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Review article

Non-invasive matrices in human biomonitoring: A review

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ABSTRACT

Humans and other living organisms are exposed to a variety of chemical pollutants that are released into the environment as a consequence of anthropogenic activities. Environmental pollutants are incorporated into the organism by different routes and can then be stored and distributed in different tissues, which leads to an internal concentration that can induce different alterations, adverse effects and/or diseases. Control measures should be taken to avoid these effects and human biomonitoring is a very useful tool that can contribute to this aim. Human biomonitoring uses different matrices to measure the target chemicals depending on the chemical, the amount of matrix necessary for the analysis and the detection limit (LOD) of the analytical technique. Blood is the ideal matrix for most chemicals due to its contact with the whole organism and its equilibrium with organs and tissues where chemicals are stored. However, it has an important disadvantage of being an invasive matrix. The development of new methodology and modern analytical techniques has allowed the use of other matrices that are less or non-invasive, such as saliva, urine, meconium, nails, hair, and semen or breast milk. The presence of a chemical in these matrices reflects an exposure, but correlations between levels in non-invasive matrices and blood must be established to ensure that these levels are related to the total body burden. The development of new biomarkers that are measurable in these matrices will improve non-invasive biomonitoring. This paper reviews studies that measure Cd, Pb, Hg, polychlorinated biphenyls (PCBs), polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), polycyclic aromatic hydrocarbons (PAHs), polybrominated diphenyl ethers (PBDEs), organochlorine pesticides and phthalates in non-invasive matrices, the most used techniques for measurements and what alternative techniques are available.

Contents

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1. Introduction

The uptake of environmental chemicals occurs by three main routes – dermal absorption, inhalation and ingestion – which lead to an internal concentration or body burden of the chemical. The body burden is determined by the physical and chemical properties of the chemical, exposure time and the physiological characteristics of the individual (individual susceptibility). The final body burden is a result of absorption, distribution (tissue binding), metabolism and excretion. An absorbed chemical can be handled in different ways. For example, it can be excreted without transformation, metabolized and excreted, stored and slowly excreted or undergo a combination of all these processes (Needham et al., 2005). The properties of the chemical and individual variability will determine the magnitude of these processes and the final fate of the chemical. Chemicals may be excreted in matrices like urine, saliva, breast milk or faeces, stored in matrices like adipose tissue or bone. It is well known that some chemicals can lead to adverse effects and different human diseases (CDC, 2005). Control measures should therefore be taken to reduce exposure as much as possible in order to avoid these adverse effects. The presence of chemicals in the environment can be determined by measurements of their concentrations in environmental matrices such as air, water, soil, food, etc. (environmental monitoring). However, chemical presence in these matrices does not necessary imply adverse effects in human health and therefore their control are not sufficient. These adverse effects are provoked by chemical concentration in the body and human biomonitoring can provide information about the body burden and therefore its potential health effects. Human biomonitoring is defined as the direct measurement of people's exposure to environmental contaminants by measuring substances or their metabolites in blood, urine, or other specimens (CDC, 2008) and is employed in different situations such as: identification and elimination of possible exposure sources (Drexler and Schaller, 1998; Duty et al., 2005); to observe time trends in chemical variations (Jin et al., 2000; Wilhelm et al., 2007a); to prove the effectiveness of bans or restrictions (Schuhmacher et al., 1996; Bates et al., 2002); to identify relationships between chemical exposure and diseases or development abnormalities (Jensen et al., 2005); to map the geographical distribution of contaminated regions (Fitzgerald et al., 1998; Campbell et al., 2003); to find relationships between chemical body burden and eating habits or workplace exposure (Paulsen et al., 1996; Schinas et al., 2000).

Biomonitoring studies can provide a wealth of information but have also some limitations. For example, some chemicals are excreted rapidly and can only be monitored for a short time after exposure. Moreover, human biomonitoring does not reveal exposure sources or routes (Pirkle et al., 1995; Needham and Wang, 2002), although there are some exceptions such as the exposure patterns of some dioxins and dioxin-like chemicals (Schecter et al., 2006). Many discussions have been focused in the correct biomonitoring study design, interpretation, and communication that imply different issues in epidemiology, analysis, ethics, etc. (Schaller et al., 2002; Bates et al., 2005; Paustenbach and Galbraith, 2006; Angerer et al., 2007). Among the numerous issues included in these discussions are the need for standardized protocols (sample collection and preparation, analysis, etc) since quality assurance is crucial to obtain comparable results. Another important question in human biomonitoring is the difficulty to interpret the results. Environmental exposure usually occurs at low levels leading to minimal internal doses and therefore difficult to connect to effects on human health. Knowledge of the toxicokinetic of the chemical and target organs is also essential when selecting the correct matrix in a human biomonitoring study.

Human biomonitoring has been used in occupational medicine since the early 1930's, with the main matrices being urine and blood (Angerer et al., 2007). Blood is an ideal matrix for most chemicals because the blood plasma is in contact with all tissues and is in equilibrium with the organs and tissues where chemicals are deposited. The main disadvantage of using blood in human biomonitoring is that it is an invasive matrix and thus can have an adverse effect on the participant response in volunteer epidemiological studies (Rockett et al., 2004). As chemicals can be stored or excreted in different tissues and organs, theoretically there are many other matrices available for human biomonitoring apart from blood. However, these matrices usually have limitations, such as the amount of matrix available or the amount of chemical deposited. The availability of new methods with much better sensitivity, simplicity and accuracy can provide new opportunities for the use of other matrices than blood.

The aim of this work is to review human biomonitoring studies that employ non-invasive matrices to analyze persistent and/or bioaccumulative chemicals, the matrices most commonly employed in human biomonitoring, and the chemicals measured in each matrix and the analytical techniques used.

