Human biomonitoring to define occupational exposure and health risks in waste incinerator plants

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Abstract: A contribution to the research on the relationship between exposure to ambient pollutants and diseases comes from human biomonitoring data collection and interpretation. The 21 biomonitoring studies reviewed are mainly aimed at providing either information on exposure amongst worker subgroups, serving as a reference, or information on the relationship between exposure and toxicity. Attention was also paid to the relationship between internal biomarker dose and environmental pollution levels through a combined use of biomonitoring epidemiological study design and environmental monitoring. Marker levels of internal dose (in blood and urine), DNA damage and oxidative stress tend to be higher mostly in highly exposed workers, i.e. those employed in furnace maintenance, residue transfer, cleaning operations, metal disposal and all activities where there is direct contact with fly ash. The presence of old furnaces or non-upgraded plants was associated with acute and chronic health problems in workers.

Keywords: biomarkers; health risk; human biomonitoring; waste incinerator; occupational exposure; workers.

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1   Introduction

Environmental epidemiology, supported by biomonitoring investigating tools, helps to clarify the possible adverse effects on the health of workers and residents that can be ascribed to anthropogenic sources of pollution. Incineration produces energy, gases which are emitted into the atmosphere and solid residues that must be disposed of. The main hazards arising from incineration are toxic metals, dioxins and particulates. The numerous epidemiological studies carried out on the contamination caused by waste incinerators, have been, over time, revised by several authors (Allsopp et al., 2001; Hu and Shy, 2001; Domingo, 2002; Rushton, 2003; Enviros Consulting Ltd and University of Birmingham, 2004; Franchini et al., 2004). Reviews reveal the existence, both for residents and workers, of possible causal links with some specific outcomes, even if results are accompanied by fairly large statistical uncertainties, and limits in the study design and in the analytical support tools used (Enviros Consulting Ltd and University of Birmingham, 2004; Franchini et al., 2004). In order to evaluate the carcinogenic effects in the residents, a possible link has been investigated with stomach, colon, liver, larynx and lung cancer, cancer in children, soft tissue sarcomas and non-Hodgkin's lymphoma and also with other outcomes of interest such as respiratory function and reproductive problems. In general, some excesses have been found nearby old plants (highly polluting due to lack of controls on emissions) for some of the outcomes in question, even if the statistical association generally was not strong enough to support a causal link with the presence of the plants. With regard to modern plants, no particular causal link was found with the incidence of cancer, respiratory symptoms or reproductive problems (Enviros Consulting Ltd and University of Birmingham, 2004). Occupational studies (reviewed in Franchini et al., 2004) provided some evidence on lung cancer, oesophageal cancer, blood poly-chlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans (PCDD/F) level; an increased risk of producing urinary mutagens in exposed workers was reported. Biomonitoring studies did not provide conclusive evidence: in some studies exposure to poly-chlorinated biphenyls (PCBs) and heavy metals were associated with reduction of thyroid hormones.

However studies on workers exposure are consistent in indicating a greater polluting body burden [dioxin, polycyclic aromatic hydrocarbon (PAH) and metals] in workers in direct contact with the source of environmental chemicals. Therefore indication of differential exposure is recognisable between groups of workers charged with specific tasks when compared to the general population (Bianchi et al., 2006). Studies at present do not provide sufficient analysis of mortality and morbidity for the category of people mostly exposed (Enviros Consulting Ltd and University of Birmingham, 2004).

Uncertainty of results is due to the complexity of investigation of the relationship between exposure to environmental pollutants and related diseases. The limited knowledge of the events taking place in the health continuum, from the point of exposure to the onset of disease, is the main source of uncertainty of the results despite the numerous studies.

Further knowledge should come from the impact assessment practice, recently undertaken, to monitor the activities of newly built plants. Results from this monitoring activity indicates a noticeable reduction in the emission of dioxins and metals, due to modern abatement systems (Lonati et al., 2007) compared to old plants, and show negligible increase of pollutants compared to background levels (Caserini et al., 2004) or compared to other sources present at the same time (Meneses et al., 2004).

Priority needs for research on health risks from waste management practices include the development and application of biomonitoring, both in human observational studies and in toxicological research, the use of pharmacokinetic models to assess the influence of factors such as metabolism and timing of exposures, and the analysis of all relevant environmental matrices, in order to evaluate chemical exposure pathways and to assess the exposure for specific subsets of the population (World Health Organization Regional Office for Europe, 2007).

2   Health risk evaluation and biomonitoring data

The planning of policies in the health sector and the programming of prevention activities are based, on one side, on the knowledge of the receptor's characteristics and on the other of environmental contamination level, of population exposure level and of the dispersion and diffusion dynamics of contaminants.

Biomonitoring, used for many years in its elective form in occupational medicine, has also been widely used, in the last 10 years, in population studies to monitor contamination levels in the human body in cases of mixed exposure and very low environmental concentration. In this exposure conditions, a descriptive approach to the biomonitoring data makes it possible to perform a comparison of exposed population with a value in a reference population, or a comparison of different exposure groups with thresholds limit values. Such a descriptive approach is not adequate to perform risk assessment (Committee on Human Biomonitoring for Environmental Toxicants, 2006).

