Human Exposure to Chemicals in Personal Care Products and Health Implications

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Abstract Human exposure to major classes of personal care products (PCPs) that include disinfectants (e.g. triclosan), fragrances (e.g. musks), insect repellents (e.g. DEET), preservatives (e.g. parabens), and UV filters (e.g. benzophenones) has been reviewed. Concentrations of these toxicants in human matrices (blood, urine, or tissues) have been compiled, alongside with relevant health implications.

Keywords Disinfectants · Fragrances · Humans · Insect repellents · Personal care products · Preservatives · UV filters

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1 Introduction

Personal care products (PCPs) contain a wide range of chemicals that are under increasing scrutiny. Current knowledge about these contaminants in PCPs has significant gaps with regard to their toxicity (towards humans), bioaccumulation, exposure, doses in humans, and biotransformation products (metabolites). Some of the contaminants in PCPs belong to chemical groups which have raised concerns regarding endocrine disruption.

An average person is exposed to numerous chemicals from cosmetics, soaps, moisturizing skin creams, lipsticks, makeup formulations, nail polishes, after-shave lotions, or hair-care products in addition to a variety of other PCPs. PCPs are widely used in our everyday life for personal hygiene and beautification purposes. Even though consumers may assume that these products are safe, some of the ingredients are untested for their safety and some are unregulated. Furthermore, ingredient labels can be misleading about the safety of the products.

Human exposure doses and sequestration of these chemicals in human bodies are key concerns for these chemicals due to their broad applications. Several ingredients of PCPs may be characterized as persistent, bioaccumulative, and toxic, while others are associated with endocrine disruption. Human exposure to these chemicals was not studied until recently. As the analytical methodologies advance, sensitive methods have been applied in the detection of these chemicals in human specimens. In this chapter, we systematically investigate the levels of selected PCPs and their metabolites in human matrices and suggest health implications from such exposures.

2 Xenobiotics: Biotransformation and Adjustment of Urinary Concentrations

Once a xenobiotic compound enters the human body, it is transformed into its metabolites by cytochrome P450 enzymes. The impact of each xenobiotic on humans differs depending on its toxicity and route of elimination from the body. Biotransformations occur mainly in the liver, lungs, intestines, and skin, and xenobiotics are subject to phase I and phase II metabolism. In general, xenobiotics are excreted as the parent compound and metabolites, and as free or conjugated species (i.e. glucuronides and sulphates). Thus, the total concentration of a xenobiotic refers to its total sum concentration of free and conjugated species.

In recent years, biomonitoring techniques have been used in the assessment of human exposure to environmental chemicals. In most biomonitoring studies, total concentrations of xenobiotics are determined in human specimens such as blood or urine. However, in the absence of analytical standards for conjugated species, a back calculation method involving analysis of concentrations of free species and "total" forms can provide information regarding the concentrations of conjugated

fraction. For the determination of total concentrations, the samples are hydrolyzed to free the conjugated fraction of the xenobiotic from the bound chemical groups (i.e. glucuronic acid). Hydrolysis is performed through the addition of a strong acid such as hydrochloric acid or through enzymatic methods. Without the hydrolysis step, only the free fraction of the chemical can be determined. When enzymatic hydrolysis is applied, the enzyme β-glucuronidase (mainly from *Helix pomatia*, since it has also sulphatase activity) is mainly used.

Urine is a most commonly used human specimen in biomonitoring studies. However, concentrations of xenobiotics in urine can vary depending on the volume of urine excreted at the time of sampling. The effect of urinary dilution/volume can be accounted for by determining the amount of the environmental chemical per amount of urinary creatinine in a given volume of urine. In addition, there are a number of normalization procedures, and the two most common ones are specific gravity and creatinine correction. Nevertheless, there are some controversies with regard to the correction of urinary concentrations of environmental chemicals to creatinine levels. Urine's specific gravity determines the content of various water-soluble molecules excreted through the kidneys into urine. On the other hand, creatinine is a by-product of skeletal muscle metabolism of creatine and is cleared from the blood plasma into the kidney at an approximately constant rate. In this chapter, unless mentioned otherwise, we report concentrations of PCPs on an unadjusted basis.

3 Exposure to Disinfectants

Triclosan (TCS) and triclocarban (TCC) are known for their extensive use as antimicrobials in PCPs [1]. They are used in PCPs, such as toothpaste, soap, shampoo, deodorant, mouthwash, and cosmetics. They can also be found in kitchen utensils, toys, and textiles. Thus, human exposure can occur through oral and dermal contact [2, 3].

TCS and TCC have been determined in urine, serum, plasma, and human breast milk. All levels are expressed in total concentrations (unconjugated and conjugated species). Urine is the most common biological media for monitoring TCS and TCC since urinary excretion is the major route of elimination [2–5] (Table 1).

Urinary TCS levels have revealed great differences in concentrations of up to three orders of magnitude (Table 1). Moreover, the detection rate is high, with most studies reporting a detection rate of >70 %. On the contrary, TCC levels, in most cases, were less frequently detected and at lower concentrations than TCS.

