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Guidelines for appropriate "biomarker of exposure" selection for EWAS studies

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HEALS

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1 Introduction

WRITTEN BY DIMOSTHENIS SARIGIANNIS & ALBERTO GOTTI (AUTH)

Historically, exposure assessments relied on: measuring the chemicals in environmental media (air, water, soil, biota) and foodstuff; collecting survey/questionnaire data on personal lifestyle, product use and food consumption; calculating estimates of contact times and incorporated quantities; and making pharmacokinetic assumptions based on animal studies.

Human Biomonitoring (HBM) data support and allow for a new approach to exposure assessment even when the quantity and quality of external exposures are unknown or ambiguous. Biomonitoring data can be used to compare exposures of the general population with special subpopulations and with toxicological animal data. Biomonitoring data also can be used in risk assessment and risk management. For risk assessment, biomonitoring/biomarker measurements are used to estimate dose, which can then be compared with toxicological parameters normally obtained from animal studies. One key task in interpreting biomonitoring data is to put in perspective exposure data with presumed toxic doses. Therefore, interpretation of human biomonitoring requires interdisciplinary expertise from several fields, including occupational and environmental medicine, toxicology, epidemiology, analytical and bioanalytical chemistry, exposure assessment, industrial hygiene, environmental fate/transport, pharmacology/pharmacokinetics and risk assessment.

Human biomonitoring can be defined as “the method for assessing human exposure to chemicals or its effect by measuring these chemicals, their metabolites or reaction products in human specimens” (CDC 2005). Biomarker data reflect the pollutant load from all exposure pathways as well as individual variability in metabolism and excretion. Thus, HBM is an important tool to support environment and health policy making since it provides useful quantitative information regarding the actual exposure of the population to existing and emerging environmental substances and the associated health effects or population susceptibility to these xenobiotic compounds.

If biomarkers are to contribute to environmental and occupational health risk assessments, they have to be relevant, informative and valid. Relevance refers to the appropriateness of biomarkers to provide information on questions of interest and importance to public and occupational/environmental health authorities and other decision-makers. The use of relevant biomarkers allows decision-makers to answer important public health questions by being used in research or risk assessments in a way that contributes useful information that cannot be obtained better by other approaches, such as questionnaires, environmental measurements or record reviews (Becker et al. 2014). In epidemiological studies, because of time and resource constraints the most informative markers are used.

For example, chronic exposure to organochlorines is better indicated by serum organochlorine levels than by market-basket studies or industrial hygiene measurements, and early kidney damage may be better indicated by a battery of urinary biomarkers than by morbidity records. Relevance also pertains to whether the questions on which a biomarker can provide information are important questions; not merely ones that can be answered, but ones that should be answered (Muscat 1996). Thus, the ability to measure a biomarker after exposure to a toxicant may not be as important a question as whether individuals with exposure to the toxicant are at increased risk of disease.

The second characteristic of potentially useful biomarkers is validity. Validity of biomarkers has been has been widely discussed (Hernberg and Aitio 1987; Schatzkin et al. 1990; Schulte and Perera 1993; Perera 1993; Bernard 1995; Boffetta 1995; Dor et al. 1999). It includes both laboratory and epidemiological aspects. Validity refers to a range of characteristics that is the best approximation of approximation of the truth or falsehood of a biomarker. It is a sense of degree rather than an all-or-all-or-none state. The validity of a biomarker is a function of intrinsic qualities of the biomarker and biomarker and characteristics of the analytic procedures (Dor et al. 1999) (see Table 1 and

Table 2 for an example of this distinction).

Additionally, three broad categories of validity can be distinguished: measurement validity, internal study validity and external validity (Schulte and Perera 1993). Measurement validity (in terms of analytical chemistry, accuracy) is the degree to which a biomarker indicates what it purports to indicate. Internal study validity is the degree to which inferences drawn from a study actually pertain to study subjects and are true. External validity is the extent to which findings of a study can be generalized to apply to other populations. The use of invalid biomarkers can lead to invalid inferences and generalizations and ultimately to erroneous risk assessments.

Table 1: Factors affecting the validity and feasibility of biomarker studies: analytical procedures (Dor et al. 1999)

- Sampling constraints (for example, timing requirements)
- Number of samples necessary for an acceptable precision
- Degree of invasiveness of the sampling procedure
- Availability of storage methods after the sample is taken (to avoid the need for immediate analysis)
- Controlling or reducing the contamination of the sample when it is taken and when it is manipulated in the laboratory
- Simplicity, possibility of routine usage, and speed of the procedure
- Trueness, precision and sensitivity
- Specificity for the component to be detected: interference must be identified to avoid misinterpretation
- Availability of reference materials, quality control schemes and standardization of the procedure to secure conditions for obtaining traceable data with stated uncertainty as a pre-condition for comparability of measurement data in time and space.

Table 2: Factors affecting the validity of biomarkers: intrinsic characteristics of the biomarker (Dor et al. 1999)

- Significance: exposure, effect, individual susceptibility
- Specificity in relation to the pollutant or pollutant family
- Sensitivity: capacity to distinguish populations with different exposure levels, susceptibilities or degrees of effect
- Knowledge of its background in the general population
- Existence of dose-response curves between exposure level and marker concentration
- Estimation of the inter- and intra-individual variability
- Knowledge of confounding factors that can affect marker

Although biomarkers have a long history in medicine and public health, the systematic development, validation and application of biomarkers is a relatively new field in environmental health (Shugart et al. 1992; Anderson et al. 1994; Schindler et al. 2014), except for biological monitoring in occupational health (Hernberg and Aitio 1987). When used

in risk assessment, information from biological markers may replace default assumptions when specific information regarding exposure, absorption and toxicokinetics is unavailable or limited (Table 3).

Table 3: Use of biomarkers to refine risk assessment information (Ponce et al. 1998)

Variable	Use of biomarkers
Exposure	Establish exposure characteristics ▪ Route of exposure ▪ Peak of exposure ▪ Total exposure
	Estimate cumulative exposure
Absorption	Establish absorption factors ▪ Inhalation ▪ Dermal exposure ▪ Ingestion
	Identify factors that influence absorption
	Identify interspecies differences
	Identify sensitive population characteristics
Toxicokinetics	Establish distribution kinetics
	Establish half-life in blood or body
	Identify interspecies differences
	Identify factors that influence distribution, metabolism or excretion
	Estimate cumulative exposure
	Estimate peak exposure variables ▪ Time ▪ Concentration
	Identify sensitive population characteristics
	Identify mechanism of toxicity at target organ
Toxicodynamics	Identify mechanism of toxicity at target organ
	Establish target organ potency
	Identify sensitive population characteristics
	Identify factors that influence target organ toxicity
	▪ Identify interspecies differences

Validity in the context of epidemiological research involving biomarkers can be defined as the relation of the biomarker test (the potentially mismeasured biomarker) to true biomarker in the population of interest. Parameters that describe the measurement error in the population are used as measures of validity (White 1997). Two indicators of measurement error are used to describe the validity of an observed measurement compared with the true measurement (Armstrong et al. 1994). The first is systematic error or bias that would occur on average for subjects measured. The second is subject-specific error, which is additional error that varies from individual to individual.

In epidemiologic studies, measurement errors include not only laboratory errors, but also errors (variations) introduced during specimen collection and storage, and due to day-to-day, month-to-month, and year-to-year within-subject variability of the biomarker. Validity and

reliability studies that aim to assess the degree of biomarker error for use of a specific biomarker in epidemiologic studies must be properly designed to measure all of these sources of error. Validity studies compare the biomarker to be used in an epidemiologic study to a perfect measure, when possible, in a group of subjects. There are numerous sources of measurement error in biomarkers; some of these are shown in Table 4.

Table 4: Examples of sources of error in biomarker measurement in epidemiological studies (White 1997)

Errors in the laboratory method as a measure of the exposure of interest

- Method may not measure all sources of the biological true exposure of interest
- Method may measure other exposures that are not the true exposure of interest
- Methods may be influenced by subject characteristics (other than the true exposure) that the researcher cannot manipulate, e.g., by the disease under study or by other diseases

Errors or omissions in the protocol

- Failure to specify the protocol in sufficient detail regarding timing and method of specimen collection, specimen handling, storage and laboratory analytical procedures
- Failure to include standardization of the instrument periodically throughout the data collection

Errors due to variation in execution of the protocol

- Variations in method of specimen collection
- Variations in specimen handling or preparation
- Variations in length of specimen storage
- Variations in specimen analysis between batches (different batches of chemicals, different calibration of instrument)
- Variation in technique between laboratory technicians
- Random error within batch

In addition to measurement error, the uncertainty of the results is affected by biological variability within subjects, i.e., short-term variability (hour to hour, day to day) in biological characteristics due 10, for example, diurnal variation, time since last meal, posture (sitting vs lying down); medium-term variability (month to month) due to, for example, seasonal changes in diet; and long-term change (year to year) due to, for example, purposeful dietary changes over time. Because of chance, different samples will produce different results and therefore must be taken into account when using a sample to make inferences about a population. This difference is referred to as the sampling error and its variability is measured by the standard error.

Probably the main achievement of HBM data is that it provides an integrated overview of the pollutant load any participant is exposed to, and hence serves as an excellent approximation of aggregate and cumulative exposure. The internal dose of a chemical, following aggregate and/or cumulative exposure has a much greater value for environmental health impact assessment as the internal body concentration is much more relevant than mere exposure data (direct Exposure-Dose-Response (EDR)-relationship in Figure 1).

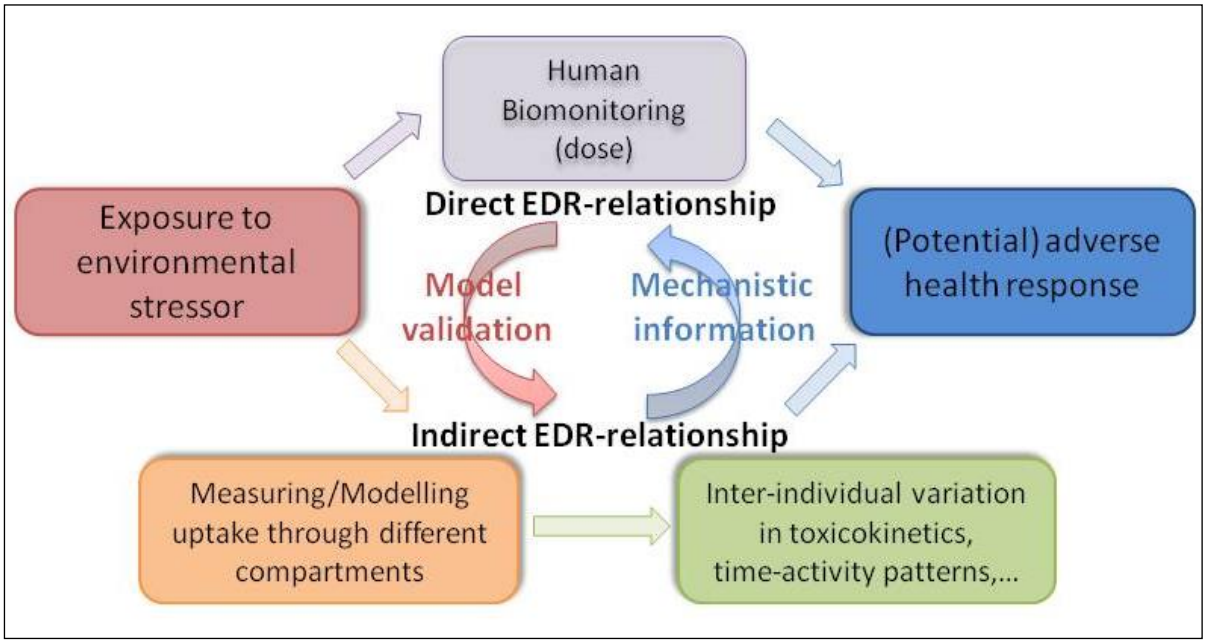

Figure 1: The Exposure-Dose-Response (EDR) Triad to evaluate the potential adverse health effects of exposure to environmental agents (adapted from Smolders and Schoeters 2007)

However, it needs to be stressed that HBM in itself cannot replace environmental monitoring and modelling data. Most often, environmental monitoring data for different environmental compartments (air, water, food and soil) provide better insight into potential sources, hence allowing the development of more informed and appropriate risk reduction strategies. At the same time, mathematical approaches to describe the pharmacokinetic and toxicokinetic behaviour of environmental agents (generally referred to as Physiologically based Pharmacokinetic [PBPK] models) offer a more mechanistic insight into the behaviour and fate of environmental agents following aggregate and/or cumulative exposure (indirect EDR-relationship in Figure 1).