2. Methods

We searched for studies that use non-invasive matrices for the determination of persistent and bioaccumulative chemicals in the Web of Knowledge (WOK) and Pubmed databases using combinations of the following words: “hair”, “nails”, “breast milk”, “saliva”, “meconium”, “urine”, “semen”, “teeth”, “sweat”, “faeces”, “placenta”, “bones”, “monitoring”, “biomonitoring”, “human monitoring”, “human biomonitoring”, “biomarker”, “heavy metals”, “Pb”, “lead”, “Cd”, “cadmium”, “Hg”, “mercury”, “MeHg”, “methyl mercury”, “POPs”, “organochlorine pesticides”, “DDT”, “DDE”, “chlordane”, “dieldrin”, “aldrin”, “endrin”, “mirex”, “toxaphene”, “heptachlor”, “hexachlorobenzene”, “hexachlorocyclohexane”, “PCB”, “ PCDDs”, “PCDFs”, “dioxin”, “PAHs”, “phthalates”, “PBDEs”, or “flame retardants”.

3. Results and discussion

The selected chemicals represent different levels of toxicity, ubiquities and industrial uses, although most of them have some characteristics in common, namely persistence, bioaccumulation, bioconcentration or long half-lives in humans and the environment. In addition, they are often found very far from their release source due to transport by the atmosphere, water and migratory species. Table 1 shows some uses of these compounds, their exposure routes, approximate half-lives and how they are released into the environment. The levels of most of these compounds have decreased over the last few years for various reasons: bans (Aldrin, Dieldrin, Endrin, Heptachlor, lead in gasoline), restrictions on their use (DDT), restrictions on their release (PCDDs, PCDFs and PCBs) or substitution and improvement of processes, while levels of others, such as PBDEs, are increasing due to their widespread use and their easy separation or leakage from the surface where they are applied (de Wit, 2002; Solomon and Weiss, 2002). The results presented here are grouped by matrix.

Table 1
Main uses, exposure sources, approximate half-lives of chemicals and how they are released into the environment

Chemical	Uses	Environmental release	Exposure sources	Half-life in the human body
Cadmium	Manufacture of batteries, pigments, coatings and plating, stabilizers for plastics nonferrous alloys.	Secondary lead smelting, primary copper smelting, primary lead production, hazardous and municipal waste incineration and petroleum refining.	Inhalation of cigarette smoke, workplace and food.	10–40 years in the kidney[5]
Lead	Manufacture of storage batteries, solders, metal alloys, plastics, leaded glass, and ceramic glazers.	Occupational and recreational sources, gasoline with lead, lead-based paint and soil contamination.	Contaminated water, inhalation of industrial and traffic smoke.	1–2 months in blood and soft tissue[5] >20 years in skeleton[5]
Mercury	Refining of mercuric sulphide cinnabar ore, electrical equipment, batteries, pigments, dental amalgams.	Combustion of fossil fuels, solid waste incineration, mining and smelting	Fish and seafood and dental amalgams.	1–3 weeks for inorganic and elemental mercury in blood[5] 50 days for methylmercury in blood[5]
PAHs	Manufacture of plastics, dyes and pesticides	Motor vehicle exhaust, residential and industrial furnaces, agricultural burning and wildfires.	Contaminated soils, water and foods, tobacco smoke, and workplace.	5 h–17 days in urine[6]
PCBs	Electrical insulating, heat-exchange fluids.	Waste sites and fires involving transformers and capacitors, fires, repairing and manufacturing transformers, capacitors and hydraulic systems.	Fatty foods (e.g. milk, fish)	1–24 years[2]
PCDDs and PCDFs	–	Incineration or burning of waste, agricultural and forest fires, bleaching processes in pulp and paper mills, chemical syntheses.	Fatty foods (e.g. eggs, animal fats, fish), breast feeding and industrial accidents.	2.9–26.9 years[1]
PBDEs	Flame and fire retardants in commercial and household products.	Household waste deposited into landfills or incinerated.	Inhalation, dermal absorption and consumption of contaminated fatty food (fish, poultry, meat and dairy products), breast milk and workplace.	BDE-153: 6.5 years in plasma [4] BDE-154: 3.3 years in plasma[4]
Organochlorine pesticides	Insecticides, fungicides and antimicrobials.	Application and runoff, disposal of contaminated waste into landfills, emissions from waste incinerators, releases from manufacturing plants.	Fatty foods (milk, dairy products, fish), breast milk, contaminated drinking water and air, workplace.	DDT: 4 years[3] DDE: 6 years[3]
Phthalates	Additives of plastics to improve flexibility and resilience. Present in personal care products, toys, blood-storage bags, plastic clothing, etc.	Direct contact with products that contain phthalates.	Ingestion, and dermal absorption and inhalation.	Non persistent

Sources: [1]EPA (1999a,[2]b), [3]Solomon and Weiss (2002), [4]Geyer et al. (2004), [5]CDC (2005); [6]BIOMONECS (2007).
Abbreviations: BDE-153: 2,2′,4,4′,5,5′-hexabromo-diphenyl ether; BDE-154: 2,2′,4,4′,5,6-hexabromo-diphenyl ether.

3.1. Hair

Human hair is a stable matrix that presents numerous advantages for human biomonitoring, such as easy collection, low cost, easy transport and storage, information about short- and long-term exposure (Barbosa et al., 2005; Angerer et al., 2007; Zhang et al., 2007) and the temporal exposure pattern by segmental analysis. The main disadvantages of this matrix are the difficulty in differentiating between external and internal exposure and variations with hair colour, hair care, race, etc. (Wilhelm and Idel, 1996; Angerer et al., 2007). Studies that use hair for human biomonitoring differ in the length of hair collected, its amount and its position on the scalp, and the hair sample preparation. The Agency for Toxic Substances and Disease Registry (ATSDR, U.S.A.) organized an expert panel for discusses the use of hair in environmental biomonitoring (ATSDR, 2001). Some of the main conclusions of this panel included the difficulty of to distinguish between external contamination and real internal dose, the absence of data for predict adverse effects in health through hair measurements, lack of reference values for correct interpretation. The absence of correlation between hair levels, blood and other target tissues and the limited data for the measure of organic chemicals in hair were also treated. The expert panel underlined the need of standardized procedures of hair analysis including hair collection, sample preparation, etc. and a better knowledge of hair biology. An exception is the measurement of methylmercury in hair that is considered to reflect the internal dose and can predict adverse effects (Harkins and Susten, 2001). Accuracy in analysis is facilitated by the availability of certified hair samples.

