

GAINING ACCESS TO LARGE QUANTITIES OF STANDARDIZED ANIMAL TESTING DATA: CONSIDERATIONS, CHALLENGES AND ARE THESE TRULY INSURMOUNTABLE BARRIERS?

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INTRODUCTION

WHY DO WE NEED TO COLLECT THIS DATA?

Cost of drug and chemical development

- New medicines could be identified from “old” data
- Using this “free” data will cut the cost and time to market
- Those old reports hold useful data for future benefits

The 3Rs

- Each animal test creates data that is valuable not just for the safety or efficacy testing of the test article that it was exposed to, but also for the potential part that it can play within computational toxicology and replacement of further animals and/or tests



THE NORTH AMERICAN
3Rs COLLABORATIVE



National Centre
for the Replacement
Refinement & Reduction
of Animals in Research

Significant legislation has been passed covering different industries by agencies and governments including

- 7th Amendment to the Cosmetics Directive (EC 2013)
- REACH (ECHA 2016)
- Frank R. Lautenberg Chemical Safety for the 21st Century Act (US Safe Chemicals Act)

Resulting in a goal to reduce the amount of animal testing needed for each safety evaluation using alternative methods and to encourage data sharing amongst companies and stakeholders

In vitro and computational models and new ways of interpreting these data are all encouraged

PRESENTATION OVERVIEW

Definitions

Case studies

- Challenges
- Potential solutions

This is not an exhaustive overview!

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WHY SHOULD WE MODEL
FROM *IN VIVO* DATA?

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Contents lists available at ScienceDirect



ELSEVIER

Toxicology and Applied Pharmacology

journal homepage: www.elsevier.com/locate/taap

Current nonclinical testing paradigm enables safe entry to First-In-Human clinical trials: The IQ consortium nonclinical to clinical translational database

Thomas M. Monticello^{a,*}, Thomas W. Jones^b, Donna M. Dambach^c, David M. Potter^d, Michael W. Bolt^e, Maggie Liu^f, Douglas A. Keller^g, Timothy K. Hart^h, Vivek J. Kadambiⁱ

Industry wide nonclinical to clinical database was created to determine how safety assessments in animal models translate to First-In-Human clinical risk

Blinded database containing 182 molecules, animal toxicology data and clinical observations from phase I human studies

The analysis supported the current regulatory paradigm of animal testing in supporting safe entry to clinical trials

This confirms the utility of using this data in computational models

COMPUTATIONAL MODELS

CAN COMPUTATIONAL TOXICOLOGY MODELS BE BUILT?

Yes, but

- The model is only as good as the data entered
- The data is only as good as the technicians and scientists
- The quality can only be guaranteed by quality procedures

LHASA LIMITED – QSAR COMPUTATIONAL MODELS



DEREK NEXUS



METEOR NEXUS



MIRABILIS



SARAH NEXUS



SETARIA



VITIC



ZENETH



ICH M7



SKIN
SENSITISATION



A good example is the products generated by companies such as Lhasa

- Data is identified & harvested from many sources; peer review journals, provided by private companies or available on public websites
- Data is graded based on it's source, quality processes, information etc.

The model is only as good as the data entered!!!

Other providers include, but not limited to: Simulations Plus, Leadscope

THE BLOCKERS

WHAT ARE THE BLOCKERS TO CREATING THESE MODELS?

The critical blockers are

- IP
- Competition
- Confidentiality
 - Business
 - Intellectual
 - Scientific
 - “Chemical”
- Ontology

But, we also need to consider

- Cost
- Time constraints

IP, COMPETITION AND CONFIDENTIALITY

These are, on the surface, the insurmountable barriers.

- Why loose IP to a competitor?
- What happens if a company discovers a blockbuster drug using data generated from a rival company?
 - Does the rival have a claim to this molecule?