As biomarker data also reflect individual accumulation, distribution, metabolism and excretion (ADME) characteristics of chemicals, HBM data offer an excellent opportunity for the validation of these PBPK models. Ultimately, combining both lines of evidence to assess exposure prove to be optimal for relating complex exposure to environmental agents to potential adverse health effects assessment.

It has to be mentioned, however, that the ability to generate biomonitoring data in recent years exceeds our ability to interpret what the data mean to public health. Today’s challenges in HBM include improved design of biomonitoring studies, interpreting what biomonitoring data mean, and understanding ethical and communication issues that are essential to the continued advancement in the field (NRC 2006; Calafat and Needham 2009; Becker et al. 2014).

There is no “gold standards” in HBM design, however, four general steps need to be carefully considered in any HBM study: study design, study conduct, data analysis and communication and interpretation of the results. Figure 2 present an outline of four steps, of which each is equally important for the success of the HBM. In HEALS the first three steps are clearly of most importance.

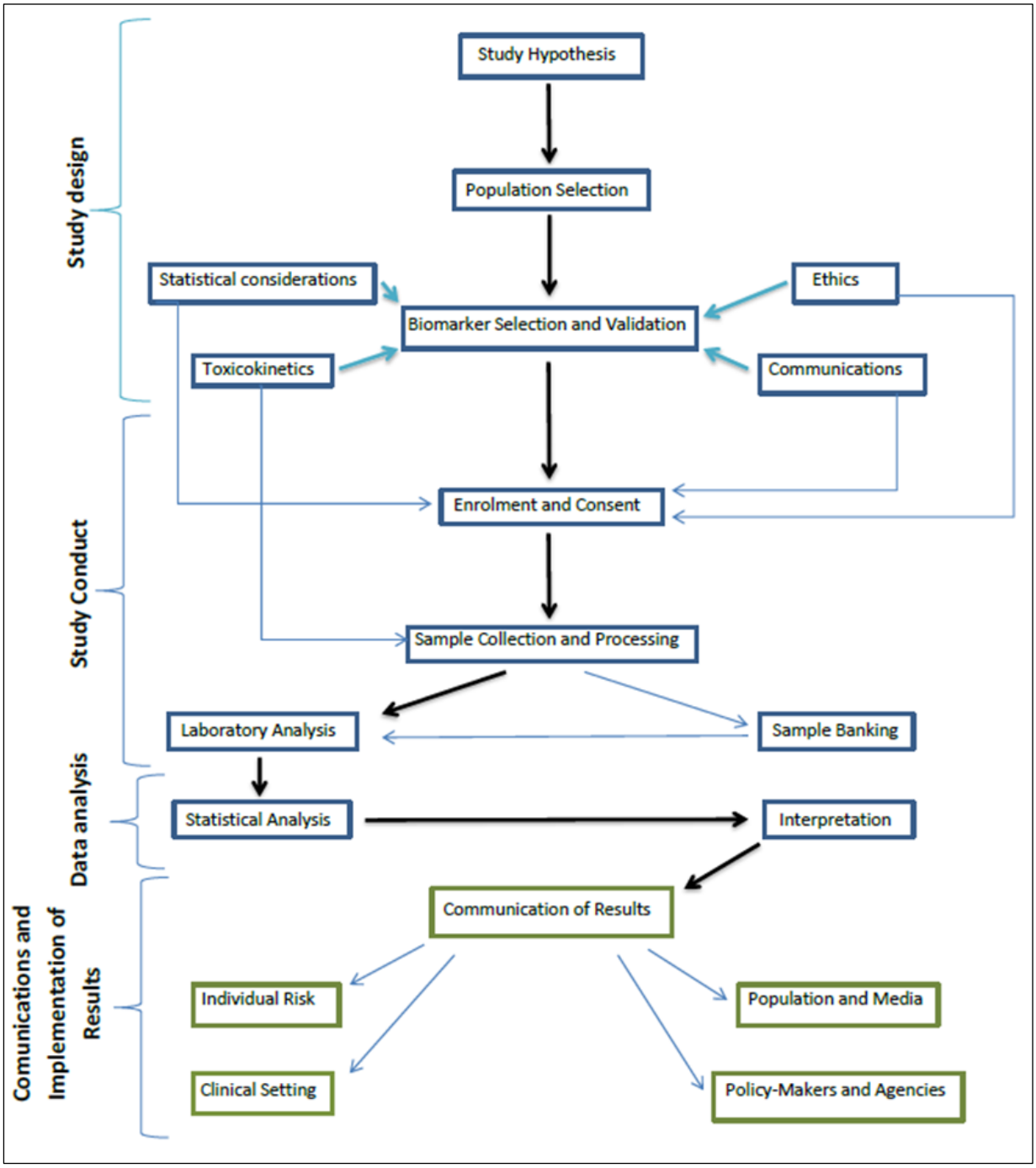

Figure 2: Stages of a human biomonitoring study (NRC 2006)

The design of any study obviously depend on its objectives and the underlying hypothesis therefore the current document provides a brief overview on the state-of-the-art of human biomonitoring, with a focus on the practical application of biomarkers in relation to the needs of HEALS, i.e. the derivation of environment-wide association studies between environmental determinants and adverse health outcomes. The main stress was given to biomarkers of exposure as these are currently best described, and have direct applicability is assessing

aggregate exposure. In the following chapters the main stressors (both chemical and not) of relevance to the HEALS project are discussed individually with the aim of providing a comprehensive guidance for the selection of appropriate “biomarkers of exposure” that can readily support Environment-wide association studies (EWAS).

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2 Stressors – Biomarkers of Exposures

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Quite often epidemiological studies utilize exposure surrogates rather than direct measurement of exposures. For environmental studies, surrogates might include geographical location such as residence for a drinking-water or air pollution study, age of housing in studies of lead-based paint exposures, or proximity of residence to electrical power lines. Occupational studies use surrogates such as job title or job group, years worked at a plant, pounds of pesticide applied per week, and tasks performed when direct measurements are not available or are limited (Stewart et al. 1991; Goldberg and Hemon 1993). The use of quantified direct measurements of personal exposures can lower uncertainty in the risk assessment process considerably compared to the use of such exposure surrogates (Schulte and Waters 1999). Biomarkers may serve to evaluate the completeness of exposure assessment information by associating environmental or source information, exposure measurements, and epidemiological and human activity data with internal dose (Dary et al. 1996). In some cases, biomarkers of exposure may be better than external measurements of exposure for situations where protective equipment has been used or when there is the possibility of dermal (or gastrointestinal) absorption.

From a general perspective, biomarkers are distinguished by whether they measure exposure, effect, or susceptibility. Biomarkers of **exposure** identify and measure chemical residues in tissue or body fluids, metabolites of the xenobiotic or physiological outcomes that are effects of exposure, often unrelated to the toxic effect of concern in humans. These data provide information on an individual’s total exposure from all sources, preceding the time of the analysis. Biomarkers of **effect** are the quantifiable changes that an individual experiences due to exposure. They are measurable biochemical, physiologic, behavioural, or other alterations in an organism that may be recognised as associated with an established or possible health outcome. Biomarkers of **susceptibility** are indicators of the natural characteristics of an organism that make it more susceptible to the effects of an exposure to a specific chemical substance (e.g. Glucose-6-phosphate dehydrogenase (G6PD) deficiency). Susceptibility biomarkers can be used to identify population subgroups potentially at greater risk from a given exposure so that protective measures can be taken.

When selecting the appropriate analyte in human specimens it is important to take into account the interaction between the matrix used and the kinetics of biomarkers. Different matrices reflect exposure over different time periods. Probably the best known examples of this phenomenon is lead (Pb), the half-life of which changes from 35 days in blood to about a year in soft tissue and twenty years in bones. Therefore, the choice of the ideal combination of biological matrix and chemical compound to be measured strongly depends on the kinetic properties of the compound. As a general rule, biomarkers of exposure to stable compounds, such as dioxins, dioxin-like PCBs and metals, are measurements of the original compound concentrations in blood, serum or urine. In the case of volatile chemicals, their concentration in exhaled breath may be assessed. For chemical classes such as organophosphate (OP) pesticides, bisphenol A (BPA) and phthalates, which are characterised by rapid metabolism and short half-lives, one or more metabolites may be chosen as biomarkers of exposure; these are measured primarily in urine.

Despite their attractiveness, there are limitations to the use of exposure biomarkers in epidemiological research for exposure and risk assessment (Schulte and Perera 1993;

Pearce et al. 1995) so that assessing exposure using only biomarkers presents some difficulties.

The first is related to the general inability of biomarkers (with some exceptions) to indicate history of the exposure events prior to the moment of sampling. Assuming that there is no additional knowledge on the activities and the related exposure events of the exposed individual, it is difficult to differentiate whether the measured value of the marker of choice represents a recent exposure peak, a periodical exposure or a steady state condition, as shown in Figure 3.

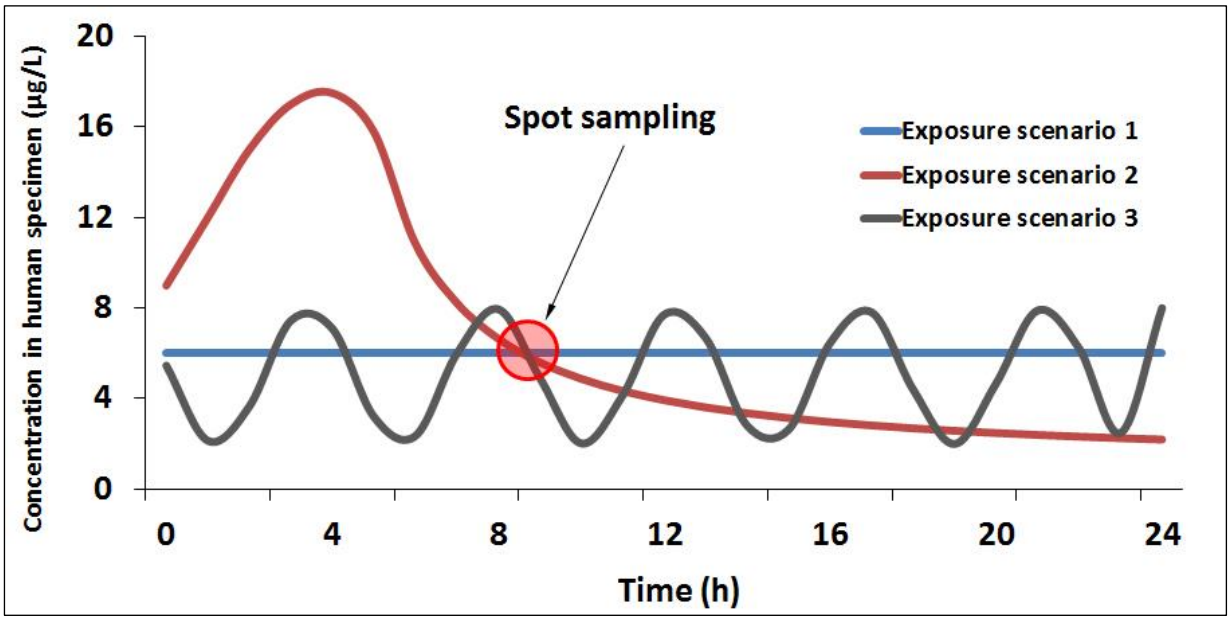

Figure 3: A generic example indicating how a single biomarker value may not be representative for exposure assessment

A second major problem is related to the biokinetic behaviour of the xenobiotic and of its metabolites. In order to accommodate the need for assessing long term exposure through spot sample biomonitoring, the marker of choice, - besides specific and sensitive which are essential requirements - needs to be characterized by well specified biokinetic characteristics. The appropriate biomarker(s) is measurable and should be measured at a time point when also the outcome of interest can be depicted or attributable to the exposure of interest. Under this perspective, the half-life time of the marker of choice is a key parameter to be taken into account to achieve representative spot sampling results.

