Organising data and knowledge to support the identification of chemicals with endocrine disruption potential

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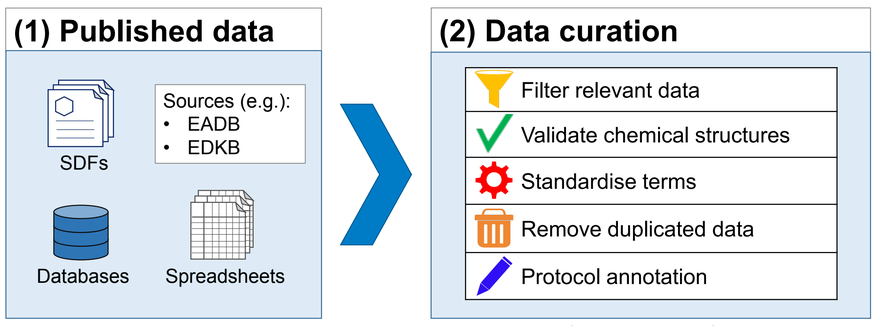
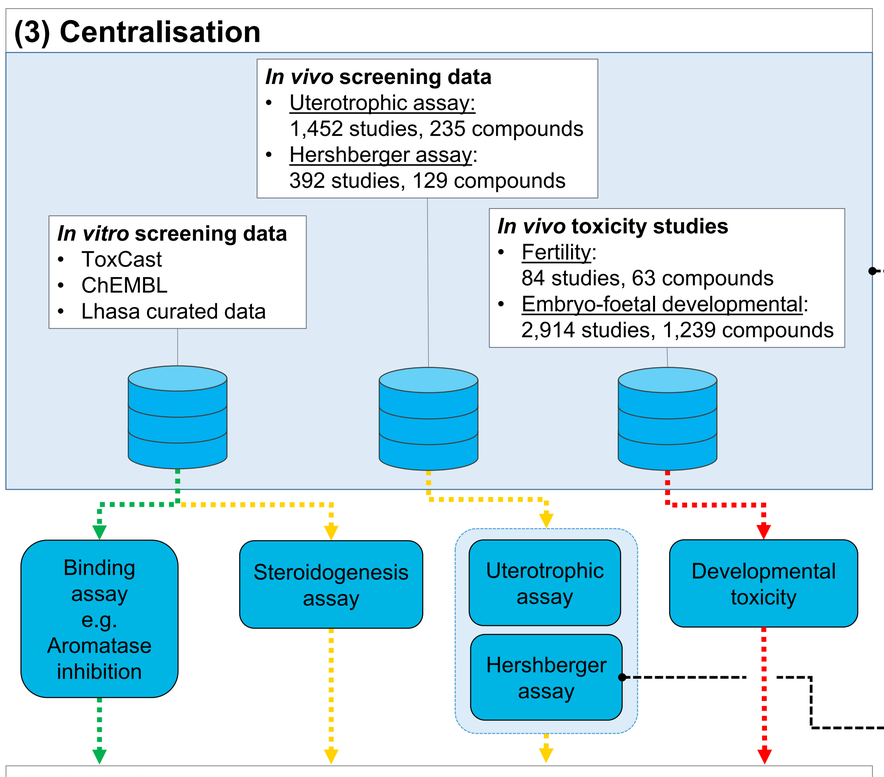
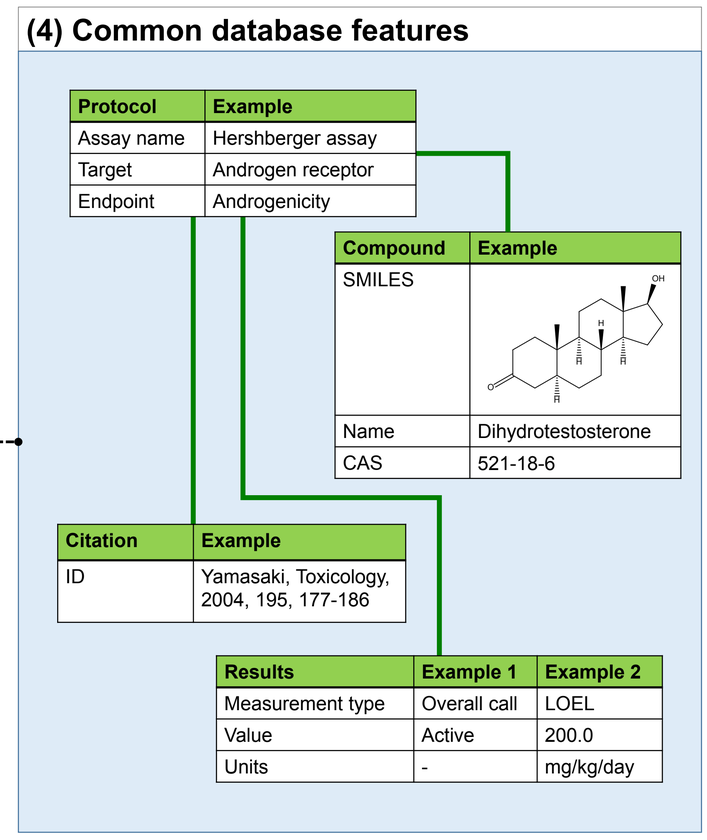
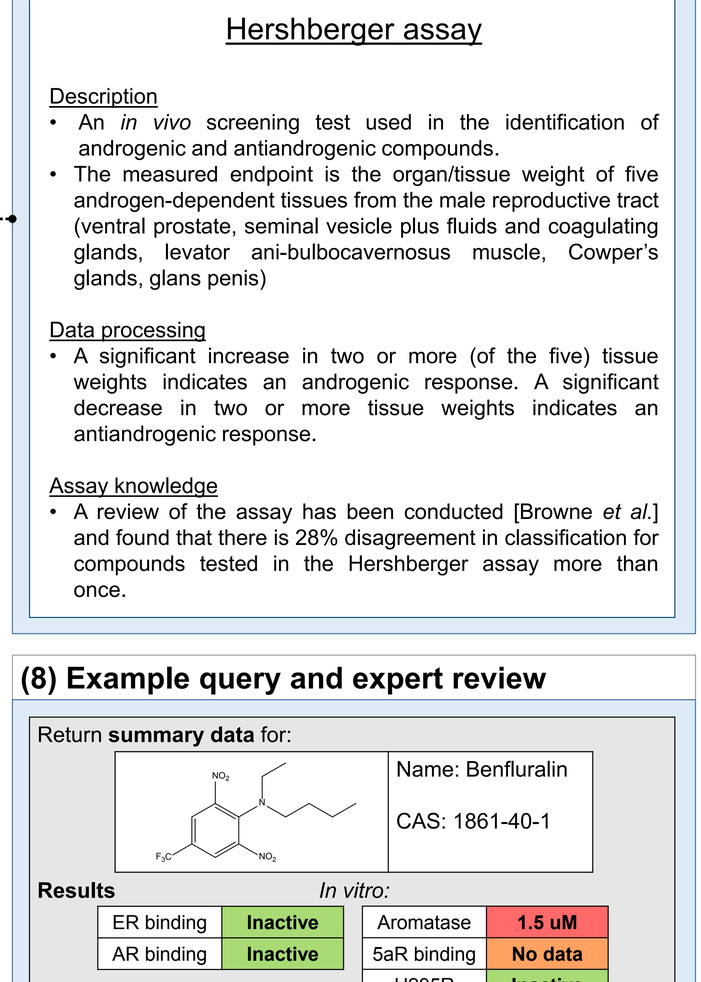
Introduction

