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## Report on access to occupational data

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### WP 8 - Targeted field work surveys and alignment at EU level

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Milla Heinälä was contributing to the collection of the data and drawing tables of aniline studies.

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## 2 Report on access to occupational data

### 2.1 General description on data sources:

Human biomonitoring is commonly applied method in occupational context. It can be used either for the assessment of exposure at workplaces or as part of health surveillance for predicting potential health effects in the absence of clinical impairments (Manno et al 2010). However, its application varies from country to country and whereas in some countries there are long traditions for its use in occupational exposure and risk assessment, in other countries biomonitoring has been regularly applied only very seldom or only for very few substances (e.g. for lead for which there is a binding biological limit value available in EU). In addition, in many such countries (like France and Germany) in which there are long traditions for the use of biomonitoring in occupational exposure and risk assessment, biomonitoring activities are scattered in different laboratories and the biomonitoring results are owned by companies or their occupational health care and not easily accessible for regulatory or scientific purposes. On the other hand, in some countries there are national databases on biomonitoring data maintained by research institutes or public laboratories. The data included in these databases is either derived from the research studies or from regular biomonitoring campaigns or biomonitoring services. These data can potentially be used to prepare overviews on the exposure in specific occupations or in the different fields of industry. Use of these databases is naturally restricted to the owners of the database.

In addition to regular biomonitoring to follow-up workers' exposure at workplaces, many institutes are performing research related to occupational chemical exposures by using biomonitoring. These scientific studies are generally published as study reports or scientific papers. As can be seen in the case of chromium and anilines (below), there are several recent studies available in which biomonitoring has been used for occupational exposure and/or risk assessment of chromium(VI) and aniline compounds. Thus, these kind of research studies are probably the main information source on occupational biomonitoring data.

Third potential data source could be data which has been gathered from the companies and their occupational health service providers by questionnaires e.g. for regulatory risk assessment purposes. Under REACH authorization process, industry has in some cases collected biomonitoring data from their member companies for exposure assessment in the context of authorization process. Summaries of these data can be found from authorization applications available at European Chemicals Agency (ECHA) webpage (<https://echa.europa.eu/>). Examples of these are given under chapter "Availability of data on anilines". However, it should be noted that this has been used only in few cases by this far.

In the following chapters we will give an overview on the situation regarding the availability of data in some European countries. Belgium, Finland, France and Netherlands are described more profoundly. The description of other countries is based on the questionnaire made under WP7.1 of the HBM4EU and complemented with additional information based on literature or interviews.

### 2.2 Examples on data sources in different countries

#### 2.2.1 Belgium

The Department of Public Health and Primary Care of the **Catholic University of Leuven (KU Leuven)** is a multidisciplinary department with a focus on community health, best practice and health policy. Within the department, the Centre for Environment and Health (CEH) studies the impact of environment on health and also the reverse, how health can affect individuals' interaction with the environment. CEH has a long tradition and extensive experience in assessing the

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exposure to environmental agents, studying the underlying mechanisms of work related disease development, and developing biomarkers. The Laboratory for Occupational and Environmental Hygiene of the centre is specialized in monitoring, sampling and analysing airborne contaminants as well as in analysing urine samples of workers. Analyses are performed for both private companies and Services for Prevention and Protection at Work. The research activities are mainly directed at the assessment of exposure and health effects. The assessment is based on environmental monitoring and biomonitoring. In recent years, a growing emphasis was laid on the study of biological effects (mainly carcinogenic, reprotoxic and neurotoxic effects) as well as studying the epigenetic changes induced by environmental agents. The CEH has a close collaboration with several national and international research centres, mutuality's and occupation health providers. The database of the Laboratory for Occupational and Environmental Hygiene (LOEH) in Leuven (Belgium) included conducting analyses of air samples and urine samples for numerous noxious chemical agents, mainly volatile organic compounds from complex mixtures, since more than 30 years. These air and urine samples were collected in a wide variety of Belgium companies, upon request of external or internal services for prevention and protection at work, or upon request of consultancy agencies. These companies and services use the data on air exposure and biomonitoring to follow-up occupational exposure of workers to chemical substances.

**IDEWE, External Service for Prevention and Protection at Work**, is the largest Belgian Occupational Health and Safety provider. In Belgium, periodic health surveillance is mandatory by law for employees exposed to occupational hazards and includes a yearly medical examination. Data from consultations are continuously recorded by about 200 occupational health nurses and more than 150 physicians of IDEWE in an electronic worker record and encoded using international or national classifications standards. Several work characteristics are encoded per worker. Occupational hazards are registered using the Belgian legislation codification system. Jobs are classified according to the International Standard Classification of Occupations of the International Labour Organization. Self-reported health complaints and sickness absence are also encoded using the International Classification of Diseases version 9 with Clinical Modifications (ICD-9-CM). Finally, the use of medication is encoded according to the index of the Belgian Compendium of Pharmaceuticals, which refers to the main pharmaceutical use of the drug. Biomonitoring is also undertaken in order to evaluate the occupational exposure of the workers, urinary and blood concentrations for a wide range of compounds being reported. On yearly bases, the occupational health and safety data on ~300.000 employees is gathered.

These two databases are available; nevertheless, cave limitations apply due to ethical and privacy constraints. In order to overcome these limitations, a request for formal approval from an Ethical Commission for the use of the data in a research context needs to be submitted.

## 2.2.2 Finland

Finnish Institute of Occupational Health (FIOH) provides biomonitoring services to Finnish workplaces. The data collected by FIOH's biomonitoring services are gathered in our database on occupational exposure to chemicals. In addition to name, sex, and identification of a person studied, and analysis result(s) the following data are stored in the database (if the requested information is given in a referral): employer, job description, exposure substance/product, duration of the exposure, sampling time, and smoking (yes/no/not available). Some additional information is also possible to store if present in a referral. Also control samples and so called zero samples (no occupational exposure) are stored in the database. On addition, limited contextual data is often a challenge. Database does not include information e.g. on the specific tasks performed, risk management measures (e.g. use of personal protective equipment) or occupational history, nor

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any detailed background information on the study subject (e.g. socioeconomic status, home location, alcohol/coffee consumption, dietary habits, use of pharmaceuticals, hobbies). It may also be that the data present in FIOH biomonitoring database is biased to describe situation in better workplaces since it represents the biomonitoring analyses ordered by the companies or their occupational health care providers i.e. it means that they have been able to identify possible hazardous exposures. Small companies with poor working practices and limited occupational health services may not be well represented in these data.

Regarding the prioritized substances in HBM4EU, the FIOH database contains urinary data on anilines [aniline, 4,4'-methylenedianiline (MDA), 4,4'-methylene-bis(2-chloroaniline) (MOCA)], chromium (urinary total chromium), cadmium and PAH metabolites (1-hydroxypyrene, 2-naphthol) from 2007–2016. The FIOH biomonitoring database is used to draw summaries on the occupational exposure in different industries in Finland. The summary data does not include information on individual subjects or companies. Examples of summary reports are urinary data on occupational exposure to chromium and chromium compounds, and cadmium and cadmium compounds in 2000–2014 covering a wide range of industry sectors (aged 18–70; a vast majority of the study subjects were men). The biomonitoring database has also been used in epidemiological cohort and case-control studies. For example, biological measurements among workers exposure to six organic solvents: styrene, xylene, toluene, trichloroethylene, perchloroethylene, and 1,1,1,-trichloroethane in 1965–1983 [number of biological measurements 21000 (urine, blood); number of workers 9031 (5809 men, 3222 women)].

In addition to expert services, FIOH performs biomonitoring as part of research projects related to the exposure of workers and general (working-aged) population. The results of these projects are published in national research reports (in Finnish, English summaries) and often also in peer-reviewed international scientific journals. Regarding the prioritized substances, recent research studies include occupational exposure to bisphenol A in 2013 (urinary total bisphenol A; n= 48, 14 women, 35 men; aged 20–62, working in five different companies), occupational exposure to some phthalates in 2015 [di(2-propylheptyl phthalate (DPHP), diisononyl phthalate (DINP), di(2-ethylhexyl) phthalate (DEHP); urinary total phthalate; n=46, 5 women, 41 men, aged 21–61, working in 5 different companies)], firefighters' exposure to PAH compounds in smoke diving in 2013–2016 (urinary 2-naphthol and 1-pyrenol; n=24) and perfluorinated compounds present in firefighting foams (blood samples from 2010; n=8). In addition, maintenance workers exposure to cadmium ash in bio power plants in 2012–2014 has been investigated (urine samples, n=12). Often a limited sample size is a challenge in occupational research studies.

### 2.2.3 France

In France, the actors in the field of the biological monitoring of occupational exposure to chemicals are:

- INRS: research studies and Biotox database
- Anses: recommendation of biological limit values (BLVs) and biological reference values (BRVs)
- Santé Publique France (ANSP): mainly environmental exposure and a limited part of occupational exposure
- Toxicology laboratories of University Hospitals (CHU) (Ex CHU Grenoble)
- Occupational physicians in companies: biomonitoring for occupational health is implemented in France under medical prescription

**Biomonitoring laboratory (BM) of INRS** provides expertise on the assessment of occupational exposure to pollutants through research studies. BM develops analytical methods primarily in urine, designs protocols for evaluation of occupational exposure (biomonitoring, atmospheric

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metrology, surface contamination, questionnaires), conducts research which comply with regulations (ethic committee, data protection law), recruits and conducts interventions in companies, develops biomarkers of exposure and early effects and proposes preventive measures for the control of exposures. Biomonitoring and atmospheric data on several chemicals are available from INRS studies (published and unpublished data). Contextual data are also available for each study: job description, specific tasks performed, use of personal protective equipment, duration of the exposure, sampling time, alcohol/coffee consumption, dietary habits.... Research studies since 2000 include: 4,4'-methylenedianiline (MDA); 4,4'-methylene-bis(2-chloroaniline) (MOCA); diisononyl phthalate (DINP); di(2-ethylhexyl) phthalate (DEHP); volatile organic compounds (toluene, benzene, ethylbenzene, xylene, dichloromethane,...); PAH metabolites; cytotoxic drugs; herbicides (diuron, isoproturon, chlorotoluron); metals (chromium, nickel, lead, manganese, cobalt, beryllium, ...); bisphenol A; bisphenol S; mycotoxins.

**Biotox database of INRS** (<http://www.inrs.fr/publications/bdd/biotox.html>) is a toolbox for occupational physicians with the inventory of biological methods available for the biomonitoring of occupational exposure to chemicals. This database provides also contact information of about 50 laboratories and some tools (or elements) to interpret biomonitoring results. Biotox list more than one hundred chemicals.

