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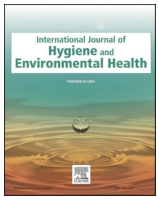

Exposure of Swedish adolescents to elements, persistent organic pollutants (POPs), and rapidly excreted substances – The Riksmaten adolescents 2016-17 national survey

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ABSTRACT

Adolescence is a period of significant physiological changes, and likely a sensitive window to chemical exposure. Few nation-wide population-based studies of chemical body burdens in adolescents have been published. In the national dietary survey Riksmaten Adolescents (RMA) 2016–17, over 13 chemical substance groups, including elements, chlorinated/brominated/fluorinated persistent organic pollutants (POPs) were analysed in blood, and in urine metabolites of phthalates/phthalate alternatives, phosphorous flame retardants, polycyclic aromatic hydrocarbons (PAHs), and pesticides, along with bisphenols and biocide/preservative/antioxidant/UV filter substances (N = 1082, ages 11–21). The aim was to characterize the body burdens in a representative population of adolescents in Sweden, and to compare results with human biomonitoring guidance values (HBM-GVs). Cluster analyses and Spearman's rank order correlations suggested that concentrations of substances with known common exposure sources and similar toxicokinetics formed obvious clusters and showed moderate to very strong correlations ($r \geq 0.4$). No clusters were formed between substances from different matrices. Geometric mean (GM) concentrations of the substances were generally less than 3-fold different from those observed among adolescents in NHANES (USA 2015–16) and GerES V (Germany 2014–17). Notable exceptions were brominated diphenyl ethers (PBDEs) with >20-fold lower GM concentrations, and the biocide triclosan and ultraviolet (UV) filter benzophenone-3 with >15-fold lower mean concentrations in RMA compared to NHANES. Exceedance of the most conservative HBM-GVs were observed for aluminium (Al, 26% of subjects), perfluorooctanesulfonic acid (PFOS, 19%), perfluorooctanoic acid (PFOA, 12%), lead (Pb, 12%), MBP (dibutyl phthalate metabolite, 4.8%), hexachlorobenzene (HCB, 3.1%) and 3-phenoxybenzoic acid (PBA, pyrethroid metabolite, 2.2%). Males showed a higher proportion of exceedances than females for Pb, HCB and PFOS; otherwise no gender-related differences in exceedances were observed. A higher proportion of males than females had a Hazard Index (HI) of substances with liver and kidney toxicity and neurotoxicity >1. Industrialized countries with similarly high standards of living, with some exceptions, show comparable average body burdens of a variety of toxic chemicals among adolescents from the general population. The exceedances of HBM-GVs and HIs strongly suggests that further efforts to limit chemical exposure are warranted.

1. Introduction

Chemicals are used in almost every aspect of society and are found ubiquitously in human exposure media, including food, drinking water, air, dust, and consumer products. There are currently over 26,000 unique substances registered with the European Chemicals Agency, of which approximately 1000 are considered potential endocrine

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Abbreviations

Al	aluminium
BBOEP	bis(2-butoxyethyl) phosphate
BBzP	butylbenzyl phthalate
BHA	3-tert-butyl-4-hydroxyanisole
BMDL1%	benchmark dose of 1% risk
BPS	bisphenol S
BPA	bisphenol A
BP3	benzophenone-3
Cd	cadmium
Co	cobalt
Cr	chromium
br-PFOS	branched perfluorooctanesulfonic acid
CNS	central nervous system
cx-MiDP	mono-carboxy-isononyl phthalate
cx-MiNP	mono-(4-methyl-7-carboxyheptyl) phthalate
cx-MINCH	cyclohexane-1,2-dicarboxylate-mono (7-carboxylate-4-methyl)heptylester
DBP	dibutyl phosphate
p,p'-DDE	1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene
p,p'- DDT	dichlorodiphenyltrichloroethane
DEP	diethyl phthalate
DEHP	diethylhexyl phthalate
DiDP	diiso-decyl phthalate
DiNCH	diisononyl-cyclohexane-1,2-dicarboxylate
DiNP	diiso-nonyl phthalate
DPHP	dipropylheptyl phthalate
EFSA	The European Food Safety Authority
GC-MS/MS	gas chromatography – triple quadrupole mass spectrometry
GM	geometric mean
HBM-GVs	human biomonitoring guidance values
HCB	hexachlorobenzene
HCH	hexachlorocyclohexane
Hg	mercury
HI	Hazard Index
HR	Hazard Ratio
ICP-MS	inductively coupled plasma mass spectrometry
LOD	limit of detection
LOQ	limit of quantification
L-PFOS	linear perfluorooctanesulfonic acid
L-PFHxS	linear perfluorohexanesulfonic acid
L-PFOA	linear perfluorooctanoic acid
MEHP	mono(2-ethylhexyl) phthalate
MEP	monoethyl phthalate
Mn	manganese
MBP	monobutyl phthalate
Ni	nickel
OCPs	organochlorine pesticides/metabolites
OH-MiNP	mono-(4-methyl-7-hydroxyoctyl) phthalate
OH-MINCH	cyclohexane-1,2-dicarboxylate-mono-(7-hydroxy-4-methyl)octyl ester
OH-MPHP	6-hydroxy monopropylheptyl phthalate
oxo-MiNP	mono-(4-methyl-7-oxooctyl) phthalate
PAHs	polycyclic aromatic hydrocarbons
PBDEs	polybrominated diphenyl ethers
PCBs	polychlorinated biphenyls
Pb	lead
PFDA	perfluorodecanoic acid
PFNA	perfluorononanoic acid
PFUnDA	perfluoroundecanoic acid
PFAS	per- and polyfluoroalkyl substances
PFOA	perfluorooctanoic acid
PFOS	perfluorooctanesulfonic acid
POPs	persistent organic pollutants
RMA	Riksmaten Adolescents
Se	selenium
SFA	Swedish Food Agency
TPP	triphenyl phosphate
TBEP	tri(2-butoxyethyl) phosphate
TCS	triclosan
TCP	trichloropyridinol
UBA	German Environment Agency
UPLC	ultra performance liquid chromatograph
US	United States
UV	ultraviolet
1-HP	1-hydroxy-pyrene
2-OH-PH	2-hydroxy-phenanthrene
3-PBA	3-phenoxybenzoic acid
4,4-BPF	bisphenol F
5-cx-MEPP	mono-(2-ethyl-5-carboxypentyl) phthalate
5-OH-MEHP	mono-(2-ethyl-5-hydroxyhexyl) phthalate
5-oxo-MEHP	mono-(2-ethyl-5-oxohexyl) phthalate

disrupting compounds (ECHA, 2022; Street et al., 2018). Furthermore, approximately 1000 new chemicals are registered with the United States Environmental Protection Agency per year (EPA, 2022), often with unknown or poorly understood safety profiles. Many chemicals are known to interfere with the human hormonal system and have previously been associated with a wide range of negative health consequences including neurologic, reproductive and other physiological effects (Braun, 2017; Wan et al., 2021; Yilmaz et al., 2020). Thus, considering both the number and effects of chemicals to which humans are exposed, understanding the variation of chemical mixture exposures within human populations (i.e., the chemical 'exposome') is of great importance.

Most studies examining human exposure to chemicals focus on single compound groups, such as elements, per- and polyfluoroalkyl substances (PFAS) and polychlorinated biphenyls (PCBs) (Marques et al., 2021; Preston et al., 2020; Roth et al., 2021), with few looking at the wider part of the chemical exposome. In reality, human exposure to chemicals is a complex process which involves multiple substances and pathways. Combination toxicity may occur when multiple chemicals occurring at sufficiently high concentrations act on a common endpoint to elicit an effect (Kortenkamp, 2014). In general, such mixtures may elicit a combination effect by either 'concentration addition' or 'independent action', although synergistic or antagonistic effects are also possible, albeit less frequently observed in experimental studies (Martin et al., 2021). 'Concentration addition' occurs when a toxicity threshold is exceeded by the sum concentration of multiple chemicals with the same mechanism/mode of action. In comparison, 'independent action' may occur when chemicals with different modes-of-action reach their individual toxicity thresholds on the same endpoint, thus eliciting a toxic effect (Kortenkamp, 2014). Concentration addition presents a unique challenge to risk assessors because individual toxic compounds may not be found in sufficiently high concentrations in study populations to pass observable health-risk thresholds, but may exceed such thresholds in combination with other chemicals sharing the same mechanism/mode of action. Further layers of complexity arise whereby chemical substances with independent modes of action can still share the same adverse health effects (Christiansen et al., 2020).

