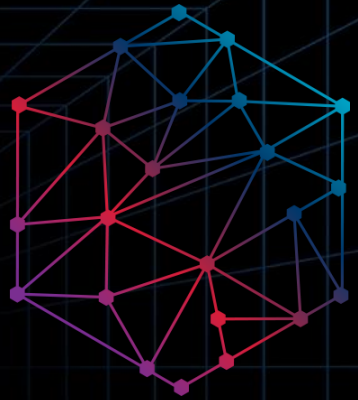
Model-Informed Drug Development

# MIDD+

2021 Virtual Conference



# Application of the DILIsym® QST drug-induced liver injury software to evaluate the carcinogenic hazard potential of acetaminophen

**Brett Howell, President of DILIsym Services Division**

SimulationsPlus

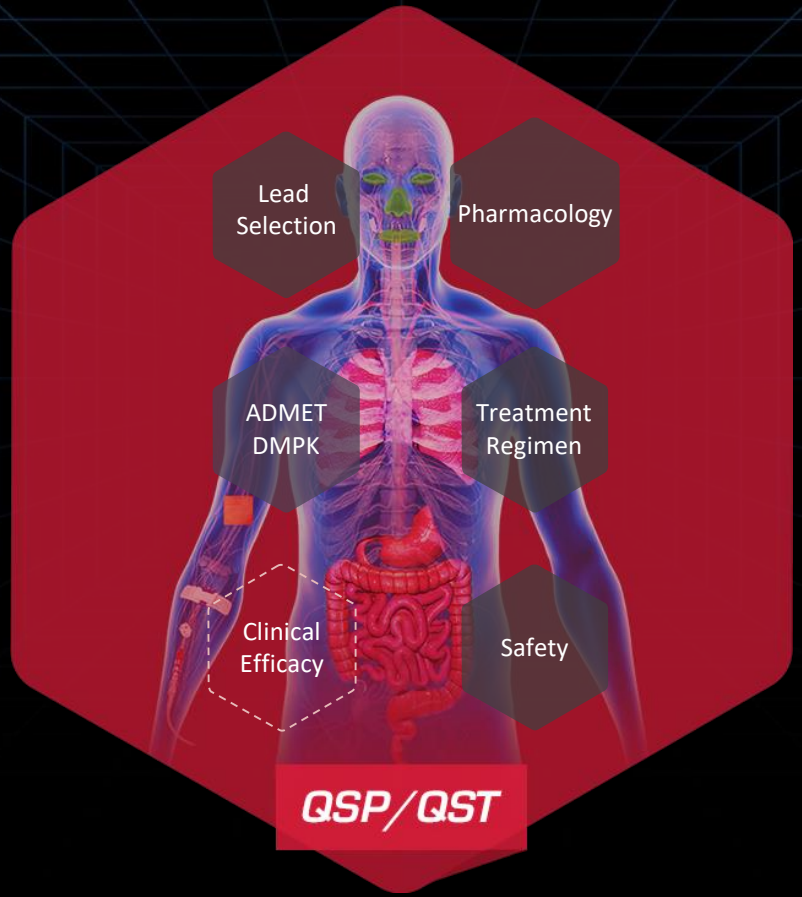
Cognigen | DILIsym Services | Lixoft

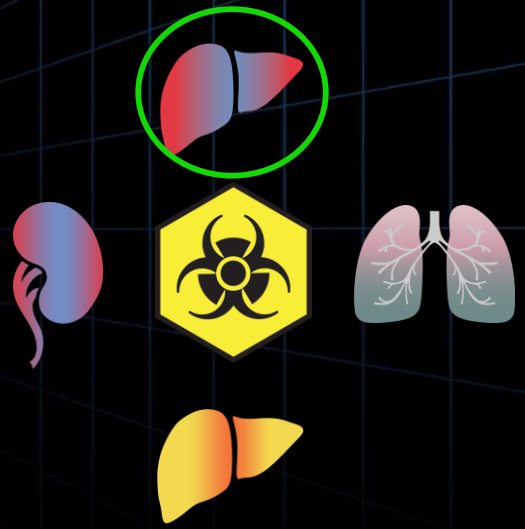
# Our *QSP/QST* Solutions Employ Comprehensive, Mechanistic Models to Address Key Drug Development Areas

DILIsym®
RENAsym®
NAFLDsym®
IPFsym™
RADAsym™

## Services

QSP Consulting
QST Consulting



Model-Informed Drug Development
MIDD+
2021 Virtual Conference

SimulationsPlus
Cognigen | DILIsym Services | Lixoft

# Executive Summary

- DILIsym is a mechanistic, mathematical model that has been constructed to support pharmaceutical risk assessment and decision making
  - Intersection of compound distribution and metabolism (PBPK), hepatotoxicity mechanisms, and patient variability

- DILIsym has been applied to support decisions related to compound DILI risk throughout the clinical development pipeline and included in regulatory submissions

- This Quantitative Systems Toxicology work supported a broader scientific weight-of-evidence assessment of the carcinogenicity hazard potential of acetaminophen
  - The results support that acetaminophen is not a carcinogenicity hazard to human health under any conditions
  - ***The FDA agreed, in writing***

# Presentation Outline

- Overview of the DILIsym Software
- DILIsym Application: Acetaminophen Risk Assessment
- General Application Take-aways or Observations
- Questions

