IPA Institut für Prävention und Arbeitsmedizin der Deutschen Gesetzlichen Unfallversicherung Institut der Ruhr-Universität Bochum

RUB

Human-Biomonitoring (HBM):

basic requirements and some practical examples

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Institute for Prevention and Occupational Medicine (IPA)

of the German Social Accident Insurance

Ruhr-University Bochum, Germany

HBM4IRE Stakeholder Forum at UCD

Dublin, October 11, 2024

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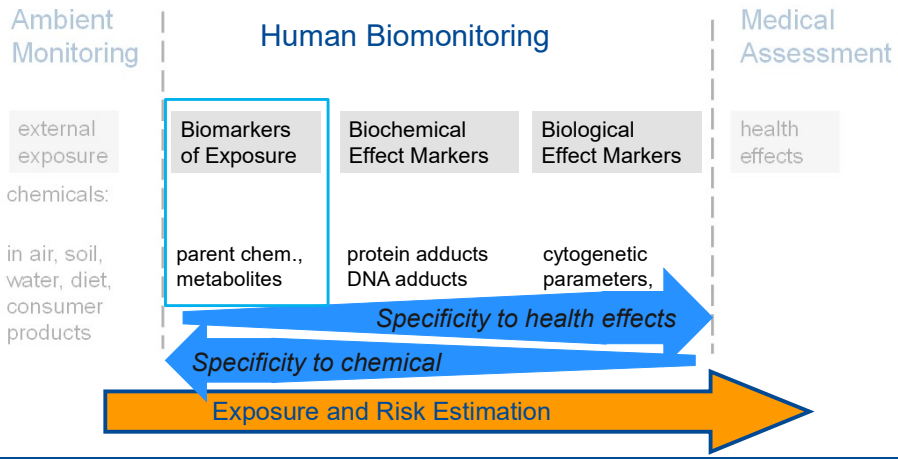
Exposure Assessment (in the exposure-disease continuum)



adapted from: Biological Monitoring- Prospects in Occupational and Environmental Medicine Angerer and Weiss (eds.), Wiley-VCH, Weinheim, 1. Edition (2002)

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HUMAN BIOMONITORING (HBM) DEFINITION

HBM is the determination of chemical substances, their metabolites and effects in human biological material with the aim

- *to determine internal exposure and health risk*
- *to compare results with reference- and limit values*
- *and if necessary to take corrective actions*

➡ ***Tool for EXPOSURE and RISK ASSESSMENT***

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HUMAN BIOMONITORING (HBM) … from another perspective

Human Biomonitoring:
pollutants that actually entered the human body
(via all known and unknown routes: oral, dermal, inhalation)

Ambient Monitoring:
pollutants that might enter the human body through known routes

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The Lead-Example I

First HBM activities of EU in Environmental medicine

- **COUNCIL DIRECTIVE**
of 29. March 1977
on the biological screening of the population for lead (77/ 312 / EEC)

„HBM necessary because of multiple sources of lead which make it difficult to determine exposure“

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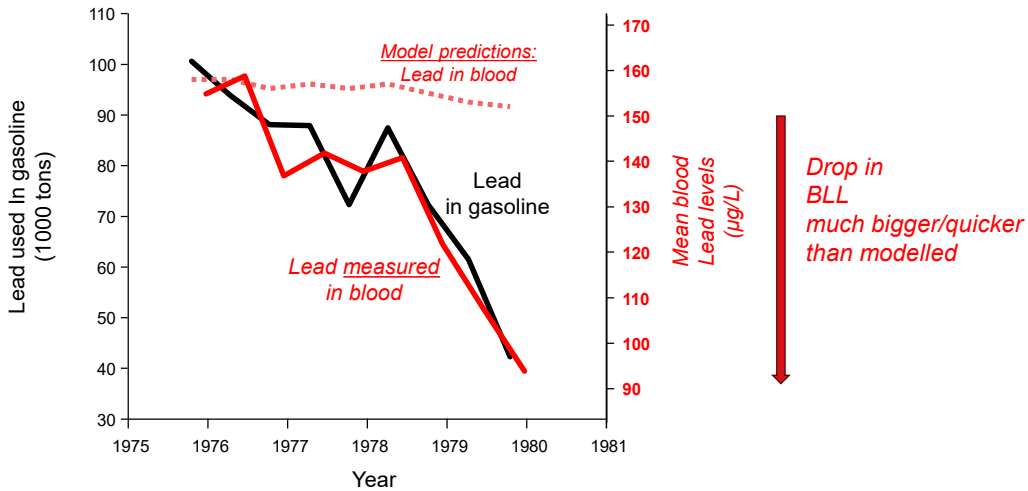
The Lead-Example II

Lead in gasoline and blood NHANES II, 1976-1980



taken with kind permission from ISEA/ISES Wesolowski Award Presentation:
Biomonitoring: An Integral Part of Exposure Analysis
Larry L. Needham, Ph.D., National Center for Environmental Health, Centers for Disease Control and Prevention

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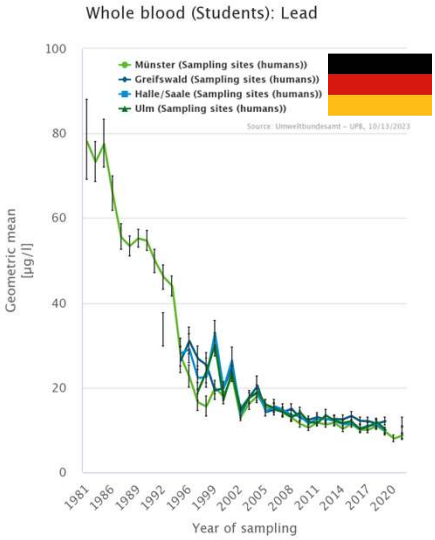
The Lead-Example III



Why blood?

