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The GENOMARK transcriptomic biomarker demonstrates a high predictivity for genotoxic hazards and utility in potency ranking in human HepaRGTM cells

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New Approach Methodologies (NAMs) and improved testing strategies are needed to modernize genotoxicity assessment and reduce reliance on experimental animals. We previously developed GENOMARK, a transcriptomic biomarker that consists of 84 genes to identify genotoxic substances in metabolically competent human HepaRG™ cells. Initial work demonstrated a high prediction performance of GENOMARK in classifying compounds as genotoxic or non-genotoxic based on qPCR gene expression data collected at a low cytotoxic concentration, the IC10. A qualitative classification of chemicals as genotoxic or non-genotoxic is generally insufficient for risk assessment. Therefore, there is growing global interest in developing quantitative methods for the analysis and interpretation of genotoxicity dose-response data. In this study, we demonstrate how GENOMARK gene expression data can be used quantitatively, i.e. for potency ranking of genotoxic chemicals. First, we evaluated the applicability of GENOMARK to higher-throughput platforms, such as RNA-Seq and TempO-Seq. These sequencing platforms generate a larger amount of gene expression data in a shorter timeframe compared to qPCR to increase the throughput and facilitate the combination of GENOMARK with other transcriptomics-based biomarkers. The work confirms that GENOMARK shows a high predictivity using these high-throughput technologies. In addition, we applied benchmark dose (BMD) analysis to demonstrate that GENOMARK can be used in ranking genotoxicants based on their potency. Finally, we compared the performance of GENOMARK and another biomarker of DNA damage, i.e. TGx-DDI, for genotoxicity hazard calls and potency ranking. Overall, the results suggest that transcriptomic biomarkers for genotoxicity such as GENOMARK can rapidly and effectively identify genotoxic hazards while simultaneously providing additional information on potency that is useful for modern risk assessment.

Keywords:
genotoxicology, quantitative assessment, benchmark dose, high-throughput toxicogenomics, new approach methodologies.