A study from China demonstrated that females had statistically higher geometric mean concentrations of TCS than males [13]. In contrast, Allmyr et al. [14] reported higher levels of TCS in serum from males than in females, and 31–45-year-old individuals had higher levels of TCS in comparison with the other age groups. TCS was also found in human breast milk but at lower levels than in plasma [15]. Milk samples from women who used TCS-containing PCPs had statistically significantly

Table 1 Reported total concentrations (or mentioned otherwise; ng mL^{-1}) and frequency of detection of triclosan (TCS) and triclocarban (TCC) in human urine

Human matrix	Population (*N*)	Origin of samples (country)	Target chemicals	Concentration ranges (and max., median, average or geometric mean if available)	Detection rates (%)	References
Urine	506 (pregnant women)	USA	TCS	19–44 ng mL^{-1} (mean: 29 ng mL^{-1})	100	[6]
Urine	46 (26 males and 20 females; average age: 34.5 years old)	Canada	Free TCS	Not detected–20 ng mL^{-1} (median: 0.07 ng mL^{-1})	95.7	[7]
			TCS-glucuronide	Not detected–702 dg mL^{-1} (median: 15 ng mL^{-1})	97.8	
			TCS-sulphate	Not detected–0.09 ng mL^{-1} (median: below detection limit)	21.7	
			TCS	Not detected–703 ng mL^{-1} (median: 15 ng mL^{-1})	100	
Urine	3,728	USA	TCS	105–127 ng mL^{-1} (mean: 116 ng mL^{-1})	100	[8]
Urine	1,870	Korea	TCS	1.5–1.9 ng mL^{-1} (mean: 1.7 ng mL^{-1})	92.6	[9]
Urine	131	Belgium	TCS	Not detected–599 ng mL^{-1} (geometric mean: 3 ng mL^{-1})	74.6	[10]
Urine	4,037	USA	TCS	Not detected–3,620 ng mL^{-1} (median: 12 ng mL^{-1})	77.3	[11]

(continued)

Table 1 (continued)

Human matrix	Population (*N*)	Origin of samples (country)	Target chemicals	Concentration ranges (and max., median, average or geometric mean if available)	Detection rates (%)	References
Urine	100	Greece	TCS	Not detected–2,583 ng mL^{-1} (geometric mean: 8 ng mL^{-1})	71	[3]
			TCC	Not detected–2 ng mL^{-1} (geometric mean: 0.6 ng mL^{-1})	4	
Urine	105 (pregnant women)	Puerto Rico	TCS	25th percentile–max: 4–2,780 ng mL^{-1}	79.0–88.9	[12]

Table 2 Estimated daily intake of TCS on the basis of biomonitoring data

Target chemicals	Origin of samples (country)	Estimated daily intake (EDI) (μg/kg BW/day)	Equation used	References
TCS	Greece	0.1–1,059 (median: 2.4)	Estimated daily intake (EDI; μg/kg BW/day) = 15.8 × [Σ_6Parabens] (μg/L) × 1.7 (L/day)/65.5 kg	[3]

higher levels of TCS compared to those women who did not use TCS-containing PCPs [15]. Pycke et al. [16] measured total TCS, TCC, and the metabolites of TCC, namely, 2′-OH-TCC, 3′-OH-TCC, and 3′-Cl-TCC in human urine. 2′-OH-TCC was present at higher detection rate amongst all three metabolites (27.1%), followed by 3′-OH-TCC (16.6%) and 3′-Cl-TCC (12.7%) [16]. The concentration ranges of 2′-OH-TCC, 3′-OH-TCC, and 3′-Cl-TCC were 0.02–0.5, 0.01–0.08, and "not detected" −0.02 ng mL^{-1}, respectively, while the precursor compound, TCC, was found at a concentration range of 37–151 ng mL^{-1} [16].

Based on the measured urinary concentrations of TCS and simple steady-state toxicokinetic model, exposure dose to TCS was estimated by Asimakopoulos et al. [3] (Table 2). It was reported that only 6.3% of TCS penetrates the human skin after dermal application. Since the major exposure route of TCS is dermal application of PCPs, a factor of 15.8 was applied in the estimation of the total intake (6.3 × 15.8–100 %) of TCS (Table 2) [3].

In 2010, TCS was removed from the EU list of provisional additives for use in plastic food-contact materials, since TCS is considered more toxic than many other disinfectants [3]. TCS is potentially genotoxic in certain types of organisms and/or

cell types [3]. Exposure to TCC was associated with methemoglobinemia in humans [3].

4 Exposure to Fragrances

Synthetic musk fragrances are widely used in PCPs, such as laundry detergents, softeners, soaps, antiperspirants, deodorants, and other cosmetics. Synthetic musks are divided into two main groups, nitro and polycyclic musks. Amongst the nitro musks, musk xylene (MX) and musk ketone (MK) are the most commonly used chemicals, followed by ambrette (MA), musk moskene (MM), and musk tibetene (MT). Amongst the polycyclic musks, celestolide (ADBI), galaxolide (HHCB), and tonalide (AHTN) are the most commonly used followed by traseolide (ATII), phantolide (AHMI), and cashmeran (DPMI). In recent years, polycyclic musks are used in higher quantities than nitro musks. In addition, the polycyclic musks are studied widely since they are suspected to act as endocrine disruptors [17]. Even though it was thought that the most likely exposure pathway is dermal exposure and absorption through the skin, research now focuses towards indoor air inhalation and indoor dust ingestion as important sources for musk exposure due to their use in diverse household products (e.g. air fresheners) and their high particle-binding affinities. Even though the overall impact of synthetic musks on human health is currently unknown, this is an active area of research [18].