For biomarkers with a half-life of less than 2 hours (h), biomonitoring is not feasible. When the half-life is in the order of 2-10 h, a sample collected at the end of the day reflects the exposure over the day, while with half-lives of 10-100 h, the optimal sampling time is at the end of the week, and the results reflect exposure during the preceding few days (HSE 1992). For chemicals with long half-lives, most authors agree that biomarkers of exposure provide clear advantages in terms of stability and need a limited number of measurements to characterize exposure.

A typical example of a very good biomarker of choice is cotinine, which is very specific and very sensitive since 85% of nicotine is transformed to cotinine (and thus to tobacco products) and has a half-life of approximately 20h. A half-life of this length allows for the detection of

exposure events occurring a few days earlier. In addition, a periodic and prolonged exposure to tobacco smoke (e.g. living with a smoker) results to urine cotinine concentration with very small intra- and inter-day fluctuation, thus making spot sampling a very efficient way to assess exposure burden to tobacco products. These are some of the main reasons why until lately the use of biomonitoring of exposure data has primarily focused mainly on assessing the effectiveness of pollution controls for relatively straightforward exposure scenarios, such as those involving inert and persistent chemicals with relatively long biological half-lives and well-defined sources of exposure (i.e. lead). For complex exposure scenarios, the use of biomonitoring data in designing and evaluating exposure reduction strategies may require significant amounts of supporting exposure information (e.g. variability in source activities and in background concentrations).

As a broad spectrum of biomarkers of exposure may be available for the same substance, including the concentration of the parent compound or its metabolite(s) in fluids, such as blood, serum, urine and exhaled air, or in other accessible tissues, such as hair and dentine pulp, or even in critical or storage tissues and organs, such as the kidney cortex for cadmium and the bone for lead, the choice of the matrix represents a further critical aspect of the problem and has to be selected according to the kinetic characteristics of the chemical of interest.

However, the representativeness of a marker of exposure is not influenced only by half-life and the matrix of choice; exposure to a xenobiotic is rarely assessed by using the parent compound in some specimen, since they usually undergo rapid metabolism. As a result, they are very sensitive to exposure events and thus representative only for short term exposure, giving very high peaks immediately after exposure and very low values a few minutes or hours later, being completely inappropriate for spot sampling purposes. Moreover, sometimes the rate of clearance might be so rapid that detection in blood of the parent compound is practically impossible, especially in the case of first pass metabolism (e.g. BPA).

Metabolism and half-life of parent xenobiotics and their metabolites are very well defined by the clearance rates, accounting for metabolism and excretion processes. For this reason, the knowledge of the metabolic pathways for a given xenobiotic should be the starting point. Knowledge of metabolic pathways and retention times in biological fluids for the possible metabolites allows us to identify the marker of choice (taking also into account the sensitivity and specificity limitations).

Under this perspective the choice of the best approach depends on the mechanistic basis of adverse effects, which may be classified as: (i) acute or chronic (on the basis of triggering exposure patterns); (ii) local or systemic; (iii) early or delayed (from the triggering exposure); (iv) reversible or irreversible; (v) threshold (dose-related in terms of probability of occurrence and severity) or non-threshold (or stochastic, i.e., depending on the dose for the probability of occurrence but not for its severity).

Other fundamental criteria would include, for example:

- Toxicokinetic properties;
- Rate of metabolism and rate of clearance;
- Age of exposed population;
- Age window of exposure for the population under study;
- Time for induction of relevant disease;
- Possibility to define the biological equivalent of toxicological threshold values such as derived no-effect levels (DNELs) and reference doses for the particular biomarker.

Additionally, the HBM strength in integrating routes of exposure also may be a weakness by introducing confounding due to source, as full use of exposure biomarkers may also require understanding of those inherited and acquired factors that influence the level of exposure biomarkers (Vineis et al. 1990). In determining whether a xenobiotic is hazardous, biomarkers may yield a more accurate determination than approaches based on less sensitive measures of exposures (e.g., job titles, as exposure proxies). In situations where exposures occurred that were variable or intermittent and the effect of exposure is integrated, biomarkers that represent accumulation of exposure might be useful (Perera 1995). A biomarker approach may allow for clarifying exposure-outcome relationships better than with classical methods, due to reduction in exposure measurement error.

Overall, the basic rationale for using exposure biomarkers is that they could provide, in some cases, a more accurate method for assessing exposure and, ultimately, risk (Figure 4) (Schulte and Waters 1999). While use of biomarkers can reduce misclassification, it is also possible that measurement error in the biomarker may contribute to bias in the measure of association (Saracci 1997; White 1997). Such error can be evaluated and its impact adjusted for, but, on balance, it is better to avoid or minimize it with good laboratory and epidemiological practices. The value of biological markers in epidemiological studies that will be useful in the hazard identification step of risk assessment depend on the quality of the design and analysis of the studies.

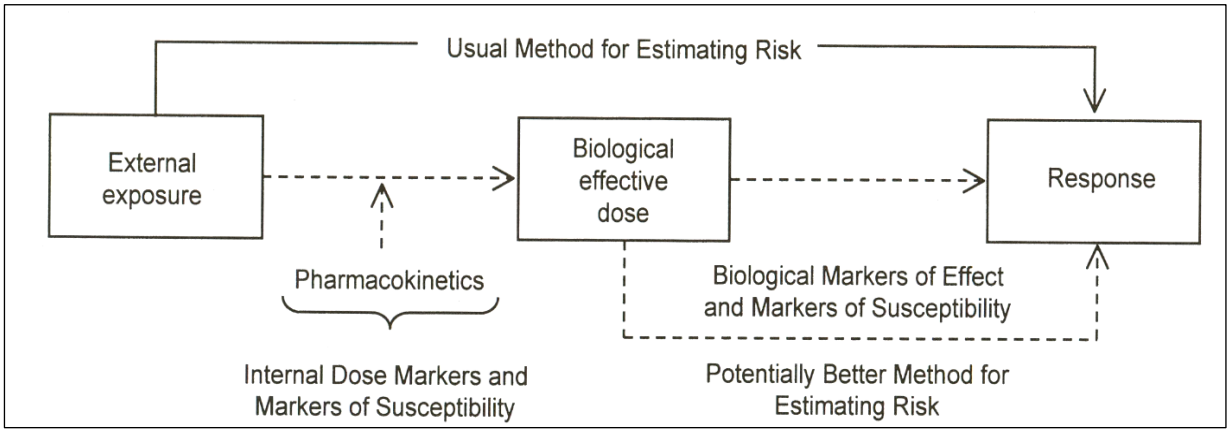

Figure 4: General approach for risk estimation (WHO-IPCS 2001)

Generally, there are two broad categories of matrices for human biomonitoring, invasive and non-invasive ones. As a rule of thumb, non-invasive biomarkers should be promoted as a superior option, when they offer the same information as invasive biomarkers.

Invasive matrices

Blood is the most frequently used invasive matrix to determine biomarkers as blood is a universal link between all tissues of the organism (Paustenbach and Galbraith 2006b). The invasive character of sampling however often negatively affects participation rates, and there are ethical issues involved in using blood. Often special consent needs to be obtained from both participants and local and national ethical oversight committees to use blood as a biomonitoring matrix. Additionally, the blood volume that can be collected is normally limited. This makes the use of blood for biomonitoring in children suboptimal. Blood analysis is often carried out for substances that are slowly excreted from the organism (Polkowska et al.

2004). An important advantage of using blood as a matrix is that concomitant with exposure markers, also many relevant biomarkers of effect can be determined in blood. Combining both exposure and effect markers in a biomarker battery, makes relating exposure, dose, effect and health impact much more relevant.

Non-invasive matrices

Urine probably is the most used matrix in which biomarkers are measured. The collection and analysis of urine carries no associated risks, sample volumes can be large and samples are obtained for different age classes, including little children with minimal impact (Kozlowska et al. 2003; Polkowska et al. 2004; Bradman and Whyatt 2005). Unfortunately, for many biomarkers, urine is not the most reliable indicator of exposure because it often contains excreted metabolites instead of parent compounds (Paustenbach and Galbraith 2006a) hence urinary biomarkers are often used for rapidly metabolized and excreted compounds such as non-persistent pesticides, BPA and other phenols, parabens, phthalates, VOCs and PAHs, as well as arsenic and inorganic mercury. Because chemicals are often slowly excreted over the course of hours or days after exposure, also toxicokinetic factors may hamper the usability of urine as a matrix. Although this can be reduced by collecting 24-hr samples rather than single spot samples, the timing of sample collection remains an essential aspect of biomonitoring using urine as a matrix (Barr et al. 2005; Kissel et al. 2005). Problems related to urine as a biological monitoring matrix are related to the wide inter-individual variability of urinary flow rate, as well as the great temporal variability in urine composition within individuals (Aylward et al. 2014). Expressing the results per g of creatinine or adjusting the measured values for the specific gravity of the compounds measured practically addresses this problem. Guidelines for creatinine adjustment and proper data interpretation are available in literature (WHO 1996; Barr et al. 2005).

Cord blood, **amniotic fluid** and **breast milk** provide an overview of the pollutant load of mothers, and at the same time provide relevant information on the in utero or early life exposure of babies (Shen et al. 2007). With the current interest in in utero and childhood exposure reflecting windows of extreme vulnerability, these matrices deserve extensive attention when preparing HBM programs. Potentially problematic issues using cord blood or amniotic fluid may arise from the fact that sampling is not always straightforward as obviously collection of HBM samples is not the first priority at time of delivery. Breast milk is a reliable matrix to monitor the presence of fat-soluble contaminants such as polychlorinated biphenyls (PCB), brominated flame retardants (BFR) or dioxins (Uehara et al. 2006; Shen et al. 2007; Yu et al. 2007) and may be the most important route of exposure to contaminants. Additionally, breast milk is a good matrix for quantification of mercury (Bose-O’Reilly et al. 2008; Bose-O`Reilly et al. 2010). Iyengar and Rapp (2001a, 2001b) provided an extensive overview on the applicability of the placenta for biomonitoring purposes, although the use of this matrix has been questioned several times because of the difficulty to collect comparable and representative samples.

Also other, less frequently used matrices have been used for biomarker quantification. Structure and histogenesis of hair and nails favours their use for biomonitoring trace elements.

Hair samples are used for identifying long term exposure to metals such as arsenic or methylmercury (Sera et al. 2002). Moreover, due to the minimal invasion required, recently efforts have been made to use of hair as a matrix for organic pollutants (Appenzeller and Tsatsakis 2012). The restricted weight of the material that can be collected (typically 50-

200 milligrams, mg) is a limiting factor for the widespread use of this matrix. In addition, external deposition of chemicals on hair (e.g. through washing) can distort the results of the analysis (Wilhelm and Idel 1996; Nielsen and Grandjean 1999).

