# The Contribution of Biomonitoring in the Assessment of Exposure and Biological Effects

IEHIA OF AIR POLLUTION AND CLIMATE CHANGE IN MEDITERRANEAN AREAS

water and health [laboratory]

Cyprus University of Technology

Cyprus International Institute for Environmental and Public Health

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# LECTURE SYNOPSIS

- Definitions and utility of human biomonitoring (HBM)
- HBM in the context of current and future environmental and occupational health research
- HBM and the exposome concept including untargeted –omics platforms
- HBM exposure limits
- Biomarker types for use in HBM and selection criteria
- HBM data interpretation and health effects
- HBM and occupational exposures including emergency response
- Examples-cases of HBM

The measurement of concentrations of chemicals or their metabolites in human biological media such as blood, urine or breast milk

including chemical and biological parameters that allow inferences about the pollutants' biological effects and endogenous processes

Why biomonitoring?

1. Assess the magnitude and variability of chemical and non-chemical exposures of the general population by measuring biospecimen concentrations for a representative population sample. This way can establish reference values for each chemical in each country.
2. obtain information about proportion and characteristics of population groups at risk as well as insight in exposure pathways and the influence of lifestyle and sociodemography via questionnaire use.
3. HBM can be used to determine early effects of harmful substances (biomarkers of effect).

Schulz C, Wilhelm M, Heudorf U, Kolossa-Gehring M. Reprint of "Update of the reference and HBM values derived by the German Human Biomonitoring Commission."International Journal of Hygiene and Environmental Health. 2012 Feb;215(2):150–8.

# What is human biomonitoring (HBM) and its main objectives

# HUMAN BIOMONITORING AND DATA ANALYSIS IN ENVIRONMENTAL HEALTH SCIENCES

Data management

Data handling and statistical analysis

Interpretation and reporting

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# Data management (i)

Is there an easy way?

1 location - 1 questionnaire - 1 interviewer - 1 dataset

| female | age | educ | inc_q | q1a | account | q2 | q3a | q3b | q4 | q5 |
|---|---|---|---|---|---|---|---|---|---|---|
| female | 85 | completed ... | second 20% | yes | yes | 1 personal ... | no | no | 2 1 - 2 times | 2 1 - 2 times |
| female | 55 | secondary | second 20% | yes | yes | 1 personal ... | no | no | 5 (dk) | 2 1 - 2 times |
| female | 26 | completed ... | middle 20% | yes | yes | 1 personal ... | yes | yes | 3 3 - 5 times | 4 6 times o... |
| female | 65 | completed ... | richest 20% | (ref) | no | . | no | no | . | . |
| male | 27 | completed ... | middle 20% | yes | yes | 1 personal ... | no | yes | 2 1 - 2 times | 4 6 times o... |
| female | 33 | secondary | second 20% | no | no | . | no | no | . | . |
| female | 42 | secondary | second 20% | no | yes | . | yes | yes | 1 0 | 1 0 |
| female | 17 | (rf) | richest 20% | no | no | . | no | no | . | . |
| female | 60 | secondary | poorest 20% | yes | yes | 1 personal ... | no | no | 2 1 - 2 times | 2 1 - 2 times |
| male | 34 | secondary | fourth 20% | yes | yes | 1 personal ... | yes | yes | 2 1 - 2 times | 4 6 times o... |
| female | 16 | secondary | middle 20% | no | no | . | no | no | . | . |
| female | 76 | completed ... | middle 20% | yes | yes | 1 personal ... | yes | yes | 2 1 - 2 times | 3 3 - 5 times |
| male | 41 | secondary | poorest 20% | no | yes | . | yes | yes | 2 1 - 2 times | 3 3 - 5 times |
| female | 75 | secondary | poorest 20% | yes | yes | 1 personal ... | | | | |
| female | 35 | completed ... | fourth 20% | yes | yes | 1 personal ... | | | | |
| female | 34 | secondary | second 20% | no | no | . | | | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 158 | | | 1 | 10 | 5 | | | | |
| 2 | 158,1 | 1 | | | 90 | 5 | 30 | 15 | 30 | 10 |
| 3 | 157 | | | 1 | | | 4 | 10 | | |
| 4 | 157,1 | | 1 | | | | | | | |
| 5 | 157,2 | | 1 | | | | | | | |
| 6 | 157,3 | 1 | | | 90 | 5 | 12 | 20 | 30 | 5 |
| 7 | 152 | | 1 | | | | | | | |
| 8 | 152,1 | 1 | | | 30 | 5 | 15 | 30 | 15 | 10 |
| 9 | 150 | 1 | | | 60 | 5 | 15 | 10 | 15 | 10 |
| 10 | 146 | | 1 | | | | | | | |
| 11 | 146,1 | | 1 | | | | | | | |
| 12 | 146,2 | | 1 | | | | | | | |
| 13 | 146,3 | | 1 | | | | | | | |
| 14 | 146,4 | 1 | | | 90 | 5 | 30 | 30 | 30 | 20 |
| 15 | 146,5 | | 1 | | | | | | | |

- **Multiple study settings - different types of data**
    - Questionnaires in different languages
        - Socio-economic and lifestyle factors
            - Questions about specific behaviors/ routines
        - Laboratory analyses - toxicological data, biomarkers

- Multiple datasets
    - Harmonization
    - Collaboration
    - Flexibility

# Data management (ii)

- **Biomarker media**
  - Hair
  - Urine
  - Blood

- **Check biomarker data**
  - Conform with definitions, units, measurements (example: values <LOQ → ½ LOQ, adjust to creatinine for urinary markers, etc.)
    - Log-transformation
    - Manage missing values
    - Calculate new variables (recode, combine etc)

# Data handling

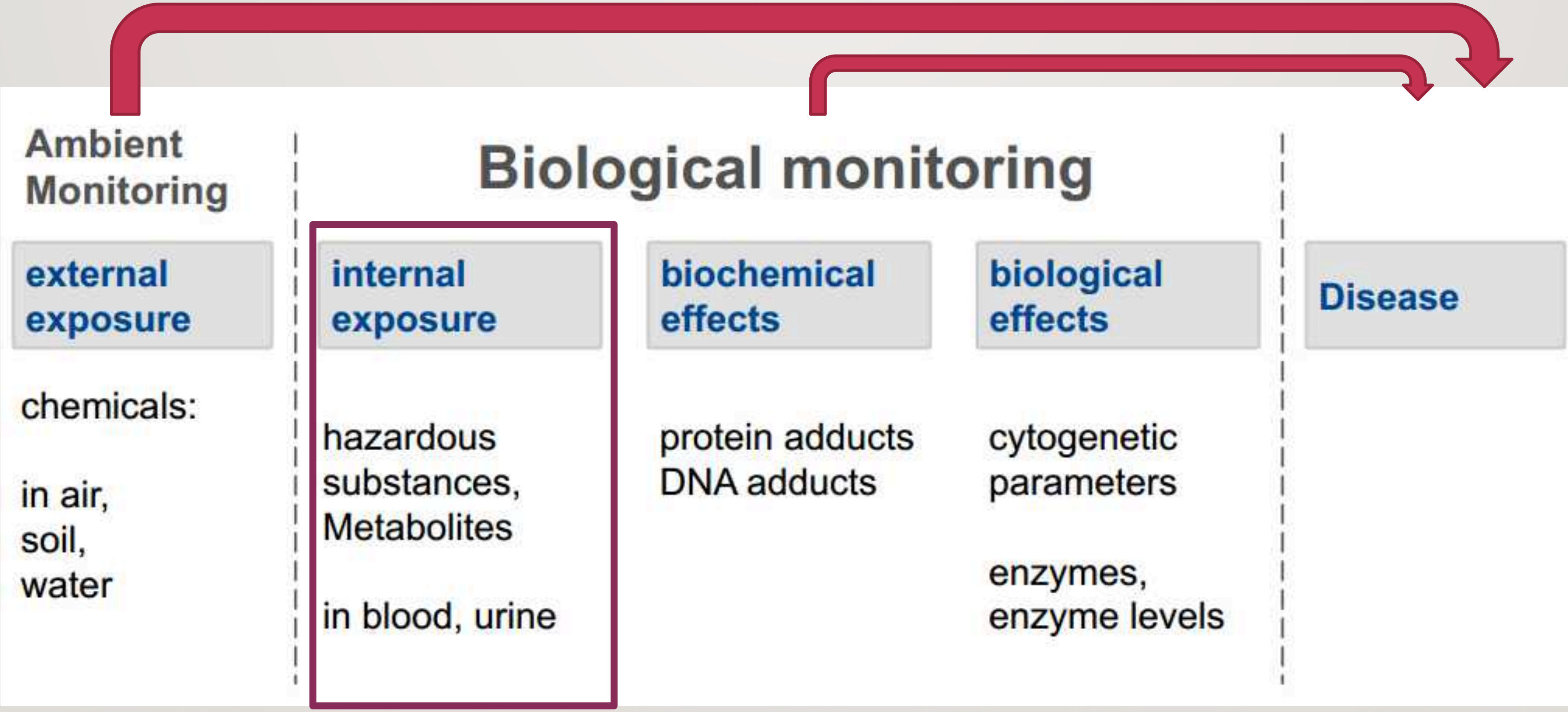
# Statistical analysis (i)