Synthetic musks maintain a lipophilic nature and low biodegradability and have been detected in human biological media (Table 3). HHCB is found at the highest median concentration in human milk, followed by AHTN and MX. Concentrations of MK were very low and often not detectable or not quantifiable (Table 3).

A downward trend in exposure to MX was observed by Covaci et al. [18], since the industry voluntarily replaced the nitro- with polycyclic musks (Table 3). Moreover, HHCB is by far the most common polycyclic musk, as its production and use increased at the same time as production and use of nitro musks decreased [18]. Women with a high use of perfume during pregnancy had elevated concentrations of HHCB in their breast milk [25, 26]. In addition, elevated concentrations of AHTN in women were observed when they reported using perfumed laundry detergent [25, 26]. Hutter et al. [25] reported higher plasma concentrations of HHCB in older individuals, and the finding was correlated to the higher use of lotions and crèmes for their skin. Polycyclic musk compounds are bioaccumulative since they are found in human fat tissues and they are very stable chemicals. However, even though humans are constantly exposed to musks, routine toxicology screens have not shown any toxicity at low-dose exposures [27].

Table 3 Reported total concentrations (ng mL^{-1} or ng g^{-1}) and frequency of detection of musk fragrances (free-form plus conjugates) in human media

Human matrix	Population (*N*)	Origin of samples (country)	Target chemicals	Concentration ranges (and max., median, average or geometric mean if available)	Detection rates (%)	References
Human milk	10	China	HHCB	12–68 ng g^{-1} lw	100	[19]
			AHTN	23–118 ng g^{-1} lw	100	
			MK	Not quantifiable	60	
Human milk	100	China	HHCB	Median: 63 ng g^{-1} lw	99	[20]
			AHTN	Median: 5 ng g^{-1} lw	75	
			MK	Median: 4 ng g^{-1} lw	60	
			MX	Median: 17 ng g^{-1} lw	83	
Human milk	54	Switzerland	HHCB	6–310 ng g^{-1} lw (median: 36 ng g^{-1} lw)	83	[21]
			AHTN	5–29 ng g^{-1} lw (median: 10 ng g^{-1} lw)	13	
			MK	0.25–12 ng g^{-1} lw (median: 0.6 ng g^{-1} lw)	63	
			MX	0.25–32 ng g^{-1} lw (median: 1 ng g^{-1} lw)	87	
Human milk	20	South Korea	HHCB	0.06–0.5 ng g^{-1} lw	100	[22]
			AHTN	0.02–0.09 ng g^{-1} lw	65	
			MK	0.02–0.2 ng g^{-1} lw	53	
			MX	0.02–0.2 ng g^{-1} lw	65	
Human milk	31	USA	HHCB	Median: 136 ng g^{-1} lw	97	[23]
			AHTN	Median: 53 ng g^{-1} lw	56	
			MK	Median: 58 ng g^{-1} lw	85	
			MX	Median: 17 ng g^{-1} lw	36	
Plasma	204	China	HHCB	Median: 0.9 ng mL^{-1}	98	[24]
			AHTN	Median: 0.5 ng mL^{-1}	85	
Plasma	53	Austria	HHCB	Max.: 7 ng mL^{-1}	89	[25]
			AHTN	Max.: 0.3 ng mL^{-1}	19	
			MK	Max.: 0.2 ng mL^{-1}	43	
			MX	Max.: 0.3 ng mL^{-1}	62	

(continued)

Table 3 (continued)

Human matrix	Population (*N*)	Origin of samples (country)	Target chemicals	Concentration ranges (and max., median, average or geometric mean if available)	Detection rates (%)	References
Serum	114	Austria	HHCB	Median: 0.4 ng mL^{-1}	91	[26]
			AHTN	Median: not detected	17	
Maternal serum	20	South Korea	HHCB	0.2–1 ng g^{-1} lw	90	[22]
			AHTN	<0.2–1 ng g^{-1} lw	35	
			MK	Not quantifiable	0	
			MX	0.2–0.5 ng g^{-1} lw	5	
Cord serum	20	South Korea	HHCB	0.7–3 ng g^{-1} lw	70	[22]
			AHTN	<0.7–3 ng g^{-1} lw	15	
			MK	Not quantifiable	0	
			MX	Not quantifiable	0	