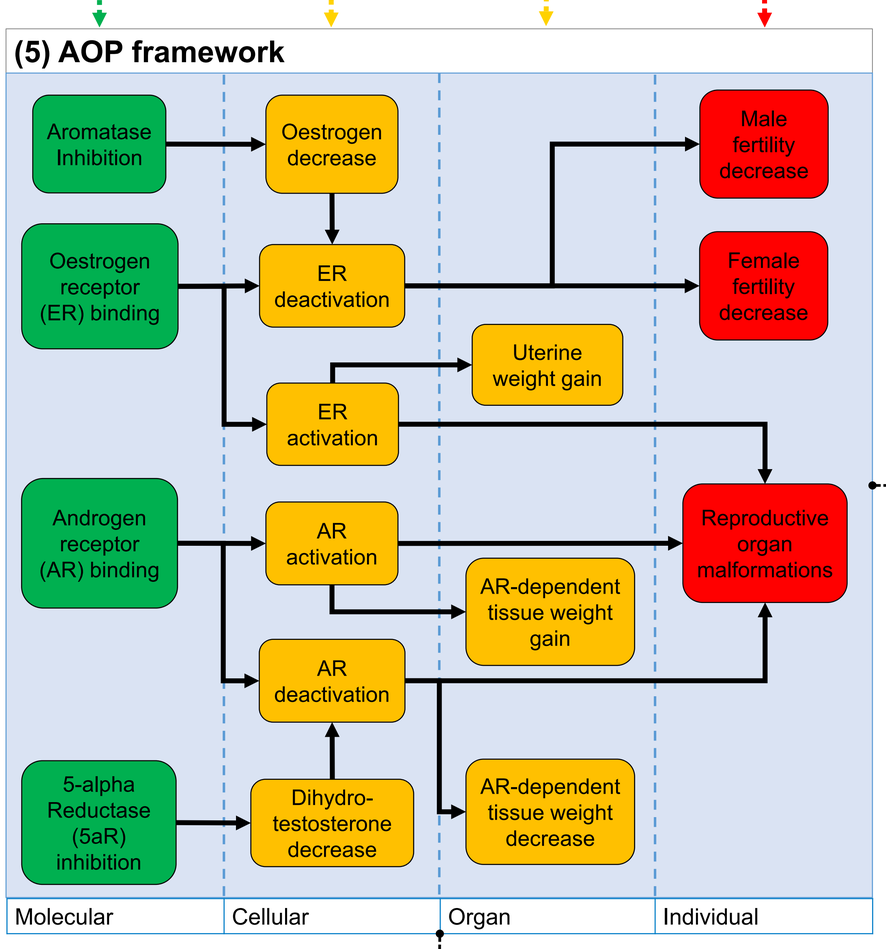
The endocrine system regulates important bodily functions including sexual development through the secretion of hormones. Disruption of these systems can lead to a range of adverse health effects. EU agencies have published guidance on how to identify molecules with endocrine disrupting properties, using the WHO definition of an endocrine disruptor [EFSA]. This definition requires the chemical to cause an adverse outcome through disruption of the endocrine system. Therefore to complete these types of assessment, both toxicity and mechanistic data are required. However, relevant data are often stored in multiple repositories, heterogeneous in nature and can lack context derived from mechanistic knowledge. Adverse outcome pathways (AOPs) provide a framework to centralise and provide context to such empirical data [Ankley *et al.*].