**Exporisq-HAP** (Grenoble University Hospital) is the only available French database (2000-2017) with individual airborne levels and biomonitoring measurements (urine) in occupational settings for **PAHs**. Occupational exposed subjects (>500) are male in general (18 and 60-year old) and urinary metabolites (1-OHP and 3-OHBaP) are investigated at different days of the workweek (pre- and end-shift), in aluminium, coke and silicon productions, manufacturing of carbon products, foundries and engine exhaust.

**Santé Publique France** (ANSP) has little data but is going to start a large study in 2 regions in France in 2018.

Biomonitoring data from **occupational physicians** in companies are scattered and quite inaccessible in France.

#### 2.2.4 Netherlands

Experts from various organizations and institutes, including universities and public agencies - (three experts from the Institute for Risk Assessment Sciences (Utrecht University), one expert from the Dutch Knowledge Center for Labor and Lung Disorders (Nederlands Kenniscentrum Arbeid en Longaandoeningen), two experts from the Dutch Centre for Occupational diseases (Nederlands Centrum voor Beroepsziekten), one expert from the Radboud University Medical Center, one expert from Inspection of Social Affairs and Employment (Inspectie Sociale Zaken en Werkgelegenheid), one expert from the National Institute for Health and Environment (Rijksinstituut voor Volksgezondheid en Milieu), and one expert from a consulting and engineering firm (RPS)) - have been asked whether they have databases available with occupational exposure biomonitoring data, or if they are conducting research activities within this field in the Netherlands.

It appears that there are very few initiatives organized in the Netherlands with regards to collecting biomonitoring data in an occupational setting. Although the Institute for Risk Assessment Sciences has conducted various research activities using biomonitoring<sup>1</sup>, they have no specific databases for human biomonitoring data.

From our own experience (TNO analytical laboratory), and from the responses of the various consulted experts listed above, we know there are various companies and industries that are

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collecting biomonitoring data within their worker population. We have no insight which biomonitoring data is collected by these industries, or what is done with the data.

Furthermore, there are a number of large scale initiatives that are using biomonitoring in The Netherlands, however not in an occupational setting. An example is the Generation R project (<https://www.generationr.nl/>) which started in 2011 and recruited over 10,000 pregnant women. Blood samples have been collected during pregnancy and at birth, and in addition urine samples of mothers have been collected and analysed for several environmental exposures, metabolites and pesticides. The children will be followed for 18 years to monitor growth and development.

Another large project is Lifelines (<https://www.lifelines.nl/researcher/about+Lifelines>) a multi-disciplinary prospective population-based cohort study which examines the health and health-related behaviours of over 167,000 persons living in the North of The Netherlands over a period of 30 years. Participants are asked to complete a follow-up questionnaire once every 1.5 years, which includes questions about work. Biomaterials collected includes urine, DNA, and blood. All samples and data are collected in a bio- and databank.

### 2.2.5 Other countries

Description of the available databases/datasets is based on the questionnaire from WP 7.1, which have been complemented by additional questions sent by email to some of the respondents. Responses to WP7.1 questionnaire were received from eight countries in addition to countries described above. Most of the reported data are single studies (some of them ongoing). It should be noted that this does not represent a comprehensive situation in whole Europe since it is based only on the data reported by those institutes included in HBM4EU project and answering the questionnaire. Responses were not received from some important countries, for example from UK.

In UK, Health and Safety Laboratory has a Biological Monitoring DataBase (BMDB), which contains exposure measurements to various (about 100) substances using biological monitoring. It has been briefly described in the report related to the development of EU occupational exposure database (HazChem@Work, Koop, 2016). The data is available for use by HSL staff.

Also in Norway, National Institute of Occupational Health (STAMI) has an EXPO database which includes biological monitoring data on blood lead and mercury levels from occupationally exposed workers starting from 1984. The database is continuously updated and a short description on it can be found from <https://stami.no/expo/> and the report by Kooperationsstelle Hamburg IFE GmbH (Koop, 2016).

In many European countries, the situation is very similar to that described for France and Netherlands. Although in some countries, like in Germany and Italy, biomonitoring is a tool which is used regularly at the workplaces, there is no central national laboratory which would do most of the biomonitoring analysis and which could have an opportunity to collect national data on the biomonitoring analysis. For example in Germany there are number of laboratories (including clinical medical laboratories) providing analysis of different metals and/or organic substances to workplaces. The same applies also to Italy.

The datasets reported by the different institutes within HBM4EU WP7.1 questionnaire are listed as follows. These concern mainly priority substances identified in HBM4EU project. Datasets described above are not repeated here. None of these represents any comprehensive database and, as described earlier, they do not represent the full set of available occupational datasets in Europe. Therefore, they should be regarded rather as examples of the datasets available in Europe.

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- From Italy Department of Public Health University of Naples Federico II (Italy) reported a single study on male welders exposed to chromium and cadmium during the manufacture of fabricated metal products (n≤100). Urine and blood samples were collected. There are also other research groups available in Italy which are conducting studies related to occupational biomonitoring in Italy but no information for datasets possibly available by them were not received.
- Related to the priority compounds, Nofer Institute of Occupational Medicine (Poland) reported a single study on male welders working in metal industry plants (n≤100). Urine, serum, and blood samples were collected. The study was conducted in 2014-2015. There is no databases on biomonitoring available in Poland.
- ESTeSL/IPL (Portugal) reported two ongoing single studies: (i) Workers of Hospital Oncology Services (nurses and pharmacy technicians) who prepared and administered antineoplastic drugs. Surface samples and blood samples were collected. Genotoxic effects (MNT and Comet Assay) were measured (in surface samples: cyclophosphamide, 5-fluorouracil, and paclitaxel). (ii) Urine and blood samples of workers from animal production (swine and poultry), slaughterhouses, cork industry, bakeries, and waste management were collected. Several mycotoxins were investigated. There are also other Portuguese laboratories, which may have data available collected in different research projects but since they are not included in the HBM4EU project, no information on these datasets are available.
- From Slovakia Constantine the Philosopher University in Nitra reported an existing database of urinary phthalate exposure (time frame 2012-2017). Type of occupation: workers in plastic industry (n=36), workers in community service (n=45), hairdressing apprentices (n=124), and firefighters (n=32). Phthalate metabolites were analysed from urine samples (MEP - monoethyl phthalate, MnBP - mono-butyl phthalate, MiBP - mono-isobutyl phthalate, MEHP - mono(2-ethylhexyl) phthalate, MEHHP - mono(2-ethyl-5-hydroxyhexyl) phthalate, MEOHP - mono(2-ethyl-5-oxohexyl) phthalate, MECPP - mono(2-ethyl-5-carboxypentyl) phthalate; MMP - mono methyl phthalate, MBzP - monobenzyl phthalate).
- IISPV (Spain) reported an ongoing occupational biomonitoring study (time frame 1998-) of cadmium and pyrene exposure of laboratory, administrative, and plant workers of the hazardous waste incinerator (n≤100). No information on other data or databases were provided.
- AICT (Switzerland) has conducted several single studies in various countries of (usually male) workers in chemical industry, automobile industry, and construction: (i) workers exposed to 4,4'-methylenedianiline, Germany; (ii) workers exposed to ammunition waste, Germany; (iii) workers exposed to 4,4'-methylenediphenyl diisocyanate in a production facility, Germany; (iv) workers exposed to polyurethanes (4,4'-methylenediphenyl diisocyanate), Germany; (v) construction workers exposed to 4,4'-methylenediphenyl diisocyanate, Germany; (vi) workers exposed to 4,4'-methylenediphenyl diisocyanate, USA; (vii) workers exposed to toluenediisocyanate, Netherlands; (ix) workers exposed to chloronitrobenzenes, China; (x) workers exposed to 2,4,6-trinitrotoluene, China; (xi) workers exposed to nitrotoluenes, China; (xii) workers exposed to aniline, 2-methylaniline, 4-aminobiphenyl, USA.; (xiii) workers exposed to benzidine, azodyes, India. Time frame was 1990-2013. Urine, blood, and air samples were collected.
- From Latvia Institute of Occupational Safety and Environmental Health (IOSEH), Agency of Rīga Stradiņš University (Latvia) reported two occupational studies: (i) male welders in metal processing and metal cutting works (n=94). Investigated chemicals were Mn, Cr, Cd, Cu, Zn. Single study in 2002-2009. (ii) Male electricians who were in contact with the transformer oils (n=25). Polychlorinated biphenyls, brominated flame retardants (BDE-47,

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BDE-99, BDE-100 and BDE-153), and pesticides (o,p'-DDE, p,p'-DDE, o,p'-DDD, p,p'-DDD, o,p'-DDT, p,p'-DDT) were investigated. Single study in 2006-2008. In both studies blood and air samples were collected.

- Lithuanian University of Health Sciences (LSMU) reported a cross-sectional study of 630 ceramic plant workers (199 men and 431 women). Lead, cadmium, chromium, and manganese were analysed in hair samples. The database was compiled in 1991-1994.

## 2.3 Availability of data: Chromium and anilines

### 2.3.1 Chromium

#### 2.3.1.1 Information on uptake, metabolism and toxicokinetics of chromium (VI) compounds

Chromium (VI) or Cr (VI) – as chromate, dichromate or chrome trioxide – is taken up in the blood via oral, pulmonary or dermal exposure, and subsequently becomes systematically available. Cr (VI) is absorbed more efficiently by the pulmonary route than chromium in its other valences. The uptake is arranged over cell membranes via chloride-phosphate canals. Cr (VI) compounds are quickly reduced, both intracellular and extracellular, to Cr (III) compounds. Cr (VI) compounds are easily transported over cell membranes (chloride-phosphate canals) and subsequently end up in blood cells, tissues, organs and bone, whereas Cr (III) compounds are taken up and eliminated less quickly by cells, hence the accumulation of chromium compounds in these cells is a reflection of systemic exposure to Cr (VI) compounds during a period of one to four months. The metabolite Cr (III) in blood is primarily excreted via the kidneys and liver. The rate of elimination (and route) depends on the route of administration, the chemical form of the Cr (VI) compound and the dose. Elimination from plasma is relatively fast in comparison to tissues (which is in the order of days to weeks). The half-life of chromium in plasma and urine is in the order of 40 hours (from studies where oral administration has been applied).

The water solubility of inhaled particles and chromium salts plays an important factor with regards to inhalation. The residence time in the lungs is variable and depends on where the deposition takes place in the lungs and the water solubility. If the salts / particles dissolve slowly, there is a prolonged period of uptake of Cr (VI) compounds in the blood, and therefore a longer elimination time. Cr (VI) is converted to Cr (III) in erythrocytes. Cr (III) is only eliminated slowly from these cells (leakage of chromium from erythrocytes is on the order of 1-2% per day) and as such erythrocytes act as a depot (more information on this is described in the following paragraph). Slow elimination from tissues and erythrocytes and delayed uptake from poorly soluble particles in the lungs lead to prolonged increase in chromium content in urine.