Mercury can be found in the body in three chemical forms: elemental, inorganic as ions, and organic as methylmercury. Methylmercury is the dominating species in hair (more than 80%), so total hair-Hg is often used as a measure of methylmercury exposure (Berglund et al., 2005). Human hair is considered to be an excellent indicator of methylmercury exposure. Food is a primary source of mercury exposure, as reflected in the numerous studies that analyze the relation between hair-Hg and diet, mainly fish consumption (Ikingura and Akagi, 1996; Barbosa et al., 2001; Dorea et al., 2003; Agusa et al., 2005; Berglund et al., 2005; Björnberg et al., 2005a; Castilhos et al., 2006). Zhang and Wong (2007) have estimated the importance of different types of fish and some foods in the mercury body burden and have found that fish consumption contributes to more than 97% of the mercury intake. Another source for exposure to mercury is the amalgam in tooth fillings (Schweinsberg, 1994; Morton et al., 2004; Berglund et al., 2005; Díez et al., 2008).

Besides mercury, other heavy metals are determined in hair, such as Cd. Some authors have employed this matrix in studies of Cd exposure in the workplace and the areas around industrial sites (Börjesson et al., 1997; Alonso et al., 2001; Domingo et al., 2001). There is no consensus, however, regarding the relationship between hair-Cd and total body burden. Thus, Nordberg and Nishiyama (1972) have reported a strong positive correlation between hair-Cd and body burden in mice whereas Ellis et al. (1981) did not consider hair-Cd to be a good indicator of body burden. Liu et al. (2001) have found that the correlation between hair-Cd and body burden is weak or moderate by comparing Cd in hair, blood and urine; they observed a stronger association between hair-Cd and urine-Cd than between hair-Cd and blood-Cd.

The other metal commonly measured in hair is Pb, and hair is generally considered to be a valuable indicator for occupational and environmental lead exposure (Wilhelm et al., 1989; Nowak and Chmielnicka, 2000; Sanna et al., 2003). Some authors have described variations in the amounts of hair-Pb with age and gender (Nowak and Chmielnicka, 2000; Souad et al., 2006). The relation between hair-Pb and blood-Pb has been studied by many authors. The results are quite divergent. Štupar et al. (2007) reported a range of hair-Pb and blood-Pb association between 0.03–0.76 from different studies and proposed that the strength of this association is related with Pb levels in the environment or at the occupational site.

Organic pollutants could also be measured in human hair. However, the analytical procedures are not well established and there is no consensus sample preparation to analyze these chemicals. Tsatsakis and Tutudaki (2004) and Schramm (2008) have discussed the main issues using hair in biomonitoring of organic chemicals including extraction methods, methods for the analysis and factors affecting levels of organic chemicals in hair. Altshul et al. (2003) have reported strong and moderate correlations between the hair and blood levels of some of the organic pollutants that they measured (e.g., *p*,*p*'-DDE, *p*,*p*'-DDT, PCB-28, PCB-74). Nakao et al. (2002) have described correlations between some PCDDs, PCDFs and coplanar PCBs levels in blood and hair.

Human hair has also been used to monitor workplace exposure to pesticides, PCDDs, PCDFs and coplanar PCBs (Cirimele et al., 1999; Covaci et al., 2002; Nakao et al., 2005; Chan et al., 2007; Zhang et al., 2007). PAHs have been measured in hair, but to a lesser extent. For example, Toriba et al. (2003) have quantitatively determined 10 kinds of PAHs in 20 subjects using different extraction methods. They found differences between the PAH levels in smokers and non-smokers. Since blood is in contact with the whole organism, it probably gives a better idea of body burden, therefore measurements of PAHs in hair should be compared with those in blood to study their intercorrelation and validate hair as a suitable matrix for determining PAH exposure.

3.2. Nails

Nails have been used historically in forensic science to determine arsenic poisoning and to a lesser extend in monitoring other inorganic chemicals such as heavy metals.

Although both fingernails and toenails can be employed, some authors consider that toenails are better than fingernails because they are less exposed to external contamination (Barbosa et al., 2005). In relation to potential contamination of fingernails, Morton et al. (2004) have investigated inorganic mercury levels in dental workers and in a non-exposed cohort by measuring levels in head hair, pubic hair, fingernails, toenails and urine. They found that fingernails were better than the other matrices for discriminating between dentists and non-exposed individuals while toenails and urine in presented similar results. They suggested that this could reflect direct finger contact with amalgams or contaminated surfaces and not the body burden. The mercury levels in nails have been compared with blood and significant correlations have been found between toenail-Hg and blood-Hg (Alfthan, 1997), and toenail-Hg and methylmercury in blood (Björkman et al., 2007). Besides occupational exposure, nail-Hg has been employed in relation with fish consumption (Ohno et al., 2007; Rees et al., 2007), residential proximity to a mine, or drinking water and soil mercury concentrations (Wickre et al., 2004).

Other metals measured in this matrix are Cd and Pb. Their levels in nails have been compared with those in hair for some authors, finding higher levels of these metals in nails than in hair (Wilhelm et al., 1991; Sukumar and Subramanian, 2007). The levels of these metals in nails have been studied in relation to smoking, health disorders, diet and drinking habits (Mehra and Juneja, 2005) They found significantly higher levels of Cd and Pb in smokers and that the presence of these metals in nails was strongly correlated with health disorders such as hypertension or mental stress.