Blood lead represents (chronic) lead exposure (bone lead) over the last couple of weeks ($t_{1/2}$= 1-2 months)

Urinary lead represents very recent (< 24h) lead exposure *(less commonly used biomarker!)*

Caveat: for Cd it is vice-versa: cadmium accumulates in the kidney and is slowly released into the urine

For this and much more data, visit: https://umweltprobenbank.de/en 7

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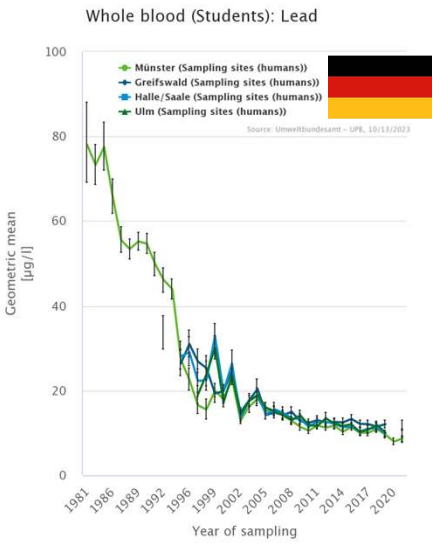
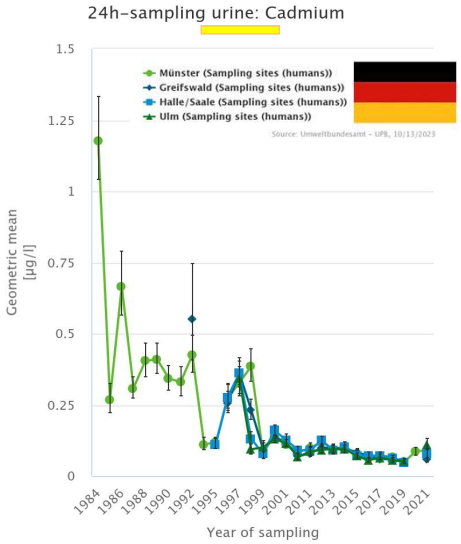
The Lead-Example III





For this and much more data, visit: https://umweltprobenbank.de/en 8

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Exposure Assessment by HBM

Knowledge on core characteristics of pollutants in the body is essential !

metabolism* and *elimination

- biomarker: pollutant or metabolite(s) ?
- matrix: blood, urine , …
- interpretation: dose-extrapolation, sampling…

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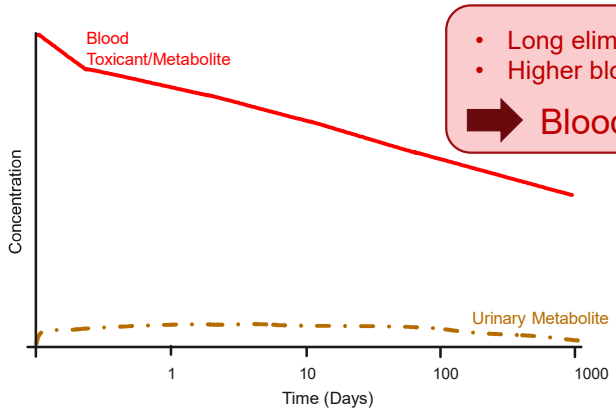
Toxikokinetics: *persistent chemicals*



- Long elimination half-times
- Higher blood levels relative to urine

Blood is preferred matix

Needham and Sexton. JEAEE 10: 611-629 (2000)
Henderson et al. Crit Rev Toxicol 20: 65-82 (1989)

taken from ISEA/ISES Wesolowski Award Presentation, Paris 2006:
Biomonitoring: An Integral Part of Exposure Analysis
Larry L. Needham, Ph.D., National Center for Environmental Health, Centers for Disease Control and Prevention

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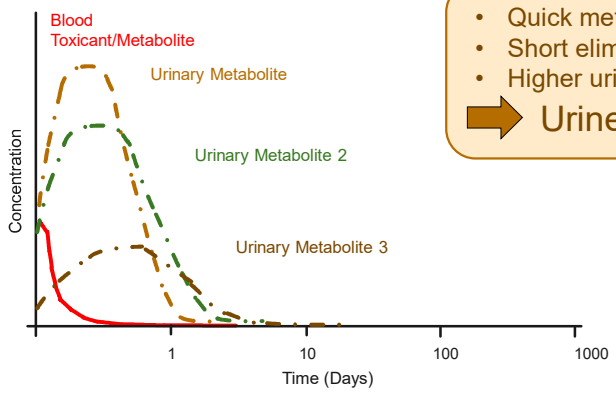
Toxikokinetics: *non-persistent chemicals*



- Quick metabolisation
- Short elimination half-times
- Higher urine levels relative to blood

➡ Urine is preferred matrix

Needham and Sexton. JEAEE 10: 611-629 (2000)
Henderson et al. Crit Rev Toxicol 20: 65-82 (1989)

taken from ISEA/ISES Wesolowski Award Presentation, Paris 2006:
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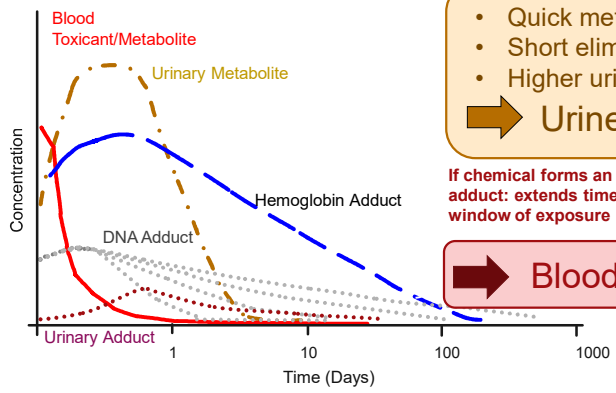
Toxikokinetics: *non-persistent chemicals*



- Quick metabolisation
- Short elimination half-times
- Higher urine levels relative to blood

➡ Urine is preferred matrix

If chemical forms an adduct: extends time window of exposure

➡ Blood possible, too

Needham and Sexton. JEAEE 10: 611-629 (2000)
Henderson et al. Crit Rev Toxicol 20: 65-82 (1989)

taken from ISEA/ISES Wesolowski Award Presentation, Paris 2006:
Biomonitoring: An Integral Part of Exposure Analysis
Larry L. Needham, Ph.D., National Center for Environmental Health, Centers for Disease Control and Prevention