Chromium levels of tissues including lungs are increased for several years after (high chronic) exposure.

#### 2.3.1.2 Measuring chromium (VI) compounds in various matrices

Cr (VI) compounds or chromium specific biomarkers can be measured in several matrices, including urine, blood, hair, nails, bone, saliva, tooth, exhaled breath condensate (EBC) and airways/ lungs (i.e. the lining fluid on the endothelia). Currently the approach is to analyze total chromium (predominantly Cr (III)) in e.g. blood and urine for which the chromium levels are an indication of enhanced occupational exposure to chromium (especially when measurements show Cr (VI) compounds in the air).

Cr (VI) compounds are demonstrable in urine very shortly after exposure. After this short period it is only possible to prove that exposure to chromium compounds has taken place, but not in which form. It is not easy to translate levels of Cr (VI) and (III) compounds in urine to a quantitative measure of exposure.

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Cr (VI) compounds are also measurable in blood, plasma and serum. Cr (VI) compounds accumulate in red and white blood cells and are immediately reduced to Cr (III) compounds which are no longer able to leave the cell. Hence the total chrome level in these cells is a measure for the uptake of Cr (VI) compounds during the lifecycle of these cells (which equals one month for white blood cells, and four months for red blood cells). This analysis is currently applied in practice to monitor exposure of employees during, or until four months after, exposure. Measuring exposure longer after this period is not yet possible via blood analysis, and, as for urine, it is not easy to translate levels of Cr VI and III compounds in blood to a quantitative measure of exposure.

Hair and nails are potentially interesting candidates to analyse exposure to chromium for a longer period (e.g. months until a year after exposure). It is, however, not possible to directly link chromium concentrations to the extent of exposure.

Bone could be used for investigated chromium exposure after an even longer period, but the disadvantage of this matrix is the invasive character.

Currently research is being conducted on measuring Cr (VI) compounds in exhaled breath condensates (EBC). This could potential be a non-invasive alternative, instead of taking lung tissue samples, to measure exposure to Cr (VI) compounds long after exposure.

### 2.3.1.3 Biomarkers of effect

Although there is a wide range of reported biomarkers (most often biomarkers of effects) - of which the most often mentioned one is DNA-protein cross-links - none of the reported biomarkers are specific for exposure to chromium (VI); i.e. other compounds can also induce an elevation of these biomarkers. Therefore it is not meaningful to analyse biomarkers of effect which are formed during internal exposure to chromium (VI) compounds.

### 2.3.1.4 Analytical techniques for determining total chromium and chromium (VI) compounds

Gómez et al. (2006) published an overview of existing and applied techniques for the analysis of chromium compounds. The authors conclude that the most commonly used methods for measuring low concentrations of chromium compounds in biological samples include: AAS (atomic absorption spectroscopy), ICP-MS (inductively coupled plasma mass spectrometry), Spectrophotometry, and AES (atomic emission spectroscopy). AAS and ICP-MS technologies have detection limits around 0.01-0.02 µg/l, which is sufficient for the analysis of chromium compounds in biological matrices given the fact that average chromium concentrations in the general population are 0.01 – 0.5 µg/l in serum, 0.24-1.8 µg/ml in urine and 200-5800 µg/kg in bone (ICPS 2013). An important aspect of chromium analysis is the possibility to distinguish different relevant chromium species, i.e. chromium (0), chromium (III) and chromium (VI). Additional technologies, together with AAS and ICP-MS, are needed for this purpose. Most of these techniques are based on physical-chemical differences in appearances of chromium (III) ( $\text{Cr}(\text{H}_2\text{O})_4(\text{OH})^{2+}$ ) and chromium (VI) ( $\text{CrO}_4^{2-}$ ,  $\text{HCrO}_4^-$ ,  $\text{Cr}_2\text{O}_7^{2-}$ ). It is beyond the scope of this report to describe these methods in more detail; more information can be found in Gómez et al. (2006).

### 2.3.1.5 Occupational exposure data on chromium

The literature review performed under WP 7.1 is reported here, in addition of the review done in WP8.5. Information provided by WP7.1 about the inventory of studies targeting occupational exposure in Europe is also reported in this paragraph.

### 2.3.1.6 Literature Review (from 2000 – 2017)

#### **Arc welding**

There are 5 scientific papers which reported chromium data in welders (Table 1). In Gube et al. (2013) and Bertram et al. (2015), subjects are voluntary exposed to welding fumes. Levels of total

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chromium in urine increased significantly after exposure in these studies, when compared to the value at baseline. Persoons et al. (2014) followed 137 welders in France. Urinary geometric mean total Cr of 0.43 mg/g creatinine was well below occupational health guidance values, but still higher than background levels observed in the general population, confirming the absorption of metals generated in welding fumes. As for Scheepers et al (2008) and Weiss et al. (2013), they also determined chromium in red blood cells.

**Table 1. Overview of studies on chromium exposure in welders**

Authors	year	Sample size	Collected samples	Investigated biomarkers	Comments
Scheepers et al.	2008	53 welders 20 controls	Urine, plasma and blood erythrocytes	Total Cr	
Weiss et al.	2013	241 welders	Airborne, urine and blood samples	Total Cr	
Gube et al.	2013	12 subjects	Urine and blood	Total Cr	Experimental exposure
Persoons et al.	2014	137 welders	urine	Total Cr	
Bertram et al.	2015	12 subjects	urine	Total Cr	Experimental exposure

### **Chromium plating**

11 scientific papers from 2000 – 2017 were found which reported chromium data in platers (Table 2). In four studies (Caglieri et al. 2006, Goldoni et al. 2006, 2010, Leese et al. 2017), levels of Cr (VI) in exhaled breath condensate (EBC) of the occupationally exposed workers were measured. Levels were significantly higher than in the control group. However, for the exposed workers no significant difference was found between the beginning and the end of the workweek in EBC samples. Leese et al. (2017) have simultaneously measured Cr(III) and Cr(VI) in EBC samples. According to these authors, EBC is a suitable matrix that can be used to investigate both Cr levels and others biomarkers.

In three studies (Benova et al. 2002, Gambelunghe et al. 2003 and Qu et al. 2008), levels of genotoxic markers in buccal cells, blood and urine increased significantly after exposure to atmospheric Cr (VI) as compared to the controls.

Levels of Cr (VI) in red blood cells (RBC) were measured in Gambelunghe et al. 2003, Qu et al. 2008 and Goldoni et al. 2010. Chromium in RBC is specific to exposure to Cr (VI) and may serve as a sensitive and reliable biomarker for long-term exposure (up to 4 months) to Cr (VI). Furthermore, Cr-RBC correlated with Cr(VI) in exhaled breath condensate (EBC). Beattie et al (2017), with dermal and surface sampling, showed the importance of a regular cleaning regime in the reduction of exposure to chromium in the electroplating industry.

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**Table 2. Overview of studies on chromium exposure in platers**

Authors	Year	Sample size	Collected samples	Investigated biomarkers	Comments
Benova et al.	2002	15 platers	Airborne, urine peripheral lymphocytes exfoliated buccal cells	Total Cr Micronuclei in cells Clastogenic and aneugenic effects	
Chen et al.	2002	57 platers	Airborne, urine	Total Cr	
Gambelunghe et al.	2003	19 platers	Urine, blood (erythrocytes, lymphocytes)	Total Cr Comet assays	
Cagliari et al.	2006	24 platers	Exhaled breath condensate (EBC)	Total Cr Hydrogen peroxide, malondialdehyde	
Kalahasthi et al.		50 platers and 50 controls	Urine plasma	Total Cr Lipid peroxidation Antioxidant enzymes	
Goldoni et al.	2006	10 platers	Airborne EBC	Cr (VI)	
Pierre et al.	2008	9 platers	Airborne urine	Total Cr	
Qu et al.	2008	195 subjects	blood	Cr in red blood cell	Identification of genotypes of band III
Goldoni et al. 2010	2010	14 workers	Urine, EBC Blood plasma	Total Cr Cr in RBC Cr(VI) in EBC	
Leese et al.	2017	58 workers 22 controls	Urine, EBC	Cr(III) and Cr(VI) in EBC Total Cr in urine	
Beattie et al.	2017		Airborne Surface and dermal samples urine	Total Cr	

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### Other sectors

There is one review (Mauriello et al. 2017) on the exposure of incinerator workers to metal including chromium. The results show that the levels of metals measured in incinerators' workers are generally low, with some notable exceptions for Cd and Pb. In the same direction, Godderis et al (2005), assessed the external exposure to fume with metal fraction and the absorbed dose of different metals in personnel from the aluminium cast house. The determination of urinary aluminium, chromium, beryllium, manganese and lead concentrations were rather low, excepting one individual had a urinary chromium excretion above the ACGIH defined biological exposure index (BEI) of 30 mg/g creatinine. Balachandar et al. (2017) identified the genetic alterations occurring in the tannery workers and surrounding inhabitants chronically exposed to hexavalent chromium [Cr(VI)]. Clear genotoxic effects were associated with Cr exposure, for both directly and indirectly exposed populations.

**Table 3. Overview of studies on chromium exposure in other sectors**

Authors	Year	Sample size	Collected samples	Investigated biomarkers	Comments
Mauriello et al.	2017	Incinerator workers			Review
Godderis et al.	2005	30 workers from an aluminium casting plant and 17 control	Airborne Urine	Total Cr	
Balachandar et al.	2010	72 tanning workers and 36 controls	Airborne Urine Blood	Total Cr Comet assay Micronuclei assay	

#### 2.3.1.7 Inventory of databases or datasets targeting occupational exposure to chromium in Europe (from WP 7.1 questionnaire)

Six countries reported occupational biomonitoring data on chromium. For Poland, Latvia, Italy and France, data are from single studies. Finland reported a database including total Cr in urine from metal workers. The Lithuania database contains data of chromium in hair from ceramic plant workers. Belgium reported a database from a continuous follow-up of workers from 2 distinct industrial setting.

