Dosing corrected for species differences in toxicokinetics using PBPK modelling predicts equivalent reactive metabolite burden following acetaminophen overdose

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Preclinical study design **informed by PBPK modelling and simulation** facilitates robust cross-species comparison of intrinsic susceptibility to toxicological hazards.

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Background & Objective

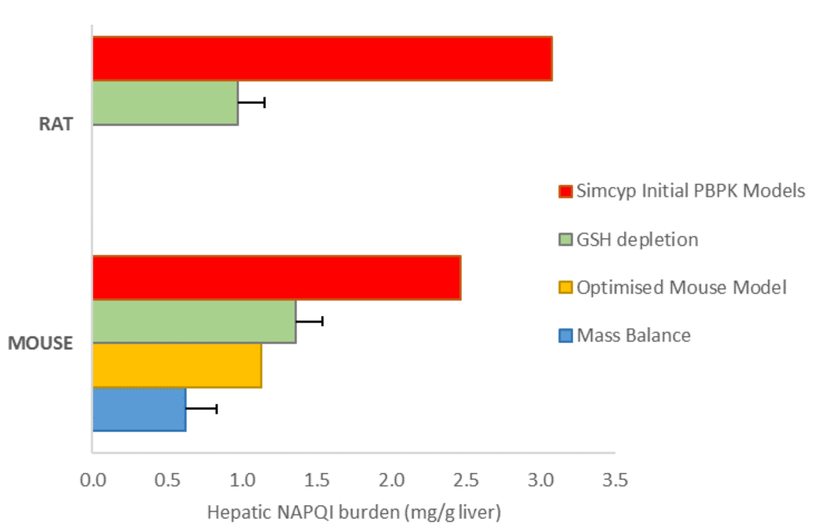
- Species differences in the metabolism of acetaminophen (APAP) affect production of the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI)
- NAPQI is primarily detoxified through conjugation with the anti-oxidant glutathione (GSH)
- Excess NAPQI production results in depletion of GSH, formation of protein adducts and eventually liver injury
- Physiologically-based pharmacokinetic (PBPK) modelling and simulation was used to predict oral equivalent doses (OED; mg/kg) of APAP in rat and mouse
- OEDs were defined as the oral APAP dose resulting in the same hepatic NAPQI burden in both species
- OEDs predicted using PBPK modelling were used to inform the design of a cross-species comparison of the intrinsic susceptibility to the toxic hazard presented by NAPQI

Methods

- PBPK models incorporating the sulphation, glucuronidation and CYP-mediated hydroxylation of APAP predicted OEDs of 300 mg/kg and 1000 mg/kg for mouse and rat, respectively
- These doses were subsequently used in a non-clinical single oral dosing study in both species. APAP and conjugated metabolite concentrations in plasma (APAP-GSH, APAP-CYS, APAP-NAC), as well as hepatic GSH concentrations were determined at 0.5, 1, 3, 6, 9 and 24 hours for mouse and 3, 6, 9 and 24 hours for rat
- Total hepatic NAPQI (NAPQI burden per gram of liver) was calculated. Mass-balance analysis calculating the AUC of all conjugated APAP metabolites in mouse was performed; assuming no protein binding, active secretion or re-absorption, and correcting for biliary clearance (Fig 4.)
- A second approach assumed 1:1 stoichiometry between GSH and NAPQI, and calculated total hepatic NAPQI burden from total hepatic GSH depletion in both rat and mouse (Fig 4.)

Results

- Calculated *in vivo* mouse:rat total hepatic NAPQI burden ratio, based on GSH depletion, was 1.4 (Fig 1)
- The ratio calculated based on mass balance in mouse and GSH depletion in rat was 0.64 (Fig 1)
- PBPK predicted OEDs resulted in cross-species total hepatic NAPQI burden within 1.6 fold (Fig 2, 3)
- Absolute values of hepatic NAPQI burden predicted from PBPK were within 3-4 fold
- Mean mouse ALT and AST concentrations increased by 67 and 44-fold, respectively, while rat levels only increased 3.5 and 7-fold, respectively.



Hepatic NAPQI Burden (mg/g liver)	MOUSE	RAT
Mass Balance	0.62 ± 0.2	NA
Simcyp PBPK prediction	1.13	3.08
GSH depletion	1.36 ± 0.18	0.97 ± 0.13
Mouse (Non-optimised) Simcyp Pred.	2.46	NA

Figure 1: Comparison of total predicted hepatic NAPQI in mouse and rat PBPK models with calculated *in vivo* NAPQI burden. Error bars denote 95% confidence interval where appropriate

Discussion

Preclinical study design informed by PBPK modelling and simulation facilitates robust cross-species comparison of intrinsic susceptibility to toxicological hazard. Predictions of oral equivalent doses led to comparable *in vivo* hepatic NAPQI burden in the subsequent non-clinical study. Despite this comparable hepatic NAPQI burden at the PBPK-informed doses, biomarker results in rat and mouse show that the mouse is intrinsically more susceptible to hepatic injury resulting from APAP overdose. Modelling informed approaches to study design can potentially reduce the number of animals required, help to refine study design, and inform on the most appropriate animal species selection for safety testing and improve extrapolation to human in risk assessment.