Biomonitoring of chemical body burdens in blood and urine provides valuable information about cumulative exposure at the time of sampling. Adolescence is likely a sensitive developmental window to

chemical exposure due to the significant physiological changes that occur. Nevertheless, few nation-wide studies have been published on adolescent exposure to a broad range of chemicals. The few well-known examples include NHANES in the United States (US) and GerES V in Germany (GerES, 2021; NHANES, 2022). Additionally, FLEHS IV in Belgium (Schoeters et al., 2022) represents another similar (albeit regional) study on the chemical exposome of adolescents. These studies, to the best of our knowledge, have not fully investigated the correlations between exposure of adolescents to the measured substances/substance groups. Knowledge of such correlations, which may be due to common exposure sources and/or similarities in toxicokinetics, are crucial when interpreting associations between health outcomes and body burdens of chemical mixtures. The previous studies have compared the observed concentrations of measured chemicals with human biomonitoring guidance values (HBM-GVs), in order to identify the chemicals with concern for adolescent health. However, they have not investigated possible gender and age differences in this context, which may be important for health development during this period of rapid physiological change. Moreover, to the best of our knowledge, no such study has attempted to investigate possible combination toxicity risks with substances with common target organs.

The overall aim of the present study is to characterize the body burdens of over 60 different substances across 13 chemical substance groups (elements (e.g., heavy metals), chlorinated, brominated, and fluorinated persistent organic pollutants (POPs), phthalates, phthalate alternatives, bisphenols, phosphorous flame retardants, polyaromatic hydrocarbons (PAH), pesticides, biocides/preservatives and UV-filters) in Swedish adolescents. To address this goal, we compared measured concentrations in whole blood, serum and urine to those reported in similar studies from the United States, Germany and the Flanders region of Belgium. We also examined correlations among individual substances, in an attempt to identify shared sources of exposure. Finally, we compared measured concentrations to published HBM-GVs and determined Hazard Indices in an effort to assess cumulative health risk (Kortenkamp and Faust, 2010).

2. Method

2.1. Study group and design

The study population was a sub-sample of Riksmaten Adolescents 2016–17 (RMA), a cross-sectional national population-based study of dietary habits and chemical exposure of Swedish adolescents, conducted by the Swedish Food Agency (SFA). Details about the recruitment process, study design and data collection are described elsewhere (Moraeus et al., 2018). Briefly, 619 schools were invited, being representative of the entire country across the 5th (median age, range: 11 years, 10–13), 8th (14 years, 11–15) and 11th (17 years, 16–21) school grades. Of these schools, 259 were invited to participate in the biomonitoring part, with 62 school classes across 57 unique schools opting-in (Moraeus et al., 2018) (Fig. S1, supplement). In total, 1305 students, out of 2377 invited, accepted to be sampled and 1082 had sufficient biomonitoring data to be included in our analysis (Table 1 & Table S1, Supplement). The study design included online-based questionnaires (RiksmatenFlexQ) addressing background factors such as age and gender (Moraeus et al., 2018).

2.2. Ethics

Ethical approval was obtained from the Regional Ethical Review Board in Uppsala (No 2015/190). Participants in grades 8 and 11 gave written informed consent to participate in the study, whilst legal guardians gave consent for 5th graders.

Table 1
Gender differences in substance concentrations among RMA participants.

Substances[a]		Geometric mean (95% CI)			p-value[b]
Abbreviation	Unit/ Matrix	Male (N = 476)	Female (N = 606)	Total (N = 1082)	
Cr	µg/L whole blood	0.58 (0.57–0.60)	0.55 (0.54–0.57)	0.57 (0.56–0.58)	0.092
Mn	µg/L whole blood	10.1 (9.67–10.4)	11.0 (10.7–11.2)	10.6 (10.3–10.8)	<0.001
Co	µg/L whole blood	0.11 (0.10–0.11)	0.14 (0.14–0.15)	0.13 (0.12–0.13)	<0.001
Ni	µg/L whole blood	0.62 (0.61–0.64)	0.62 (0.61–0.64)	0.62 (0.61–0.63)	0.466
Se	µg/L whole blood	94.7 (91.8–97.7)	95.0 (93.9–96.1)	94.8 (93.4–96.3)	0.141
Cd	µg/L whole blood	0.11 (0.11–0.12)	0.13 (0.13–0.14)	0.12 (0.12–0.13)	<0.001
Hg	µg/L whole blood	0.75 (0.69–0.81)	0.60 (0.56–0.64)	0.66 (0.63–0.69)	<0.001
Pb	µg/L whole blood	8.17 (7.77–8.58)	6.72 (6.49–6.97)	7.32 (7.11–7.55)	<0.001
HCB	pg/mL serum	47.3 (45.8–48.9)	38.5 (37.3–39.8)	42.2 (41.2–43.2)	<0.001
p,p'-DDE	pg/mL serum	124 (115–133)	99.7 (93.2–107)	110 (104–115)	<0.001
PCB-118	pg/mL serum	7.01 (6.67–7.36)	6.41 (6.14–6.70)	6.67 (6.45–6.89)	0.006
PCB-138	pg/mL serum	30.3 (28.6–32.2)	23.3 (22.1–24.6)	26.2 (25.2–27.2)	<0.001
PCB-153	pg/mL serum	49.0 (46.1–52.1)	36.9 (34.9–39.0)	41.8 (40.0–43.6)	<0.001
PCB-170	pg/mL serum	13.7 (12.8–14.7)	9.86 (9.24–10.5)	11.4 (10.9–12.0)	<0.001
PCB-180	pg/mL serum	27.7 (25.7–29.8)	19.7 (18.5–21.1)	22.9 (21.8–24.1)	<0.001
PCB-187	pg/mL serum	6.14 (5.71–6.61)	4.49 (4.20–4.80)	5.15 (4.90–5.41)	<0.001
L-PFOA	ng/g serum	1.26 (1.21–1.31)	1.17 (1.13–1.22)	1.21 (1.18–1.25)	0.001
PFNA	ng/g serum	0.39 (0.37–0.41)	0.34 (0.32–0.35)	0.36 (0.35–0.37)	<0.001
PFDA	ng/g serum	0.15 (0.14–0.16)	0.15 (0.14–0.16)	0.15 (0.14–0.16)	0.219
L-PFHxS	ng/g serum	0.55 (0.50–0.61)	0.39 (0.36–0.42)	0.45 (0.43–0.48)	<0.001
L-PFOS	ng/g serum	2.43 (2.29–2.59)	1.92 (1.82–2.03)	2.13 (2.05–2.22)	<0.001
br-PFOS	ng/g serum	1.12 (1.05–1.19)	0.85 (0.80–0.90)	0.96 (0.92–1.00)	<0.001
MEP	ng/mL urine	31.5 (28.8–34.6)	51.0 (46.4–56.2)	41.3 (38.6–44.2)	<0.001
MBP	ng/mL urine	38.9 (36.5–41.3)	43.7 (41.6–45.9)	41.5 (39.9–43.1)	0.001
MBzP	ng/mL urine	6.33 (5.73–6.99)	7.61 (6.98–8.30)	7.02 (6.57–7.49)	0.006
MEHP	ng/mL urine	1.61 (1.52–1.71)	1.82 (1.72–1.93)	1.73 (1.66–1.80)	0.005
5OH-MEHP	ng/mL urine	7.81 (7.35–8.29)	8.19 (7.69–8.73)	8.02 (7.67–8.38)	0.230
5oxo-MEHP	ng/mL urine	5.98 (5.62–6.37)	6.69 (6.31–7.10)	6.37 (6.10–6.65)	0.033
5cx-MEPP	ng/mL urine	6.80 (6.39–7.24)	7.69 (7.25–8.16)	7.29 (6.98–7.61)	0.010
2cx-MEHP	ng/mL urine	2.05 (1.92–2.18)	2.18 (2.06–2.32)	2.12 (2.03–2.22)	0.120
OH-MiNP	ng/mL urine	4.23 (3.89–4.61)	4.93 (4.52–5.38)	4.61 (4.33–4.91)	0.042
oxo-MiNP	ng/mL urine	1.94 (1.79–2.09)	2.34 (2.16–2.54)	2.15 (2.04–2.28)	0.001

(continued on next page)

Table 1 (*continued*)