lw lipid weight

5 Exposure to Preservatives

Parabens are the most commonly used preservatives found in PCPs, and in fact, they are regarded as the most common ingredients in cosmetics. They are present in approximately 80% of PCPs surveyed [28]. In a study conducted by Rastogi et al. [29], parabens were found in approximately 80% of rinse-off and 100% of leave-on cosmetics. Although commercially used parabens are of synthetic origin, it is known that some organisms are able to produce them naturally [30]. An acceptable daily intake (ADI) of <10 mg/kg-body weight (bw)/day was suggested for methylparaben (MeP), ethylparaben (EtP), and propylparaben (PrP) by the Joint Food and Agriculture Organization (FAO) and World Health Organization (WHO) Expert Committee on Food Additives (JECFA) [2, 3]. Estrogenic activities have been reported in numerous bioassays for MeP, EtP, PrP, and butyl paraben (BuP) [2, 3]. Recently, epidemiological studies showed an association between human exposure to parabens and adverse health effects [31, 32]. In 2007, the ADI set for PrP was withdrawn by JECFA, and in 2011, Denmark banned the use of PrP and BuP in children's cosmetic products [2, 3]. Other parabens that are applied in PCPs, but less extensively, are benzylparaben (BzP) and heptylparaben (HeptP). Recently, methyl-protocatechuate (OH-MeP) and ethyl-protocatechuate (OH-EtP) were documented as novel metabolites of exposure to methyl- and ethyl-paraben, respectively [33]. Following oral or dermal administration, parabens are rapidly hydrolyzed by non-specific esterases and widely distributed in the body (i.e. skin, subcutaneous fat tissue, and digestive system). Several parabens end up in two common metabolites, p-hydroxybenzoic acid (4-HB) and protocatechuic acid (3,4-dihydroxybenzoic acid; 3,4-DHB) [33].

Parabens, once they enter into the bloodstream through oral or dermal application, are excreted through urine, as free-form or glycine, glucuronide, or sulphate conjugates [30]. Therefore, parabens are mainly determined in human urine and blood serum [30] (Table 4). In a biomonitoring study in Greece, Asimakopoulos et al. [3] measured the total concentrations of parabens (Σ_6Parabens: [MeP] + [EtP] + [PrP] + [BuP] + [BzP] + [HeptP]) in urine from 100 individuals. Considerable differences in concentrations were revealed, ranging from 2 to 1012 ng mL^{-1}, with a geometrical mean value of 24 ng mL^{-1}. All parabens were found in urine, and the rank order of detection rate (DR) was MeP (100%) > EtP (87%) > PrP (72%) > BuP (46 %) > BzP (6%) > HeptP (4%). This pattern of detection rate of parabens is in accordance to previous studies on human biologic media [3]. The distribution profiles of paraben concentrations in urine followed the order of MeP >> PrP > EtP, which was also similar to those reported in previous studies on human biologic media [3]. Moreover, MeP and PrP are used in combination in many PCPs, and therefore, a significant correlation was found between these two parabens in urine samples across a number of studies [45].

For the first time, alkyl protocatechuates were determined and quantified by Wang and Kannan [33]. They found that in the urine of children, the concentrations of OH-MeP were an order of magnitude lower than the concentrations of MeP,

Table 4 Reported total concentrations (ng mL^{-1} or ng g^{-1}) and frequency of detection of parabens and metabolites (free-form plus conjugates) in human specimens

Human matrix	Population (N)	Origin of samples (country)	Target chemicals	Concentration ranges (and max., median, average or geometric mean if available)	Detection rates (%)	References
Urine	506	USA	MeP	Mean: 104 ng mL^{-1}	100	[6]
			PrP	Mean: 19 ng mL^{-1}	98.4	
Urine	100	USA	MeP	5–95th percentiles: 4–680 ng mL^{-1}	99	[34]
			EtP	5–95th percentiles: not detected–48 ng mL^{-1}	58	
			PrP	5–95th percentiles: 0.2–279 ng mL^{-1}	96	
			BuP	5–95th percentiles: not detected–30 ng mL^{-1}	69	
			BzP	5–95th percentiles: not detected–0.5 ng mL^{-1}	39	
Urine	2,548	USA	MeP	10–95th percentiles: 6–974 ng mL^{-1}	99	[35]
			EtP	10–95th percentiles: not detected–57 ng mL^{-1}	42	
			PrP	10–95th percentiles: 0.3–299 ng mL^{-1}	93	
			BuP	10–95th percentiles: not detected–20 ng mL^{-1}	47	
Urine	60 (males)	Denmark	MeP	Not detected–2,002 ng mL^{-1}	98	[36]
			EtP	Not detected–564 ng mL^{-1}	80	
			PrP	Not detected–256 ng mL^{-1}	98	
			BuP	Not detected–68 ng mL^{-1}	83	
			BzP	Not detected–2 ng mL^{-1}	7	
Urine	120 (pregnant women)	Spain	MeP	Median: 191 ng mL^{-1}	100	[37]
			EtP	Median: 9 ng mL^{-1}	98	
			PrP	Median: 30 ng mL^{-1}	88	
			BuP	Median: 2 ng mL^{-1}	90	
Urine	30 (children)	Spain	MeP	Median: 150 ng mL^{-1}	100	[37]
			EtP	Median: 8 ng mL^{-1}	100	
			PrP	Median: 22 ng mL^{-1}	80	
			BuP	Median: 1 ng mL^{-1}	83	

