Corporate Health Management

Chief Medical Officer: Prof. Dr. Stefan Lang



# Human Biomonitoring of urinary Bisphenol S

## Method development and results of a pilot study among German adults

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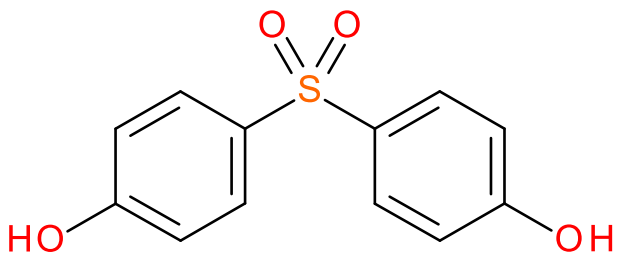
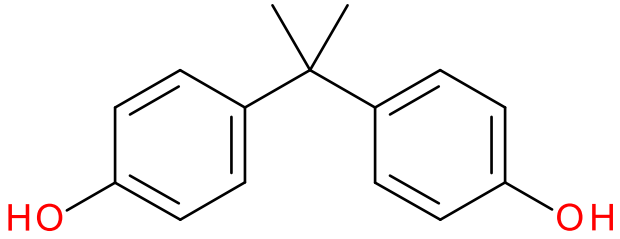
# Bisphenol S (BPS)




4,4’-Dihydroxydiphenylsulfone CAS-Nr. 80-09-1

production EU tonnage band 1.000 – 10.000 t/a

- ❑ polymer syntheses (e.g. polyarylethersulfones)
- ❑ substitute for Bisphenol A (e.g. thermal paper)
- ❑ ...

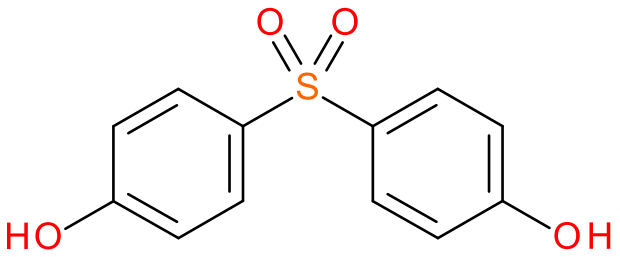


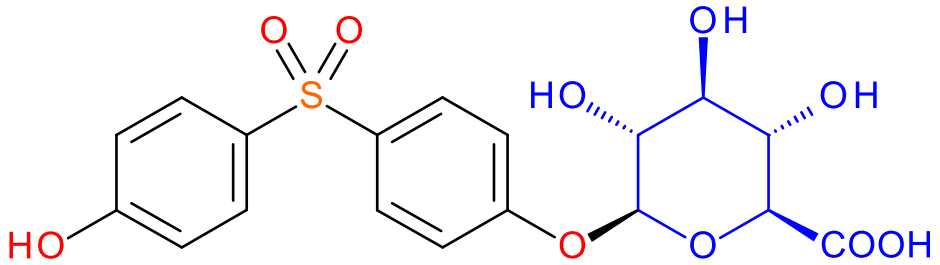

discussion structural (toxicological) similarity with Bisphenol A

- ❑ systemic toxicity ?
- ❑ reproductive toxicity ?
- ❑ endocrine effects ?

# Metabolism of Bisphenol S

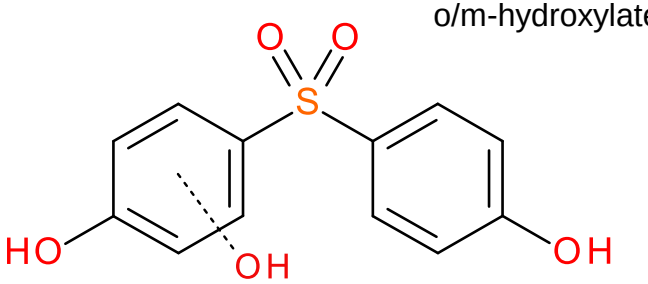
according to Skledar und Mašič (2016) Environ Int 112: 127-133

