Human biomonitoring in urine samples from the Environmental Specimen Bank reveals an increasing exposure to the UV filter DHHB between 2000 and 2021

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UV filter DHHB

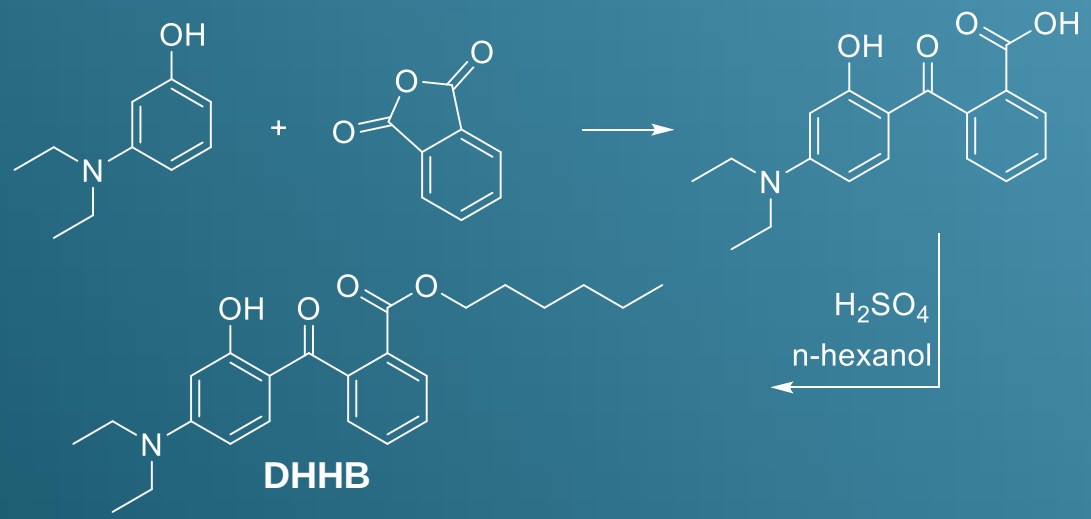
- **D**iethylamino **h**ydroxybenzoyl **h**exyl **b**enzoate
- IUPAC: Hexyl 2-[4-(diethylamino)-2-hydroxybenzoyl]-benzoat; CAS-No: 302776-68-7
- 2005: Authorization as UV filter in the EU

Main application

UV filter in sunscreens
Additive in **cosmetics** like body lotions, lip stick
Maximum concentration of 10% (w/w)

Possible **exposure** in the **general population**

Establishment of analytical method for the **exposure assessment** in **HBM** studies



Human Biomonitoring (HBM)

Collaboration between the BMUV and the VCI since 2010 ⇨ new HBM methods for chemicals of concern

OBJECTIVE

Improving knowledge about substances to which the population may be **increasingly exposed** and which are of **potential relevance to human health**

Elucidation of their metabolism in humans and **establishment of sensitive analytical methods** to detect the exposure in the general population

Establishment of new HBM methods for up to 50 chemicals

⇨ 2016: Selection of DHHB

Bundesministerium für Umwelt, Naturschutz, nukleare Sicherheit und Verbraucherschutz

Verband der Chemischen Industrie e.V.
Wir gestalten Zukunft.

VCI

HBM

UV filter

Fragrances

Flame retardants

Plasticizer

HBM of DHHB

Human metabolism study:

Elucidation of the human metabolism in a study with 5 volunteers after defined oral administration

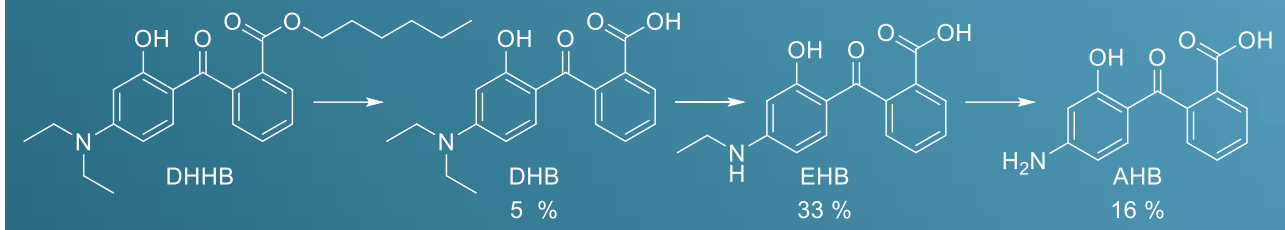
Establishment of LC-MS/MS methods for the quantification of the major metabolites
LLOQ = 0.1 µg/L (AHB, EHB); 0.05 µg/L (DHB)