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**Table 4. Available databases/datasets on chromate exposure**

Institution / organisation	Country	Type of study	Population (sample size)	Period of data collection	Collected samples	Investigated Biomarkers
Nofer Institute of Occupational Medicine (NIOM)	Poland	Single study	Welders (<100)	2014 - 2015	Urine, serum, blood	Total chromium; Retinol Binding protein; b2-microglobulin
Finish Institute of occupational health (FIOH)	Finland	Database	Workers of metal industry and metalworkers industry	2000 - 2014	urine	Total chromium;
Environmental Health, Agency of Riga Stradins University (RSU)	Latvia	Single study	Welders (148)	2002 - 2009	Blood; air	Sox-oxidation of plasma; tga – oxidation speed
Lithuanian University of Health Sciences (LSMU)	Lithuania	Database (cross-sectional survey)	Ceramic plant workers (630)	1991 - 1994	Hair	Total chromium;
Department of public health University of Naples	Italy	Single study	Welders (<100)	2018	Urine; blood	
French Institute of occupational safety (INRS)	France	Single studies (4 studies)	Painters (233) Workers of metal industry (125) Plating workers (118) Plating workers (29)	2005 – 2009; 2005 – 2010; 2007 – 2011; 2010 – 2015;	Urine; Air; Hair	Total chromium
University of Leuven (KU Leuven) / External Service for Prevention and Protection at Work (IDEWE)	Belgium	Database (continuous ongoing workers follow-up)	Worker in the industry producing paints and coatings for Railway Industry and Aluminum cast-house workers	2004 - present	Urine; Air	Total chromium

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### 2.3.1.8 Background exposure data

The general population is mostly exposed to Cr(III) by inhaling ambient air, ingesting food, smoking and drinking water containing chromium. The primary route of exposure, however, is food ingestion. Chromium is found in many vegetables, fruits, meats, grains, and yeast. Chromium content in foods varies greatly and depends on the processing and preparation. The concentration of chromium in water also varies according to the type of the surrounding industrial sources and the nature of the underlying soils.

### 2.3.1.9 Summary on chromates data

Chromium, whether measured in total blood, plasma or urine as total Cr, is not specific to occupational exposure to Cr(VI) and also includes exposure to Cr(III) by inhalation and/or the dietary route. Recent studies have focused on exhaled breath condensate (EBC) and red blood cell (RBC) chromium levels. Only Cr(VI) is able to penetrate the membrane of the erythrocytes before being reduced to Cr(III), thus RBC chromium levels are specific to exposure to Cr(VI). In EBC, simultaneous detection Cr(III) and Cr(VI) was reported by some authors. These matrixes (RBC and EBC) seem promising to investigate specific exposure to Cr(VI). More, in one study, a correlation between Cr-RBC and Cr-EBC was established. Since the data using these Cr(VI) specific biomarkers is still very limited, there is need for further studies, which would integrate and evaluate both Cr-RBC and Cr-EBC as biomarkers for occupational exposure to Cr(VI).

### 2.3.2 Anilines

There is a wide variety of aniline compounds. Anilines are also formed as degradation products from e.g. azo-colourants, pharmaceuticals and from aromatic isocyanates used for polyurethane polymers, lacquers, foams and adhesives. Selection of the most relevant anilines for review was based on the information found in ECHA website. The candidate list of substances of very high concern (SVHCs) and the list of Substances restricted under REACH were screened for anilines. "Search for chemicals" was also used with the search word "Aniline". From 2032 search results substances with Brief Profile and health hazard (not just irritation/corrosion or harmful) were selected. The final selection from these anilines was made based on the amounts manufactured and/or imported in the European Economic Area. HPV substances, e.g. those manufactured or imported in EU at amounts above 1000 tonnes were selected for closer look and literature review. These included: aniline (CAS 62-53-3), o-toluidine (CAS 95-53-4), p-toluidine (CAS 106-49-0), 4,4'-methylenebis[2-chloroaniline] (MOCA) (CAS 101-14-4), 4,4'-methylenedianiline (MDA) (CAS 101-77-9), 1,3-diphenylguanidine (CAS 102-06-7), p-phenylenediamine (CAS 106-50-3).

Literature review was performed under HBM4EU WP7.1. Data sources included databases PubMed, Web of Science; publication date from 1.1.2000 to 31.12.2016. Information on questionnaires performed under WP7.1 was also screened to find out any occupational exposure datasets on anilines.

#### 2.3.2.1 General description on data sources

In the case of aniline compounds main data sources are occupational studies published as scientific papers (including usually method development and general population exposure). Some data may be available in the databases of laboratories performing biomonitoring of these compounds, but in the questionnaire performed under WP7.1 only Finnish Institute of Occupational Health (FIOH) reported some measurements of aniline compounds. For MOCA (and to a limited extent MDA) some biomonitoring data can be found also related to authorization applications available at ECHA webpage. This is the data which have been gathered and reported by the industry applying authorization for the use of these authorised chemicals. Compound specific overview of biomonitoring data is presented below.

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### 2.3.2.2 Aniline (CAS 62-53-3):

There are 14 publications available on aniline at publication date from 1.1.2000 to 31.12.2016. There are two reviews: one on biomonitoring of arylamines (published 2002) and the other on the presence of paracetamol (the major metabolite of aniline) in urine (published 2014). There are publications reporting haemoglobin and serum albumin adducts in workers in a nitrobenzene reduction plant, method development in determination of various aromatic amines in urine for low level exposure (general population), method development for urine p-Aminophenol and its application in workers at a rubber plant, presence of hemoglobin adducts in workers exposed to benzidine and azo dyes, biomonitoring of percutaneous absorption of aromatic amines in rubber industry workers, biomonitoring of monocyclic arylamines in urine in the general population to yield reference values, case of methemoglobinemia induced by dermally absorbed aniline, experimental study between aniline in air with the formation of Met-Hb in blood and the elimination of aniline in urine, investigation on human metabolism and excretion kinetics of aniline after a single oral dose. There is also a publication on method development of determination of N-acetyl-4-aminophenol (paracetamol) in urine and its application in general population, a related publication on method development of determination of N-Acetyl-4-aminophenol (paracetamol), N-acetyl-2-aminophenol and acetanilide in urine and its application in general population, individuals exposed to aniline and paracetamol users and a third publication reporting a body burden of the Danish school children and their mothers to N-acetyl-4-aminophenol (paracetamol) measured by methods described in two earlier studies.

Most of the relevant studies seemingly have been published before year 2000. However, data is still quite scarce regarding occupational exposure. Major use of aniline is as an intermediate in the production of different chemicals, including rubber chemicals, dyes, some pesticides, drugs and polyurethane based polymers. According to ECHA registration information, its production/import in EU is 1-10 million tonnes. According to the ECHA database it is also used in pH regulators and water treatment products. Aniline may also be formed in the degradation of MDI-based polyurethane and reactions in rubber industry (EU, 2004). Also general population is known to be ubiquitously exposed to aniline. Thus, assessment of aniline exposure is of both occupational and environmental relevance.

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**Table 5. Overview on the occupational exposure studies on aniline.**

Authors	Year	Sample size	Collected samples	Investigated biomarkers	Comments
Thier, R., Lewalter, J., Selinski, S., Bolt, H.M.	2001	80 employees	blood	aniline, 4-aminodiphenyl (4-ADP) and benzidine adducts of haemoglobin (Hb) and human serum albumin (HSA), levels of methaemoglobin (Met-Hb) and of carbon monoxide haemoglobin (CO-Hb)	
Chen, C.-F., Tseng, Y.-T., Tseng, H.-K., Liu, T.-Z.	2004	255 rubber plant workers	urine	p-aminophenol (4-aminophenol)	
Beyerbach, A., Rothman, N., Bhatnagar, V.K., Kashyap, R., Sabbioni, G.	2006	group of Indian workers	blood	Bz, N-acetylbenzidine (AcBz), 4-aminobiphenyl (4ABP) and aniline adducts of haemoglobin	
Korinth, G., Weiss, T., Penkert, S., Schaller, K.H., Angerer, J., Drexler, H.	2007	51 rubber plant workers	urine, blood, air	aniline and o-toluidine, haemoglobin adducts	
Kafferlein, H.U., Broding, H.C., Bungler, J., Jettkant, B., Koslitz, S., Lehnert, M., Marek, E.M., Blaszkewicz, M., Monse, C., Weiss, T., Bruning, T.	2014	19 (+4 in pilot study) volunteers	air, blood, urine	aniline, Met-Hb	the association between aniline in air with the formation of Met-Hb in blood and the elimination of aniline in urine was studied
Dierkes, G., Weiss, T., Modick, H., Kafferlein, H.U., Bruning, T., Koch, H.M.	2014	31 (controls), 6 (occupational exposure to aniline but no paracetamol medication) and 2 (no occupational aniline exposure, paracetamol users)	urine	N-acetyl-4-aminophenol, N-acetyl-2-aminophenol and acetanilide	

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### 2.3.2.3 4,4'-methylenebis[2-chloroaniline] (MOCA) (CAS 101-14-4)

11 publications on MOCA at publication date from 1.1.2000 to 31.12.2016 including a review on biomonitoring of arylamines (published 2002). Some older data have been summarized by SCOEL (2013). Three articles were found concerning occupational exposure to MOCA in the United Kingdom. One was about how research studies can be used to develop biological monitoring guidance values and the other two were to investigate exposure levels on workers in workplaces known to be using MbOCA (polyurethane industry). There were three method development publications: one was on determination of aliphatic and aromatic diamines in urine and plasma, the other was on analyzing MOCA and N-acetyl-MOCA in urine and the third was on analyzing MOCA in urine. One study was on genotoxicity in urothelial cells and in lymphocytes of workers exposed to Methylenebis-(2-chloroaniline) (MOCA) in polyurethane manufacture. One was a case of occupational bladder cancer among workers in MOCA manufacturing company with 10 urine samples analyzed. One study on workers in four MOCA producing factories included Plasma 8-hydroxydeoxyguanosine (8-OHdG) level (marker of oxidative stress) and urinary MBOCA concentration measurements in estimation of oxidative DNA damage. Another study on workers in four MOCA producing factories explored the association between 8-OHdG and genetic polymorphism of the carcinogen-metabolizing enzyme N-acetyltransferase 2 (NAT2).

Many of the relevant studies have been published before year 2000. The main use of MOCA is as a curing agent in the manufacturing of polyurethane products. In UK, HSL has offered MOCA biomonitoring to companies for 30 years and published follow up data on the exposure to MOCA in polyurethane production from this period of time on the basis of the data gathered in their databases (Cocker et al., 2009). Also the Finnish Institute of Occupational Health (FIOH) publishes results from the biomonitoring analysis made in Finnish workplaces. According to FIOH analysis cited in SCOEL (2013) the total number of MOCA measurements during the years 2000–2008 was 49. Most of the samples were derived from workers involved in the manufacturing of polyurethane coatings. Most of the values were < 5 µmol/mol creatinine, the range being between below the LOD (1 µmol/mol creatinine) and 10 µmol/mol creatinine (FIOH 2000-2008). The 95th percentile of these measurements (n = 49) was 3.4 µmol/mol creatinine. Since then the use of MOCA has decreased and finally ceased in Finland. In 2007-2008 only 8 samples were analysed and after 2008 there has been no samples for the biomonitoring of MOCA in Finland.