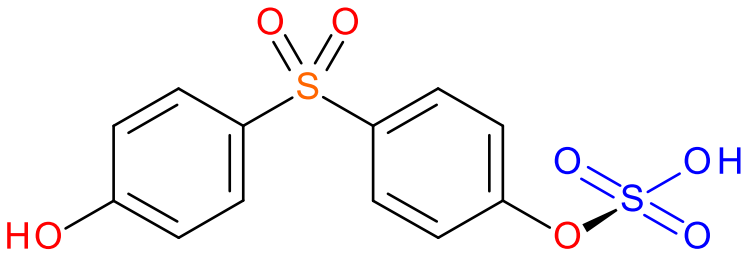



BPS glucuronide (~ 85.8 %)

o/m-hydroxylated BPS



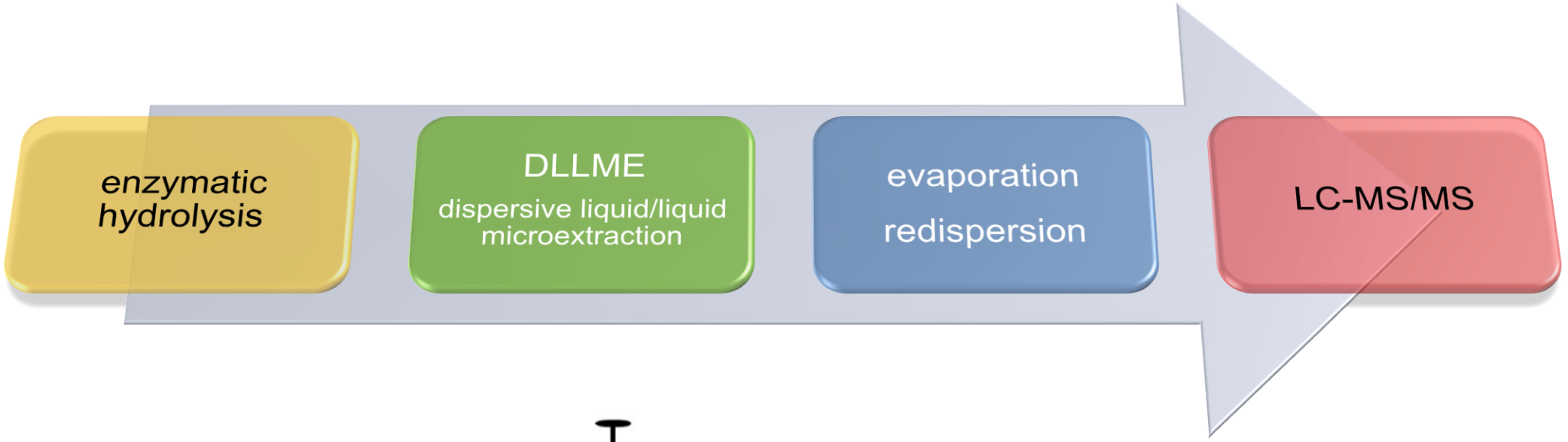




BPS sulfate (~ 10.5 %)

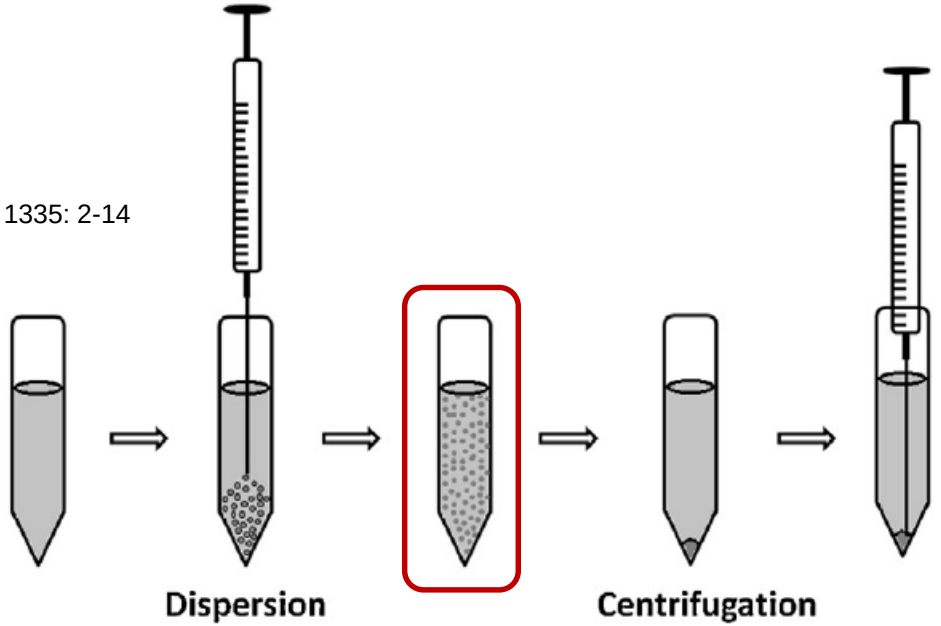
# Objectives of the Human Biomonitoring (HBM) project