3.3. Breast milk

This is a very commonly used matrix in human biomonitoring as breast milk measurements give information concerning the exposure levels of both the mother and her child. Breast milk is usually employed for monitoring lipophilic chemicals due to its high fat content. Lipophilic chemicals are stored and equilibrated in the body in different tissues with high fat content and can pass into the breast milk for their excretion. As the lipid concentration of breast milk is not constant, a lipid adjustment (amount of chemical per gram of lipid in human milk) is necessary to compare chemical levels within mothers and between mothers (LaKind et al., 2004). When breast milk is employed for human biomonitoring, it is important to take into account the process of depuration, that is, the reduction of chemicals in milk during lactation (LaKind et al., 2001; Björnberg et al., 2005b; Ettinger et al., 2006).

Although most studies determine organic pollutants, some studies have also determined the level of heavy metals in breast milk. Unlike POPs, heavy metals tend to accumulate in blood more than in breast milk. Sharma and Pervez (2005) have reported that Cd has a lesser tendency to associate with blood and breast milk than Pb and Hg. A significant association has been found to exist between Cd in breast milk and smoking (Solomon and Weiss, 2002). More than 90% of Pb body burden is accumulated in skeleton (WHO, 1995) so the mobilization of Pb from bones during pregnancy and lactation is an important process to mobilise lead in the body (Hernandez-Avila et al., 1996; Ettinger et al., 2004). Gulson et al. (1995, 1997, 1998) and have studied the influence of bone turnover on Pb-blood levels during pregnancy and lactation. They found that bone remodelling is higher in lactation than in pregnancy. Besides pregnancy and lactation, other situations can increase bone turnover and increase Pb levels in blood. Examples are menopause in women, (Silbergeld et al., 1988; Symanski et al., 1995; Berglund et al., 2000), rapid growth (Leggett, 1993; O'Flaherty, 1994), or pathological states (Goldman et al., 1994; Osterloh and Clark, 1993).

The presence of mercury in breast milk has also been studied in relation to amalgam fillings, diet and mercury exposure in polluted areas (Grandjean et al., 1995, Drexler and Schaller, 1998; Ramirez et al., 2000).

POPs have been determined in breast milk in numerous studies. The World Health Organization (WHO) is following the presence of POPs in breast milk since 1976 through The Global Environment Monitoring System/Food Contamination Monitoring and Assessment Programme (GEMS/food Programme). Furthermore, WHO carried out additional surveys measuring PCDDs, PCDFs and dioxin-like PCBs (WHO, 2007). LaKind et al. (2004) have discussed the following issues regarding POPs in breast milk: the levels of most POPs appear to decline during lactation; the levels of these compounds appear to decrease with successive lactation; POP levels increase with the age of the mother; and consumption of fish and marine mammals from polluted waters is associated with levels of some of these compounds.

Breast milk has also been employed monitoring different pesticides and others compounds included in The Stockholm Treaty (Dewailly et al., 1996; Smith, 1999; Norén and Meironyté, 2000; Romero et al., 2000; Campoy et al., 2001; Moreno Frías et al., 2004; Ribas-Fito et al., 2005; Damgaard et al., 2006; Tanabe and Kunisue, 2007). Emerging chemicals such as phthalates and PBDEs can be found in breast milk (Calafat et al., 2004; Kalantzi et al., 2004; Andersson et al., 2006; Main et al., 2006; Inoue et al., 2006; Gómara et al., 2007). Fig. 1 shows the differences in the number of studies biomonitoring these chemicals.

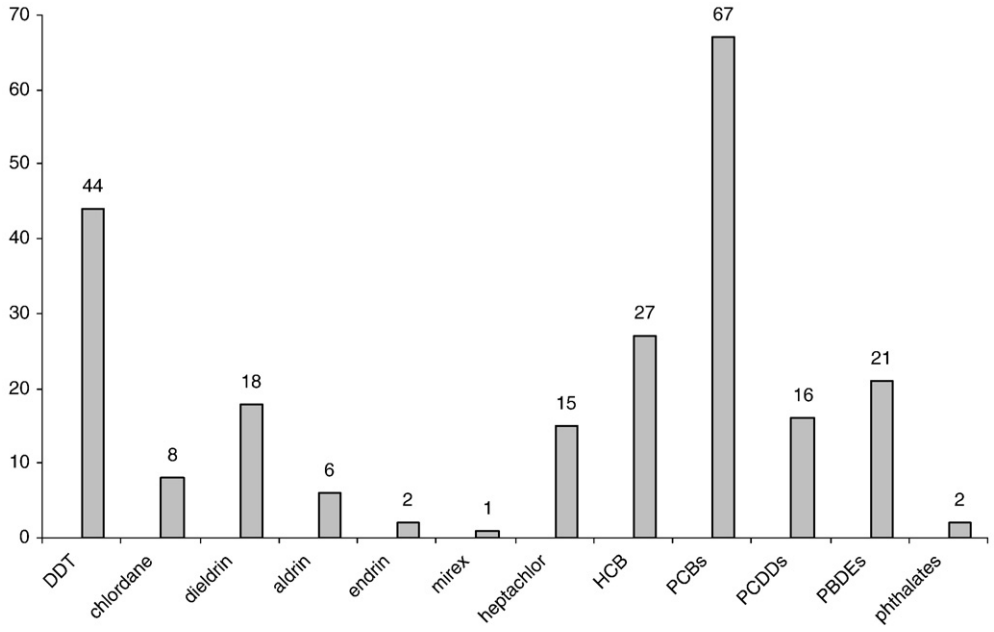

Fig. 1. Number of articles in PubMed using humans like limits and search terms: "respective chemical" and "breast milk" and "monitoring".

3.4. Saliva

This is an easy-to-collect low-cost matrix that is very useful for screening large populations (Kaufman and Lamster, 2002). Saliva is excreted by the salivary glands, which have high blood flow, and chemicals and their metabolites pass into the saliva by different mechanisms (Höld et al., 1995). The presence of a chemical in saliva depends on its chemical characteristics, both lipophilic and non-ionized molecules pass from blood to saliva better than hydrophilic and ionized molecules (Kaufman and Lamster, 2002). Saliva has a very high water content and low protein content, which means that strongly protein-bound chemicals are unlikely to be present in this matrix (Silva et al., 2005). Many factors, such as circadian rhythms, exercise, medication or age, can influence the flow and physiological characteristics of saliva (Dawes, 1981; Aps and Martens, 2005), and this has to be considered when saliva is used for biomonitoring. On the other hand, these changes in saliva flow do not influence all substance concentrations to the same degree (Vining et al., 1983). Blood contamination must be avoided when saliva is collected because this fact can lead to overestimation of chemicals if their concentrations are higher in blood than in saliva.

