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*Molecular Sciences*

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*Project report*

# The GOLIATH project: Towards Internationally Harmonised Approaches for Testing Metabolism Disrupting Compounds

***SUPPLEMENTARY TABLES AND FIGURES***

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Supplementary Table 1: Overview of the reported associations between (early life) exposure to the initial set of GOLIATH chemicals and metabolic disorders in human epidemiological studies. For PFOA, TCS, p,p'-DDE, and BPA, studies of 2016 onwards were selected.

| Chemical | Endpoint | Epidemiologic design | Population | Statistically significant associations / Findings | First Author + Year of publication |
|---|---|---|---|---|---|
| **TBT** | **Growth and Ponderal Index** | Prospective (Outcome ~ TBT placenta) | Newborns followed in childhood, Finland | Weight gain during the first three months of life (positive); no significant associations between placenta OTC concentrations and child length, weight or PI at any time point were found | Rantakokko, 2014 [1] |
| | | | | | |
| **PFOA** | **Liver disease** | Cross-sectional | Adults, China | Serum adipocytokines: TNF-alpha (negative); CK18 M30 (positive) | Bassler, 2019 [2] |
| **PFOA** | **Gestational diabetes (GD)** | Prospective: GD ~ PFOA in early pregnancy | Healthy US women | Positive association with GDM among women with a family history of T2D | Rahman, 2019 [3] |
| **PFOA** | **Overweight** | Cross-sectional | Adults, China | Higher prevalence of overweight and positive association with waist circumference, more pronounced in women | Tian, 2019 [4] |

| Chemical | Endpoint | Epidemiologic design | Population | Statistically significant associations / Findings | First Author + Year of publication |
|---|---|---|---|---|---|
| **PFOA** | **Lipids/lipoproteins** | Cross-sectional | NHANES 2005-2014, adults | Total (positive) and LDL cholerterol (positive). Greater susceptibility to elevated total and LDL cholesterol in obese participants, with differences between men and women. | Jain, 2019 [5] |
| **PFOA** | **Childhood adiposity** | Meta-analysis of Prospective cohorts | 10 cohort studies, N = 6076 | Childhood body mass index (positive) | Liu, 2019 [6] |
| **PFOA** | **Birth antropometric measures** | Cross-sectional | Newborns, US (KIDS) | No significant associations | Bell, 2019 [7] |
| **PFOA** | **Type 2 diabetes** | Prospective cohort: T2D ~ dietary exposure | Adults, France (E3N) | U-shape association | Mancini, 2019 [8] |
| **PFOA** | **Glucose related outcomes** | Prospective birth cohort: outcome gestational week 28 ~ PFOA gestational week 11 | Pregnant women, Denmark (Odense Child Cohort) | PFOA was not associated with glucose related outcomes (other PFASs were) | Jensen, 2018 [9] |
| **PFOA** | **Cord blood DNA methylation** | Cross-sectional | Mothers and newborns, Japan (Sappora cohort, Hokkaido Study) | DMP: ZBTB7A, USP2-AS1, TCP11L2, NTN1; DMR: ZFP57, CYP2E1, SMAD3, SLC17A9, GFPT2, DUSP22, and TCERG1L | Miura, 2019 [10] |
| **PFOA** | **Type 2 diabetes** | Prospective nested case-control | Adults, US, NHSII | Risk of type 2 diabetes (positive) | Sun, 2018 [11] |

| Chemical | Endpoint | Epidemiologic design | Population | Statistically significant associations / Findings | First Author + Year of publication |
|---|---|---|---|---|---|
| **PFOA** | **Body weight and resting metabolic rate** | Randomnised clinical trial | Adults, US | Participants lost an average of 6.4 kg of body weight during the first 6 months (weight-loss period) and subsequently regained an average of 2.7 kg of body weight during the period of 6-24 months (weight regain period).Examine associations of PFAS exposure with changes in body weight and resting metabolic rate (RMR) in a diet-induced weight-loss setting. Higher baseline levels of PFASs were significantly associated with a greater weight regain, primarily in women | Liu, 2018 [12] |
| **PFOA** | **Lipids (total cholesterol, HDL, LDL) and alanine aminotransferase** | Prospective cohort: outcome childhood ~ prenatal exposure maternal plasma preganancy | Children, US | Higher TC and LDL in girls; Higher ALT in boys and girls; Lower ALT in boys and girls (the latter two predict better cardiovascular health) | Mora, 2018 [13] |
| **PFOA** | **Metabolic outocmes: impaired glucose tolerance (IGT), gestational diabetes mellitus (GDM),** | Prospective/cross-sectional: outcome ~PFOA 1st trimester | Pregnant women, Spain (INMA) | total cholesterol (positive) | Matilla-Santander, 2018 [14] |

| Chemical | Endpoint | Epidemiologic design | Population | Statistically significant associations / Findings | First Author + Year of publication |
|---|---|---|---|---|---|
| | **first-trimester serum levels of triglycerides, total cholesterol, and C-reactive protein (CRP)** | | | | |
| **PFOA** | **Metabolic Syndrome** | Cross-sectional | Adults, China | increased risk of metabolic syndrome, systolic blood pressure (positive), hypertriglyceridemia (positive), obesitry (positive) | Yang, 2018 [15] |
| **PFOA** | **Bone density; cardio-metabolic risk factors** | Cross-sectional | Children, 2017 | Total and LDL cholesterol (positive) | Khalil, 2017 [16] |
| **PFOA** | **Glycemic indicators and diabetes index** | Prospective | Diabetes Prevention Program Trial, US | Evaluated adjusted associations for plasma PFAS concentrations with diabetes incidence and key glycemic indicators measured at baseline and annually over up to 4.6 y. Baseline: homeostatic model assessment of insulin resistance (HOMA-IR) (positive); β-cell function (HOMA-β) (positive); fasting proinsulin (positive); glycated hemoglobin (HbA1c) (prositive) | Cardenas, 2017 [17] |