- ❑ Development of an analytical procedure for the determination of urinary Bisphenol S (and other polyarylethersulfone monomers)
- ❑ key assumption: similar metabolism of BPS and BPA
- ❑ analysis of urinary BPS in a control study group (company internal, i.e. employees without occupational exposure to bisphenols)
- ❑ derivation of assessment values for HBM (background & workplace)
- ❑ workplace studies

# Sample preparation




source: Leong et al. (2014) JCB 1335: 2-14



# Analysis by LC-MS/MS (I)

© Waters

Waters Aquity UPLC

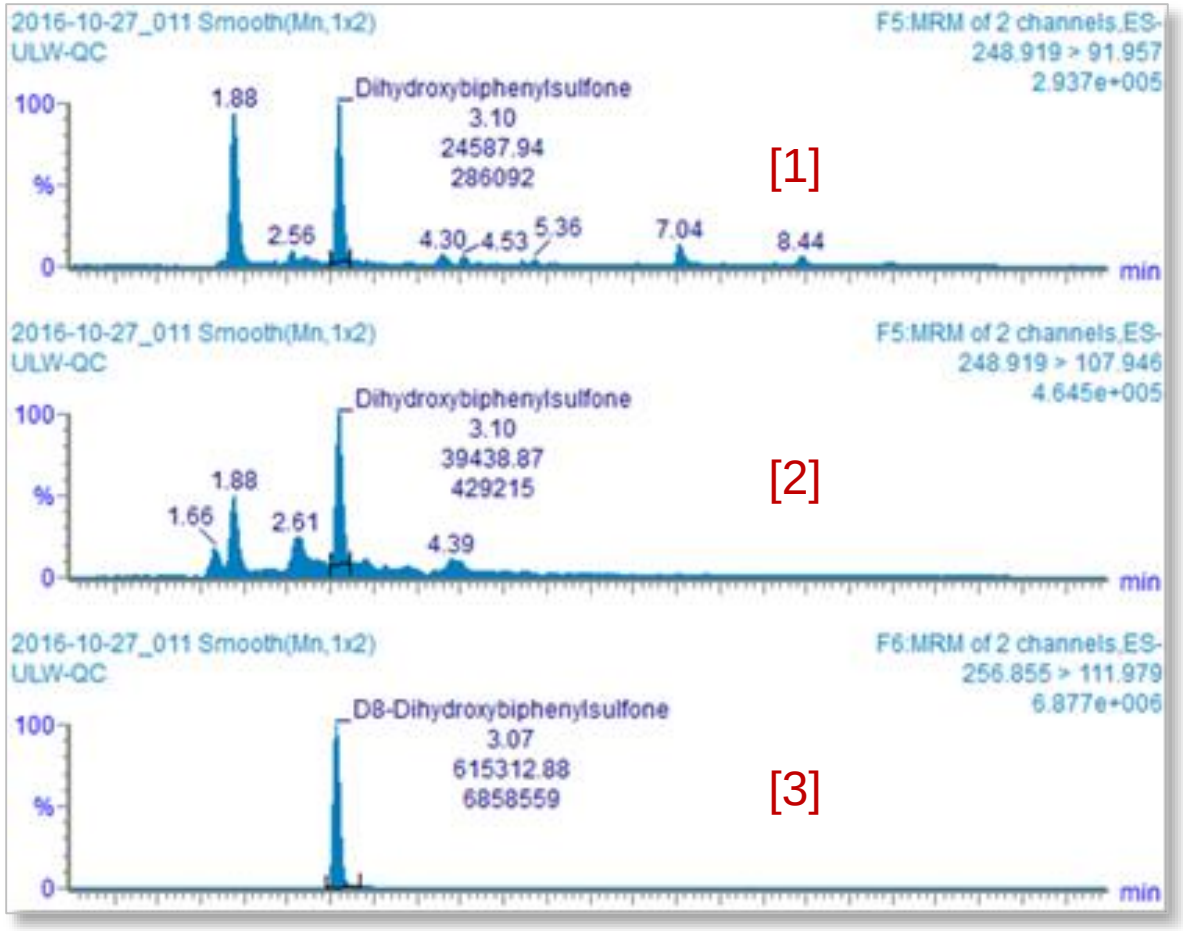
Waters Xevo TQ-S

Agilent Zorbax SB-C8 RRHD 2.1 x 150 mm, 1.8 µm

| min | mL/min | % $H_2O$ | % MeOH |
|---|---|---|---|
| 0 | 0.2 | 50 | 50 |
| 5.0 | 0.2 | 10 | 90 |
| 8.5 | 0.2 | 10 | 90 |
| 9.0 | 0.2 | 50 | 50 |
| 12.0 | 0.2 | 50 | 50 |

| parameter | setting |
|---|---|
| injection volume | 10 µL |
| column temp | 30°C |
| ionisation mode | ES (neg.) |
| detection mode | MRM |
| capillary voltage | 2.90 kV |
| cone voltage | -76 V |
| cone gas flow | 150 L/h |
| source temp | 150°C |
| desolvation temp | 500°C |
| desolvation gas flow | 1000 L/h |
| collision gas | Argon |
| collision gas flow | 0.15 mL/h |

# Analysis by LC-MS/MS (II)




| | $t_R$ (min) | mass transition | status |
|---|---|---|---|
| Bisphenol S | 3.10 | 248.919 → 91.957 | quantifier [1] |
| | | 248.919 → 107.946 | qualifier [2] |