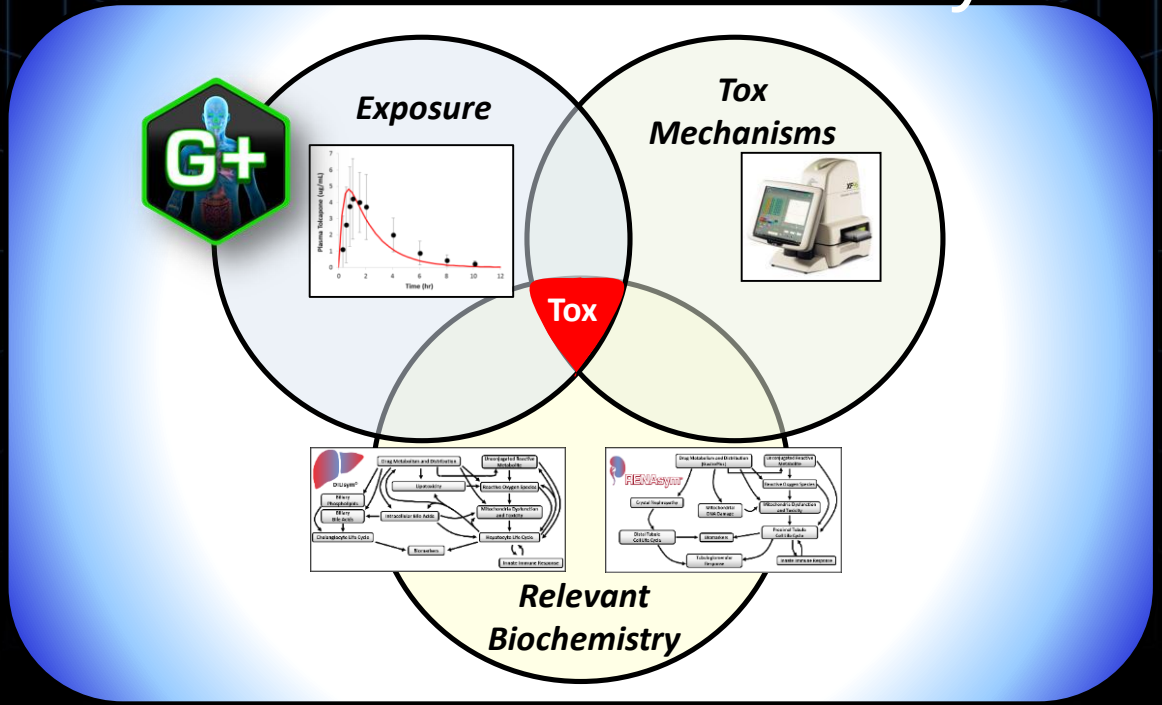
# DILIsym Services QST and QSP Models


- Predicts drug-induced liver disease
- v8A released Q1 2019
- Includes mechanistic representation of normal hepatic biochemistry
- Evaluated >80 compounds with 40+ companies

***So how can DILIsym help my organization?***

- Predict DILI liabilities beforehand and save $$$
- Choose the lead candidate ***most likely to succeed*** from a DILI standpoint
- Communicate with regulators on safety issues with information they have requested from others numerous times and from a platform they license (FDA)
- ***Keep patients safer….***

# QST Predicts Tox via the Intersection Between Exposure, Mechanisms, and Inter-Patient Variability



# The DILI-sim Initiative is a Partnership Between DILIsym Services and Pharmaceutical Companies to Minimize DILI



DILIsym Services
A SIMULATIONS PLUS COMPANY

janssen
gsk GlaxoSmithKline
GILEAD
DILIsym
abbvie
SERVIER

Select Sample of Current Companies Licensing DILIsym

For a comprehensive review of progress, see
***Watkins 2019: Clin Transl Sci***

- *Overall Goals*
  - *Improve patient safety*
  - *Reduce the need for animal testing*
  - *Reduce the costs and time necessary to develop new drugs*
- *History*
  - *Officially started in 2011*
  - *20 major pharmaceutical companies have participated*
  - *Members have provided compounds, data, and conducted experiments to support effort*
  - *Over $10 million total invested in project*
- ***At least 29 cases of use for regulatory purposes***
- ***Over 30 publications***

# Top DILIsym Related Content from 2020

## U.S. FDA Renews Annual DILIsym Software Licenses

*FDA Maintains Access to Leading Liver Injury Software Program*

May 06, 2020 08:30 AM Eastern Daylight Time

RESEARCH TRIANGLE PARK, N.C.--(BUSINESS WIRE)--DILIsym Services, Inc., a Simulations Plus company (Nasdaq: SLP) and a leading provider of simulation and modeling software for pharmaceutical safety and efficacy, today announced that the U.S. Food and

Available online at www.sciencedirect.com
ScienceDirect
Current Opinion in Toxicology

## DILIsym: Quantitative systems toxicology impacting drug development

Paul B. Watkins

Pharm Res (2020) 37:24
https://doi.org/10.1007/s11095-019-2726-0

RESEARCH PAPER

## Comparison of the Hepatotoxic Potential of Two Treatments for Autosomal-Dominant Polycystic Kidney Disease Using Quantitative Systems Toxicology Modelin

J. L. Woodhead[1] • L. Pellegrini[2] • L. K. M. Shoda[1] • B. A. Howell[1]

OXFORD SOT Society of Toxicology
academic.oup.com/toxsci
TOXICOLOGICAL SCIENCES, 177(1), 2020, 84–93
doi: 10.1093/toxsci/kfaa093
Advance Access Publication Date: 24 June 2020
Research Article

## Mechanistic Investigations Support Liver Safety of Ubrogepant

Brenda Smith,* Josh Rowe,*,1 Paul B. Watkins,† Messoud Ashina,‡ Jeffrey L. Woodhead,§ Frank D. Sistare,¶ and Peter J. Goadsby‖

*Allergan plc, Irvine, California; †Eshelman School of Pharmacy and Institute for Drug Safety Sciences, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; ‡Department of Neurology, Danish Headache Center, Faculty of Health and Medical Sciences, University of Copenhagen, København, Denmark; §DILIsym Services, Durham, North Carolina; ¶Merck & Co., Inc., West Point, Pennsylvania and ‖NIHR-

ELSEVIER
Regulatory Toxicology and Pharmacology
journal homepage: www.elsevier.com/locate/yrtph