Procedures to assess the risk of adverse health effects on the basis of daily intake of a given chemical, make use of an approach that is rated highly complex in the logic of epidemiological research, since it requires a prior explanation of the mechanisms leading to the onset of early biological effects. When traditional tools are unable to evaluate the risk because of poor knowledge of the contamination pathways, it can be estimated measuring the level of chemicals absorbed and levels of effective dose (in this case the knowledge of individual susceptibility to a certain level of contaminant will improve the quality of results). The epidemiological study design with the support of pharmacokinetic models, linking individual concentrations measures with the exposure dose, contributes to the definition of biomarker–effect relationship. Measurement of spatial and temporal variation in burden levels, validation of new predictive biomarkers of a disease, are also allowed through this alternative approach to risk evaluation (Committee on Human Biomonitoring for Environmental Toxicants, 2006).

A new research area in public health, called 'molecular epidemiology', develops the knowledge of the interaction between genetics and environment, using 'high throughput' biomarkers and techniques in molecular biology as investigating tools, to evaluate the health risks caused by environmental exposure on an affected population.

A list of the main activities of biomonitoring, already in place or planned at an international level and recorded by Albertini et al. (2006) shows a rapid increase, in the first 5 years of the twentieth century, in the use of biomarkers as a valid tool to evaluate environmental exposure for risk assessment purposes. However, due to the different sources of variability and error that characterise the use and the interpretation of biomonitoring data, a critical approach must accompany the evaluation of epidemiological studies based solely on biomonitoring data. At present, several Programmes are being used for the evaluation and standardisation of this new epidemiological tool.

A recent publication in Italian reviewed 32 publications on the issue of incineration and related health risks (Bianchi et al., 2006). It showed that most of the studies assessed the individual exposure using biomarkers, while 'traditional' epidemiological studies, based on surrogate exposure metrics, appeared to be decreasing in number.

The present paper is a revision of the studies published over the period 2003–2007 on environmental and biological monitoring in relation to health risk identification for waste incinerator workers. It has the scope of highlighting:

- the different interpretative options on the use of biomonitoring still aimed at improving the definition of risk exposure for workers (Table 1);

- study design both aiming at looking for early measurable alteration (biochemical, morphological or functional alterations) and at identifying indicators of any individual predisposition to develop pathologies associated with exposure to xenobiotics;

- the possible contribution of measuring human biomarkers in risk assessment.

The present paper proposes to clarify data gaps and new knowledge about occupational health in the framework of biomonitoring tool in epidemiology research.

Table 1   Major biomarker case-example to illustrate interpretative options

Chemical	*Biomarker*	*Interpretative option of biomonitoring study*	*Ref.*
Metals and organic substances, PBDEs, PCDD/Fs and PCBs	Urinary and blood metals and organic metabolites, hair dioxins and congeners	Comparison between subgroups or with a reference population or with Threshold Limit Value (TLV) to obtain exposure information	Agramunt et al. (2003); Maitre et al. (2003); Hu et al. (2004); Nakao et al. (2005); Lee et al. (2007); Mari et al. (2007)
PAH, dioxins, lead, dust	Blood lead, biological tests, DNA damage, gene expression profiles, protein expression, urinary metabolite, leukocyte subpopulation, serum immunoglobulins and cytokines	Comparison of subgroups to evaluate biological functions, morbidity, toxic effect	Hours et al. (2003); Kim et al. (2004); Oh et al. (2005)

Table 1 Major biomarker case-example to illustrate interpretative options (continued)

Chemical	Biomarker	Interpretative option of biomonitoring study	Ref.
PAH, dioxin	CYP1B1 gene expression	Comparison of exposure groups with controls to develop dose–response relationship	Toide et al. (2003); Hu et al. (2006)
PAH	1-OHPG	Use of epidemiology study to estimate exposure dose from amount excreted in urine. Susceptibility	Lee et al. (2003)
Dioxin, Fly ash	Blood PCDD/Fs, malondialdehyde and lipid peroxide; urinary 8-OH-dG and biopyrrins	Use of epidemiology studies to develop dose–response relationship	Yoshida et al. (2003); Shih et al. (2006)
Dioxins, PAH	Blood/serum PCDD/F, DNA damage, urinary/leukocytic 8-OH-dG, urinary mutagenicity	Use of epidemiology studies to develop biomarker–response relationship	Sul et al. (2003); Hu et al. (2003); Toide et al. (2003); Yoshida et al. (2005); Yoshida et al. (2006); Shih et al. (2006)
Dioxin	Blood dioxin	Use of exposure assessment to put biomonitoring results into risk context	Lim et al. (2004)

3 Materials and methods

This review covers papers published from 2003 to 2007. It focuses on biomonitoring studies of groups that are occupationally exposed in the context of waste incineration. A research undertaken by way of free terms search on the internet and using specific query records on Medline database or through private journals access, returned numerous publications responding to and/or combinations of main keywords such as: biomarkers, dioxins, health risk, human biomonitoring, waste incineration, occupational exposure, workers. Only peer-reviewed publications were included.