| $d_8$-Bisphenol S | 3.07 | 256.855 → 95.988 | ISTD |
| | | 256.855 → 111.979 | ISTD [3] |

native urine specimen (c = 0.38 µg/L)

# Analytical performance

| | 0.5 µg/L | 2 µg/L | 10 µg/L |
|---|---|---|---|
| imprecision within series (pooled urine, n = 6) | 10.0 % | 6.4 % | 2.1 % |
| imprecision between series (pooled urine, n = 6) | 14.5 % | 5.0 % | 4.6 % |
| recovery (pooled urine, n = 3) | 94.7 % | 97.8 % | 106.1 % |

| | |
|---|---|
| matrix effect* | 98 ± 5 % |
| LOD limit of detection** | 0.01 µg/L |
| LOQ limit of determination** | 0.05 µg/L |
| calibration range (linear) | 0.1 – 50 µg/L |

* 10 individual urine specimens (creatinine 0.4 – 2.3 g/L, spiked with 2 µg/L Bisphenol S)

** LOD/LOQ according to DIN 32645, calibration curve method

# Study group

request for spot urine samples from employees of three departments

without occupational exposure to bisphenols

- ❑ voluntary participation
- ❑ short questionnaire
- ❑ informed consent, data protection

exclusion criteria

- ❑ urinary creatinine ≤ 0.3 g/L or ≥ 3.0 g/L
- ❑ multiple sampling
- ❑ any task/stay in plants using BPA/BPS

| total | 142 samples |
|---|---|
| men (n) | 95 |
| women (n) | 47 |
| median age (years) | 48 |
| age range (years) | 21 – 64 |
| nonsmokers (n) | 131 |
| smokers (n) | 11 |
| morning sampling (n) | 79 |
| afternoon sampling (n) | 61 |
| not specified (n) | 2 |