**Table 1.** Select characteristics of study participants.

| # | Characteristic | Quartiles (or Categories) | Overall | |
|---|---|---|---|---|
| | | | n | % |
| 1 | Gender | Female | 200 | 61 |
| | | Male | 126 | 39 |
| 2 | Area[a] | High risk | 167 | 51 |
| | | Low risk | 159 | 49 |
| 3 | Age (y) | <36 | 79 | 24 |
| | | 36-63 | 167 | 51 |
| | | >63 | 80 | 25 |
| 4 | BMI ($Kg\ m^{-2}$) | <25 | 137 | 42 |
| | | 25-30 | 134 | 41 |
| | | >30 | 54 | 17 |
| 5 | Marital status | Single | 44 | 14 |
| | | Married | 253 | 78 |
| | | Divorcee | 7 | 2 |
| | | Widower | 19 | 6 |
| 6 | Education | Primary | 103 | 32 |
| | | Secondary | | |
| | | University | | |
| 7 | Smoking status | Current smoker | | |
| | | Never smoker | | |
| | | Ex-smoker | | |

**Table 2.** Distribution of THM concentration classes in tap water (n = 193) and participants' urine samples (n = 326).

| | **Medium** | **Trihalomethane** | **Mean (Deviation)*** | **Percentile** | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Min. | $10^{th}$ | $25^{th}$ | Median | $75^{th}$ | $90^{th}$ | Max. |
| 1 | Water ($\mu g\ L^{-1}$)# | Chloroform | 16 (7) | 1 | 8 | 12 | 16 | 21 | 25 | 38 |
| | | Bromodichloromethane | 21 (8) | 1 | 11 | 17 | 22 | 25 | 30 | 39 |
| | | Dibromochloromethane | 22 (9) | 1 | 8 | 18 | 24 | 27 | 31 | 46 |
| | | Bromoform | 7 (3) | 1 | 2 | 5 | 7 | 9 | 11 | 17 |
| | | Brominated THM | 50 (19) | 2 | 21 | 42 | 53 | 60 | 71 | 98 |
| | | Total THM | 67 (25) | 3 | 29 | 55 | 69 | 80 | 95 | 129 |
| 2 | Creatinine-unadjusted urinary concentration ($ng\ L^{-1}$)## | | | | | | | | | |
| | | Chloroform | 332 (3) | $47^a$ | $47^a$ | 311 | 456 | 601 | 783 | 3008 |
| | | Bromodichloromethane | 73 (2) | $23^a$ | $23^a$ | $68^b$ | $68^b$ | $68^b$ | 165 | 1934 |
| | | Dibromochloromethane | 54 (1) | $47^b$ | $47^b$ | $47^b$ | $47^b$ | $47^b$ | 117 | 195 |
| | | Bromoform | 23 (1) | $20^a$ | $20^a$ | $20^a$ | $20^a$ | $20^a$ | $60^b$ | $60^b$ |
| | | Brominated THM | 161 (2) | 90 | 90 | 135 | 135 | 188 | 283 | 2156 |
| | | Total THM | 560 (2) | 137 | 182 | 480 | 625 | 797 | 1001 | 5163 |
| 3 | Urinary Creatinine ($g\ L^{-1}$) | | 1.2 (0.8) | 0.1 | 0.3 | 0.6 | 1.1 | 1.8 | 2.3 | 3.9 |




Human Biomonitoring Conference - German approach for setting human biomonitoring (HBM) values and reference values - Holger Koch - German HBM Commission, Germany

http://www.lne.be/en/environment-and-health/human-biomonitoring-conference/conference-day-1-27th-of-october

# Interpretation and reporting – The big picture

# EXPOSOME

- Definition by Miller and Jones (Emory Univ.) :

- The cumulative measure of environmental influences and associated biological responses throughout the lifespan including exposures from the environment, diet, behavior, and endogenous processes.

- Coupling external with internal exposures a key concept within Exposome to improve characterizing exposures implicated with disease process

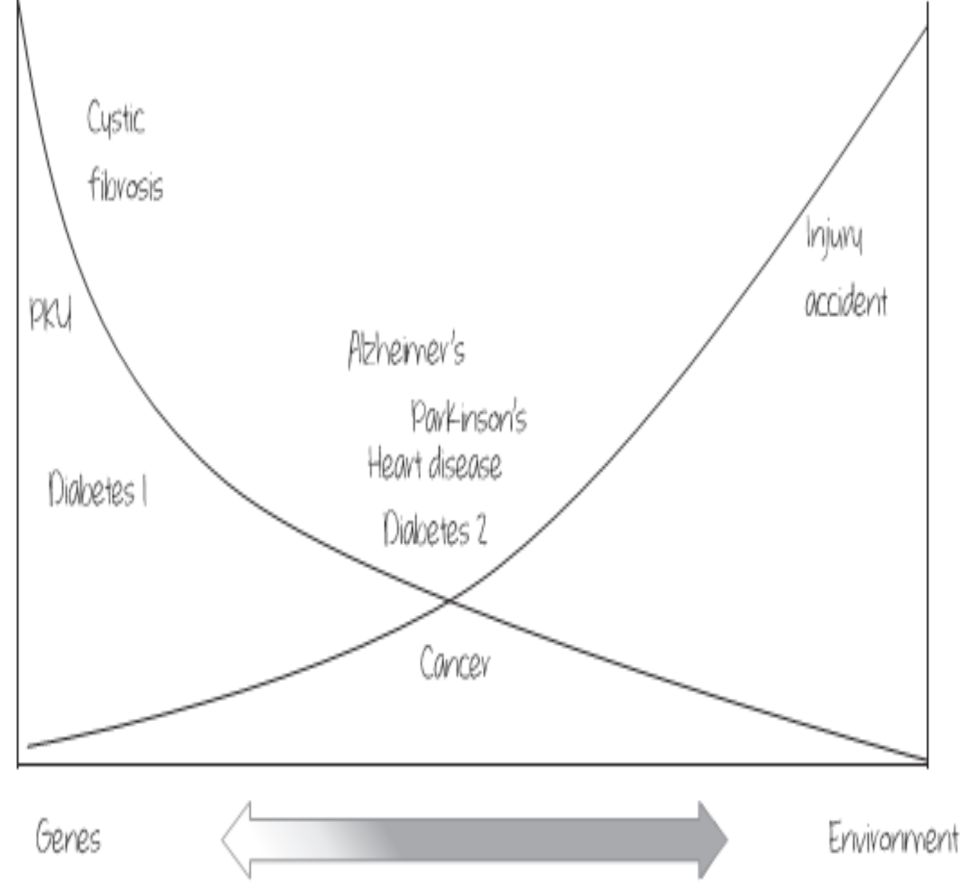



*Figure 2.1 The gene–environmental continuum. There are numerous diseases that result exclusively from genetic abnormalities. These are depicted on the left side of the graph. There are also outcomes that result exclusively from external or environmental sources, shown on the right side of the graph. The vast majority of disease though resides at the interface. They may be 80% genetic and 20% environmental or vice versa. The past few decades have generated superb data on the genetic causation of disease. In order to address the majority of diseases at the interface we must have more comprehensive environmental data (i.e., exposome).*