A selection of 21 studies was made responding to the need to characterise the health status of workers in waste incinerators plants, through at least one of the following methods:

- a direct measuring of the presence of a contaminant (or its marker) in the body fluids or tissues
- the identification of morpho-functional alterations in cells or tissues
- the identification of early biological symptoms in the systems that are principally involved (respiratory, cardiovascular, reproductive)
- an evaluation of individual susceptibility to chemicals
- an assessment of the health risk based on daily intake levels.

4   Results

4.1   Human biomonitoring and evaluation of occupational exposure

The large production of occupational studies is justified by the necessity of controlling workplace conditions in order to ensure a level of health safety for the personnel. Generally the interest of studies focuses on atmospheric measurement of dioxins (dioxins and/or dioxin like substances), through permanent strategic stations in the area near the plant or through personal devices, and on dioxins absorbed by the human body measured as blood or urinary markers. Other studies aim at identifying interaction between the body and different levels of exposure by measuring biomarkers of effects or of susceptibility.

A study done in Japan on 57 incinerator workers showed that the lymphocytic 8-hydroxydeoxyguanosine (8-OH-dG) correlated negatively ($p < 0.05$) to the levels of dioxin in the serum (average level of 38.9 pg TEQ/g lipids, comparable to that of Japan's general population), in particular with the foremost marker of dioxins produced by a waste incinerator [i.e. 1,2,3,4,6,7,8-heptachlorinated dibenzofuran (HpCDF)], proposed by Kumagai et al. (2000). The urinary genotoxicity markers (8-OH-dG, mutagenicity level) showed no significant correlation, apart from that of urinary 8-OH-dG with the Body Mass Index (BMI). The author points out that although the 1,2,3,4,6,7,8-HpCDF marker had an average level six times above that of the general population, this had no significant effect on the total Toxic Equivalent (TEQ) of exposed subjects whose results were compatible with the average levels of the population. A more significant effect is observed in relation to cigarette smoke than for dioxins in terms of oxidation damage of DNA (Yoshida et al., 2006).

Another study, done on the same exposed group, assessed the alteration in the levels of urinary metabolites of estrogens according to different concentration of dioxin in the blood. This showed an increment in the average oestriol concentration according to three levels of dioxins in the serum ($p = 0.036$) (Yoshida et al., 2005).

A study done in Korea compared workers with the general population living in the area for not less than 5 years and within 5 km from the plant. The workers of two plants showed concentration of PCDD/Fs and PCB significantly lower than the residents (17.73 pg/p lipids vs. 21.52 pg/p lipids, $p < 0.05$) (Kim et al., 2005).

A second Korean study, similar to the previous, found no significant difference in the values of total TEQ of PCDD/Fs in workers (3.14 pg TEQ/lipid) and residents living nearby the plants for not less than 3 years and within 300 m from some waste incinerators (3.14 pg TEQ/lipids) (Moon et al., 2005).

In a category of maintenance workers directly exposed to residual ashes (cleaning of the oven and repair of emissions control devices), significant increase in the levels of dioxin in the blood were seen at the end of the operations (1 month), in particular, the difference was significantly greater in those who never performed these operations (a greater increase is observed in congener 2,3,4,6,7,8-HxCDF). The author of this study suggested a possible modification in the metabolic mechanisms in those exposed to high concentrations, since the dioxins chromatographic patterns observed in individuals and in the volatile ashes were heterogeneous (Shih et al., 2006a).

The concentration of dioxin in the blood of 72 workers in some incineration plants was measured to study the correlation between exposure to environmental dioxin and the production of mRNAs of CYP1B1. Findings suggested an effect of the dioxin on the induction of the CYP1B1 gene (involved in the enzymatic activation process of the PAH

in carcinogenicity). It was also shown that, in the Japanese population, the correlation between the quantity of mRNA and dioxin resulted higher in the group with higher inducibility and lower in the group of intermediate inducibility (the inducibility of CYP1B1 mRNA in leukocytes is defined as the ratio of CYP1B1 mRNA to the plasma concentration of dioxins and varied amongst the subjects) (Toide et al., 2003).

Other observations are consistent with these results demonstrating that the levels of expression of the CYP1B1 gene (but not CYP1A1) are significantly higher in those exposed than in a control group (Hu et al., 2006).

The effect of dioxins and furans on blood lipids and on hepatic function was studied in 133 workers divided into groups receiving different levels of exposure. Those receiving a greater exposure show total cholesterol levels significantly higher than the group receiving a lower exposure (OR = 2.895%; CI = 1.0–7.9) and also chronically higher (but not significantly) levels of several hepatic enzymes. The hepatic function was not altered by possible interactions between hepatitis B and dioxins (Hu et al., 2003).

An immunotoxic effect through the increase of activated T-lymphocytes and the suppression of cytokine IL-4 expression was observed in a group of workers exposed to PAH and dioxins. Significant differences were also detected in the level of urinary metabolites (1-OHP and 2-naphthol). The association between DNA damage (in mono- and polynucleotide blood cells), the urinary markers and the leukocyte population was not significant. Tobacco smoke did not result in a difference in DNA damage between those individuals who were exposed and those who were not (Oh et al., 2005).