Nails are largely constituted of keratin-rich proteins, which incorporate trace elements in proportion to dietary intakes and other exposures (He 2011). Use of nails for biomonitoring offers the advantage of integrating a relatively long-term intake and exposure into a single specimen, specimen collection is non-invasive, and sample shipping and storage are easy. Disadvantages of using nails for biomonitoring include the lack of sensitivity for several compounds, potential contamination through the use of medication, nail polish and nail cutters and the small nail mass samples, (e.g. nail masses of 20 milligrams or less).

Deciduous **teeth** have been used as markers of contamination to metals such as lead, strontium, zinc and magnesium in children (Grobler et al. 2000; Farmer et al. 2006; Robbins et al. 2010). In fact, high spatial resolution laser ablation ICP-MS (Inductively Coupled Plasma Mass Spectrometry) coupled with dental histology has delivered useful information on the life-time exposure of children to lead (Shepherd et al. 2012), shedding thus light to epigenetic effects of heavy metals associated with endocrine disruption. As such deciduous teeth can be a very useful biomarker for cumulative exposure to metals of high toxicological interest.

Identifying biomarkers in **saliva** is a promising approach for HBM, even if only few substances showed a satisfying correlation with exposure data or established biomonitoring matrices such as blood, plasma and urine. Saliva has been proven to be particularly suitable for substances of low molecular weight such as organic solvents, selected pesticides, cotinine, and for specific trace elements. Besides the advantage offered by the non-invasive nature of sampling, serious problems and limitations have been identified in the use of saliva for biological monitoring. These are mainly related to its lack of sensitivity to various exposure levels (Michalke et al. 2014).

Exhaled breath is a non-invasive biomonitoring matrix, which facilitates the direct association of inhaled air compounds to exhaled concentrations of biological and toxicological relevance. Considering that the respective biomarker (either of exposure or effect) comes directly from the respiratory system, this allows the assessment of actual internal dose at the tissue of interest. However, information is limited to target tissues in the respiratory tract primarily and the applicability domain covers specific types of compounds (volatile compounds) for a short exposure regime, such as the disinfection by-product trihalomethane (Lindstrom and Pleil 2002; Gordon et al. 2006).

The use of non-invasively collected matrices can be a valuable alternative to, or addition for, invasive matrices for most contaminants discussed. Generally, there is good agreement between invasive and non-invasive biomarker values (Esteban and Castano 2009). However, the applicability of non-invasively collected matrices is sometimes hampered by incomplete knowledge of, for example, toxicokinetics and validated sampling, sample treatment and analysis procedures. On the other hand, non-invasively collected matrices can offer substantial advantages for practical and routine implementation, such as increased participation rates, repetitive sampling, more efficient inclusion of susceptible and vulnerable populations, and improved cost-efficiency (Smolders et al. 2009).

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2.1 Persistent Organic Pollutants (POPs)

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Persistent organic pollutants (POPs) are synthetic chemical substances either intentionally produced for agricultural and industrial applications or non-intentionally formed as by-products of industrial processes or as compounds released in the air by combustion processes. They have in common five major characteristics: persistence in the environment; long-range transport; lipophilic behaviour; accumulate in food chain and possess significant toxicity to life forms (Secretariat of the Stockholm Convention 2008b).

POPs are very persistent in the environment because of their high resistance to chemical, physical and biological degradation. Therefore, they remain intact for long periods of time. POPs are also semi-volatile compounds, a characteristic that promotes their long-range transport. They can be transported through the atmosphere globally, being volatilized in

warm areas and condensed in cold regions (Figure 5). This process, known as the global distillation effect (Figure 6), has allowed these pollutants to become widely distributed throughout the planet (Simonich and Hites 1995), including regions where they have never been used or produced, like the polar region and high-mountain areas (Wania and Mackay 1993; AMAP 1998; Grimalt et al. 2001).

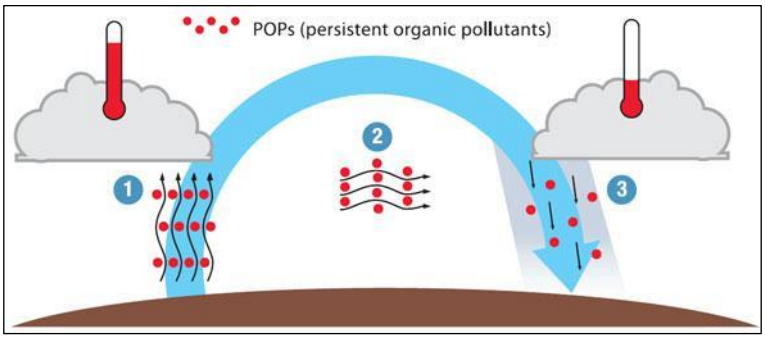

Figure 5: Long-range transport of persistent organic pollutants (POPs). (1) In warm temperatures POPs evaporate. (2) POPs move in air by winds to colder places such as the Poles and mountain tops. (3) In cold temperatures POPs condense to fall to earth (Contaminants & Remediation Directorate 2004, p. 1)

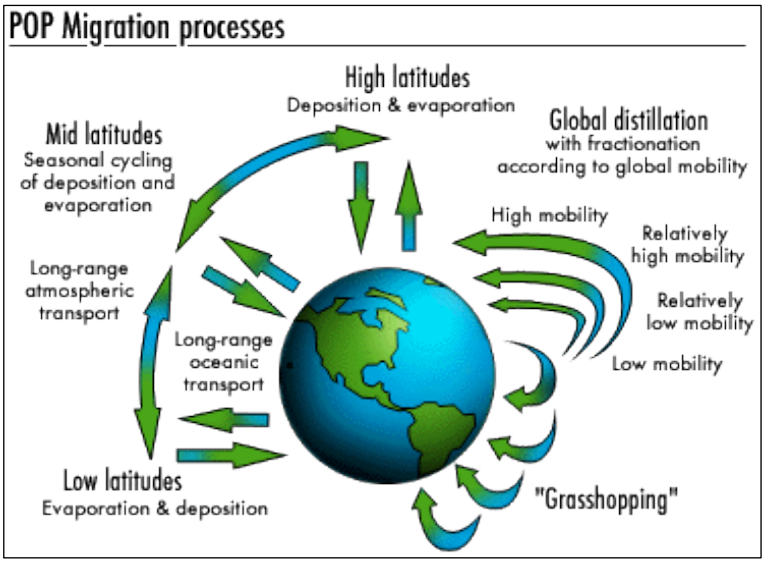

Figure 6: Global distillation effect (Greenpeace 1999)

POPs are highly lipophilic compounds. POPs have a great capacity to bio accumulate in fatty tissues of living organisms and biomagnify up along the food chain (Papadopoulos et al. 2004). The highest concentrations are found in the top organisms of the food web, particularly humans (Costopoulou et al. 2006; Vassiliadou et al. 2010).

Finally, POPs exhibit significant toxicity potential, posing a threat to the human and animal health. Human exposure to POPs can lead to serious adverse effects, including cancer, birth defects, immune and reproductive system dysfunctions, behavioural effects, among others (Porta et al.; Grimalt et al. 1994; Longnecker et al. 2001; Ribas-Fitó et al. 2002; Howsam et al. 2004; Yáñez et al. 2004; Turyk et al. 2007).

Due to their persistence, POPs can accumulate to during long term exposure to relatively low levels of these compounds and can reach levels that are toxic. However, acute toxicity has been reported after high-level exposure to some of the organochlorine pesticides (e.g. aldrin, dieldrin and toxaphene) and in cases of mass poisoning by exposure to POPs. Two such examples are the "Yusho" and "Yu Cheng” food poisoning incidents in Japan and Taiwan respectively, both due to high polychlorinated biphenyl (PCB) concentration in rice oil. Pregnant women exposed had no or minor symptomatology, but their children presented adverse effects and developmental disorders as most POPs can pass the placenta barrier (Sala et al. 2001).

Because of the high toxicity of POPs, limits of tolerance intake have been proposed for several of them. The EU Scientific Committee on Food (SCF) has established a safety limit for tolerable intake of Dioxins and PCBs, in a weekly basis (tolerable weekly intake, TWI) at 14 pg TEQ (toxic equivalency) per kg bw (SCF 2000).

Given the wide geographic distribution of POPs and their toxic properties, in 1995 the United Nations called for a global action to be taken on POPs. Accordingly, the Stockholm Convention on Persistent Organic Pollutants was adopted in 2001, with the aim of eliminating or reducing the production and use of twelve initially selected POPs, called the *"dirty dozen"*. With time, further POPs have been added to the list of banned or restricted compounds (Secretariat of the Stockholm Convention 2008a). Yet, despite the discontinuation of the use and production of many POPs, due to their use in old installations, inadequate storage or presence in waste-dumps, they are still present in the environment posing a threat to human health.

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2.1.1 Polychlorinated biphenyls (PCBs)

WRITTEN BY MERCÈ GARÍ & JOAN O. GRIMALT (IDAEA-CSIC)

Polychlorinated biphenyls (PCBs) are part of the so-called organochlorine compounds (OCs), synthetically manufactured because of their insulating and dielectric properties. They were first synthesized in Germany in 1881, but their industrial production did not start until 1930s. The use of these compounds in industrial and commercial applications quickly spread due to their properties, which included high chemical stability, non-flammability, low electrical conductivity and insulating properties, high resistance to acids and oxidation, and low

solubility in water, among others. All these properties made them highly adaptable to various uses, such as heat exchangers, dielectric fluids for transformers and capacitors, plasticizers in paints and plastics, pigments and dyes and many other industrial and commercial applications (Hutzinger et al. 1974).

Chemistry

PCBs are a group of 209 individual compounds, known as congeners, which are formed by chlorination of ten possible positions of a biphenyl structure (Figure 7). The congeners' name specifies the total number and position of chlorine atoms in the chemical structure, based on the IUPAC (International Union of Pure and Applied Chemistry) system.

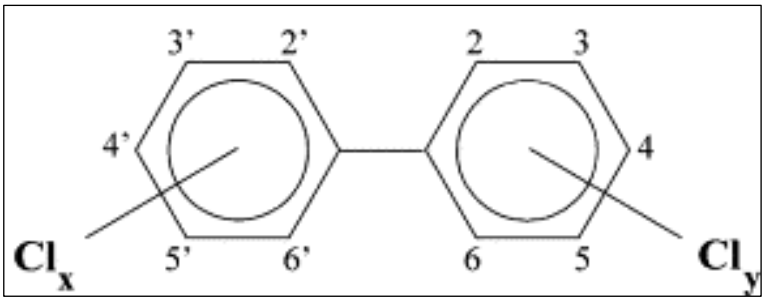

Figure 7: Structure of polychlorinated biphenyl (PCB) and numbering system.

The degree of chlorination and the position of chlorine atoms in the biphenyl molecule determine their physical-chemical properties. For instance, if ortho positions (positions 2 and 6) have no chlorine atoms, the molecule assumes a coplanar structure and is called non-ortho substituted or coplanar PCB. If the molecule has an ortho substitution in one of the phenyl rings, the PCB is called mono-ortho substituted and has still planar properties. The rest of the structures are non-coplanar PCBs. Both coplanar and mono-ortho substituted PCBs are called dioxin-like PCBs because their biological action is similar to dioxins. Coplanarity is of major environmental and analytical importance because these congeners present higher toxicity than ortho substituted PCBs.

Effects on Biological Systems

Dioxin-like PCBs are classified as probable human carcinogens (Group 2A) by the International Agency for Research on Cancer (IARC 1987). In 2013, PCBs have been reclassified as carcinogenic to humans (Group 1; see Glossary) (Lauby-Secretan et al. 2013). In studies on humans exposed to PCBs, effects on sperm motility, foetal growth rate (lower birth weight, smaller head circumference) and development (shorter gestational age, neuromuscular immaturity), and neurological functions of the offspring (impaired autonomic function, increased number of abnormally weak reflexes, reduced memory capacity, lower IQ (Intelligence Quotient) scores, and attention deficit) have been observed. Some of the neurological deficiencies at early ages may disappear later during childhood (WHO 2003).