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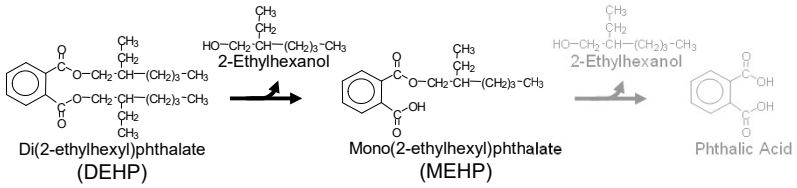
DEHP: metabolism and urinary excretion

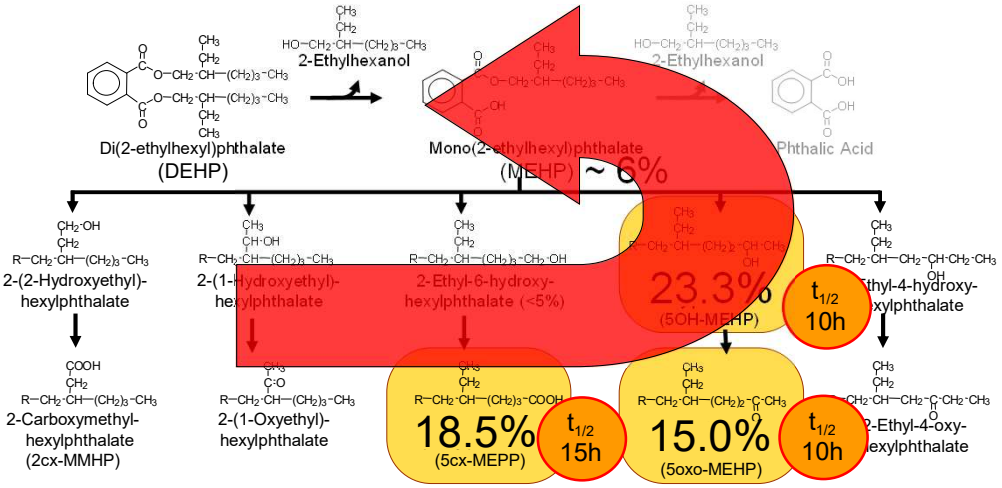


Metabolite is the toxic species (!)

- Rapid metabolism does NOT mean „detoxification“
- Non-persistent chemicals not *per se* less toxic than persistent chemicals
- Exposure biomarkers for reverse-dosimetry

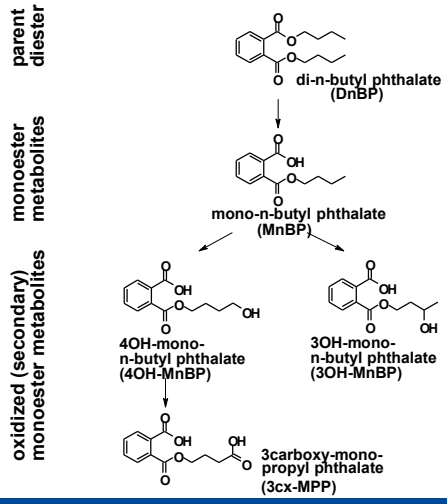
Koch et al. (2004) Arch Tox 78, 123.
Koch et al. (2005) Arch Tox 79, 367.
Wittassek et al. (2011) Mol Nut F Res 55(1), 7.
Koch et al. (2017) IJHEH 220: 130.

DEHP: metabolism and urinary excretion



Koch et al. (2004) Arch Tox 78, 123.
Koch et al. (2005) Arch Tox 79, 367.
Wittassek et al. (2011) Mol Nut F Res 55(1), 7.
Koch et al. (2017) IJHEH 220: 130.

Toxikokinetics: *n-butyl phthalate*



Koch et al (2012) Arch Tox 86, 1829-1839.
Lorber and Koch (2013) Environ Int 59, 469–477.

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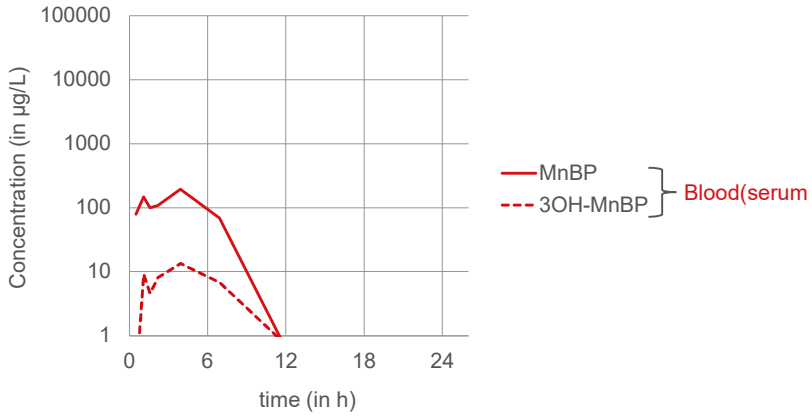
Toxikokinetics: *n-butyl phthalate*

5mg D4-DnBuP (oral, one human volunteer)



Koch et al (2012) Arch Tox 86, 1829-1839.
Lorber and Koch (2013) Environ Int 59, 469–477.

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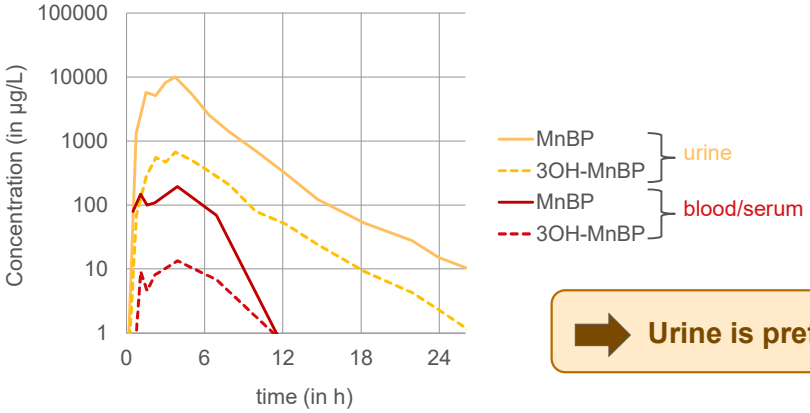

Urine is preferred matrix

Koch et al (2012) Arch Tox 86, 1829-1839.
Lorber and Koch (2013) Environ Int 59, 469–477.