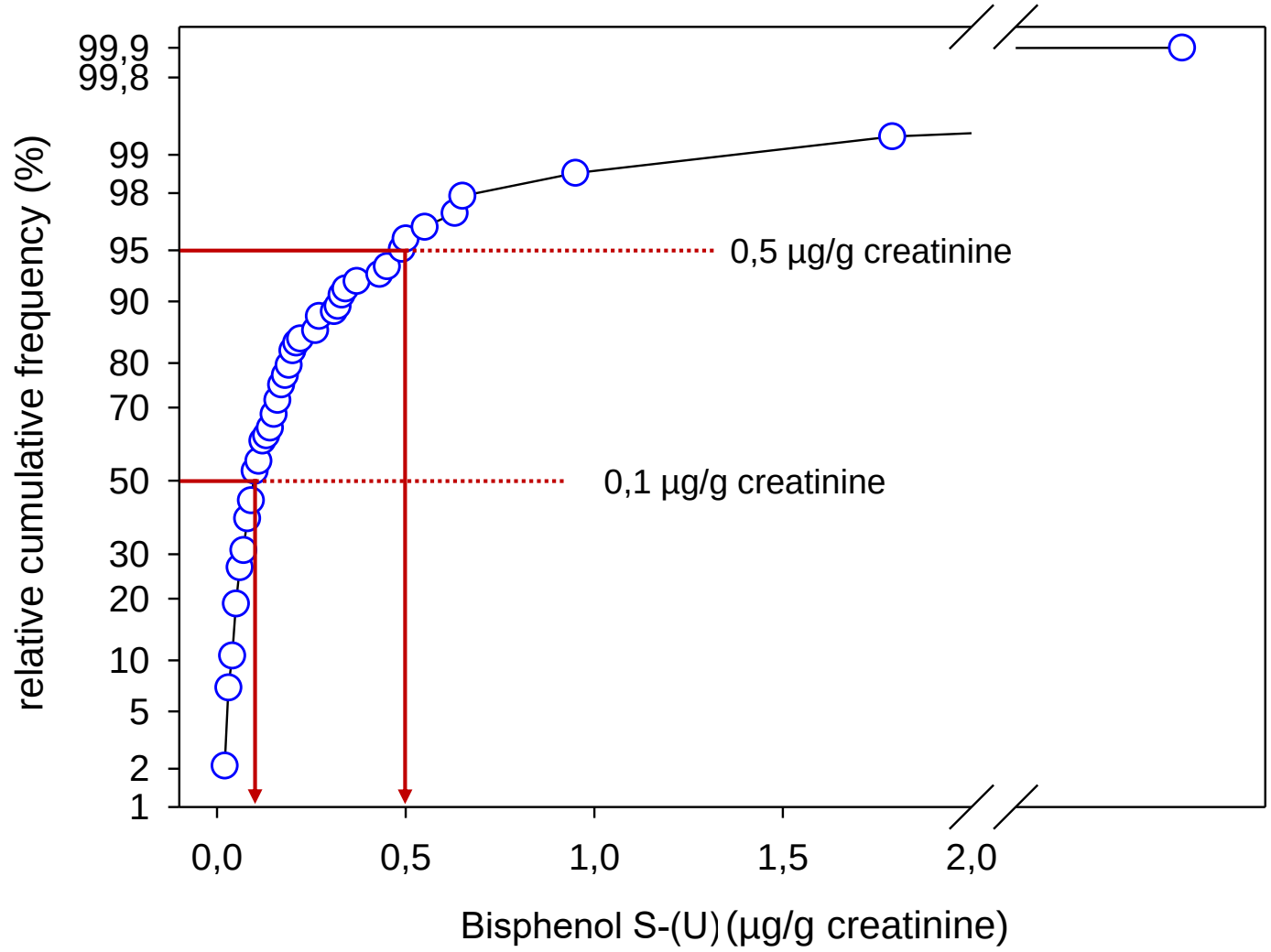
# Results (I)

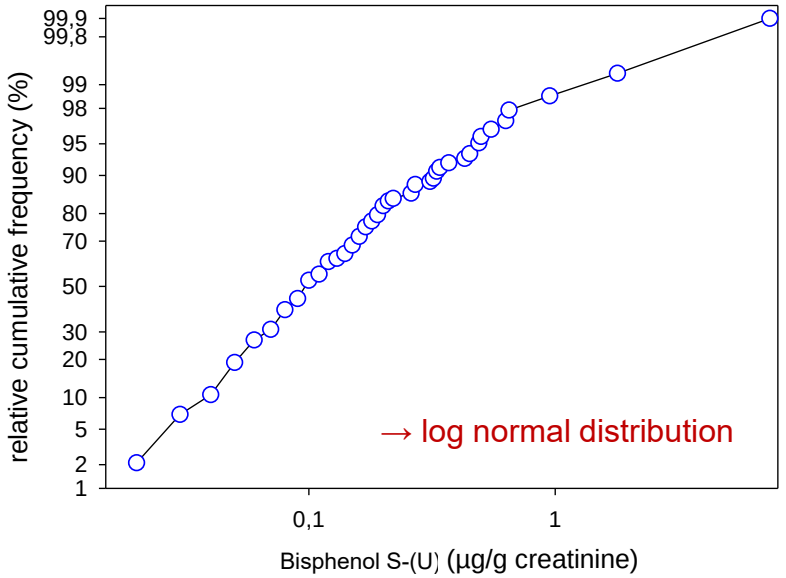
| Bisphenol S | total | |
|---|---|---|
| samples (n) | 142 | |
| n > LOQ (0.05 µgL) | 86 % detects | |
| | | |
| | µg/L | µg/g creatinine |
| mean (x ± s) | 0.18 ± 0.29 | 0.21 ± 0.64 |
| median | 0.10 | 0.10 |
| 95$^{th}$ percentile | 0.68 | 0.50 |
| range | <0.05 – 2.75 | <0.05 – 7.43 |