Two cases of contamination by PCBs and other chemical compounds such as polychlorodibenzodioxins and dibenzofurans occurred in Japan and Taiwan, due to consumption of contaminated oil. These incidents produced symptoms such as acne-like eruptions (chloracne), hyperpigmentation of the skin and eye discharge, as well as other adverse effects in liver and the nervous systems.

One study found that mono-ortho substituted PCBs may contribute to colorectal cancer development through mutation of the *k*-ras oncogene (Howsam et al. 2004). PCBs are found to act as endocrine disruptors, causing alterations in the nervous and reproductive systems, liver disorders, immunotoxicity and alterations of thyroid function, since they have a structure similar to thyroxin (T4 thyroid hormone).

Possible Exposure Routes

PCBs are widespread in the environment and in foodstuffs. Humans can be exposed to these compounds by air (both indoor and outdoor) and by ingesting contaminated water and food (Domingo and Bocio 2007; Lauby-Secretan et al. 2013). PCBs can cross the placenta to the foetus and infants can be exposed from lactation with human milk and/or formula milk (Ribas-Fitó et al. 2003; Costopoulou et al. 2013).

Absorption

Oral ingestion (e.g. dietary intake) is certainly the major human exposure route to PCBs, particularly through consumption of contaminated foodstuffs with high lipid content like fatty fish or red meat and poultry (WHO 2003; Domingo and Bocio 2007). PCBs are readily absorbed and distributed in the body, and accumulate in the adipose tissue (Lauby-Secretan et al. 2013).

Elimination

The main PCB elimination routes are through the faeces and urine (WHO 2003). PCBs can be metabolized by the cytochrome P450 system into polar metabolites. The rate of metabolism of PCBs is determined by several factors, which are mainly due to their degree of chlorination and position of chlorine atoms in the molecule (Safe 1994). Higher chlorinated congeners, such as 138, 153 and 180, have higher half-lives and a longer retention trend tendency than the lower chlorinated congeners such as PCB-118, hence being more difficulty metabolized or excreted by the organism (Wolff et al. 1992; van Larebeke et al. 2001; Grandjean et al. 2008). PCBs can be excreted by women during gestation, child delivery and lactation (Sala et al. 2001; Ribas-Fitó et al. 2003; Carrizo et al. 2007). However, as shown in a PBPK model for assessing the life-time exposure to some POPs (including PCB-153 and PCB-180), despite lactation periods and weight changes – when women are more likely to decrease their OC concentrations – mature women may reach similar concentrations irrespectively of maternity records (Verner et al. 2008).

Reference values

The French Agency for Food, Environmental and Occupational Health and Safety (ANSES) recommends setting the critical concentration threshold for pregnant women, women of childbearing age, breastfeeding women and children under three years of age at 700 ng of total PCB per gram of plasma lipids (ANSES 2013). The German Human Biomonitoring Commission has established reference values (RV_{95}) for total PCBs in whole blood of children and adults, as well as for breast-feeding women, of 1-7.8 µg/l and 0.5 mg/kg fat, respectively (Schulz et al. 2011).

Specimens for analysis

Human biomonitoring of PCBs include several matrices, such as blood or serum, adipose tissue, breast milk and placenta in women, and meconium in newborns. The most abundant

PCB congeners' in human matrices are 28, 52, 101, 118, 126, 138, 153, 156, 157 and 180 (Costopoulou et al. 2006; Garí et al. 2014; Vizcaino et al. 2014). Median concentrations of total PCBs in serum found in several studied adult populations from Europe are in the range of 170-550 ng/g lipid (e.g. UK, Germany, Sweden, Spain, Romania) although certain locations (e.g. Slovakia and Czech Republic) have shown higher concentrations (in the range of 1,000-1,900 ng/g lipid) (Garí et al. 2014).

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2.1.2 Organochlorine Pesticides (OCPs)

WRITTEN BY MERCÈ GARÍ & JOAN O. GRIMALT (IDAEA-CSIC)

Organochlorine pesticides (OCPs) encompass a wide range of chemicals with different structures. They have been used extensively in agriculture and for mosquito control (Manaca et al. 2012). The following OCPs are included in the Stockholm Convention on POPs: dichlorodiphenyltrichloroethane (DDT), hexachlorobenzene (HCB), hexachlorocyclohexanes (HCHs), aldrin, endrin, dieldrin, mirex, toxaphene, chlordane, chlordecone, heptachlor and endosulfans (Secretariat of the Stockholm Convention 2008).

DDT is a powerful insecticide currently used for malaria control (WHO 2011; Manaca et al. 2012). It was first synthesized in 1874, but its insecticide properties were not discovered until 1930s. DDT was widely used during World War II to protect people from diseases such as malaria, typhus and dengue, among other insect-borne diseases. After the war, DDT continued to be used to control disease vectors, and it was also used extensively in agriculture.

HCB is a potent fungicide that was first used in 1945 for seed treatment. It is also a by-product of the manufacture of certain industrial chemicals and a known impurity of some pesticide formulations.

HCHs were synthesized for the first time in 1825, but their insecticide properties were not identified until 1942 (Willett et al. 1998). The main use of HCH has been as a broad-spectrum insecticide for seed and soil treatment, foliar applications, tree and wood treatment and as an agent against the parasites in both pharmaceutical and veterinary products. The gamma isomer, called lindane, was the active ingredient of many soaps and shampoos to treat lice and scabies.

Cyclodiene organochlorine pesticides, which include aldrin, dieldrin, chlordane, endrin and heptachlor, are potent insecticides that inhibit GABA (γ-aminobutyric acid) mediated neurotransmission.

Chemistry

HCB belong to the group of chlorobenzenes (Figure 8). It is formed by a benzene ring attached to six chlorine atoms. HCB is chemically very stable and resistant to degradation.

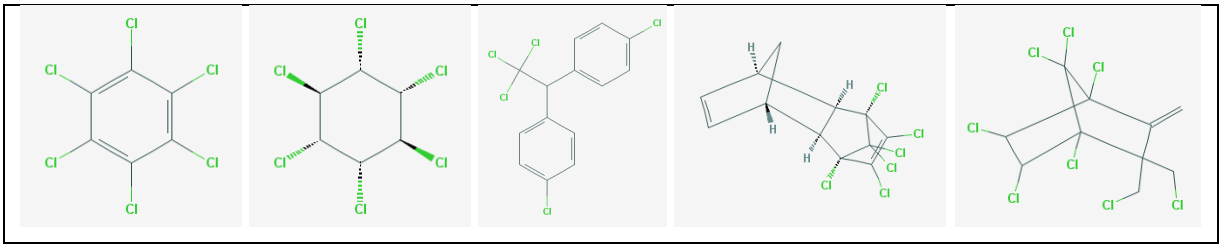

Figure 8: Chemical structure of certain organochlorine pesticides (OCPs). From left to right: hexachlorobenzene (HCB), lindane (γ-HCH), dichlorodiphenyltrichloroethane (DDT), aldrin and toxaphene (NCBI 2014)

HCH is a synthetic chemical that consist of eight isomers (Safe 1994) (Figure 8; y-HCH). These isomers have very different physical-chemical properties, depending on the position of the hydrogen and chlorine atoms in the chemical structure. HCHs are produced commercially by photochemical chlorination of benzene. Only α, β, δ and y-HCH isomers are of commercial significance. The technical mixture of HCH consists of approximately 65% α-HCH, 8% β-HCH, 13% γ-HCH, 8% δ-HCH and 3% ε-HCH (Kutz et al. 1991).

The technical mixture of DDT contains three isomers of the molecule in the following composition: 4,4'-DDT in 85% (it is the most active isomer, Figure 8), 2,4'-DDT in 15% and 2,2'-DDT at trace levels. DDT is slowly degraded to DDD (dichlorodiphenyldichloroethane) and DDE (dichlorodiphenyldichloroethylene), which are also very persistent and have similar physical-chemical and toxicological properties to the original product.

Cyclodiene organochlorine insecticides are derived from hexachlorocyclopentadiene (Figure 8). They possess a structure based on two 3-dimensional carbon ring units, one of which is heavily chlorinated.

Effects on Biological Systems

In the Turkish Kurdistan, a mass poisoning by consumption of HCB treated seeds generated a large number of deaths and the appearance of a variety of symptoms including photosensitive skin lesions, hyperpigmentation, hirsutism, colic and severe weakness (Gocmen et al. 1989). Several thousands of people developed a metabolic disorder called porphyrinuria. Exposure to moderate levels of HCB have a negative effect on reproduction (Ribas-Fitó et al. 2002). Moreover, a chronic exposure to this compound has also been related with thyroid cancer (Grimalt et al. 1994) and disturbances of the thyroid hormones (Sala et al. 2001).

Concerning HCHs, all the isomers are toxic to mammals. The IARC has classified the γ-HCH, together with the technical mixture of HCHs, in Group 2B (see Glossary) as a probable human carcinogenic (IARC 1987). Chronic exposure to this compound has been associated with adverse effects in humans, affecting the entire central nervous system (Willett et al.

1998). In addition, this group of compound can produce alterations in the reproductive, immunologic and endocrine systems (Willett et al. 1998; Alvarez-Pedrerol et al. 2008).

Long-term exposures to DDT have been associated with chronic health effects including reproductive disorders, neurotoxicity, immunotoxicity and metabolic disorders (Ribas-Fitó et al. 2006; Alvarez-Pedrerol et al. 2008).

Possible Exposure Routes

OCPs are ubiquitous in the environment and can be found in air, soil and water. Diet is the main route of human exposure to these compounds, particularly through the ingestion of fatty foods (e.g. fish and dairy products) (Falcó et al. 2008). Humans can be exposed to OCPs by drinking-water and air, but to a lesser extent. Children are exposed to these compounds through breast milk (Ribas-Fitó et al. 2003; Carrizo et al. 2007).

Absorption

OCPs can be incorporated in the human body by ingestion (thus they are absorbed in the intestinal tract), by inhalation (through the respiratory system) and by dermal contact (across the skin). HCHs, endosulfan and the organochlorine cyclodienes (e.g. aldrin, dieldrin, chlordane, endrin and heptachlor) are efficiently absorbed across the skin. HCB can be easily inhaled in contaminated sites (Sala et al. 1999).

Elimination

OCPs are highly lipid soluble. Metabolic biotransformation may allow the release of OCPs and their metabolites into bile or plasma, allowing their elimination by urine of faeces (To-Figueras et al. 1997, 2000; Moser and McLachlan 2001; Jandacek and Tso 2007). OCPs can be excreted by women during gestation, child delivery and lactation, as these compounds are found in placenta, cord blood and breast milk (Sala et al. 2001; Ribas-Fitó et al. 2003; Vizcaino et al. 2014).

Reference values

The German Human Biomonitoring Commission has established reference values (RV_{95}) for some organochlorine (OC) compounds in whole blood of children and adults and in human breast milk (Schulz et al. 2011). Specifically, these RV_{95} in whole blood are in the range of 0.3-0.9 µg/l for β-HCH, 0.3-5.8 µg/l for HCB, and 0.7-31 µg/l for DDE, depending on the age of individuals (Schulz et al. 2011). RV_{95} for breast-feeding women are 0.07 mg/kg fat for β-HCH, 0.06 mg/kg fat for HCB and 0.5 mg/kg fat for total DDT (Schulz et al. 2011).