Substances[a]		Geometric mean (95% CI)			p-value[b]
Abbreviation	Unit/ Matrix	Male (N = 476)	Female (N = 606)	Total (N = 1082)	
cx-MiNP	ng/mL urine	6.34 (5.84–6.88)	7.89 (7.27–8.57)	7.17 (6.76–7.60)	0.001
cx-MiDP	ng/mL urine	0.36 (0.34–0.39)	0.44 (0.42–0.47)	0.41 (0.39–0.43)	<0.001
OH-MPHP	ng/mL urine	1.07 (1.00–1.15)	1.16 (1.08–1.24)	1.12 (1.07–1.18)	0.189
oxo-MiNCH	ng/mL urine	1.20 (1.07–1.33)	1.36 (1.24–1.50)	1.29 (1.20–1.38)	0.032
cx-MINCH	ng/mL urine	0.88 (0.78–0.98)	1.01 (0.92–1.12)	0.95 (0.88–1.03)	0.034
OH-MINCH	ng/mL urine	0.92 (0.82–1.03)	0.99 (0.89–1.10)	0.96 (0.89–1.03)	0.321
DPP	ng/mL urine	1.82 (1.71–1.93)	2.13 (2.01–2.25)	1.99 (1.91–2.07)	0.001
DBP	ng/mL urine	0.13 (0.12–0.14)	0.17 (0.15–0.18)	0.15 (0.14–0.16)	<0.001
BPA	ng/mL urine	0.87 (0.80–0.95)	0.88 (0.81–0.95)	0.88 (0.83–0.93)	0.536
BPS	ng/mL urine	0.12 (0.11–0.13)	0.16 (0.15–0.18)	0.14 (0.14–0.15)	<0.001
4,4BPF	ng/mL urine	0.09 (0.08–0.11)	0.11 (0.10–0.13)	0.10 (0.09–0.11)	0.026
2-OH-PH	ng/mL urine	0.16 (0.15–0.17)	0.17 (0.16–0.19)	0.17 (0.16–0.18)	0.160
TCP	ng/mL urine	1.24 (1.16–1.31)	1.35 (1.28–1.43)	1.30 (1.25–1.35)	0.021
3-PBA	ng/mL urine	0.27 (0.25–0.29)	0.29 (0.28–0.31)	0.28 (0.27–0.30)	0.029
TCS	ng/mL urine	0.25 (0.23–0.29)	0.33 (0.30–0.37)	0.30 (0.27–0.32)	0.002
BHA	ng/mL urine	0.27 (0.21–0.36)	1.33 (1.05–1.69)	0.66 (0.55–0.80)	<0.001
BP3	ng/mL urine	0.64 (0.56–0.73)	1.56 (1.35–1.81)	1.05 (0.95–1.17)	<0.001

[a] Substances with over 50% of samples < LOQ or LOD are not included in this table. For the purpose of calculating geometric means and 95% confidence intervals (CI), determined concentrations < LOQ or < LOD were used and concentrations determined to be 0 were converted to the lowest concentration above 0 divided by sqrt(2) (see section Handling of data below LOQ/LOD). When LOD was available PFAS concentrations < LOD were converted to LOD/sqrt(2), else concentrations < LOQ were converted to LOQ/sqrt(2).

[b] Wilcoxon rank sum test on comparison of concentrations by gender. p-values <0.05 indicate significant difference of concentration between genders.

2.3. Sample collection

One single-spot non-fasting blood and urine sample, along with anthropometric data, were collected from each participant by trained staff during school visits on weekdays throughout 2016 (September)-2017 (May). Blood samples (10 ml) for serum were collected in Vacutainer serum tubes with coagulation activator (Becton Dickinson, article # 367896, Sweden), centrifuged at 1500×*g* for 10 min and then aliquoted to cryotubes. Whole blood samples (4 ml) were collected in lithium-heparin Vacuette tubes (Greiner Bio-one, article# 454056, Germany). Urine samples were collected in acetone-rinsed paper cups by the individual participants during the school visit, and these samples were then aliquoted to polypropylene tubes. All aforementioned samples were promptly frozen at −20 °C at the site of collection and shipped frozen to the SFA where they were stored at −80 °C until being sent to external laboratories for analysis. None of the samples analysed in this study had known disruptions in the cold chain.

2.4. Sample analysis

Full names and abbreviations of the analysed substances, CAS numbers, and their main uses are provided in Table S2 (Supplement). Decisions on inclusion of substances were made by experts from the SFA at the time of study design and were based on toxic properties of the substances and presence in food and/or drinking water. Some essential/suspected essential elements were also included based on suspected interactions with non-essential toxic elements in the body (chromium (Cr), manganese (Mn), selenium (Se), cobalt (Co)) (Table S2, supplement).

2.5. Elements

Samples were analysed for Cr, Mn, Co, nickel (Ni), Se, cadmium (Cd), mercury (Hg), lead (Pb), and aluminium (Al) by the Department of Laboratory Medicine, Lund University, Lund, Sweden (Table S2, Supplement). Concentrations of Pb, Cd and Hg in RMA have been published previously (Almerud et al., 2021). Sample analyses were performed in duplicate. In short, the samples were treated as previously described (Barany et al., 1997). The concentrations were determined by inductively coupled plasma mass spectrometry (ICP-MS; iCAP Q, Thermo Fisher Scientific, Bremen, GmbH) equipped with collision cell with kinetic energy discrimination and helium as collision gas. The limit of detection (LOD) varied from 0.05 to 5.0 μg/L. Method precision varied from 2.8 to 15% depending on analyte.

2.6. PCBs, organochlorine pesticides/metabolites (OCPs) and polybrominated diphenyl ethers (PBDEs)

The Department of Health Security, National Institute for Health and Welfare, Kuopio, Finland analysed the chlorinated and brominated POPs in serum (Table S2, Supplement) as described previously (Gasull et al., 2019). Some results from the analyses have been published previously (Zamaratskaia et al., 2022). In brief, concentrations were measured using gas chromatography – triple quadrupole mass spectrometry (GC-MS/MS). The instrument used was an Agilent 7010 GC-MS/MS system (Wilmington, DE, U.S.), GC column DB5MS UI (J&W Scientific, 20m, ID 0.18 mm, 0.18 μm). Limits of quantification (LOQ) ranged from 5 pg/mL for PCB congeners and trans-nonachlor to 40 pg/mL for 1, 1-dichloro-2,2-bis(p-chlorophenyl)ethylene (p,p'-DDE). Two blank samples and two control samples (NIST SRM 1958) were included in each batch of samples. Measured concentrations of chlorinated and brominated POPs in SRM1958 were 80–105% of the certified/reference concentrations. The coefficient of variation (CV%) from SRM 1958 (n = 18) was <3.6% for all compounds.

2.7. PFAS

Serum samples were analysed for PFASs by the Department of Environmental Science, Stockholm University, Sweden (Table S2, Supplement). Details of the extraction and instrumental analysis are described in Nyström et al. (2022). Briefly, samples were fortified with a suite of isotopically-labelled internal standards and then extracted twice with acetonitrile in an ultrasonic bath, followed by clean-up with acidified graphitized carbon. The cleaned-up extract was diluted and fortified with volumetric standards and thereafter stored at −20 °C prior to analysis. Instrumental analysis was carried out on a Acquity ultra performance liquid chromatograph coupled to a Waters Xevo TQS triple quadrupole mass spectrometer operated in negative electrospray ionisation, multiple reaction monitoring mode. Quantification was based on isotope dilution or an internal standard approach (see Nyström et al. (2022) for details). LOQs are summarized in Table S3 (Supplement). In the present study only data on selected perfluoroalkyl acids: linear perfluorooctanoic acid (L-PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), linear perfluorohexanesulfonic acid (L-PFHxS), branched and linear perfluorooctanesulfonic acid (br-PFOS, L-PFOS), were used due to the low detection frequency of other PFASs analysed in RMA (Nyström et al., 2022).

2.8. Substances measured in urine

Analyses were performed at the Department of Laboratory Medicine, Lund University, Sweden, as previously described (Alhamdow et al., 2017; Cequier et al., 2014; Liljedahl et al., 2021) with some modifications. In brief, the samples were analysed on a liquid chromatography triple quadrupole mass spectrometry (LC-MS/MS; QTRAP 5500, AB Sciex, Framingham, MA, USA). Two urinary quality control samples were included in the analysis, one authentic and one spiked. The CV% calculated from QC samples included in all sample batches (N = 34) as a between-run precision, did not exceed 20% for almost all compounds with the exception of mono-carboxy-isononyl phthalate (cx-MiDP, 27% at concentration of 0.6 ng/mL), bisphenol S (BPS, 25% at concentration of 0.8 ng/mL), dibutyl phosphate (DBP, 41% at concentration of 0.1 ng/mL) and 3-tert-butyl-4-hydroxyanisole (BHA, 21% at concentration of 0.8 ng/mL). The analyses of bisphenol A (BPA), 1-hydroxy-pyrene (1-HP), benzophenone-3 (BP3), triclosan (TCS), 3-phenoxybezoic acid (3-PBA), trichloropyridinol (TCP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (5-OH-MEHP), mono-(2-ethyl-5-oxohexyl) phthalate (5-oxo--MEHP), is part of G-EQUAS inter-laboratory control program (University of Erlangen-Nuremberg, Germany). The laboratory also participates in the HBM4EU QA/QC program, and has qualified as HBM4EU laboratory for the analysis of: BPA, BPS, BPF, 1-HP, monobenzyl phthalate (MBzP), mono-(2-ethylhexyl) phthalate (MEHP), 5-OH-MEHP, 5-oxo--MEHP, mono-(2-ethyl-5-carboxypentyl) phthalate (5-cx-MEPP), mono-(4-methyl-7-hydroxyoctyl) phthalate (OH-MiNP), mono-(4-methyl-7-oxooctyl) phthalate (oxo-MiNP), mono-(4-methyl-7-carboxyheptyl) phthalate (cx-MiNP), cyclohexane-1,2-dicarboxylate-mono (7-carboxylate-4-methyl)heptylester (cx-MINCH), cyclohexane-1,2-dicarboxy late-mono-(7-hydroxy-4-methyl)octyl ester (OH-MINCH). Urine concentrations were adjusted for individual differences in urine density in the RMA population as described by (Carnerup et al., 2006). LODs are summarized in Table S4 (Supplement).