But, benefits should be considered to evaluate if they outweigh these costs

- IP and confidentiality will be retained by legal agreements
- Companies are already sharing data

CASE STUDY 1: NANO TOXICITY

DATA

data.eNanoMapper.net is a public database hosting nanomaterials characterization data and biological and toxicological information. The database provides various possibilities to search and explore information, and to download data in various standard formats. The database supports data upload through configurable Excel templates. *(Contact the eNanoMapper team for support)*

Search data:

ENM APPLICATIONS

- [> ONTOLOGY](#)
- [> DATA](#)
- [> MODELLING](#)
- [> ALL](#)

ENANOMAPPER

eNanoMapper was an FP7 EU funded project completed in January 2017

- It delivered data and computational infrastructure; it was not a data generation project instead data was provided by other projects (<https://search.data.enanomapper.net/enm/>)
- Later, the NANoREG project used the eNanoMapper database to transfer nanosafety data generated by **60 partners** under **open license** (https://search.data.enanomapper.net/nanoreg_about.html)

OK, but what about industry with competition and IP to consider?

GAINING ACCESS TO HIGH QUALITY DATA

WHAT IS THE DEFINITION OF HIGH QUALITY DATA?

Published in a peer review journal?

- What quality processes were incorporated into this research project?
- What was the quality of the peer review?
- Was the work performed GLP-like?

Generated under GLP?

- Is there a national accreditation scheme?
- Is there regular auditing by authorities?

I digress, so I define Quality Data as generated under GLP

WHAT IS THE DEFINITION OF STANDARDIZED ANIMAL TESTING DATA?

Regulatory toxicology generates most of its data from

- Standardized methods
 - OECD Test Guidelines, ICH Guidance, Regulatory Guidance
- In-bred animals
 - Charles River CD Rat

The laboratories performing GLP regulatory tests perform many tests on

- a huge variety of test articles
- but reproducibly following
 - standardized protocols
 - standard operating procedures

With independent Quality Auditing

GAINING ACCESS TO ANIMAL DATA

CASE STUDY 2:
LUECHTEFELD *ET AL* (2018)



SOT | Society of
Toxicology
www.toxsci.oxfordjournals.org



TOXICOLOGICAL SCIENCES, 2018, 1–15

doi: 10.1093/toxsci/kfy152

Advance Access Publication Date: July 11, 2018

Research Article

Machine Learning of Toxicological Big Data Enables Read-Across Structure Activity Relationships (RASAR) Outperforming Animal Test Reproducibility

Thomas Luechtefeld,^{*,†} Dan Marsh,[†] Craig Rowlands,[‡] and Thomas Hartung^{*,§,1}

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NEWS · 11 JULY 2018

Software beats animal tests at predicting toxicity of chemicals

Machine learning on mountain of safety data improves automated assessments.

Richard Van Noorden

To improve the software, Hartung's team created a giant database with information on roughly 10,000 chemicals based on some 800,000 animal tests. These data were originally collected by the European Chemicals Agency (ECHA) in Helsinki as part of a 2007 law known as REACH

Hartung's team extracted the available data into a machine-readable database. This led to a legal dispute between Hartung and ECHA, because the agency said the study details belonged to the companies that conducted the tests.

In 2017, Hartung agreed not to publish his own database. The ECHA also released key study outcomes — but not all data — in a separate public file.

CASE STUDY 3: REPEAT DOSE TOXICITY

Arch Toxicol (2018) 92:587–600

<https://doi.org/10.1007/s00204-017-2067-x>

REGULATORY TOXICOLOGY

Predicting in vivo effect levels for repeat-dose systemic toxicity using chemical, biological, kinetic and study covariates

**Lisa Truong^{1,3} · Gladys Ouedraogo² · LyLy Pham¹ · Jacques Clouzeau² ·
Sophie Loisel-Joubert² · Delphine Blanchet² · Hicham Noçairi² · Woodrow Setzer¹ ·
Richard Judson¹ · Chris Grulke¹ · Kamel Mansouri^{1,4} · Matthew Martin^{1,5}**