Urine	194 (males)	USA	MeP	10th percentile-maximum: 5–1.080 ng mL^{-1}	100	[31]
			PrP	10th percentile-maximum: 0.4–294 ng mL^{-1}	92	
			BuP	10th percentile-maximum: not detected–65 ng mL^{-1}	32	
Urine	860	USA	MeP	0.5–14.900 ng mL^{-1}	NA	[32]
			EtP	0.5–1,110 ng mL^{-1}	NA	
			PrP	0.1–7,210 ng mL^{-1}	NA	
			BuP	0.1–1,240 ng mL^{-1}	NA	
Urine	653	USA	MeP	Not detected–23.200 ng mL^{-1}	99.7	[38]
			PrP	Not detected–2,870 ng mL^{-1}	96.5	
			BuP	Not detected–998 ng mL^{-1}	65.4	
Urine	30 (adults)	USA	MeP	0.8–240 ng mL^{-1}	100	[33]
			OH-MeP	Not quantified–40 ng mL^{-1}	98	
			EtP	0.1–24 ng mL^{-1}	100	
			OH-EtP	Not quantified–6 ng mL^{-1}	60	
			4-HB	81–6,220 ng mL^{-1}	100	
			3,4-DHB	8–2,960 ng mL^{-1}	100	
	40 (children)		MeP	2–5,240 ng mL^{-1}	100	
			OH-MeP	2–94 ng mL^{-1}	100	
			EtP	Not quantified–8 ng mL^{-1}	60	
			OH-EtP	0.6–107 ng mL^{-1}	100	
			4-HB	134–2,900 ng mL^{-1}	100	
			3,4-DHB	9–6,780 ng mL^{-1}	100	
Urine	879 (females)	USA	MeP	Not detected–4,282 ng mL^{-1}	99.9	[39]
			EtP	Not detected–3,010 ng mL^{-1}	60	
			PrP	Not detected–1,002 ng mL^{-1}	98	
			BuP	Not detected–309 ng mL^{-1}	65	

(continued)

Table 4 (continued)

Human matrix	Population (N)	Origin of samples (country)	Target chemicals	Concentration ranges (and max., median, average or geometric mean if available)	Detection rates (%)	References
	970 (males)		MeP	Not detected–7,909 ng mL^{-1}	99.5	
			EtP	Not detected–771 ng mL^{-1}	38	
			PrP	Not detected–1,486 ng mL^{-1}	91	
			BuP	Not detected–723 ng mL^{-1}	28	
Urine	108 (pregnant women)	Japan	MeP	Not detected–1,238 ng mL^{-1}	94	[40]
			EtP	Not detected–2,022 ng mL^{-1}	81	
			PrP	Not detected–5,380 ng mL^{-1}	89	
			BuP	Not detected–82 ng mL^{-1}	54	
Urine	46 (pregnant women)	Korea	MeP	25–75th percentiles (specific gravity adjusted concentrations): 61–452 ng mL^{-1}	98	[41]
			EtP	25–75th percentiles (specific gravity adjusted concentrations): 17–203 ng mL^{-1}	100	
			PrP	25–75th percentiles (specific gravity adjusted concentrations): 0.9–65 ng mL^{-1}	98	
			BuP	25–75th percentiles (specific gravity adjusted concentrations): not detected–0.5 ng mL^{-1}	28	
	46 (newborn infants)		MeP	25–75th percentiles (specific gravity adjusted concentrations): 40–272 ng mL^{-1}	100	
			EtP	25–75th percentiles (specific gravity adjusted concentrations): 1–8 ng mL^{-1}	98	
			PrP	25–75th percentiles (specific gravity adjusted concentrations): 0.8–15 ng mL^{-1}	100	
			BuP	25–75th percentiles (specific gravity adjusted concentrations): not detected–2 ng mL^{-1}	41	

Urine	100 (50 males and 50 females)	Greece	MeP	1–803 ng mL^{-1}	100	[3]
			EtP	<0.5–61 ng mL^{-1}	87	
			PrP	<0.5–575 ng mL^{-1}	72	
			BuP	<0.5–113 ng mL^{-1}	46	
			BzP	<0.2–0.8 ng mL^{-1}	6	
			HeptP	<0.2 ng mL^{-1}	4	
			OH-EtP	<2–71 ng mL^{-1}	87	
Serum	15	–	MeP	0.4–301 ng mL^{-1}	100	[42]
			EtP	Not detected–5 ng mL^{-1}	53	
			PrP	Not detected–67 ng mL^{-1}	80	
			BuP	Not detected	–	
			BzP	Not detected	–	
Urine	60 (males)	Denmark	MeP	Not detected–60 ng mL^{-1}	95	[36]
			EtP	Not detected–21 ng mL^{-1}	30	
			PrP	Not detected–6 ng mL^{-1}	93	
			BuP	Not detected–0.9 ng mL^{-1}	3	
			BzP	Not detected–3 ng mL^{-1}	3	
Urine	261 (123 males and 138 females)	Belgium	MeP	0.3–7,576 ng mL^{-1} (geometric mean: 19 ng mL^{-1})	100	[43]
			EtP	Not detected–887 ng mL^{-1} (geometric mean: 2 ng mL^{-1})	96.6	
			PrP	Not detected–692 ng mL^{-1} (geometric mean: 2 ng mL^{-1})	83.1	
			BuP	Not detected–81 ng mL^{-1} (geometric mean: NA)	41	
Urine	71	USA	MeP	5–95th percentiles: 10–1,830 ng mL^{-1}	100	[44]
			EtP	5–95th percentiles: not detected–347 ng mL^{-1}	59	
			PrP	5–95th percentiles: 0.5–589 ng mL^{-1}	100	
			BuP	5–95th percentiles: not detected–58 ng mL^{-1}	70	

