Potential For Metabolomics-based Markers Of Exposure: Encouraging Evidence From Studies Using Animal Models

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Abstract # 341

Background

Direct measure of human exposure to environmental contaminants in real time is rare and difficult to obtain.

This frustrates exposure assessments, and investigations into the link between chemical exposure and human disease.

But, we can measure "markers" (both xenobiotic and 'omic-based) of past chemical exposure in human biofluids.

EPA risk assessments could be improved if these biomarkers are used to reconstruct previous exposures, and to predict the future likelihood of adverse effects.

'omic-based biomarkers, when used in conjunction with traditional biomarkers, offer great promise for both exposure reconstruction and for elucidating the linkages between exposures and adverse outcomes.

Goals and Objectives

- Discover mode-of-action specific 'omic biomarkers, including those based on genes, proteins, and endogenous metabolites.
- Early focus on endogenous metabolites measured by NMR spectroscopy (i.e., metabolomic-based biomarkers).
- Develop approaches for characterizing the "normal" levels of endogenous metabolites and their variance components in the healthy human population.
- Evaluate the potential for using 'omic-based biomarkers for exposure reconstruction.
- Incorporate biological outcome variables into all exposure assessment studies.

Methods/Approach

To Reconstruct Exposures:

many biomarkers (e.g., from 'omic measurements) are better than one or a few biomarkers (e.g., from the xenobiotic)

Consider this Hypothetical Case: Human Exposure to Chemical A:

Concentration of A in urine is a well-characterized biomarker

its ADME parameters are known:

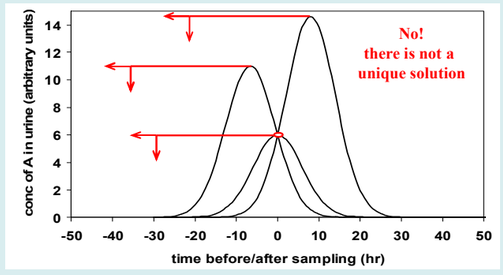
maximum concentration of A in urine = 20% of exposure concentration

it takes 30 hours to reach this maximum concentration

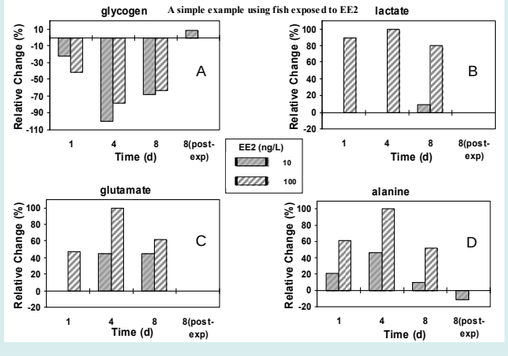
Chemical A is quantified in a urine sample from a human subject

We do not know the time or the concentration of the exposure

Can we reconstruct the exposure scenario with only this information?



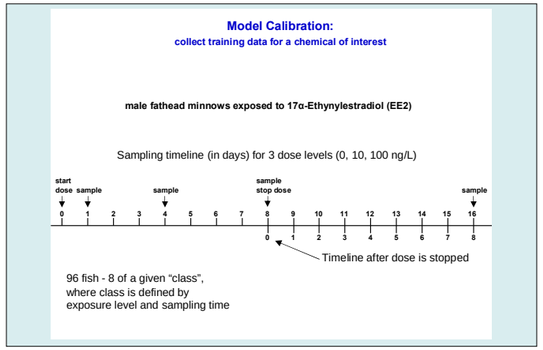
With metabolomics, many endogenous metabolite changes can be tracked. Including this information yields a better chance of reconstructing exposure scenarios.