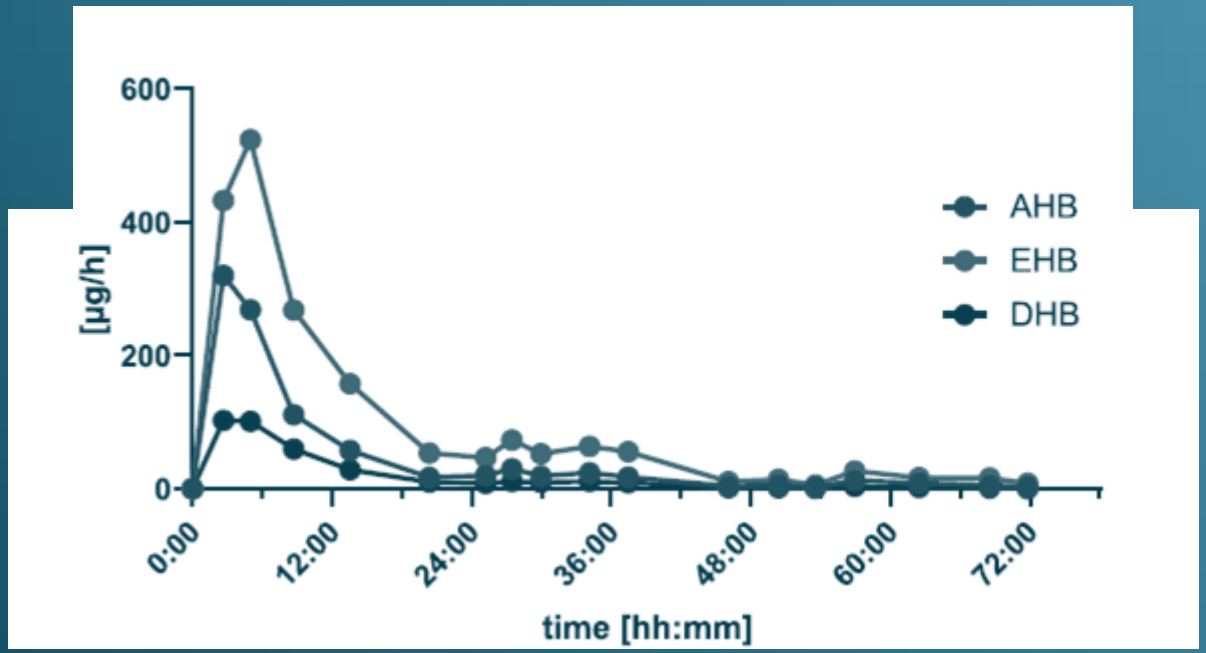
Pilot study with 58 volunteers:

Location: Bavaria, 31 ♂ / 27 ♀, 18-83 years

~**35%** of urine samples with metabolite conc. > LLOQ

⇨ Exposure to DHHB
⇨ Sufficient sensitivity of the method





Stoeckelhuber, M., Scherer, M., Peschel, O., Leibold, E., Bracher, F., Scherer, G., Pluym, N., 2020. Human metabolism and urinary excretion kinetics of the UV filter Uvinul A plus® after a single oral or dermal dosage. IJHEH 227, 113509.
Stoeckelhuber, M., Pluym, N., Bracher, F., Leibold, E., Scherer, G., Scherer, M., 2019. A validated UPLC-MS/MS method for the determination of urinary metabolites of Uvinul® A plus. ABC

HBM of DHHB

24h-urine samples, stored in the Environmental Specimen Bank (**ESB**) and provided by the German Environment Agency (Umweltbundesamt, **UBA**)

OBJECTIVES

Monitor **time trends**

Identification of possible **sex differences**

Estimation of the **daily intake**

Study years

2000 → 2008 → 2012 → 2016 → 2021

Male to female split 50/50

250 24h urine samples

Location: Münster (Germany); Age: 20-29 years

Values < LLOQ set to LLOQ/2

Significance test: Mann Whitney U test, $\alpha = 0.05$

Normalization for 24h urine volume → urinary excretion rate / d

Daily intake (DI) based on excretion of DHB/EHB:
Fractional urinary excretion (F_{ue}) of 35.7 %

