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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.

Keywords

Biomarkers; Sensors; Non-invasive; Computational modeling

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Conflict of interest

The authors have nothing to disclose.

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 Fig. 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 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].

2. Minimally-invasive methods

As noted by Esteban and Castano [6], blood is probably the most ideal matrix for biological monitoring; however, the invasive nature of venipuncture is a significant disadvantage, particularly when considering the need for multiple measurements over time. Further, there are sensitive populations, such as premature infants, where extensive blood sampling for biomonitoring is not feasible without injury/health risk. An estimated 75% of infants born at 25 weeks gestation, and over 90% born at 27–28 weeks gestation survive [7]. As a consequence, iatrogenic pain in the newborn intensive care unit is commonplace.

These patients experience an average of 10–14 painful procedures per day [8,9], including heel-sticks, the most common painful procedure in the newborn intensive care unit, and venipuncture. Both procedures are used as the clinical standard to sample blood to evaluate therapeutic drug concentrations. Effects of exposure to painful procedures such as these in premature infants include a decrease in white and gray matter growth and a reduction in cortical thickness [10]. These brain abnormalities are implicated in altered sensory, motor, and cognitive development with profound, negative, long-term health outcomes, including altered sensitivity to pain, behavioral problems, learning disorders, vision problems, lower IQ, depression, and more [11-13]. Diagnostic blood sampling can also lead to anemia in premature infants [14]. Hence, non-invasive methods have been advocated, and saliva has been suggested as an ideal body fluid that can be substituted for blood in biomonitoring both drugs and environmental contaminants [15-23]. For many of these xenobiotics, saliva concentration readily correlates with blood so it is feasible to utilize computational modeling to estimate systemic dose and biological response based upon a saliva measurement [24]. In this context, our research group has pioneered the development of life-stage computational models, which enable prediction of pharmacokinetics at different stages of biological maturation [16,25,26]. Mechanisms of absorption, distribution, metabolism, and excretion all develop at different rates which could lead to age-dependent discrepancies in both pharmacokinetics and pharmacodynamics after exposure to drugs. PBPK models provide a computational framework to quantitatively incorporate age-dependent changes in physiology and mechanisms of xenobiotic disposition to predict net effects on target-tissue dosimetry and biological response.

This begs the question, if saliva correlates with blood concentrations, why has it not become a more routine matrix for biomonitoring? Although there are a number of contributing factors, the overarching problem relates to our inability to detect low concentrations (potentially much lower than in blood) of parent chemicals and or metabolites at occupationally and environmentally relevant concentrations. Likewise, the lack of adequate studies evaluating the mechanisms by which chemicals are taken up in salivary glands and subsequently secreted in saliva has likewise contributed to the problem. Nonetheless, we do have some general understanding of the physiological processes in play [24]. Salivary glands are highly perfused [27] and the primary mechanism by which xenobiotics leave the blood and enter saliva is thought to involve paracellular transport, passive transcellular diffusion, or trancellular active transport [28]. Paracellular transport (i.e. ultrafiltration) favors small (MW ~300 Da) polar lipid insoluble molecules that generally have a low (i.e. <1.0) saliva/plasma (S/P) ratio. Whereas, transcellular diffusion or active transport are favored by lipid soluble materials that can readily cross cell membranes [29]. However, the majority of drugs and xenobiotics are cleared from plasma into saliva by a passive diffusion process that is a function of concentration gradient, surface area, membrane thickness, and diffusion constants [30]. Of particular importance may be the extent by which target analytes are bound to plasma proteins, since it appears that transport from blood to saliva glands is primarily a function of “free” concentration [24,31,32]. In this regard, the identification of exposure and response biomarkers that are ideal candidates for saliva biomonitoring requires some understanding of the clearance mechanism which has primarily been determined *in vivo* in animal model systems [16,31-33]. However, these *in vivo* model systems are not

ideal for screening a broader range of biomarkers for salivary clearance; hence, alternative (simpler) experimental systems are warranted.

3. Challenges to saliva biomonitoring

To utilize saliva for biomonitoring, the relationship between blood and saliva concentrations for target analytes needs to be well established [17,24]. Secondly, for saliva biomonitoring to be more broadly utilized, there is a need to rapidly identify a comprehensive range of chemicals that can readily be quantified in saliva and utilized to predict systemic dose based upon these saliva measurements. To date, a major limitation of the experimental and modeling strategy has been the dependence upon *in vivo* animal model systems [16,31,33,34] as a means of identifying and screening chemical/drug candidates for salivary clearance. These *in vivo* models are limited by relatively low throughput and experimental complexity; hence, there utility as a general screen is poor. In this regard, consideration of alternative systems such as *in vitro* salivary gland epithelial cell based Transwell® assay to enable broad based screening of uptake and clearance mechanisms associated with both diffusional and active transport mechanisms [24,35] and the utilization of computational models to enable dosimetry quantification is needed.