MOCA is currently authorized under REACH. There is one application for authorization for MOCA, which covers up to 89 sites in EU using MOCA as a curing agent in polyurethane production (ECHA, 2016a). Estimated number of exposed workers in EU is about 200 and the authorization is applied for 12 years. The application is available at ECHA website, but the commission decision or the ECHA committees (Risk Assessment Committee (RAC) and Committee for Socio-Economic analysis (SEAC)) recommendation on the authorization of MOCA is not available yet. The applicant has used biomonitoring data to assess the workers' exposure to MOCA. Data have been gathered by questionnaires directly from companies using MOCA as a curing agent (ECHA, 2016a). According to the application, total of 17 companies answering to the questionnaire had performed biomonitoring. Data was, however, presented only from 11 companies in the application. Since there are ready-to-use substitutes for MOCA available for the use in polyurethane production, the use of MOCA may cease within becoming years when companies are able to move to the substitutes. Taking this into account, MOCA is not a good candidate for further research under HBM4EU although laboratories performing biomonitoring of MOCA are still needed in EU as long as it is used.

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**Table 6. Overview on the occupational exposure studies on MOCA.**

Authors	Year	Sample size	Collected samples	Investigated biomarkers	Comments
Marand, A., Karlsson, D., Dalene, M., Skarping, G.	2004	10 urine and 6 plasma samples from workers exposed to isocyanates	urine, plasma	methylene diamine (MDA), toluene diamine (TDA), naphthalene diamine (NDA), hexamethylene diamine (HDA), isophorone diamine (IPDA), methylenedi(cyclohexylamine) (HMDA) and 4,4'-methylene-(2-chloroaniline)(MOCA)	
Murray, E.B., Edwards, J.W.	2005	Twelve men employed in polyurethane manufacture, twelve bitumen road layers, and eighteen hospital stores personnel (controls)	blood, urine	genotoxicity in urothelial cells and in lymphocytes of workers	
Chen, H.I., Liou, S.H., Ho, S.F., Wu, K.Y., Sun, C.W., Chen, M.F., Cheng, L.C., Shih, T.S., Loh, C.H.	2007	four MBOCA-producing factories (158 subjects)	blood	8-hydroxydeoxyguanosine (8-OHdG)	association between oxidative DNA damage and MBOCA exposure was studied
Cocker, J., Cain, J.R., Baldwin, P., McNally, K., Jones, K.	2009	80 inhalation, 79 urine samples (from workplaces known to be using MbOCA)	air samples, surface wipes, gloves, and urine samples	All samples were analysed for MbOCA and urine samples were additionally analysed for isocyanate metabolites	
Keen, C., Coldwell, M., McNally, K., Baldwin, P., McAlinden, J., Cocker, J.	2012	Urine samples (n = 446) were collected from 90 different workers, 19 companies in from polyurethane industry (seventeen MbOCA users and two suppliers)	urine	MbOCA	
Lin, I.S., Fan, P.L., Chen, H.I., Loh, C.H., Shih, T.S., Liou, S.H.	2013	57 MBOCA-exposed workers and 101 unexposed control workers	blood	8-hydroxydeoxyguanosine (8-OHdG), enzyme N-acetyltransferase 2 (NAT2)	study explored the association between a marker of oxidative stress, 8-OHdG, and genetic polymorphism of the carcinogen-

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					metabolizing enzyme NAT2 among MBOCA- exposed workers

#### 2.3.2.4 4,4'-methylenedianiline (MDA) (CAS 101-77-9):

There are 4 publications on the exposure to MDA and its biomonitoring at publication date from 1.1.2000 to 31.12.2016 including a review on biomonitoring of arylamines (published 2002). There was one method development study on the determination of aliphatic and aromatic diamines in urine and plasma and its application in workers exposed to isocyanates. One publication was on workers exposure in rotor blade production. One recent article was on determination of albumin adducts of 4,4'-methylenediphenyl diisocyanate in workers of a 4,4'-methylenedianiline factory, where albumin adducts of MDI have been found in subjects classified as 4,4'-methylenedianiline (MDA) workers.

Most of the studies seemingly have been published before year 2000. These have been summarized in SCOEL (2012). The use of MDA is authorized under REACH and there is only two applications for authorization concerning 1) the industrial use of an epoxy resin hardener containing technical MDA aimed at immobilizing spent ion exchange resins in a high containment matrix and 2) the formulation of MDA mixtures for this use (ECHA, 2017ab). For these uses, there are RAC and SEAC opinions available and a 12 years review period was proposed for this use (ECHA, 2017ab). Total number of exposed workers in these uses is 56. The applicant of an authorization provided biomonitoring data on the exposure of workers in these uses, and these data were used by RAC in the assessment of excess cancer risk to workers. Due to the limited use and limited number of workers exposed to MDA, exposure to MDA *in the use of MDA* is not a good candidate for further work under HBM4EU.

However, MDA is the degradation product and one of the main metabolites of methylene diphenyldiisocyanate (MDI, CAS 101-68-8). Urinary MDA can be used also to measure exposure to MDI. Similarly, toluene diamine (TDA) can be used as a marker for exposure to toluene diisocyanate (TDI, CAS 584-84-9). These diisocyanates are widely used in different applications (e.g. foams, sealants, coatings) throughout the EU, with the total tonnage of about 2.5 million tonnes per year (ECHA, 2016b). They are common respiratory sensitizers causing several thousand new cases of respiratory allergies (mainly asthma) annually in Europe. The use of these di-isocyanates has been recently proposed to be restricted in EU unless specific conditions for workers training and risk management measures apply. The aim of the restriction is not to ban the use of diisocyanates but rather to improve the control of di-isocyanate use by obligatory training for good working practices and risk management. Therefore, for the biomonitoring of di-isocyanates sensitive methods to measure diamine levels in urine are still needed in future and there may be a need to study the effectiveness of the possible restriction on the occupational exposure to diisocyanates via different exposure routes.

In the questionnaire performed under WP7.1. Finnish Institute of Occupational Health (FIOH) reported 38 MDA measurements, which were performed in Finland between 2007 and 2016. Majority of these analysis came from the polyurethane workers, meaning that it reflects the exposure to MDI rather than to MDA itself.

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**Table 7. Overview on the occupational exposure studies on MDA/MDI.**

Authors	Year	Sample size	Collected samples	Investigated biomarkers	Comments
Marand, A., Karlsson, D., Dalene, M., Skarping, G.	2004	10 urine and 6 plasma samples*	urine, plasma	methylene diamine (MDA), toluene diamine (TDA), naphthalene diamine (NDA), hexamethylene diamine (HDA), isophorone diamine (IPDA), methylenedi(cyclohexylamine)(HMDA) and 4,4'-methylene-(2-chloroaniline)(MOCA)	* workers exposed to isocyanates
Weiss, T., Schuster, H., Muller, J., Schaller, K.H., Drexler, H., Angerer, J., Kafferlein, H.U.	2011	7 workers in rotor blade production	air, urine	MDA	
Sabbioni, G., Dongari, N., Sepai, O., Kumar, A.	2016	MDA-workers		isocyanate specific adducts	
Sabbioni, G., Wesp, H., Lewalter, J., Rumler, R.	2007	40 non-exposed and 45 exposed construction site workers*	blood, urine	4,4'-Methylenedianiline (MDA) and N-acetyl-4,4'-MDA (AcMDA), Hb-MDA	MDI exposure
Kaaria, K., Hirvonen, A., Norppa, H., Piirila, P., Vainio, H., Rosenberg, C.	2001	57 workers	air, urine	MDI, MDA	MDI exposure
Gries, W., Leng, G.	2013		blood	hemoglobin adduct 5-isopropyl-3-[4-(4-aminobenzyl)phenyl]hydantoin (ABP-Val-Hyd)	MDI exposure

### 2.3.2.5 o-Toluidine (CAS 95-53-4):

Five occupational publications on o-toluidine starting from the year 2000. Older data have been summarized in SCOEL (2017). Some data exists on the exposure of hairdressers to o-toluidine showing exposure of hairdressers when using hair dyes. Skin absorption in rubber industry workers, as well as in vulcanisation process of rubber products in a components supplier plant for automobile industry has been studied. There was also a method development in determination of various aromatic amines in urine for low level exposure (general population) and biomonitoring monocyclic arylamines in urine in the general population to yield reference values.

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**Table 8. Overview on the occupational exposure studies on o-toluidine.**

Authors	Year	Sample size	Collected samples	Investigated biomarkers	Comments
Korinth, G., Weiss, T., Penkert, S., Schaller, K.H., Angerer, J., Drexler, H.	2007	51 workers manufacturing rubber products for the automobile industry	air, urine, blood	aniline and o-toluidine	
Carreon, T., Hein, M. J., Hanley, K. W., Viet, S. M., Ruder, A. M.	2014	1875 workers, rubber chemical manufacturing plant			bladder cancer study
Johansson, G.M., Jonsson, B.A., Axmon, A., Lindh, C.H., Lind, M.L., Gustavsson, M., Broberg, K., Boman, A., Meding, B., Liden, C., Albin, M.	2015	295 hairdressers, 32 users of hair dyes and 60 controls	blood	ortho-, meta (m)- and para (p)-toluidine; 2-, 3- and 4-ethylaniline, 2,3- and 3,4-dimethylaniline as haemoglobin adducts	

### 2.3.2.6 p-toluidine (CAS 106-49-0):

Only two occupational publications on p-toluidine starting from 2000 was found. One was the same study on hairdressers as for o-toluidine. No occupational exposure to p-toluidine was detected. The other was a case report on exposure to p-toluidine and aniline while maintaining 4,4'-methylene diphenyl diisocyanate (MDI) storage tank.

**Table 9. Overview on the occupational exposure studies on p-toluidine.**

Authors	Year	Sample size	Collected samples	Investigated biomarkers	Comments
Johansson, G.M., Jonsson, B.A., Axmon, A., Lindh, C.H., Lind, M.L., Gustavsson, M., Broberg, K., Boman, A., Meding, B., Liden, C., Albin, M.	2015	295 hairdressers, 32 users of hair dyes and 60 controls	blood	ortho-, meta (m)- and para (p)-toluidine; 2-, 3- and 4-ethylaniline, 2,3- and 3,4-dimethylaniline as haemoglobin adducts	

### 2.3.2.7 Other high volume aniline compounds with hazardous properties

P-phenylenediamine (p-PDA, CAS 106-50-3) is a common contact allergen present in cosmetics and e.g. in hair dyes. It has not been regularly biomonitored, but there studies in which analytical methods for the analysis of it or its metabolites in urine or blood has been described. In these studies exposure of hairdressers to p-PDA has been described. In addition, some of these studies describe potential exposure to other sensitizing aromatic diamines, like 2,5-TDA, m- and p-aminophenols due to the hair dyes.