| Chemical | Endpoint | Epidemiologic design | Population | Statistically significant associations / Findings | First Author + Year of publication |
|---|---|---|---|---|---|
| **PFOA** | **Weight gain; BMI; Waist circumference; blood pressure** | Prospective | Childran, Spain (INMA) | Little or no evidence of associations between low prenatal PFAS exposures and outcomes related to cardiometabolic risk in a cohort of Spanish children followed from birth until 7 y | Manzano-Salgado, 2017 [18] |
| **PFOA** | **Biochemistry profiles of metabolic syndrome** | Cross-sectional | Adults, US (NHANES 2013-2014) | Increased linear PFOA was associated with increases in total cholesterol, serum albumin and an enhancement of beta cell function as well as a decrease in the serum globulin. Increased branched PFOA was significantly associated with increased fasting glucose. All isomers of PFOA were positively associated with high-density lipoprotein-cholesterol (HDL-C) and negatively associated with glycohemoglobin (HbA1C). | Liu, 2018 [19] |
| **PFOA** | **Birth antropometric outcomes and maternal glucose and lipids** | Prospective: Outcome ~ PFOA mid pregnancy | Mothers and newborns, US (Healthy Start) | Birth weight (negative); Adipositiy (negative); maternal glucose mid pregnancy (negative). Mediation effect of maternal glucose on | Starling, 2017 [20] |

| Chemical | Endpoint | Epidemiologic design | Population | Statistically significant associations / Findings | First Author + Year of publication |
|---|---|---|---|---|---|
| | | | | association between PFAS and neonatal adiposity | |
| **PFOA** | **DNA methylation cord blood** | Prospective: Outcome ~ PFOA mid pregnancy | Mothers and newborns, US | among top20 genes: RASA3; OPRD1 | Kingsley, 2017 [21] |
| **PFOA** | **Body fat at age 9 in girls** | Prospective: Outcome ~ PFOA maternal mid pregnancy | Mothers and children, UK (Avon) | BF age 9 (positive) | Hartman, 2017 [22] |
| **PFOA** | **Fetal growth** | Prospective case-cohort: outcome ~PFOA early second trimester | Mothers and newborns, Sweden and Norway | Higher odds for small for gestational age (SGA) birth | Lauritzen, 2017 [23] |
| **PFOA** | **Cord blood transcriptome** | Cross-sectional | Newborns, Belgium | Transcription factor enrichment analysis: Progesteron Receptor Signaling; Gene: ICA1; Cell signaling: Natural killar cell signaling | Remy, 2016 [24] |
| **PFOA** | **Metabolic function** | Prospective (Outcome ~ PFOA early pregnancy) | Mothers and children, US (Project Viva) | HOMA-IR (negative), more pronounced in females | Fleish, 2017 [25] |
| **PFOA** | **Adiposity and glucose metabolism** | Prospective | Children followed until young adulthood, Denmark (European Youth Heart Study) | PFOA exposure in childhood was associated with decreased β-cell function at 15 years of age. No associations observed between exposure during adolescence and | Domazet, 2016 [26] |

| Chemical | Endpoint | Epidemiologic design | Population | Statistically significant associations / Findings | First Author + Year of publication |
|---|---|---|---|---|---|
| | | | | indicators of adiposity and glucose metabolism in young adulthood. | |
| **PFOA** | **Adiposity** | Prospective (Outcome ~ PFOA early pregnancy) | Mothers and children, US (Project Viva) | In girls, mid childhood (7 tears): Body mass index (positive), subscapular and triceps skinfold thickness (positive), DXA total fat mass index (positive); no associations for boys and early childhood | Mora, 2017 [27] |
| **PFOA** | **Beta cell deficient diabetes** | Cross-sectional | Adults, US (C8 health project) | Diabetes (negative), strongest for type 1 diabetes | Conway, 2016 [28] |
| **PFOA** | **Glucose tolerance and diabetes** | Cross-sectional | Adults, Taiwan | Potential protective effect against glucose intolerance and the risk of diabetes | Su, 2016 [29] |
| **PFOA** | **Adiposity** | Prospective (Outcome ~ PFOA pregnancy) | Mothers and children, US (HOME study) | Adiposity 8y (positive), waist circumference 8y (positive), BMI gain 2y-8y (positive) | Braun, 2016 [30] |
| | | | | | |