(continued)

Table 4 (continued)

Human matrix	Population (N)	Origin of samples (country)	Target chemicals	Concentration ranges (and max., median, average or geometric mean if available)	Detection rates (%)	References
Amniotic fluid	69		MeP	5–95th percentiles: not detected–3 ng mL^{-1}	42	
			EtP	Not detected	–	
			PrP	5–95th percentiles: not detected–1 ng mL^{-1}	58	
			BuP	5–95th percentiles: not detected–0.3 ng mL^{-1}	6	
Urine	109	China	MeP	0.4–608 ng mL^{-1} (geometric mean: 7 ng mL^{-1})	100	[45]
			EtP	0.1–439 ng mL^{-1} (geometric mean: 2 ng mL^{-1})	100	
			PrP	0.1–202 ng mL^{-1} (geometric mean: 4 ng mL^{-1})	100	
			BuP	0.01–129 ng mL^{-1} (geometric mean: 0.1 ng mL^{-1})	60	
			BzP	0.01–0.1 ng mL^{-1} (geometric mean: 0.01 ng mL^{-1})	19	
Urine	105 (pregnant women)	Puerto Rico	MeP	25th percentile–maximum: 39–7,550 ng mL^{-1}	99.5–100	[12]
			PrP	25th percentile–maximum: 5–3,490 ng mL^{-1}	98.1–99.3	
			BuP	25th percentile–maximum: <0.2–188 ng mL^{-1}	58.4–74.8	
Breast tumours	20	UK	MeP	Mean: 13 ng g^{-1}	NA	[46]
			EtP	Mean: 2 ng g^{-1}	NA	
			PrP	Mean: 3 ng g^{-1}	NA	
			BuP	Mean: 3 ng g^{-1}	NA	
			BzP	Not detected	NA	

Table 5 Estimated daily intake of parabens through human biomonitoring studies

Target chemicals	Origin of samples (Country)	Estimated daily intake (EDI) (μg/kg BW/day)	Equation used	References
Σ_6Parabens ([MeP] + [EtP] + [PrP] + [BuP] + [BzP] + [HeptP])	Greece	2.1–1,313 (median: 23.8)	Estimated daily intake (EDI; μg/kg BW/day) = 50 × [Σ_6Parabens] (μg/L) × 1.7 (L/day)/65.5 kg	[3]
MeP, EtP, PrP, ΣParabens ([MeP] + [EtP] + [PrP])	China	MeP: geometric mean: 6.69 for males	Estimated daily intake (EDI; μg/kg BW/day) = 50 × Ci (μg/L) × 1.7 L (L/day) / BW	[45]
		Geometric mean: 15.9 for females	(C_i : measured urinary concentration of individual parent parabens; BW: 62.7 kg for males and 54.8 kg for females)	
		EtP: geometric mean: 2.50 for males		
		Geometric mean: 3.06 for females		
		PrP: geometric mean: 3.63 for males		
		Geometric mean: 8.94 for females		
		Σparabens: geometric mean: 18.4 for males		
		Geometric mean: 40.8 for females		

whereas in the urine of adults, the total concentrations of OH-MeP were higher than those of MeP, suggesting a potential difference in metabolism between these two age groups [33]. Moreover, 4-HB and 3,4-DHB, two established endocrine-disrupting compounds, were found to be predominant in the urine of children and adults [33].

Based on the measured urinary concentrations of parabens and simple steady-state toxicokinetic models, exposure to parabens was estimated by Asimakopoulos et al. [3] and Ma et al. [45]. Higher concentrations of parabens in females than in males have been associated with high use rates of PCPs by the former group (Table 5) [45].

6 Exposure to UV Filters

UV filters are used as sunscreen agents in PCPs for the protection of skin and hair from UV irradiation [47]. Even though UV filters are designed for external application on the skin or hair, some of them can be absorbed in the human body, further metabolized, and eventually bioaccumulated and/or excreted. Thus, for adequate consumers' protection, the maximum allowed concentrations of UV filters have been regulated worldwide by legislation. The absorption of these chemicals by the human body is linked to various adverse health effects, such as allergic contact dermatitis and endometriosis [47, 48]. Chisvert et al. [47] categorized the UV filters into 9 classes:

1. *p*-Aminobenzoic acid (PABA) and derivatives (i.e. ethylhexyl dimethyl *p*-aminobenzoic acid (EDP) and PEG-25 *p*-aminobenzoic acid (P25))
2. Benzimidazole derivatives (i.e. phenylbenzimidazole sulphonic acid (PBS) and disodium phenyl dibenzimidazole tetrasulfonate (PDT))
3. Benzophenone derivatives (i.e. benzophenone-3 (BZ-3) and diethylamino hydroxybenzoyl hexyl benzoate (DHHB))
4. Benzotriazole derivatives (drometrizole trisiloxane (DTR) and methylene bis-benzotriazolyl tetramethylbutylphenol (MBT))
5. Camphor derivatives (3-benzyliden camphor (3BC), 4-methylbenzylidene camphor (MBC), benzylidene camphor sulphonic acid (BCS) polyacrylamidomethyl benzylidene camphor (PBC), camphor benzalkonium methosulfate (CBM), and terephthalylidene dicamphor sulphonic acid (TDS))
6. Methoxycinnamates (ethylhexyl *p*-methoxycinnamate (EMC) and isoamyl *p*-methoxycinnamate (IMC))
7. Salicylates (ethylhexyl salicylate (ES) and homosalate (HS))
8. Triazine derivatives (diethylhexyl butamido triazone (DBT), ethylhexyl triazone (ET), and bis-ethylhexyloxyphenol methoxyphenyl triazine (EMT))
9. Other filters (butyl methoxydibenzoylmethane (BDM), octocrylene (OCR), and polysilicone-15, P15)