The same exposed cohort showed an alteration in the genic expression (over-expression of 11 genes and under-regulation of 4 genes) and in protein expression (8 over-expressed and 1 under-regulated) with significant damage to the DNA of mononucleate cells (Kim et al., 2004).

Another study showed DNA damage in T- and B-lymphocytes and granulocytes and contemporary significant difference of urinary metabolite levels (1-OHP, 2-naphthol) in the exposed group compared to the control group ($p > 0.05$) (Sul et al., 2003).

A significant alteration in the number of spermatozoa was observed in those exposed to dioxin and PAH compared with the control group, in a large-scale investigation on the effects of reproductive toxicity (Oh et al., 2005).

An evaluation of workers exposure to polybrominated diphenyl ether (PBDEs) (on top of PCDD/Fs and PCBs) was undertaken for the first time in Korea. The concentration of total PBDEs was sampled in the blood of workers at two different incinerators and in residents living within 5 km of the incinerators. Workers blood PBDEs levels were slightly higher than those from the general population (average values respectively of 19.33 ng/g lipids vs. 15.06 ng/g lipids). The levels found for the workers and the population on average were higher than in other countries suggesting the possibility of a poor performance of the incinerator ventilation system, although no data regarding the air near the plants were available for confirmation. Furthermore, the study showed that the BDE 47 is an excellent indicator of the total PBDE, that the BDE183, to which the workers are significantly exposed, is correlated to the presence of octa-BDE in waste reaffirming the PCB 153 as indicator of the total PCB (Kim et al., 2005).

A subsequent investigation revealed that the blood levels and profiles of PBDE congeners, in three waste incinerators in Seoul (one of them dealing with industrial waste), were no different between workers and the general population. Lifestyle factors and personal behaviour examined for their contribution to PBDE exposure appeared to be key factors with respect to occupational exposure of incinerator workers (Lee et al., 2007).

A higher concentration of blood dioxins was found in employees (in an industrial waste incinerator) who had worked for a long period dealing with fly ash handling, with respect to new employees working with industrial waste. A direct connection is that provided with direct handling of dioxins contaminated residues. The high exposure burden could be ascribed to poor maintenance of the plant (concentration of PCDD/Fs > 68.68 pg I-TEQ/g lipids in personnel working for over 100 months) (Kim et al., 2005).

Exposure to PAH in an incineration plant for hospital waste was evaluated by measuring the variation of 1-hydroxy pyrene glucuronide (1-OHPG) in urine at the end of the work shift. No significant difference was noted between exposed and non-exposed other than amongst GSTM1 ± subjects. Higher levels of urinary 1-OHPG were observed in GSTM1 negative subjects. The effect of tobacco smoking on 1-OHPG levels showed an increase in dose–response relationship relative to the amount of tobacco smoked (Lee et al., 2003).

Amongst the various monitoring activities on the only existing dangerous waste incinerator in Spain and active since 1999, the comparison between the exposure of 102 workers, after three years of activity, with baseline values, showed no difference in the concentration of hexachlorobenzene (HCB), PCBs, PCDD/Fs and metals (Be, Mn, Hg, Pb) in plasma, and of dicalcium/tricalcium phosphate (DCPs), TCPs 1-HP and metals (Cd, Cr, Ni, V) in urine (Agramunt et al., 2003).

The result was confirmed after 3 more years of the plant's activity (Mari et al., 2007).

An occupational investigation made in France between exposed (selected from two plants) and reference groups, showed no significant difference in the levels of urinary metabolites, both organic and inorganic, measured before and after a work shift. In one of the plants, the chronically higher urinary concentrations observed, measured over a long period of work activity, were due to the presence of an old dismantling furnace. The level of atmospheric exposure measured for the workers (by means of individual air sampling devices) were below the limits set by French regulations, and only reached the maximum values for the maintenance of the furnace (the highest source of contamination). The main sources for atmospheric particles and metals [10–100 times higher in Municipal Waste Incinerator (MWIs) than at the control site] were cleaning operations for particles, and residue transfer and disposal operations for metals. The atmospheric metals were lower when compared to old plants (Maitre et al., 2003).

The study on the association of oxidative stress markers with the duration of engagement in fly ashes exposed jobs showed an upward trend of urinary 8-OH-dG ($p < 0.05$). This marker demonstrated that it was more sensitive than the molecule measured in the leukocytes (the author of the investigation suggested that the repair mechanisms of the oxidative damage in the blood altered the measuring of leukocytic 8-OH-dG). Other systemic indicators measured [malondialdehyde (MDA), lipid peroxidation (LPO)] did not seem sensitive to oxidative stress levels as they are prone to react in the body, concealing the effective levels of oxidative stress (Yoshida et al., 2003).