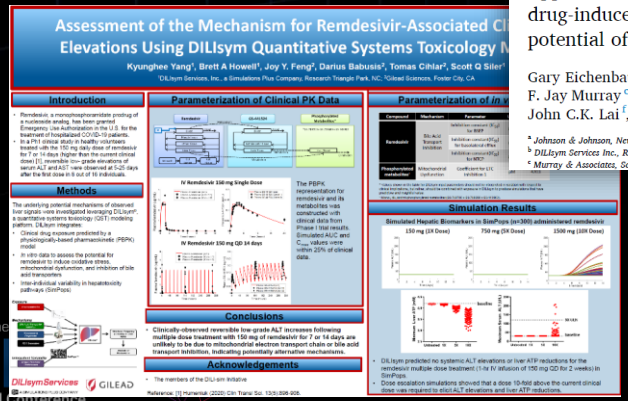
## Application of the DILIsym® Quantitative Systems Toxicology drug-induced liver injury model to evaluate the carcinogenic hazard potential of acetaminophen

Gary Eichenbaum[a,*], Kyunghee Yang[b], Yeshitila Gebremichael[b], Brett A. Howell[b], F. Jay Murray[c], David Jacobson-Kram[d], Hartmut Jaeschke[e], Edwin Kuffner[a], Cathy K. Gelotte[a], John C.K. Lai[f], Daniele Wikoff[g], Evren Atillasoy[f]

[a] Johnson & Johnson, New Brunswick, NJ, 08901, USA
[b] DILIsym Services Inc., Research Triangle Park, NC, 27709, USA
[c] Murray & Associates, San Jose, CA, 95138, USA

## Assessment of the Mechanism for Remdesivir-Associated Cl Elevations Using DILIsym Quantitative Systems Toxicology M

Kyunghee Yang[1], Brett A Howell[1], Joy Y. Feng[2], Darius Babusis[2], Tomas Cihlar[2], Scott Q Siler[1]
[1]DILIsym Services, Inc., a Simulations Plus Company, Research Triangle Park, NC; [2]Gilead Sciences, Foster City, CA




## First Approved Cancer Treatment for TGCT Included DILIsym Simulations in FDA Review

*FDA Review Cites DILIsym Results as Part of Turalio® Submission*

October 27, 2020 08:30 AM Eastern Daylight Time

RESEARCH TRIANGLE PARK, N.C.--(BUSINESS WIRE)--DILIsym Services, Inc., a Simulations Plus company (Nasdaq: SLP) and a leading provider of modeling and simulation software for pharmaceutical safety and efficacy, today announced that simulations using their DILIsym® software were noted in a U.S. Food and Drug Administration (FDA) review of the New Drug Application for Pexidartinib (Turalio®, marketed by Daiichi Sankyo, Inc.), which was subsequently approved as the first systemic therapy for treatment of symptomatic tenosynovial giant cell tumor (TGCT). The FDA review also included the general comment

# DILI-sim Initiative

Consortium Distributing and Developing Software for
Predicting and Preventing Drug-Induced Liver Injury (DILI)

**Dr. Paul B. Watkins**
Director, DILI-sim Initiative;
Chair, Scientific Advisory Board

DILIsym®

## *Join Today and Support Cutting Edge Research to Make Patients Safer!*

### *Benefits of Stage 4 DILI-sim Membership*

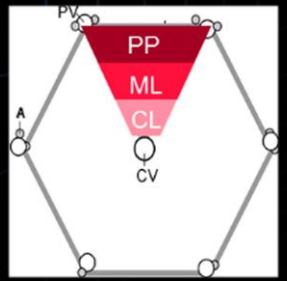
- Two global, floating end-user licenses to the current version of the DILIsym® software package
- Includes integrated GastroPlus® version, when available
- Licenses to an add-on feature of DILIsym that enables use of server/cloud parallel computing with unlimited nodes (upcharge for non-members)
- 31% discount on consulting services related to DILIsym
- 10 total hours of private training for employees of the Member company related to DILIsym use
- The right to vote on DILIsym software development items going forward
- Attendance at DILI-sim research, development, and software update meetings/discussions (typically held quarterly)
- Access to the DILIsym Discovery Support Program (DDSP), a Members-only, lower cost program for enabling internal software use

*Now includes **RENAsym™ Consortium** membership at no additional cost!*

DILIsym Services
A SIMULATIONS PLUS COMPANY

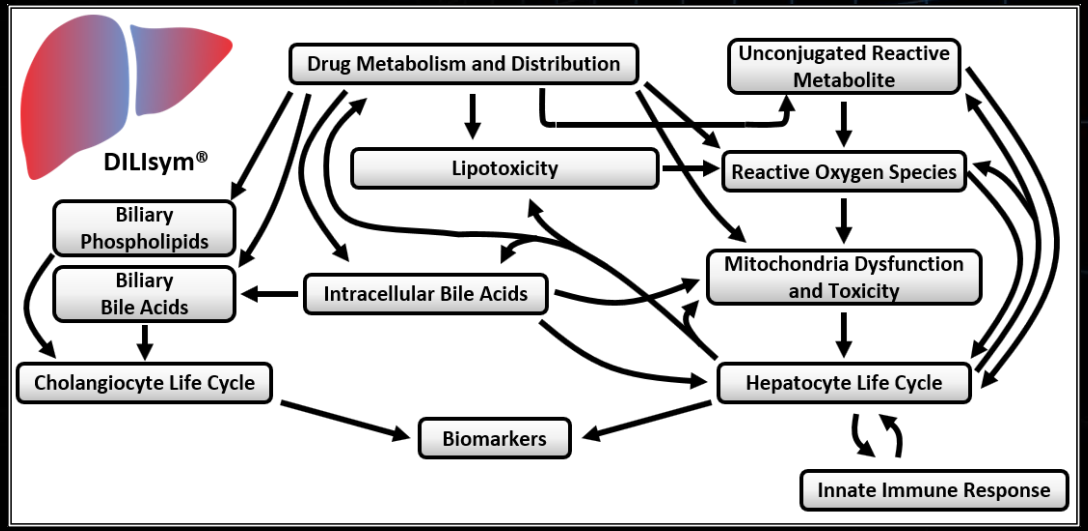
# DILIsym Software Overview

- **Multiple species: human, rat, mouse, and dog**
  - Population variability
- **The three primary acinar zones of liver represented**
- **Essential cellular processes represented to multiple scales in interacting sub-models**
- **Over 80 detailed representations of optimization or validation compounds with ~80% success**
- **Single and combination drug therapies**