Specimens for analysis

Human biomonitoring of OCPs include several matrices, such as blood or serum, adipose tissue, breast milk and placenta in women, and meconium in newborns (Ortega García et al. 2006; Vizcaino et al. 2014). Measurements of these chemicals include the parent compound and, for certain organochlorines (HCB, HCHs), some metabolites can also be detected in urine (e.g. pentachlorophenol) (To-Figueras et al. 1997). Median concentrations of several OCPs in individuals from several countries in Europe (e.g. UK, Germany, Sweden, Belgium, Spain, Italy) are in the range of 100-800 ng/g lipid for 4,4’-DDE (the major metabolite of DDT), 10-200 ng/g lipid for HCB and 10-100 ng/g lipid for β-HCH (Garí et al. 2014). These concentrations are below the RV_{95} values set by the German Commission (Schulz et al. 2011).

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2.1.3 Polybromodiphenyl Ethers (PBDE)

WRITTEN BY MERCÈ GARÍ & JOAN O. GRIMALT (CSIC)

Polybromodiphenyl ethers (PBDEs) have been used as flame retardants for some decades in a wide range of products such as plastics, electronics and textiles. They have been distributed in three commercial mixtures of congeners with different levels of bromination (penta-BDE, octa-BDE and deca-BDE), which are named after the dominating homologue group.

The pentabromo formulation is dominated by BDE-47, BDE-99 and BDE-100 congeners. It has been mainly employed as additive of polyurethane foams in furniture, carpets and bedding.

The octabromo mixture is dominated by BDE-183, followed by BDE-153 and BDE-154, being used in flame-retard thermoplastics, such as high impact polystyrene.

The decabromo product is essentially composed of decabromodiphenyl ether (BDE-209) and has been predominantly used for textiles, as well as in plastics for a variety of electronic products, in particular televisions and computers (EBFRIP 2008). According to the PBDE global market demands in 2001, the deca-BDE formulation was the dominant one (83%), followed by penta-BDE (11%) and octa-BDE (6%) (La Guardia et al. 2006).

Chemistry

PBDEs occur in mixtures of the 209 possible congeners that vary by the number and position of the bromine atoms in the molecular structure. Similarly to PCBs, they are named under the IUPAC system, based on the position and number of the bromine atoms (Figure 9).

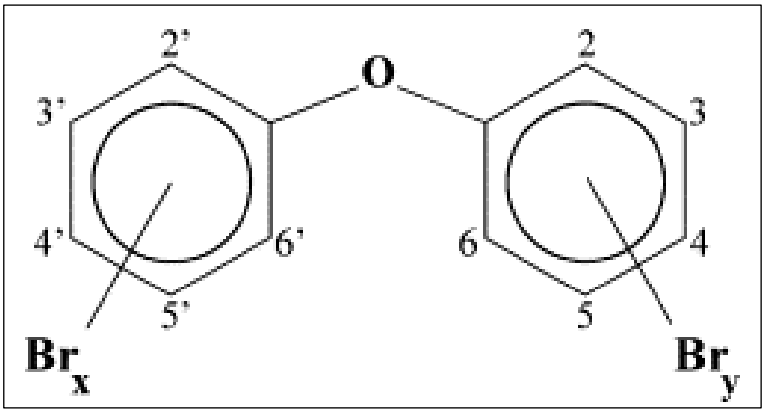

Figure 9: Structure of polybromodiphenyl ether (PBDE) and numbering system

Effects on Biological Systems

Adverse health effects of human exposure to PBDEs include endocrine disruption (Darnerud 2003; Herbstman et al. 2008; Legler 2008; Turyk et al. 2008), developmental neurotoxicity (Herbstman et al. 2010; Gascon et al. 2011; 2013) and other detrimental effects (Main et al. 2007; Akutsu et al. 2008).

Possible Exposure Routes

PBDEs have been found in various environmental compartments (Simonich and Hites 1995). Human exposure to PBDEs may occur in many daily life situations. Diet is one of the main sources of PBDEs, e.g. fatty fish or red meat and poultry (Sjödin et al. 2000; Domingo and Bocio 2007; Fraser et al. 2009). Several studies reporting the concentrations of PBDEs in a number of foodstuffs are available (Bocio et al. 2003; Domingo et al. 2006; Gómara et al. 2006). PBDEs are ubiquitous in the indoor environment due to their use in consumer products, e.g. electronics, mattresses, furniture and carpets (Schecter et al. 2005). Ingestion, inhalation and dermal contact of indoor air and dust particles are also a substantial contributor to PBDE exposure (Lorber 2008; Zota et al. 2008; Johnson-Restrepo and Kannan 2009). Children are exposed to PBDEs through breastfeeding (Carrizo et al. 2007).

Absorption

PBDEs are incorporated into humans by ingestion of foodstuffs and dust, which are then absorbed in the intestinal tract and accumulated in fatty tissues. PBDEs are also

incorporated into humans through the respiratory system, by inhalation of dust particles and indoor air (Lorber 2008; Zota et al. 2008). Dermal absorption of PBDEs can also occur, but to a lesser extent.

Elimination

Information on human metabolism and elimination of PBDEs is scarce. However, PBDE congeners containing seven to ten bromine atoms have relatively short biological half-lives in humans (Thuresson et al. 2006). Debromination of more brominated congeners can occur. In fact, metabolic enrichment of BDE-153 upon exposure to deca-BDE has been observed in mammals (e.g. polar bears; (Sørmo et al. 2006) and fish (Kierkegaard et al. 1999)), involving increases of both BDE-153 and BDE-154 in the latter. Therefore, higher brominated PBDEs are metabolized to lower brominated products and excreted mainly in faeces.

Reference values

The US EPA set a safe daily exposure level for PBDEs ranging from 0.1 to 7 µg per kg bw per day. Biomonitoring equivalent (BE) concentration for BDE-99 in serum is set to 520 ng/g lipid (Aylward et al. 2013).

Specimens for analysis

Human biomonitoring of PBDEs include several matrices, such as blood or serum, adipose tissue and, in women, breast milk and placenta. The most abundant PBDE congeners' in human matrices are 28, 47, 85, 99, 100, 138, 153, 154, 183 and 209 (Garí and Grimalt 2013; Vizcaino et al. 2014). Median concentrations of total PBDEs and BDE-99 in serum from adult populations in several countries in Europe are in the range of 2-15 ng/g lipid and 0.16-2.4 ng/g lipid, respectively (Garí and Grimalt 2013).

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2.1.4 Perfluorinated Compounds (PFC)

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Perfluorinated compounds (PFCs) have found a wide use in industrial products and processes and in a vast array of consumer products. PFCs are molecules made up of carbon chains to which fluorine atoms are bound. Due to the strength of the carbon/fluorine bond, the molecules are chemically very stable and are highly resistant to biological degradation; therefore, they belong to a class of compounds that tend to persist in the environment.

These compounds can bioaccumulate and also undergo biomagnification. Within the class of PFC chemicals, perfluorooctanoic acid and perfluorosulphonic acid are the most studied as they have been produced in highest amounts for several decades in the past. Meanwhile, PFCs can be detected almost ubiquitously, e.g., in water, plants, different kinds of foodstuffs, in animals such as fish, birds, in mammals, as well as in human breast milk and blood (EFSA 2008; Vassiliadou et al. 2010). Numerous publications refer to the negative effects of PFCs on human health: carcinogenesis, genotoxicity and epigenetic effects, reproductive and developmental toxicities, neurotoxicity, effects on the endocrine system, immunotoxicity and potential modes of action with combinational effects.

PFCs do not occur naturally in the environment. They have been manufactured for more than 50 years. These compounds are commonly used in numerous industrial and consumer products. PFOA (perfluorooctanoic acid) is used as a starting material to produce fluoropolymers, substances with special properties that have hundreds of important manufacturing and industrial applications. Fluoropolymers present valuable properties, including fire resistance and oil, stain, grease, and water repellency. They are used to

provide non-stick surfaces on cookware and waterproof, breathable membranes for clothing, and are used in many industry segments, including the aerospace, automotive, building/construction, chemical processing, electronics, semiconductors, textile industry and cosmetic industry (Stahl et al. 2011).

Chemistry

Polyfluorinated alkylated substances (R-X) are compounds consisting of a hydrophobic alkyl chain, R, of varying length (typically C4 to C16) and a hydrophilic end group, X. The hydrophobic part may be fully or partially fluorinated. When fully fluorinated the molecules are called perfluorinated substances.

The hydrophilic end group can be neutral, or positively or negatively charged. The resulting compounds are non-ionic, cationic or anionic surface active agents due to their amphiphilic character. Examples of anionic end groups are the sulfonates ($-SO_3^-$), which include perfluorooctanesulfonic acid (PFOS) (Figure 10), the carboxylates ($-COO^-$) which include PFOA (Figure 10), and the phosphates ($-OPO_3^-$). In cationic PFAS, the fluorinated hydrophobic part is attached to e.g. a quaternary ammonium group. Examples of neutral end groups X are: -OH, $-SO_3NH_2$. Both PFOS and PFOA are perfluorinated compounds and appear to be highly persistent, because of the strong covalent C-F bond.

PFOS potassium salt at normal temperature and pressure is a white powder, with molecular weight of 538 g/mol and solubility in pure water of 519 mg/l (20 ± 0.5ºC) or 680 mg/l (24-25ºC). PFOS is a fully fluorinated anion, which is commonly used in its salt form (potassium, sodium, ammonium) or incorporated into larger polymers.

PFOA at normal temperature and pressure is a white powder/waxy white solid, with molecular weight of 414.1 g/mol and solubility in pure water of 4.1 g/l (22°C) or 9.5 g/l (25°C). PFOA is a completely fluorinated organic acid. The free acid group is expected to completely dissociate in aqueous solutions, leaving the anionic carboxylate in the water surface and the perfluoroalkyl chain on the air/water interface. At pH 4, about 6% of the molecules will be undissociated. The dissociated acid (PFO) has a negligible vapour pressure, high water solubility, and moderate sorption to solids. Based on these properties, accumulation in surface waters is expected.

The main characteristics of polyfluorinated compounds are the replacement of most hydrogens by fluorine in the aliphatic chain structure. The fluorine-carbon bonds are extremely stabile conferring these substances with very high thermal and chemical stability. Because of their extraordinary properties (chemically inert, non-wetting, very slippery, nonstick, highly fire resistant, very high temperature ratings, highly weather resistant, etc.), they are applied in fluoropolymer-coated cookware, sports clothing, extreme weather-resistant military uniforms, food handling equipment, medical equipment, motor oil additives, fire-fighting foams, paint and ink as well as water-repellent products.

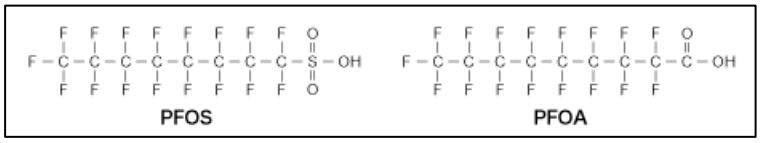

Figure 10: PFOS (perfluorooctanesulfonic acid) and PFOA (perfluorooctanoic acid)

Biological Systems Affected

Unlike dioxin compounds, PFOS and PFOA are weakly lipophilic, water soluble and bind preferentially to proteins.

Based on the results of animal experiments, the acute toxicity is considered moderate. Diverse toxic effects were observed in long-term animal tests. Hepatotoxic effects have often been described. In addition, lipid metabolism was often affected in experimental animals. Epidemiological studies have indicated effects of PFCs on glucose, urea, and/or uric acid metabolism; therefore, it would seem that further studies on PFCs and metabolic processes are necessary. Tumour growth has been observed in experimental animals after chronic exposure. Most commonly the liver, Leydig cells, and mammary gland tissue have been involved (Stahl et al. 2011).

Evidence of the occurrence of particular cancer diseases – most often urinary bladder and prostate cancers – have been observed in individual epidemiological studies. The target organs of animals and humans appear to differ, aside from the pancreas that was seen to be prone to cancerous growth both in humans and in animals. In regard to carcinogenesis, a genotoxic mechanism cannot be assumed for PFOS and PFOA, but rather a tumour promoting effect and/or epigenetic process come into question. Animal studies show unmistakable reproductive and developmental toxic effects that were only partially found in epidemiological studies. There is presently no evidence of teratogenic effects. To more thoroughly understand the influence on human fertility and the development of newborn children, the results on reproductive toxicity from animal studies should be taken into consideration. Considering the results of animal experiments, neuro- and immunotoxic effects will have to be examined in future epidemiological studies.

