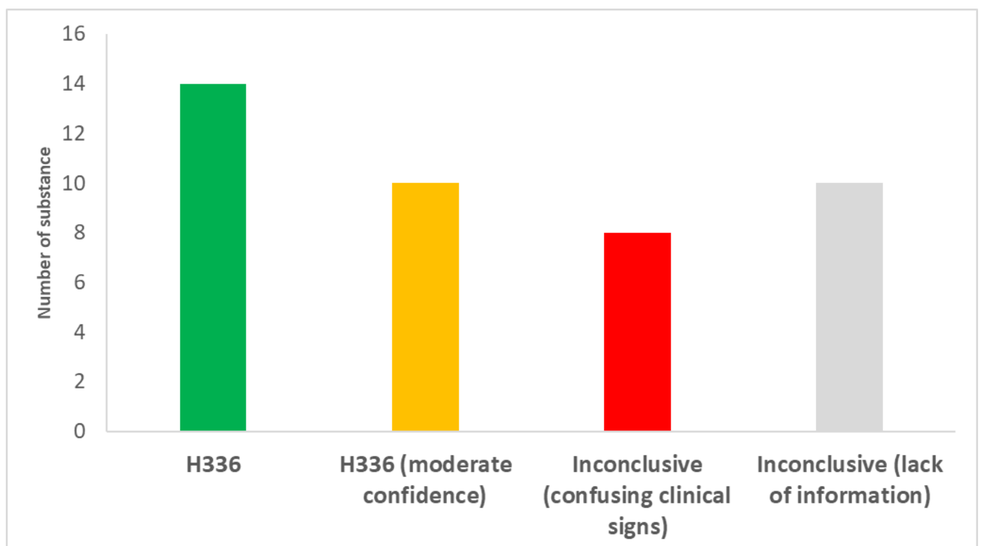
- H336: substance with harmonised classification H336 or for which clinical signs of narcosis were clear.
- H336 (moderate confidence): mixed clinical signs of toxicity, but sufficiently reliable indications of narcosis for classification.
- Inconclusive: clinical signs were not described, absence of clinical signs related to narcosis or potential indications of narcosis were covered by other toxic effects.

RESULTS

As represented on **Figure 1A and 1B**, the 42 substances correlated perfectly with baseline ecotoxicity in fish and daphnid acute toxicity studies. This was confirmed mathematically as the mean deviation was 0.13 in Log scale for both species, corresponding to less than 1.5 fold difference between predicted and experimental values. The maximal observed deviation was a factor of 2.6 in fish for chloroform. The MechoA profiler predicted all the substances to be non-polar narcotics for all species (i.e., MechoA 1.1). In addition to MechoA 1.1, 6 halogenated substances were also predicted to be bioactivated to reactive species (*i.e.,* MechoA ma4.3 or maC4.3) leading to genotoxicity or oxidative stress only associated with chronic adverse effects in mammals.

According to ECHA dossiers, only 5 out of 42 substances were classified H336. The results of the in-house classification are presented on **Figure 2**. Twenty-eight substances were classified H336 with high or moderate confidence. No conclusion could be reached for 10 substances because of poorly described studies, while clinical signs confusing with neurotoxicity or severe irritation were observed for 8 substances. Among the 6 halogenated substances, 3 were classified H336 without any restriction. No reliable conclusion could be established for the 3 others.

Figure 2. Count of H336 in-house classification based on rodent acute toxicity studies available in online REACH Dossiers.



CONCLUSION

In cases where the lack of information was not detrimental to in-house classification, 75% of substances predicted non-polar narcotics by the MechoA scheme and confirmed narcotics with iSafeRat® ecotoxicity QSARs were also classified H336 based on rodent studies. Additionally, narcosis could still be observed for substances associated with another mechanism of toxic action. Altogether, these clear results demonstrate the universality of non-polar narcosis across species and the usefulness of the MechoA scheme for cross-species hazard extrapolation. Narcosis could not be ascertained for the remaining 25% of substances, but it cannot be totally excluded as many acute toxicity studies on rodents consisted of limit tests at or near to lethal doses and adverse effects may camouflage narcotic symptoms.

Another possible application of the MechoA scheme is its use for H336 classification. As many of the substances were not classified according to CLP while clear clinical signs of narcosis were described in rodent studies, this Structure-Activity Relationship (SAR) could greatly help industrial toxicologists to identify narcotic effects and possibly other adverse effects related to critical classification (*e.g.* CMR). Further research will examine whether the universality of MechoA 1.1 is also observed for other MechoAs.

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