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eTOX at EMA – Safety Working Party Meeting

(1st October 2013, London)



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

An update on the **eTOX** database and the prediction system was provided to the CHMP Safety Working Party (SWP) at EMA. The main focus was to develop a common understanding on the use of the system and expectation for validation of the systems. National representatives of the SWP expressed interest in accessing the database. In order to explore ways of cooperating between **eTOX** and regulatory authorities it was agreed to start a so-called Scientific Advice Procedure.

PROJECT NEWS

Modelling technical workshop in Barcelona, Spain

In July, FIMIM organized a hands-on workshop to present the eTOXlab, a framework for scaling up models to “industrial production” stage, to the modelers team in order to fit all models building requirements.

4th eTOXsys user meeting in Berlin, Germany, September 26th

The meeting reported on the progress of implementation of the virtual machines developed for several modules of eTOXsys, which were previously only available as web services. Most of the EFPIA companies were able to install the prototype of eTOXsys, which means that they now can access and use eTOXsys behind their firewalls. Integration of additional models and interfacing the database within eTOXsys will soon be available to the EFPIA partners – a major progress in the usability of the tools developed so far. In addition, agreement was achieved with regard to the use and license procedure for third party software needed in some of the predictive models. Since the numbers of available *in vivo* reports in the database have significantly increased, it was also discussed which organs or endpoints should be modeled first from the existing data sets.

KEYNOTE

Data and Knowledge Management is advancing Drug R&D

Message from IMI Principal Scientific Manager: Ann Martin

The recent approval of an extension for eTOX is not only an acknowledgement of the project's achievements, but also instrumental for connecting with other IMI projects for a more integrated collaboration and, ultimately, enhanced results for patients and society at large. Deeper connections with, for example, Open Phacts, MIP-DILI and EMIF are foreseen.



In Open Phacts, the time for answering a simple medicinal chemistry query was reduced from 6 days to mere seconds as a result of addressing the interoperability of public databases collaboratively. MIP-DILI is focused on early detection of drug-induced potential liver toxicity issues. In EMIF, the metadata of electronic health records in observational data sources are being catalogued to aid researchers in identifying relevant data to address particular research questions.

In turn, these projects enable connections with, for example, EHR4CR (where electronic health record systems of hospitals are queried simultaneously to identify the numbers of patients that meet e.g. eligibility criteria for clinical trials), eTRIKS (where the open low cost technical infrastructure TRANSMART is being rolled out to assist collaborative IMI and other projects with their KM platform needs) and ADVANCE (on creating a framework for vaccine benefit-risk assessment). This constellation of efforts, of which eTOX is a central pillar, can contribute through integrative efforts to a new understanding of toxicity as a continuum over the drug life cycle. Whereas Knowledge Management is not a goal in itself, it is a key means to allow this ecosystem to flourish, with derived improvements in drug discovery and development processes.

With this I want to end with a big thank you to the data scientists dedicated to the hard and often tedious tasks of data and knowledge management.

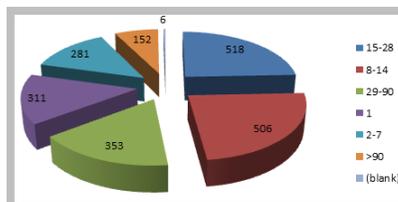


ACHIEVEMENTS

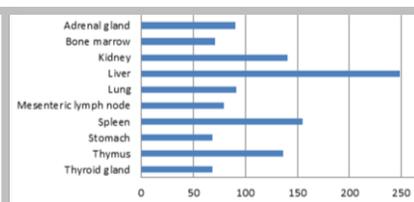
- Mid August 2013, Lhasa Limited launched the **sixth release of the Vitic Nexus eTOX database**, with 831 structures (584 confidential) linked to 2,127 study records contributed by **all** EFPIA partners of the eTOX consortium. In addition, it contains data from the **third release of the ChOX database** (162,287 substances and 701,181 records) and **OPEN TG GATES database** (170 substances and 304 records).

Vitic Nexus eTOX database 2013.3

Study duration in days

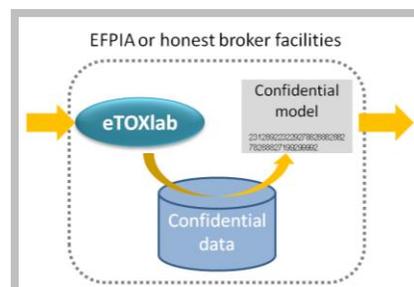


Top 10 – Organ Pathology Findings



- FIMIM has developed the **eTOXlab**, a framework for scaling up models to “industrial production” stage, which facilitates the simple generation and implementation of predictive models developed elsewhere. It is automatically accessible by the **eTOXsys**, offers easy model maintenance (including model re-training with new compounds and model versioning management) and takes into account the structure normalization, checks structural identity (i.e., if the query compound is in the training series?) and reports on Reliability Indexes and Applicability Domain information. On top of these features, it is overcoming the need to mask confidential information shared in the **Vitic Nexus eTOX database**.

eTOXlab

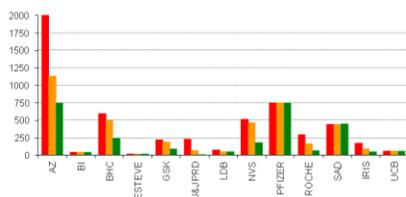


- DTU and FIMIM have integrated the expression data at different layer (system, organs, tissue, cells) for each of the 226 PPI shown in the **Tox-PPI**, a network visualization tool for toxicity-related protein-protein interactions.

REPORT-O-METER

5430

Up to date, 5430 reports have passed the clearance step and all EFPIA partners have data in Vitic **eTOX** database.



Cleared Reports submitted to CROs or in-house facilities for data extraction
Extracted Reports with processing by CROs or in-house facilities completed
Vitic Reports with data available at Vitic Nexus database

PUBLICATIONS

A full list of publications is available on <http://www.etoxproject.eu>

- ARTICLE-(FIMIM): Improving data and knowledge management to better integrate healthcare and research. Cases M, et al. *J Intern Med* 2013;274(4):321-8.
- ARTICLE-(DTU): The effect of network biology on drug toxicology. Gautier L, Taboureau O, Audouze K. *Expert Opin Drug Metab Toxicol*. In press. doi:10.1517/17425255.2013.820704.
- ARTICLE-(LJMU): Hepatotoxicity: A scheme for generating chemical categories for read-across, structural alerts and insights into mechanism(s) of action. Hewitt M, Enoch SJ, Madden JC, Przybylak KR, Cronin MTD. *Crit Rev Toxicol* 2013;43:537-58.

UPCOMING EVENTS

- 15-17.10.13** | 2nd International Conference on Medicinal Chemistry & Computer Aided Drug Designing, Las Vegas (USA). Info: <http://www.omicsgroup.com/conferences/medicinal-chemistry-computer-aided-drug-designing-2013/>
- 30-31.10.13** | Management Knowledge of Tissues Brussels, Annual Congress of the European Society for Translational Medicine. Brussels (Belgium). Jointly organised by the IMI projects DDMoRe, Open PHACTS and eTOX. Info: <http://www.eutranslationalmedicine.org/preliminary-agenda-2>
- 04-08.11.13** | CDISC International Interchange. Bethesda, MD (USA). Info: <http://www.cdisc.org/interchange?a=2438#2438>
- 16-17.01.14** | FutureToxII: *In Vitro* Data and *In Silico* Models for Predictive Toxicology. Chapel Hill, North Carolina (USA). Info: https://www.toxicology.org/ai/meet/cct_futureToxII.asp#program