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

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 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 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.

OVERDOSE LEVELS

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

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REFERENCES