A comparison between the health indicators in two populations of workers, exposed and non-exposed, showed no differences in the general symptoms evaluated. The blood lead levels resulted higher in the exposed group (9.11 ± 5.5 μg/100 ml vs. 6.32 ± 3.4 μg/100 ml; $p < 0.05$) and presented a positive trend significantly associated with the duration of the employment. Amongst workers with different tasks, the most exposed and selected according to atmospheric measurements in the workplace (maintenance workers, cleaners and treatment workers, people working at the furnace),

presented a statistically significant excess in respiratory symptoms and an evident decrease in pulmonary function (a significant positive trend associated with the length of employment, $p < 0.01$) also with skin irritations (smoking and age were included as confounders variables) compared to non-exposed groups (Hours et al., 2003).

In a study for the validation of biomarkers, the use of hair proved to be an effective monitoring method to measure exposure to atmospheric dioxins. The exposure of MSW workers came from flue gas and electrostatic precipitator ash from the incineration facility because the TCDF (tetrachlorinated dibenzo-p-dioxin) chromatogram patterns of the workers were similar to the electrostatic precipitator ash pattern. A comparison of workers chromatogram congeners and that of the population highlighted a different source of exposure for the two groups and also TEQ values in the workers higher in PCDDs, PCDFs and coplanar polychlorinated biphenyls (Co-PCB) respectively of 3.1, 3.6 and 1.6. Examining differences in exposure levels in terms of occupational category a higher exposure was detected in those doing maintenance and checking inside the incinerator, with levels of PCDD double compared to those working in the conveyance of incinerated materials. The hair confirmed the body burden of isomers as shown by serum levels (Nakao et al., 2005).

Differences in exposure to dioxins in groups of workers have been evaluated in three different plants. Differences between plants were found both in environmental concentration (PCDD/Fs on average between 0.08 and 3.01 pg I-TEQ/m^3) and in the blood of workers independently of the job contents, duration of employment and time activity in those plants. The measurement of specific congeners of dioxins in the blood appeared higher in workers in one of the three plants that did not conform to regulations – the possibility that the difference from the other groups could be due to the type and length of activity was excluded. Dioxins levels in workers from plants that had been updated were equal to a reference population (Hu et al., 2004).

Two summarising tables are shown to provide an overall evaluation of the revised studies (reporting quantitative results and describing the methodological approach) and to compare the results. Table 1 groups the studies according to the type of chemical being assessed indicating which biomarkers are mainly used in the course of the investigations. Each group is accompanied by a description of the approach to the biomonitoring data used.

Table 2 summarises some of the above-reported results. It shows (in accordance with the classification of results from biomarkers studies reported in Srám and Binková, 2000) 17 studies that highlight an interaction between the body and a specific chemical by measuring differences in the levels of appropriate markers of exposure and measuring the effects in occupationally exposed groups. The letter E in the table is used to report a significative effect of exposure on levels of biomarkers of exposure (i.e. metabolites in fluids, DNA adduct, protein adduct, comet essay parameters, immunotoxicity parameters) and to report the existence of a significative effect on the levels of biomarkers of effect (i.e. genes and proteins expression, parameter of altered organ function). The description of the studies is also accompanied by the indication of use/not use, of additional measurement of exposure (atmospheric air or inhaled). One case evaluates the effect on levels of hepatic function and one more case an individual genetic susceptibility. Studies evaluating exposure to dioxins are those more numerous (12 out of 17 studies).

Table 2   Effect of exposure and genotypes on biomarkers and effects on occupationally exposed groups

Reference of the study/ sample size	Exposure		Effect of exposure on biomarkers								Effect of biomarkers of susceptibility
	Type of chemical	Measured in air	Urine[a]	Blood/ plasma/serum[a]	Mutagenicity[b]	Immuno-toxicity[b]	Comet[c]	Genes expression	Proteins expression	Of effect	
Yoshida et al. (2006) Exp = 57	Dioxins	No	No E[d]	E[d]	No E	–	–	–	–	–	–
	Tobacco smoke										
Yoshida et al. (2005) Exp = 57	Dioxins	No	E	–	–	–	–	–	–	–	–
Kim et al. (2005) Exp = 13; C = 22	Dioxins	No	E	No E	–	–	–	–	–	–	–
	PBDEs		–	E[e]	–	–	–	–	–	–	–
Moon et al. (2005) Exp = 28; C = 75	Dioxins	No	–	No E	–	–	–	–	–	–	–
Shih et al. (2006a) Exp = 35	Dioxins	No	–	E	–	–	–	–	–	–	–
Toide et al. (2003) Exp = 72	Dioxins	No	–	–	–	–	–	E CYP1B1 No E CYP1A1	–	–	–
Hu et al. (2006) Exp = 112	Dioxins, PAH	No	–	–	–	–	–	E CYP1B1 No E CYP1A1	–	–	–
Hu et al. (2003) Exp = 133	Dioxins	No	–	E	–	–	–	–	–	No E	–
Oh et al. (2005) Exp = 31; C = 84	Dioxins, PAHs	Personal Ambient	E	–	–	E	E	–	–	E	–
	Tobacco smoke		–	–	–	–	No E	–	–	–	–

Table 2 Effect of exposure and genotypes on biomarkers and effects on occupationally exposed groups (continued)