2.9. Handling of data below LOQ/LOD

The number of samples with concentrations below LOQ/LOD for each substance are presented in Tables S3 and S4 (Supplement). Except for PFASs, concentrations below LOQ or LOD were handled as previously described (Darnerud et al., 2015; Gyllenhammar et al., 2017; Svensson et al., 2021). Briefly, concentrations above 'background noise' in the analyses were determined to the concentration estimated in the analytical run. When a concentration was estimated not to be above 'background noise' in the chemical analyses, the concentration was set to zero (AMC, 2001). In the case of PFAS, concentrations below LOQ but above LOD were used when available, while concentrations below LOD were set to zero. Concentrations determined to be below LOD or LOQ are more uncertain and should be regarded as semi-quantitative. Nevertheless, the use of these determined concentrations in statistical analyses, as opposed to using substituted or imputed data, is generally considered to result in less statistical bias (AMC, 2001; Bergstrand and Karlsson, 2009). Fig. S2 (Supplement) provides examples of Al, PCB-183 and bis(2-butoxyethyl) phosphate (BBOEP) showing the change in concentration distribution of the substances after replacement of concentrations < LOQ or LOD with determined concentrations instead of fixed concentrations at LOQ or LOD/$\sqrt{2}$. Nevertheless, it is important to be aware of that use of data with a large proportion of determined concentrations below LOQ or LOD will add uncertainty in the interpretation of the results. For GM calculations, concentrations determined to be zero were by necessity further converted to the lowest determined concentrations above zero divided by $\sqrt{2}$. In these cases, PFAS concentrations below LOQ or LOD were set to LOQ or LOD/$\sqrt{2}$.

2.10. Statistical analysis

Analysis was performed using *R* (ver: 4.0.2). In the cluster analysis, the 'varclus' function from the 'hmisc' package (ver: 4.4–0) was used to visualise the clustering of the chemical substances using spearman correlation coefficients with complete linkage. Correlation analyses of relationships between substance concentrations were assessed using Spearman Rank Correlation coefficients. By using results from the cluster analysis in combination with the correlation analysis it is possible to get a more comprehensive description of the relationships between individual substances. It is usually not probable that the cluster analysis identifies clusters including all substances that are similarly correlated to one another. In this case, the correlation analysis provides information about correlations between substances separated in different clusters. In both the cluster and the correlation analysis, substances with more than 70% of concentrations above zero were included in the analyses (Tables S3 and S4, supplement), with the full range of values used for calculations. The strength of the correlations was assessed using definitions proposed by (Schober et al., 2018), where a correlation coefficient of 0.00–0.39 is classified as negligible to weak, 0.40–0.69 is moderate, 0.70–0.89 is strong, and 0.90–1.00 is a very strong correlation. Wilcoxon rank sum and signed rank test ($\alpha = 0.05$) was used to analyse if there were gender-related differences in concentrations, and a Kruskal-Wallis rank sum test ($\alpha = 0.05$) to analyse if there are significant concentration differences in at least one of the school grades compared to the others. The Chi-Squared Test was used to test if there were gender- or school grade-related differences in proportions of exceedances of HBM-GVs and HI > 1 (see section 'Comparisons with HBM-GVs and HI assessment' below).

2.11. Study comparison

The literature was searched for nation-wide population-based studies that analysed the larger chemical exposome in both blood and urine amongst adolescents during the same period as RMA. We found two studies matching this criteria, United States NHANES 2015–17 (NHANES, 2022), German GerEs V 2014–17 (GerES, 2021), and additionally the regional Flemish Belgium FLEHS IV 2016–2020 (FLEHS, 2020).

Concentrations for NHANES were mostly reported as weighted GMs. In the case of chlorinated and brominated POPs, concentrations were instead reported as arithmetic means of pooled samples from separate ethnic groups and genders. We therefore included the reported minimum and maximum ethnical group/gender mean concentrations reported in NHANES 2015-17 within our comparison table (Table 2). Values for GerES V were reported as GMs but sometimes included younger children than those included in RMA in the reporting of certain substances. Values for FLEHS IV were reported as GMs for the adolescent study population, ages 14–15. Comparatively, we reported the RMA results as GMs including all ages (ages 10–21) analysed within our study population.

2.12. Comparisons with HBM-GVs and HI assessment

To assess the potential health concerns associated with chemical exposure in Swedish adolescents, HBM-GVs were obtained for the investigated substances from the peer-reviewed literature. We focussed on published values from the German Environment Agency (UBA) and the HBM4EU project (Apel et al., 2020; UBA, 2015) (Table 4). If HBM-GVs were published by both organizations, the HBM4EU value was used. In certain cases when HBM-GVs from these two sources were lacking we used published biomonitoring equivalents (Hays and Aylward, 2009), or published health-based values from other sources that could be used when comparing with our observed concentrations (Table 4). While the search for HBM-GVs was not exhaustive, data were obtained for many of the substances in the present work.

In order to examine possible combination toxicity of measured substances, the HI assessment approach was used (Borg et al., 2013). This approach assumes concentration addition between measured substances

Table 2
Comparison of geometric mean (GM) of substance concentrations in whole blood and serum observed in RMA with those reported for 12–19 years old adolescents from NHANES, USA, 3–17 years old children/adolescents from GerES V, Germany, and 14–15 years old adolescents from the Flemish regions of Belgium (FLEHS IV)[a].

Substances[b]	RMA (2016–2017) GM (N = 1082)	NHANES (2015–2016) Weighted GM[e] (N = 353–565)	GerES (2014–2017) GM (age) (N = 516–2256)		FLEHS IV (2016–2020) GM (N = 428)
Whole blood (μg/L)					
Mn	11	11			9.4
Se	95	190			
Cd	0.12	0.13	<0.12	(12–17)	0.19
Hg	0.66	0.40			
Pb	7.3	4.7	8.4	(12–17)	7.7
Serum (pg/ml)[c]					
HCB	42	24–37000 (NHBF – AHM)	<70	(14–17)	25
beta-HCH	3.1	<4–60 (NHBF - AHM)	<20	(3–17)	3.7
Oxychlordane	0.13	<4–7900 (NHBF - AHM)			4.0
trans-Nonachlor	2.9	9.3–12000 (NHBF – AHM)			2.5
p,p'-DDT	0.16	<4–16000 (NHBF - AHM)	<20	(14–15)	5.9
p,p'-DDE	110	160. – 690000 (NHBF - AHM)	134	(14–17)	135
PCB-74	3.5	<2–51 (NHWF - NHWM)			
PCB-99	3.9	0.2–3800 (MAF - AHM)			
PCB-118	6.7	4.1–5500 (MAF - AHM)	<20	(3–17)	
PCB-138	26	6.2–10000 (MAF - AHM)	45	(14–17)	
PCB-153	42	8.2–13000 (MAF - AHM)	62	(14–17)	
PCB-156	3.8	<0.8–6.2 (NHBF - NHWM)			
PCB-170	11	2.1–2900 (NHBF - AHM)			
PCB-180	23	4.1–7000 (MAF - AHM)	32	(14–17)	
PCB-183	2.1	<0.8–4.1 (NHBF - AM)			
PCB-187	5.2	2.1–2300 (MAF - AHM)			
∑PCB-138, 153, 180	92		140		71
BDE-47	0.78	27–83 (AF - NHBM)			<1
BDE-99	0.29	7.9–20 (AF - MAM)			<1
BDE-153	0.68	16–54 (AF - NHBM)			<1
Serum (ng/g serum)[d]					
L-PFOA	1.2	1.1	1.1	(12–17)	1
PFNA	0.36	0.47	<0.49	(3–17)	0.3
PFUnDA	0.10	<0.10	<0.24	(3–17)	
PFHxS	0.45	0.89	0.35	(12–17)	0.47
L-PFOS[f]	2.1	2	2.4	(12–17)	2.1
br-PFOS	0.96	0.85			

[a] (GerES, 2021; NHANES, 2022; Schoeters et al., 2022).
[b] For the purpose of calculating geometric means in RMA, determined concentrations < LOQ or < LOD were used and concentrations determined to be 0 were converted to the lowest concentration above 0 divided by sqrt(2) (see section Handling of data below LOQ/LOD). When LOD was available, PFAS concentrations < LOD were converted to LOD/sqrt(2), else concentrations < LOQ were converted to LOQ/sqrt(2).
[c] NHANES/GerES/FLEHS; ng/g lipid of chlorinated and brominated POPs converted to pg/ml serum using average lipid content of serum in RMA of 0.33%.
[d] NHANES/GerES/FLEHS; PFAS ng/mL converted to ng/g using the specific gravity of serum (1.0275) (Sunderman and Boerner, 1949).
[e] Chlorinated POPs; arithmetic mean in pooled samples (N = 2–11, each consisting of 8 individuals) from different ethnical groups: NHBF = non-hispanic black females. AHM = all hispanic males. MHWF = non-hispanic white female. NHWM = non-hispanic white male. MAF = mexican american females. AM = asian male. AF=Asian female. MAM = Mexican american male.
[f] GerES & FLEHS linear + branched isomers.