4. Cell based experimental system

To help address these challenges Weber et al. [35] developed a serous-acinar (rat derived) Transwell® model systems that is capable of rapidly screening chemicals for salivary cell uptake and clearance, and also capable of providing kinetic parameters (uptake/clearance constants) to support pharmacokinetic modeling (Fig. 3A). A key consideration for determining cellular uptake and clearance kinetics is the need to have a system that can maintain barrier function. In this regard, the serous-acinar cells have been shown to be highly resilient forming reliable tight junctions capable of withstand subtle stress without loss of epithelial barrier function [35]. Utilization of these cell systems to predict salivary clearance for a broad range of xenobiotics requires that they are well characterized for tight junction formation/integrity, toxicity response (can impact barrier) and expression of tissue-specific transporters and metabolic enzymes [36,37]. Once these cell based systems have been adequately validated, they can readily be exploited for rapid evaluation of *in vitro* salivary chemical clearance, including the evaluation of complex mixtures. Hence, the experimental platform is critical for the development of individual analyte and multiplex sensor arrays capable of quantifying a broad range of biomarkers [38-40].

4.1. Cell model

Cellular based systems, such as Caco-2 cells and Madin–Darby canine kidney (MDCK) cells, have previously been developed to measure chemical and drug permeation in cells [41-44]. Smith et al. [45] has recently developed a cellular transport computational model to describe chemical uptake and clearance in salivary cells. The model describes the time course of chemical transport in the Transwell® system from the basolateral cell culture medium (bottom chamber), into the cells and transport into the apical cell culture medium (top chamber; Fig. 3A). Transport across compartments can be modeled as passive diffusion or active transport which is determined using the *in vitro* experimental results. The amount

of chemical in each compartment is calculated by integrating the differential rate equation, and concentration is determined by normalizing the amount by each compartments volume.

5. Physiologically based pharmacokinetic (PBPK) model

Although the cellular transport model provides critical information on the rates and extent of salivary cell uptake and clearance of xenobiotics, it cannot provide quantitative assessment of *in vivo* dosimetry and biological response. Hence as illustrated in Figure 3C integration of the cellular transport model into a PBPK model structure enables predictions of systemic dose and biological response based upon non-invasive biomarker assessment [45].

6. Example: pesticide chlorpyrifos

Based upon the above rationale we have suggested that rapid biomonitoring can be achieved utilizing multiplex sensor platforms to evaluate chemical exposure and response non-invasively in the field. So, is this a plausible approach? Over the last decade our research group has been working to develop such a system using the organophosphate insecticide chlorpyrifos as the initial test chemical. Since chlorpyrifos toxicity results from the inhibition of cholinesterase (ChE) in brain, blood, and tissues, it is feasible to develop biomonitoring approaches that quantify both dosimetry and biological response concurrently.

6.1. Sensor platforms

For rapid detection and quantification of dosimetry and biological response biomarkers, a number of sensor platforms have been developed. These include a quantum dot-based immunochromatographic biosensor for quantifying the chlorpyrifos metabolite trichloropyridinol (TCPy), a carbon nanotube-enhanced flow-injection detection system for quantifying ChE activity, and a multiplexed electrochemical immunosensor platform for detection of phosphorylated ChE enzyme [3,46,47]. Of particular importance is the ability to couple a simple sample separation strategy with a parallel multiplex sensor array for simultaneous analyte analysis and to increase detection limits using quantum dot-based biosensors over more conventional ELISA methods [48].