Excretion rates

- Differences in the detection rates between metabolites
  - AHB detectable since 2000
  - DHB/EHB detectable since 2012

AHB	EHB	DHB
87%	17%	13%

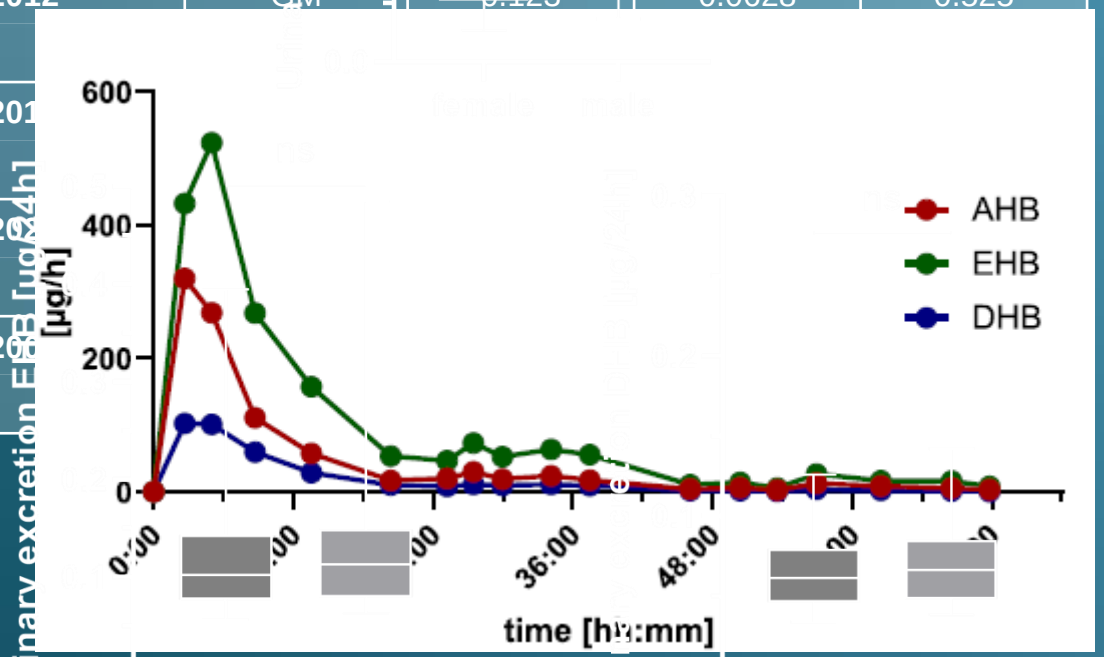
- Excretion rates:
  AHB >> EHB > DHB

AHB	EHB	DHB
0.542 µg/24h	0.132 µg/24h	0.068 µg/24h

- Contradicting previous metabolism study:
  EHB > AHB >> DHB
- Higher excretion rates of AHB in men
- No difference in excretion rates between sexes for EHB/DHB

Excretion rate [µg/24h]

Year	Parameter	EHB	DHB	AHB
2000	GM	0.0835	0.0501	0.394
	N > LOQ	0 (0 %)	0 (0 %)	43 (86 %)
2008	GM	0.073	0.0583	0.426
	N > LOQ	0 (0 %)	0 (0 %)	38 (76 %)
2012	GM	0.123	0.0628	0.525



Excretion rates

- Increasing detection rates over time for EHB/DHB
- **Time trend:** Significant **increase** since 2012 (EHB) and 2016 (DHB/AHB)