Saliva collection can be done directly from the salivary glands or using whole saliva, which is a complex mixture of oral fluids, including secretions from the salivary glands, gingival crevicular fluid, expectorated bronchial and nasal secretions, serum and blood derivatives from oral wounds, etc. (Kaufman and Lamster, 2002). There are many methods for saliva collection, including spitting into a collection vial, wiping the oral cavity with a swab or other collection devices either with or without stimulation (Silva et al., 2005). Saliva stimulation can change saliva composition due to a number of active salivary glands. For example, parotid gland in unstimulated conditions contributes 20% and in stimulated parotid saliva is 50% (Edgar, 1990).

Saliva is widely employed for biomonitoring medicines, drugs, narcotics, hormones and some clinical analysis (Aps and Martens, 2005) although is not currently used for environmental exposure biomonitoring to the same extend and there is no consensus in its use for this aim. Pb level has been measured in saliva and its level in this matrix is about 15–50% of Pb levels in whole blood (Koh and Koh, 2007). González et al. (1997) have detected Pb and Cd in saliva and considered it a potential technique for monitoring recent exposure to environmental pollutants; Similarly, White et al. (1992) have measured Cd in this matrix and suggested that saliva-Cd may reflect recent exposure to this metal. However, many authors subsequently studied the use of saliva for Pb and Hg monitoring in different situations and found that saliva was not a good matrix for this aim (Pesch et al., 2002; Wilhelm et al., 2002; Zimmer et al., 2002; Koh et al., 2003; Barbosa et al., 2006). Omokhodion and Crockford (1991a) have found a poor relation between lead levels in saliva and those in blood.

Few studies determine organic chemicals in saliva. Ogawa et al. (2003), for example, have analyzed PCBs and PCDDs levels in saliva and blood. They have detected different PCBs and PCDDs in saliva finding higher levels for 2,3′,4,4′,5-pentachlorobiphenyl (PCB 118) and 1,2,3,4,6,7,8,9,-octachlorodibenzo-*p*-dioxin (OCDD). Levels of dioxins and coplanar PCBs were lower in saliva than those in blood.

Other organic chemicals measured in saliva include phthalates and their metabolites. For example, Silva et al., 2005 compared phthalates levels measured in saliva with levels in urine and blood in other studies and concluded that salivary levels were lower than urinary but comparable with phthalate levels in blood.

3.5. Meconium

The main advantage of this matrix is its easy collection, the large amount of sample that can be collected and the information it can give regarding long-term exposure. A foetus can be exposed to different chemicals, most of which are deposited and accumulated in the meconium. This process occurs through bile secretion and/or foetal swallowing of amniotic fluid, starting from the 12th week of gestation (Ostrea et al., 1989). An individual or pool sample can be used for the measurement, although when sporadic exposures are to be studied the collection of a pool sample of meconium is advisable because the chemical deposition is also sporadic and the chemical is more likely to be detected (Ramirez et al., 2000).

Pb, Cd and Hg have been detected in meconium by different authors (Ramirez et al., 2000; Ostrea et al., 2002; Turker et al., 2006; Unuvar et al., 2007), although differences in the presence of these heavy metals in meconium and blood were found: Ramirez et al. (2000), for example, did not detect Hg in some maternal blood samples but detected Hg in their infants' meconium.

Ostrea et al. (2008) have analysed the presence of several organochlorine pesticides in this matrix. They compared meconium with infant hair and cord blood and concluded that meconium was the best matrix for the determination of foetal exposure to pesticides. Other authors have also measured organochlorine pesticides (Ostrea et al., 1998; Hong et al., 2002; Ostrea et al., 2002; Garcia et al., 2006; Zhao et al., 2007) as well as PCBs (Zhao et al., 2006, 2007) and phthalates (Kato et al., 2006a,b) in meconium.

3.6. Urine

This is probably the second most common matrix for human biomonitoring, particularly for water-soluble chemicals. Two different types of urine samples can be collected, namely spot samples or 24-h samples. The collection of spot samples is easier, therefore they are employed more often. However, spot samples have the disadvantage of varying volume and chemical concentration (Barr et al., 2005a), both of which mean that spot samples must be adjusted. This adjustment can be performed by different methods, but the most commonly used is the creatinine concentration adjustment (Barr et al., 2005b).

Urine is the preferred non-invasive matrix in heavy metals biomonitoring (Fig. 2).Moon et al. (1999) have studied the correlation between Pb and Cd in blood and urine and concluded that urine-Cd is a better biomarker than urine-Pb for general population biomonitoring. Barbosa et al. (2005) have reported that the use of urine for monitoring lead exposure is limited to long-term occupational exposures. Urine-Hg has been related to several factors, such as amalgam fillings, occupational exposure, fish consumption, environmental pollution, etc. Berglund et al. (2005) have studied total, inorganic and organic mercury levels in urine and their relationship with the levels in other matrices; they found that more than 98% of the mercury present in urine was inorganic and that its level in urines highway strongly correlated with those in blood, plasma and red blood cells.

Urine is not a useful matrix for monitoring POPs, although some authors have studied POP exposure by measuring their metabolites, such as DDT and DDA [2,2-bis(*p*-chlorophenyl)acetic acid] (Edmundson et al., 1970) or HCH and chlorophenols (Angerer et al., 1983; Drummond et al., 1988; Mari et al., 2007). Other authors have studied POP exposure by indirect measurements, such as the case of organochlorine pesticides, PCBs and TCDD, with D-glucaric acid (Hunter et al., 1972; Ideo et al., 1985; Apostoli et al., 2003; Ayotte et al., 2005).