Miller, G. (2014). *Exposome: a primer*.

# STUDY TYPES FOR THE EXPOSOME

## Exposure assessment - Experimental studies

Exposome approach

- Multi-omics
- Personal monitoring

Interventions

- Randomized and non-randomized

- Panel studies
- Time series

## Population/observational studies
## Surveillance (disease-mapping, spatial epidemiology)

- Cohorts
- Case-control studies
- Cross-sectional studies

- Prospective and retrospective
- Continuous monitoring

## Urban environment studies

| Infrastructure | Physical environment | City planning |
| --- | --- | --- |

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# Example: Trihalomethanes exposure assessment (outcome: small for gestational age)

| Estimation from monitoring only | Estimation from monitoring levels and questionnaire | Tap water analysis at participant's residence and estimation of exposure | Estimation based on routinely collected data + questionnaire and biomonitoring |
|---|---|---|---|
| **5/9** | **1/5** | **1/1** | **0/1** |
| Kramer et al 1992 (N)<br>Bove et al 1995 (Y)<br>Dodds et al 1999 (Y)<br>Wright et al 2003, 2004 (Y)<br>Hinckley et al 2005 (Y)<br>Porter et al 2005 (N)<br>Yang et al 2007 (N)<br>Horton et al 2011 (N) | Infante-Rivard 2004 (Y)<br>Hoffman et al 2008 (N)<br>Villanueva et al 2011 (N)<br>Grazuleviciene et al 2011 (N)<br>Danileviciute et al 2012 (N) | Levallois et al 2012 (Y) | Costet et al, 2012 (N) |

## How common is the HBM use in population health studies?

water and health laboratory

Main data processing

Integration of external and internal metrics with participant characteristics

External exposures

- Demographics
- Anthropometrics
- Questionnaire data

Internal exposures

- Targeted exposure measurements
- Untargeted metabolomics data (identification of differentially expressed metabolites)

Exploratory analysis

Summary statistics

Group comparisons

Regression analysis

Modelling

Associations between the differentially expressed metabolites and exposures or health endpoints

Database search

Literature

Pathway analysis

Validation

# TARGETED BIOMONITORING AND UNTARGETED METABOLOMICS PLATFORMS

# BIOMONITORING-BASED EXPOSURE LIMITS

- Helping national authorities in decision making using HBM surveys

## Human Biomonitoring Values (HBM values)

HBM value definition → most reliable using epidemiological data; also possible using toxicokinetic extrapolation in the absence of human data

What if there are no human studies available? ⇒ Biomonitoring equivalents (BEs)
or, Health-Based guidance values based on WHO guidance values

The concentration of a substance or its metabolites corresponding to tolerable intake dose - acceptable daily intake (ADI) or tolerable daily intake (TDI) - derived by recognized experts or authoritative organizations (WHO, EFSA)

Schulz C, Wilhelm M, Heudorf U, Kolossa-Gehring M. Reprint of "Update of the reference and HBM values derived by the German Human Biomonitoring Commission."International Journal of Hygiene and Environmental Health. 2012 Feb;215(2):150–8.

| Damage to health | Recommendation |
|---|---|
| Possible | Care by experts |
| | Immediate action |
| **HBM II (“action” value)** | |
| | Identification of specific sources of exposure |
| | Reduction on exposure |
| **HBM I (“control” value)** | |
| No risk (current knowledge) | No actions recommended |

**Risk increase for adverse health effects**

Negligible health risk assumed, if the concentration of a substance in urine or blood is < HBM I level. A health risk cannot be excluded if the concentration of a substance in urine or blood is between HBM I and HBM II. An increased risk for adverse health effects is presented if biomarker concentration > HBM II ( Schulz et al., 2011).

http://www.umweltbundesamt.de/en/reference-hbm-values

C. Schulz, et al., Update of the reference and HBM values derived by the German Human Biomonitoring Commission, Int J. Hyg. Environ. Health, 215 (2011), pp. 26-35

# Exposure Limit Estimates and Interpretation

**Table 13**
Human biomonitoring (HBM) values for cadmium, mercury, pentachlorophenol, thallium and DEHP in urine or blood.

| Parameter and medium | Population group (age range) | HBM I value | HBM II value |
|---|---|---|---|
| Based on epidemiological studies | | | |
| Cadmium in urine (HBM Commission, 2011c) | Children and adolescents | 0.5 µg/l | 2 µg/l |
| | Adults | 1 µg/l | 4 µg/l |
| Lead in blood (Wilhelm et al., 2010) | General population incl. children ≤12 years, women of reproductive age | Suspended | Suspended |
| Mercury in urine (Schulz et al., 2007) | Children and adults | 7 µg<br>5 µg/g creatinine | 25 µg/l<br>20 µg/g creatinine |
| Mercury in blood (Schulz et al., 2007) | Children and adults*<br>* Derived from women of reproductive age. The value is recommended for other groups | 5 µg/l | 15 µg/l |
| Pentachlorophenol in serum (Schulz et al., 2007) | General population | 40 µg/l | 70 µg/l |
| Pentachlorophenol in urine (Schulz et al., 2007) | General population | 25 µg/l<br>20 µg/g creatinine | 40 µg/l<br>30 µg/g creatinine |
| Thallium in urine (HBM Commission, 2011a) | General population | 5 µg/l | / |
| Based on TDIs | | | |
| Sum of the metabolites of di(2-ethylhexyl)phthalate DEHP: | Children aged 6–13 years | 500 µg/l | / |
| 5-oxo- and 5-OH-MEHP in urine (HBM Commission, 2007b) | Women of reproductive age | 300 µg/l | / |
| | Males ≥14 years, general population | 750 µg/l | / |

# Interpretation and reporting (examples of HBM values)

**Reference values** ($RV_{95}$): the 95th population percentile of the concentration level of the respective parameter in the matrix obtained from the reference population

- rounding off the 95th population percentile within the 95% CI
- statistically defined reference value - describes exposure or body burden in the general population at a given time, has NO whatsoever relevance to human health

If $RV_{95}$> HBM I -- no immediate action needed, BUT indication of high levels of exposure.

- "In such a situation, the persons or population groups affected should be informed as soon as possible yet without creating undue concern."