| Bisphenol A | total | |
|---|---|---|
| samples (n) | 142 | |
| n > LOQ (0.5 µg/L) | 83 % detects | |
| | | |
| | µg/L | µg/g creatinine |
| mean (x ± s) | 1.6 – 2.3 | 1.9 ± 4.0 |
| median | 1.0 | 1.1 |
| 95$^{th}$ percentile | 5.1 | 6.0 |
| range | <0.5 – 19.8 | <0.5 – 43.2 |

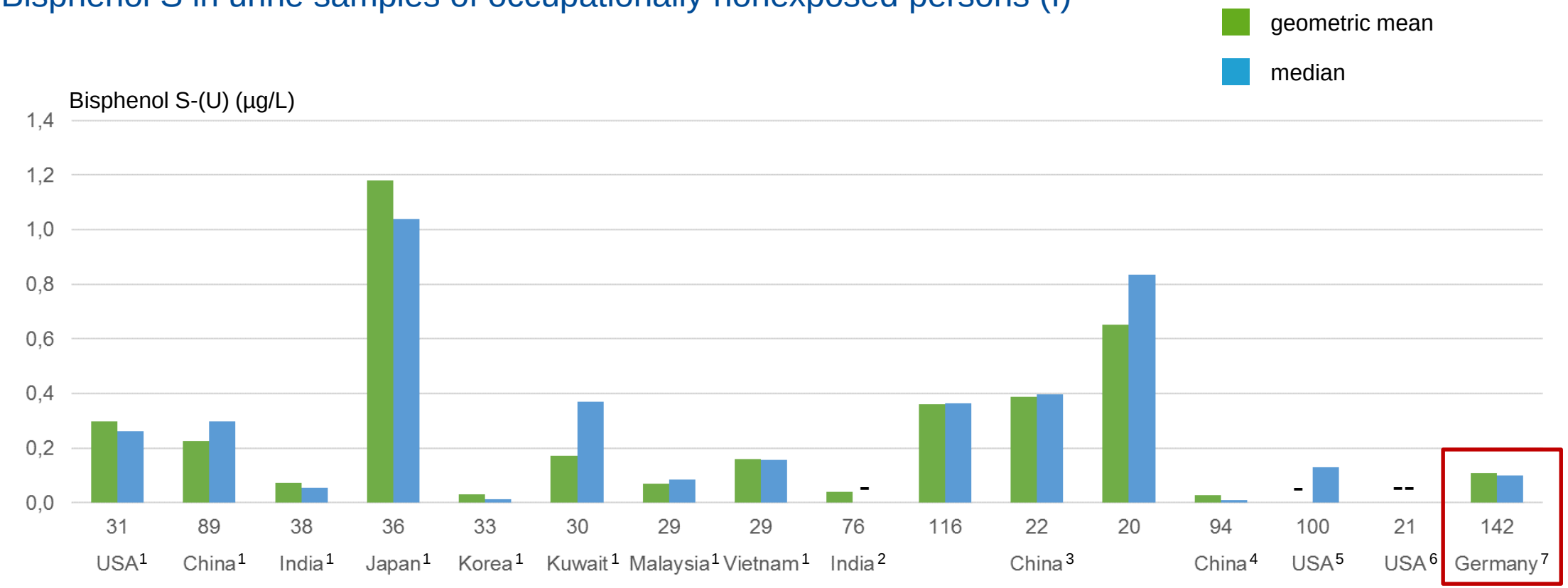
| | | |
|---|---|---|
| 95$^{th}$ percentile (Germany, 20 – 29 years) | 7 | ~ 5.8 |

# Results (II)


99,9
99,8
99
98
95
90
80
70
50
30
20
10
5
2
1
relative cumulative frequency (%)
0,5 µg/g creatinine
0,1 µg/g creatinine
0,0
0,5
1,0
1,5
2,0
Bisphenol S-(U) (µg/g creatinine)