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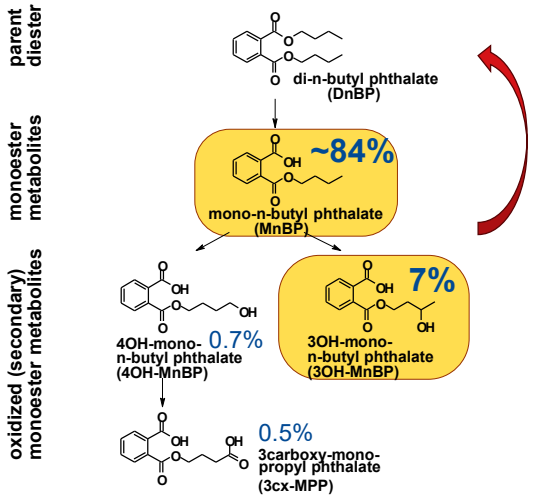
Toxikokinetics: *n-butyl phthalate*



Koch et al (2012) Arch Tox 86, 1829-1839.
Lorber and Koch (2013) Environ Int 59, 469–477.

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Urinary Exposure Biomarkers for Phthalates

Chain length	Phthalate	Monoester Metabolite	$f_{ue\text{-}pm}$	Secondary metabolite	$f_{ue\text{-}pm}$	reference
2	DEP	MEP	80%			*estimated*
4	DnBP	MnBP	84%			*Koch et al. (2012), Anderson et al. (2001)*
4	DiBP	MiBP	71%			*Koch et al. (2012) Anderson et al. (2001)*
6	BBzP	MBzP	73%			*Anderson et al. (2001)*
8	DEHP	MEHP	6%			*Koch et al. (2005), Anderson et al. (2011), Kessler et al. (2012)*
				5OH-MEHP	23%	
				5oxo-MEHP	15%	
				5cx-MEPP	18%	
9	DiNP	MiNP	1%			*Koch et al. (2007), Anderson et al. (2011)*
				OH-MiNP	18%	
				oxo-MiNP	10%	
				cx-MiNP	9%	
10	DPHP /DiDP			OH-MPHP	12%	*Schütze et al. (2014), Wittassek and Angerer (2008)*
				oxo-MPHP	14%	
				cx-MPHP	0.5%	

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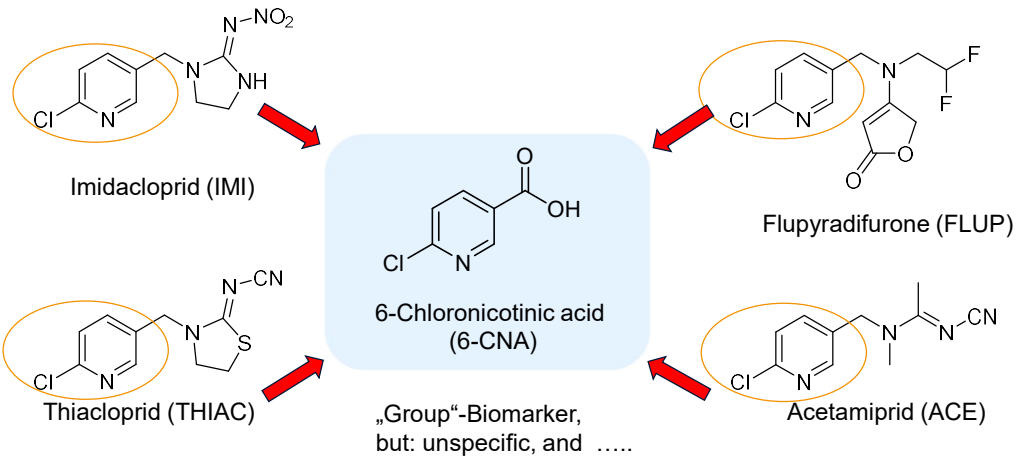
Specificity of biomarkers: neonicotinoids



„Group"-Biomarker,
but: unspecific, and …..

Wrobel S et al. (2023) Environ Res. 226:115609.

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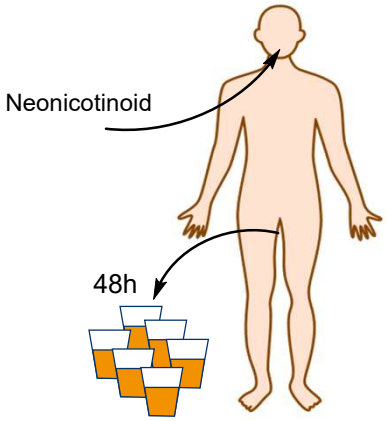
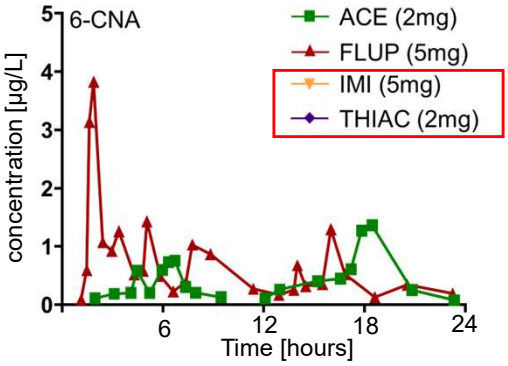
6-CNA: Literature vs. research





- *varying 6-CNA shares for ACE and FLUP*
- *no 6-CNA for IMI and THIAC*

Wrobel S et al. (2023) Environ Res. 226:115609.