| Chemical | Endpoint | Epidemiologic design | Population | Statistically significant associations / Findings | First Author + Year of publication |
|---|---|---|---|---|---|
| **TCS** | **Blood pressure (BP)** | Prospective birth cohort (Outcome and TCS measured in 3 trimesters of pregnancy) | Pregnant women, China | In the women carrying male fetuses, urinary TCS concentrations were associated with a slight change of SBP during pregnancy. In the women carrying female fetuses, no chemical was associated with SBP, while urinary concentration of triclosan was inversely associated with DBP, though the magnitude was small. | Liu, 2019 [31] |
| **TCS** | **Fetal and early childhood growth** | Prospective birth cohort (Outcome ~ TCS 3 trimesters of pregnancy | Mothers and children, China | Girls: third-trimester estimated fetal weight (increase), 2 year-old weight z-score (increase); early and middle stage of pregnancy may be the windows of vulnerability | Wu, 2019 [32] |
| **TCS** | **Child adiposity** | Prospective birt cohort (Outcome at 8 y ~ TCS during pregancy and annually from 1-5 years and at 8 years) | Mothers and children, US | Girls: Child adiposity at 8y ~ Prenatal triclosan | Kalloo, 2018 [33] |
| **TCS** | **Gestational diabetes (GD) and birth weight** | Cross-sectional | Pregnant women, China | Birth weight (positive, female infants) | Ouyang, 2018 [34] |
| **TCS** | **Fetal growth** | Prospective birth cohort (Outcome ~ TCS during | Mothers and newborns, US (LIFECODES) | Estimated fetal weight and birth weight (negative, male infants) | Ferguson, 2018 [35] |

| Chemical | Endpoint | Epidemiologic design | Population | Statistically significant associations / Findings | First Author + Year of publication |
|---|---|---|---|---|---|
| | | pregnancy) | | | |
| **TCS** | **Gestational diabetes, impaired glucose tolerance, gestational weight gain, fetal markers of metabolic function** | Prospective birth cohort (Outcome ~ TCS first trimester pregnancy) | Mothers and newborns, Canada (MIREC) | No support of an association between triclosan concentrations in pregnancy and fetal metabolic markers, glucose disorders of pregnancy, or excessive gestational weight gain | Shapiro, 2018 [36] |
| **TCS** | **Birth outcomes** | Cross-sectional | Mothers and newborns, China | No statistically significant associations after adjustment for covariates | Huo, 2018 [37] |
| **TCS** | **Adiposity** | Prospective (Outcome up to 15 years ~ TCS 6-8y) | Children followed until 15 y, US | Adiposity (posity, only among overweight girls) | Deierlein, 2017 [38] |
| **TCS** | **Birth outcomes** | Prospective (Outcome ~ TCS 3rd trimester pregnancy) | Mothers and newborns, US | No associations oberserved for TCS | Geer, 2017 [39] |
| **TCS** | **Childhood fat mass** | Prospective (Outcome ~ TCS 3rd trimester pregnancy) | Mothers and children, US | No assosiation observed for TCS | Buckley, 2016 [40] |
| **TCS** | **Birth athropometric measures** | Prospective (Outcome ~ TCS pregnancy) | Mothers and newborns, Denmark (Odense Child Cohort) | Head circumference (negative, boys); abdominal circumference (negative, borderline signifcant boys) | Lassen, 2017 [41] |
| | | | | | |

| Chemical | Endpoint | Epidemiologic design | Population | Statistically significant associations / Findings | First Author + Year of publication |
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| **p,p'-DDE** | **Blood pressure; hypertension** | Repeated measures of Outcome and Exposure 10 years apart | Adults, Sweden (Västerbotten Intervention Programme) | DDE levels were significantly associated with odds of hypertension when BMI was not included in the model as a covariate. | Donat-Vargas, 2018 [42] |
| **p,p'-DDE** | **Type 2 Diabetes** | Prospective (Outcome ~p,p'-DDE 11 years earlier) | Adults, US (Nurses' Health Study II) | T2D (positive, upper vs lower tertile exposure) | Zong, 2018 [43] |
| **p,p'-DDE** | **Body weight; body composition** | Prospective (Outcome 1-2 y ~ p,p'-DDE mother near delivery) | Children, South Africa (VHEMBE) | p,p'-DDT, girls: body composition (positive); body weight (positive) | Coker, 2018 [44] |
| **p,p'-DDE** | **Obesity** | Prospective (Outcome 70-75-80y ~ Exposure 70y) | Adulsts, Sweden (PIVUS) | Fasting glucose (postive), BMI (positive), hypertension (positive) | La Merrill, 2018 [45] |
| **p,p'-DDE** | **Obesity** | Systematic Review; Meta-analysis | 7 Prospective Studies for meta-analysis | BMI z-score (positive) | Cano-Sancho, 2017 [46] |
| **p,p'-DDE** | **Adiposity** | Prospective (Outcome 12y ~ p,p'-DDE prenatal mother) | Children, US (CHAMACOS) | 12y, boys: o,p'-DDT, p,p'-DDT, and p,p'-DDE: BMI z-score (positive) | Warner, 2017 [47] |
| **p,p'-DDE** | **Metabolic Syndrome** | Cross-sectional | Adults, US (Anniston Community Health Survey) | Metabolic Syndrom (positive, for p,p'-DDT across multiple quintiles; for p,p'-DDE for the highest quintile relative to the first) | Rosenbaum, 2017 [48] |
| **p,p'-DDE** | **Gestational diabetes, birth size** | | Pregnant women, Faroe Islands | Gestational diabetes (positive); head circumference (positive) | Valvi, 2017 [49] |