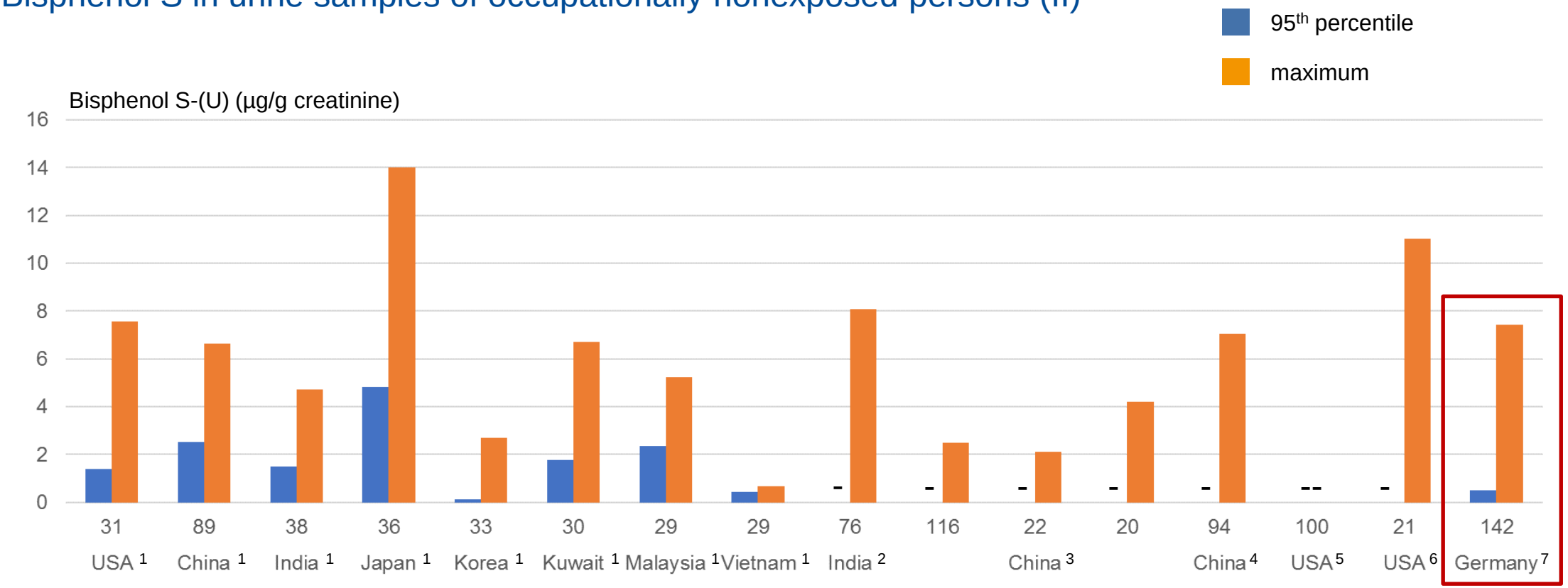

99,9
99,8
99
98
95
90
80
70
50
30
20
10
5
2
1
relative cumulative frequency (%)
→ log normal distribution
0,1
1
Bisphenol S-(U) (µg/g creatinine)

# Bisphenol S in urine samples of occupationally nonexposed persons (I)




[1] Liao et al. (2012) Environ Sci Technol 46: 6860-6866
[2] Xue et al. (2015) Environ Res 137: 120-128
[3] Zhang et al. (2016) Environ Sci Technol 50: 4045-4053
[4] Yang et al. (2014) Chemosphere 112: 481-486
[5] Zhou et al. (2014) J Chrom B 944: 152-156
[6] Thayer et al. (2016) Environ Health Perspect 124: 437-444
[7] this study (2018)

# Bisphenol S in urine samples of occupationally nonexposed persons (II)

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# Conclusions

- ❑ reliable and sensitive LC-MS/MS method for BPS quantification in human urine

- ❑ internal reference group — 95$^{th}$ percentile — 0.7 µg/L or 0.5 µg/g creatinine
  median — 0.1 µg/L or 0.1 µg/g creatinine

- ❑ results accord with other studies on background exposure (DE: ‘lower midrange’)

- ❑ current background: urinary BPS ~ 1/10 of urinary BPA

- ❑ next step: occupational field studies (incl. ambient air monitoring)

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We create chemistry