6.2. Computational modeling

There has been a significant effort over the last decade towards developing and validating PBPK/pharmacodynamic (PD) models in animal model systems and humans to describe the uptake, metabolism and elimination of the organophosphate insecticide chlorpyrifos which is likewise capable of predicting biological response associated with ChE inhibition. Models have been developed to directly address a number of key issues including: life-stages [26,49,50], mixtures [51], dietary exposure [25,52], and saliva clearance [16,17,45]. All these models were conceptualized and built on the PBPK/PD model developed by Timchalk et al. [53] which was capable of simulating the time course of the parent pesticide chlorpyrifos, it's major metabolite (trichloropyridinol) and ChE inhibition in blood (plasma & RBC) and brain in both rats and humans. As previously noted (Fig. 3) recent efforts by Smith et al. [45] has now integrated a cellular transport computational model into

the chlorpyrifos PBPK/PD model which is capable of simulating TCPy concentrations in blood, saliva and predict the extent of ChE inhibition (Fig. 4). Overall, this approach demonstrates the utility of a combination cellular and computational approach to predict chemical transport in saliva increasing the utility of future salivary biomonitoring.

7. Summary

The overarching strategy outlined above represents an important approach for developing and deploying biomonitoring sensor platforms capable of quantifying exposure and biological response at the level of the individual. The strategy is multidisciplinary in scope requiring expertise in: nanotechnology, sensors, pharmacokinetics, computational modeling, bioanalytical chemistry and exposure science. The multiplex sensor systems will enable a more accurate prediction of exposures and once validated the sensor array can be employed to assess dosimetry and biological response to a broad range of chemicals in support of biomonitoring and epidemiology studies.

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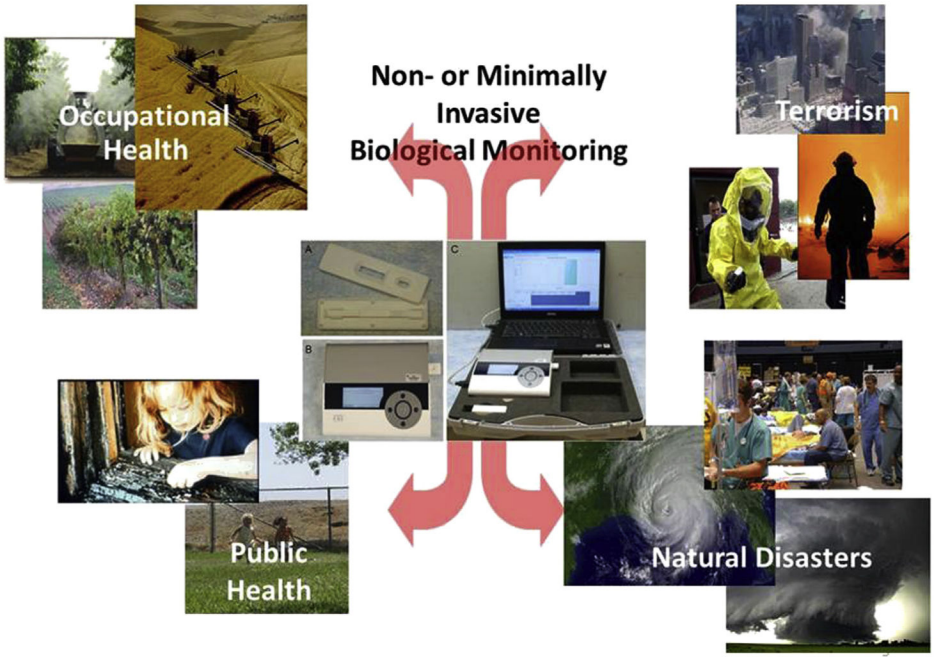

Fig. 1.
Biomarkers of exposure and response have a potential broad range of occupational and environmental applications.

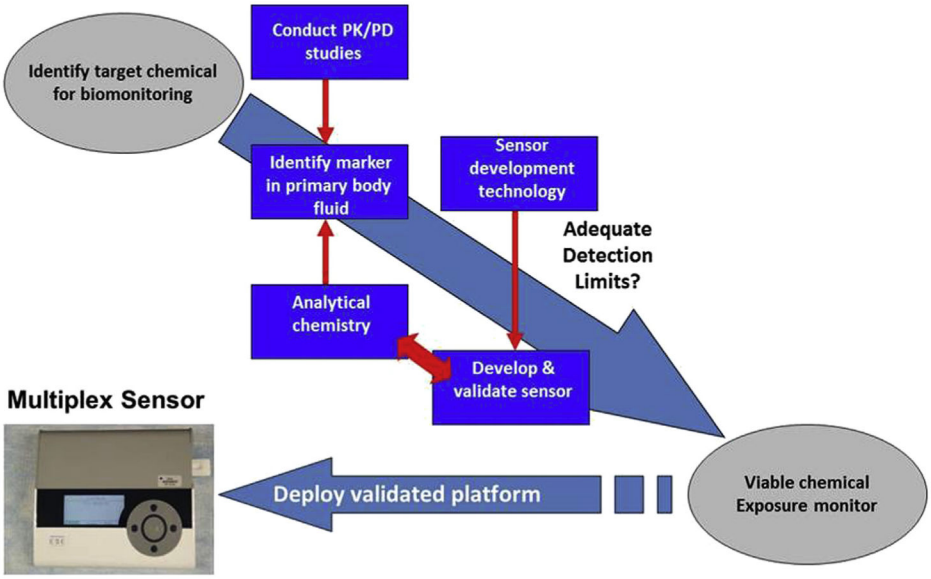

Fig. 2.
Sensor development strategy.