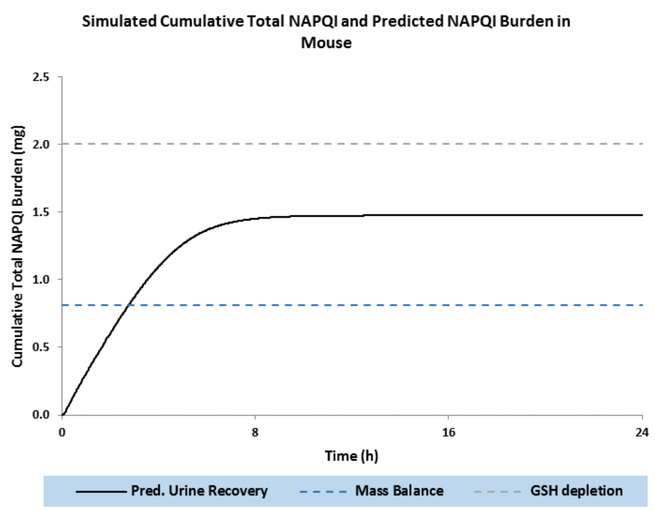


Figure 2: Comparison of cumulative NAPQI recovery over time with calculated *in vivo* NAPQI burden in mouse

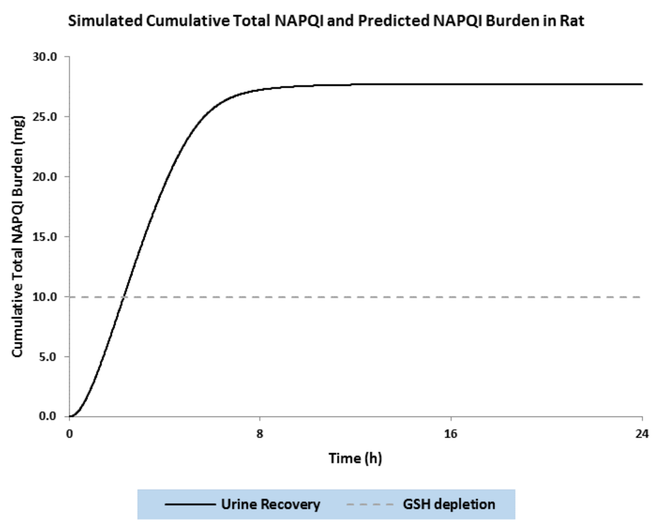


Figure 3: Comparison of cumulative NAPQI recovery over time with calculated *in vivo* NAPQI burden in rat

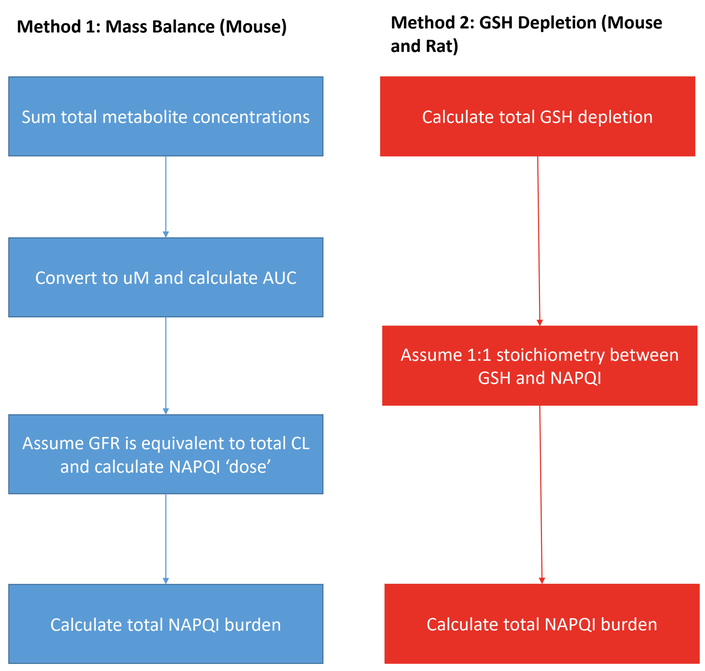


Figure 4: Workflows for calculation of NAPQI burden from preclinical *in vivo* data

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