Reference of the study/ sample size	Exposure		Effect of exposure on biomarkers								Effect of biomarkers of susceptibility
	Type of chemical	Measured in air	Urine[a]	Blood/ plasma/serum	Mutagenicity[b]	Immuno-toxicity	Comet[c]	Genes expression	Proteins expression	Of effect	
Kim et al. (2004) Exp = 31; C = 84	Dioxins, PAHs	Personal	–	–	–	–	–	E	E	–	–
		Ambient	–	–	–	–	E	E	E	–	–
Sul et al. (2003) Exp = 28; C = 43	PAHs	Personal	E	–	–	–	E	–	–	–	–
		Ambient	E	–	–	–	–	–	–	–	–
	Tobacco smoke		E	No E	–	–	No E	–	–	–	–
Lee et al. (2007) Exp = 30; C = 51	PBDEs	No	–	No E	–	–	–	–	–	–	–
Lee et al. (2003) Exp = 28	PAHs	No	No E	–	–	–	–	–	–	–	GSTM1 E GSTT1 No E
	Tobacco smoke		E	–	–	–	–	–	–	–	–
Agramunt et al. (2003) Exp = 102	Dioxins, HCB, metals	No	No E	No E	–	–	–	–	–	–	–
Maitre et al. (2003) Exp = 29; C = 17	Particles, metals, organic compounds	Personal Ambient[f]	No E	–	–	–	–	–	–	–	–
Yoshida et al. (2003) Exp = 81	Fly ash	No	E	No E	–	–	–	–	–	–	–
Hours et al. (2003) Exp = 102; C = 94	Lead	Ambient	–	E	–	–	–	–	–	E	–

[a]metabolites in urine; [b]*umu* assay; [c]DNA damage; [d]correlation between dioxins levels and urinary/leukocytic metabolites; [e]BDE 183; [f]workstations measures of PM, metals, PAH, aldehyde, VOC.

Abbreviations: –, biomarkers was not analysed; C, number of subjects in control group; E, statistically significant effect of exposure and/or genotype on biomarkers of exposure and effect; Exp, number of subject in exposed group.

5   Discussion

Biomonitoring studies contribute to the risk evaluation characterising not only the individual exposure but also identifying those areas for which there is scantiness of data, erroneous assumptions, misclassification of exposure and factors influencing the variability of exposure in the population. The biomonitoring studies on incinerator exposure respond to some shortage in the application and interpretation of this type of data in the epidemiological field, as placed in evidence elsewhere (Albertini et al., 2006). Some contributions are particularly useful:

- the definition of the reference intervals for biomarkers in populations and workers exposed (like in a programme of human biomonitoring around waste incinerator plant in Spain, with follow-up of a group of workers);

- the validation of specific biomarkers (as through the identification of the characteristic emission patterns of dioxins and PCBs congeners both in workers or population, the selection of the best markers for exposure to PAH, the validation of the use of hair to measure exposure to dioxins);

- the application of molecular biology for the evaluation of the genic expression (search for mRNA and proteins correlated to a immune or detoxifying function);

- the definition of the inter-individual variability to better predict possible health effects (induction of the expression of those genes activating the intermediate metabolites to toxic substances or involved in the detoxifying process);

- the identification of exposed workers groups according to length of employment and type of activity and of the exposure–toxicity effect relationship (comparing tasks, length of engagement, plants conditions and local communities).

The studies shown in Table 2 evaluate the effect of exposure on biomarkers (measuring internal levels or studying the correlation of endpoints of interest with measured levels of chemicals) giving a result in terms of statistic significance. Of these, 12 evaluate the effect of dioxins (71%) but only in four of them (23%) a measure of personal and environmental exposure is available and environmental only for two (12%). The individual monitoring of the air breathed has been used to determine exposure to dioxins, PAH, metals, particles, aldehydes, Volatile Organic Compounds (VOCs).

5.1   Dioxins

This review demonstrates that amongst the undesirable by-products of waste incinerators, dioxins represent the focus on which research is concentrated because of their toxicity for humans and the environment.

It emerges that both the concentration of dioxin in the serum and the total TEQ are comparable in workers and residents in the vicinity of incinerators (Hu et al., 2004; Yoshida et al., 2006) or inferior in workers (Kim et al., 2005; Moon et al., 2005). Higher levels of contamination can be noticed using hair of workers as indicator compared to the general population (Nakao et al. 2005). Employees in maintenance operations show a significant increase in the levels of serum dioxins at the end of the shift (Shih et al., 2006a) and of inhaled particles and metals above all during the maintenance of the

furnace (Maitre et al., 2003). Environmental measurement confirm a higher level of exposure for these workers (Hours et al., 2003). The dioxin chromotographic pattern, evaluated in samples of workers hair, individuates different sourcers of exposure for workers with respect to the general population (exposure coming from occupational sources, i.e. electrostatic precipitator of ashes) (Nakao et al., 2005). Some inconsistencies observed in the composition of congeners between serum and air samples in the working area suggests that poorly understood and evaluated phenomena are involved in determining both the effective absorption of toxic chemicals (volatile compounds disperse more easily) and levels measured in the body (an effect of the metabolic rate of chemicals elimination can be present) (Shih et al., 2006b; Maitre et al., 2003).