Many metabolites of PAHs can be measured in urine (Table 2). Recent exposure to PAHs, for example, is often determined by the presence of 1-hydroxypyrene (1-OHP) (Ptashekas et al., 1996; Strickland et al., 1996; Domingo et al., 2001; Schuhmacher et al., 2002; Agramunt et al., 2003; Campo et al., 2006; Mari et al., 2007; Wilhelm et al., 2007b). Although 1-OHP is a metabolite of pyrene, it is considered a suitable surrogate marker of PAH exposure because this exposure frequently occurs with a mixture of PAHs where pyrene is present (Mucha et al., 2005).

Phthalate metabolites are also usually measured in urine. Phthalates are widespread and their assessment can lead to erroneous values due to contamination of the samples, which is why their metabolites are measured instead of the parent compounds (Latini, 2005). In addition, phthalates are rapidly metabolized. Table 2 shows some of the most used phthalates and their monoester and other oxidized metabolites assessed in urine. Many authors have used the measurement of phthalate metabolites to assess phthalate exposure (Liss et al., 1985; Blount et al., 2000; Koch et al., 2003; Kato et al., 2004; Silva et al., 2004; Duty et al., 2005; Weuve et al., 2006; Fromme et al., 2007a; Wittassek et al., 2007). However, this is not a good assessment method when the phthalates concerned have side chains containing eight or more carbon atoms. For example, Kato et al. (2005) have developed a method for determining total exposure to phthalates by measuring the concentration of phthalic acid in urine, although this technique has the disadvantage that it does not give information about the parent phthalate.

The presence of PBDEs in urine has also been employed for human biomonitoring, although less frequently. The Integrated Exposure Assessment Survey (INES, Germany) includes PBDE measurements in urine, but the results are not available at present (Fromme et al., 2007b).

Urine is widely employed in large environmental studies such as the German Environmental Survey for Children (GerES) and the National Health and Nutrition Examination (NHANES). The Third National Report on Human Exposure to Environmental Chemicals

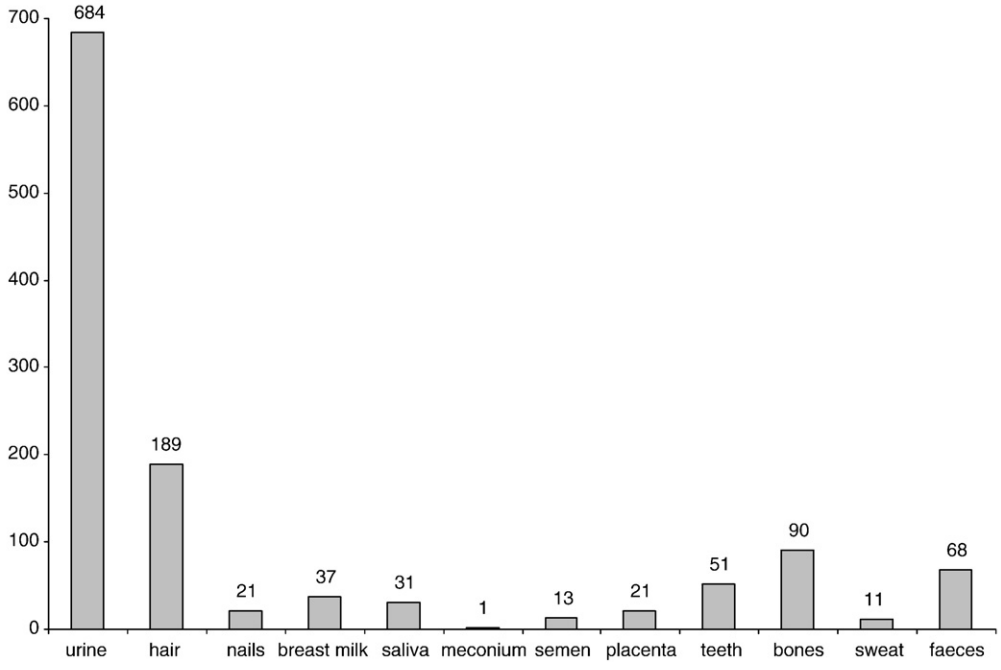

Fig. 2. Number of articles in PubMed using humans like limits and search terms: “respective matrix” and “heavy metals” and “monitoring”.

Table 2
Some PAHs and phthalate metabolites measured in urine

Chemical	Metabolite
PAHs	
Benz[a]anthracene	1-Hydroxybenz[a]anthracene; 3-Hydroxybenz[a]anthracene and 9-Hydroxybenz[a]anthracene
Benzo[c]phenanthrene	1-Hydroxybenzo[c]phenanthrene; 2-Hydroxybenzo[c]phenanthrene; 3-Hydroxybenzo[c]phenanthrene
Chrysene	1-Hydroxychrysene; 2-Hydroxychrysene; 3-Hydroxychrysene; 4-Hydroxychrysene; 6-Hydroxychrysene
Fluoranthene	3-Hydroxyfluoranthene
Fluorene	2-Hydroxyfluorene; 3-Hydroxyfluorene; 9-Hydroxyfluorene
Phenanthrene	1-Hydroxyphenanthrene; 2-Hydroxyphenanthrene; 3-Hydroxyphenanthrene 4-Hydroxyphenanthrene; 9-Hydroxyphenanthrene
Pyrene	1-Hydroxypyrene
Benzo[a]pyrene	3-Hydroxybenzo[a]pyrene
Naphthalene	1-Hydroxynapthalene; 2-Hydroxynapthalene
Phthalates	
Dimethyl phthalate (DMP)	Monomethyl phthalate (MMP)
Diethyl phthalate (DEP)	Monoethyl phthalate (MEP)
Dibutyl phthalates (DBP)	Mono-*n*-butyl phthalate (MnBP); Monoisobutyl phthalate (MiBP)
Benzylbutyl phthalate (BzBP)	Monobenzyl phthalate (MBzP) (some mono-*n*-butyl phthalate)
Dicyclohexyl phthalate (DCHP)	Monocyclohexyl phthalate (MCHP)
Di-2-ethylhexyl phthalate (DEHP)	Mono-2-ethylhexyl phthalate (MEHP); Mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP); Mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP)
Di-*n*-octyl phthalate (DOP)	Mono-*n*-octyl phthalate (MOP); Mono-(3-carboxypropyl) phthalate (MCPP)
Diisononyl phthalate (DiNP)	Monoisononyl phthalate (MiNP)

Sources: adapted from the Third National Report on Human Exposure to Environmental Chemicals (CDC, 2005).