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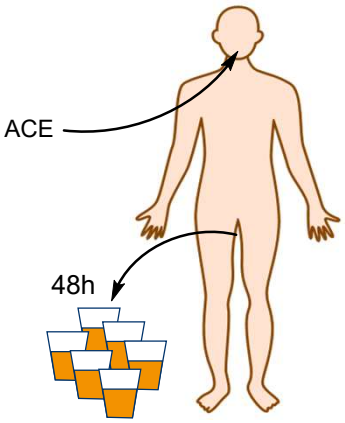
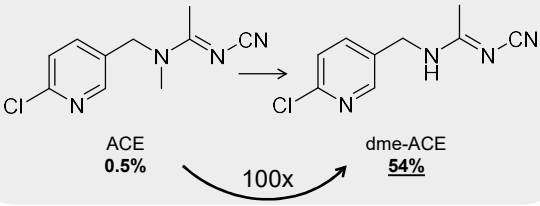
Metabolism of Acetamiprid (ACE)





Wrobel S et al. (2023) Environ Res. 226:115609.

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Urinary excretion of Neonicotinoids

Dosage	Parent	*N*-dealkylation	Hydroxylation
ACE	0.5%	54%	n.d.
FLUP	33%	26%	24%
IMI	8%	n.d.	31%
THIAC	0.4%	n.d.	23%
CLO	84%	14%	n.d.
THIAM	50%	0.3%	n.d.
SULF	51%	n.d.	n.d.

First practical application in HBM-study with UCD/Prof. Connolly

Wrobel S et al. (2022) Arch Toxicol. 96(1):121-134.
Wrobel S et al. (2023) Environ Sci Technol. 57(48):19285-19294.

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Exposure route investigations …

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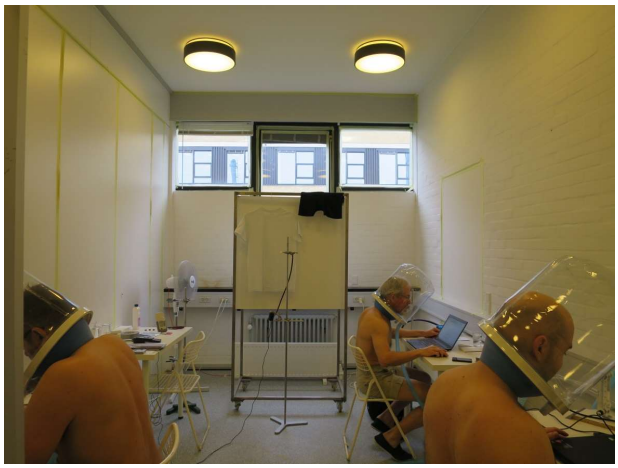
Transdermal uptake of phthalates (experimental chamber study)



Indoor air exposure:

~250 µg/m³ for DEP
~125 µg/m³ for DnBP

8h-exposure:
- *With hood (clean air)*
- *Without hood*

Human Biomionitoring:
Urine samples collected
- before entering the chamber
- continuously for 54 hours thereafter

Schripp et al., Sci. Total Environ (2014)
Weschler et al., EHP (2015)

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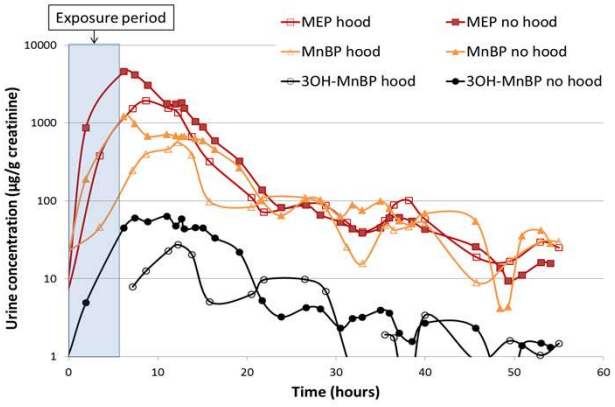
Transdermal uptake of phthalates (experimental chamber study)



Schripp et al., Sci. Total Environ (2014)
Weschler et al., EHP (2015)

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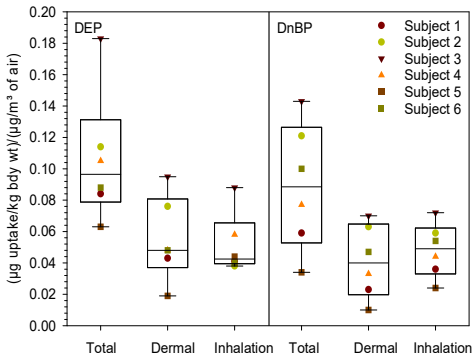
Transdermal uptake of phthalates (experimental chamber study)

reverse-dosimetry
to phthalate uptake



Proof, that transdermal uptake can lead to exposures comparable to inhalation.

Assuming only inhalation exposure would underestimate total exposure

Schripp et al., Sci. Total Environ (2014)
Weschler et al., EHP (2015)

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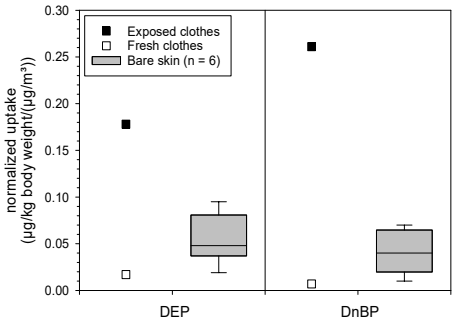
Transdermal uptake … and the role of clothing:



Significance of multiple exposure routes

"dirty" protective gear can be counter-protective

Morrison et al. J Expo Sci Environ Epidemiol. 26(1), 113-118 (2016)

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New, emerging exposures:

Unexpected

Hexyl-Phthalate (DnHexP)