**Table 3**
Reference values ($RV_{95}$) for metabolites of organophosphorus insecticides (DMP, DMTP, DMDTP, DEP, DETP) in urine (Heudorf et al., 2006; Schulz et al., 2009).

| Parameter | Population group (age range) | Study period | $RV_{95}$[a] |
|---|---|---|---|
| DMP | Children (3–14 years) | 2003–2006 | 75 µg/l |
| | General population (not a strictly representative sample) | 1998 | 135 µg/l |
| DMTP | Children (3–14 years) | 2003–2006 | 100 µg/l |
| | General population (not a strictly representative sample) | 1998 | 160 µg/l |
| DMDTP | Children (3–14 years) | 2003–2006 | 10 µg/l |
| DEP | Children (3–14 years) | 2003–2006 | 30 µg/l |
| | General population (not a strictly representative sample) | 1998 | 16 µg/l |
| DETP | Children (3–14 years) | 2003–2006 | 10 µg/l |

[a] Uncertainty of analysis must be taken into account; DMP: dimethylphosphate; DMTP: dimethylthiophosphate; DMDTP: dimethyldithiophosphate; DEP: diethylphosphate; DETP: diethylthiophosphate.

Schulz C, Wilhelm M, Heudorf U, Kolossa-Gehring M. Reprint of "Update of the reference and HBM values derived by the German Human Biomonitoring Commission."International Journal of Hygiene and Environmental Health. 2012 Feb;215(2):150–8.

# Reference values

## Comparison with other large national BM surveys

| Biomarker | **Reference value ( $\mu$ g/g creatinine)** | | | |
|---|---|---|---|---|
| | **UK (this study)** | **US NHANES (Year)** | **Germany (GerES)** | **Other** |
| **Metals** | | | | |
| Cadmium | 0.9<br>N=435 | 1.05 (2007/08)<br>N = 1857 | 0.7 (1998)<br>N = 4728 | |
| Mercury | 2.8<br>N=435 | 2.56 (2007/08)<br>N = 1861 | 2.0 (1998)<br>N = 4730 | |
| **Pesticides** | | | | |
| Pyrethroids | | | | |
| 3PBA | 4.3<br>N=405 | 3.2 (01/02)<br>N = 1128 | | ~2 German HBM |
| cisCl2CA | 0.7<br>N=405 | 0.9 (01/02)<br>N = 1128 | | ~1 (1998) German HBM |
| transCl2CA | 1.8<br>N=405 | 2.6<br>(01/02) N = 1123 | | ~2 (1998) German HBM |

Bevan R, Jones K, Cocker J, Assem FL, Levy LS. Reference ranges for key biomarkers of chemical exposure within the UK population. International Journal of Hygiene and Environmental Health. 2013 Mar;216(2):170–4.

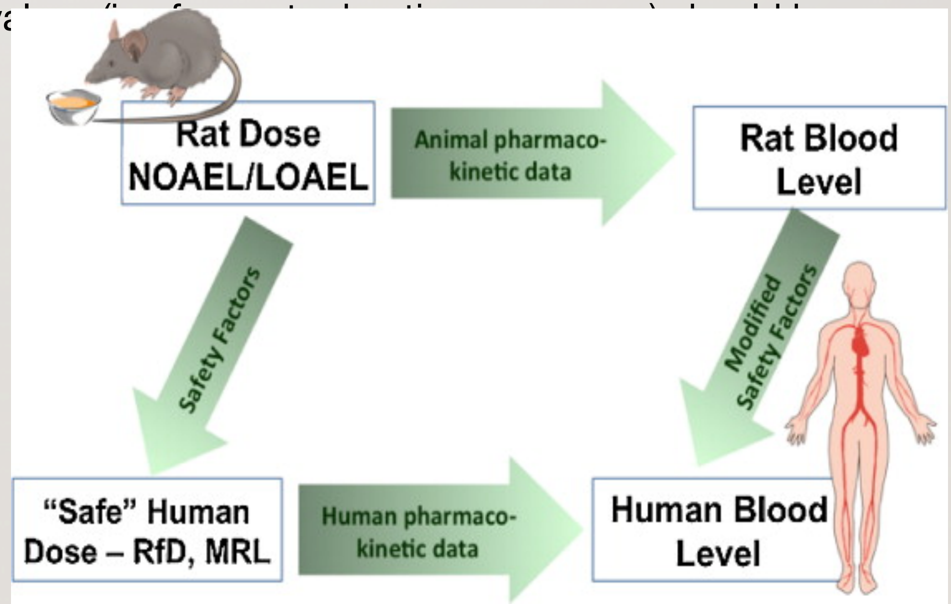
**Biomonitoring Equivalents (BEs)**

- the concentration or range of concentrations of a chemical or its metabolites in a biological medium (blood, urine, or other medium) that is consistent with an existing health-based exposure guidance value such as a Reference Dose (RfD) or Tolerable or Acceptable Daily Intake (TDI or ADI).

- **Utility:** screening tool to put biomonitoring data into a health risk context

**Selection of exposure guidance values**

- RfDs (reference doses), RfCs (reference concentrations), MRLs (minimal risk levels), TDIs (tolerable daily intake)
- preference to values with more recent toxicological evaluations and values applicable to country, population etc
- BE values derived from specific guidance va
used only in comparable situations




Hays SM, Aylward LL. Interpreting human biomonitoring data in a public health risk context using Biomonitoring Equivalents. International Journal of Hygiene and Environmental Health. 2012 Feb;215(2):145–8.

# Biomonitoring Equivalents (BEs) -- unified model

## Starting points for BE derivation (ii)

- Pharmacokinetic data requirements
  - fully developed PBPK models are desirable but not necessary
  - animal data can be used to form an internal dose-based derivation of a BE that is consistent with the exposure guidance value
    - Uncertainty factors (UFs)
    - Data informing the use of animal and human data in the derivation of a BE: data on active compound (parent or metabolite), model of action, critical dose metric

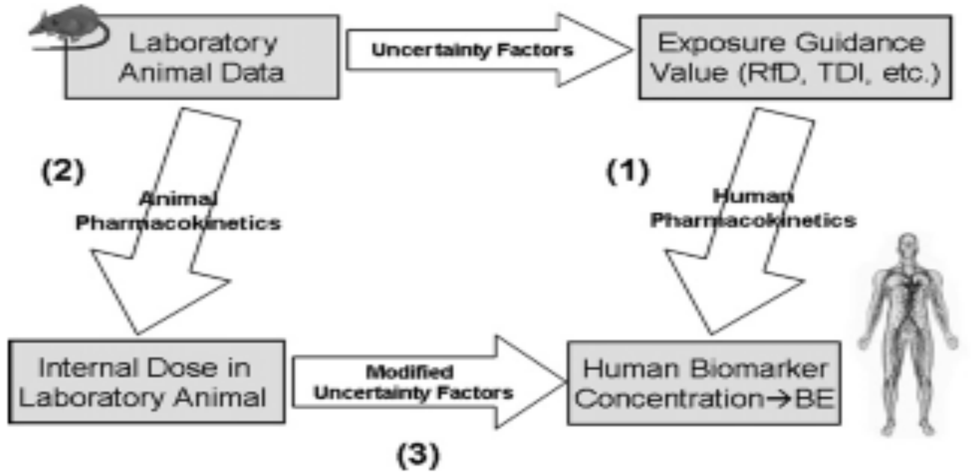



**Fig. 1.** Schematic diagram showing parallelogram concept for calculating BEs and possible routes for deriving a BE.

**Table 2**
Example summary table for presentation of BE values

| Underlying exposure guidance value | Analyte | Biological matrix | Human equivalent $BE_{POD}$ | Target BE | Confidence |
|---|---|---|---|---|---|
| USEPA RfD | Parent<br>Metabolite | Blood<br>Urine | 120 ng/mL<br>30–60 µg/g creatinine | 40 ng/mL<br>3–6 µg/g creatinine | High[a]<br>Medium[a] |

The underlying exposure guidance values, and the methods used to estimate the BE values, would be described in more detail in accompanying text and table(s).
[a] A summary of the considerations leading to the confidence rating can be presented here.