For very few UV filters, BZ-3, MBC, EDP, and PABA, their metabolic pathways are elucidated in vivo and/or in vitro studies [47]. BZ-3 is biotransformed amongst others into 2,4-dihydroxybenzophenone (2,4-OH-BP; or BP-1), 2,2′,4,4′-tetrahydroxybenzophenone (2,2′,4,4′-OH-BP or BP-2), 2,2′-dihydroxy-4-methoxybenzophenone (2,2′-OH-4MeO-BP; or BP-8), 4-hydroxybenzophenone (4-OH-BP), and 2,3,4-trihydroxybenzophenone (2,3,4-OH-BP) [2, 3]. MBC is mainly biotransformed to 3-(4-carboxybenzylidene)camphor (CBC) and four isomers of 3-(4-carboxybenzylidene)hydroxycamphor (CBC-OH) (3-(4-carboxybenzylidene)-6-hydroxycamphor (CBC-6OH) is the major one) [47]. EDP is mainly biotransformed to *N*,*N*-dimethyl-p-aminobenzoic acid (DMP) and *N*-monomethyl-p-aminobenzoic acid (MMP) [47], while PABA is mainly biotransformed to *p*-aminohippuric acid (PAH), *p*-acetamidobenzoic acid (PAcB), and *p*-acetamidohippuric acid (PAcH) [47].

Table 6 Reported total concentrations (ng mL^{-1} or μg g^{-1}) and frequency of detection of BP-UV filters and metabolites (free-form plus conjugates) in human urine and other bodily fluids

Human matrix	Population (*N*)	Origin of samples (country)	Target chemicals	Concentration ranges (and max., median, average, or geometric mean if available)	Detection rates (%)	References
Urine	440 (females)	USA	BP-3	Geometric mean (creatinine-corrected weighted): 27 μg g^{-1}	NA	[49]
Urine	100 (50 males and 50 females)	Greece	BP-1	<1–1,117 ng mL^{-1}	78	[3]
			BP-2	<1–54 ng mL^{-1}	40	
			2,3,4-OH-BP	<1–41 ng mL^{-1}	33	
			BP-8	<2–25 ng mL^{-1}	24	
			4OH-BP	<0.7–47 ng mL^{-1}	23	
Urine	US children (38)	USA and China	BP-3	0.2–713 ng mL^{-1} (geometric mean: 10 ng mL^{-1})	97	[50]
			4-OH-BP	0.1–61 ng mL^{-1} (geometric mean: 0.9 ng mL^{-1})	100	
			BP-1	<0.08–738 ng mL^{-1} (geometric mean: 4 ng mL^{-1})	87	
			BP-2	0.1–18 ng mL^{-1} (geometric mean: 0.2 ng mL^{-1})	29	
			BP-8	<0.2–8 ng mL^{-1} (geometric mean: 0.3 ng mL^{-1})	68	
	US adults (30)		BP-3	0.5–413 ng mL^{-1} (geometric mean: 16 ng mL^{-1})	100	
			4-OH-BP	0.07–6 ng mL^{-1} (geometric mean: 0.3 ng mL^{-1})	93	
			BP-1	0.08–67 ng mL^{-1} (geometric mean: 4 ng mL^{-1})	100	
			BP-2	<0.2–2 ng mL^{-1} (geometric mean: 0.3 ng mL^{-1})	60	
			BP-8	<0.1–1 (geometric mean: 0.2 ng mL^{-1})	53	
	Chinese children (70)		BP-3	0.3–6 ng mL^{-1} (geometric mean: 0.6 ng mL^{-1})	100	
			4-OH-BP	<0.07–0.7 ng mL^{-1} (geometric mean: 0.08 ng mL^{-1})	83	
			BP-1	<0.08–2 ng mL^{-1} (geometric mean: 0.1 ng mL^{-1})	81	
			BP-2		39	

(continued)

Table 6 (continued)