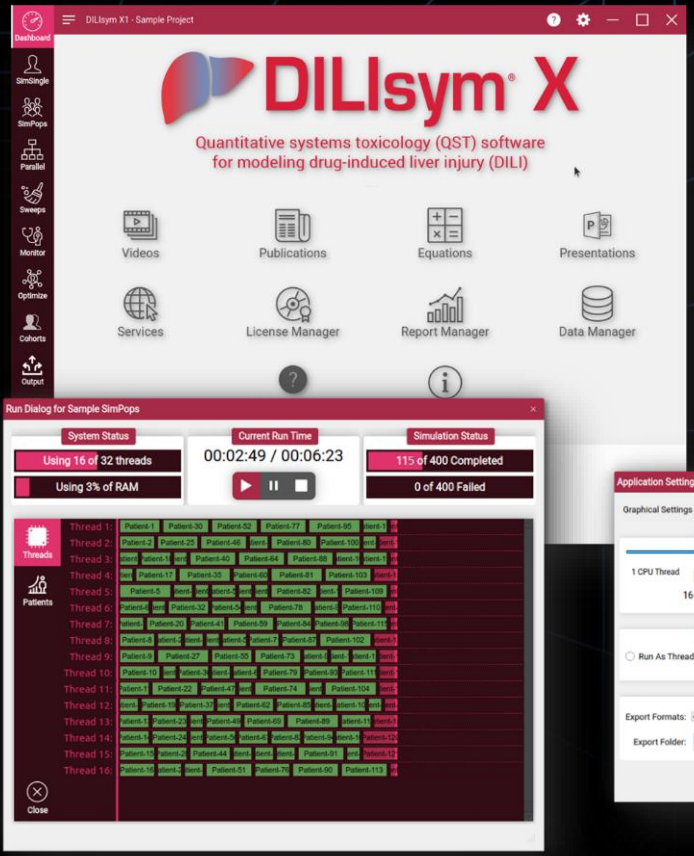


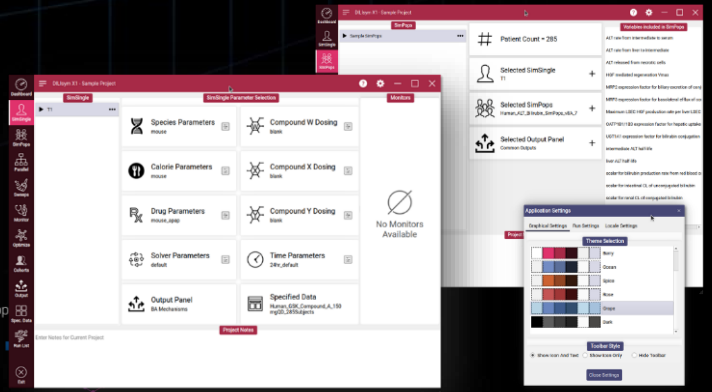
*eDISH*



# Highlights of DILIsym Version X (DSX)

- Completely new software platform!
  - Much faster and more user friendly
  - Command line and GUI options
  - No reliance on MATLAB runtime or base MATLAB
  - Server/cloud computing capability coming soon…..
- 4 NEW exemplar Compounds included with varying clinical presentations
  - PF-04895162 *(Generaux 2019)*
  - Efavirenz
  - Anastrozole
  - Tamoxifen
- 2 New SimCohorts that include variability in susceptibility to liver injury and biomarker-related parameters (ALT and bilirubin)



# DILIsym Utilizes Various Data Types to Inform Decisions

***Exposure Data***

**PBPK Modeling**

- **Compound Properties**
  - Tissue partition coefficients
- **Tissue penetration studies**
  - *Liver to blood ratio*
- **Pharmacokinetic data**
  - *Absorption, extra-hepatic clearance, metabolites*
- ***in vitro* data**
  - *Metabolite synthesis, active uptake*

***Modeling & Simulation***

**Simulations and Assays inform:**

- **Prediction of DILI risk**
- **Participating DILI mechanisms**
- **Characteristics of patients at risk for DILI**
- **Drug dosing paradigms**
- **DILI monitoring strategies**

***In vitro Mechanistic DILI Data***

**Assays performed to determine quantitative aspects of DILI mechanisms**

- **Oxidative stress**
  - *Direct and reactive metabolite-mediated*
- **Mitochondrial toxicity**
  - *ETC inhibition*
  - *Uncoupling*
- **Bile acid / phospholipid transporter inhibition**
  - *BSEP, MRP3 and 4, NTCP, (MDR3)*
- **Bilirubin transport/metabolism**
  - *OATP1B1, OATP1B3, UGT1A1, MRP2, MRP3*