(i) The identification of the point of departure (POD) used for deriving the external exposure reference value (e.g., TDI or RfD).

(ii) uncertainty factors that account for interspecies extrapolation (animal to human) and, if needed, the lowest observed adverse effect level (LOAEL) to no observed adverse effect level (NOAEL) extrapolation, are used to calculate the human-equivalent POD.

(iii) Using pharmacokinetic modelling, we estimate the expected concentration at the matrix of interest, assuming an intake equal to the human-equivalent POD. For rapidly metabolized compounds, when a urinary metabolite is identified, the daily urinary excretion of the compound normalized by average urine volume and average creatinine excretion at the daily exposure rate equal to the human-equivalent POD has to be estimated. For this we have to make an assumption on the percentage of intake that is eliminated via the urinary tract. In both cases, the result of the toxicokinetic calculation helps us to derive the biological matrix-related BE (POD).

(iv) Uncertainty factors related to intraspecies differences have to be applied on the BE (POD). When a detailed toxicokinetic model is available, intraspecies variability can be directly incorporated in the relevant anthropometric (i.e. bodyweight, body mass index) and biochemical (e.g. metabolic rates based on the genetic polymorphisms of the cytochrome P450 [CYP] isozymes) parameters.

# Derivation steps of a BE

Steckling et al., 2018, Env. Res.

**Table 1**
Chemicals for which BEs have been derived.

| Completed and published | |
|---|---|
| 2,4-D | n-Nonane |
| Cyfluthrin | 1,1,1-Trichloroethane |
| Cadmium | 1,1,2-Trichloroethane |
| Inorganic arsenic | n-Decane |
| Hexachlorobenzene | 1,2,3-Trichloropropane |
| Bisphenol A | 1,1,1,2-Tetrachloroethane |
| Triclosan | 1,1,2,2-Tetrachloroethane |
| Diethyl phthalate | 1,2-Dibromoethane |
| Dibutyl phthalate | Hexachloroethane |
| Benzyl butyl phthalate | 1,1-Dichloroethene |
| Di-2(ethylhexyl) phthalate | cis-1,2-Dichloroethene |
| Dioxin TEQ | trans-1,2-Dichloroethene |
| Acrylamide | Trichloroethene |
| Chloroform | Tetrachloroethene |
| Bromoform | Benzene |
| Dibromochloromethane | Toluene |
| Bromodichloromethane | Styrene |
| Methylene chloride | Ethylbenzene |
| Carbon tetrachloride | Xylenes, mixed |
| Dibromomethane | Acrylonitrile |
| n-Hexane | Furan |
| 1,1-Dichloroethane | Tetrahydrofuran |
| 1,2-Dichloroethane | 1,4-Dioxane |
| n-Heptane | Methyl-tert-Butyl Ether (MTBE) |
| n-Octane | Methyl isobutyl ketone |
| Hexabromocyclododecane | PBDE 99 |
| Di-isononylphthalate | Deltamethrin |
| DDT/DDE/DDD | |



Hays SM, Aylward LL. Interpreting human biomonitoring data in a public health risk context using Biomonitoring Equivalents. International Journal of Hygiene and Environmental Health. 2012 Feb;215(2):145–8.

**<u>BEs</u>**

- could be calculated with a variety of approaches and datasets
- could be targeted to a number of biological matrices and analyses

*carry uncertainties
*may change

Use of population representative biomonitoring data to prioritize amongst chemicals by assessing the relative levels of detected biomarker concentrations in comparison to the chemical specific BE values

**Hazard quotient (HQ) = [biomarker]/BE**

**HQ<1 → exposure below the guidance value**

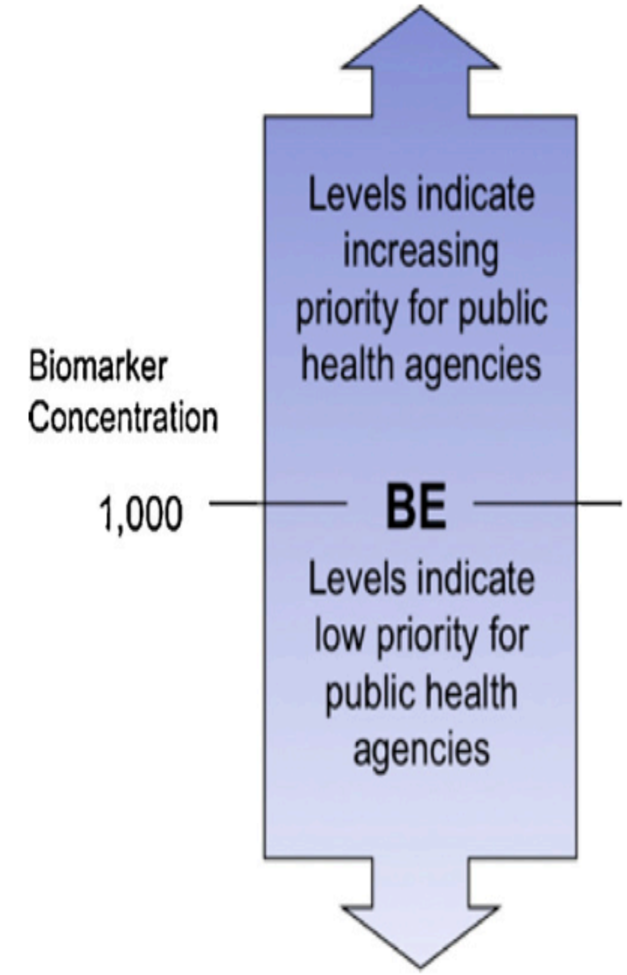



**Fig. 2.** BE communication model. The model is intended to convey several messages, particularly that BE values are not bright lines between safe and unsafe exposure levels and that the interpretation should be made in terms of relative priority for risk assessment follow-up.

# Use of Biomonitoring Equivalents in prioritizing health risk management

Urinary excretion rate (UER) of an analyte is calculated by multiplying the measured biomarker concentration in urine by the volume of the bladder void and divided by the duration of time that the void was accumulating in the bladder (collection time – time of last urination) (Rigas et al., 2001,Toxicological Sciences, 61:374-381).

Despite its attractiveness, assessing exposure using only biomarkers also presents difficulties. A metabolite measured in urine must, for example, be specific to the parent toxic agent of interest. Further, the relationship between metabolite concentrations in urine and particular exposure events is often unclear.