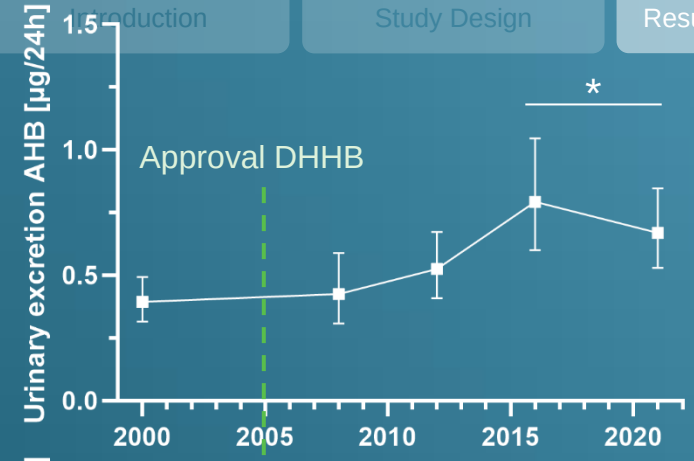
2000-2021 ↑ **x1.7-2.3**

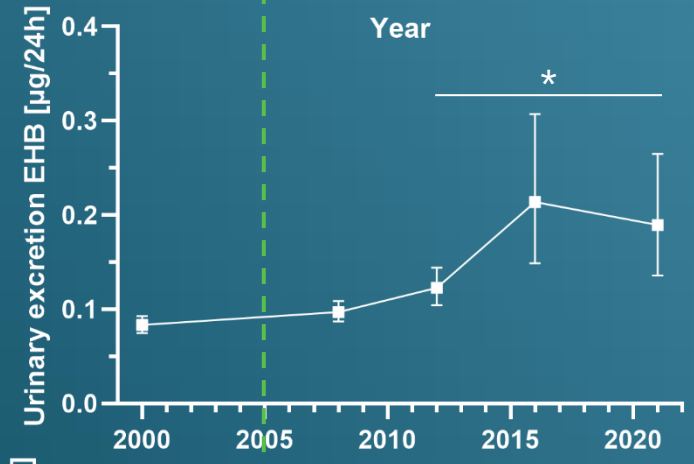
- High AHB detection rates already in 2000
- **Strong correlation** only between **EHB/DHB**

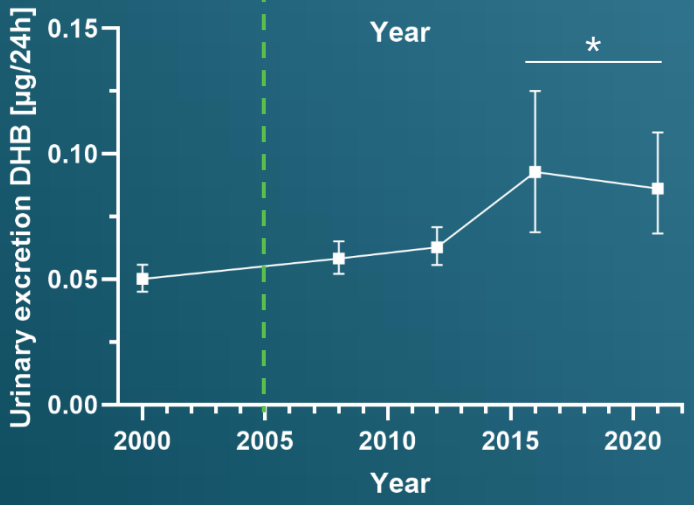
EHB/DHB	EHB/AHB	DHB/AHB
0.928	0.251	0.215

Potential other sources for AHB

DHB/EHB specific biomarkers of DHHB exposure







GM ± 95% CI

AHB GM 2021:
0.670 µg/24h

EHB GM 2021:
0.190 µg/24h

DHB GM 2021:
0.086 µg/24h

Daily intakes

Fractional urinary excretions (F_{ue}) of the metabolites determined in metabolism study

+

Consideration of the body weight (bw)

