



UNIVERSITÀ degli STUDI di CATANIA
Dipartimento di Scienze Mediche, Chirurgiche
e Tecnologie Avanzate
"F. G. Ingrassia"

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E.N.P.A.B.
ENTE NAZIONALE DI PREVIDENZA E ASSISTENZA
A FAVORE DEI BIODICI



Ordine dei Tecnologi Alimentari
di Sicilia e Sardegna

WORKSHOP

LA QUALITÀ DELLE ACQUE MINERALI NATURALI
THE QUALITY OF NATURAL MINERAL WATER

Bisphenol A in Plastic Contact Materials and Evidence of Human Metabolic Alterations

**La presenza di bisfenolo A nei contenitori in materia plastica ed effetti sul
metabolismo umano**

MSc Corina Konstantinou – Cyprus University of Technology



Lifelong
Learning
Programme

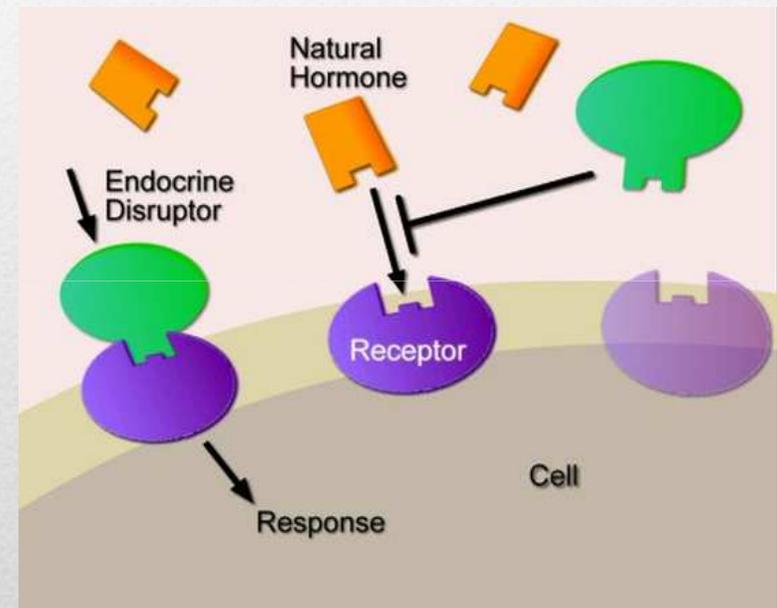
Catania (Italy), 19 March 2015

Overview

- Endocrine-disrupting chemicals (EDCs) in bottled water
 - Economic burden from EDCs in the EU
 - Diabetes - facts & figures
 - Association of BPA with diabetes
 - Factors affecting BPA leaching in bottled water
 - Research recommendations
-

Why so much concern for EDCs?

- Show structural similarities to natural hormones
- Interact with the endocrine system by mimicking or blocking natural hormones
- Interfere with the production, secretion, or metabolism of endogenous hormones and/or their nuclear receptors
- Dysregulate reproduction, homeostatic mechanisms and development



Estrogenic activity in bottled water

- Widespread estrogenic contamination of commercially available bottled water
 - ‘Traditional EDCs’
 - BPA, phthalates
 - Might not be responsible for the endocrine activity in bottled water
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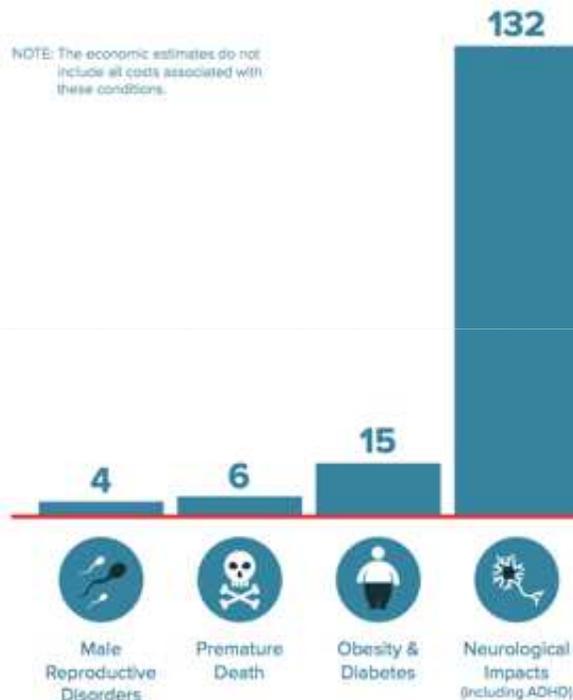
Presence of other EDCs in bottled water