***Clinical Data***

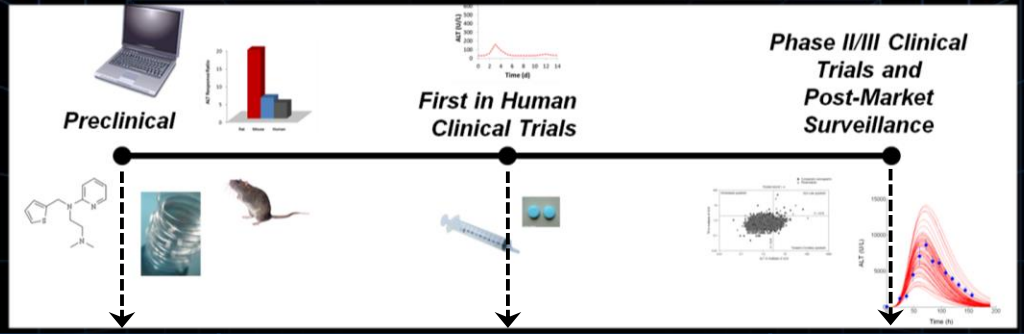
- **Dosing Protocols, fasting/fed state, meal times**
- **Anthropometric data**
  - **Body weight, age, ethnicity**
- **Pharmacokinetic data**
  - **Absorption, extra-hepatic clearance, metabolites**

# Presentation Outline

- Overview of the DILIsym Software
- DILIsym Application: Acetaminophen Risk Assessment
- General Application Take-aways or Observations
- Questions

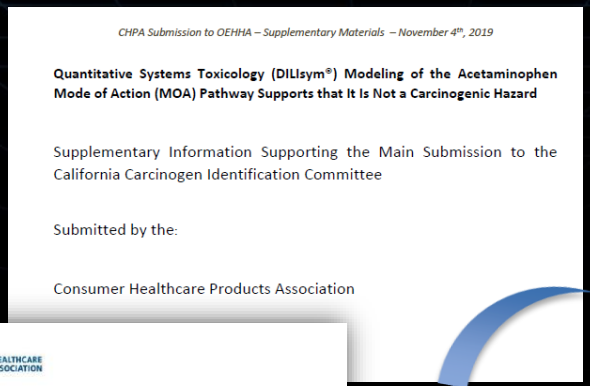
# Applications of DILIsym Along the Drug Development Pipeline

Predictions of hepatotoxicity for humans and preclinical animal models




| Preclinical | First in Human Clinical Trials | Phase II/III Clinical Trials and Post-Market Surveillance |
|---|---|---|
| • Mechanism exploration<br>• Rank candidates for DILI potential<br>• Extrapolation from animal and *in vitro* findings to humans | • Dose optimization (risk versus presumed benefit)<br>• Infer magnitude of injury based on measured biomarkers<br>• Extrapolation from healthy volunteers to patient groups<br>• Guide incorporation of emerging biomarker measurements in clinical trials<br>• Analysis of mechanisms underlying observed liver signals | • Inform choice and timing of biomarker measurement<br>• Aid identification of risk factors leading to personalized medicine approaches<br>• **Analysis of mechanisms underlying observed liver signals** |

# Acetaminophen (Paracetamol) Under CA OEHHA Review for Carcinogenicity

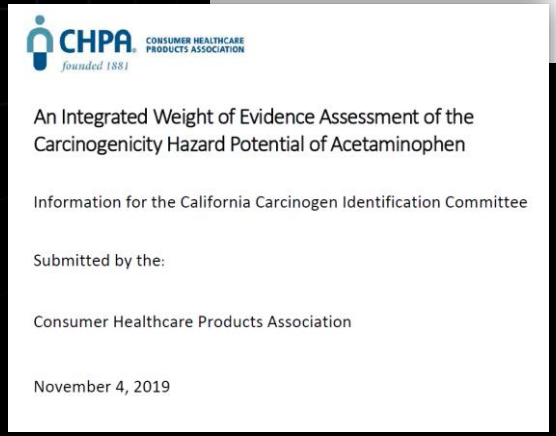


CHPA Submission to OEHHA – Supplementary Materials – November 4th, 2019

**Quantitative Systems Toxicology (DILIsym®) Modeling of the Acetaminophen Mode of Action (MOA) Pathway Supports that It Is Not a Carcinogenic Hazard**

Supplementary Information Supporting the Main Submission to the California Carcinogen Identification Committee

Submitted by the:

Consumer Healthcare Products Association


CHPA CONSUMER HEALTHCARE PRODUCTS ASSOCIATION
founded 1881

An Integrated Weight of Evidence Assessment of the Carcinogenicity Hazard Potential of Acetaminophen

Information for the California Carcinogen Identification Committee

Submitted by the:

Consumer Healthcare Products Association

November 4, 2019

- Acetaminophen has a long history of safe use at therapeutic doses, but can cause liver injury at very high doses
- The CA OEHHA recently called for a scientific review of the carcinogenicity hazard potential of acetaminophen
- This QST work supported this review as part of a broader scientific weight-of-evidence assessment
- Publication followed submission


ELSEVIER

Regulatory Toxicology and Pharmacology

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

Application of the DILIsym® Quantitative Systems Toxicology drug-induced liver injury model to evaluate the carcinogenic hazard potential of acetaminophen

Gary Eichenbaum [a,*], Kyunghee Yang [b], Yeshitila Gebremichael [b], Brett A. Howell [b], F. Jay Murray [c], David Jacobson-Kram [d], Hartmut Jaeschke [e], Edwin Kuffner [a], Cathy K. Gelotte [f], John C.K. Lai [f], Daniele Wikoff [g], Evren Atillasoy [f]

[a] Johnson & Johnson, New Brunswick, NJ, 08901, USA
[b] DILIsym Services Inc., Research Triangle Park, NC, 27709, USA
[c] Murray & Associates, San Jose, CA, 95138, USA