in the assessment of possible cumulative health concerns. A conservative approach was used by grouping substances with the same target organ of critical effects (Table 4), specifically in this present study kidney toxicity, liver toxicity and neurotoxicity. Each participant's Hazard Ratio (HR) of the substance in question was calculated by dividing the measured concentration of the substance and its most conservative HBM-GV. Each individual's HRs were summed together to a HI according to the shared target organ of critical effects (see formula below). A potential concern to human health exists if the HI is > 1 for each target organ. See Table 5 for selected substance HRs included within each HI.

$$\text{Hazard Index} = \frac{C1}{GV1} + \frac{C2}{GV2} + \frac{C3}{GV3} + \ldots\ldots\ldots\frac{Ci}{GVi}$$

C_i: concentration of substance i in serum/whole blood/urine. GV_i: the HBM-GV for substance i (see Table 4). Hazard Index = the sum of the HRs of each substance in an individual with the same target organ of critical effects (see Table 5)

3. Results and discussion

RMA showed ubiquitous exposure of Swedish adolescents to mixtures of many of the studied elements, chlorinated pesticides, PCBs, and PFASs (Table 1 & Table S3, Supplement). Moreover, >50% of the participants had quantifiable concentrations of urinary metabolites of phthalates/phthalate alternatives, as well as metabolites of phosphorous flame retardants, PAHs, and pesticides, and bisphenols, and biocide/preservative/UV filter chemicals (Table 1 and Table S4, Supplement). This is in line with results from similar studies on adolescents from Germany and the USA (GerES, 2021; NHANES, 2022), and the regional study in Belgium (Schoeters et al., 2022).

Many of the studied elements and POPs have half-lives in the human body ranging from months to years (Nordberg et al., 2014; Verner et al., 2009); consequently, concentrations are representative of medium-to long-term cumulative exposure prior to sampling. In contrast, urine substances have short elimination half-lives (i.e., hours to a few days) and are therefore representative of very recent exposure (Perrier et al., 2016). Nevertheless, the almost ubiquitous quantification of these 'short-lived' substances in adolescent urine suggests that exposure

Table 3
Comparison of geometric means (GM) of substance concentrations in urine observed in RMA, with those reported for 12–19 years old adolescents from NHANES and 14–17 years old adolescents from GerES.

Substances	RMA (2016–2017) GM (N = 1082)	NHANES (2015–2016)[a,b] Weighted GM (N = 405)	GerES (2014–2017)[c] GM (N = 516–2256)	FLEHS IV (2016–2020)[d] GM (N = 416)
Urine (ng/mL)				
MEP	41	35	26	38
MBP	42	12	21	20
MBzP	7	6.1	3.1	3
MEHP	1.7	1.2	1.4	1.1[e]
5OH-MEHP	8	5.8	11	6.7
5oxo-MEHP	6.4	3.8	7.6	4.2
5cx-MEPP	7.3	9.4	12	16
OH-MiNP	4.6		6.9	3.9[e]
oxo-MiNP	2.2	2.6	2.8	
cx-MiNP	7.2		5.9	1.7[e]
cx-MiDP	0.41	2.2	0.9	1.2[e]
OH-MPHP	1.1		0.3	
oxo-MiNCH	1.3		0.93	
cx-MINCH	0.95	0.58	1.1	0.98[e]
OH-MINCH	0.96	0.97	2.3	1.2[e]
DPP	2	1.4		
DBP	0.15	0.21		
BPA	0.88	1.2	1.9	1.1
BPS	0.14	0.37		0.13
4,4BPF	0.10	<0.2		0.17
2-OH-PH	0.17	0.06	0.09	
1-HP	0.07	0.16	0.12	
3-PBA	0.28	0.64		
TCS	0.30	5.2	<1	
BP3	1.1	16	<2	

[a] DPP and DBP from 2013 to 2014 instead. 2-OH-PH from 2011 to 2012 instead. 1-HP and 3-PBA from 2013 to 2014 instead.
[b] (NHANES, 2022) Volumes II & III, updated March 2021.
[c] (Murawski et al., 2020; Schwedler et al., 2020a, 2020b; Tschersich et al., 2021).
[d] (Schoeters et al., 2022).
[e] (Bastiaensen et al., 2021).

occurred on a more-or-less daily basis in Sweden during the RMA study period. However, the use of a single-spot urine sample from each participant makes it difficult to estimate individual long-term exposure due to large intra-individual temporal variation in exposure (Perrier et al., 2016). Nonetheless, the RMA results give estimates of the overall exposure situation among adolescents in Sweden 2016–17 (Aylward et al., 2017).

3.1. Correlations between substance concentrations

This is, to the best of our knowledge, one of the most comprehensive studies of relationships between whole blood, serum and urine concentrations of chemicals in a national population study of adolescents. In the cluster analysis, most elements with diverging dietary exposure sources (Livsmedelsverket, 2017), did not form clear cluster groupings and in most cases negligible to weak correlations were observed (Fig. 1 and Fig. S3, Supplement). Moreover, with a few exceptions, correlations between elements and POPs were negligible to weak (Fig. S3, Supplement), most likely due to differences in toxicokinetics (much shorter half-lives of most elements, many POPs being lipid soluble) (Andersen et al., 2021; Nordberg et al., 2022; Verner et al., 2009) and/or exposure sources (mainly plants-based foods vs foods of animal origin) (Livsmedelsverket, 2017). Within-group clusters were observed among the POPs with similar dietary exposure patterns (Krauskopf et al., 2017; Lignell et al., 2011; Livsmedelsverket, 2017; Nyström et al., 2022) and toxicokinetics (Andersen et al., 2021; Verner et al., 2009) (Fig. 1). However, no overlaps were observed between the chlorinated, brominated and fluorinated POPs (Fig. 1). As suspected from the very short half-lives and diverging exposure sources, the urine substances did not cluster together with any of the substances measured in blood (Fig. 1) and correlations were negligible to weak (results not shown). Among substances measured in urine, metabolites of diethylhexyl phthalate (DEHP), diiso-nonyl phthalate (DiNP), and diisononyl-cyclohexane-1, 2-dicarboxylate (DiNCH) clustered separately from one another and displayed moderate to strong correlations within a given cluster (Fig. 1 & Fig. S4, Supplement). Se and Hg, and Co and Cd, formed separate clusters among the elements (Fig. 1). Hypothetically, Se and Hg relationships could be due interactions between these elements in the body (Bárány et al., 2003; Bates et al., 2006; Glynn and Lind, 1995; Ralston and Raymond, 2010). For Co and Cd similar dietary exposure sources (cereals and sugar/sweets) (Livsmedelsverket, 2017) and toxicokinetics (sharing of iron-transporting mechanisms) (Bárány et al., 2005) may have contributed. Hexa-to hepta-chlorinated PCBs clustered separately from tetra-to penta-chlorinated PCBs as well as from the chlorinated pesticides (Fig. 1). The indoor environment may still be a significant exposure source of the latter PCBs (Johansson et al., 2003; Meyer et al., 2013; Wingfors et al., 2006). For HCB, hexachlorocyclohexane (HCH) and p,p'-DDE, fish consumption has been a less important dietary source than for PCBs in Sweden (Livsmedelsverket, 2017; Törnkvist et al., 2011). BDE-47 and -99 formed a cluster separate from BDE-153 (Fig. 1), whereas BDE-153 was moderately correlated with highly chlorinated PCBs (Fig. S3, Supplement), as also observed among nursing women from Sweden (Lignell et al., 2011). The indoor environment appears to be a more significant source of human BDE-47 and BDE-99 exposure than of BDE-153 exposure (Björklund et al., 2012; Fromme et al., 2016). Among young Swedish women, BDE-153 body burdens were significantly related to consumption of fish (as was the case for certain PCBs), whereas no such relationship was found for BDE-47 and -99 (Lignell et al., 2011). As in a previous RMA study using PCA clustering (Nyström et al., 2022), L-PFHxS, L-PFOS and br-PFOS clustered separately from L-PFOA, PFNA, and PFDA (Fig. 1), which was suggested to be due to exposure to the former PFASs from drinking water (Nyström et al., 2022).

Apart from phthalates/phthalate alternatives with common 'mother

Table 4
Estimated fraction (%) of exceedances of toxic substance concentrations among RMA participants (N = 1082) in relation to non-cancer HBM-GVs, gender and school grade differences in exceedances, and critical effects of the HBM-GVs.

