EXECUTIVE SUMMARY

Understanding inter- and intra-individual variability in human biomonitoring spot samples (CEFIC-LRI HBM4)

INTRODUCTION and AIMS

In many large-scale human biomonitoring (HBM) surveys, single samples of blood, urine or other bodily matrices are collected from individuals recruited from the general population. When a single sample is collected however, it is very difficult to understand whether this biomarker measurement is truly representative for an individual's long term average exposure, or whether it may be due to a recent peak exposure. This may lead to misclassification of individuals with high/low exposures and is of particular concern if the exposure pattern is discontinuous and the compounds have a short half-life in the biological matrix.

This project aimed to develop an easy-to-use software model that predicted inter- and intra-individual variability in biomarker concentrations that could be used to determine the most important drivers affecting the representativeness of single biomarker samples for assessing an individual's internal dose. In order to test and validate the software tool the project aimed to generate new fit-for-purpose biomarker data from a human volunteer study.

MAIN OUTCOMES

A literature review provided an overview of factors that, apart from external exposure magnitude, may influence inter- and intra-individual variation in biomarker concentrations:

- Characteristics of the **specific chemical** of interest;
- Characteristics of the likely **route(s) and frequency of exposure**;
- **Physiological characteristics** of the biomonitoring matrix (in our case primarily urine).

Intra-individual variation in biomarker concentrations may be markedly affected by:

- The relationship between the elimination half-life and the intervals between exposure events;
- Variation in characteristics of the biomonitored media such urinary flow rate.

Variation across individuals may occur due to:

- Differences in time of sampling relative to exposure events;
- Physiological differences influencing urinary flow or creatinine excretion rates;
- Differences in metabolic rate or other factors influencing the absorption/excretion of a compound.

An **easy-to-use software model** was developed to allow researchers and regulators to quickly investigate the representativeness of spot biomonitoring samples in relation to different exposure patterns, chemical-related properties including half-life, and estimate how this is affected by e.g. creatinine correction or multiple sampling strategies. This tool also provides reverse dosimetry calculations that estimate an individual's likely exposure given their measured biomarker concentration.

Parallel to the development of the software tool, a human volunteer study was conducted in which **8 individuals collected each individual urine sample over a 6-day period**, while also recording dietary information and the use of personal care products. As target compounds, four different metals (As, Cd, Mn, Ni), 15 organic compounds (incl. 9 parabens, triclosan, triclocaban, chlorophenone-1, -3, -8, and Bisphenol A), creatinine and specific gravity were quantified.

Testing of the software model using both biomarker data from the human volunteer study and additional datasets retrieved from literature (16 datasets covering organics and metals, a large variability in half-lives and exposure frequencies, and different exposure routes) found **very good agreement between predicted and observed intraclass correlation coefficients** (ICCs) with an R^2 of 0.76.

The details of the software tool and the results of the model evaluation will also be available in a peer-reviewed publication.

CONCLUSIONS

When designing, implementing and interpreting biomonitoring studies, one should be aware of the factors driving inter- and intra-individual variability of biomarkers. At the same time however, these sources of variability are often less than the uncertainties associated with conventional external dose-based exposure assessments. With the appropriate understanding and appreciation of the relevant factors and corresponding

EXECUTIVE SUMMARY

enhancements to study design and data interpretation, some sources of variability can be accounted for in the interpretation of biomonitoring study findings.

Based on the results of our study, we could put forward the following conclusions:

- There are large differences in daily urine production, both within and between individuals. One forward approach to improve the interpretation of biomarker values is the additional collection of:
  - The entire volume of a sample rather than just a fixed volume from e.g. the midstream urine;
  - Registration of the time till last void, as this allows calculating urine production rates.
- Adjustment for specific gravity was more closely correlated with excretion rate than creatinine;
- As there often is a clear correlation between exposure episodes and biomarker levels , the intricate link between exposure frequency and toxicokinetics needs to be understood to improve their value for epidemiological studies;
- When evaluating the effect of different sampling strategies, FMV – spot sampling – 24-h samples, and creatinine- or SG-adjustment on the interpretation of biomarker values, there were noticeable differences between the metal and the organic biomarkers measured. This made it difficult to identify one common approach to an optimal sampling strategy;
- The project's software model accurately predicts the intra-class correlation coefficients (ICCs) of the 16 biomarkers tested, and should be highly valuable during the design phase of a biomonitoring studies.

PROJECT TEAM

Roel Smolders (VITO, Mol, Belgium; coordinator)
Holger M. Koch (IPA, Ruhr-University Bochum (IPA) Germany)
John Cocker, Kate Jones, Nick Warren (Health Safety Laboratory, Buxton, United Kingdom)
Len Levy, Ruth Bevan (Cranfield University, Cranfield, United Kingdom)
Sean M. Hays, Lesa L. Aylward (Summit Toxicology, LLP, Allenspark, CO and Falls Church, VA, USA)