The trigger for hepato- and immuno-reproductive, reproductive, and developmental effects as well as carcinogenesis of PFCs may be partially or completely attributed to the activation of the PPARa (peroxisome proliferator-activated receptor alpha). Correspondingly, a change in expression of the genes that control lipid metabolism, energy homeostasis, cell differentiation, and peroxisome proliferation might be involved.

Apparently, different PFCs exhibit different toxicities. PFOS and linear isomers appear to be more toxic than PFOA and branched chain compounds, i.e., in comparison, PFOS and linear isomers exhibit a longer half-life than do PFOA and branched chain compounds and cause adverse effects at lower dosages. The data presently available regarding toxicology of PFCs other than PFOS and PFOA is in comparison meagre, non-homogeneous, and fragmentary, particularly in light of the diversity of PFCs occurring in biological matrices (Stahl et al. 2011).

Epidemiological studies have been primarily carried out on groups of people who are occupationally exposed to PFCs. These took place, for example, in the course of medical monitoring studies of workers in the fluorochemical industry. The workers were principally from the PFC manufacturing company, 3M, in Decatur, Alabama, USA and Antwerp, Belgium. In particular, biochemical parameters for liver damage or interference with lipid metabolism were examined. Furthermore, hormonal changes and cancer death rates and/or tumour

incidence were at the centre of interest. Recent studies have also examined possible reproductive toxicities. The significance of these epidemiological studies is, however, limited because of the small number of participants, mostly males due to the working structure in the companies and the problematic assessment of exposure (US EPA 2013).

Possible Exposure Routes

The present general opinion is that the main route of PFC uptake is dietary with contaminated fish, game and drinking water constituting a majority of the exposure. Nonetheless, representative data that would allow an estimation of dietary exposure is not available. Among other things, the migration of PFCs from packaging material into foodstuffs is to be studied further (Zafeiraki E et al. 2014).

Additionally, other less studied pathways such as skin contact with PFC-treated utensils and inhalation of indoor air in particular should also be further studied. Comparatively, little data is, however, presently available on these paths of exposure. According to previous studies, the total daily PFC uptake is in the range of 2 to 200 ng/kg bw/day for PFOS and 3 to 14 ng/kg bw/day for PFOA. Admittedly, other PFCs such as FTOH or FOSE/FOSA may contribute to the internal contamination of humans. As a result of their lower body mass and increased hand-to-mouth contact, it may be assumed that the internal PFC contamination per kilogram body mass of children is greater than that of adults (Hölzer et al. 2008).

The quantitatively dominant component of PFCs in the human blood is PFOS. The PFOA concentrations are generally somewhat lower in the blood than PFOS concentrations. The linear forms of both so-called reference components are most commonly identifiable in blood samples. Geographic differences have been found for PFC serum concentrations in humans. Individual studies show a possible influence of diet on the degree of contamination with PFCs. An unequivocal correlation between age and blood PFC concentration is not evident. Gender-dependent differences are, however, probable. Men generally show a higher contamination with PFCs than women. The serum concentrations of these compounds appear to have risen over the last decades. Whether this trend will continue is presently unknown.

Animal experiments suggest that PFCs are relatively well taken up by the organism both orally and by inhalation.

In addition, PFOS and PFOA can cross the placental barrier and can pass into breast milk.

PFC exposure of the foetus (prenatal) and nursing infants (postnatal) has also been shown in studies of mother-child pairs. PFOS was detected in cord blood samples in studies from Northern Canada, Germany, Japan, the USA, Canada, and Denmark. PFCs are considered to cross the placental barrier. This was also shown in animal studies (Stahl et al. 2011).

Various studies were carried out to compare PFOS concentrations in the mother’s blood with the cord blood of the foetus. The concentration in the maternal blood varied from 4.9 to 17.6 µg/l, whereas the cord blood concentration had a PFOS level of 1.6 to 5.3 µg/l. A strong correlation was found between the PFOS concentration in the mother’s blood and in cord blood. In this study, PFOA was only found in the mother’s blood. The presence of PFOS and PFOA in human breast milk was demonstrated in studies from Sweden and China among others. According to the results of these studies, nursing contributes to PFC exposure of infants. The mechanism by which these compounds pass from the mother’s blood to the milk is not fully understood. Bonding to proteins would appear likely. Contamination of baby food

is likely the result of migration of the compounds from the packaging or containers used during production.

Absorption

Since these substances are both lipophobic and hydrophobic, they do not accumulate in adipose tissue like most POPs, but mainly in blood, liver and kidneys through binding to proteins. An explanation of the mechanism by which this distribution takes place involves the preferred binding of PFCs to serum albumin and to b-lipoproteins or fatty acid binding proteins in the liver.

Elimination

The half-life of PFOS and PFOA in human serum is considered long (about 5 and 3.5 years, respectively) and in the organs it is probably longer. Differences in the excretion of PFCs have been found for different compounds and different species. PFOS is excreted more slowly than PFOA so that the latter has a shorter elimination half-life and higher rate of excretion (EFSA 2008).

It can be assumed that branched chain molecules are more rapidly excreted than the linear isomers, which therefore tend to accumulate more. According to current knowledge, short-chain PFCs such as PFBS are also excreted more rapidly than long-chain PFCs. An active and sex-hormone-regulated mechanism for renal excretion of PFOA has been demonstrated in rats. Enterohepatic circulation appears to reduce the excretion rate of PFOS and PFOA as also shown in an experiment on rats (Hölzer et al. 2008).

Reference values

According to EFSA, the estimate of PFOS diet uptake for adults is 60 to 200 ng/kg bw/day. The estimate of PFOA diet uptake for adults is 2 to 6 ng/kg bw/day, whereas PFOS resulting from outdoor air is estimated at 0.001 to 0.004 ng/kg bw/day and PFOA is estimated at 0.006 to 0.14 ng/kg bw/day (EFSA 2008).

Specimens for analysis

PFCs have been detected in fish, meat, milk products, plants, water, vegetables, fruits, different kinds of foodstuffs, food packaging as well as in biological samples such as human breast milk and plasma/serum.

Data on serum concentrations in the general population have only been available since 1998. The mean PFOA concentration in the blood for the European population is within the range of 4 to 20 µg/l; the mean PFOS serum concentration is within the range of 4 µg/l (Italy) and 55 µg/l (Poland). Higher PFOS and PFOA concentrations have been detected in samples from the USA in contrast to China, Korea, Malaysia and Japan where somehow lower concentrations were measured. PFOS is the quantitatively dominant PFC in all of the blood samples measured worldwide. The lowest PFOS concentrations were measured in samples from India (<3 µg/l) (Stahl et al. 2011).

For food items, mean upper bound values range between 0.05-1.60 ng/g for PFOA and 0.05-30.00 ng/g for PFOS, whereas for drinking water mean upper bound values are 2-5 ng/l for PFOA and 2-4 ng/l for PFOS (EFSA 2012).

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2.1.5 Dioxins and Furans

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Polychlorinated dibenzo-*p*-dioxins (PCDDs, dioxins) and polychlorinated dibenzofurans (PCDFs, furans) are persistent organic pollutants that accumulate in the environment and cause many toxic effects. They have caused great concern because of their severe health effects in humans following chronic exposure. Due to their similar chemical properties and biological actions, these two groups of compounds are studied together and are often collectively referred to as “dioxins”.

Chemistry

PCDDs and PCDFs constitute two groups of tricyclic, planar, aromatic compounds. PCDDs have two benzene rings connected by two oxygen atoms and PCDFs have two benzene rings connected by one oxygen atom (Figure 11). Depending on the position and number of chlorine atoms, exist 210 different congeners (75 PCDDs and 135 PCDFs).

Figure 11: a: Polychlorinated dibenzo-*p*-dioxins (PCDDs), b: polychlorinated dibenzofurans (PCDFs)

Dioxins and furans are characterized by high polarity and lipophilicity and are stable in the presence of acids, bases, oxidative and reductive agents. They are extremely stable at high temperatures and scarcely soluble in water (ATSDR 1998)

Biological Systems Affected

Toxic actions in humans include reproductive and developmental effects, neurological and behavioural effects, dermal toxicity, immunomodulatory and carcinogenic effects (ATSDR 1998). The toxic and biological effects of PCDD/Fs are mediated through the aryl hydrocarbon receptor (AhR), a cytosolic receptor protein present in most vertebrate tissues. This receptor has a high affinity for PCDD/Fs and some non-ortho substituted PCBs. In order to assess the effects of PCDD/Fs on biological systems, the toxic equivalency factors (TEF) approach has been adopted. This approach is based on the assumption that congeners exert toxicity through a common mechanism mediated by the aryl hydrocarbon receptor, and that the effects of mixtures of different congeners are additive. The TEF value of 1 has been assigned to the most toxic of these compounds, 2,3,7,8-TCDD (tetrachlorodibenzo-p-dioxin), and all other congeners have been assigned lower values according to their toxicity relative to 2,3,7,8-TCDD. A system for toxic equivalency (TEQ) values for PCDD/Fs and PCBs was initially proposed in 1998 (Van den Berg et al. 1998), and was re-evaluated in 2005 (Van den Berg et al. 2006). The TEQ of a mixture of congeners is the sum of the concentrations of all congeners multiplied by their TEF.

Possible Exposure Routes

Dioxins and furans are not produced intentionally and have no industrial use. They enter the environment as products of incomplete combustion of organic materials in the presence of chlorine. This is the case in waste incineration, burning of fuels such as coal or wood, metallurgical processing, manufacturing of some herbicides, pesticides and petroleum products. Other high temperature sources are cement kilns and poorly controlled combustion sources such as building fires. Non-industrial emission sources include domestic solid fuel combustion, accidental fires and incineration of house-hold and medical waste.

After entering the environment through the air, these compounds are deposited on soil or enter the food chain, where their biomagnification leads to high tissue concentrations in various animal species consumed by humans. In population non occupationally exposed more than 90% of exposure to PCDDs and PCDFs is due to food intake, mainly meat, eggs, milk and dairy products, fish and seafood (Papadopoulos et al. 2004; Domingo and Bocio 2007; Perelló et al. 2012). Much lower levels are present in food with lower lipid content, such as fruit and vegetables. Factors affecting PCDD/Fs and dl-PCBs levels in humans are eating habits, environmental exposure, age, sex, severe change of weight, and breast-feeding (Liem et al. 2000).
Other less significant sources of exposure to dioxins are indoor and outdoor air and contact with contaminated soils. Drinking water is not considered a significant source of exposure to dioxins and furans (ATSDR 1998).

In addition, PCDDs and PCDFs exposure of the foetus and nursing infants has also been shown in studies of mother-child pairs (ref). PCDDs and PCDFs can cross the placental barrier (ATSDR 1998) and are excreted into breast milk. Studies in several countries have shown that breast milk contains non-negligible levels of PCDDs and PCDFs (Costopoulou et al. 2006). According to the results of these studies, breast feeding contributes to infant exposure to dioxins and furans (Costopoulou et al. 2013).

Absorption

Absorption of dioxins and furans in humans occurs through oral, dermal and pulmonary exposure. Oral and pulmonary absorption have been shown to be more effective than dermal

exposure. The transpulmonary absorption of 2,3,7,8-TCDD has been calculated somewhat more effective than gastrointestinal absorption by oral consumption (Diliberto et al. 1996). However, dermal exposure is extremely important in cases of occupational exposure in people involved in the production and handling of chlorinated compounds or in activities where dioxins are produced, such as chlorination processes at pulp and paper mills, operation of municipal solid waste or hazardous waste incinerators. Equally important are cases of populations exposed to PCDD/Fs through accidents in the chemical industry. In these populations, dioxin exposure occurs through breathing of contaminated air and skin contact with hazardous products (Tuomisto and Tuomisto 2012).