| Chemical | Endpoint | Epidemiologic design | Population | Statistically significant associations / Findings | First Author + Year of publication |
|---|---|---|---|---|---|
| **p,p'-DDE** | **Diabetes** | Cross-sectional | Adults, Canadian Arctic, Adult Inuit Health Survey | Diabetes (positive, highest versus mowest quartile); Fasting glucose (positive, highest versus mowest quartile) | Singh, 2017 [50] |
| **p,p'-DDE** | **Disruption adipose tissue oxidative microenvironment** | Cross-sectional | > 16 years, Spain | lipid peroxidation (TBARS, positive); SOD acitivity (positive) | Artacho-Cordón, 2016 [51] |
| **p,p'-DDE** | **Birth Outcomes** | Cross-sectional | Newborns, China | birth weigth (positive) | Xu, 2017 [52] |
| **p,p'-DDE** | **Metabolomics** | Intervention study | Adults, UK (FoodCAP research project) | Sphingolipids and Glycerophospholipids lipids families were identified and found significantly ($p < 0.05$) different between high and low POPs exposure levels. | Carrizo, 2017 [53] |
| **p,p'-DDE** | **Infant growth** | Cross-sectional | Mothers and newborns, Australia | For the first time no significant association was found between p,p'-DDE concentrations in human milk and infant growth outcomes such as weight, length, head circumference and percentage fat mass. (N = 40) | Du, 2017 [54] |

| Chemical | Endpoint | Epidemiologic design | Population | Statistically significant associations / Findings | First Author + Year of publication |
|---|---|---|---|---|---|
| **p,p'-DDE** | **Cord blood transcriptome** | Cross-sectional | Newborns, Belgium | Transcription factor enrichment analysis: Glucocorticoid Receptor; Pathway Enrichment: 'insulin receptor signaling', 'acute phase response signaling', 'Interleukin(IL)-6 signaling', 'prolactin signaling' | Remy, 2016 [24] |
| **p,p'-DDE** | **Diabetes** | Cross-sectional | Adults, US | Differences in diabetes prevalence between quartiles of exposure | Aminov, 2016 [55] |
| **p,p'-DDE** | **Metabolomics** | Cross-sectional | Adults, Sweden (PIVUS) | The majority of the significant metabolites belong to lipid metabolism pathways and include fatty acids, glycerophospholipids, sphingolipids, and glycerolipids. | Salihovic, 2016 [56] |
| | | | | | |
| **BPA** | **Cardiometabolic impairement** | Case-control | Children and adolescents, Iran | Higher odds ratio of cardiometabolic risk factors | Mansouri, 2019 [57] |
| **BPA** | **Type 2 diabetes** | Case-control | Adults, India | Serum levels of BPA were significantly higher in patients with T2DM compared to control individuals and positively correlated to poor glycemic control and insulin resistance. | Soundararajan, 2019 [58] |

| Chemical | Endpoint | Epidemiologic design | Population | Statistically significant associations / Findings | First Author + Year of publication |
|---|---|---|---|---|---|
| **BPA** | **Birth outcomes** | Prospective (Outcome ~ BPA third trimester mother) | Mothers and newborns, Taiwan | neonatal head circumference (marginally significant) | Chang, 2019 [59] |
| **BPA** | **Metabolic syndrome** | Cross-sectional | Adults, South Korea (Korean National Environmental Health Survey II 2012-2014) | Metabolic syndrome (negative) | Shim, 2019 [60] |
| **BPA** | **Glucose** | Cross-sectional | Adults, China (e-waste recycling and reference area) | Results suggest BPA exposure might be associated with abnormal fasting blood glucose in participants living in e-waste sites | Song, 2019 [61] |
| **BPA** | **Type 2 diabetes** | Case-control | Adults, China | Type 2 diabetes (positive for 2nd and 3rd quartile, but not for 4th quartile) | Duan, 2018 [62] |
| **BPA** | **Type 2 diabetes** | Meta-analysis | 16 studies; 41,320 subjects | Type 2 diabetes (positive) | Hwang, 2018 [63] |
| **BPA** | **Type 1 diabetes** | Case-control | Children, Turkey | No significant association with T1D; Birth Weight (negative) | Rahmani, 2018 [64] |
| **BPA** | **Type 2 diabetes** | Case-control | Adults, Saudi Arabia | Type 2 diabetes (positive (3rd quartile) | Li, 2018 [65] |
| **BPA** | **Insulin resistance** | Intervention study (not wearing and do wearing gloves 1 week) | Women, Korea (Cashiers) | Insulin (positive); Insulin resistance (positive); wearing gloves shown to be protective for exposure levels | Lee, 2018 [66] |