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We also searched for the data 1,3-diphenylguanidine (CAS 102-06-7), which is also manufactured and/or imported in the European Economic Area in 1 000 - 10 000 tonnes per year. No biomonitoring studies was found, only few occupational contact allergy studies. 1,3-diphenylguanidine is classified as suspected of damaging fertility. It is used in polymers and manufacturing of rubber.

**Table 10. Overview on the occupational exposure studies on p-phenylenediamine.**

Authors	Year	Sample size	Collected samples	Investigated biomarkers	Comments
Geens, T., Aerts, E., Borguet, M., Haufroid, V., Godderis, L.	2016	11 hairdressers		PTD, PPD	
Gube, M., Heinrich, K., Dewes, P., Brand, P., Kraus, T., Schettgen, T.	2011	52 hairdressers, 19 controls	urine	2,5-toluylene diamine (2,5-TDA) and p-phenylene diamine (p-PDA)	
Hueber-Becker, F., Nohynek, G. J., Dufour, E. K., Meuling, W. J., de Bie, A. T., Toutain, H., Bolt, H. M.	2007	18 hairdressers	plasma, urine, air*	PPD	*also hand residues, waste, equipment, gloves and coveralls were measured

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## Inventory of studies targeting occupational exposure to anilines in Europe (from WP 7.1 questionnaire)

Institution / organisation	Country	Type of study	Population (sample size)	Period of data collection	Collected samples	Investigated Biomarkers
Environment and Health, KU Leuven	Belgium	Single study	Polyurethanes factory (<100)	2017 - 2018	Urine, blood, air	Aniline, toluidines, MOCA, MDA, TDA
Finnish Institute of Occupational Health (FIOH)	Finland	Existing database	Aniline exposure, not specified.	2007 - 2016	Urine	Aniline in urine
AICT	Switzerland	Single study	Chemical industry, automobile industry, construction (<100)	1990-2013	Urine, blood, air	Urinary metabolite, hemoglobin adducts or albumin adducts
Finnish Institute of Occupational Health (FIOH)	Finland	Existing database	NACE classifications: 13.96 (<100)	2007 - 2016	Urine	MOCA in urine
Finnish Institute of Occupational Health (FIOH)	Finland	Existing database	NACE classifications: 28.9 - 25.1, 22.2 - 28.2 (<100)	2007 - 2016	Urine	MDA in urine

### 2.3.3 Summary on anilines

For anilines, a part of the lack of structural databases and of national or European wide studies, the scientific publications are highlighting also other knowledge gaps.

#### 2.3.3.1 Biomarkers

Suitability of the biomarkers to accurately reflect exposure to specific aniline compound need to be ensured. Challenges have been faced e.g. in the case of workers' co-exposure to both anilines and diisocyanates (Gries et al., 2013, Sabbioni et al., 2000; Cocker, 2011; Jones et al., 2017). Another example is the biomonitoring of aniline and confounding effect of paracetamol intake if N-Acetyl-4-aminophenol is used as a biomarker for aniline.

Due to their closely related chemical structures, some diisocyanates are metabolized in the human body to anilines (MDI to MDA; TDI to TDA). Considering this, urinary metabolites of MDA might reflect both the exposure to MDA and MDI (Tinnerberg et al., 2008; Cocker, 2011; Sabbioni et al., 2010; Jones et al., 2017), which is an issue from a regulatory point of view. Nevertheless, the use of MDA is decreasing due to the REACH authorization, but, despite that, this compound can be

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even generated by the process of degradation of MDI that naturally occur in the work environment (Six, C. and Richter, F., 2003). In order to establish threshold limits as well as potential causative relationship between MDA exposure and health illness occurrence in occupational setting, where complex exposures might occur, an accurate biomonitoring is required. To tackle this issue, two main approaches have been proposed to distinguish between the anilines and isocyanates exposure. On one hand, it was proposed the simultaneous evaluation of air exposure and human biomonitoring (Tinnerberg et al., 2008; Jones et al., 2017). Even if this approach is suitable to better evaluate exposure and allows to confirm exposure to either anilines or isocyanates, it does not allow completely to distinguish their respective contribution to the overall body burden as reflected by biomonitoring. On the other hand, the use of adducts (e.g. albumin, hemoglobin or DNA adducts) of anilines and isocyanates has been proposed as alternative. The adducts evaluation is providing several advantages, among which the most relevant one for regulatory evaluation is their half-life ranging from about 20 days for albumin adducts up to 120 days for hemoglobin adducts, thus reflecting a chronic constant exposure over a longer period of time than urinary concentrations that might reflect up to 48h of exposure (Sabbioni et al., 2010). Furthermore, adducts might be considered as both biomarkers of exposure and effect, since their occurrence might be the first step towards future cytotoxic and genotoxic effects (Sabbioni et al., 2010). There are specific adducts identified for diisocyanates (e.g. MDI-Lys, AcMDI-Lys) whereas aniline adducts can be formed both due to the exposure to anilines and isocyanates (e.g. MDA-Val-Hyd, AcMDA-Val-Gly-Gly) (Gries et al., 2013; Sabbioni et al., 2000&2010 & 2016).

### 2.3.3.2 Occupational settings

Among the various scenarios in which occupational exposure to anilines and diisocyanates occurs, we can distinguish between large companies and medium/small companies. Different studies are already made by different organizations/institutions in order to evaluate the occupational exposure to anilines and diisocyanates, but most of them are mainly focused on large companies such as polyurethanes industries or paint factories in which the protective personal equipment (PPE) and the safety procedure are well established (Schnorr et al; 1996). Nevertheless, there is an increasing interest to assess the occupational exposure in the small/medium companies (SMEs) or micro-sized companies (hairdressing shops, car painting shops, construction painters, etc.) where the exposure of workers can be more relevant due to reduced attention of workers regarding the safety procedures and the correct use of PPE (Geens et al., 2016; Johansson et al., 2015). For instance, a significant reduction of the systemic exposure was obtained through the improvement and the correct use of PPEs (Geens et al., 2016). If the restriction proposal on diisocyanates (ECHA, 2017c) is going to become in force, it should have an impact on the exposure to diisocyanates but the SMEs may still pose a challenge. Therefore, there is a need to follow-up its effects especially in SMEs.

Aniline compounds can be found also from different pigments or colorants (e.g. hair dyes and tattoo inks). For example, aniline compound p-PDA is a common cause of occupational allergies in e.g. hairdressers. Some aniline compounds have been also found as impurities in hair dyes or are formed as degradation products of dyes or pigments. Limited data on exposures, however, exists. There are limited data available on the exposure of workers, including e.g. hairdressers to these different aniline compounds.

Taking into account these different challenges, there is a need of developing integrated European wide biomonitoring studies in different occupational settings, with a special focus on small/medium companies where the personal protective equipment and the safety procedures are not well established. These studies should be focused on gathering as much insight of the extent of human exposure using both air and biological monitoring, as well as to evaluate the most suitable biomarkers.

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### 3 General challenges related to the available occupational biomonitoring data

From the description of different available data in different European countries, it appears that there are very few national initiatives organized with regard to the collection of biomonitoring data in occupational settings. Furthermore, to the best of our knowledge there are no European wide studies for the biomonitoring of human exposure in occupational settings. Only individual studies data or workers annual follow-up may give some insights on workers exposure as reflected by biomonitoring.

The majority of the available occupational biomonitoring data comes from the research studies performed by the different research institutes. These data have been published as research papers. The main problem related to many research studies on occupational exposure is the size of the sample, which is often small especially if some specific occupations and tasks are concerned. On the other hand, in the case of larger occupational studies, contextual data, including descriptions on specific tasks undertaken, risk management measures like the use of personal protective equipment and detailed background information on the subjects (and possible confounding exposures) may be limited and the way these are presented varies between the studies. Although in some studies also air and surface sampling has been done, in other studies information on external exposure is limited, which makes it difficult to draw conclusions on the exposure routes resulting in elevated blood or urinary levels. Proper characterization of exposure routes is, however, an important aspects in the viewpoint of workers' protection. For example in the case of use of hexavalent chromium in chromium electroplating, there are data available on the significance of skin and surface contamination to the systemic chromium levels, which should be taken into account in the risk assessment and management.

Only in few member states there are such national biomonitoring databases, which include several substances and biomonitoring samples which have been taken as part of workplace exposure assessment or workers' health surveillance. These countries include Belgium, Finland and UK. In some countries, there are databases available on biomonitoring analyses of some specific compounds. However, even in Finland where Finnish Institute of Occupational Health (FIOH) is almost the only laboratory performing occupational biomonitoring analyses, FIOH database does not cover all the biomonitoring analyses performed at Finnish workplaces, since companies are increasingly buying these services from laboratories outside Finland. Thus, the current coverage of the database is unknown. In addition, the data which is based on the analyses ordered by the companies (or their occupational health services) may be biased to describe situation in better workplaces since small companies with poor working conditions and limited occupational health services may not have realized the need for biomonitoring. One additional challenge related to these databases is that they contain often very limited contextual information related to the exposure. Although this kind of data can be used to prepare overviews on the exposure to specific substances, the uncertainties described above should be taken into account when interpreting the results.

In the case of many countries there are several laboratories providing biomonitoring analyses to workplaces or to occupational health services, and there are no systems to collect national data on the occupational biomonitoring analysis. Thus, even though occupational biomonitoring is actively done by companies and their occupational health services, the results are only accessible for them and it is not possible to get an overview on the national situation. Naturally, it could be possible to gather data by questionnaires from individual companies, which has been done in some cases by the industry in the context of e.g. REACH authorization process, but this demands non-individualized, summarized data and the overall response rate may remain low.

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Even though there might be biomonitoring data available on the occupational exposure to specific substances from individual countries, extrapolation from one country to other countries should be made with caution. It should be noted that occupational exposure limit values may differ widely between countries, which may result in differing levels of protection and exposures at workplaces. In order to get an overview on the exposure in EU, the data from several countries, covering different parts of Europe is preferable.

One general challenge related to the biomonitoring is the specificity of the available biomarkers. For the substances described in this document, this issue concerns especially hexavalent chromium where usually total urinary chromium has been used as a biomarker for hexavalent chromium exposure. In tasks where there is simultaneous exposure also to trivalent chromium (like welding), it is not possible to identify the exposure to carcinogenic hexavalent chromium from trivalent chromium exposure when using urinary total chromium. Also in the case of biomonitoring of MDA, proportion of the urinary MDA may reflect exposure to diphenyl methyl diisocyanate. Naturally, in those cases in which only either one of these chemicals is used in the workplace, or is present in the air of the workplace, it can be assumed that these biomarkers represent exposure specifically to that substance.