Some studies did not detect any correlations between task, length of employment and the levels of dioxin in the serum (Agramunt et al., 2003; Hu et al., 2004). A possible explanation could be that the biological monitoring before and after exposure is not a valid method for evaluating occupational exposure since chemical levels at the incinerator plant are low (Maitre et al., 2003).

With regard to the oxidative damage, the interpretation of the biological essay is complex. The sensitivity of systemic or urinary markers of oxidative damage from dioxins is being evaluated. The variability in responsiveness of the genes involved in the body's primary defences or in the DNA repair mechanisms of the oxidative damage, need to be further explored to define proper exposure indicators. Urinary 8-OH-dG represents the average level of oxidative DNA damage throughout the body (excreted quantity of the delated oxidative DNA damage through repair process in the whole body) but it neither correlates with the serum dioxin level nor do the individuals' dioxin levels increase the urinary 8-OH-dG level by oxidative DNA damage, as an activation of the repairing system and/or the upregulation of the primary defences with oxidative damage, might have occurred. However, the urinary 8-OH-dG shows a significant upward trend with the duration of the activity in the presence of fly ashes (Yoshida et al., 2003). The lymphocytic 8-OH-dG represents the level of oxidative damage only in the blood (a condition of equilibrium between production and repair of oxidative DNA damage) and negatively correlates with the serum dioxin level because it is rapidly affected by the over-regulation induced in the genes that repair the oxidative damage (Yoshida et al., 2006). Other systemic indicators measured (MDA, LPO) did not yield results appropriate (Yoshida et al., 2003) to identify the level of oxidative stress of the entire body. A better interpretation of the measurements taken with markers of oxidative stress could be achieved by evaluating highly exposed subjects (Yoshida et al., 2006).

Maitre et al. (2003) assume that the detoxification mechanisms act speedily and, in condition of non-acute exposure, it becomes impossible to detect significant variations in the urinary markers used (Agramunt et al., 2003; Maitre et al., 2003). It seems that biological markers could better evaluate the effects of long duration exposure.

Isolated results observed for some effects of plasmatic dioxins on the levels of estrogens (Yoshida et al., 2005) and on urinary mutagenicity (Yoshida et al., 2006), need further clarification or a more in depth study. It seems a valid method to compare isomeric patterns of dioxin-like compounds to distinguish between occupational and non-occupational exposure and to characterise workers exposure in different work stations (Agramunt et al., 2003).

5.2 PAH

The studies on individual susceptibility confirm that the level of expression of the CYP1B1 gene is a marker of the effective biological dose for occupational exposure to PAH and dioxins. Moreover the polymorphism with which the gene is present in the population, which is responsible for a different inducibility by the polluting agent, is responsible for a different individual susceptibility to develop pathologies (Hu et al., 2006). It also seems that there is a dioxin concentration threshold responsible for the induction of the gene in human leukocytes (it has been calculated to be 6.5 pg TEQ/g in lipids), (Toide et al., 2003). High levels of CYP1B1 gene expression recorded for occupational exposure are not recognised for environmental exposure (Hu et al., 2006). The genotype GSTM1+ is confirmed as protective against the genotoxicity of the PAH (Lee et al., 2003).

The best biomarker for PAH exposure, between lymphocytes T-, B- and granulocytes, proves to be the lymphocyte B that is more affected by damage to the DNA (Sul et al., 2003). Patterns of altered genic expression are individuated in relation to exposure to dioxins and PAH. In response to oxidative stress there is an over-expression of antioxidant proteins and of immune defence regulating proteins. Transferrin is greatly over-represented in the exposed groups justifying a possible role as a biomarker of exposure to dioxins and PAH (Kim et al., 2004). A toxic effect of the PAH on the immune system is confirmed but the alteration of the immunological parameters (immunoglobulins, cytokines, leukocyte subpopulations) is not related to urinary metabolites or to DNA damage levels (Oh et al., 2005). In the same study similar negative results were also produced in terms of the relationship between DNA damage and age or working period (Sul et al., 2003).

6   A note on ethical issues

It is noteworthy that the increasing introduction of the measurement and use of biomarkers of exposure, susceptibility and disease in the epidemiological studies, to replace traditional environmental indicators, has brought along the need to address ethical issues in terms of informed consent and confidentiality. The US National Research Council in the recent publication entitled 'Human Biomonitoring for Environmental Chemicals' (Committee on Human Biomonitoring for Environmental Toxicants, 2006) provided a specific recommendation to review bioethical issues confronting the future of biomonitoring, including confidentiality, informed consent, reporting of results and public health or clinical follow-up. Because of the challenges posed by informed consent for studies that use high-output, high-throughput technologies, the committee recommended research that develops, evaluates and disseminates methods that ethically and practically inform study subjects during recruitment and during later communication of study results.