- Combination of bioassays and high-resolution MS
 - Detection of antiestrogenic and antiandrogenic activity in majority of bottled water products
 - Identification of DEHF (antiestrogenic but not antiandrogenic)
 - Other unidentified EDCs must contribute to the antagonistic effect of bottled water
 - Maleate/fumarate isomers
 - Biologically active & structurally highly similar to phthalates
 - Might represent a novel group of EDCs
-

HEALTH EFFECTS FROM ENDOCRINE DISRUPTING CHEMICALS COST THE EU 157 BILLION EUROS EACH YEAR.

This is the tip of the iceberg: Costs may be as high as €270B.

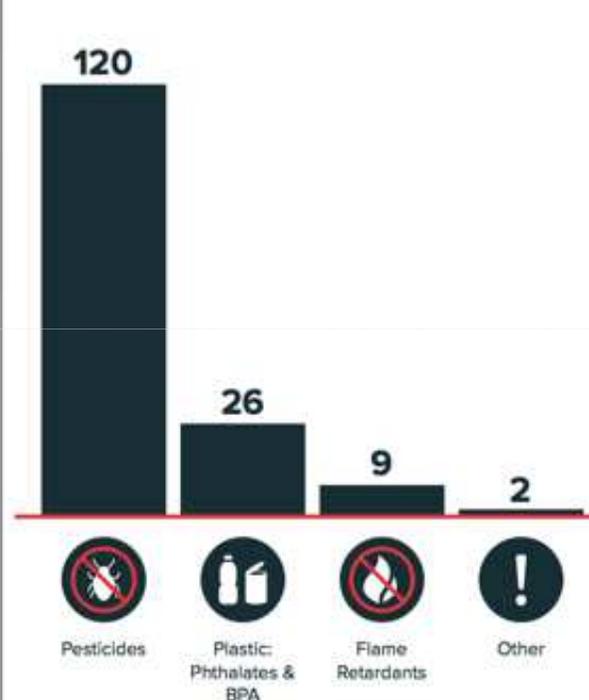
€157B Cost by Health Effect



SOME EDC-RELATED HEALTH OUTCOMES NOT INCLUDED:

- Breast Cancer
- Prostate Cancer
- Immune Disorders
- Female Reproductive Disorders
- Liver Cancer
- Parkinson's Disease
- Osteoporosis
- Endometriosis
- Thyroid Disorders

€157B Cost by EDC Type



SOME EDCs NOT INCLUDED:

- Atrazine
- 2, 4-D
- Styrene
- Triclosan
- Nonylphenol
- Polycyclic Aromatic Hydrocarbons
- Bisphenol S
- Cadmium
- Arsenic
- Ethylene glycol



Endocrine Disrupting Chemicals (EDCs) interfere with hormone action to cause adverse health effects in people.

"THE TIP OF THE ICEBERG"