Human matrix	Population (*N*)	Origin of samples (country)	Target chemicals	Concentration ranges (and max., median, average, or geometric mean if available)	Detection rates (%)	References
				<0.2–1.3 ng mL^{-1} (geometric mean: 0.2 ng mL^{-1})		
			BP-8	<0.1–1.4 ng mL^{-1} (geometric mean: 0.09 ng mL^{-1})	20	
	Chinese adults (26)		BP-3	<0.2–9 ng mL^{-1} (geometric mean: 1 ng mL^{-1})	96	
			4-OH-BP	<0.07–6 ng mL^{-1} (geometric mean: 0.08 ng mL^{-1})	77	
			BP-1	0.3–14 ng mL^{-1} (geometric mean: 0.9 ng mL^{-1})	100	
			BP-2	<0.2–23 ng mL^{-1} (geometric mean: 0.9 ng mL^{-1})	77	
			BP-8	<0.1–2 (geometric mean: 0.2 ng mL^{-1})	65	
Urine	506	USA	BP-3	Mean: 60 ng mL^{-1}	100	[6]
Whole blood	101 (children, fetuses, pregnant women, adults)	China	BP-3	<0.4–3 ng mL^{-1}	30–83	[51]
			4OH-BP	0.2–2 ng mL^{-1}	100	
			BP-1	<0.06–0.2 ng mL^{-1}	0–10	
Urine			BP-3	<0.1–45 ng mL^{-1}	25	
			4OH-BP	<0.06–8 ng mL^{-1}	61	
			BP-1	<0.07–20 ng mL^{-1}	57	
Urine	71	USA	BP-3	5–95th percentiles: 4–6,740 ng mL^{-1}	100	[44]
Amniotic fluid	69			5–95th percentiles: not detected–16 ng mL^{-1}	61	
Urine	261 (123 males and 138 females)	Belgium	BP-3	Not detected–663 ng mL^{-1} (geometric mean: 1 ng mL^{-1})	82.8	[43]
Urine	105 (pregnant women)	Puerto Rico	BP-3	25th percentile–maximum: 8–39,700 ng mL^{-1}	99.5–10	[12]
Urine	625 (females)	USA	BP-3	<0.3–5,900 ng mL^{-1}	99	[48]
			BP-1	<0.08–3,200 ng mL^{-1}	93.3	
			4OH-BP	<0.08–22 ng mL^{-1}	83.8	

Table 7 Estimated daily intake of BP-UV filters through biomonitoring data

Target chemicals	Origin of samples (country)	Estimated daily intake (EDI) (μg/kg BW/day)	Equation used	References
Σ_5 BP-UV filters ([BP-1] + [BP-8] + [BP-2] + [2,3,4-OH-BP] + [4OH-BP])	Greece	0.6–1,458 (median: 5.8)	Estimated daily intake (EDI; μg/kg BW/day) = 50 × [Σ_6Parabens] (μg/L) × 1.7 (L/day)/65.5 kg	[3]

The rank order of the studied human biological media for BP-UV filters in descending order is urine > blood plasma or serum > faeces, breast milk, and semen > tissues (liver, kidney, intestine, spleen, brain, heart, testes, placental, skin, and adipose tissue). The most studied class of UV filters is the "benzophenone derivatives" class, and the majority of studies by far are focused on BP-3 (and metabolites) (Table 6).

Calafat et al. [52] determined the total concentrations of BP-3 in 2,517 urine samples (between 2000 and 2004). The concentrations ranged from 0.4 to 21,700 ng mL^{-1}, with a mean value of 23 ng mL^{-1}. Kunisue et al. [48] determined the total concentrations of BP-3 in urine samples from 625 women in ranges from <0.3 to 5,900 ng mL^{-1}. In a biomonitoring study in Greece, Asimakopoulos et al. [3] measured the total concentrations of BP-UV filters (Σ_5BP-UV filters: [BP-1] + [BP-2] + [2,3,4-OH-BP] + [BP-8] + [4OH-BP]) in urine from 100 individuals and also revealed great differences in concentrations, ranging from 0.5 to 1,120 ng mL^{-1}, with a geometrical mean value of 4 ng mL^{-1}. Moreover to our knowledge, the study of Asimakopoulos et al. [3] is the first in which the concentrations of BP-UV filters are expressed on three different bases (volume-, specific gravity-, and creatinine-adjusted bases).

The daily intake assessment of BP-UV filters is more complicated than the other PCPs because of the lack of clear knowledge on metabolic pathways; for example, BP-1 and BP-8 can be found in urine as parent compounds, as they are used directly in sunscreens, but they can also be formed as metabolic products of BP-3 [3]. Thus, taking into consideration that a maximum of 2 % of BP-3 applied on human skin could reach the bloodstream, a factor of 50 was applied to estimate the total exposure amount (50 × 2 = 100 %) [3] (Table 7).

7 Exposure to Insect Repellents

N,*N*-diethyl-m-toluamide (DEET) is the most common active ingredient in insect repellents, and is routinely detected in the environment. Because these insect repellents are sprayed directly on the skin, human exposure is inevitable. DEET is currently registered for use in 225 products in the USA, and it is estimated that the annual usage exceeds 1.8 million kg [53]. DEET is metabolized in the human body

and excreted in urine [54, 55]. Although DEET metabolism is not fully understood, some dealkylated and oxidized metabolites have been reported [1]. The studies on human biomonitoring of DEET are a few compared to the other PCPs. In a study on the general population of the USA (2001–2002), urine samples from 2,535 individuals were analyzed and demonstrated a 95th percentile value of 0.18 ng mL^{-1} [1].

8 Concluding Remarks and Future Perspectives

On the basis of the information presented in this chapter, humans are exposed to a range of chemicals present in PCPs. Toxicological significance of exposure to complex mixture of these chemicals on human health is not known. More information is needed, mostly regarding the importance of the exposure pathways and the factors that affect these exposures. Linking adverse health effects to various PCPs is a very difficult and complicated, and more epidemiological studies are deemed necessary.

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