Model-Informed Drug Development
MIDD+
2021 Virtual Conference



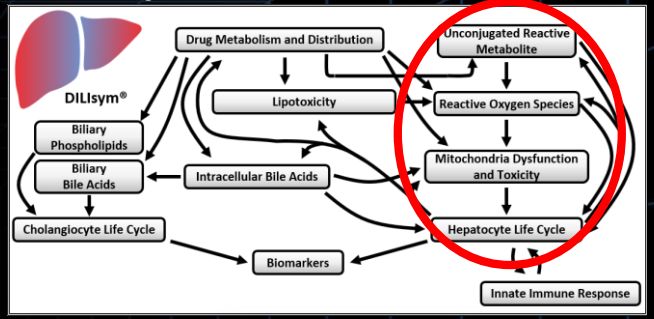
Cognigen | DILIsym Services | Lixoft

# DILIsym Validation Submitted: Fit for Purpose Focus

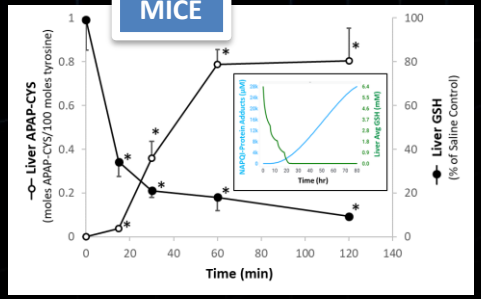
- DILIsym was applied to model acetaminophen drug exposure, metabolism and mechanisms of cell death
- The model was qualified using clinical and experimental data
- Validation of the model was focused on the compound and processes of interest

| Parameter/Endpoint | Experimental data supporting Kinetics | Experimental data supporting dose response | Model comparison to experimental data |
|---|---|---|---|
| Acetaminophen ADME and PK | √ | √ | Refs [1-3] |
| GSH depletion | √ | √ | Refs [1-3] |
| Hepatotoxicity | √ | √ | Refs [1-3] |
| Oxidative stress/ROS generation | √ | √ | Refs [1-3] |
| Mitochondrial inhibition/dysfunction | √ | √ | Refs [1-3] |
| Protein adduct formation | √ | √ | Refs [1-3] |

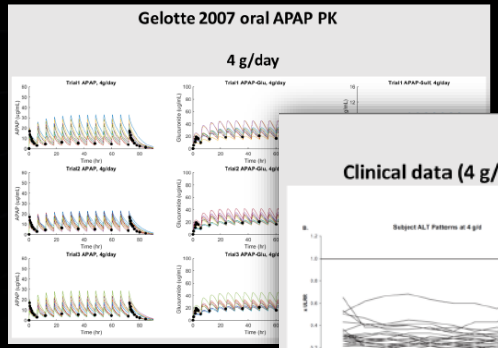
***DILIsym Mechanism-Based Model***



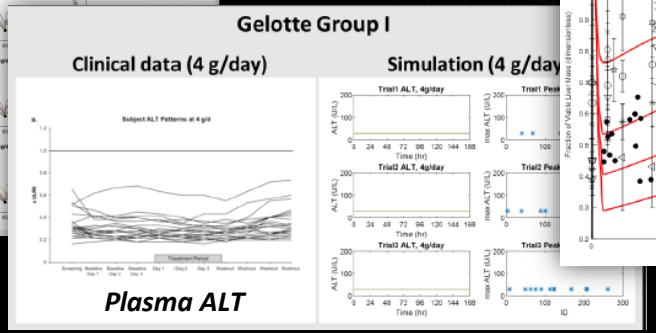

**MICE**

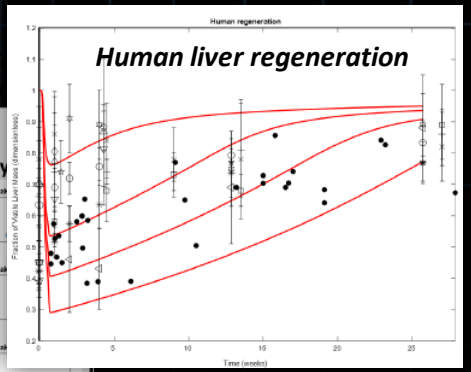



***Mice Treated with Acetaminophen at a Hepatotoxic Dose of 300 mg/kg i.p. [4]***




**HUMANS**





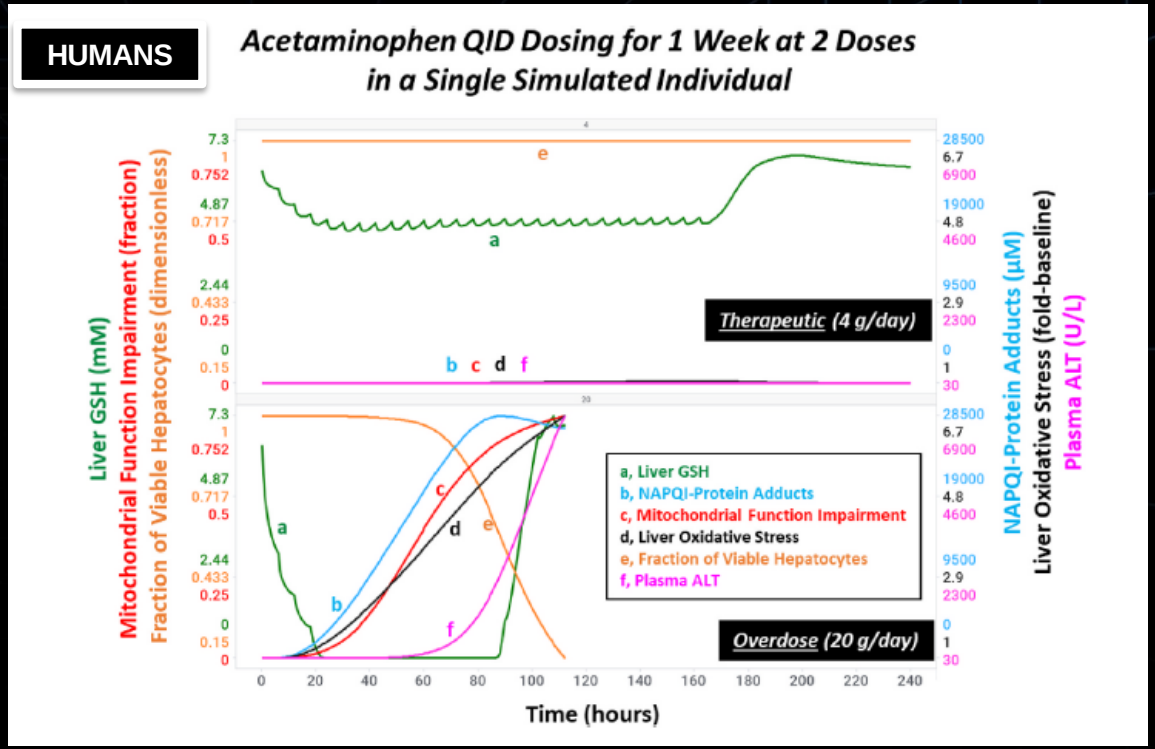
[1] Howell et al., J Pharmacokinet Pharmacodyn. 2012 Oct;39(5):527–4
[2] Howell et al., Toxicol Lett. 2014 Apr 21;226(2):163–72
[3] Woodhead et al., J Pharmacol Exp Ther. 2012 Aug;342(2):529–40
[4] Muldrew et al., Drug Metab Dispos. 2002 Apr;30(4):446–51




