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Converging Degradation Pathways as a Basis for Grouping & Read-Across

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Introduction

Since the REACH legislation, Read-Across became a frequently used option for predicting toxicity and properties of chemicals. While (Quantitative)-Structure-Property-Relationships ((Q)SPR) have achieved some regulatory acceptance (e.g., for concluding of explosive properties or estimating vapour pressure of substances with a melting point above 200 °C), the derivation of biological effects is often not very solid and gets refused.

Formaldehyde Releasers are a good example for a straight-forward applicable Read-Across. The cleaving of Formaldehyde (CAS 50-00-0) is often the intended property of chemicals. It represents an important and rather fast primary degradation step. The remainder of the parent molecule normally does not degrade fast and shows little bioactivity, while Formaldehyde is readily biodegradable (ECHA registered dossier 15858). Therefore, short-term effects after (in relation to the formed Formaldehyde) isomolar exposure are likely to be comparable. In contrast, long-term effects to low doses can be expected to be influenced by the other degradation products.

Any grouping must be precisely defined and justified in agreement with the guidance documents of the authorities. The applicability domain may comprise only few or just one well defined endpoint. This is particularly necessary if the grouping is based on metabolism/transformation, but the group members differ in terms of degradation times and the number of required transformation steps.

Nonetheless, more complex grouping could be based on converging pathways (leading with at least one branch to an identical toxicophoric chemical), where the relevant metabolite or transformation product is formed after some antecedent degradation steps.

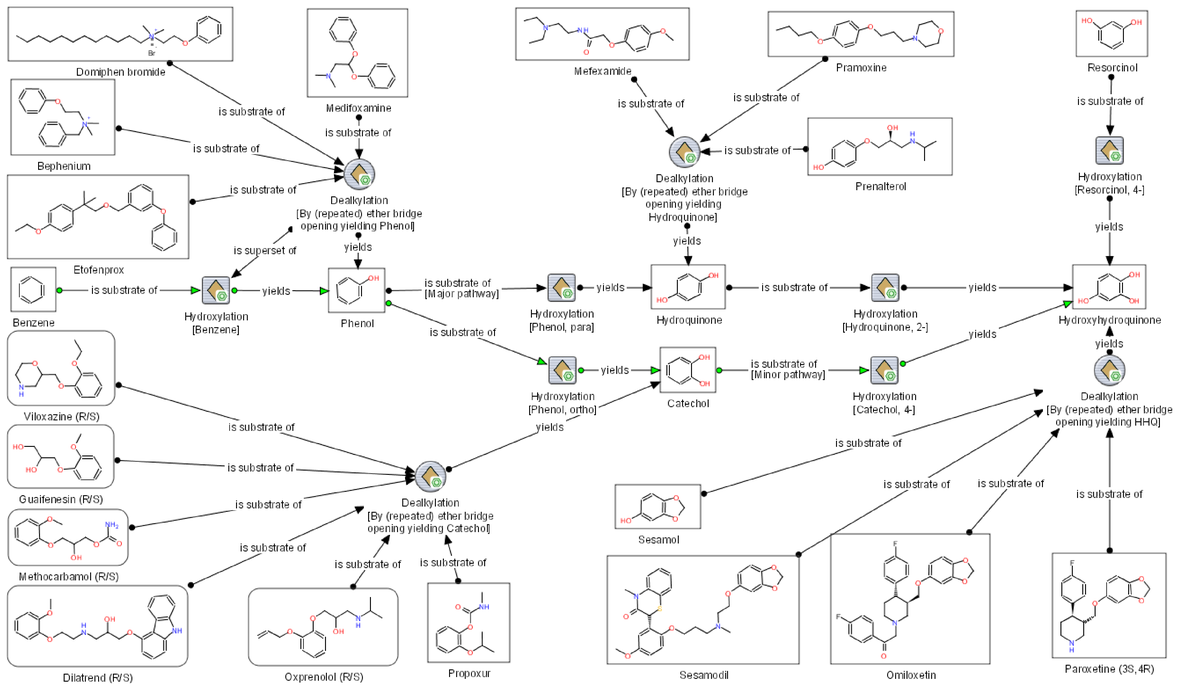

Figure 1: Groups of substances potentially able to converge with the metabolic pathway of benzene at different levels.

Materials and Methods

As illustration of the approach and as a basis for discussion, Benzene (CAS 71-43-2) degradation was selected, because metabolism is necessary for its toxicity (Kalf 1989, Ross 2000). Epidemiological data (Bove et al. 1995) show correlation between low level (2 µg/L) drinking water contamination during pregnancy and birth outcome, i.e., neural tube defects (NTD) and major cardiac defects (MCD). This could indicate specific developmental toxicity at low levels to susceptible organisms. If verified, a point of departure for safe concentrations could be established.

A variety of substances could potentially converge in the metabolic pathway of Benzene, as illustrated in Figure 1. The compilation is a first approximation based on generally possible metabolization/transformation steps. Only some of the pathway steps have been evidenced in the literature yet (Bourin et al. 2001, Carmona et al. 2009, Inoue et al. 1989, Kalf 2000, Kim et al. 2006, Lévay & Bodell 1992, Philipp & Schink 1998, Snyder & Hedli 1996).

While most of the compounds shown in Figure 1 could converge at the level of Phenol (CAS 108-95-2, group 1), other groups go via Hydroquinone (HQ, CAS 123-31-9, group 2), Catechol (CAS 120-80-9, group 3) or Hydroxyhydroquinone (HHQ, CAS 533-73-3, group 4).

HHQ is a minor metabolite of Benzene (Inoue et al. 1989), but it shows specific bioactivity (Hiramoto et al. 1998, Zhang et al. 1998) and its potential precursors (HQ and Catechol) show specific toxicokinetics (Irons 1985). Therefore, it could potentially be a critical molecule in the toxification (metabolic activation) of Benzene and for substances of the groups 1 to 4.

Group 4 includes Paroxetine (CAS 61869-08-7), a pharmaceutical active ingredient intensively investigated for birth defects. In case of a relevantly converging pathway and HHQ being the critical compound, production of effects comparable to Benzene should occur. Due to the established pharmacovigilance systems, this would be recorded. To check this, FDA black box warnings and literature were searched for NTD and MCD.

Results

In December 2005, the US Food and Drug Administration (FDA) cautioned that the use of paroxetine, as individual SSRI during the first trimester of pregnancy may increase the risk of MCD (Gao et al. 2018). An earlier meta-analysis found an increased prevalence of MCD with first trimester paroxetine use (Bérard et al. 2016). The more comprehensive investigations of Gao et al. (2018) did support the association.

In contrast NTD was not found being correlated with paroxetine in the scientific literature.

Discussion & Conclusion

The hypothesis did not work for paroxetine, but the falsification was rather simple achievable. In general, the chosen case was unlikely to produce sufficiently strong evidence for regulatory purposes and safe level derivation, but a verification could have indicated a basis for a common mode of action.

Nonetheless, shorter pathways may be conclusive even if conversion does occur with the second or later degradation step, particularly if a PBT compound would be formed.

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