Exposures

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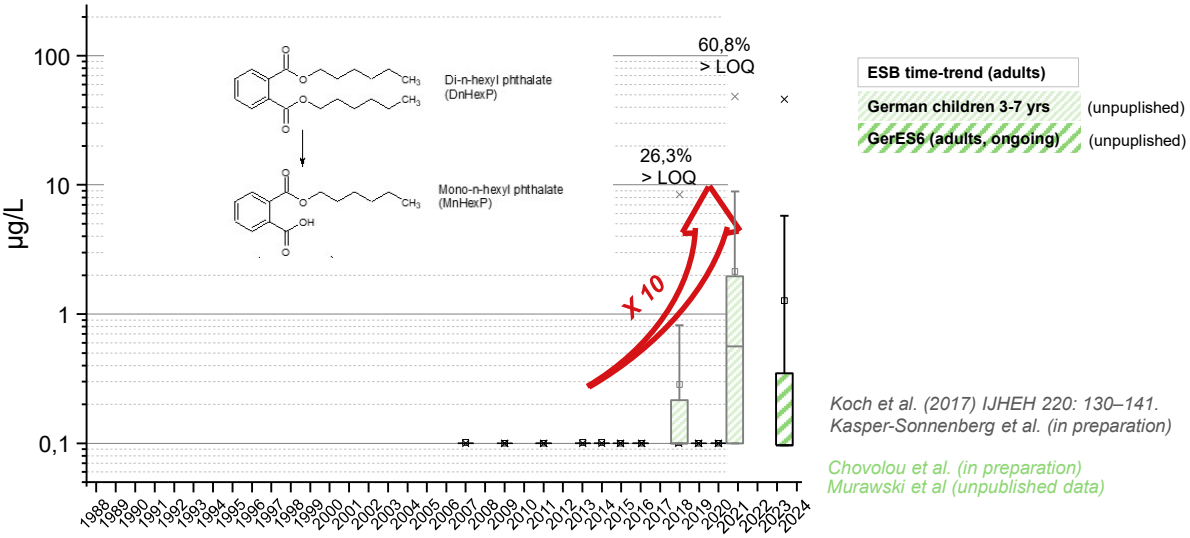
Phthalate: MnHexP

Marike`s wish : „HBM-surveillance of all EU-regulated phthalates (enocrine disruptors)“



ESB time-trend (adults)

German children 3-7 yrs (unpuplished)

GerES6 (adults, ongoing) (unpuplished)

Koch et al. (2017) IJHEH 220: 130–141.
Kasper-Sonnenberg et al. (in preparation)

Chovolou et al. (in preparation)
Murawski et al (unpublished data)

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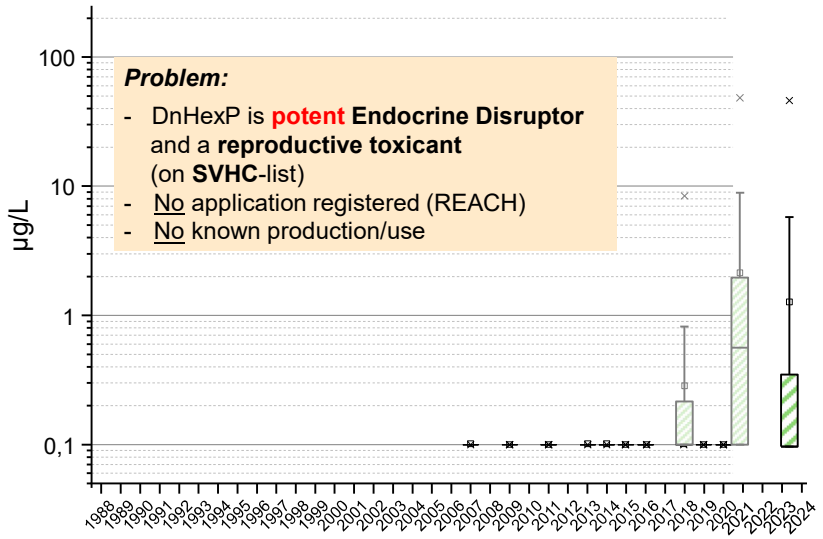
Phthalate: MnHexP



Problem:

- DnHexP is **potent** **Endocrine Disruptor** and a **reproductive toxicant** (on **SVHC**-list)
- No application registered (REACH)
- No known production/use

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Chovolou et al. (in preparation)
Murawski et al (unpublished data)

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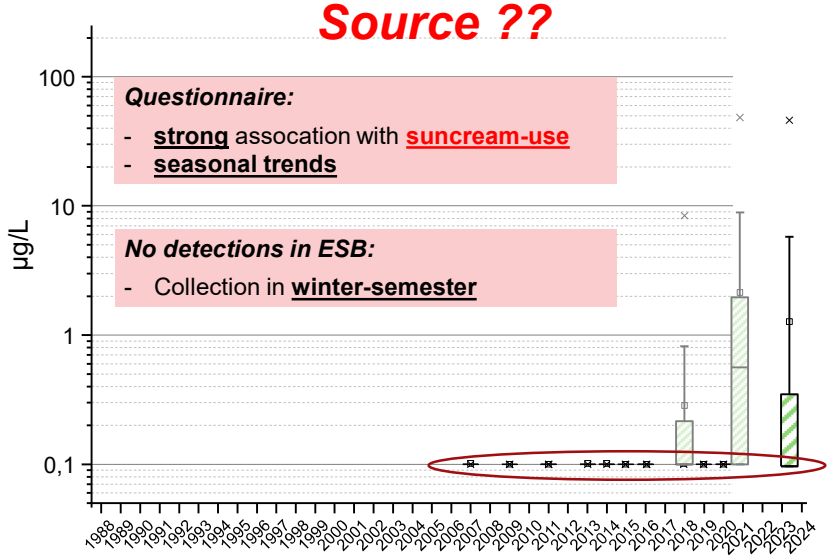
Phthalate: MnHexP

Source ??