**UER calculation using external dose estimates – example of CHLORPYRIFOS**

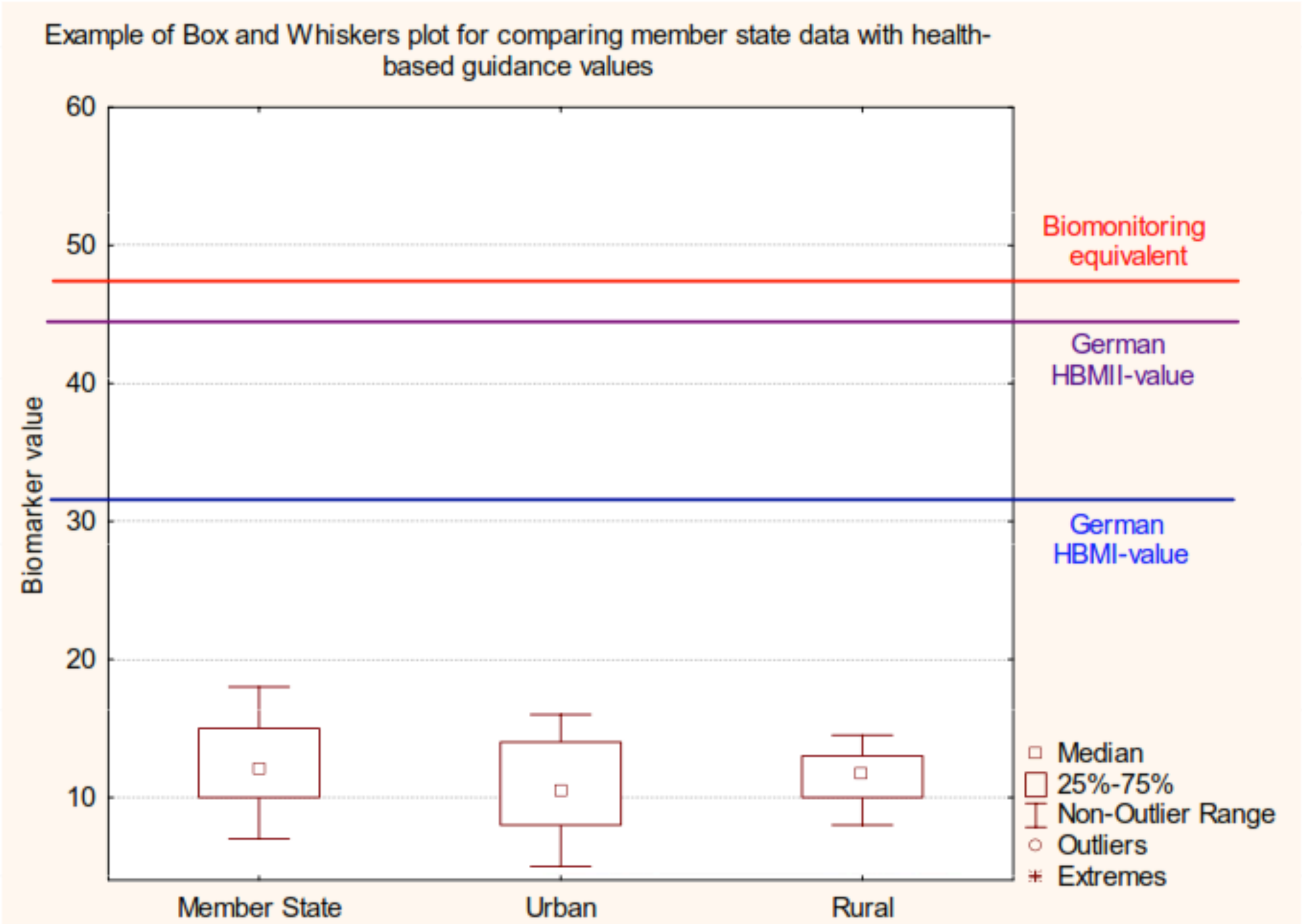
*The assumptions for the exposure estimates imply steady-state chronic exposure*. Average absorption rate must be equal to the average elimination rate, accounting for mass differences between TCPy and chlorpyrifos. We used the assumption that 70% of an oral dose is absorbed (Nolan et al., 1984) and 3% of a dermal dose is absorbed (U.S. EPA, 1997b). Then, the average urinary excretion rate (UER) of TCPy in mg/h is related to the exposure assumptions as

$$\mathbf{UER = 198.5/350.57(0.03Dp + 0.7Rp + 0.70Ip)/24,}$$

the molecular weight of TCPy is 198.5 mg/mmol and the molecular weight of chlorpyrifos is 350.57 mg/mmol. Dp and Ip are the daily dermal and ingestion doses, respectively. The absorption fraction of 0.7 for respiratory exposures from Buck et al. (2001).

# Example UER derivation

# Data interpretation at group level: comparison with guidelines




Den Hond (2013) - Statistical analysis of human biomonitoring data

# Biomonitoring in emergency response

## Acute Exposure Guideline Levels & Intervention Values for Emergency Response

**TABLE 2. Characteristics of AEGLs**

| CATEGORY | CHARACTERISTICS |
|---|---|
| Death or Life-threatening Effects | Death or life-threatening effects immediately or soon after exposure |
| AEGL-3---(LETHAL) | |
| Disability | External assistance needed:<br>➨persons disabled by exposure<br>➨persons acquire permanent or long-lasting effects |
| AEGL-2---(DISABLING) | |
| Discomfort | Person's condition does not:<br>➨impair escape<br>➨produce disablement<br>➨result in permanent or long-lasting effects |
| AEGL-1---(NON-DISABLING) | |
| Detectability | Perceived only by smell, taste, sight, or by sensations. No direct effects of exposure on health |

Rusch GM et al., Process Safety Progress. 2000;19(2):98–102.
Scheepers PT et al., J Expos Sci Environ Epidemiol. 2011 May; 21(3):247–61.

**Health effects and corresponding intervention values for emergency response (IVERs) in the US and The Netherlands**

| | |
|---|---|
| Death | |
| AEGL-3 | Danger-to-life threshold |
| Disability (irreversibility/impairment), | |
| AEGL-2 | Public alert threshold |
| Discomfort (mild CNS depression, some slight irritation) | |
| AEGL-1 | Public information guidance value |
| Detectability (very slight CNS depression, some slight sensory awareness) | |

- Specificity - analytes specific markers of exposure to the chemical of interest (i.e. toluene in blood is specific biomarker, urinary markers of toluene - ortho-cresol and hippuric acid are non-specific)
- Relevance to toxicity - analytes most relevant to the toxic endpoint of interest (i.e. toluene in blood is directly relevant to nervous system responses)
- Relevance to exposure
- Stability
- Acceptability - the less invasive collection procedure (i.e. hair, urine) is preferable
- Ease of interpretation

Hays SM, Aylward LL, LaKind JS, Bartels MJ, Barton HA, Boogaard PJ, et al. Guidelines for the derivation of Biomonitoring Equivalents: report from the Biomonitoring Equivalents Expert Workshop. Regul Toxicol Pharmacol. 2008 Aug;51(3 Suppl):S4–15.

# Target Biomarker/Analyte Selection Characteristics

| **Biomarker** | **S-phenyl mercapturic acid (SPMA)** | ***trans,trans*-muconic acid (*tt*MA)** | **benzene (parent)** |
|---|---|---|---|
| **Molecular weight** | 239.29 | 142.11 | 78.11 |
| **Enzymatic metabolism** | CYP2E1 and GST | CYP2E1 and GST | - |
| **Biological material** | Urine | Urine | Alveolar air |
| **Type of sample** | Spot urine | Spot urine | End-exhaled breath |
| **Sampling collection** | Collect multiple samples over 1-2 days | Collect multiple samples over 1-2 days | Collect multiple samples over 1-2 days; exposure to 10 ppm was detected until 45 h (Pekari et al. 1992) |
| **Excretion pattern** | Biphasic elimination: 9.0 ± 4 (Boogaard and van Sittert, 1995) and 45 ± 4 h workers in the petrochemical industry (DFG, 2008) | Monophasic elimination: 5.1 ± 2.3 h (workers in the petrochemical industry) (Boogaard and van Sittert, 1995) | Triphasic elimination: 0.9h, 3h and 15 h (Nomiyamia and Nomiyama 1974b) and 55-61 min, 3.2-5.9 h and 14-19.7 h (Pekari et al. 1992) |

