Letters to the Editor

Comprehensive Toxicology Risk Assessment for Genotoxic Impurities

Dear Editor:

We believe that the publication by Yang et al.[1] provides an important methodology for eliminating genotoxic impurities from drug substances. However, we recommend that the risk assessment presented for methyl and ethyl chloride go beyond the staged TTC guidance as referenced in the manuscript.

Dr. David Snodin's letter to the editor[2] highlighting the need for a comprehensive risk assessment for specific genotoxic impurities is relevant to the recent Yang et al. manuscript. One reason to conduct a genotoxicity test is to predict potential carcinogenicity. We acknowledge that the TTC has been an effective risk assessment tool to provide a conservative acceptable dose for genotoxic compounds when no adequate carcinogenicity information is available. However, if available, carcinogenicity data should be used to evaluate the risk.

Both methyl and ethyl chloride are examples of genotoxic compounds with carcinogenicity data critical to the toxicology evaluation. The United States Environmental Protection Agency (USEPA) review of the carcinogenicity data[3] for methyl chloride indicates that renal tumors observed in male mice are a species-specific effect with limited relevance in humans and categorizes methyl chloride as a Group D compound (i.e., "Not classifiable as to its carcinogenicity"). USEPA has not developed an oral permissible daily exposure (PDE also referred to as a reference dose) for noncarcinogenic effects because methyl chloride exists primarily as a gas and no adequate oral toxicity data exist. While an oral PDE could be developed from inhalation data given the high rate of absorption from an inhalation perspective, the result would be several orders of magnitude greater than the TTC.[3,4] In addition, ambient exposures are well in excess of the TTC.[4] Given this information, one should consider applying the ICH Q3A(R2)/Q3B(R2) guidelines[5,6] for an oral pharmaceutical. These guidelines are intended to address impurities without unusual toxicity or potency and rely on qualification of the impurity via the toxicity test for the drug substance.

In contrast, ethyl chloride exposure results in uterine tumors in female mice that could be relevant to humans, but the carcinogenicity data indicate ethyl chloride is a low potency carcinogen (TD_{50} = 1810 mg/kg/day).[7] The California Environmental Protection Agency (CalEPA)[8] considers the nonsignificant risk level to be 150 μg/day, which corresponds to a 1 in 100,000 excess risk of cancer if exposure occurs over a lifetime. Therefore, a carcinogenicity risk assessment of ethyl chloride supports an acceptable daily intake 100-fold higher than the 1.5 μg/day TTC for chronic exposure. A higher acceptable daily intake also exists for short-term exposure as well.

In conclusion, we believe that genotoxic compounds should be removed as low as reasonably practicable, and Yang et al. describes how this can be performed for methyl and ethyl chloride. However, considering a comprehensive risk assessment may allow for more flexibility in establishing appropriate limits for genotoxic impurities.

Sincerely,

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