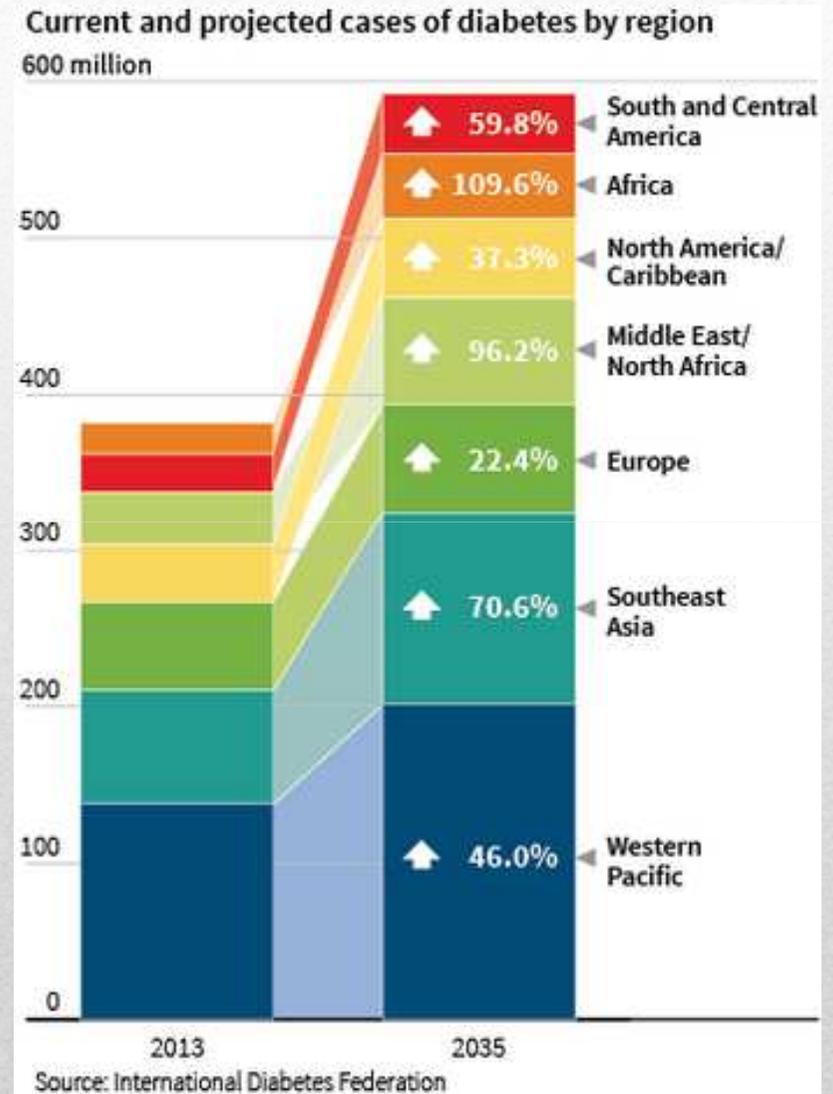
The data shown to the left are based on fewer than 5% of likely EDCs. Many EDC health conditions were not included in this study because key data are lacking. Other health outcomes will be the focus of future research.

See Terasande et al. The Journal of Clinical Endocrinology & Metabolism
<http://press.endocrine.org/edc>

Estimated Costs of EDCs for the EU

Diabetes

- In 2014: global prevalence of 9%
- In 2012: 1.5 million deaths caused by diabetes
- >80% of diabetes deaths: in low- & middle-income countries
- Projections: it will be the 7th leading cause of death in 2030