Substance (metabolite)	Type of HBM-GV[a]	Matrix	HBM-GV	Participants exceeding HBM-GV (%)	Male/female participants exceeding HBM-GV (%)	Participants in grade 5/8/11 exceeding HBM-GV (%)	Critical effect	Reference for HBM-GV
Se	Biomonitoring equivalents (BE)	Whole blood	400 µg/L	0			Selenosis	Hays et al. (2014)
Cd	BE	Whole blood	1.4 µg/L	0.8			Kidney toxicity	Hays et al. (2008)
Hg	Human biomonitoring I (HBM I) children/adults	Whole Blood	5 µg/L	0.4			Neurotoxicity	Apel et al. (2017)
	HBM II children/adults	Whole blood	15 µg/L	0			Neurotoxicity	Apel et al. (2017)
Pb	BMDL1% developmental neurotoxicity children	Whole blood	12 µg/L	12	17/8.8*	12/13/11	Neurotoxicity	EFSA (2010)
	BMDL1% systolic blood pressure	Whole blood	15 µg/L	7.1	8.4/6.1	7.3/7.4/6.6	Hypertension	EFSA (2010)
	BMDL10% chronic kidney disease	Whole blood	36 µg/L	0.4			Kidney toxicity	EFSA (2010)
Al	Occupational threshold adverse effects	Serum	6.8 µg/L	26	27/25	27/26/25	Neurotoxicity	Riihimäki et al. (2000)
HCB[b]	BE	Serum	80 pg/mL	3.1	5.9/1.2*	2.7/4.4/2.3	Liver toxicity	Aylward et al. (2010)
p,p'-DDE[b]	Safe level developmental effects	Serum	12.8 ng/mL	0			Reproductive toxicity	WHO (2012)
NDL-PCB[c]	HBM I (138 + 153+180x2)	Serum	3.5 ng/mL	0			Neuro-/immunotoxicity	Apel et al. (2017)
	HBM II	Serum	7 ng/mL	0			Neuro-/immunotoxicity	Apel et al. (2017)
PBDE-99[b]	BE	Serum	1.7 ng/mL	0			Neurotoxicity	Krishnan et al. (2011)
PFAS[d]	PFOA + PFNA + PFHxS + PFOS at TWI young women	Serum	6.9 ng/mL	21		34/15/20*	Immunotoxicity	EFSA (2020)
PFOA[d]	HBM I general population	Serum	2 ng/mL	12	12/13	16/6.9/14*	Mixed toxicity	Hölzer et al. (2021)
	HBM II general population	Serum	10 ng/mL	0			Mixed toxicity	Schümann et al. (2021)
	HBM II females child-bearing age	Serum	5 ng/mL	0.3			Developmental toxicity	Schümann et al. (2021)
PFOS[d]	HBM I general population	Serum	5 ng/mL	19	27/14*	25/19/18*	Mixed toxicity	Hölzer et al. (2021)
	HBM II general population	Serum	20 ng/mL	1.7	1.7/1.8	5.5/0.25/0*	Mixed toxicity	Schümann et al. (2021)
	HBM II females child-bearing age	Serum	10 ng/mL	3.6		9.8/1.8/1.4*	Developmental toxicity	Schümann et al. (2021)
DEP	BE (MEP)	Urine	18000 µg/L	0			Body growth	Aylward et al. (2009)
DBP	HBM guidance value (HBM-GV), children (MBP)	Urine	120 µg/L	4.8	5.5/4.5	5.2/4.0/5.8	Reproductive/developmental toxicity	Lange et al. (2021)
	HBM-GV adults/adolescents	Urine	190 µg/L	1.5	1.7/1.3	1.2/1.7/1.4	Reproductive/developmental toxicity	Lange et al. (2021)
BBzP	HBM-GV children (MBzP)	Urine	2000 µg/L	0			Reproductive/developmental toxicity	Lange et al. (2021)
	HBM-GV adults/adolescents	Urine	3000 µg/L	0			Reproductive/developmental toxicity	Lange et al. (2021)
DEHP	HBM-GV children (5-oxo-MEHP+5-OH-MEHP)	Urine	340 µg/L	0.2			Reproductive/developmental toxicity	Lange et al. (2021)
	HBM-GV adults/adolescents	Urine	500 µg/L	0.09			Reproductive/developmental toxicity	Lange et al. (2021)
	HBM-GV children (5cx-MEPP+5-OH-MEHP)	Urine	380 µg/L	0.2			Reproductive/developmental toxicity	Lange et al. (2021)
	HBM GV adults/adolescents	Urine	570 µg/L	0.09			Reproductive/developmental toxicity	Lange et al. (2021)

(*continued on next page*)

Table 4 (*continued*)

Substance (metabolite)	Type of HBM-GV[a]	Matrix	HBM-GV	Participants exceeding HBM-GV (%)	Male/female participants exceeding HBM-GV (%)	Participants in grade 5/8/11 exceeding HBM-GV (%)	Critical effect	Reference for HBM-GV
DPHP	HBM GV adults (OH-MPHP)	Urine	220 μg/L	0			Thyroid toxicity	Lange et al. (2021)
	Children	Urine	140 μg/L	0			Thyroid toxicity	Lange et al. (2021)
DiNP	BE (OH-MiNP + oxo-MiNP + cx-MiNP)	Urine	14700 μg/L	0			Liver toxicity	Hays et al. (2011)
DiNCH	HBM GV children (OH-MINCH + cx-MINCH)	Urine	3000 μg/L	0			Kidney toxicity	Lange et al. (2021)
	Adults/adolescents	Urine	4500 μg/L	0			Kidney toxicity	Lange et al. (2021)
BPA	HMB GV children	Urine	135 μg/L	0			Kidney toxicity	Ougier et al. (2021)
	HMB GV adults	Urine	230 μg/L	0			Kidney toxicity	Ougier et al. (2021)
3-PBA	BE Tier 1	Urine	1.7 μg/L	2.2	2.3/2.5	3.3/1.2/2.9	Neurotoxicity	Aylward et al. (2018)
	BE Tier 2	Urine	87 μg/L	0			Neurotoxicity	Aylward et al. (2018)
TCS	HBM I children	Urine	2000 μg/L	0			Haemato-/spleen toxicity	Apel et al. (2017)
	HBM I adults	Urine	3000 μg/L	0			Haemato-/spleen toxicity	Apel et al. (2017)

[a] HBM I is the threshold for early warning and concern, whereas HBM II is the threshold for an increased risk for adverse health effects.
[b] Recalculated from concentration in blood lipids to concentration in serum using a mean lipid content in RMA serum of 0.33%. *p ≤ 0.05, Chi-square test.
[c] Non-dioxin like.
[d] PFAS ng/g converted to ng/mL using the specific gravity of serum (1.0275) (Sunderman and Boerner, 1949).

Table 5
Hazard index (HI) in RMA (N = 1082) based on the same target organ critical effect.

Target organ[a]	Composition	Total N with hazard index >1 (%)[b]	Median (range) of HI	Median (range)[c] of HI > 1
Liver	HCB, DiNP	35 (3.2)	0.53 (0.15–93)	1.1 (1.01–93)
Kidney	Cd, Pb, DiNCH, BPA	16 (1.5)	0.31 (0.01–4)	1.64 (1.08–4)
Central nervous system	Hg, Pb, Al, NDL[d]-PCB, PBDE-99, 3-PBA	1018 (94)	1.82 (0.58–15)	1.86 (1–15)

[a] Critical effect target for HBM-GVs as seen in Table 4.
[b] HI calculated per target organ critical effect by dividing participants blood/serum/urine concentrations with corresponding HBM-GV (hazard ratio, HR) from Table 4, then summing HR together. Total numbers of those with HI > 1 shown.
[c] Median and range calculated for participants with HI > 1.
[d] Non-dioxin-like.

substances', the dibutyl phthalate (DBP) metabolite monobutyl phthalate (MBP) and the butylbenzyl phthalate (BBzP) metabolite MBzP formed a cluster suggesting common exposure sources (Fig. 1). MBP and MBzP were also moderately correlated with the DEHP metabolites (Fig. S4, Supplement), as correspondingly observed for MBzP among Swedish and Danish children, and for MBP among Flemish adolescents (Bastiaensen et al., 2021; Langer et al., 2014; Larsson et al., 2014). Common exposure from building materials/consumer products may contribute to the observed relations (KEMI, 2015). As among Swedish and Danish children, and Flemish adolescents (Bastiaensen et al., 2021; Langer et al., 2014; Larsson et al., 2014), in RMA only negligible/weak correlations were observed between the metabolite of diethyl phthalate (DEP), monoethyl phthalate (MEP), and the other phthalate metabolites (Fig. S4, Supplement). DEP is currently the main phthalate used in cosmetic products in the EU (KEMI, 2015). DiNP, diiso-decyl phthlate (DiDP) and dipropylheptyl phthalate (DPHP) have been introduced on the European market more recently than the other phthalates (Fréry et al., 2020), and the metabolites of these three phthalates were moderately correlated with each other (Fig. S4, Supplement). DiNP and DPHP metabolites were also moderately correlated with the DEHP metabolites (Fig. S4, Supplement), also observed for DiNP and DEHP metabolites in Flemish adolescents (Bastiaensen et al., 2021). DiNP is a direct alternative to DEHP as a general plasticizer and are used together with both DiNP and DPHP in PVC production (KEMI, 2015). The two PAH metabolites 2-hydroxy-phenanthrene (2-OH-PH) and 1-HP formed a cluster and were moderately correlated (Fig. 1 & Fig. S4, Supplement), as expected due to the common exposure sources (Murawski et al., 2020)