(CDC, 2005) lists urinary levels of Pb, Cd, Hg, PAH metabolites and phthalates, and GerES IV (Umweltbundesamt, 2008) includes Cd, Hg and PAH metabolite measurements in urine. This latter study highlights the relationship between urine-Cd and age, urine-Cd and smoking, urine-Hg and amalgam fillings, and urine-1-OHP and smoking.

3.7. Other non-invasive matrices

Other non-invasive matrices, such as deciduous teeth or sweat, can also be used but have the drawback of low availability or are difficult to collect. Despite these drawbacks, some authors have employed them, for example, for lead biomonitoring (Omokhodion and Howard, 1991b; Nowak and Chmielnicka, 2000). Faeces are another rarely used non-invasive matrix that has, however, been used for the biomonitoring of metals as Cd (Kikuchi et al., 2003), and Pb (Claeys-Thoreau et al., 1987), or chemicals like PCDDs, PCDFs (Schrey et al., 1998), PCBs and organochlorine pesticides (Moser and McLachlan, 1999).

Semen is used to assess effect biomarkers in most studies. Exposure biomarkers are measured in other matrices and then related with semen quality parameters. A minority of studies, however, determine heavy metals in semen or seminal plasma (Hanf et al., 1996; Alexander et al., 1998; Xu et al., 1993,2003), organochlorinated pesticides (Kumar et al., 2000; Younglai et al., 2002; Pant et al., 2007), dioxins (Schecter et al., 1996), phthalates (Kato et al., 2006a; Zhang et al., 2006).

Placenta can be employed for human biomonitoring. This matrix is easy to collect, provides large amounts of sample for analysis and presents the same advantages as blood. The use of placenta in human biomonitoring was proposed as far back as 1974 (Baglan et al., 1974). Placenta has been employed for human biomonitoring by many authors, with Cd and Pb being measured more than Hg (Iyengar and Rapp, 2001). Organic chemicals, mainly organochlorine pesticides, have also been measured in this matrix (Falcón et al., 2004; Lopez-Espinosa et al., 2007; Shen et al., 2007a,b; Galassi et al., 2008). Similarly, exposure to PCDDs, PCDFs and PCBs (Wang et al., 2005; Chan et al., 2007), PAHs (Madhavan and Naidu, 1995; Gladen et al., 2000), PBDEs (Gómara et al., 2007) and phthalates (Mose et al., 2007) has been determined in placenta.

Bones are employed as a non-invasive matrix in Pb monitoring. Skeletal lead can be considered in two different ways: as a repository — providing an estimation of the level of Pb accumulated in bones — or as a source — increasing the endogenous exposure due to increase in bone turnover. Hu et al., 1998 have discussed the importance of these two paradigms of skeletal lead. Lead concentration in bone can be determined by two types of X-ray fluorescence (XRF), LXRF (L-line X-ray fluorescence) or KXRF (K-line X-ray fluorescence), being KXRF most used and validated (Hu et al., 1998). Measurements of Pb levels in bones have been compared with those in blood and studied in relation to different diseases or adverse effects. Some studies report significant relations between Pb-bone and adverse effects, while this is not always the case with Pb-blood (Hu et al., 1994, 1996; González-Cossío et al., 1997). Therefore Pb-bone is considered a better indicator of Pb dose than Pb-blood in some situations.

4. Conclusion

In general and although many matrices can be employed in human biomonitoring, none of them is useful in every situation and therefore there is not and unique ideal matrix. This ideal matrix should have several characteristics, for example, must be accessible in sufficient amounts for the analysis, must not pose a health risk for the donor, must contain chemical levels detectable by the techniques available and must reflect the body burden. An additional characteristic is its ease of collection and storage. Moreover, that ideal matrix should be useful for the determination of any chemical.

Blood is an ideal matrix for most chemicals as it is in continuous contact with the whole organism and in equilibrium with the organs and tissues where chemicals are deposited. However, blood is not ideal to trace bioaccumulated chemicals. In addition, blood is an invasive matrix and the amounts that can be collected are limited, whereas other matrices such as urine can be collected in larger amounts and by non-invasive methods. Despite these disadvantages blood is widely employed for human biomonitoring even though its use is restricted in some cases, such as biomonitoring studies in children and newborns.

Non-invasive matrices do not present this limitation but present other disadvantages. The main disadvantage for hair and nails is the possibility of external contamination — these matrices are exposed to the environment and therefore chemicals can easily be deposited on them. This problem can be eliminated by washing hair and nails samples, although this complicates the analysis to rather a large extent.

Breast milk is probably the most invasive matrix of the non-invasive ones. The main drawback of this matrix is its availability restricted to lactating women. The same limitation is found in the use

of placenta and meconium. Despite this, breast milk, placenta and meconium can still provide useful information about time trends in chemical exposure.

The disadvantage of saliva is related to its flow, which is influenced by many factors. Saliva flow does not influence all substance concentrations to the same degree, so it can still be a useful matrix for non-flow-dependent chemicals.

The variability of urine volume and chemical concentration are the main drawbacks of urine measurements; these can be corrected by using creatinine concentration as a neutral marker for urine production.