## 4 Conclusions and proposals

### 4.1 Conclusions

- The current occupational biomonitoring data is scattered and its coverage is limited. Therefore, there is clearly a need for the collection of EU-wide, more comprehensive biomonitoring data on occupational chemical exposures in different occupations/industries. Thus, the importance of EU wide occupational biomonitoring studies is highlighted. The data from these studies would support not only implementation of occupational health and safety legislation but also EU chemicals legislation (REACH).
- Similarly to general population studies, also in the case of occupational biomonitoring studies, there is a need to standardize common protocols, and harmonize methods for example for the collection of contextual data
- Efforts to collect EU wide data to an European database should be supported. The database should include both the available data on research studies and when possible summary data from national databases. It should be noted that DG Employment funded recently the development of the database Hazchem@work (Koop, 2016), which forms a platform for a database aimed to be used for the gathering occupational exposure data, both air and biomonitoring data, from different European countries.
- In the case of chromates, majority of available occupational biomonitoring data comes from the use of total chromium measurements. Since this is not specific for hexavalent chromium, there is need for EU wide data, which would use new Cr(VI) specific biomarkers, Cr-RBC and Cr-EBC for the assessment of occupational exposure to Cr(VI) in different industries. This would give more accurate and better picture on the Cr(VI) exposure especially in the cases in which there is significant co-exposure to the trivalent chromium than only the measurement of total urinary chromium. This supports the already planned study with more specific markers for Cr(VI). Given the complexity of developing a biomonitoring study in which blood samples are collected, a dried blood spot approach may be useful. A thorough evaluation of available matrices for the proposed markers will be needed beforehand. The measurement strategy should be based on data on variability in markers levels and availability of the populations.

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- In the case of anilines, occupational exposure to anilines formed from diisocyanates, MDA/TDA as markers for diisocyanate exposure and effects for regulatory measures on the exposure to these substances, especially in small and medium sized companies, needs further data. Although some studies exist, the data is still limited. There are also some data on the occupational exposure to specific anilines through e.g. hair dyes but the biomonitoring data on these exposures, which may concern large number of workers, is still limited. This supports the already planned study where we intend to measure both known and new biomarkers, together with the simultaneous assessment of the air and dermal monitoring for anilines and whenever appropriate for diisocyanates. As for chromates, a thorough evaluation of available data and available evaluation tools will be needed beforehand. The measurement strategy should be based on data on variability in markers levels and availability of the populations. Furthermore, a standardized integrated approach is foreseen in order to have consistent and comparable data European wide.

## 4.2 Detailed Proposals

- HBM4EU shall make efforts to collect EU wide occupational biomonitoring data on a database which should include both the available data on research studies and when possible summary data from national databases.
  - This data should be linked to Hazchem@work database. WP8 will start to make links to this initiative.
- Study on chromates exposure shall be performed as planned in Y2 and as outlined above. A thorough evaluation of available matrices for the proposed markers shall be done beforehand. A detailed research plan for chromates will be developed AD8.2 (M12) (FIOH Leads). The study will also include testing of the applicability of dried blood spot approach for biomonitoring of Cr(VI).
- Study on aniline exposure shall be performed as outlined above. Planning of the study will be performed beginning of Y2 and samplings will be made during at Y2-Y3. A standardized integrated approach is foreseen in order to have consistent and comparable data European wide. Biomonitoring of anilines as biomarkers for anilines and diisocyanates exposure is foreseen together with the assessment of the air and dermal exposure that will allow to account for this simultaneous exposure and different exposure routes, whenever appropriate. New biomarkers specific for anilines and diisocyanates will be investigated. A special interest will be given to anilines and diisocyanates exposures at small and medium companies.
- Evaluation of the need for occupational studies on other priority chemicals shall be done in Y2; for example on PAHs, bisphenols and phthalates.
- New occupational studies performed under HBM4EU should use standardized common protocols, and harmonized methods for example for the collection of contextual data. The coordination of occupational studies and harmonization of methods should be developed under HBM4EU.

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## 6 Annexes

### 6.1 Literature review on chromium and abstracts

#### Arc welding

- 1- P.T.J. Scheepers, G.A.H. Heussen, P.G.M. Peer, et al. Characterisation of exposure to total and hexavalent chromium of welders using biological monitoring. *Toxicology Letters* 178 (2008) 185–190  
Netherlands; 53 welders and 20 references; 2008  
Total Cr, RBC and urine  
Spot urine sample was collected just before the start of the shift and another sample directly after the 8 h shift. On the same day also a blood samples were collected. Total Cr in pre-shift urine, blood plasma and blood erythrocytes are not primarily determined by recent exposure but instead reflect long-term exposure to Cr. It is suggested to use these biomarkers in future epidemiology studies.
- 2- Weiss T, Pesch B, Lotz A, et al. the WELDOX Group. Levels and predictors of airborne and internal exposure to chromium and nickel among welders—Results of the WELDOX study. *International Journal of Hygiene and Environmental Health* 216 (2013) 175– 183.  
Germany; 241 Welders; 2007-2009;  
Airborne, urine and blood samples (for Cr VI determination in erythrocytes in 15 stainless steel welders) - Total Cr and Ni.  
Lung function measurements  
Each welder was examined after 2 p.m. on a Tuesday, Wednesday, or Thursday.  
Cr in erythrocytes as a biomarker of Cr(VI) exposure was only detected in 15 out of 150 stainless-steel welders.
- 3- Gube M, Brand P, Schettgen T et al. Experimental exposure of healthy subjects with emissions from a gas metal arc welding process-part II : biomonitoring of chromium and nickel. *Int Arch occup Environ Health*, 2013, 86, 31-37.  
12 healthy male non-smokers; Experimental exposure  
Blood and urine samples before and after a 6-h exposure to three concentrations of welding fumes  
Although the internal exposure to Cr was comparatively low, significantly dose dependent increased concentrations of Cr in urine compared to the values at baseline are observed  
The relationship between ambient and biological exposures from welding fumes provides a good basis for evaluating future biological threshold values for these metals in welding occupation. Welding fume exposure under controlled and standardized conditions.

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- 4- Persoons R, Arnoux D, Monssu T, et al. Determinants of occupational exposure to metals by gas metal arc welding and risk management measures: A biomonitoring study. Toxicology Letters 231 (2014) 135–141  
France; 137 welders  
Total Cr in urine – Post-shift/end of the working week samples  
Urinary geometric mean total Cr of 0.43 mg/g creatinine was well below occupational health guidance values, but still higher than background levels observed in the general population, confirming the absorption of metals generated in welding fumes.
- 5- Bertram J, Brand P, Schettgen T et al. Human biomonitoring of chromium and nickel from experimental exposure to manual metal arc welding fumes of low and high alloyed steel. Ann Occup Hyg, 2015, 59(4), 467-480.  
12 male subjects; Experimental exposure to welding fumes for 6 h;  
Total Cr in urine; before and after exposure urine  
Urine analysis for total Cr was performed before and after exposure.  
Six-hour exposure to 2.5 mg m<sup>-3</sup> high alloyed manual metal arc welding fumes lead to elevated urinary Cr levels from 0.27 µg l<sup>-1</sup> to 18.62 µg l<sup>-1</sup> with a range 7.11–34.16 µg l<sup>-1</sup> directly after exposure. Single exposure experiment shows that a welding work related Cr exposure can be measured immediately after the work shift.

### Chromium plating

- 1- Benova D, Hadjidekova V, Hristova R, et al. Cytogenetic effects of hexavalent chromium in Bulgarian chromium platers. Muta Res, 2002, 514, 29-38.  
15 workers; Bulgaria  
Atmospheric and urine sample (end of workshift)  
Classical cytogenetic and molecular cytogenetic analyses of peripheral lymphocytes and exfoliated buccal cells  
Relationship between atmospheric Cr and urinary Cr :  $\log(\text{Cr}_u) = 0.96 \log(\text{Cr}_{atm}) + 0.51$  ( $R^2=0.35$ ,  $n=11$ ). Arithmetic means: 18 µg/m<sup>3</sup> for Cr atm and 73 µg/L for urinary Cr.  
Significant increase in the number of cells with micronuclei (MN) in peripheral lymphocytes from chromium exposed workers as compared to the controls.  
Cr(VI) appears to have both clastogenic as well as aneugenic effects in humans.
- 2- Chen JH, Guo YL, Tsai PJ, Su LF. Use of inhalable Cr(VI) exposures to characterize urinary chromium concentrations in plating industry workers. J Occup Health, 2002, 44, 46-52.  
27 and 30 workers from decorative plating and hard-surface plating operation.  
Personal sampling and urine samples (end of work week)

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Hard-surface plating workers had higher atmospheric Cr (arithmetic mean  $\approx 25.2 \mu\text{g}/\text{m}^3$ ) than decorative plating workers (arithmetic mean  $\approx 1.91 \mu\text{g}/\text{m}^3$ ).

Relationship between atmospheric Cr and urinary Cr: urinary Cr =  $1.86 \text{ Cr atm} - 0.21$  ( $R^2=0.87$ ,  $n=57$ ).

Considering that no BEI has been suggested for chromium plating industries, the result obtained in this study will be helpful in introducing a new BEI in the future.

- 3- Gambelunghe A, Piccinini R, Ambrogi M et al. Primary DNA damage in chrome-plating workers. *Toxicology*, 2003, 188, 187-195.

DNA damage (strand-breaks and apoptosis in peripheral lymphocytes) and occupational exposure to Cr (VI).

19 chrome-plating workers.

Concentrations of Cr in urine, erythrocytes and lymphocytes.

18 hospital workers (control group I) and another 20 university personnel (control group II).

Chrome-plating workers have higher levels of Cr in urine, erythrocytes and lymphocytes than unexposed workers.

Measurements of Cr in erythrocytes and lymphocytes may provide useful information about recent and past exposure to hexavalent chromium at the workplace. The increase in DNA strand-breaks measured by comet assay suggests this test is valid for the biological monitoring of workers exposed to genotoxic compounds such as Cr (VI).

- 4- Caglieri A, Goldoni M, Acampa O, et al. The effect of inhaled chromium on different exhaled breath condensate biomarkers among chrome-plating workers. *Environ Health Perspec*, 2006, 114(4), 542-546.

EBC samples from 24 chrome-plating workers

Cr levels in exhaled breath condensate (EBC) of workers exposed to Cr(VI) and analysis of EBC biomarkers of oxidative stress, namely, hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) and malondialdehyde (MDA).