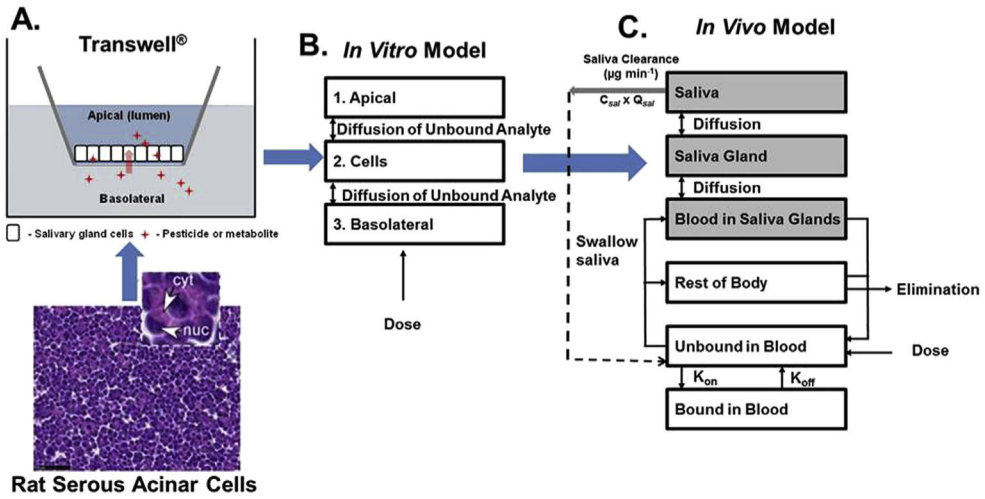

Fig. 3.
Salivary gland clearance model.

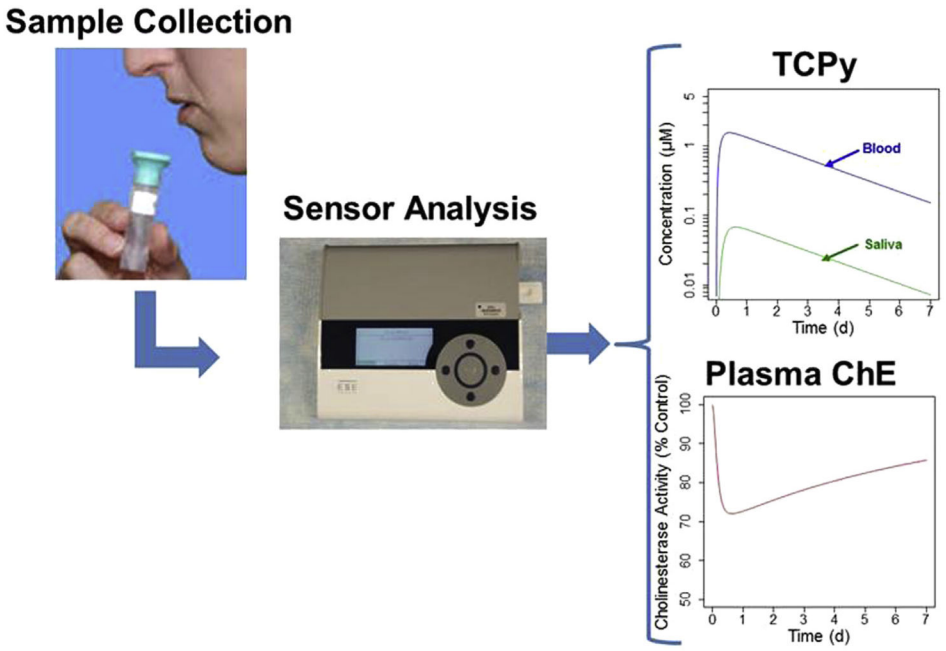

Fig. 4.
Non-invasive quantitative dosimetry.