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Response to request

Expert-based *in silico* approaches are able to identify potential developmental toxicants and impart knowledge of a potential mechanism of action alongside a prediction. The expert rule-based *in silico* toxicity prediction system Derek Nexus contains structural alerts for developmental and reproductive toxicity endpoints[1]. The endpoint of teratogenicity has been developed through review of publicly available data and the identification of structure-activity relationships. The teratogenicity model within Derek Nexus contains over 50 structural alerts, which have been trained on teratogenic studies in animals, relevant *in vitro* data (e.g. embryo culture assays) and human case reports on teratogenicity, including FDA pregnancy categories. Structure-activity relationships were identified by experts who also considered both mechanistic evidence and chemical properties (such as reactivity). These relationships are captured in alerts which also outline relevant animal and human data and potential mechanisms leading to toxicity. By reporting this information to the user, Derek Nexus provides highly transparent predictions to support decision-making. In addition to alerts trained on toxicity data, the endpoint of teratogenicity is linked to alerts which predict for known mechanisms leading to malformations, such as 5alpha-reductase inhibition and glucocorticoid receptor agonism. When alerts of this type are present on a query compound, an extrapolation is made to provide a prediction for the endpoint of teratogenicity. Structural alerts such as these were developed from curation and expert analysis of non-adverse bioactivity data[2].

The approach of linking models for key events to apical toxicity endpoints aligns to the adverse outcome pathway (AOP) concept[3]. Organising models in such a way allows expansion of the chemical and biological space covered by prediction systems for complex *in vivo* endpoints of regulatory significance, such as developmental toxicity. Lhasa Limited aims to further improve it's *in silico* approaches for identifying developmental toxicants by generating additional models for AOPs leading to developmental and reproductive toxicity. Constructing a predictive AOP framework consisting of a suite of relevant AOPs and associated models can help support the development of integrated approaches to testing and assessment (IATA) for developmental toxicity endpoints using alternative assays[4].

The development of AOP-based models can be accelerated by data sharing, which enables a greater (and more relevant) coverage of the chemical space described by such models. Lhasa Limited is well-positioned to promote this, as we are a not-for-profit organisation and educational charity that facilitates collaborative data sharing projects in the pharmaceutical, cosmetics and chemistry-related industries. A core component of various data sharing initiatives is Vitic Nexus[5], which is a chemical database and information management system developed by Lhasa Limited. Examples of data sharing initiatives facilitated by Lhasa Limited, include the sharing of proprietary mutagenicity data amongst

a consortium[6], which enabled validation of *in silico* models and supports the reduction of unnecessary testing of chemicals where data already exists.

References

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