**Biomonitoring – based biomarker availability and media**

| Biomarker | S-phenyl mercapturic acid (SPMA) | *trans,trans*-muconic acid (*tt*MA) | benzene (parent) |
|---|---|---|---|
| **Materials** | 250 mL polyethylene container with screw cap | 250 mL polyethylene container with screw cap | Bio-VOC, Tenax TA-tubes |
| **Transportation** | At ambient temperature | At ambient temperature | At ambient temperature |
| **Storage** | Stable at 4°C if acidified to pH 2 with 6 M of HCl | Stable at 4°C if acidified to pH 2 with 6 M of HCl | < 2 h transfer to TENAX; preferably sealed in a plastic bag to avoid contact with ambient air |
| **Stability** | > 1 month | > 1 month | > 1 month |
| **Measurement principle** | Gas chromatography mass spectrometry (GC-MS) | HPLC-UV (absorption at 259 nm) | Gas chromatography – flame ionization detector (GC-FID) or GC-MS |
| **Aliquot for 1 analysis** | 2 mL | 2 mL | 100 – 300 mL |
| **Limit of quantification** | 1 µg/L (GC-MS) | 25 µg/L (HPLC-UV) | 0.01 µg/L (GC-MS) |
| **Recommended adjustments** | creatinine | creatinine | n/a |

| Incident | Chemical(s) | Biomarkers | Delay of sample collection (in days after cessation of exposure) | Method of detection | Result |
|---|---|---|---|---|---|
| **Industrial accident at chemical production plant Seveso, Italy (July 10, 1976)** | Dioxin | Dioxin in serum | Several moments until 11 years after the incident | LC-MS | Confirmation of exposure status with distance from source |
| **Workers in coma after exposure to solvent mixture in unvented room** | Organic solvents | Toluene in end-exhaled air and in blood | 36 – 112 h | GC | Half life for elimination of toluene in blood and alveolar air (~ 20 h) |
| **Fire at storage facility, Schweizerhalle, Switzerland, November 1, 1986** | Mercury and others | Mercury in blood, urine and hair | 23 and 29 | Not specified | No enhanced values observed |
| **Fire at storage facility in St. Bastile Le Grand, Canada (August 23, 1988)** | PCBs | PCBs in blood | 3 | Not specified | Not reported |

# Biological monitoring after chemical incidents

**Calculation of the elapsed time between the end of the environmental exposure and the last sample collection**

Concentration at the time of sampling collection $C_{t_s} \geq LOQ$

**First-order elimination**
typical elimination
_log-linear decline

$$C_{t_s} = \frac{C_e}{2^{t_s/t_{1/2}}} \Longrightarrow C_e \geq 2^{t_s/t_{1/2}} LOQ$$

the factor by which the concentration at the end of the exposure has decreased as a function of the half-lives between the end of the exposure and the sampling

*LOQ: can be replaced by another criterion i.e. $P_{95}$ - the 95 percentile background of the biomarker level in the general population

**When exposure ends, how can we assess possible biological effects using HBM?**

**Benzene** - biomarker: SPMA (*S*-phenyl mercapturic acid)

$t_{1/2}$=9.0±4.5 h and $P_{95}$=7.3μg/g (used instead of the LOQ)

For 8-h TWA occupational exposure:

$$[\mathrm{SPMA}]_{\mathrm{urine}}\ (\mathrm{mg/g\ creatinine}) = 0.045\ [\mathrm{benzene}]_{\mathrm{air}}\ (\mathrm{p.p.m.}) - 0.001\ (r = 0.999)$$

For 8-h AEGL-2 exposure to 200ppm

$C_e$=9000μg/g creatinine (9000μg/l)

$$C_{t_s} = \frac{C_e}{2^{t_s/t_{1/2}}}$$

$C_{ts}$=$P_{95}$ in the critical longest period of sampling ($t_s$)

$$t_s = \frac{t_{1/2}}{0.30}\log\left(\frac{C_e}{P_{95}}\right)$$

$t_s$=93 h

## Example--First-order elimination

# Zero-order elimination

## Biomarkers captured in blood cells

Loss of adduct per day:

$$C_{t_s} = -\alpha\, C_e\, t + C_e$$

for $t = t_s$:

$$t_s = \frac{C_e - C_{t_s}}{\alpha C_e}$$

α ⇒ slope -- dependent on the lifespan of hemoglobin - equal to the lifespan of erythrocyte ($t_{er}$=126 days)

$$\alpha = \frac{1}{t_{er}} \approx 0.008$$

Lifespan of adduct - 2-fold the biomarker half-life

$$\alpha = \frac{1}{2t_{1/2}}$$

---

$$t_s = \frac{C_e - C_{t_s}}{\alpha C_e} \xrightarrow{\alpha = \frac{1}{2t_{1/2}}} t_s = 2t_{1/2}\frac{C_e - C_{t_s}}{C_e} \xrightarrow{\text{LOQ (or } P_{95}) \ll C_e} t_s \cong 2\, t_{1/2}$$

*$C_{ts}$=$P_{95}$ (or LOQ) in the critical longest period of sampling ($t_s$)

**Zero-order elimination**
**Acrylonitrile** - biomarker: Cyanothylvaline adduct

$t_{1/2}$~ 75 days

$$[\text{Cyanoethylvaline}]_{\text{blood}}(\mu g/l) = 140.1\ [\text{acrylonitrate}]_{\text{air}}\ (\text{p.p.m.}) - 1.360\ (r = 0.999)$$

1-h AEGL-2 exposure to 58ppm → $C_e$= 8124.44μg/l

LOQ=0.5μg/l

LOQ<<$C_e$

$$t_s \cong 2\,t_{1/2}$$ → $t_s$=2*75 =150 days

$$t_s = 2t_{1/2} \frac{C_e - C_{t_s}}{C_e}$$

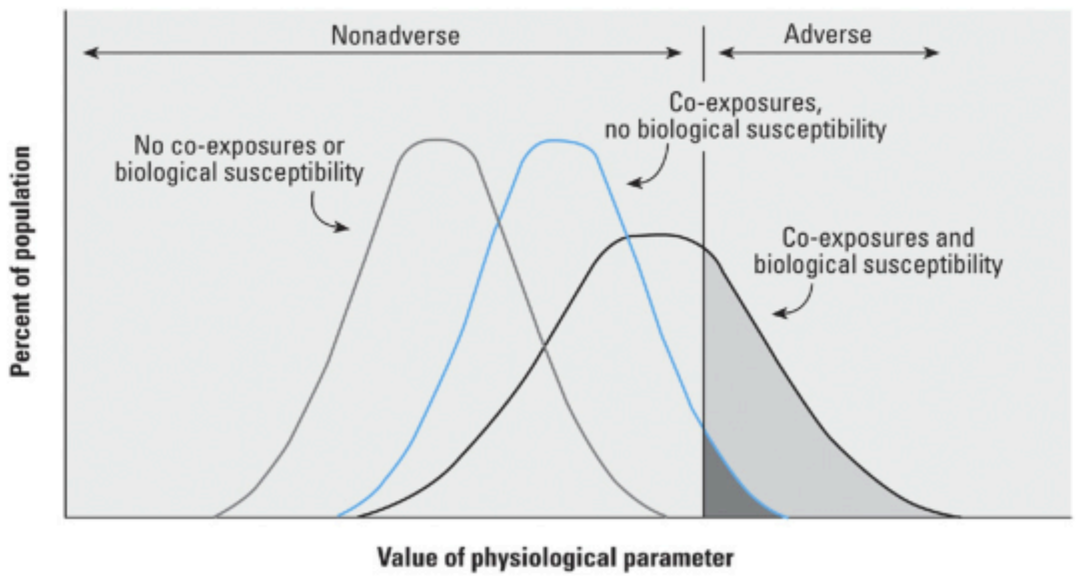
$$\text{LOQ (or } P_{95}) \ll C_e$$ → $$t_s \cong 2\,t_{1/2}$$

# Example -- zero order elimination

# Utility of Biomonitoring for new chemicals

**FIGURE 1**

**The effect of biologic susceptibility and coexposure to other chemicals on the relationship between individual chemical exposure and adverse health outcomes**