7   Conclusions

The elevated number of recently published studies on human biomonitoring demonstrates a great scientific interest to explore the validity of biomonitoring data to further knowledge about occupational health. Approaches ranging from descriptive to risk-based

are alternatively used (Committee on Human Biomonitoring for Environmental Toxicants, 2006). The studies performed seem to be mainly aimed at providing either information on who is more and who is less exposed, or on the levels at which exposed individuals and groups are placed compared to the reference populations (compared to a general population and also to the levels set by regulations), or on the relation between exposure and toxicity. Some attention is also given to provide a possible explanation of the relationship between biomarker level and exposure (internal dose and pollutant concentration) trying to combine together the biomonitoring epidemiological investigation and the contaminant concentration measured in the environment. These two different sets of data need to be systematically coupled in order to obtain a good classification of exposure and to achieve a valid interpretation of biomonitoring data with the aim of risks evaluation (a complex interaction between mechanisms and dynamics of dispersion, absorption and degradation, in the environment or in the human organism, is still not well elucidated to enable explanation of the observed health effects). The informative potential for risk evaluation grows as it progresses from descriptive studies to those that aim at characterising the biomarker–toxicity effect relationship. Further studies on biomonitoring can be of great help in evaluating the risk since some limitation still remain when interpreting results. Some observations are put forward to highlight these areas of uncertainty or lack of information:

- Levels of dioxin in the blood are rapidly affected by the activation of detoxification mechanisms and in conditions of non-acute exposure, this biological dosage shows no difference between exposed and non-exposed workers or the general population.

- It must be considered that some biomarkers of exposure are better than others (as it is the case of urinary oxidative stress markers compared to systemic ones), or markers should be preferred to others for their sensitivity in highlighting toxicity effects (as it is the case of DNA damage, genic response and alteration of the immunological parameters).

- A correct study design should be able to rank workers exposure because a great variability in exposure is experienced according to different tasks. It is possible to get inconsistent results when comparing groups of subject unless there is an appropriate selection of reference population.

- Jobs and tasks are individuated that imply elevated increases in urinary and plasmatic metabolites (time spent in maintenance and cleaning work proves to be a high risk factor). Also it is possible that for short exposure period a differential is not detected. For example, after an 8-hour work shift, recorded differences are only dependent on factors other than occupational (lifestyle, other types of exposure such as tobacco smoke, etc.).

- Environmental measurements within the plants indicate higher levels of chemicals than outdoors, even if they are always inferior to workplace threshold values, and that only in some working stations and only after some types of activities there is a significant increase in the concentration of pollutants (dioxins, VOCs, metal, particles, etc.) (Maitre et al., 2003; Hours et al., 2003). Also is it possible not to find correlation between environmental measurements and individual biomarker levels when the actual presence of the operator in the area sampled with fixed stations is not carefully considered.

- In some cases, tobacco smoke proves to be a relevant confounding factor and a greater exposure risk can be attributed to this factor than to occupation (Lee et al., 2003; Sul et al., 2003; Yoshida et al., 2006).

- The study of the relationship dose–biomarkers of effect and the interpretation of related results are noticeably complex. Biological mechanisms repairing the intra-cellular balance and the genetic damage are subjected to individual variability that introduce a great uncertainty in the effects of exposure measured as internal variation of marker levels and in the estimation of the related dose. Some of the studies pay particular attention to individuating polymorphic genes and valid markers (those less affected by the mechanisms of detoxification and therefore better indicators).

The present review describes a scientific research context that focuses considerable attention on the main themes of dioxin contamination and risk estimate. The monitoring of environmental dioxins levels in the surroundings confirms the safety of modern incinerating plants being able to contain ambient air dispersion of these pollutants (Sul et al., 2003; Kim et al., 2004; Oh et al., 2005; Shih et al., 2006b). Nonetheless there is very insufficient assessment available of the carcinogenic risk estimated from the daily dose absorbed by workers (Lim et al., 2004), otherwise biomonitoring studies on residents are already providing this kind of data (Yoshida and Nakanishi, 2003; Karademir, 2004; Lim et al., 2004; Van Gerven et al., 2004).

Biomonitoring as investigating tool in the environmental epidemiology has the potential to play a role of great importance for health prevention and early diagnosis as it becomes possible to integrate biomonitoring data with the knowledge on pollutants toxicity effects and toxicity mechanisms, which at present is still limited.

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List of abbreviations

1-HP	1-hydroxypyrene
1-OHPG	1-hydroxy pyrene glucuronide
8-OH-dG	8-hydroxydeoxyguanosine
BMI	Body mass index
CI	Confidence interval
CYP	cytochrome P450
Co-PCB	Coplanar polychlorinated biphenyls
DCP	Dicalcium/ Tricalcium Phosphate
GSTM	class Mu glutathione S-transferase genes
HCB	hexachlorobenzene
HpCDF	Heptachlorinated dibenzofuran
HxCDF	hexachlorinated dibenzofuran
MDA	malondialdehyde
MWI	Municipal waste incinerator
LPO	lipid peroxidation
OR	Odds ratio
PAH	Polycyclic aromatic hydrocarbon
PBDE	Polybrominated diphenyl ether
PCB	Poly-chlorinated biphenyls
PCDD/F	Poly-chlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans
TCDF	Tetra-chlorinated dibenzofuran
TEQ	Toxic equivalent
TLV	Threshold Limit Value
VOCs	Volatile organic compounds