Predicting hazardous properties of substances from related substances – some recent cases

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INTRODUCTION

ECHA's Committee for Risk Assessment (RAC) started its work on assessing proposals for harmonised classification in 2009 and has since developed opinions on such proposals for over 200 substances.

Endpoint-specific information for one or more substances ('source') has been used by dossier submitters to predict the potential hazard for another substance ('target') with similar physico-chemical, environmental fate and/or (eco)toxicological/kinetic properties.

Recent analysis of harmonised classification and labelling (CLH) dossiers (n=99) prepared under the CLP Regulation[1] that were submitted to ECHA and processed, between 2013-2015, showed that approximately 35 % of the these CLH proposals employed information from related substances (Figure 1).

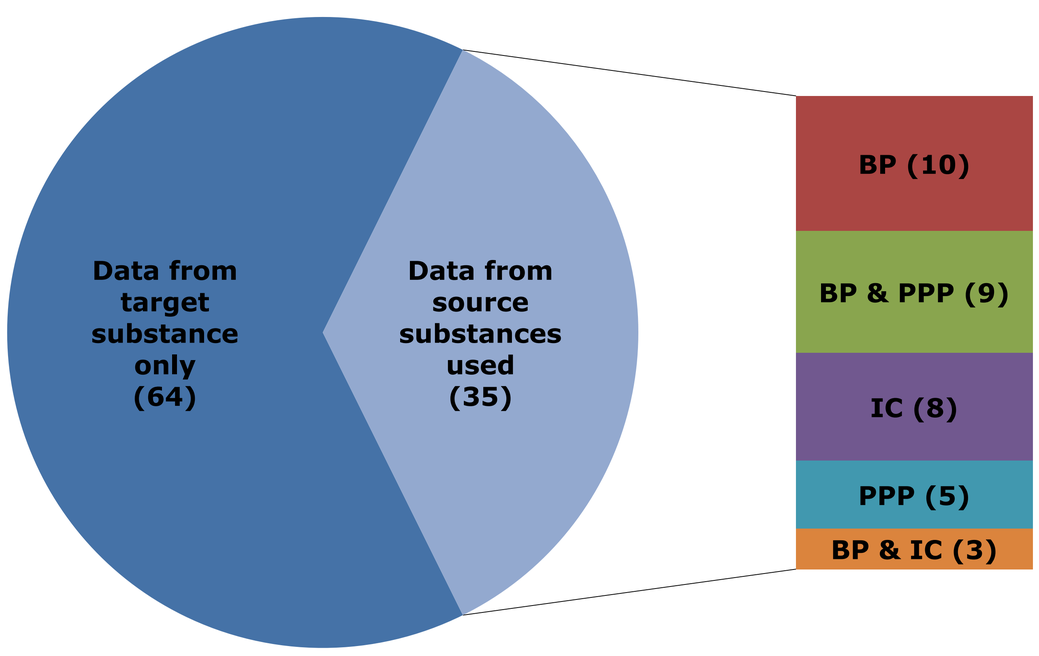


Figure 1. CLH dossiers (n = 99) submitted between 2013-2015 using data from related substances (Number of CLH dossiers in parenthesis). BP, Biocidal Products; PPP, Plant Protection Products; IC, Industrial Chemicals.

In some of those cases, data on source substances was used as supportive information and part of a weight of evidence approach; in others it was driving the classification. On a case-by-case basis, RAC took data on metabolic precursor substances, substances with physico-chemical and structural similarities, data on substances formed and released after chemical reaction, as well as substances acting via identical modes of action for classification purposes into consideration.

RECENT CASES

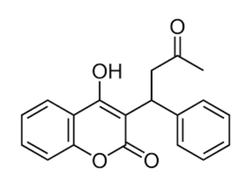
In several CLH opinions, RAC concluded on harmonised classification proposals for target substances based on data derived from source substances. Here, we present four case reports of different ways in which this has been achieved:

1. Hydrolysis

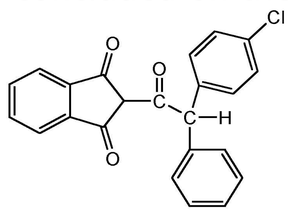
RAC used data on dibutyltin chloride (DBTC) to classify dibutyltin dilaurate (DBTDL) for the systemic human health endpoints STOT RE, mutagenicity and reproductive toxicity via oral exposure. The classification was based on the perception that DBTDL is rapidly hydrolysed into dibutyltin in the stomach producing DBTC, which was supported by an *in vitro* study showing DBTDL hydrolysis of 87.8 % within 2h.

2. Mode of action

Anticoagulants from the warfarin type with an anti-vitamin K (AVK) mode of action (MoA) are used mainly as active substances for pest control of rodents. Warfarin has been shown to cause developmental toxicity in humans. RAC concluded on the classification for developmental toxicity for seven AVK rodenticides, including warfarin based on the assumption that all AVK rodenticides share the same MoA, namely inhibiting vitamin K epoxide reductase (VKOR).



Warfarin



Chlorophacinone

3. Solubility and bioavailability

The systemic toxicity of inorganic cadmium compounds was considered to result from the intrinsic properties of the Cd^{2+} ion and thus those compounds from which the Cd^{2+} ion is bioavailable will share common hazards. RAC agreed with the proposal to use data from very soluble inorganic cadmium compounds to classify the slightly soluble cadmium hydroxide since there was evidence for bioavailability.

4. Analogue approach

The analogue approach was used to fill in data gaps for substances that are expected to behave in a similar manner for a specific endpoint. RAC used perfluorooctanoic acid (PFOA) and its ammonium salt (APFO) as source substances for the CLH opinion of the structurally similar target substances perfluorononanoic acid (PFNA) and perfluorodecanoic acid (PFDA) and their respective ammonium and sodium salts for various endpoints, including reproductive toxicity.

CONCLUSIONS

- A significant number of the CLH proposals submitted to ECHA use information from related substances.
- This information is used by RAC to conclude on the hazardous properties of the substances under evaluation.
- Overall, this approach allows classification of substances with limited or no data also on CMR endpoints.

REFERENCES

[1] CLP Regulation (EC) No 1272/2008
RAC Opinions to find under: http://echa.europa.eu/opinions-of-the-committee-for-risk-assessment-on-proposals-for-harmonised-classification-and-labelling