Tox Strategies

Biological Plausibility Assessment of Acetaminophen and Occurrence of Developmental Neurological Outcomes in Humans

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Abstract:

Background and Purpose: Causal pathways for neurodevelopmental disorders, including attention-deficit and hyperactivity disorder (ADHD), are complex and currently understood to be a likely result of a combination of factors including genetics and environmental effects on brain function. In utero exposure to acetaminophen and potential relationships with neurodevelopmental disorders has been reported in epidemiological studies. The observational nature of the studies, and in particular, factors such as the potential for exposure misclassification (e.g., lack of quantifiable exposure information) and confounding, limit the ability to assess causal relationships. Assessment of biological plausibility and experiment are critical aspects of assessing the potential for, as well as the nature of, causal relationships. Biological plausibility can be assessed by assembling mechanistic data across biological levels of organization to evaluate both the plausibility as well as the strength of a potential relationship between exposure and outcome. As such, the objective of this evaluation is to systematically identify, assess, and integrate mechanistic data to inform on the plausibility of neurodevelopmental disorders being causally related to prenatal acetaminophen exposure.

Methods: Biological pathways (i.e., adverse outcome pathways; AOPs) proposing molecular, cellular, and organ events associated with adverse neurological outcomes were utilized as a framework for data evaluations. A protocol was developed for the identification and evaluation of data suitable for evaluation of the biological plausibility of acetaminophen induced adverse neurological effects based on the key events (KEs) identified in the AOPs. Using an AI-facilitated screening workflow to reduce the corpus of >25,000 articles to ~10,000 articles, followed by combined use of machine-learning and manual review, a database of ~300 studies was established using specific inclusion criteria. Data were extracted from studies and organized around biological level of organization (e.g., molecular, cellular, organ-level), species, study design, and other attributes. Lines of evidence were synthesized for each KE, and each biological pathway, based on life stage as a measure of directness; data were considered sufficient if at least 2 studies were available for a KE. A weight-of-evidence assessment was conducted for the totality of data in a stepwise fashion which included considerations of key event/key event relationships, dose, toxicokinetics, and study construct/model relevance.

Results: From the ~300 studies included, almost all data identified were assessing cellular responses. These data assessed measures mapped to 16 KEs of interest: altered neurotransmission, altered BDNF levels, altered calcium levels, cellular injury, GABA modulation, gene expression, glutamate modulation, inflammatory mediators, mitochondrial effects, altered hippocampus anatomy, altered thyroxine levels, oxidative stress, and neuroinflammation, altered neurotransmission, receptor effects, neuronal activity, and neurodegeneration. No mechanistic data were identified within the human gestation life stage, the

most direct model. No human data in postnatal or adult models were identified; human data were limited to in vitro studies of cellular response in which only single experiments were identified for three of 16 KEs. Most data available were from rodent studies. In gestational and postnatal models, the only key event with sufficient information was glutamate modulation; studies reported contradictory findings for activity. The majority of data identified were for adult exposures in rodents or in vitro rodent models. These data reported contradictory findings for altered neurotransmission, cellular injury, and altered hippocampus anatomy. Fewer than 5 studies assessed key event relationships and/or relationships with adverse outcomes in the same studies, limiting the ability to assess pathway concepts such as evaluation of essentiality of event modulation (i.e., evidence that modulation of a down-stream event directly leads to modulation of an up-stream event). Overall activity, while inconsistent, also did not mimic prototypical stressors for KEs of interest.

Conclusions: The limited data available do not consistently or clearly demonstrate a biologically plausible relationship between acetaminophen and neurological outcomes, particularly when considering dose and model relevance. The lack of studies utilizing models that would allow for direct correlation of mechanistic events to adverse outcomes evaluated in epidemiological studies is an important limitation, as are the general limitations in understanding biological mechanisms underpinning behavioral outcomes such as ADHD. Taken together, the biological plausibility of acetaminophen and occurrence of developmental neurological outcomes in humans has not been established with available data.