Questionnaire:

- **strong** assocation with **suncream-use**
- **seasonal trends**

No detections in ESB:

- Collection in **winter-semester**

ESB time-trend (adults)

German children 3-7 yrs (unpuplished)

GerES6 (adults, ongoing) (unpuplished)

Koch et al. (2017) IJHEH 220: 130–141.
Kasper-Sonnenberg et al. (in preparation)

Chovolou et al. (in preparation)
Murawski et al (unpublished data)

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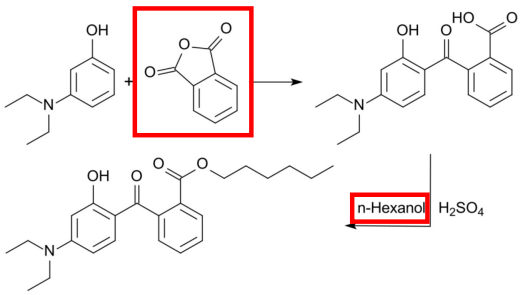
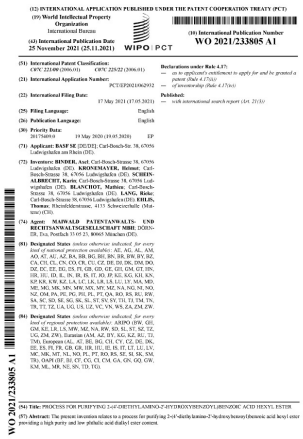
Source: UV-filter DHHB

DHHB (Diethylamino hydroxybenzoyl hexyl benzoate)




(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)
(19) World Intellectual Property Organization
International Bureau
(10) International Publication Number
WO 2021/233805 A1
(43) International Publication Date: 25 November 2021 (25.11.2021)
WIPO | PCT
WO 2021/233805 A1

BASF Patent 2021/23: DnHexP impurity
50-150 ppm (mg/kg)

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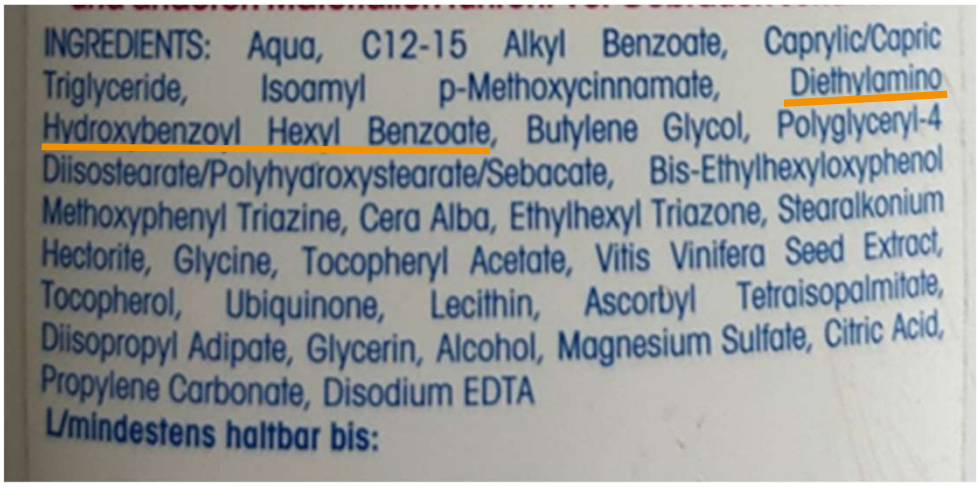
Source: UV-filter DHHB

DHHB (Diethylamino hydroxybenzoyl hexyl benzoate)


INGREDIENTS: Aqua, C12-15 Alkyl Benzoate, Caprylic/Capric Triglyceride, Isoamyl p-Methoxycinnamate, Diethylamino Hydroxybenzoyl Hexyl Benzoate, Butylene Glycol, Polyglyceryl-4 Diisostearate/Polyhydroxystearate/Sebacate, Bis-Ethylhexyloxyphenol Methoxyphenyl Triazine, Cera Alba, Ethylhexyl Triazone, Stearalkonium Hectorite, Glycine, Tocopheryl Acetate, Vitis Vinifera Seed Extract, Tocopherol, Ubiquinone, Lecithin, Ascorbyl Tetraisopalmitate, Diisopropyl Adipate, Glycerin, Alcohol, Magnesium Sulfate, Citric Acid, Propylene Carbonate, Disodium EDTA
Mindestens haltbar bis:

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State Surveillance Lab …..

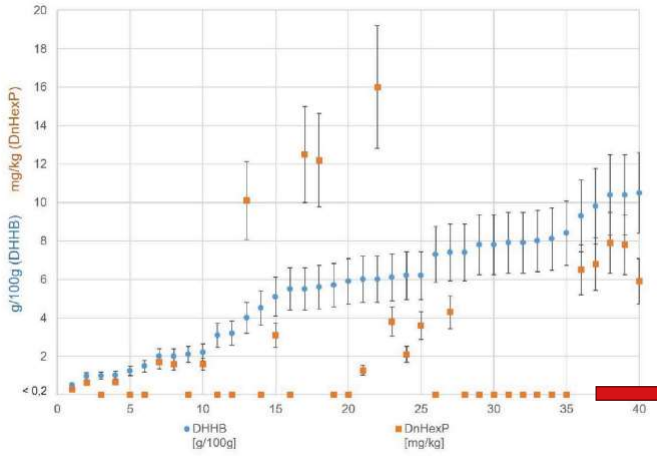

Abb.3: Graphische Darstellung der Gehalte an DnHexP (mg/kg) und DHHB (g/100g) in 40 Sonnenschutzprodukten mit DHHB als UV-Filter mit Messunsicherheit

Analyses of 57 Sunscreens (40 with DHHB, 17 without)