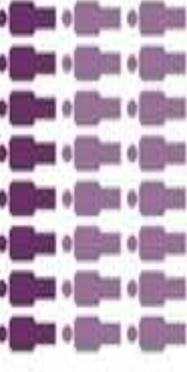


46.3% undiagnosed

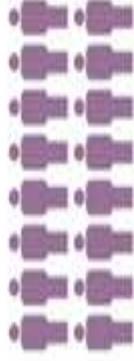


expected increase

+205 MILLION



2035



2014



1/12 people with **DIABETES**

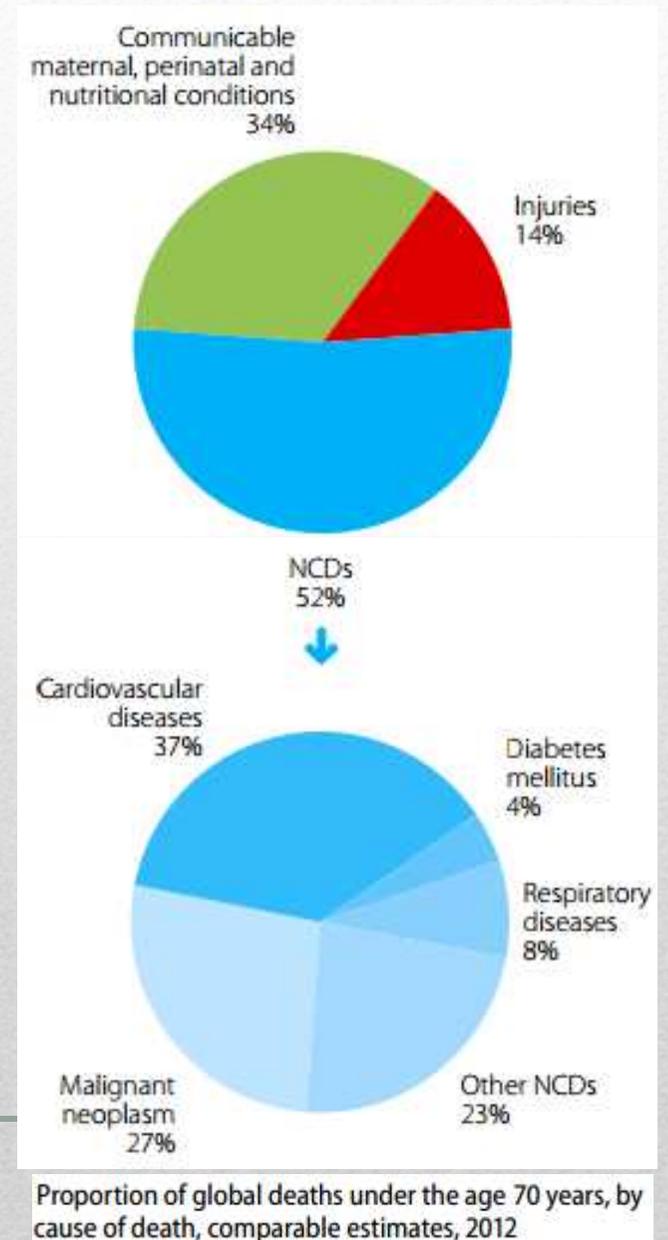
1 healthcare

in 9 IS SPENT ON DIABETES

in 2014 diabetes expenditure reached US\$12 trillion

Type 2 Diabetes Mellitus

- Formerly called non-insulin-dependent or adult-onset
- Body's ineffective use of insulin.
- Comprises 90% of people with diabetes around the world
- Largely the result of excess body weight and physical inactivity
- The disease may be diagnosed several years after onset, once complications have already arisen
- Until recently, only in adults but now also occurring in children.



Bottled water chemicals and diabetes

- Based on NTP workshop discussions

A. Phthalates

- Discussion of 3 cross-sectional studies
- Positive associations but not sufficient evidence
- However, phthalate exposure was found to have a 40-69% probability of causing 20 500 new-onset cases of diabetes in older women with €607 million in associated costs.

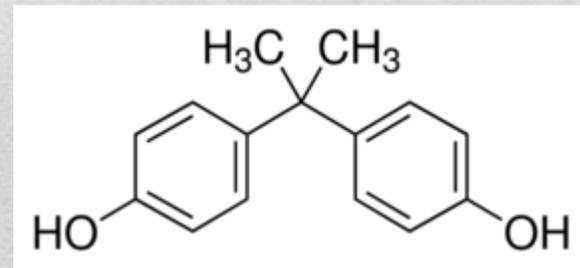
B. BPA

- Animal and in vitro studies
 - Suggest effect of BPA on glucose homeostasis, insulin release, cellular signaling in pancreatic β cells and adipogenesis
 - Human studies: Too limited to draw conclusions
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BPA

- **Bisphenol A (BPA)**

- Monomer used in the production of polycarbonates and epoxy resins
- Found in thermal receipt papers
- One of the highest volume chemicals produced worldwide (>6 billion pounds/y)
- Considered as important organic pollutant
- Endocrine-disrupting chemical: estrogenic activity



