

Challenges Faced in Interpreting Biomonitoring Data in a Risk Context

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Challenges – how to interpret results.

What does a biomonitoring level mean? Is it high, are we at risk? Are these levels safe? Are these levels at the dose that makes them a poison? Disconnect between regulations on concentrations in the external environment due to technology limitations – now we have the technical ability to measure levels in people. How do we consolidate the two? Calculate from external known safe concentration to internal or vice versa? Which is best?

Concentration of target tissue is the most relevant dose measure. Calculating exposure to yield biomonitoring level – lots of uncertainty – don't know exposure situation, also there is variability in exposure needed to cause a certain level, historical exposure versus snapshot of level.

If you put biomonitoring levels in a health risk context, need to forward calculate from external to internal.

To calculate – use information gathered for workplace toxicity. Can use human or animal PK studies, 1 compartment models or PBPKs. ACGIH has set BEIs for 42 chemicals, not all are quantitative, the ones that are have data to extrapolate from TLV to safe external concentration. BATs (German) - has set them for around 800 chemicals. Is biomarker level linear? Can we extrapolate to low levels? Need to determine from published literature and studies. Be careful of observational studies – some have sloppy exposure monitoring. Lots of PK studies dating back to the 50's – human studies on volunteer exposure and blood / urine measurements. Can use this information as a starting point to calculate safe biomonitoring levels. NTP information of NOEL also can be used for extrapolation to humans. 1 compartment model is simplistic but it works. Need half-life, volume of distribution, and bioavailability. Can calculate steady state concentration associated with exposure. Inhalational exposure is a similar relationship with different parameters needed for model – inhalation concentration (RfC), ventilation rate, etc. Dioxin example – parameters are known, safe biomonitoring level calculated to 8ppt lipid. Toluene – parameters are known, safe biomonitoring level calculated to 1.3 ug/L blood. Advantage of steady state model is that most data needed are readily available from PK studies and Toxicological Profiles. Can use it as a first approximation of safe levels. PBPK modeling is more complex (compartments for all body organs) but more robust. Can calculate biomonitoring levels for each tissue to be sampled. Lots of chemicals have had PBPK models developed. PBPK modeling can account for variability. Data on distributions of parameters can be used to run Monte Carlo simulations, and come up with distribution of internal dose – then develop the level recommended to protect public health (50, 75, 95th percentiles).

Extrapolating from BEI

Pros – Approach is established for some

Cons – assure linearity or know shape for extrapolation

PK Studies

Pros - Direct method if data are appropriate, Historical data exists, new protocols will develop a lot of data in animals

Cons – Extrapolation because studies are not always conducted at steady state.

Steady state PK Modeling

Pros – Easy to use for screening, minimal information required

Cons – Simplistic, not as useful for metabolites, urine is difficult

PBPK Modeling

Pros – Most robust and comprehensive, powerful tool for various scenarios, exist for many chemicals

Cons – Costly to develop from scratch

Should some uncertainty factors from RfC, and other regulatory estimates be removed?

Some conservatism could be minimized by using internal dose measurements.

Characteristics of useful biomarkers – health risk context – moderate half life, easy medium to sample, specific to chemical of interest, best if related to toxicity of compound, should be easy medium to interpret – close to critical (target) dose measurement. Easy medium to collect are usually not very relevant to toxicity (hair, nails). Suggest exhaled breath, blood, breast milk (for risk of infant only). Exhaled breath most useful for volatile compounds, urine for metabolites, blood for parent compounds.

Challenges with communicating the interpretation – presence does not equal risk but still need to determine safe biomonitoring levels.

What's in a name? – for biomonitoring levels – consider what you are trying to convey. (concern, safety, action, exposure, etc.) Prefers “Biomonitoring Equivalent” can have one for each regulatory guideline ex. BE_{RfC} .

Biomonitoring can become the gold standard for exposure assessment and risk management if you have the tools to interpret what you're measuring. Do have the methods to calculate safe levels.