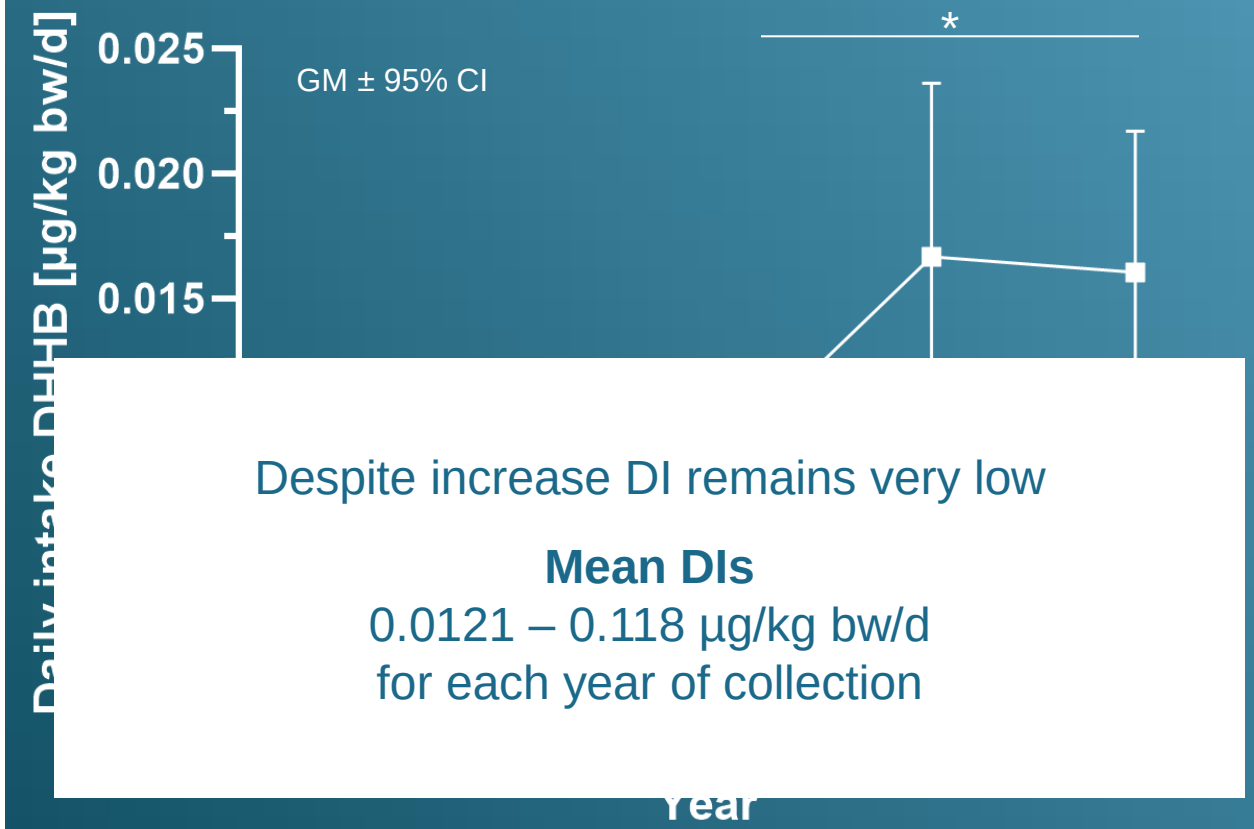
↷

Calculation of daily intake ⇨ DI [µg/kg bw/d]

- **No differences** in **DAILY INTAKE** in males vs females
- Significant **increase** in **DAILY INTAKE** since 2012

2000-2021 **↑ x2.3**

F_{ue} EHB/DHB: 35.7%



Despite increase DI remains very low

Mean DIs
0.0121 – 0.118 µg/kg bw/d
for each year of collection

Risk Assessment

DNEL (derived no-effect levels): toxicological threshold value for chronic exposure
(no health consequences below this value)