| Chemical | Endpoint | Epidemiologic design | Population | Statistically significant associations / Findings | First Author + Year of publication |
|---|---|---|---|---|---|
| **BPA** | **Glucose levels** | Prospective (Outcome ~ BPA 1st & 2nd trimester) | Pregnant women, US (Lifecodes pregnancy cohort) | No associations in the overall population. Moderately high BPA concentrations were associated with increased glucose levels among overweight/obese women | Bellavia, 2018 [67] |
| **BPA** | **Type 2 diabetes** | Prospective nested case-control study | Adults, China (environment, inflammation and metabolic diseases study (2008-2013)) | BPA is not associated with a 5-year T2D incidence. | Shu, 2018 [68] |
| **BPA** | **Gestational Diabetes** | Prospective | Mothers and newborns, China | Gestational Diabetes (negative); birth weight (negative); ponderal index (negative) | Wang, 2017 [69] |
| **BPA** | **Glucose levels** | Prospective | Subfertile pregnant women, US | Blood glucose (positive) | Chiu, 2017 [70] |
| **BPA** | **Metabolic syndrome** | Cross-sectional | Adults, Prague | There was no significant relation of bisphenol A level to diabetes, hypertension, dyslipidemia, age, and BMI. | Piecha, 2017 [71] |
| **BPA** | **Diabetes** | Cross-sectional | Adult men, Canada | glycated hemoglobin (HbA1c, positive), diabetes melitus (positive) | Stojanoska, 2017 [72] |
| **BPA** | **Metabolism biomarkers** | Prospective (Outcome ~ BPA pregnancy and at | Children 8-14y, Mexico (ELEMENT) | Leptin (positive, boys) | Watkins, 2016 [73] |

| **Chemical** | **Endpoint** | **Epidemiologic design** | **Population** | **Statistically significant associations / Findings** | **First Author + Year of publication** |
|---|---|---|---|---|---|
| | | follow-up) | | | |

Supplementary Table 2: BPA, p,p'-DDE, PFOA, and TCS levels in the Flemish Environment And Health Studies (FLEHS) [74–81]

| Chemical | CAS Number | Study Acronym + link IPCHEM metdata page | Year | Matrix | Unit of Measure | N | N Below LOD/LOQ | FREQ sex | Population | P05 | P10 | P25 | P50 | P75 | P90 | P95 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| BPA | 80-5-7 | FLEHS 3 Ref Adult | 2014 | Urine-spot | µg/L | 194 | 7 | FEMALE , N = 101 ; MALE , N = 93 | Adults | 0.28 | 0.35 | 0.61 | 1.12 | 1.96 | 3.57 | 5.14 |
| BPA | 80-5-7 | FLEHS 3 Ref Adult | 2014 | Urine-spot | µg/g creatinine | 194 | 7 | FEMALE , N = 101 ; MALE , N = 93 | Adults | 0.40 | 0.63 | 1.02 | 1.57 | 2.58 | 4.17 | 6.44 |
| BPA | 80-5-7 | FLEHS 3 Ref Adult | 2014 | Urine-spot | µg/L adjusted for specific gravity (SG) | 194 | 7 | FEMALE , N = 101 ; MALE , N = 93 | Adults | 0.53 | 0.82 | 1.44 | 2.10 | 3.50 | 5.74 | 8.14 |
| | | | | | | | | | | | | | | | | |

| Chemical | CAS Number | Study Acronym + link IPCHEM metdata page | Year | Matrix | Unit of Measure | N | N Below LOD/LOQ | FREQ sex | Population | P05 | P10 | P25 | P50 | P75 | P90 | P95 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PFOA | 335-67-1 | FLEHS 2 Ref Nb | 2008-2009 | Cord blood-plasma | µg/L | 220 | 0 | FEMALE , N = 109 ; MALE , N = 111 | Newbornw | 0.80 | 0.90 | 1.10 | 1.50 | 2.00 | 2.50 | 2.91 |
| PFOA | 335-67-1 | FLEHS 3 Ref Nb | 2013-2014 | Cord blood-plasma | µg/L | 269 | 0 | FEMALE , N = 130 ; MALE , N = 139 | Newbornw | 0.48 | 0.64 | 0.89 | 1.27 | 1.57 | 2.14 | 2.40 |
| PFOA | 335-67-1 | FLEHS 2 Hotspot M | 2010-2011 | Blood Serum | µg/L | 197 | 0 | FEMALE , N = 83 ; MALE , N = 114 | Teenagers | 1.52 | 1.77 | 2.13 | 2.60 | 3.00 | 3.60 | 3.98 |
| PFOA | 335-67-1 | FLEHS 2 Ref Adult | 2008-2009 | Blood Serum | µg/L | 201 | 0 | FEMALE , N = 107 ; MALE , N = 94 | Adults | 1.20 | 1.70 | 2.50 | 3.50 | 4.50 | 5.80 | 6.30 |
| PFOA | 335-67-1 | FLEHS 3 Ref Adult | 2014 | Blood Serum | µg/L | 205 | 0 | FEMALE , N = 108 ; MALE , N = 97 | Adults | 1.20 | 1.59 | 2.13 | 2.94 | 3.69 | 4.89 | 6.31 |

| Chemical | CAS Number | Study Acronym + link IPCHEM metdata page | Year | Matrix | Unit of Measure | N | N Below LOD/LOQ | FREQ sex | Population | P05 | P10 | P25 | P50 | P75 | P90 | P95 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | | |
| p,p'-DDE | 72-55-9 | FLEHS 1 Ref Nb | 2002-2004 | Cord blood-plasma | µg/L | 1114 | 20 | FEMALE , N = 532 ; MALE , N = 582 | Newborns | 0.05 | 0.07 | 0.13 | 0.22 | 0.38 | 0.62 | 0.91 |
| p,p'-DDE | 72-55-9 | FLEHS 1 Ref Nb | 2002-2004 | Cord blood-plasma | µg/g lipid | 1112 | 20 | FEMALE , N = 532 ; MALE , N = 580 | Newborns | 0.03 | 0.04 | 0.06 | 0.11 | 0.19 | 0.33 | 0.51 |
| p,p'-DDE | 72-55-9 | FLEHS 2 Ref Nb | 2008-2009 | Cord blood-plasma | µg/L | 253 | 0 | FEMALE , N = 125 ; MALE , N = 128 | Newborns | 0.06 | 0.07 | 0.09 | 0.15 | 0.24 | 0.38 | 0.52 |
| p,p'-DDE | 72-55-9 | FLEHS 2 Ref Nb | 2008-2009 | Cord blood-plasma | µg/g lipid | 250 | 0 | FEMALE , N = 125 ; MALE , N = 125 | Newborns | 0.03 | 0.03 | 0.05 | 0.07 | 0.13 | 0.20 | 0.27 |