Along with the specific limitations for each matrix there are limitations that are common to every matrix and must be taken into account, such as the levels of chemicals present. The target chemical must be present in the chosen matrix at levels that are measurable by the techniques currently available. The development and refinement of analytical techniques provides lower limits of detection, which allows lower chemical concentrations to be measured. A good example of these analytical techniques is ICP-MS, which allows the detection of nanogram quantities of multiple elements in hair (Goullé et al., 2005; Rodrigues et al., 2008), nails (Batista et al., 2008), urine (Goullé et al., 2005; Minnich et al., 2008), or GC-HRMS, which can measure femtogram or picogram quantities of POPs in breast milk (Barr et al., 2005a). The measurements of these low concentrations imply very strict laboratory conditions due to the risk of contamination of the samples and therefore these techniques are not suitable for routine analysis. There are many techniques employed in chemical determinations which have different characteristics, therefore, they should be chosen depending on the matrix employed, chemical levels expected, type of studies, etc. Table 3 shows the most common analytical techniques for human biomonitoring of heavy metals and organic chemicals in non-invasive matrices.

Besides these common analytical techniques, various alternative analytical techniques are available. These methods can be novel or old ones that are used in special situations. ALA (δ-aminolevulinic acid), for example, has been widely used to determine lead exposure in working place environments. Its use is currently limited to parts of the world where economic resources are limited and high environmental lead exposure is likely. Urinary ALA measurements can only be applied to monitor exposure situations resulting in blood-Pb levels higher than 400 μg/L (Graziano, 1994), which means that this technique is not suitable for general population biomonitoring. Khan et al. (2007), for example, have developed a novel method for the trace determination of Pb based on the reaction between dithizone and Pb^{II} in acid solution, which produces a violet chelate product and cationic micelles. These authors compared their results with levels in urine and blood measured with atomic absorption spectrometry and obtained good agreement.

Table 3
Common analytical methods employed in human biomonitoring

Chemical	Analytical techniques
Inorganic chemicals	AAS
	NAA
	ICP-OES
	ICP-MS
Organic chemicals	CE-MS
	GC-EC
	GC-MS
	GC-HRMS
	GC-MS/MS
	HRGC-HRMS
	HPLC-MS/MS

Abbreviations: AAS: atomic absorption spectrometry; NAA: neutron activation analysis; ICP: inductively coupled plasma; OES: optical emission spectrophotometry; CE: capillary electrophoresis; GC: gas chromatography; EC: electron capture; MS: mass spectrometry; HRMS: high-resolution mass spectrometry; HRGC: high-resolution gas spectrometry; MS/MS: tandem mass spectrometry; HPLC: high-performance liquid chromatography.

Some of the samples were from traffic police and non-exposed adults, whose urine-Pb levels, as obtained by AAS, were 20.0 and 0.08 μg/L respectively. The respective values obtained by their proposed method were 20.8 ± 1.2 and 0.09 ± 0.03 μg/L. Yantasee et al. (2007) have developed a microanalyzer based on the flow-injection/voltammetric analysis of Pb, which is a new field-portable method for lead detection in a non-invasive matrix such as urine.

Another possibility for determine the chemical exposure in non-invasive matrices is to measure chemical metabolites or even other molecules. An example, is PAHs exposure which can be assessed by DNA adducts in urine (Angerer et al., 2007), semen (Paracchini et al., 2005) or exfoliated ductal ephitelial cells present in breast milk (Thompson et al., 1998). Biochemical techniques such as the enzyme-linked inmunosorbent assay (ELISA) have been also employed for human biomonitoring. Sugawara et al. (1998) have developed an immunoassay based on polyclonal antibodies for PCDDs and PCDFs and have employed this method for the determination of dioxins in breast milk (Sugawara et al., 2002). They proposed that their method could be used as a TEQ screening method for PCDDs and PCDFs. ELISA has also been employed for the determination of trichlorophenols (TCPs), which are considered to be potential exposure biomarkers of many organochlorinated chemicals, in urine (Galve et al., 2002; Nichkova and Marco, 2006). ELISA has also been employed to determine environmental exposure to heavy metals by measuring metallothionein levels in urine (Swierzeck et al., 2004). Another alternative technique for human biomonitoring in non-invasive matrices is the chemically activated luciferase expression (CALUX) bioassay, which allows the detection of Ah receptor agonists such as PCDDs, PCDFs and dioxin-like PCBs. This bioassay has been used for human biomonitoring of these compounds in breast milk (Laier et al., 2003; Soechitram et al., 2003; Hui et al., 2007). Both, ELISA and CALUX are useful and specific techniques but has been sometimes criticised because they do not give information about specific chemicals but related group of chemicals. On the other hand and for control purposes biomarkers of Chemicals Groups are very useful because they can give a good idea of trends variations.

Other important issue is the relationship between chemical levels in a matrix and the real body burden. The presence of a chemical in a matrix reflects exposure to this chemical, but the concentration measured might not be related to the body burden. It is therefore necessary to validate the measurements in these matrices. Blood, for example, is considered to be a good reflection of the internal chemical concentration, which means it is a good matrix for comparison and validation studies. Many studies have analyzed the associations between matrices and age, gender, diet, amalgam fillings, etc. Other studies have involved chemical measurements in different matrices, although not many have analyzed the correlations between blood and non-invasive matrices.

5. Final remarks

Human biomonitoring studies are a useful tool to assess environmental chemical exposure in population such as POPs and bioaccumulative metals, and are necessaries in order to impose measures to avoid or minimize their presence in the environment and their subsequent health effects. These studies imply the use of biological matrices and if those are non-invasive the control will be less disturbing for the donors and consequently would have a greater acceptance in volunteer studies.

There is not an ideal matrix useful in every situation. Depending on the target chemical, toxicokinetic of the chemical, LODs, available amounts, etc. one matrix will be more suitable than the others.

Chemicals leave a trace in the organism after exposure, for some chemicals this trace can be easily followed but not for others, therefore it is essential to continuously investigate and improve the development of new exposure or effect biomarkers that allow this trace to be

detected and the extent of exposure determined. Furthermore, since some restrictions and bans are focused on groups rather than on specific chemicals, the development of group biomarkers is especially important for biomonitoring studies designed for those purposes.

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