*Pre-clinical and Clinical Data, Simulation Results*

# Kinetics of APAP Examined: Clear Delineation Between Therapeutic and Overdose Case

- GSH stores are adequate in avg. person at therapeutic dose levels, but clearly depleted with 20g+
- Clear inflection point where GSH (green) goes down and ROS (black) goes up
- ***Sharp transition from safe to mitochondrial damage suggests lack of sustained DNA damage zone***



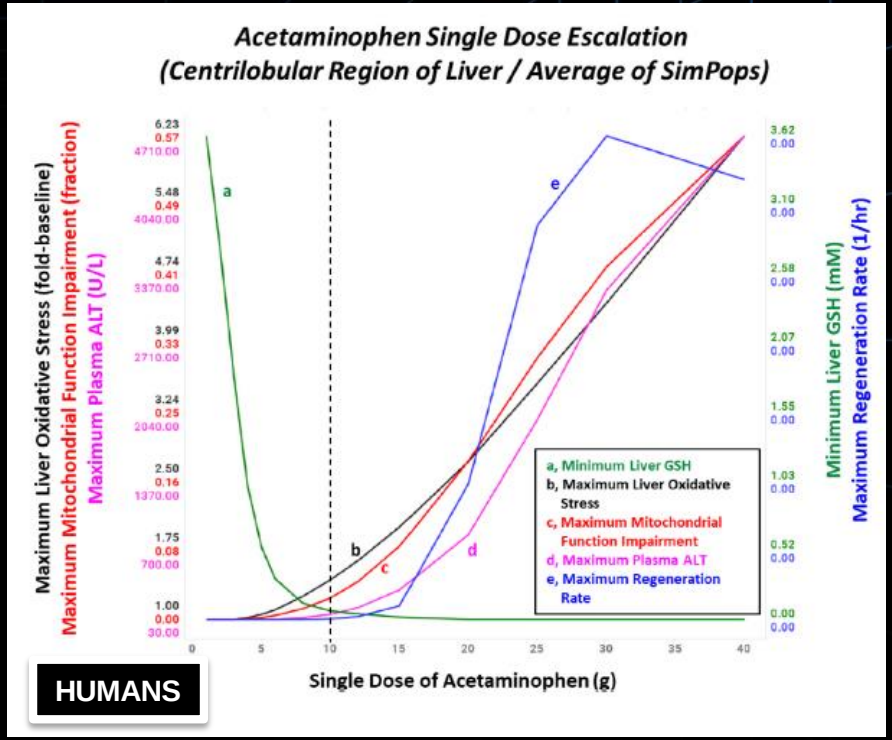




[1] Howell et al., J Pharmacokinet Pharmacodyn. 2012 Oct;39(5):527–4
[2] Howell et al., Toxicol Lett. 2014 Apr 21;226(2):163–72
[3] Woodhead et al., J Pharmacol Exp Ther. 2012 Aug;342(2):529–40
[4] Muldrew et al., Drug Metab Dispos. 2002 Apr;30(4):446–51

# Dose-Response of APAP Examined: Clear Delineation Between Therapeutic and Overdose Case

- As single dose level increases, GSH nadir drops sharply
- Clear inflection point where GSH (green) goes down and ROS (black) goes up at around 10g single dose in average person
- ***Dose-response suggests that perhaps APAP has a built-in mechanism against carcinogenicity (self-destruction)***



