ToxGPS® Prediction

Expert System for Toxicity Predictions

ToxGPS® Prediction is a toxicity knowledgebase providing *in silico* prediction models for the major human health and regulatory relevant endpoints. The predictions are based on mechanistically informed, probabilistic QSAR models and endpoint-specific structural knowledge (expert rules) which are combined in a final weight-of-evidence approach to minimize the uncertainty in the prediction.

Toxicity Endpoints

- Genetic toxicity
  - Bacterial reverse mutagenicity (Ames), *in vitro* chromosome aberration, *in vivo* micronucleus
- Carcinogenicity
  - Rat and mouse tumorigenicity
- Developmental and reproductive toxicity
  - Cleft palate, pregnancy loss
- Dermal toxicity
  - Skin irritation and sensitization (hazard & potency)
- Hepatotoxicity
  - Mammalian steatosis and mitochondrial toxicity, human drug-induced liver injury
- Acute toxicity (consumer products)

Training Sets

- Data preferentially collected from regulatory sources: US NTP, EPA and FDA, SCCS, HESS, ECETOC, ECHA, EFSA and open literature
- Different training sets for QSAR models and chemotype alerts (rule-based prediction), *e.g.*, for bacterial reverse mutagenicity
  - 2,864 compounds for QSAR models
  - 9,391 compounds for chemotype alerts
- Further details available in the respective ToxGPS® model documentations

ToxGPS Prediction

Prediction Components

- Combined QSAR and rule-based system with probabilistic outcome by weight-of-evidence
  - Global and MOA-based QSAR models including applicability domain check
  - Endpoint-specific chemotype alerts including severity scores (odds ratios)
- Nearest neighbor analysis of query linked to study data in ChemTunes Database

Modeling Approach

Statistical Modelling Methods	▪ Partial least squares & logistic regression ▪ *k*-nearest neighbors ▪ Random forest
Descriptors	▪ Structural rules (chemotypes) ▪ Physicochemical descriptors and QM parameters ▪ Biological assays
Training Set	▪ Curated structures and data ▪ Mechanistic/MOA categories ▪ Diversity for broad applicability domain

Contacts Molecular Networks GmbH, Nuremberg, Germany
Altamira LLC, Columbus, OH, USA
www.mn-am.com
+49 911 597 424 00
+1 614 824 4586
info@mn-am.com

MN AM