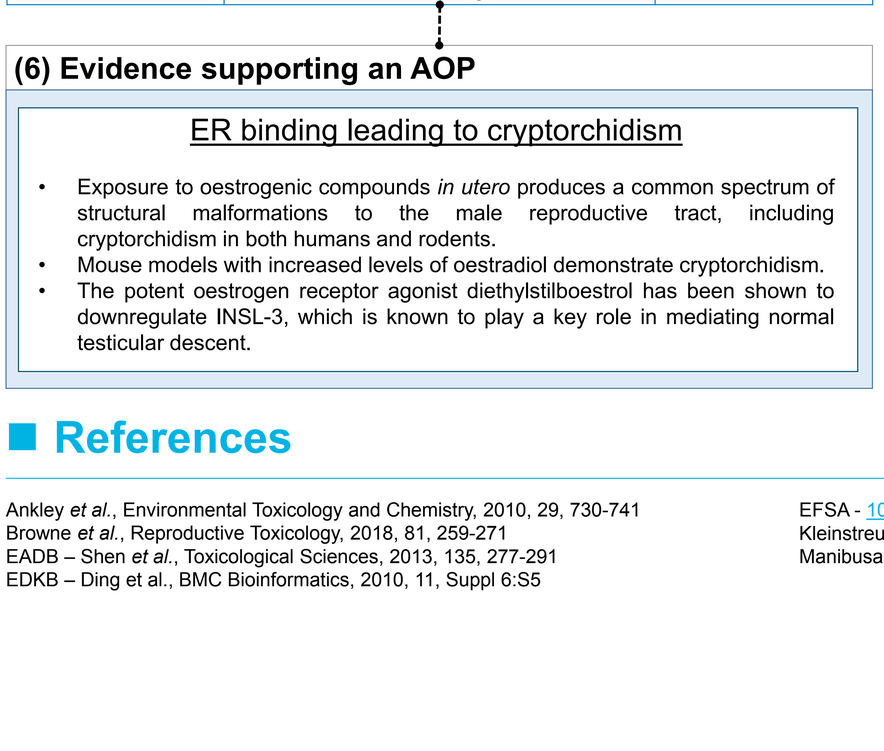












Assay data

- Numerous assays exist which can provide information on the endocrine disruption properties of a chemical [Manibusan and Touart]. Typically, these results are published in different locations and in a variety of formats **(1)**, which hinders risk assessors gathering relevant data to perform weight of evidence assessments.
- Literature searches were performed to identify repositories of Hershberger and Uterotrophic assay data. Identified datasets were downloaded and stored locally [Browne *et al.*, EADB, EDKB, Kleinstreuer *et al.*].
- The datasets were curated using a series of in-house curation rules **(2)**. These rules normalised both the chemical and protocol information, allowing for the data to be aggregated and the identification of duplicate entries from different sources.
- The standardised data was stored in a database designed to hold summary information for *in vivo* screening assays **(3)**. The database contains information on the structure of the tested compound, citations, protocol details and results for Uterotrophic assay and Hershberger assay studies **(4)**.
- This database can be used alongside other databases to store relevant compound information for an endocrine assessment, such as *in vitro* screening data (e.g. ToxCast) and developmental toxicity studies (in-house database).

AOP framework

- Mechanistic information can provide additional context to assay data. AOPs are able to act as repositories for such context and enable assay results to be related to one another.
- Literature review enabled developmental and reproductive toxicity AOPs stemming from binding to the oestrogen receptor, androgen receptor, aromatase and 5-alpha reductase to be synthesised **(5)**.
- Standardisation of the AOPs facilitated the creation, and storage in a database, of an AOP network.
- Each AOP contains key events annotated with relevant assays and key event relationships which document the evidence supporting the causal relationship between events **(6)**. Descriptions were created for each assay, which provide information on the protocol and reproducibility **(7)**. As assays are instances in the assay databases, the results for chemicals can be directly associated to relevant parts of the AOP.

Querying the data

- Organising assay data into an AOP framework enables a range of structure-based and pathway-centric queries to be performed. The results from such queries can be used to generate supporting evidence for risk assessments. For example, a risk assessor may want to retrieve relevant endocrine disruption data for a specific compound **(8)**.
- Database queries can be structured to meet the needs of the risk assessors, such as returning each piece of evidence separately to support a weight of evidence assessment. Alternatively, additional contextualisation can be placed on the data to summarise a range of studies for an individual compound or a number of compounds from a substructure query.

Conclusions

AOP networks associated with assay databases allow rapid retrieval of relevant empirical data and mechanistic evidence, to support assessments addressing the endocrine disruption potential of a compound. Future work will focus on the curation of additional endocrine-relevant AOPs and associated assays, followed by storage of the data in the AOP-based platform Kaptis, which is designed to support chemical risk assessments.

References

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