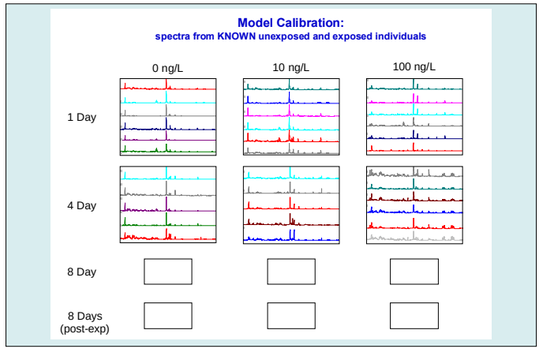


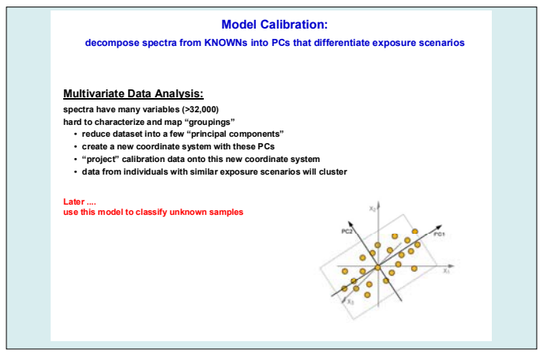
Exposure Reconstruction with Metabolomics:

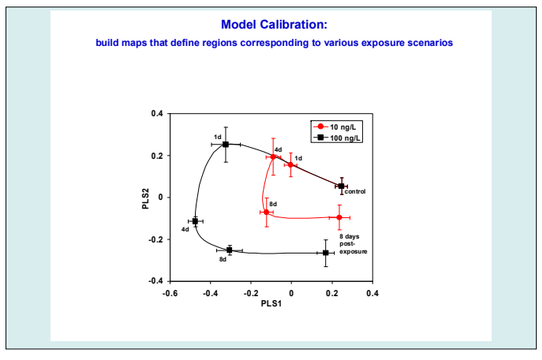
Proof of Concept - male fathead minnows exposed to 17α-Ethynylestradiol (EE2)

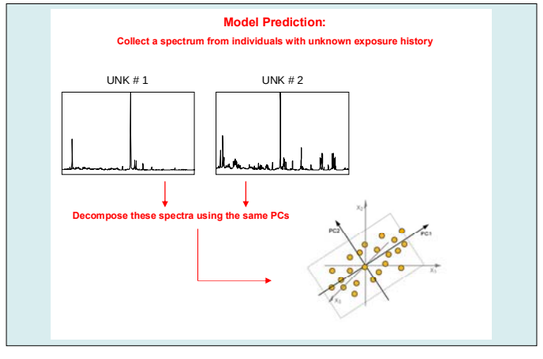
NMR spectra of polar liver extracts

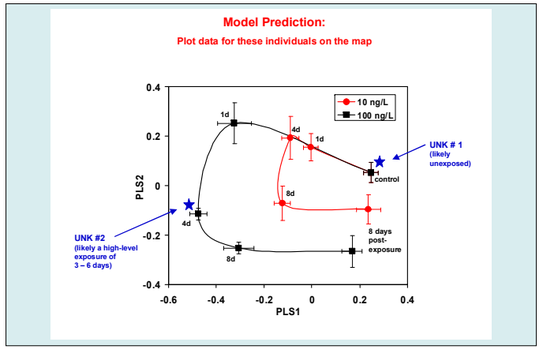












Future Directions

This is a new research proposal, with the following activities envisioned:

- Conduct studies with model animals exposed to model toxicants using a variety of exposure scenarios. Investigate reliability, sensitivity, selectivity, quantification, etc. Can exposures be adequately reconstructed?
- Conduct studies using cell cultures from both model animals and humans. Investigate cross species similarities and differences.
- Conduct mixture studies to assess the extent to which markers of specific toxicants can be observed in the presence of other chemicals.
- Conduct temporal studies where both conventional biomarkers and 'omic markers are collected. How do they compare and contrast over time following an exposure event?
- Incorporate modeling of pharmacokinetics and biomolecular interactions to aid in exposure reconstruction
- Conduct studies with human exposure samples where available.

Impact and Outcomes

Comprehensive information on exposure patterns is rarely available when conducting chemical assessments.

The ability to retrospectively reconstruct exposure scenarios would be a valuable capability for EPA's risk assessors.

Also, the ability to forecast adverse effects due to a given exposure scenario would enable better chemical and risk management practices.

Incorporating 'omic technologies into a program on exposure biomarkers offers great promise for advancing these applications.

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