No hazard identified for exposure in the general population

DNEL for workers (dermal exposure): 2,900 mg/kg bw/d

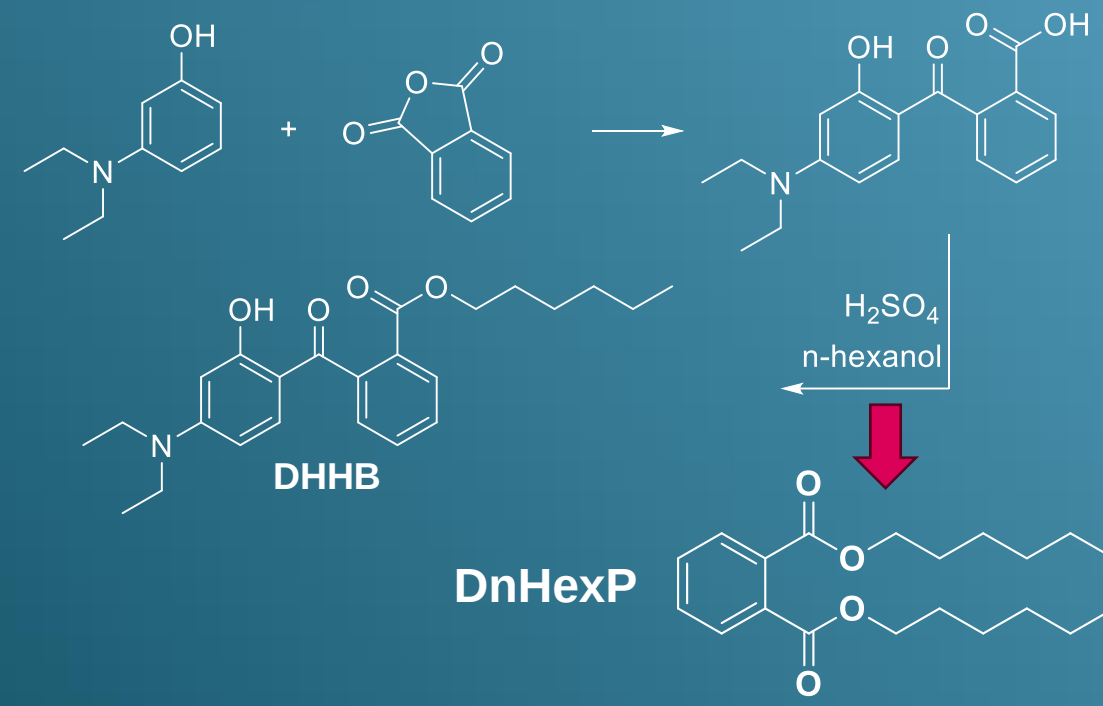
Maximum DI in ESB samples:

4.32 µg/kg bw/d

0.0015 ‰ of **DNEL** for **workers**

Based on available data, risk is considered very low

Potential contamination of DHHB

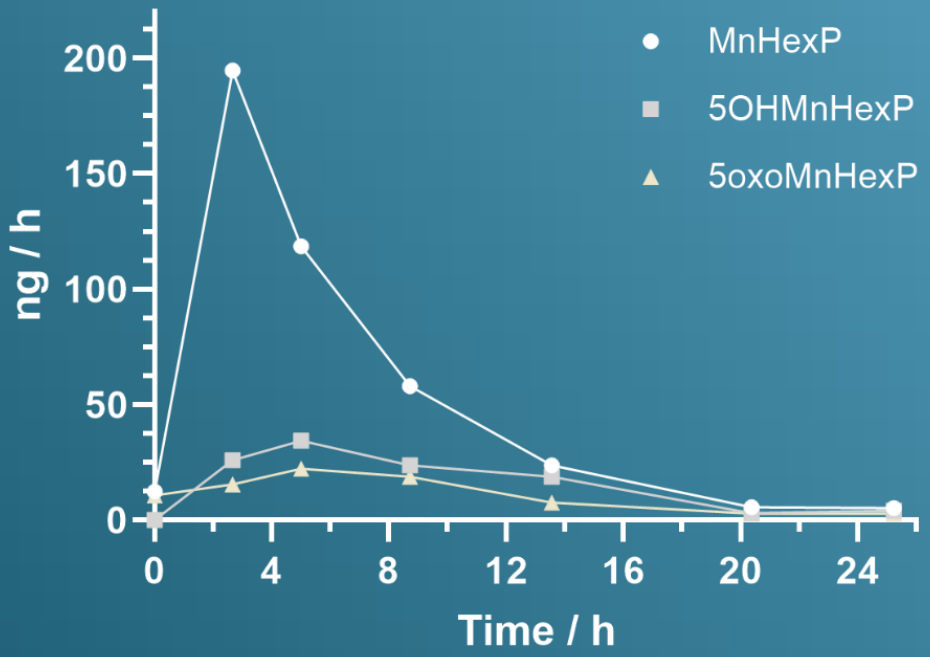


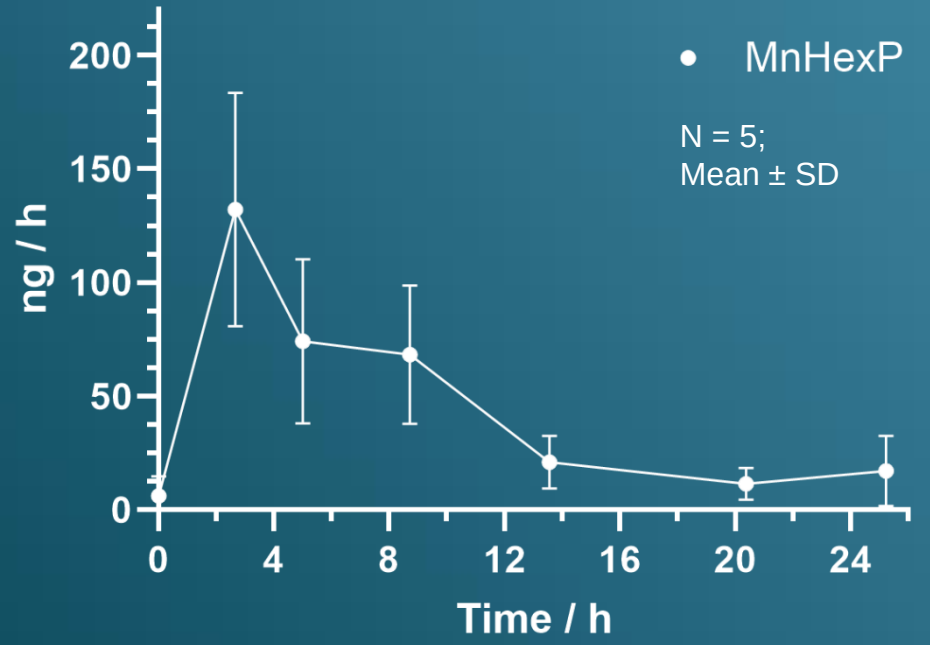
Possible exposure to **DnHexP**: **Substance of very high concern**

Excretion kinetics of DnHexP after oral administration of DHHB

- Determination of DnHexP metabolites after defined oral dose of DHHB
- Fast excretion: C_{max} in 1st (MnHexP) and 2nd urine fraction (5OHMnHexP, 5oxoMnHexP)
- Dose-dependent excretion kinetics

DnHexP intake from contaminated DHHB must be considered in risk assessment of DHHB exposure



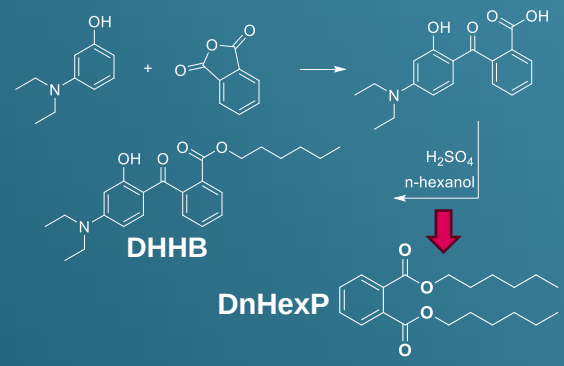


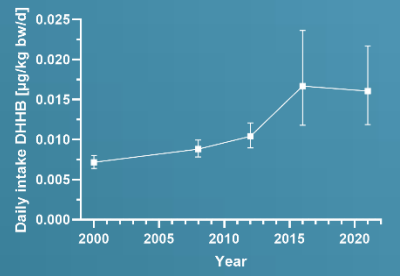
Conclusion

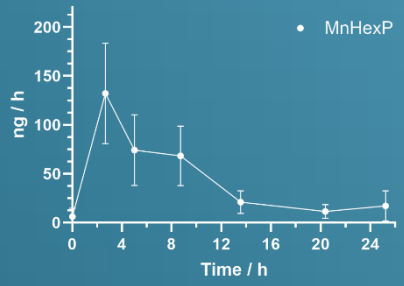
- Elucidation of human metabolism of DHHB
- First comprehensive HBM in 250 urine samples
- Identification of EHB / DHB as specific metabolites of DHHB exposure
- Further sources for AHB?
- Calculation of **Daily intake** based on urinary excretion of EHB / DHB

Significant increase in **DHHB exposure since 2012** following its approval as UV filter in 2005 in the EU

Further HBM ongoing (GerES VI, ESB, LANUV)
- ⇨ monitor **time trend** and **exposure sources**
- ⇨ Establish **reference** and **guidance values**
- ⇨ **Correlation** with **DnHexP** to identify major source of rising DnHexP exposure







Establishment of **new HBM methods** within the BMUV/VCI collaboration adds important exposure data

Low intake of DHHB

Increasing exposure over time identified in ESB samples **calls for action** regarding the possible co-exposure to the phthalate **DnHexP, toxic to reproduction**

Expanding the HBM toolbox crucial for a sound **risk assessment** and **evidence-based policymaking**

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