BPA association with T2DM

Study	Sample Population	Methods	Analysis	Results
Sun et al., 2014	971 incident T2D case-control pairs from the NHS (mean age, 66y) and NHSII (mean age, 46y)	Urinary BPA concentrations and T2D risk	In the NHSII, after adjustment of BMI OR= 2.08 (95% CI: 1.17-3.69; p(trend) = 0.02). In the NHS OR= 0.81; 95% CI: 0.48-1.38; p(trend) = 0.45)	BPA exposures may be associated with the risk of type 2 diabetes among middle-aged women, but not older women
Melzer et al., 2010	n=1455 (NHANES 2003/04) and n=1493 (NHANES 2005/06) adults aged 18-74 y	Urinary BPA concentrations and health status	Associations with diabetes did not reach significance in 2005/06, but pooled estimates remained significant (OR = 1.24, CI: 1.10-1.40, p = 0.001)	Significant association between BPA and diabetes in pooled data (NHANES 2003-06)
Lang et al., 2008	1455 adults aged 18-74 y from NHANES 2003-2004	Urinary BPA concentrations and health status	OR per 1-SD increase in BPA concentration, 1.39; 95% CI: 1.21-1.60; P < .001	Higher BPA concentrations were associated with diabetes
Shankar & Teppala, 2011	3967 participants (51.7% women), 467 of whom had diabetes from NHANES 2003-2008.	Urinary BPA levels and diabetes mellitus	Compared to quartile 1 (referent), the multivariate-adjusted odds ratio (95% CI) of diabetes associated with quartile 4 was 1.68 (1.22-2.30) (p-trend = 0.002)	Urinary BPA levels are found to be associated with diabetes mellitus independent of traditional diabetes risk factors.

BPA association with T2DM

Study	Sample Population	Methods	Analysis	Results
Silver et al., 2010	4,389 adults from three NHANES cycles (2003-2008)	Urinary BPA and T2DM. T2DM was defined as having a HbA1c \geq 6.5% or use of diabetes medication	Two-fold increase in urinary BPA was associated with an OR of 1.08 of T2DM (95% CI, 1.02-1.16), after controlling for potential confounders. A statistically significant association was found only in the 2003/04 cycle (n = 1,364, OR = 1.23 (95% CI, 1.07-1.42) for each doubling in urinary BPA)	Although higher urinary BPA was associated with elevated HbA1c and T2DM in the pooled analysis, it was driven by data from only one NHANES cycle.
Sabanayagam et al., 2013	3,516 subjects from NHANES 2003-2008.	Urinary BPA levels and prediabetes	Compared to tertile 1 (referent), the multivariate-adjusted odds ratio (95 % confidence interval) of prediabetes associated with tertile 3 of BPA was 1.34 (1.03-1.73), p-trend = 0.02. In subgroup analysis, this association was stronger among women and obese subjects.	Positive association between higher levels of urinary BPA and prediabetes, independent of potential confounders including body mass index, alcohol intake, blood pressure and serum cholesterol levels.

BPA association with T2DM

Study	Sample Population	Methods	Analysis	Results
Ning et al., 2011	3423 Chinese adults, median age 59 y, 40% men and 1087 had type 2 diabetes	Urinary concentrations of BPA and fasting plasma glucose concentration, plasma glucose concentration 2 hours after an oral glucose tolerance test and serum insulin concentration	Multivariable analyses showed no clear association between BPA levels and type 2 diabetes. The adjusted OR of type 2 diabetes was slightly increased for participants in the second BPA quartile (0.48 -0.81 ng/mL) (adjusted OR, 1.30 [95% CI, 1.03-1.64]) and the fourth quartile (>1.43 ng/mL) (adjusted OR, 1.37 [CI, 1.08-1.74]) but not the third quartile (0.82-1.43 ng/mL) (adjusted OR, 1.09 [CI, 0.86-1.39]), and a test of the trend of the association was not statistically significant.	No association between urinary BPA levels and self-reported type 2 diabetes.
Kim & Park, 2013	Korean adults (n=1210) aged 40-69 years, mean age 53 y and 42% were men. From the 2009 KNHBS.	Urinary BPA concentration and prevalence of type 2 diabetes	Among BPA quartiles, no clear association was found between BPA levels and type 2 diabetes. Although the adjusted odds ratio of type 2 diabetes was slightly increased for participants in the upper BPA quartile, the association was not statistically significant.	A high body BPA burden may not be associated with an increased prevalence of type 2 diabetes in Korean adults

