Abstracts

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Development of Pharmacokinetic and Non-invasive Biomonitoring Approaches to determine Dosimetry and Assess Risk in Potentially Sensitive Sub-populations Following Exposure to Individual Chemicals and Mixtures

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There is an ongoing need to develop approaches for quantitatively assessing risk associated with occupational exposures to a broad-range of chemical agents and to determine the potential implications of these occupational exposures to human health, particularly with regards to sensitive sub-populations. In this regard, efforts are underway to develop state-of-the-art physiologically based pharmacokinetic and pharmacodynamic (PBPK/PD) modeling approaches to assess dosimetry and biological response following exposure to single agents or more complex mixtures. These models have also been used to assess risk in potentially sensitive populations such as children and individuals with a genetic polymorphism associated with critical detoxification pathways. In addition, the development of non-invasive biomonitoring approaches that utilize readily obtainable fluids like saliva have been coupled with PBPK models to readily determine systemic chemical exposure by the rapid analysis of "spot" saliva specimens. A PBPK/PD model has been developed for the organophosphate (OP) insecticides chlorpyrifos and diazinon utilizing available data from rats and humans. These OP insecticides share common metabolic activation/detoxification pathways and a common mechanism of neurotoxicity associated with excessive cholinergic stimulation, due to the inhibition of acetylcholinesterase in nerve tissues. Therefore, these two models have been combined into a binary OP PBPK/PD model to quantitatively assess dosimetry and response due to occupational exposure to these chemical mixtures that are routinely encountered in the workplace. This binary model facilitates understanding the mixture interactions and the potential for additivity, synergism or antagonism from multi-OP exposures for assessing risk. In addition, these models have been extended to incorporate age- and polymorphism-dependent changes and have been successfully used to quantitatively determine the dose-dependent impact of OP exposure on potentially susceptible sub-populations. To advance the application of non-invasive biomonitoring a portable microfluidic/electrochemical device has also been developed for the rapid analysis of lead (Pb), based on square wave anodic stripping voltametry. Appropriate pharmacokinetic analyses have been used to quantitate systemic dosimetry based on determination of saliva Pb concentrations. The PBPK model for Pb is capable of predicting blood and saliva Pb concentration based on a limited data set obtained in rats. In addition, saliva has recently been used to quantitate chlorpyrifos exposure in a rodent model system by measuring the major metabolite, trichloropyridinol, and saliva cholinesterase inhibition following acute exposures. These results suggest that technology developed for non-invasive biomonitoring can provide a sensitive, and portable analytical tool capable of assessing exposure and risk in real-time. By coupling these non-invasive technologies with advanced PBPK modeling it is feasible to quantitatively assess occupational exposure to a broad range of chemical agents involving multiple routes of exposure (i.e. skin, ingestion, inhalation) that are routinely encountered in the work environment. In summary, it is envisioned that once fully validated, these monitoring and modeling approaches will be a very useful for accessing exposure and health risk to a wide range of occupationally exposed individuals. Supported by: CDC/NIOSH 1 R01 OH03629-01A2; EPA-STAR R828608; NIEHS 1 R01ES/OH10976-01A2; and DOE contract DE-AC06-76RLO-1830.

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