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Species-specific developmental toxicity in rats and rabbits: generation of a reference compound list for development of alternative testing approaches

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Highlights

- Study comparison based entirely on publically available data
- An overall similar sensitivity of developmental toxicity in rat and rabbits was confirmed
- Only 10% of compounds were selective developmental toxicants in one of the species
- Maternal toxicity and pharmacokinetics are crucial for assessment of interspecies differences
- A list of reference compounds was provided to evaluate the potential of in vitro approaches

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Abstract

For regulatory information requirements, developmental toxicity testing is often conducted in two mammalian species. In order to provide a set of reference compounds that could be used to explore alternative approaches to supersede testing in a second species, a retrospective data analysis was conducted. The aim was to identify compounds for which species sensitivity differences between rats and rabbits are not caused by maternal toxicity or toxicokinetic differences. A total of 330 compounds were analysed and classified according to their species-specific differences. A lack of concordance between rat and rabbit was observed in 24% of the compounds, of which 10% were found to be selective developmental toxicants in one of the species. In contrast to previously published analyses the presented comparison is based entirely on publically data allowing validating and comparing alternative approaches for developmental toxicity testing. Furthermore, this list could be useful to identify mechanisms leading to species differences.

Abbreviations: FP, fluoroprostaglandin; DPP, dipeptidyl peptidase; HPPD, 4-Hydroxyphenylpyruvate dioxygenase. *Rat and rabbit showed no difference for the NOEL (fold change <10) for this compound, differences for the LOEL may have just been produced by selection of different concentrations for testing.

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