

Predictive Models for Acute Oral Systemic Toxicity Workshop – End User Application

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Disclaimer

The views expressed are those of the author and do not necessarily reflect the official policy or position of the Air Force, the Department of Defense, or the U.S. Government.

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Introduction

- **Exposure Science in the 21st Century: A Vision and a Strategy (NAS, 2012)**

“long-term vision for exposure science motivated by the advances in analytical methods, sensor systems, molecular technologies, **informatics, and computational modeling**. That vision was to inspire a transformational change in the breadth and depth of exposure assessment that would improve integration with and responsiveness to toxicology and epidemiology”
- **Using 21st Century Science to Improve Risk-Related Evaluations (NAS, 2017)**

“a future in which toxicology relied primarily on high-throughput in vitro assays and **computational models** based on **human biology** to evaluate potential **adverse effects** of chemical exposures”

Operational Toxicology

- **Applied toxicology that is part of the DoD operational process and in my case especially the USAF mission focus areas, both in the training environment and deployed exposure scenarios – for new or unknown chemicals, often requires a rapid “Operational” decision so as to provide information for decision makers in the command chain.**

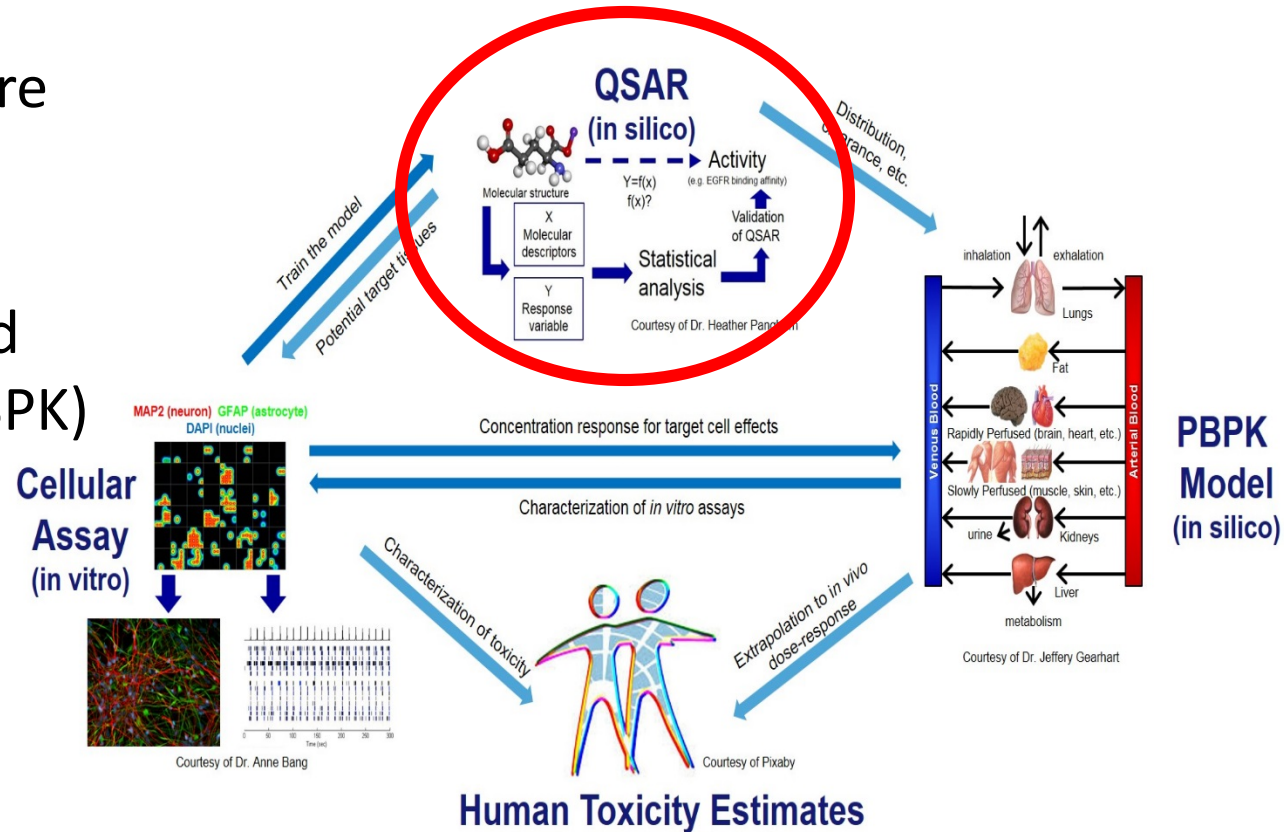
Extreme operational environments... High altitude (low pressures), divers (high pressures), G forces, special operations etc..

Goal

- Our overarching goal is to deliver a rapid, more cost effective means by which to determine occupational and deployment human exposure standards and health risk estimates for chemical toxicological exposures with high scientific fidelity.

In vitro to *in vivo* Extrapolation

- Quantitative Structure Activity Relationship (QSAR) Modeling
- Physiologically-Based Pharmacokinetic (PBPK) Modeling
- In vitro models – cellular assays



Questions Posed

- **What factors should be considered when evaluating computational approaches for use in predictive toxicology?** *Robust, Rapid, Cost efficient, Human centric predictions*
- **At what point is a computational approach suitable for an actual risk assessment?** *This depends upon the application... for Operational settings, we often need a rapid response that may be of a lower predictability, but for early phases is acceptable, later stages and moving from Operational to more “Occupational” Standards, more precise processes can be employed.*

Questions Posed

- **Should regulatory agencies be required to use open source and freely available software (as in no cost) when making a screening, regulatory or policy decision?**

There are pros and cons for open source vs proprietary software – cost, free from restrictions, crowd sourcing innovation vs defined product, security, functionality... in practice we all use both in one fashion or another

Questions Posed

- **Other than model performance, what are the key drivers for acceptance of these types of approaches?**

*The key priorities and mission focus of each organization answering the toxicological question being posed. Scope of the universe of known chemical entities and their unknown risks, limited or unknown nature of relying purely on rodent animal acute lethality toxicity responses in light of the drive for mechanistic **Mode of Action** and **Adverse Outcome Pathway** health risk approaches.*

Questions Posed

- **When is mechanistic information essential in order to accept predictions, and when is having a good performing model is enough?**

*Ideally **mechanistic information** should be the basis of the first toxicity estimates, but this will be dictated by knowledge of the chemical domains considered, priorities of questions to be answered.*

As discussed at this meeting, currently model performance is being limited by lack of experimental details, limited mechanistic information, or limited chemical data numbers....

Questions??

Debate??

Questions Posed

- **Industry perspectives about what their experiences are when it comes to computational approaches, how they see the use of machine learning models in product development and regulatory submissions, and what they can or cannot use.**

Regulatory Toxicology

- Regulatory toxicology is the process whereby information relevant to the evaluation of the toxicity of agents is obtained by organizations and evaluated by or on behalf of governmental or international organizations.
- The aim is to protect workers, consumers, the public generally and the environment.
- The requirements of many regulatory systems are closely defined in terms of both the studies required and the interpretations to be placed upon the results obtained.

Illing et al, "Regulatory Toxicology", In: General, Applied and Systems Toxicology, 2011