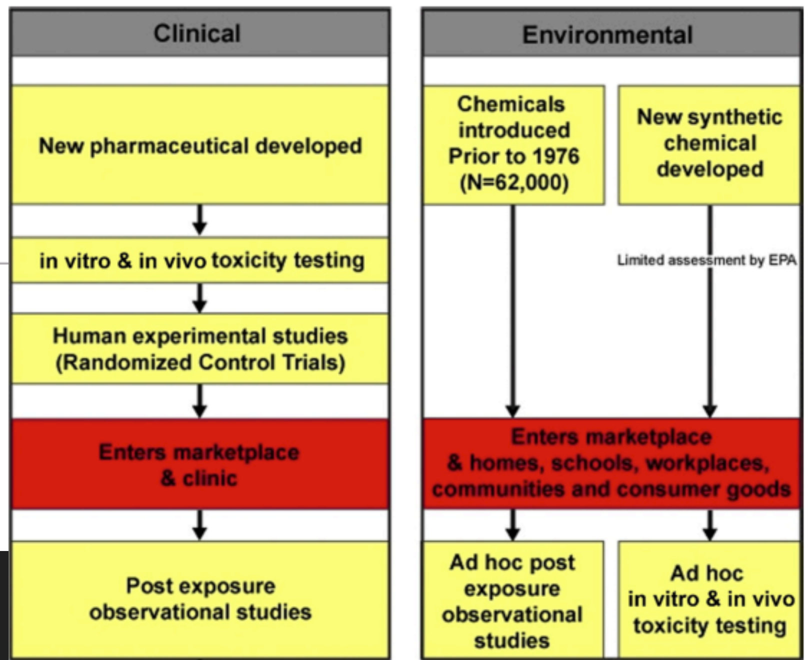

Reproduced, with permission, from Woodruff et al.[71]

*Sutton. Toxic matters. Am J Obstet Gynecol 2012.*

Low-dose exposure to environmental chemical → different - population's degree of exposure

**FIGURE 3**

**Comparison of the evidence streams that are needed in clinical and environmental health sciences for an exogenous chemical to enter the marketplace**




*EPA*, Environmental Protection Agency.
Adapted, with permission, from Woodruff et al.[146]

*Sutton. Toxic matters. Am J Obstet Gynecol 2012.*

Sutton et al 2012

Environmental stressors to reproductive health

- social
- physical
- nutritional environment
- chemical agents

*interactions among them
*interactions with intrinsic biologic factors

→ Individual and Population health outcomes

Health Disparities →

major health consequences

- e.g. communities with high exposures and no access to healthcare or education

Sutton, P., Woodruff, T. J., Perron, J., Stotland, N., Conry, J. A., Miller, M. D., & Giudice, L. C. (2012). Toxic environmental chemicals: the role of reproductive health professionals in preventing harmful exposures. *American Journal of Obstetrics & Gynecology*, *207*(3), 164–173. doi:10.1016/j.ajog.2012.01.034

# Developmental vulnerability

_ exposures during sensitive periods (extensive developmental changes)
ex.: embryogenesis → adolescence ⇒ central nervous system development;
periods of neuronal proliferation, differentiations etc
disruptions = permanent damage

_ wide range of adverse health outcomes

_ exposure of pregnant women to endocrine-disrupting chemicals (EDCs)
found in food, water, air, house dust, personal care products
phthalates, BPA, PBDEs, perchlorate, some pesticides
critical to human reproduction (disturbing hormonal regulation)

Sutton et al 2012

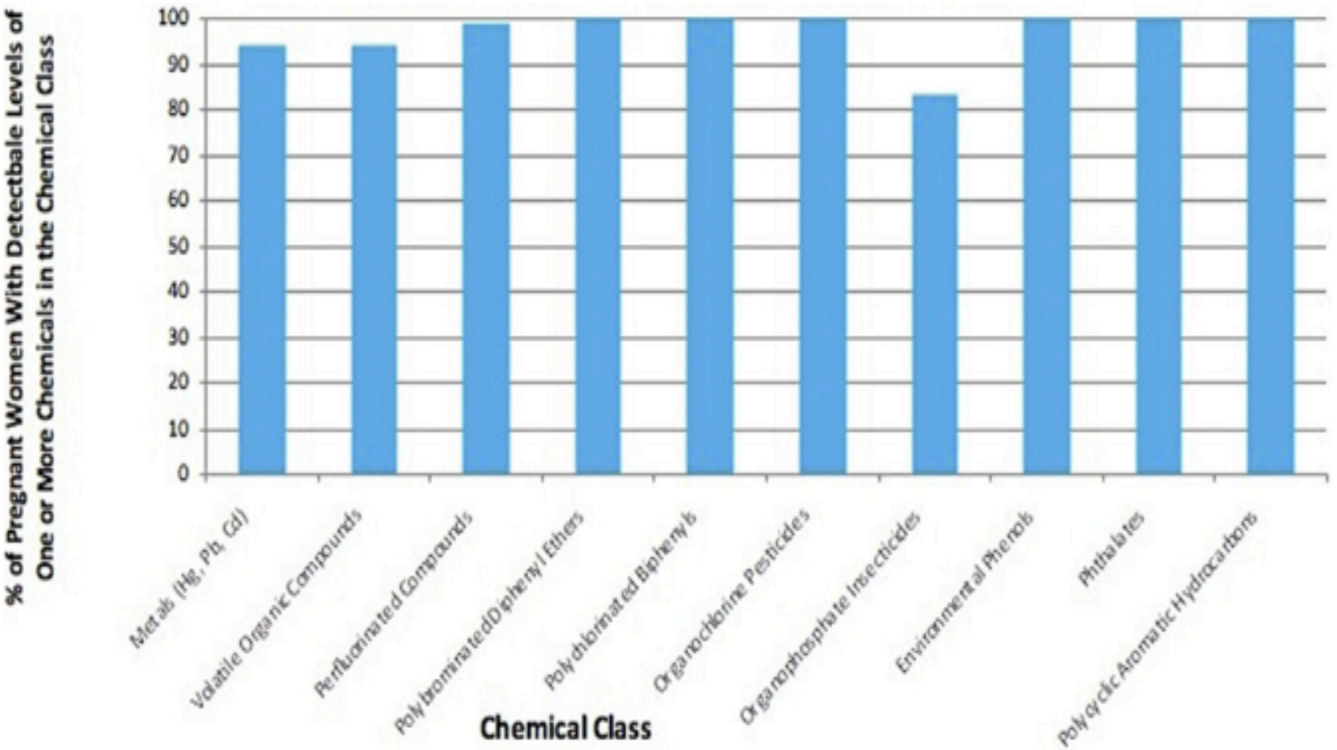
water and health [laboratory]

Cyprus University of Technology

Cyprus International Institute for Environmental and Public Health

**FIGURE 2**

**Environmental chemicals in pregnant women in the United States**




Adapted, with permission from Woodruff et al.[30]

*Sutton. Toxic matters. Am J Obstet Gynecol 2012.*

- Metals (Hg, Pb, Cd)
- Volatile organic compounds
- Perfluorinated compounds
- Polybrominated Diphenyl Ethers
- Polychlorinated Biphenyls
- Organochlorine Pesticides
- Organophosphate Insecticides
- Environmental Phenols
- Phthalates
- Polycyclic Aromatic Hydrocarbons

**Virtually all pregnant women in the US are exposed to potentially harmful chemicals**

Sutton et al 2012

# Pregnant women: exposure to environmental chemicals and the utility of HBM


# Ευχαριστώ !

## Details about our Master in Public Health here:

## [www.cut.ac.cy/cii](http://www.cut.ac.cy/cii)

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