| Chemical | CAS Number | Study Acronym + link IPCHEM metdata page | Year | Matrix | Unit of Measure | N | N Below LOD/LOQ | FREQ sex | Population | P05 | P10 | P25 | P50 | P75 | P90 | P95 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| p,p'-DDE | 72-55-9 | FLEHS 3 Ref Nb | 2013-2014 | Cord blood-plasma | µg/L | 276 | 0 | FEMALE , N = 135 ; MALE , N = 141 | Newborns | 0.04 | 0.05 | 0.06 | 0.10 | 0.16 | 0.29 | 0.49 |
| p,p'-DDE | 72-55-9 | FLEHS 3 Ref Nb | 2013-2014 | Cord blood-plasma | µg/g lipid | 273 | 0 | FEMALE , N = 134 ; MALE , N = 139 | Newborns | 0.02 | 0.03 | 0.04 | 0.06 | 0.09 | 0.14 | 0.27 |
| p,p'-DDE | 72-55-9 | FLEHS 1 Ref Ado | 2003-2004 | Blood Serum | µg/L | 1653 | 1 | FEMALE , N = 778 ; MALE , N = 875 | Teenagers | 0.15 | 0.19 | 0.27 | 0.41 | 0.72 | 1.50 | 2.30 |
| p,p'-DDE | 72-55-9 | FLEHS 1 Ref Ado | 2003-2004 | Blood Serum | µg/g lipid | 1653 | 1 | FEMALE , N = 778 ; MALE , N = 875 | Teenagers | 0.03 | 0.04 | 0.06 | 0.09 | 0.16 | 0.33 | 0.52 |
| p,p'-DDE | 72-55-9 | FLEHS 2 Hotspot GenkZ | 2010 | Blood Serum | µg/L | 196 | 0 | FEMALE , N = 107 ; MALE , N = 89 | Teenagers | 0.08 | 0.10 | 0.13 | 0.19 | 0.30 | 0.54 | 0.75 |

| Chemical | CAS Number | Study Acronym + link IPCHEM metdata page | Year | Matrix | Unit of Measure | N | N Below LOD/LOQ | FREQ sex | Population | P05 | P10 | P25 | P50 | P75 | P90 | P95 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| p,p'-DDE | 72-55-9 | FLEHS 2 Hotspot GenkZ | 2010 | Blood Serum | µg/g lipid | 196 | 0 | FEMALE , N = 107 ; MALE , N = 89 | Teenagers | 0.02 | 0.02 | 0.03 | 0.04 | 0.07 | 0.11 | 0.18 |
| p,p'-DDE | 72-55-9 | FLEHS 2 Hotspot M | 2010-2011 | Blood Serum | µg/L | 197 | 0 | FEMALE , N = 83 ; MALE , N = 114 | Teenagers | 0.08 | 0.10 | 0.13 | 0.19 | 0.32 | 0.54 | 0.75 |
| p,p'-DDE | 72-55-9 | FLEHS 2 Hotspot M | 2010-2011 | Blood Serum | µg/g lipid | 197 | 0 | FEMALE , N = 83 ; MALE , N = 114 | Teenagers | 0.02 | 0.02 | 0.03 | 0.04 | 0.07 | 0.11 | 0.17 |
| p,p'-DDE | 72-55-9 | FLEHS 2 Ref Ado | 2008-2009 | Blood Serum | µg/L | 210 | 0 | FEMALE , N = 89 ; MALE , N = 121 | Teenagers | 0.12 | 0.13 | 0.18 | 0.26 | 0.46 | 0.79 | 1.22 |
| p,p'-DDE | 72-55-9 | FLEHS 2 Ref Ado | 2008-2009 | Blood Serum | µg/g lipid | 208 | 0 | FEMALE , N = 88 ; MALE , N = 120 | Teenagers | 0.02 | 0.03 | 0.04 | 0.06 | 0.11 | 0.19 | 0.30 |