Systemic effect levels were curated from EPA ToxRefDB, HESS-DB and COSMOS data bases covering 4379 *in vivo* studies with 1247 chemicals

Systemic effects in mammalian models are a complex function of chemical dynamics, kinetics and inter and intra-individual variability

Systemic effect levels were modelled at the study level by leveraging study covariates such as

- study type, strain, administration route

in addition to multiple descriptor sets including

- chemical
- biological
- kinetic, metabolism, gene expression, oxidative stress & cytotoxicity

The building of a predictive model of *in vivo* effect levels for repeat-dose systemic toxicity is a complex process due, in part, to varying experimental design and endpoint inclusion

This generated an predictive model of systemic effect levels for use as a safety assessment tool generating predictions for over 30,000 chemicals

How easy is it to obtain the large amounts of high quality data and is there an opportunity to gain?

CASE STUDY 4: SEND

SEND

FDA COMPLIANT DATA SUBMISSION FOR TOXICOLOGY

Study Reports	Carcinogenicity
Pharmacology	Long-Term Studies
Primary Pharmacodynamics; <i>in vitro</i> and <i>in vivo</i>	Short- or Medium-Term Studies
Secondary Pharmacodynamics	Other Studies
Safety Pharmacology; <i>in vitro</i> and <i>in vivo</i>	Reproductive and Developmental Toxicity
Pharmacodynamic Drug Interactions	Fertility and Early Embryonic Development
Pharmacokinetics	Embryo-Fetal Development
Analytical Methods and Validation Reports	Prenatal & Postnatal Development including maternal function
Absorption	Studies in which Juvenile animals are dosed and/or further evaluated
Distribution	Local Tolerance
Metabolism	Other Toxicity Studies
Excretion	Antigenicity
Pharmacokinetic Drug Interactions	Immunotoxicity
Other Pharmacokinetic Studies	Mechanistic Studies
Toxicology	Dependence
Single-Dose Toxicity	Metabolites
Repeat-Dose Toxicity	Impurities
Genotoxicity; <i>in vitro</i> and <i>in vivo</i>	Other

SEND SUMMARY

IN SCOPE DATASETS FOR APPLICABLE STUDY TYPES IN SCOPE FOR SEND 3.0

Default Study Details

- Study plan information
- Subject elements
- Exposure/ dosing
- Relationship datasets
- Comments

Body weights

Body weight gains

Clinical signs including ophthalmology

Food and water consumption

Clinical Pathology

- Hematology
- Clinical chemistry
- Urinalysis
- Coagulation
- Body fluids
- Urine chemistry
- Bone marrow smear evaluations

Bioanalysis Evaluation

Toxicokinetic Evaluation

Electrocardiography

Vital Signs

- Body temperature
- Diastolic blood pressure
- Heart rate
- Automated heart rate
- Mean Arterial Pressure
- Respiratory Rate
- Systolic blood pressure
- SpO2 value
- Respiratory rate

Palpable masses

Organ weights

Necropsy/ macroscopic findings

Histopathology findings

Tumor findings

Mortality/ disposition

SEND

Ontology (Terminology) is the Key!

Raw data collected electronically *e.g.* Provantis

Toxicology study report generated

SEND then “data-mines” the raw data based on Charles River fixed ontology

There are **10,242 separate commands** in this fixed ontology

This was an expensive programme to develop and is an added price industry is paying to run. **Cost** could be the insurmountable obstacle!

Is SEND a solution already in place to mine the data?

Note: I do not know if ontology is Charles River specific or specified by FDA

CONCLUSIONS

CONCLUSION

There are opportunities and barriers for gaining access to large quantities of standardized animal testing data

The benefits and opportunities far outweigh the barriers

The barriers are not insurmountable

- Businesses & authorities can create the environment to share this data
- Protected by the computational models themselves

The computational technology is available

There are solutions such as SEND which can be used to data-mine

Cost and time could be the biggest problem of all



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