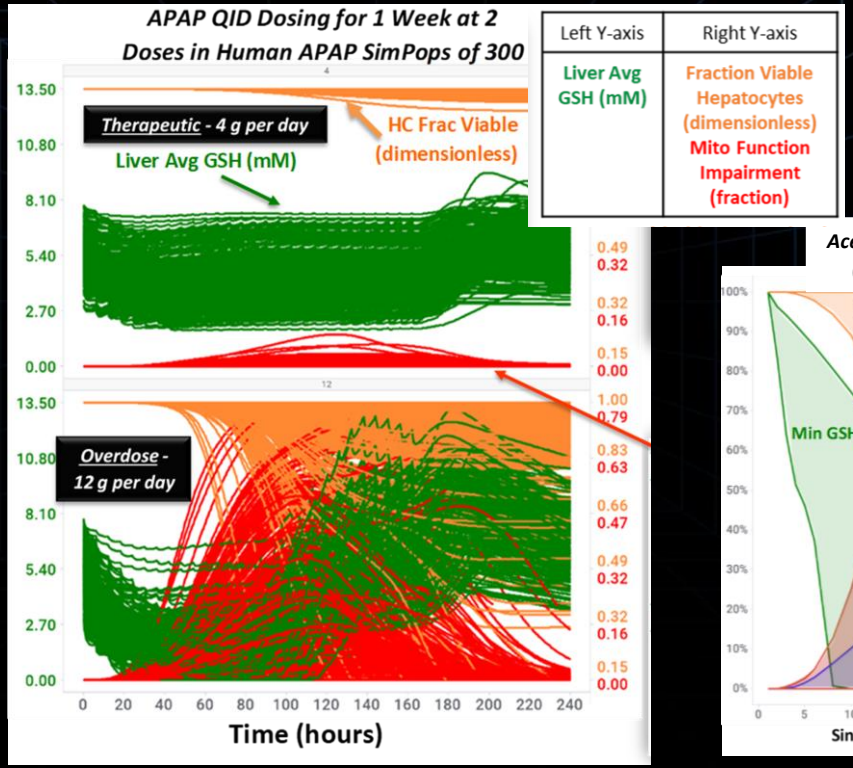




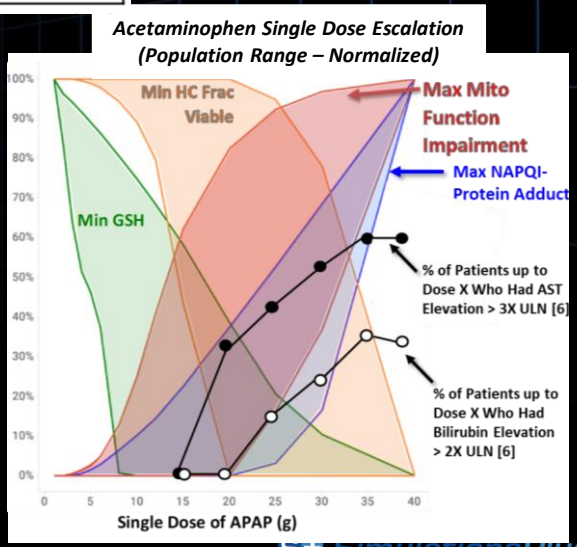
[1] Howell et al., J Pharmacokinet Pharmacodyn. 2012 Oct;39(5):527–4
[2] Howell et al., Toxicol Lett. 2014 Apr 21;226(2):163–72
[3] Woodhead et al., J Pharmacol Exp Ther. 2012 Aug;342(2):529–40
[4] Muldrew et al., Drug Metab Dispos. 2002 Apr;30(4):446–51

# Population Level Analysis of APAP Liver Effects Confirms Sharp Transition to Cell Death

- A full simulated population with variability avoids significant liver cell stress at 4 g per day
- The threshold for reaching cell death is different across individuals at 12 g per day, but the inflection point is preserved (shifted left or right)
- ***Simulations including population variability support that across a wide array of patient backgrounds, acetaminophen exposure only results in significant oxidative stress or DNA effects under conditions that cause cell death***

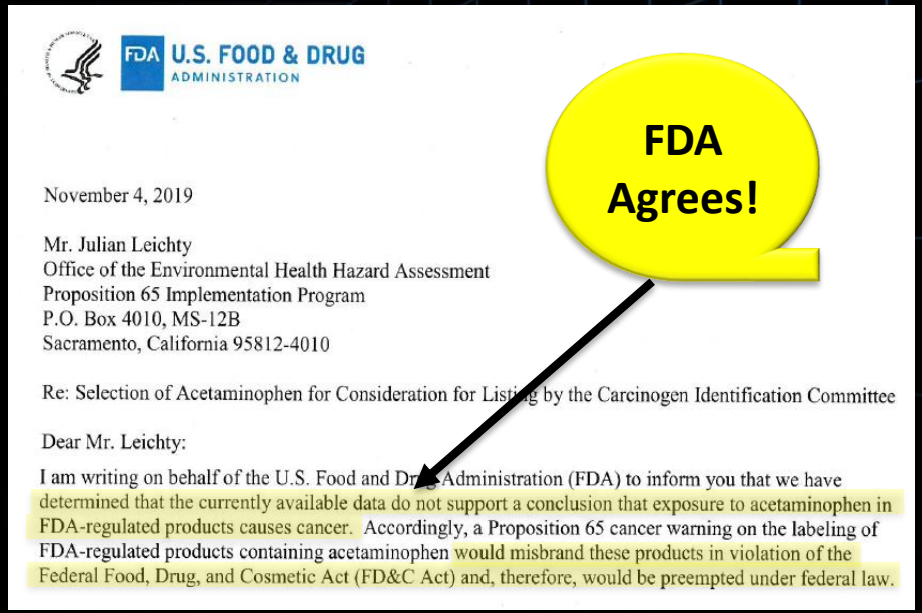



HUMANS



# QST Modeling of Acetaminophen Cellular Pathways for Liver Toxicity: **Conclusions**

- Simulations results support that:
  - ➢ At therapeutic acetaminophen doses, cellular GSH deactivates the NAPQI metabolite and there is sufficient buffering capacity to prevent any meaningful protein adduct formation or oxidative stress
  - ➢ Following overdose of acetaminophen, cell death occurs before any adverse conditions occur (e.g. oxidative stress or DNA damage) that could result in carcinogenicity
- ***These results support that acetaminophen is not a carcinogenicity hazard to human health***



# Presentation Outline

- Overview of the DILIsym Software
- DILIsym Application: Acetaminophen Risk Assessment
- General Application Take-aways or Observations
- Questions

# Important General Take-aways from This Application

- Fit-for-purpose validation is very effective and easier to defend
- Integrated, global responses that include modeling results and data alongside one another are more convincing
- Publication of results in parallel with submission to regulators can provide credibility
- M&S tools can be used in a myriad of ways, some of which are outside of the typical main-stream intent or purpose

# Presentation Outline

- Overview of the DILIsym Software
- DILIsym Application: Acetaminophen Risk Assessment
- General Application Take-aways or Observations
- Questions

# Q&A

Questions & Answers

Model-Informed Drug Development

# MIDD+

2021 Virtual Conference

**Learn More!** www.simulations-plus.com

SimulationsPlus

Cognigen | DILIsym Services | Lixoft