| Chemical | CAS Number | Study Acronym + link IPCHEM metdata page | Year | Matrix | Unit of Measure | N | N Below LOD/LOQ | FREQ sex | Population | P05 | P10 | P25 | P50 | P75 | P90 | P95 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| p,p'-DDE | 72-55-9 | FLEHS 3 Hotspot GKZ | 2013-2014 | Blood Serum | µg/L | 199 | 0 | FEMALE , N = 99 ; MALE , N = 100 | Teenagers | 0.07 | 0.08 | 0.12 | 0.19 | 0.35 | 0.93 | 1.40 |
| p,p'-DDE | 72-55-9 | FLEHS 3 Hotspot GKZ | 2013-2014 | Blood Serum | µg/g lipid | 198 | 0 | FEMALE , N = 99 ; MALE , N = 99 | Teenagers | 0.02 | 0.02 | 0.03 | 0.04 | 0.08 | 0.22 | 0.35 |
| p,p'-DDE | 72-55-9 | FLEHS 3 ref Ado | 2013 | Blood Serum | µg/L | 205 | 1 | FEMALE , N = 111 ; MALE , N = 94 | Teenagers | 0.06 | 0.09 | 0.12 | 0.20 | 0.35 | 0.77 | 1.09 |
| p,p'-DDE | 72-55-9 | FLEHS 3 ref Ado | 2013 | Blood Serum | µg/g lipid | 205 | 1 | FEMALE , N = 111 ; MALE , N = 94 | Teenagers | 0.02 | 0.02 | 0.03 | 0.05 | 0.08 | 0.16 | 0.28 |
| p,p'-DDE | 72-55-9 | FLEHS 1 Ref Adult | 2004-2005 | Blood Serum | µg/L | 1577 | 6 | FEMALE , N = 803 ; MALE , N = 774 | Adults | 0.54 | 0.82 | 1.60 | 2.92 | 5.60 | 9.95 | 13.00 |

| Chemical | CAS Number | Study Acronym + link IPCHEM metdata page | Year | Matrix | Unit of Measure | N | N Below LOD/LOQ | FREQ sex | Population | P05 | P10 | P25 | P50 | P75 | P90 | P95 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| p,p'-DDE | 72-55-9 | FLEHS 1 Ref Adult | 2004-2005 | Blood Serum | µg/g lipid | 1577 | 6 | FEMALE , N = 803 ; MALE , N = 774 | Adults | 0.09 | 0.14 | 0.27 | 0.49 | 0.91 | 1.58 | 2.15 |
| p,p'-DDE | 72-55-9 | FLEHS 3 Ref Adult | 2014 | Blood Serum | µg/L | 206 | 0 | FEMALE , N = 109 ; MALE , N = 97 | Adults | 0.26 | 0.34 | 0.72 | 1.37 | 2.44 | 4.20 | 6.00 |
| p,p'-DDE | 72-55-9 | FLEHS 3 Ref Adult | 2014 | Blood Serum | µg/g lipid | 202 | 0 | FEMALE , N = 105 ; MALE , N = 97 | Adults | 0.05 | 0.06 | 0.13 | 0.24 | 0.38 | 0.64 | 1.05 |
| | | | | | | | | | | | | | | | | |
| TCS | 3380-34-5 | FLEHS 2 Ref Ado | 2008-2009 | Urine-morning urine | µg/L | 197 | 0 | FEMALE , N = 84 ; MALE , N = 113 | Teenagers | 0.22 | 0.30 | 0.56 | 1.29 | 4.89 | 63.52 | 152.49 |

| Chemical | CAS Number | Study Acronym + link IPCHEM metdata page | Year | Matrix | Unit of Measure | N | N Below LOD/LOQ | FREQ sex | Population | P05 | P10 | P25 | P50 | P75 | P90 | P95 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TCS | 3380-34-5 | FLEHS 2 Ref Ado | 2008-2009 | Urine-morning urine | µg/g creatinine | 196 | 0 | FEMALE , N = 84 ; MALE , N = 112 | Teenagers | 0.17 | 0.20 | 0.37 | 0.92 | 3.71 | 48.50 | 97.48 |
| TCS | 3380-34-5 | FLEHS 2 Ref Ado | 2008-2009 | Urine-morning urine | µg/L adjusted for specific gravity (SG) | 196 | 0 | FEMALE , N = 84 ; MALE , N = 112 | Teenagers | 0.27 | 0.33 | 0.62 | 1.35 | 5.16 | 68.32 | 166.97 |
| TCS | 3380-34-5 | FLEHS 3 Ref Adult | 2014 | Urine-spot | µg/L | 194 | 23 | FEMALE , N = 101 ; MALE , N = 93 | Adults | | | 0.18 | 0.39 | 1.30 | 12.08 | 46.12 |
| TCS | 3380-34-5 | FLEHS 3 Ref Adult | 2014 | Urine-spot | µg/g creatinine | 194 | 23 | FEMALE , N = 101 ; MALE , N = 93 | Adults | | | 0.23 | 0.59 | 1.65 | 18.23 | 71.88 |

| Chemical | CAS Number | Study Acronym + link IPCHEM metdata page | Year | Matrix | Unit of Measure | N | N Below LOD/LOQ | FREQ sex | Population | P05 | P10 | P25 | P50 | P75 | P90 | P95 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TCS | 3380-34-5 | FLEHS 3 Ref Adult | 2014 | Urine-spot | µg/L adjusted for specific gravity (SG) | 194 | 23 | FEMALE , N = 101 ; MALE , N = 93 | Adults | | | 0.35 | 0.73 | 2.11 | 20.53 | 103.60 |

Legend: N = Number of samples; LOD = Limit of Detection; LOQ = Limit of Quantification; FREQ = Frequency table; P05, P10, P25, P50, P75, P90, P95 = 5$^{th}$, 10$^{th}$, 25$^{th}$, 50$^{th}$, 75$^{th}$, 90$^{th}$, 95$^{th}$ percentile respectively

Supplementary Table 3: Human biomonitoring data on TBT and TPP obtained from literature.