BPA association with T2DM

Study	Sample Population	Methods	Analysis	Results
Ahmadkhaniha et al., 2014	239 Iranian adults, median age 52 y and 119 of them had type-2 diabetes mellitus	Urinary BPA concentrations and diabetes diagnosis	The multi variable-adjusted odds ratio for type-2 diabetes mellitus associated with the group 1 (referent), of urinary BPA was 57.6 (95% CI: 21.10-157.05; P-value < 0.001).	Higher urinary BPA concentrations, are consistently associated with diabetes in the general adult population of the Iran.
Aekplakorn et al., 2015	2581 serum samples from the Thai National Health Examination Survey (2009)	Serum BPA concentrations and diabetes diagnosis (or fasting plasma glucose)	After adjusting for potential confounders, compared with the first quartile (≤ 0.071 ng/mL), the overall adjusted OR of serum BPA concentration in the third and fourth quartiles ($0.319-0.745$ and ≥ 0.746 ng/mL, respectively) for IFG were 1.72 (95% CI 1.19-2.49) and 1.23 (95% CI 0.80-1.89), respectively; for diabetes, the adjusted OR were 1.88 (95% CI 1.18-2.99) and 1.83 (95% CI 1.12-2.95) respectively	Serum BPA concentrations were not associated with IFG, but were positively associated with diabetes in the Thai population.

Factors affecting BPA leaching in bottled water

- Scratched or discolored polycarbonate
 - Alkaline water
 - Can degrade the PC plastic
 - Dishwashing, boiling and brushing of PC bottles:
 - May be due to polymer degradation but TDI was not exceeded for infants
 - However, in another study, it was shown that brushing of the bottle does not seem to increase the release of BPA
-

Factors affecting BPA leaching in bottled water

- Temperature
 - The critical factor favouring BPA migration from PC bottles to water
 - Higher temperature and longer testing period in PC bottles
 - For PC reusable water bottles, filling with hot water or heating in the microwave to high temperatures
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Study on the leaching of BPA from PC bottles

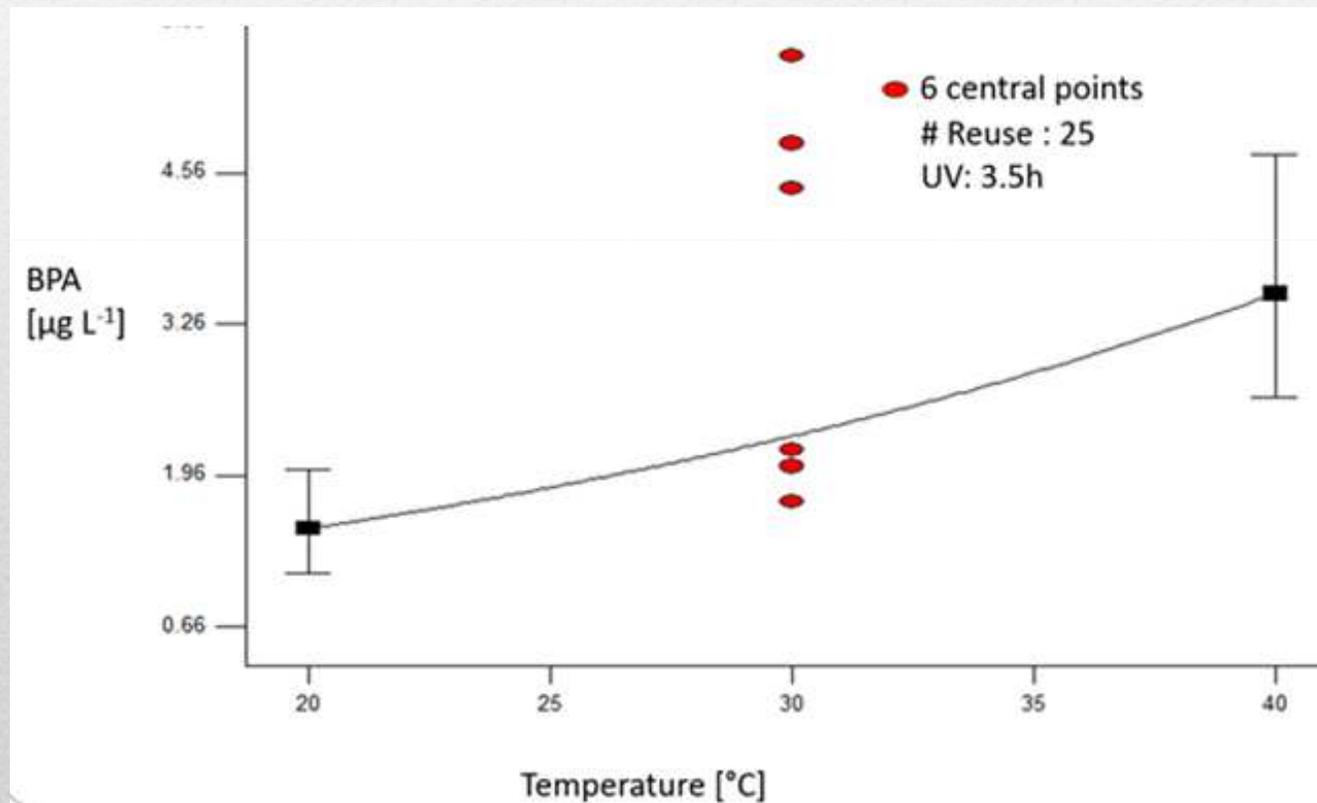
- **Aim:** Investigate the leaching behavior of BPA from PC-bottles into bottled water under various environmental conditions such as varying temperatures, number of reuse cycles and UV-light irradiation
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Study on the leaching of BPA from PC bottles

