Using Data on Human Polymorphisms and Variability in Risk Assessment

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The objectives of this project include (1) collecting data on known polymorphisms in genes that encode enzymes responsible for the metabolism of environmentally-relevant chemicals, and the population frequency of the polymorphisms, and (2) developing an approach for using physiologically based pharmacokinetic (PBPK) modeling to incorporate these data into standard risk assessment methods, taking into account other aspects of interindividual variability. Results from this project will aid in determining the quantitative relationship between human genetic variability and variability in response to toxic chemicals. The first publication of this project integrated data on the relative activities of key metabolic enzymes encoded by polymorphic alleles, the frequency of the altered phenotypes in the general population, and information on the metabolic pathway for representative chemicals. The second publication presents the results of combining PBPK modeling and Monte Carlo analyses for two case study chemicals, warfarin and parathion, to determine variability in tissue dose resulting from genetic polymorphisms in the genes associated with relevant metabolic enzymes. Results suggest that polymorphisms in the PON1 gene, which is involved in the metabolism of paraoxon (a metabolite of parathion), make a minor contribution to the overall variability in paraoxon tissue dose, while polymorphisms in the CYP2C9 gene, the major metabolic enzyme for warfarin, account for a significant portion of the overall variability in (S)-warfarin tissue dose. These data were used to estimate Chemical-Specific Adjustment Factors (CSAFs) for the human variability in toxicokinetics for both parathion and warfarin, and implications of options in the calculation of CSAFs were explored.

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Presentation(s):


Haber, L. T. (2002). Quantitative consideration of data on human polymorphisms and variability in risk assessment. Presentation for the RIVM (National Institute of Public Health and the Environment, the Netherlands), Bilthoven, the Netherlands, September.


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