| Chemical | CAS Number | Country Name | Year | Population | Matrix | Unit of Measure | Number of Samples | Median | First Author + Year of Publication |
|---|---|---|---|---|---|---|---|---|---|
| DPHP | 838-85-7 | China | 2016-2017 | e-waste dismantling area, pregnant women | Maternal Urine | μg/L | 15 | 1.2 | Bai, 2019 [82] |
| DPHP | 838-85-7 | China | 2016-2017 | e-waste dismantling area, pregnant women | Amnionic Fluid | μg/L | 15 | 0.18 | Bai, 2019 [82] |
| DPHP | 838-85-7 | China | 2016 | Children and adults | Urine, first morning | μg/L | 323 | 0.3 | Zhang, 2018 [83] |
| DPHP | 838-85-7 | US | 2016 | Toddlers | Urine | μg/L adjusted for SG | 21 | 3.4 | Thomas, 2017 [84] |
| DPHP | 838-85-7 | US | 2016 | Toddlers | Urine | μg/L adjusted for SG | 20 | 8.2 | Thomas, 2017 [84] |
| DPHP | 838-85-7 | China | 2015 | Pregnant women | Urine | μg/L | 23 | 0.83 | Feng, 2016 [85] |
| TPP | 115-86-6 | US | 2014 | Adults | Hair | ng/g | 50 | 220 | Liu, 2016 [86] |
| TPP | 115-86-6 | US | 2014 | Adults | Fingernail | ng/g | 50 | 370 | Liu, 2016 [86] |
| TPP | 115-86-6 | US | 2014 | Adults | Toenail | ng/g | 50 | 1080 | Liu, 2016 [86] |
| | | | | | | | | | |
| TBT | 1461-22-9 | US | 1998 | Adults | Blood | μg/L | 32 | 5.8 | Kannan, 1999 [87] |
| TBT | 1461-22-9 | Denmark | 1997-2001 | Newborn | Placenta | ng/g fw | 129 | 0.01 | Rantakokko, 2013 [88] |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TBT | 1461-22-9 | Finland | 1997-2001 | Newborn | Placenta | ng/g fw | 56 | 0.38 | Rantakokko, 2013 [88] |

Supplementary Table 4**.** Examples of (Q)SAR models predicting activity related to nuclear receptors involved in metabolic disruption by MDCs

| Nuclear Receptor | Method | Dataset | Data type | Chemical domain | statistics | references |
|---|---|---|---|---|---|---|
| PPAR$\alpha$ | multiple linear regressions (MLR) and partial least squares (PLS) | 46 | pEC50 | phenylpropanoic acid derivatives | Training: $R^2$ = 0.784, $Q^2$= 0.774, Test: $R^2$= 0.841 | Verma and Chouhan, 2016 [89] |
| | Multivariate Data Analysis | 71 | gene transactivation data (expressed as EC50) | carboxylic acid derivatives | Training: $R^2$ = 0.721, $Q^2$= 0.476, Blind test: Residuals $\Delta$ <1.5 | Vallianatou, 2013 [90] |
| PPAR$\gamma$ | 3D-QSAR | 170 | pEC50 | PPAR$\gamma$ full agonists | Training: $R^2$ = 0.821, $Q^2$= 0.610, Test: $R^2$ = 0.552 | Al Sharif, 2017 [91] |
| PXR | k-nearest neighbor (k-NN) | 2724 | competing potency to hPXR | various chemicals | Training: Ac = 0,708 Sp= 0,704 Se= 0,702 | Yin, 2017 [92] |
| | partial logistic regression | 631 | human PXR binding assay | environmental chemicals | Training: Ac = 0,835 Sp= 0,85 Se= 0,82 Test: Ac= 0,696 Sp=0,839 Se=0,579 | Dybdahl, 2012 [93] |
| CAR | 3D-QSAR | 35 | reporter gene assay with HepG2 cells transfected | Various chemicals (including bisphenol A and | Training: $R^2$ = 0,99, $Q^2$= 0.74, Test: $R^2$= 0.71 | Kato, 2017 [94] |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | with a chimerical construct of hCAR (hCAR1þA | triphenyl phosphate) | | |
| LXRα | multidimentional QSAR | 52 | LXR binding affinity | heterocyclic phenylacetic acid compounds and compounds derived from podocarpic acid | Training set: $R^2$=0,849 Test set: $R^2$= 0,744 | (Spreafico, 2010)[95] |
| LXRβ | stepwise method combined with linear discriminant analysis | 41 | ABCA1 promoter activation assay | ABCA1 up-regulators | Within domain: Q = 100%, Sp= 100% Se= 100% | Chen, 2018a [96] |
| FXR | k-nearest neighbors based on molecular fingerprints | 1224 | qHTS assays for agonists and antagonists of FXR | Various chemicals | Training: Ac = 0,76 Sp= 0,80 Se= 0,73 Test: Ac=0,79 Sp=0,77 Se=0,90 | Chen, 2018b [97] |
| | Structural fragments | 103 | FXR-bla transactivation assay and FXR-SRC2 coactivator assay | avermectin anthelmintics, dihydropyridine calcium channel blockers, 1,3-indandione rodenticides, and | area under the receiver operating characteristic (AUC-ROC) >0.78 (AUC≤0.5 for random data) | Hsu, 2016 [98] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | pyrethroid pesticides |

Ac: predictive accuracy, Sp: specificity, Se: sensitivity

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