- **Method:**
 - Central Composite Design
 - Factors assessed
 - Temperature: 20-40°C
 - Number of bottle reuse: 20-40 times
 - UV-A light irradiation: 1-6h (365nm)
 - 6 Central points (30°C, 25 times reuse, 3.5 h UVA-light)
 - Medium used:
 - Bottled spring mineral water
 - Tap water
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Study on the leaching of BPA from PC bottles

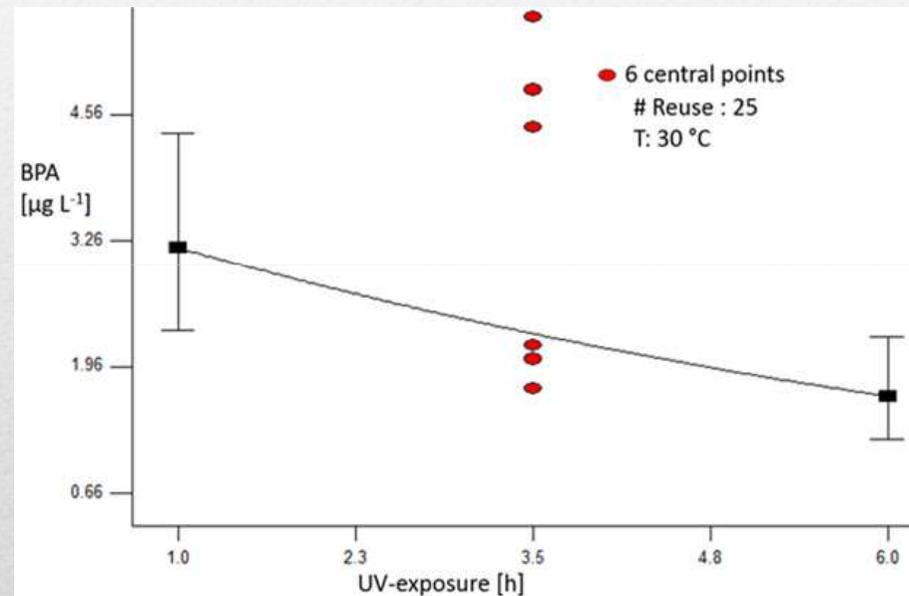
- **Results:**
 - Increased BPA migration with increasing T



Study on the leaching of BPA from PC bottles

- **Results:**

- Negative correlation between UV-exposure duration and BPA concentration, but not significant



- No effect of bottle reuse on BPA concentration was found.
 - No interaction effect of temperature, bottle reuse and UV-exposure was found.
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Research Recommendations

- Large-scale prospective studies are needed to evaluate the relationship between BPA and diabetes
 - Evaluation of the dose-response relationship, the role of chemical mixtures and critical growth periods
 - Elucidate the role(s) of effect modifiers, confounding factors and specific genetic contributions
 - Further research on the novel group of EDCs in bottled water
 - Constantly update and extend the list of EDCs in bottled water
 - Promotion of collaborative projects, workshops and biomonitoring worldwide
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Thank You

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