3.2. Comparisons with other studies

Comparisons of RMA results with other studies of adolescents are somewhat uncertain due to differences in study design/populations and analytical methods. Nevertheless, mean concentrations of elements, POPs and urine substances with a few exceptions varied less than 3-fold between RMA against NHANES (USA), GerES (Germany) and FLEHS (Flanders, Belgium) (Tables 2 and 3). The relatively small differences in average exposure of adolescents between the four studies are most probably due to the similarly high standard of living in these populations, in combination with world-wide distribution of chemicals and products. NHANES showed large ethnic differences in mean serum concentrations of chlorinated and brominated POPs, in some cases up to several orders of magnitude (Table 2) (NHANES, 2022). In RMA, mean concentrations of chlorinated POPs were within these ranges or somewhat lower (Table 2). The concentrations of the three PBDEs were in most cases below the LOQ (<20 pg/ml serum) in RMA (Table S3, supplement). However, the determined concentrations below LOQ in RMA strongly suggested considerably lower mean serum PBDE concentrations than in NHANES, with a minimum of a 23-fold difference (BDE-153) (Table 2) (NHANES, 2022). The higher body burdens of PBDE in the US than in Sweden and other European countries is in line with studies of adults (Fromme et al., 2016). Differences in PBDE legislation between the US and Europe most likely contributes to the exposure differences (Horton et al., 2013). The mean concentration of

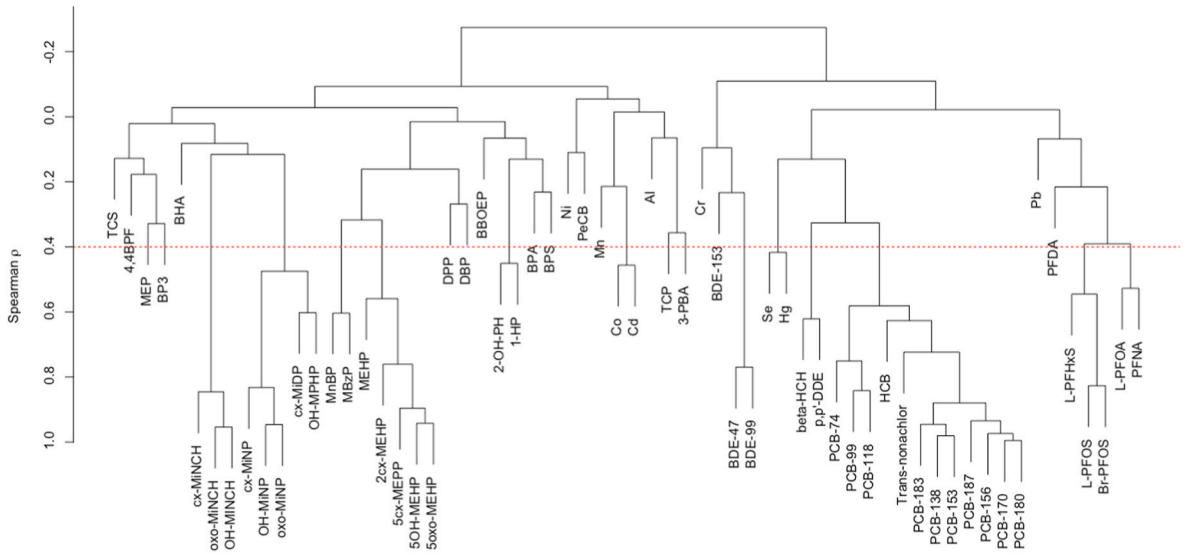

Fig. 1. Cluster analyses of correlations between toxic substance concentrations among adolescents in RMA (N = 1082). Correlation coefficients should be read at where branches separate and not on the names. Figure shows absolute spearman correlation coefficients with both negative and positive correlations. The dotted red line represents the set cut-off for moderate correlation. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

dichlorodiphenyltrichloroethane (p,p'- DDT) was reported to be 37-fold higher in FLEHS compared to RMA, but the concentration of the DDT metabolite p,p-DDE did not differ markedly (Table 2). Studies of breast milk suggest similar average p,p'-DDT exposures among women in child-bearing age in Sweden and Belgium around the same time period as the RMA study (Aerts et al., 2019; Kallerman et al., 2021). Further studies are needed to determine the reason behind the large differences in p,p'-DDT concentrations in RMA and FLEHS.

The average concentrations of phthalate metabolites in urine did in many cases not differ more than 3-fold between RMA and the other studies, suggesting similar exposure levels among the adolescents (Table 3). Among the European adolescents this may be due to the common plastics regulation within the EU (CEP et al., 2022; Pereira et al., 2022). Nevertheless, the exceptions to the <3-fold difference were MBP, cx-MiNP, cx-MiDP and 6-hydroxy monopropylheptyl phthalate (OH-MPHP). The mean MBP concentrations in NHANES, GerES and FLEHS were lower than in RMA (Table 3), at most being 3.6-fold lower in NHANES compared with RMA. Similarly, the mean cx-MiNP was also lower in GerES and FLEHS (not reported in NHANES), occurring at a 4.2-fold lower mean concentration in FLEHS. However, the differences in mean concentrations of the other DiNP metabolites were less than 3-fold and RMA did not consistently show the highest concentrations (Table 3). cx-MiDP was lowest in RMA, at most 5.4-fold lower than in NHANES (Table 3), and OH-MPHP was 3.7-fold lower in GerES than in RMA. There was no consistent pattern in the observed differences in mean concentrations of the four phthalate metabolites between RMA and the other three studies, suggesting diverging substance-related exposure sources. The largest differences of concentrations of urine substances were observed for TCS and BP3, being on average about 15-fold higher in NHANES adolescents compared to RMA (Table 3). Although concentrations of these substances were below LOQ in GerES, they were also clearly lower than in NHANES. Differences in the levels of TCS and BP3 in consumer products and also in usage patterns, between Germany and the US were suggested as explanations of divergence in TCS exposure between GerES and NHANES (Tschersich et al., 2021), and is likely also the reason for the large difference between RMA and NHANES.

3.3. Comparisons with HBM-GVs and HI assessment

We surveyed the literature for HBM-GVs and found several from multiple sources (Table 4). There are uncertainties when comparing the different proposed HBM-GV, in part due to variation in the quality of the toxicological database, in procedures used in the development of the different values, safety margins used between point-of-departure of critical effect concentrations and HBM-GVs, and the fact that some of them have not been updated based to the most recent risk assessments.

Moreover, some HBM-GVs listed in Table 4 were specifically developed for distinct sub-populations like children, adolescents, adults or women in childbearing age. UBA, Germany (see Table 4 references) developed HBM I and HBM II values, and in the view of UBA there is no risk of adverse health effects if concentrations of substances are below HBM I. If the concentrations are above HBM I, but below HBM II, efforts should be made to search for potential sources of exposure and to mitigate identified exposure sources. An exceedance of HBM II is by UBA regarded as an increased health risk, and therefore there is a need for acute action to reduce exposure and biomedical advice should also be provided. Biomonitoring Equivalent (BE) values are based on existing health-based guidance values, such as tolerable intakes, and exceedances of BE may be regarded as a health concern (Hays et al., 2007). HBM4EU has developed HBM-GVs that in reality are equivalent to UBA's HBM I values (Apel et al., 2020). The values for Pb, Al, and $PFAS_4$ (Table 4) were based on benchmark concentrations/effect level concentrations in humans without any safety factors (EFSA, 2020; Riihimäki et al., 2000). Moreover, the Al value was based on relationships between occupational exposure and health among aluminium welders (Riihimäki et al., 2000). Despite all these uncertainties, as a conservative measure, exceedances of the HBM-GVs among the RMA participants were regarded as indications of a health concern.

The largest degree of exceedance of HBM I, HBM-GVs for children, and benchmark concentrations/effect levels were observed for Al, $PFAS_4$, PFOS, PFOA and Pb in declining order, all being ≥12% of the adolescent population when looking at the most conservative values (Table 4). Based on the size of the adolescent population in Sweden during 2016 for ages 12, 15 and 18 (N = 324776) (SCB, 2022), the number of adolescents exceeding the HBM-GVs can be estimated to range from 32700 ($PFAS_4$, females only) to 84400 (Al). For HCB, MBP and 3-PBA percent exceedances corresponded to 10000, 16300 and

7100 adolescents, respectively (Table 4). The percentages of exceedances of PFASs are likely overestimated since 5% of the participants were living in areas with a history of PFAS contamination of drinking water (Nyström et al., 2022), which is disproportionally high from a nation-wide population perspective. To the best of our knowledge, the PFAS contamination in some areas of Sweden is a special case not representative for the other substances included in our study. Nevertheless, contribution of unknown local hotspot contamination of other substances to the exceedances of HBM-GVs cannot be excluded. Exceedances were also observed for Cd, Hg, DEP, and DEHP, although to a lesser degree (Table 4). Overall, 54% of the participants exceeded at least one of the HBM-GV, 18% at least two, and 5% at least three. Taken together the results show that a significant fraction of the adolescent population had overall high exposures to several of the toxic substances in relation to the HBM-GVs. When using HBM-GVs for adults and/or adolescents (Pb, DBP, DEHP) or HBM II values (Hg, PFOS) the percentages exceeding the HBM-GVs were less frequent (Table 4). Considering that the concentrations of toxic substances in RMA, GerEs V and FLEHS were comparable (Tables 2 and 3), it is not surprising that GerES and FLEHS also reported exceedances of HBM-GVs of Cd, Pb (FLEHS), Hg (GerES), HCB (FLEHS), PFASs, DBP, DEHP (GerES) and 3-PBA (FLEHS) (Schwedler et al., 2020b; Vogel et al., 2021).

