Drug Safety Database

The eTOX project has developed a drug safety database that holds unpublished toxicology reports donated by 13 members of the pharmaceutical industry and public toxicology data. The database currently includes over 1,800 substances and 7,000 studies which may be explored through a customised interface: eTOXsys.

This new system allows data mining for structurally similar compounds, for toxicological endpoints and pharmacological mode of action (for the latter see Table 1).

Ontologies & Compatibility with SEND

The eTOX database is linked to an ontology which has been developed by pathologists and toxicologists and is integrated with the SEND and INHAND initiatives (Table 2). Mapping of verbatim terms collected to the ontologies and code lists is done using OntoBrowser (Fig. 1).

In the interests of continued data donation during the sustainability phase we have also developed a tool to allow data in SEND submission format to be directly imported into the eTOX database.

Predictive Models

The eTOX computational modellers have developed well documented and verified predictive models (that are also accessible from within this interface) for endpoints including ADME (e.g. transporter inhibition), organ toxicity (e.g. cardiotoxicity, phospholipidosis, hepatotoxicity) and target safety pharmacology.

These models have been built on a chemical space with high relevance to drug development and that has relevance for other industry sectors.

Use case 1 (Bayer) – Framework for Early Drug Candidate Assessment

A framework consisting of four key approaches, each accessible through eTOXsys, was introduced to the early small molecule drug development pipeline of Bayer Pharma in September 2015 (Fig.6).

60 projects have been assessed so far at the transition point from hit to lead against this framework (as of May 2016).

Results for target search:

- Identical targets found for 10 projects (17%);
- Similar/related targets (down-stream targets, antagonists ↔ agonists) for 10 projects (17%);

Results for chemical similarity search:

- > 50% similarity in 34 projects (57%);
- > 60% similarity in 8 projects (13%);
- > 70% similarity in 3 projects (5%).

Use case 2 (Sanofi) – Relevance of Histopathology Findings Observed in a Rat Toxicity Study

Renal papillary necrosis was observed in a rat toxicity study. eTOXsys was searched for compounds with the same effect (Fig.7):

- 49 compounds (81 studies) where renal papillary necrosis was observed - for dogs, only 3 for dogs;
- 30 compounds with annotated pharmacology: 53% were EGF or VEGF inhibitors;
- Further literature research established a link between EGF receptors and renal papillary necrosis.

Conclusion and Outcome:

- Inhibiting EGF/VEGF (on- or off-target) could be related with the induction of renal papillary necrosis;
- Rats are more susceptible to chemically induced renal papillary necrosis compared to dogs/other species.
- Both conclusions used for assessment of relevance of renal papillary necrosis in rat for the human situation.

Use case 3 (Bayer) – Consideration of Potential Target Related Effects in Preclinical Screening

Bayer are currently investigating antagonists for specific receptors within the PDK, receptor family due to their prominent role in nicotinase. Searching eTOXsys for structurally similar compounds led to the retrieval of Fluopyram, a fungicide (Fig.8).

Reported treatment-related organ effects included:

- Liver (hypertrophy) in the mid-dose;
- Thyroid (hypothyrosis) in the high dose.

These effects are mechanistically well characterized and considered to be species-specific without relevance for human safety (Rouquié et al., 2014).

Conclusion and Outcome:

- The study director was advised to include thyroid in the screening panel (normally not included).
- If comparable liver or thyroid effects are observed during screening or pivotal 4-week toxicity studies, these can be de-risked based on the knowledge obtained from both eTOXsys and the literature.


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