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The need for non- or minimally-invasive biomonitoring strategies and the development of pharmacokinetic/pharmacodynamic models for quantification

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Abstract

Advancements in Exposure Science involving the development and deployment of biomarkers of exposure and biological response are anticipated to significantly (and positively) influence health outcomes associated with occupational, environmental and clinical exposure to chemicals/drugs. To achieve this vision, innovative strategies are needed to develop multiplex sensor platforms capable of quantifying individual and mixed exposures (i.e. systemic dose) by measuring biomarkers of dose and biological response in readily obtainable (non-invasive) biofluids. Secondly, the use of saliva (alternative to blood) for biomonitoring coupled with the ability to rapidly analyze multiple samples in real-time offers an innovative opportunity to revolutionize biomonitoring assessments. In this regard, the timing and number of samples taken for biomonitoring will not be limited as is currently the case. In addition, real-time analysis will facilitate identification of work practices or conditions that are contributing to increased exposures and will make possible a more rapid and successful intervention strategy. The initial development and application of computational models for evaluation of saliva/blood analyte concentration at anticipated exposure levels represents an important opportunity to establish the limits of quantification and robustness of multiplex sensor systems by exploiting a unique computational modeling framework. The use of these pharmacokinetic models will also enable prediction of an exposure dose based on the saliva/blood measurement. This novel strategy will result in a more accurate prediction of exposures and, once validated, can be employed to assess dosimetry to a broad range of chemicals in support of biomonitoring and epidemiology studies.

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Biomarkers, Sensors, Non-invasive, Computational modeling.

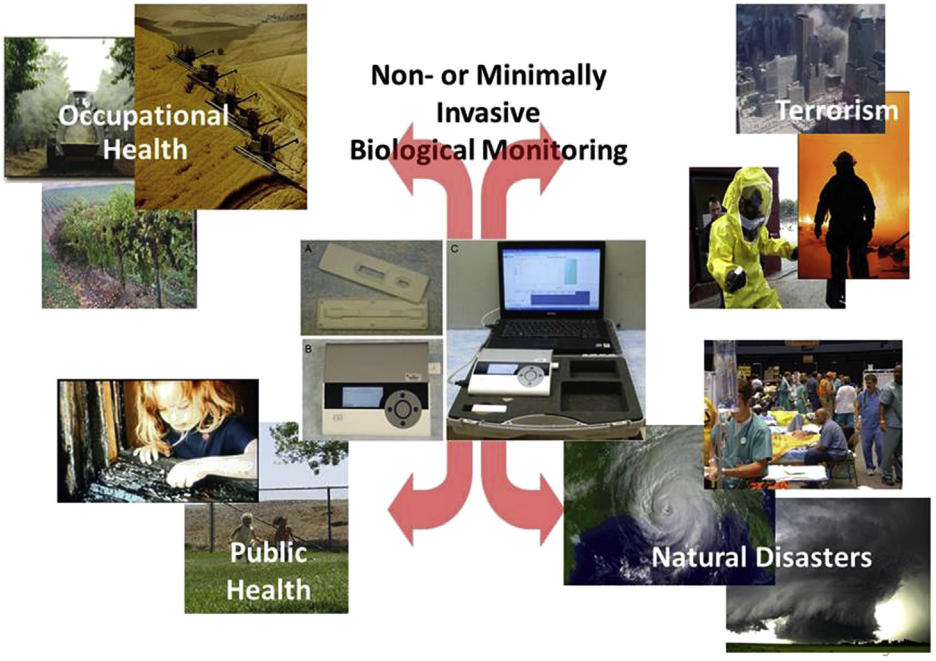
1. Sensor platforms

Clinically, recent advances in Point-of-Care (POC) technologies enable patients to be rapidly diagnosed for a broad range of diseases including: cardiovascular, cancer, diabetes and chronic respiratory disease among others [1]. However, the application of these types of diagnostic tools for the assessment of environmental exposures and biomarkers of toxicological response has yet to be fully realized. As suggested by the National Research Council of the National Academies report, *Exposure Science in the 21st Century*: *A Vision and a Strategy*, exposure and biological response biomarkers are critically important for linking across toxicological and exposure health assessments and therefore are of fundamental importance for many disciplines including: toxicology, epidemiology, occupational health, environmental regulation, environmental planning, and disaster management (see Figure 1).

Technologies that enable real-time quantitative evaluation of these biomarkers in easily obtainable biological fluids (e.g., saliva, capillary bleed) will enable these approaches to have the broadest impact [2]. For example, the interpretation of epidemiology studies would be significantly enhanced if they could be designed to quantitatively integrate chemical exposure (pharmacokinetics) with biological effect (pharmacodynamics) endpoints [3]. However, a major impediment has been the lack of field deployable technologies capable of quantifying both chemical exposure and response markers (biomarkers) using minimally-invasive biological fluids [4]. To address these limitations, inexpensive microanalytical-based sensors are needed to accurately and precisely process small amounts of biological fluids [4,5]. As reviewed by Weis et al. [4], multiplex microsensor platforms, capable of measuring multiple analytes simultaneously, offer great promise because they have the potential to provide rapid, accurate, and quantitative detection of exposure and biological response for individuals [3].

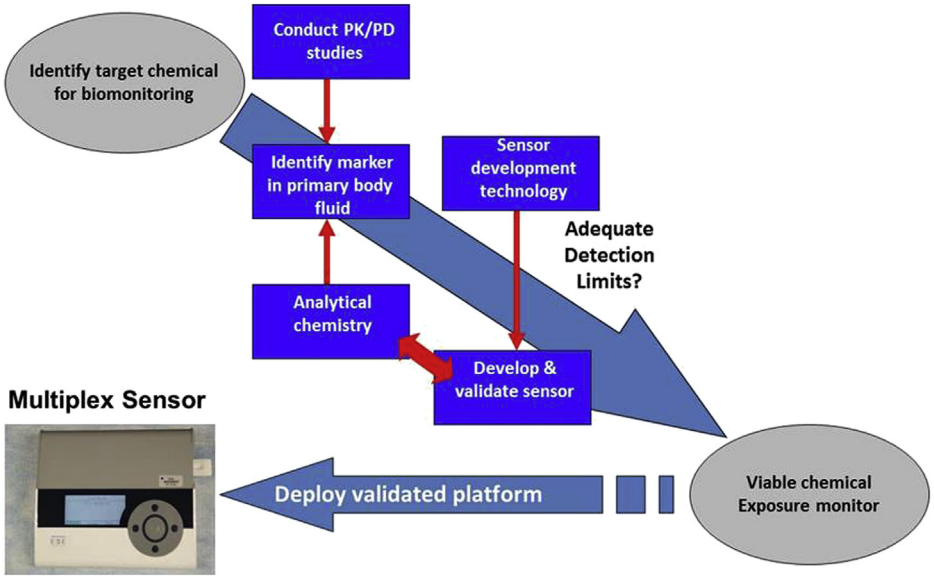
An overarching strategy for the development, validation, and deployment of a chemical biomonitoring platform is illustrated in Figure 2. Key criteria include: evaluation of the pharmacokinetics of biomarkers in complex matrices, such as blood, urine or saliva; validation of sensor performance against standard analytical methodology; and integration of the sensor technology into a user friendly platform. Validation

Figure 1



Biomarkers of exposure and response have a potential broad range of occupational and environmental applications.

Figure 2



Sensor development strategy.

should not only include characteristics of instrument performance (e.g., limit of detection, limit of quantification, linear performance, reproducibility, matrix effects, etc.), but the biomarker(s) should have positive predictive value that link chemical exposures with adverse health effects [3].