Sampling before and after the Friday work shift and before the work shift on the following Monday

Cr-EBC levels increased from the beginning ( $5.3 \mu\text{g}/\text{L}$ ) to the end of Friday ( $6.4 \mu\text{g}/\text{L}$ ) but were considerably lower on Monday morning ( $2.8 \mu\text{g}/\text{L}$ ).

A similar trend was observed for  $\text{H}_2\text{O}_2$ -EBC levels (which increased from  $0.36 \mu\text{M}$  to  $0.59 \mu\text{M}$  on Friday and were  $0.19 \mu\text{M}$  on Monday morning) and MDA-EBC levels (which increased from  $8.2 \text{ nM}$  to  $9.7 \text{ nM}$  on Friday and were  $6.6 \text{ nM}$  on Monday).

Cr-EBC levels correlated with those of  $\text{H}_2\text{O}_2$ -EBC ( $r = 0.54$ ,  $p < 0.01$ ) and MDA-EBC ( $r = 0.59$ ,  $p < 0.01$ ), as well as with urinary Cr levels ( $r = 0.25$ ,  $p < 0.05$ ).

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EBC is a suitable matrix that can be used to investigate both Cr levels and biomarkers of free radical production sampling the epithelial-lining fluid of workers exposed to Cr(VI).

- 5- Kalahasthi RB, Rao RH, Murthy RB, et al. Effect of chromium(VI) on the status of plasma lipid peroxidation and erythrocyte antioxidant enzymes in chromium plating workers, 2006, 164(3), 192-199.

Fifty subjects and an equal number of age–sex matched subjects working in administrative units formed the control group

Urinary Cr levels, plasma lipid peroxidation and erythrocyte antioxidant enzymes.

A significant increase of plasma lipid peroxidation and a significant decrease of superoxide dismutase and glutathione peroxidase levels in the study group as compared with the controls. The level of plasma lipid peroxidation was positively and erythrocyte antioxidant enzymes were negatively and significantly correlated with chromium levels in urine.

Increased plasma lipid peroxidation and decreased antioxidant enzymes (superoxide dismutase and glutathione peroxidase) in Cr-exposed workers could be used as biomarkers of oxidative stress.

- 6- Goldoni M, Caglieri A, Poli D et al. Determination of hexavalent chromium in exhaled breath condensate and environmental air among chrome plating workers. *Analytica Chimica Acta*, 2006, 562, 229-235.

Personal air samples and EBC were collected from 10 chrome platers.

Determination of Environmental and EBC Cr(VI) levels

Kinetic data showed that airborne Cr(VI) was reduced by 50% in airway lining fluid sampled at the end of exposure and that there was a further 50% reduction after about 15 h. The persistence of Cr(VI) in EBC supports the use of EBC in assessing target tissue levels of Cr(VI).

- 7- Pierre F, Diebold F, Baruthio F. Biomonitoring of two types of chromium exposure in an electroplating shop. *Int Arch Occup Environ Health*, 2008, 81, 321-329.

Airborne Cr (water soluble Cr(VI), water total soluble Cr and water insoluble Cr) and urinary Cr for a-one week period.

Exposed population: chromium plating and polishing functions

Differences between the two groups appear in relation to the type of exposure.

Urinary Cr varied according to a 24 h cycle in similar manner in both groups throughout the monitoring week. Minimum values (3–10 µg/g crea) occurred when starting a work shift, following by a rapid rise as soon as exposure commenced, whilst maximum values (12–30 µg/g crea) were recorded towards the end of the work shift.

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- 8- Qu Q, Li X, An F, et al. Cr<sup>VI</sup> exposure and biomarkers : Cr in erythrocytes in relation to exposure and polymorphisms of genes encoding anion transport proteins. *Biomarkers*, 2008, 13(5), 467-477.

195 subjects, including 141 exposed workers and 54 farmers.

Chromium (Cr) in erythrocytes as a biomarker of exposure to CrVI.

The levels of Cr in red blood cells (RBC) were remarkably elevated even in a group of workers routinely exposed to CrVI as low as 5–15 µg m<sup>-3</sup> and showed a significant exposure–response trend over the exposure range from 0.002 to 1152 µg m<sup>-3</sup> (p<0.0001). Female subjects had lower Cr in RBC, compared with their male counterparts for about the same exposure levels (p<0.05).

The genotypes of band III, which encodes for anion transport protein and may regulate across cell membranes, were also identified and included for analysis. The ratios of Cr in RBC to CrVI exposure were higher in subjects with a wild genotype than in those who had heterozygous or homozygous variant alleles. However, the difference was not statistically significant probably due to the limited number of participating subjects.

In addition, 15 of the 141 workers were selected for multiple exposure monitoring and blood sample collections to evaluate the inter- and intra-individual variations of Cr in RBC.

Compared with the personal exposure levels, Cr in RBC had small intra-individual variations with a reliability coefficient of 0.88. The study suggests that Cr in RBC may serve as a sensitive and reliable biomarker for long-term exposure to CrVI.

- 9- Goldoni M, Caglieri A, De Palma G, et al. Chromium in exhaled breath condensate (EBC), erythrocytes, plasma and urine in the biomonitoring of chrome-plating workers exposed to soluble Cr(VI). *J. Environ. Monit.*, 2010, 12, 442–447.

Italy; 14 male workers

Exhaled breath condensate (EBC), urine, Red Blood Cells, plasma. Total Cr and Cr(VI). Beginning (36 h after last exposure) and end of worksift samples.

In post sift samples, Cr-U correlated with Cr-P whereas Cr-RBC correlated with EBC-Cr

These findings reinforce the idea that measuring Cr in exhaled breath condensate (EBC) can significantly contribute to traditional biomonitoring by providing specific information at the target organ level and integrating our knowledge of Cr toxicokinetics.

- 10- Leese E, Morton J, Gardiner P.H.E, Carolan V.A. The simultaneous detection of trivalent & hexavalent chromium in exhaled breath condensate: A feasibility study comparing workers and controls. *Int J Hyg Environ Health*, 2017, 220, 415-423.

Cr(III) and Cr(VI) in exhaled breath condensate(EBC) samples and total Cr in urine.

58 workers occupationally exposed to Cr(VI) and 22 unexposed volunteers (control group).

Pre and post working week samples for both EBC and urine were collected in tandem.

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The results showed that the occupationally exposed workers had significantly higher levels of Cr(III) and Cr(VI) in their EBC samples than the control group, as well as higher levels of total chromium in their urines samples. However, for the exposed workers no significant difference was found between pre and postworking week EBC samples for either Cr(III) or Cr(VI).

No correlations of log transformed data between post working week total Cr in urine and Cr(III), Cr(VI) and the sum of Cr(III) and Cr(VI) in post working week EBC samples.

This study has established that Cr(III) and Cr(VI) can simultaneously be detected and measured in 'real' EBC samples and will help in understanding inhalation exposure

- 11- Beattie H, Keen C, Coldwell M , et al. The use of bio-monitoring to assess exposure in the electroplating industry. *J Expo Sci Environ Epidemiology*, 2017, 27, 47-55.

BM was performed on multiple occasions over 3 years, at 53 electroplating companies in Great Britain. Surface and dermal contamination was also measured, and controls were assessed. Air monitoring was undertaken on repeat visits where previous BM results were of concern. There were significant reductions in urinary nickel and chromium levels over the lifetime of this work in the subset of companies where initially, control deficiencies were more significant. Increased risk awareness following provision of direct feedback to individual workers and targeted advice to companies is likely to have contributed to these reductions. This study has shown that exposures to chromium VI and nickel in the electroplating industry occur via a combination of inhalation, dermal and ingestion routes. Surface contamination found in areas such as canteens highlights the potential for transferal from work areas, and the importance of a regular cleaning regime.

## Other sectors

- 1- Mauriello MC, Sbordone C, Montuori P, et al. Biomonitoring of toxic metals in incinerator workers: A systematic review. *Toxicology letters*, 2017, 272, 8-28.

Systematic review investigating the levels of different toxic metals, including As, Be, Cd, Cr, Pb, Mn, Hg, Ni and V, measured in the main biological matrices (blood, urine, hair) of incinerator workers.

The results show that the levels of metals measured in incinerators' workers are generally low, with some notable exceptions for Cd and Pb.

Non-occupational exposure, including diet, area of residence and others, and/or by a number of methodological limitations can be confounders. Future work should focus on an integrated approach, using ideally both biological and environmental monitoring. A particular emphasis should be given to the measurement of the different granulometric fractions of the dust containing metals, i.e. inhalable, thoracic, respirable and ultrafine

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fractions. Moreover, an accurate description of the work tasks and the characteristics and levels of non-occupational exposure should always be provided.

- 2- Balachandar V, Arun M, Devi SM, et al. Evaluation of the genetic alterations in direct and indirect exposures of hexavalent chromium [Cr(VI)] in leather tanning industry workers North Arcot District, South India. *Int Arch occup Environ Health*, 2010, 83, 791-801.

Identify the genetic alterations occurring in the tannery workers and surrounding inhabitants chronically exposed to hexavalent chromium [Cr(VI)].

108 samples which includes 72 exposed subjects [36 directly exposed (DE) subjects and 36 indirectly exposed (IE) subjects] and 36 controls.

Cr levels in air (total and VI) and in urine.

Total Cr in air (mean  $\pm$  SD) : 0.101  $\pm$  0.003, 0.089  $\pm$  0.003 and 0.014  $\pm$  0.004 mg/m<sup>3</sup>; Cr (VI) in air : 0.021  $\pm$  0.003, 0.013  $\pm$  0.005 and 0.006  $\pm$  0.001 mg/m<sup>3</sup>; Cr in urine : 2.11  $\pm$  1.01, 1.81  $\pm$  0.88 and 0.54  $\pm$  0.39  $\mu$ g/L for DE, IE subjects and controls, respectively.

Cell cultures from blood samples (5 ml from each subject).

Micronucleus (MN) assay and comet assay (CA) were used to identify the genetic alterations of individuals exposed to Cr(VI) in comparison with the controls.

A higher degree of total CA [12  $\pm$  8.49 (21–25 years)] and MN [18.69  $\pm$  7.39 (11–15 years)] was found in DE subjects compared to other groups.

In IE subjects, elevated levels of CA [5.67  $\pm$  1.15 (51–60 years)] and MN [25  $\pm$  9.89 (71–80 years)] were observed. As expected, controls exhibited minimal number of alterations.

Clear genotoxic effect associated with Cr exposure, both directly and indirectly. Higher sensitivity of cytogenetic assays for the biomonitoring of occupationally exposed populations.

Strong need to educate the workers and importance of using protective measures.