No DHHB-free Suncream contained DnHexP

50% of the DHHB-containing Suncreams contain DnHexP (0.3-16 mg/kg)*

Technically avoidable

** In the meantime, some suncreams have been found with higher concentrations (>35 mg/kg)*

Source: CVUA Karlsruhe

https://www.ua-bw.de/pub/beitrag.asp?subid=2&Thema_ID=4&ID=3940&lang=DE&Pdf=No

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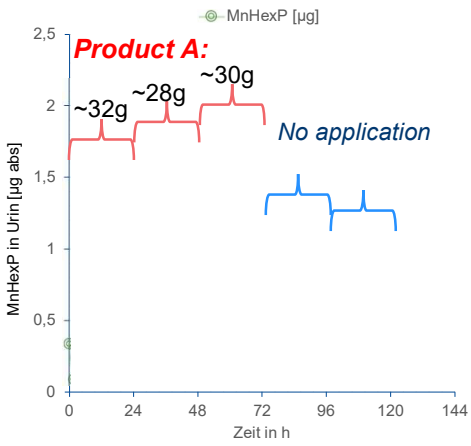
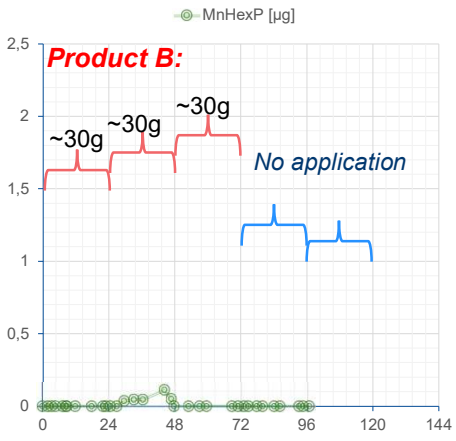
Application-Study

3-day-application (Sun Cream Kids SPF 50+)





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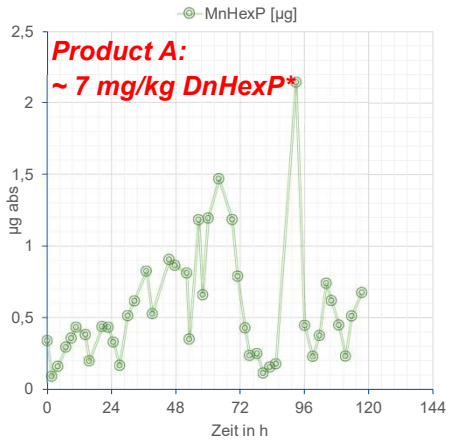
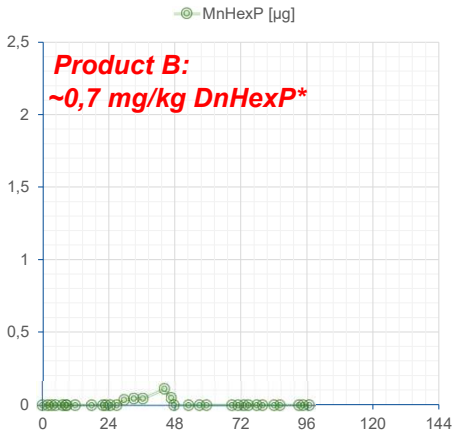
Application-Study

3-day-application (Sun Cream Kids SPF 50+)





* Analyes performed by state-lab

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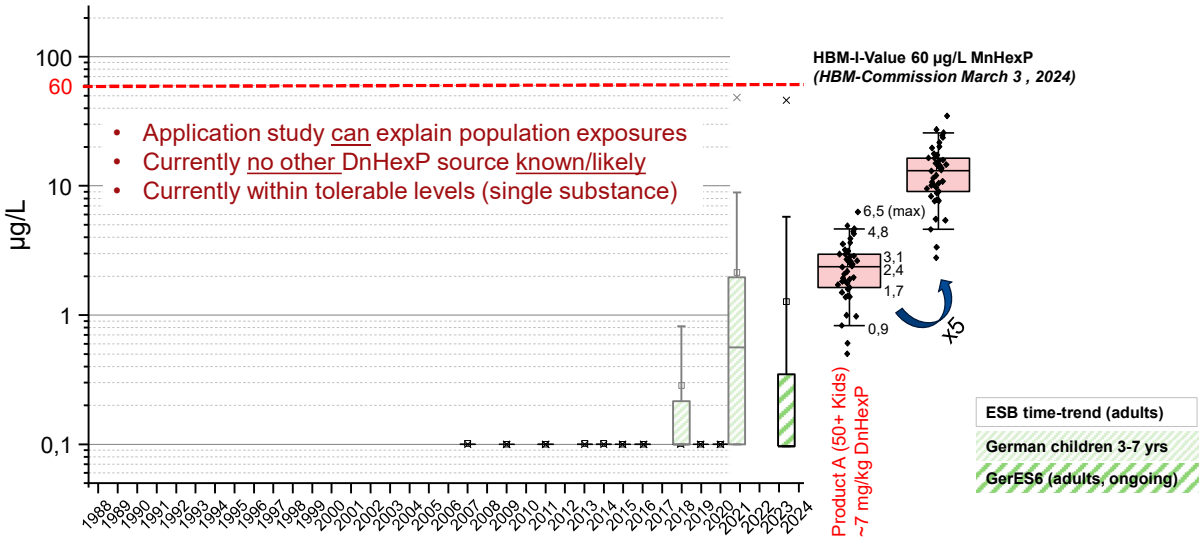
Application-Study



Koch et al. (2017) IJHEH 220: 130–141.
Kasper-Sonnenberg et al. (Eingereicht)

Chovolou et al. (in preparation)
Murawski et al (unpublished data)

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Summary

Human Biomonitoring: *what you need*

- Thorough understanding of ADME (absorption, distribution, metabolism, excretion)
- Wise selection of Biomarker and Matrix
  - *Specificity, Sensitivity, Feasibility*
- Analytical chemistry infrastructure (GC-MS/MS; LC-MS/MS …)
- Multi-disciplinary environment for interpretation
  - *analytical, medical, toxicological, statistical, …*

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Human Biomonitoring: *what you get*

- method of choice to capture ***actual/effective*** exposure
- captures even ***complex/unknown routes*** of exposure (dermal, oral, inhalation)
- captures ***environmental/life-style/occupational*** exposures

HBM objectifies exposures *(no worst case!)*
- valuable addition to ambient data and probabilistic models

Integral Exposure Assessment

Wholistic Risk Assessment

Indicator for regulatory/political measures (need for, success/failure)

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Human-Biomonitoring (HBM):
basic requirements and some practical examples

Holger M. Koch
Institute for Prevention and Occupational Medicine (IPA)
of the German Social Accident Insurance
Ruhr-University Bochum, Germany

Thank you!

HBM4IRE Stakeholder Forum at UCD
Dublin, October 11, 2024

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Hello from …

… the HBM-group at the IPA in Bochum …

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