Quantitative systems toxicology (DILIsym) modeling of the acetaminophen (paracetamol) mode of action (MOA) pathway for hepatotoxicity supports that acetaminophen is not a carcinogenic hazard in humans

Brett A. Howell[a], Kyunghee Yang[a], Yeshi Gebremichael[a], Gary Eichenbaum[b]

[1]DILIsym Services Inc, an SLP Company, 6 Davis Drive, Research Triangle Park, North Carolina, USA

[b]Johnson & Johnson, New Brunswick, NJ 08901

PURPOSE

- Acetaminophen has a long history of safe use at therapeutic doses, but can cause liver injury at very high doses
- The California Office of Environment Health Hazard Assessment (OEHHA) recently called for a scientific review of the carcinogenicity hazard potential of acetaminophen
- This Quantitative Systems Toxicology work supported this review as part of a broader scientific weight-of-evidence assessment of the carcinogenicity hazard potential of acetaminophen

OBJECTIVE(S)

- DILIsym was applied to model acetaminophen drug exposure, metabolism and mechanisms of cell death
- The model was qualified using clinical and experimental data

METHOD(S)

- DILIsym was used to simulate exposure to acetaminophen at therapeutic (≤ 4 g/day), supratherapeutic (> 4-12 g/day), and overdose (> 15 g) conditions across representative populations with the goal of determining whether it's liver injury MOA represents a carcinogenic hazard
- The simulations accounted for variability in baseline GSH levels, pharmacokinetics, and the capacity of hepatic antioxidants to reduce oxidative stress.

RESULT(S)

- The simulations support that at therapeutic doses, cellular GSH binds to NAPQI providing sufficient buffering capacity to limit oxidative stress and subsequent protein adduct formation. With repeated supratherapeutic exposures >8 – 12 g/day for an extended period or acute doses > 15 g, cell death precedes DNA damage that could result in carcinogenicity.
- The simulations herein align with many previous investigations showing that oxidative stress caused by acetaminophen in overdose scenarios is associated with liver toxicity and cell death rather than carcinogenicity
- The simulations illustrate that oxidative stress and the other KCCs associated with acetaminophen do not represent a carcinogenic hazard due to: (1) the presence of excess buffering capacity through GSH and cytosolic proteins, which prevent any ROS or injury by deactivating the reactive NAPQI at therapeutic doses, or (2) toxicity induced hepatocyte death in the event of complete depletion of GSH following chronic supratherapeutic and acute overdose exposures.
- Specifically, the simulations demonstrate that cell death begins just as the liver GSH is depleted to 30% or less, coincident with ROS increases, protein adduction, and mitochondrial dysfunction.

CONCLUSION(S)

- ***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***

REFERENCES

[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

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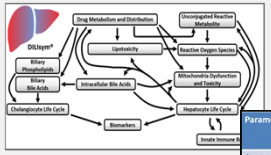
Simulations evaluating repeated high-level supratherapeutic exposures or acute overdoses of acetaminophen indicate that cell death precedes DNA damage that could result in carcinogenicity and ***thus acetaminophen does not present a carcinogenicity hazard to humans at any dose.***

VALIDATED QST SOFTWARE UTILIZED

DILIsym Software APAP Representation

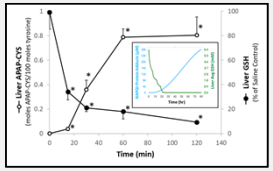
- DILIsym was applied to model acetaminophen drug exposure, metabolism and mechanisms of cell death
- The model was qualified using clinical and experimental data



Summary of Experimental data that have been used to develop and validate the DILIsym simulations

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]

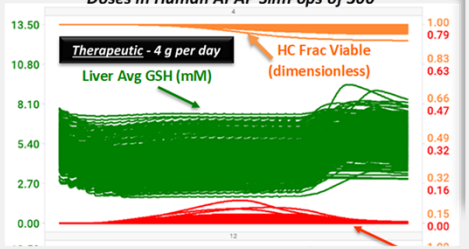
Mice Treated with Acetaminophen at a Hepatotoxic Dose of 300 mg/kg i.p. [4]



CLINICAL DOSES

Clinically relevant exposures of acetaminophen do not lead to meaningful cellular stress that would cause carcinogenicity

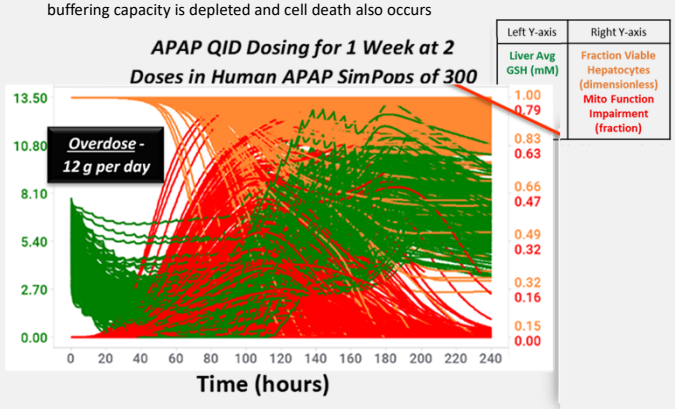
APAP QID Dosing for 1 Week at 2 Doses in Human APAP SimPops of 300



OVERDOSE LEVELS

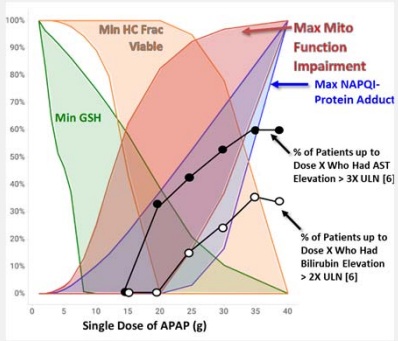
At higher doses when cellular stress does occur, the buffering capacity is depleted and cell death also occurs

APAP QID Dosing for 1 Week at 2 Doses in Human APAP SimPops of 300



WINDOW FOR CARCINOGENICITY WITH APAP NON-EXISTENT

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



CONTACT INFORMATION: bhowell@DILIsym.com