As suggested by the higher GM concentrations of Pb, HCB, and PFOS among males than females in RMA (Table 1), fewer females exceeded the benchmark dose of 1% extra risk (BMDL1%) for neurotoxicity of Pb in children, the BE for HCB, and the HBM I value for PFOS (Table 4). However, observed gender differences in concentrations of the toxic substances (Table 1) did not necessarily result in gender differences in exceedances of HBM-GVs, as observed for PFOA, the DBP metabolite MBP, and 3-PBA (Table 4). Moreover, no gender differences in exceedances of HBM-GVs were observed for Al, and for less conservative HBM-GVs of Pb, PFOS, and MBP. When looking at age-dependent differences in exceedances in relation to observed associations between age and concentrations there were no general trend, except in the case of PFASs that showed a higher degree of exceedances among 5th graders (Table 4), most probably due to a particular subset of the 5th-grade participants (N = 58) having a known high exposure of PFHxS and PFOS from drinking water in Uppsala and Ronneby (Nyström et al., 2022).

Efforts to eliminate environmental pollution of Pb, HCB, PFOA, PFNA, PFHxS and PFOS have resulted in slowly declining temporal trends in different Swedish populations (Gyllenhammar et al., 2021; Lundh et al., 2020; Miaz et al., 2020; Norén et al., 2021; Wennberg et al., 2017). Similar efforts to reduce Cd pollution have not resulted in declining Cd exposures during the last few decades, whilst mixed trends for Hg exposure (no decrease/slow decrease) have been reported (Kippler et al., 2021; Lundh et al., 2020; Wennberg et al., 2017). Taken together, further efforts to reduce exposures to Pb, Hg, Cd, Al, HCB and PFASs in Sweden are clearly needed. A study of young women in Sweden have reported decreasing exposures to DEP, DBP and DEHP over the last few decades, suggesting that the exposure situation also is slowly improving for these rapidly metabolized substances (Gyllenhammar et al., 2017).

In accordance with the RMA findings of exceedances of HBM-GVs of Pb, Hg (methyl-Hg), Al, and PFASs, The European Food Safety Authority (EFSA) concluded that the tolerable intakes of these substances from the diet were exceeded by parts of the EU population at the time of risk assessment (EFSA, 2012a, 2012b, 2010, 2008). Regarding phthalates, EFSA stated that the group tolerable intake of DBP, BBP, DEHP and DiNP (as DEHP equivalents) were not exceeded by EU populations even when considering the worst-case total dietary intake mainly originating from plastic food contact materials (CEP et al., 2019). However, diet is only one of several potential exposure sources of these phthalates, and the contribution of the additional sources most likely contributes to the high concentrations of metabolites observed in a small fraction of the RMA participants (Bastiaensen et al., 2021; Langer et al., 2014; Larsson et al., 2014; Schwedler et al., 2020b). However, considering that RMA only included single-spot urine sample there are still uncertainties about the risks of long-term individual exceedances of the HBM-GVs for these phthalates among adolescents in Sweden.

BPA concentrations in urine did not exceed the published HBM-GV, the GM concentration being 148-fold lower than the HBM-GV for children (Tables 1 and 4). However, in 2021 an EFSA draft opinion on health risks of BPA in foods proposed a considerably lower tolerable intake compared to the pervious assessment in 2015 (EFSA, 2021). It was proposed that populations with both average and high exposures to BPA in all age groups exceed the new tolerable intake. The publication of the final risk assessment will reveal if the exposure of the Swedish adolescent population will be regarded as too high or not from a health risk assessment perspective.

In the cumulative health risk assessment liver toxicity, including HCB and DiNP, showed a median HI (range) of 0.53 (0.15–93), with 3.2% of the participants showing a HI > 1 (Table 5). HCB was the driver of the health concern contributing with 99.9% (median, range: 98.8–100%) to the HI among participants with HI > 1. As with HCB alone, the highest proportion of participants with a health concern HCB was observed among males (5.9%), with a significantly lower proportion among females (1.2%, Chi-square test $p \leq 0.05$). In the case of kidney toxicity, the median HI (range) was estimated to 0.31 (0.006–4.0) and 1.5% of the participants had a HI > 1 (Table 5). Cd contributed 76.3% (3.1–91%) to the HI among participants with HI higher than 1, followed by Pb 23% (7.7–96%). The proportion of males and females with a HI higher than 1 was 1.6% and 1.3%, respectively, with gender difference not being statistically significant. Neurotoxic substances consisting of Hg, Pb, Al, NDL-PCB, PBDE-99 and 3-PBA showed a higher median HI of 1.8 (range: 0.58–15) compared to substances with liver and kidney toxicity, with 94% of the participants showing a health concern (HI > 1). Al contributed the most 39.5% (0–93%) to the HI among participants with HI higher than 1, followed by Pb 33.8% (0–96%). As with liver and kidney toxicity males showed a higher proportion of 96% exceeding HI = 1, whereas the proportion of females was 93% (Chi-square test $p \leq 0.05$). The HI analysis indicates that if the assumption of cumulative additive target organ toxicity effect holds true, significant portions of the adolescent population may be at risk of having too high cumulative exposures to neurotoxic substances. However, granted that the target organ of the central nervous system (CNS) is highly complex and the neurotoxicity of each individual contributing substance may affect different sections or processes of the CNS, the observation should be considered preliminary.

3.4. Strengths and limitations

As previously eluded to, a major strength of this nation-wide population-based study of adolescents is the inclusion of wider groups of toxic substances. There are some minor demographic/life-style differences between the RMA participants and the adolescent population in Sweden, yet participants are still considered as representative of the adolescent population in Sweden with regard to school type/size, and parental education and income (Moraeus et al., 2018). The urine substances have very short half-lives in comparison to the elements and POPs. As a consequence there is intra-individual variation of urine substance concentrations depending on timing of sampling. Other studies have shown that there may be seasonal differences in concentrations for some of the substances in urine (Bastiaensen et al., 2021). Although the possibility of seasonal differences in concentrations were not analysed statistically in the present study, the present results may be regarded as representative for the general adolescent population in Sweden during the sampling period. While aspects of the present work are comparable to prior studies (e.g. NHANES and GerES) some caution is warranted when comparing between studies due to potential differences in study design, analytical methods, and data processing/analyses. Human biomonitoring initiatives of toxic substances has been increasingly moving

towards combination and mixture effects. Yet, most studies still only focus on single substances/substance groups. Inclusion of a wider portion of exposome as in the present study, uncovered patterns of chemical body burdens that are valuable for interpretation of future RMA health studies. In the analyses of urine substances, the precision of cx-MiDP, BPS, DBP and BHA was >20%. This introduced an additional uncertainty in the statistical analyses, and in comparisons with other studies and HBM-GV.

The HBM4EU initiative, as well as UBA, has made steady progress to developing HBM-GVs for the general population (Apel et al., 2020), but nevertheless many toxic substances currently lack established HBM-GVs. We attempted to include the HBM-GVs appropriate for a general adolescent population, but if unavailable we instead used either those developed for children/adults or values proposed for occupational exposure (Al), making comparison of the results uncertain. Moreover, there are uncertainties connected to our limited HI approach of grouping of substances with the same target critical effect organs, and the HI results therefore should be considered as hypothesis generating for future studies of possible combination effects of the included chemicals.

4. Conclusion

Although many biomonitoring studies are available involving a range of individual chemical substances, our study is one of the few attempts at looking at the wider chemical exposome within a single study of adolescents, giving a more holistic and clearer picture of the current state of the chemical body burden in Swedish adolescents. With few exceptions, chemical body burdens in the present work were similar to those observed in adolescents from Germany and the US, showing a similar exposome for adolescents in these economically and industrially developed countries from two different continents. In RMA, the moderate to strong correlations between substances within the same chemical groupings were most likely due to common sources of exposure and/or similar toxicokinetics. However, while the chlorinated, brominated and fluorinated POPs included here share common properties of environmental persistence and bioaccumulation in humans, measured concentrations of the different contaminant classes were rarely correlated. Moreover, no correlations were generally observed between substances measured in different matrices. These observations are important for better interpretation of results in future evaluations of RMA data with regards to possible combination effects. The gender patterns observed, with generally higher average body burdens of neurotoxic Pb, Hg and some POPs in males compared to females, reflected in males having higher proportions of HI $>$ 1 for neurotoxicity also adds important knowledge for future combination effect studies. Our results give support to further efforts to reduce human exposures to toxic chemicals.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2023.114196.

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