Due to their lipophilicity dioxins and dioxin-like PCBs tend to accumulate in adipose tissue (Schecter et al. 1991). A correlation between serum and adipose tissue, whole blood and adipose tissue, and whole blood and mother milk has been demonstrated (Patterson et al. 1988).
In the gastrointestinal system, animal studies have suggested that TCDD is absorbed largely via uptake by the lymphatic system in association with chylomicrons. Passage across the intestinal wall is predominantly limited by molecular size and solubility. As soon as dioxins and furans pass in the systematic circulation, their main carriers in human plasma are serum lipids and lipoproteins. The liver and adipose tissue are their major storage sites. Tissue deposition is congener-specific and depends on the dose, the route of administration, and age (ATSDR 1998).

Elimination

The major routes of elimination of PCDD/Fs are the bile and the faeces. Smaller amounts are excreted via the urine. In mammalians species, lactation is an alternative route for eliminating PCDD/Fs. Placental transfer has also been reported. The elimination half-life of 2,3,7,8-TCDD in humans has been reported to be about 7 years (ATSDR 1998).

Reference values

The European Union has set maximum limits for PCDDs/Fs and dioxin like PCBs in food products which are specified in EC Regulation 1259/2011. In 2001, the EU Scientific Committee on Food established a group tolerable weekly intake (TWI) of 14 pg WHO TEQ/kg bodyweight (SCF 2000). Moreover, the Joint FAO/WHO Expert Committee on Food Additives (JEFCA 2002)provided a provisional tolerable monthly intake (PTMI) of 70 pg TEQ/kg body weight (JEFCA 2002).

Specimens for analysis

PCDD/F exposure can be monitored in humans by their measurement in breast milk and serum. According to existing literature, the mean concentrations in human serum of PCDD/Fs are between 6.8 and 37 pg/g fat WHO-TEQ and of dioxin-like PCBs between 1.2 and 6.4 pg/g fat WHO-TEQ. In breast milk, PCDD/F concentrations vary between 3.3 and 22.3 pg/g fat WHO-TEQ, dioxin-like PCBs between 1.7 and 19.9 pg/g fat WHO-TEQ and indicator PCBs between 17 and 502 ng/g fat (Costopoulou et al. 2006).

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2.2 Other organic contaminants

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Phthalates, bisphenol A (BPA) and parabens are synthetic compounds considered as endocrine disrupting chemicals (EDCs) widely used in numerous consumer products from construction material, furniture, food contact material, toys to personal care and cosmetic products. In general, endocrine disrupting chemicals can affect the endocrine (hormonal) system, and certain endocrine disruptors may also interfere with the developmental processes in humans and wildlife. Phthalates do not seem to act via direct hormonal mimicking, while BPA and parabens are known for their oestrogenic activity; BPA interacting also with androgen and thyroid receptors.

EDCs represent a challenge, as their effects depend on both the level and timing of exposure, being especially critical when exposure occurs during development. It was summarized by WHO, UNEP and the International Labour Organization, in the report developed in 2002 entitled *Global Assessment of the State-of-the-Science of Endocrine Disruptors* that "*although it is clear that certain environmental chemicals can interfere with normal hormonal processes, there is weak evidence that human health has been adversely affected by exposure to endocrine-active chemicals. However, there is sufficient evidence to conclude that adverse endocrine-mediated effects have occurred in some wildlife species. Laboratory studies support these conclusions"* (WHO-IPCS 2002). Since 2002, intensive scientific work has improved our understanding of the impacts of EDCs on human and wildlife health. Recent scientific reviews have concluded that there is emerging evidence for adverse reproductive outcomes (infertility, cancers, malformations) from exposure to EDCs, and there is also mounting evidence for effects of these chemicals on thyroid function, brain function, obesity and metabolism, and insulin and glucose homeostasis (UNEP and WHO 2012).

Several phthalates and their metabolic products have been shown to be developmental and reproductive toxicants affecting particularly *male* reproductive development (Koch and Angerer 2012), causing a decrease in fertility, genital efects, and also premature births. Metabolites in human urine, particularly of the higher-molecular-weight phthalates, have been associated with allergies and asthma in multiple studies (North et al. 2014). Similarly, elevated levels of BPA are linked to fertility and developmental problems, but also to cardiovascular disorders and diabetes. The weight of evidence suggests that BPA increases cancer susceptibility (Keri et al. 2007). Parabens have possible effect on the *male* reproductive system (Kirchohof and de Gannes 2013), and have been suspected of increasing breast cancer incidence (Abbas 2010) and also causing allergic reactions including skin irritation and contact dermatitis on sensitive or already damaged skin (Kirchohof and de Gannes 2013). However, studies investigating the health effects of parabens are conflicting and there is insufficient amount of data suggesting serious consequences from paraben use and exposure to warrant drastic avoidance measures or government regulations (Kirchohof and de Gannes 2013). To assess the exact health effects of long-term exposure to low levels of EDCs in humans, it is clear that further research is needed.

Organophosphates (OP) and pyrethroids (PYR) are synthetic compounds widely used as pesticides in agriculture, household and gardening. They are considered as nonpersistent pesticides as they have much shorter environmental half-lives and tend not to

bioaccumulate, in relation to persistent pesticides such as organochlorine pesticides (OCPs, see chapter 2.1.2). In fact, both OP pesticide and pyrethroid usage increased rapidly in the 1970’s, when the application of OCPs was banned or restricted due to their persistence in the environment. Organophosphate pesticides (OPPs) and pyrethroids are the most widely used pesticides and are also called contemporary pesticides or current-use pesticides (Barr 2008).

These pesticides are known to be neurotoxic compounds, as they interfere with the nervous system by inhibiting acetyl cholinesterase (in the case of OPPs) or by modulating sodium channel voltages (in the case of PYR) (Barr 2008; Kavvalakis and Tsatsakis 2012). Once human exposure occurs, these compounds are rapidly metabolized and their metabolites are excreted in urine. Therefore, measuring these metabolites in urine samples can provide useful information on recent pesticide exposure (Olsson et al. 2004; Roca et al. 2014). Human biomonitoring of neurotoxic pesticides such as OPPs and pyrethroids is appropriate not only in occupationally-exposed populations (e.g. agricultural workers) but also in the general population as people can be exposed to these compounds by consumption of contaminated food or household use of pesticides for mosquito control or in gardening.

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2.2.1 Phthalates

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Phthalates are manmade chemicals that are produced worldwide in millions of tons each year, and are used in the manufacture of plastics, to make them soft and flexible, and in personal care products. Typical products containing phthalates are building and construction materials, flooring and roofing materials, cables and wires, clothing, furniture, car interiors and car underbody coatings, children’s toys, glow sticks, modelling clay, automobiles, lubricants, waxes, cleaning agents, insecticides and also food contact materials. Within soft PVC (polyvinyl chloride), the plasticizing phthalate content can be up to 40% (Heudorf et al. 2007; Koch and Angerer 2012).

Phthalates have received considerable attention over recent years because of their proven toxicity in animal studies and because of their ubiquitous presence in the environment and in humans (Koch and Angerer 2012). Continuous and repeated exposure to high levels is associated with changes in the hormonal system, causing a decrease in fertility, premature births and genital effects, among other consequences. More research is needed to assess the exact health effects of long-term exposure to low levels of phthalates.

Chemistry

The term phthalates describes a class of chemicals which are dialkyl- or alkylarylesters of ortho-benzenedicarboxylic acid (phthalic acid). Depending on the alcohol that makes up the alkyl chain, and therefore depending on their physical properties, phthalates have a wide range of applications. The long chain phthalates di(2-ethylhexyl) phthalate (DEHP), di-iso-nonyl phthalate (DiNP), di-iso-decyl phthalate (DiDP) and di(propylheptyl) phthalate (DPHP) are used primarily in PVC polymer and plastisol applications. DEHP is also the major plasticizer for PVC-containing medical devices such as bags for blood or parenteral nutrition, tubing and catheters. Short chain phthalates, such as dimethyl phthalate (DMP), diethyl phthalate (DEP), butyl benzyl phthalate (BBzP), di-n-butyl phthalate (DnBP), and di-iso-butyl phthalate (DiBP), are often used in non-PVC applications such as industrial solvents and lubricants, additives and the textile industry, pesticide formulations, personal care products, paints and adhesives. DEP and DnBP are also used in the pharmaceutical field as a constituent of the enteric coating of some medications. DiBP is also used in dispersion adhesives in paper and cardboard packaging. During recycling processes DiBP can end up in paper and paper packaging with direct food contact and can migrate into the foodstuff. In Europe the phthalates DEHP, DnBP, DiBP and BBzP are all prohibited from use in cosmetics owing to their classification as substances that are potentially carcinogenic, mutagenic or reproductive toxicants. Despite that ban, the above-mentioned phthalates can still be found in such products sold in Europe (Koch and Angerer 2012).

Biological Systems Affected

Some phthalates, such as DEHP, DnBP, DiBP, BBzP, DPP and DiNP are developmental and reproductive toxicants in rodent studies. Several phthalates and their metabolic products have been shown to be developmental and reproductive toxicants affecting particularly male reproductive development. Phthalates do not exhibit any intrinsic hormonal activity and thus do not seem to act via direct hormonal mimicking. However, some phthalates clearly have to be regarded as endocrine disruptors, as they have been shown to modulate the endogenous production of foetal testicular testosterone and also influence insulin-like factor 3 and follicle-stimulating hormone production (Latini 2005; Koch and Angerer 2012).
Some recent epidemiological studies suggest that internal exposure to some phthalates at environmental levels may be associated with a decreased anogenital distance in male infants, reduced reproductive hormone levels in adult men, alterations in semen parameters, DNA damage in sperm, abdominal obesity and insulin resistance, conduct or attention-deficit hyperactivity disorders or less male-typical behaviour in young boys (Koch and Angerer 2012).

The most critical window of exposure is in foetal life, during the androgen (testosterone) regulated sexual differentiation. In humans, this most critical period would correspond to foetal exposure during the end of the first trimester of pregnancy (Koch and Angerer 2012).

Phthalates are primarily known as endocrine disrupting compounds, but have been associated also with oxidative stress and alterations in cytokine expression. Metabolites in human urine, particularly of the higher-molecular-weight phthalates, have been associated with allergies and asthma in multiple studies (Jaakkola and Knight 2008; Tsai et al. 2012; Braun et al. 2013; North et al. 2014).

Possible Exposure Routes

The general public is exposed to significant levels of phthalates via diet, pharmaceuticals, phthalate-containing products, and ambient indoor environment via air and dust. Intravenous exposures occur through medical equipment.

Consumer products containing phthalates can result in human exposure through direct contact and use, indirectly through leaching into other products, or general environmental contamination. Humans are exposed through ingestion, inhalation, and dermal exposure during their whole lifetime, including during intrauterine development (Heudorf et al. 2007).

Food is generally regarded as a major source of exposure to the long chain phthalates such as DEHP and DiNP in the general population. For the short chain phthalates other life-style dependant pathways of exposure (e.g. cosmetics, body care products) seem to be of relevance in addition to foodstuffs (Koch and Angerer 2012).

The contamination of foodstuff occurs mainly with the long chain phthalates, because these phthalates are either purposely or accidentally used in products or materials during processing, handling, transportation, packaging and storage. There is considerable variability in the degree of phthalate contamination of food depending, for example, on packaging and processing practices and the lipid content. Relatively high phthalate levels have been found in some fatty foods as a result of direct contact with the gaskets of twist-off lids (Koch and Angerer 2012).

In infants and toddlers, mouthing of toys and other items made of phthalate plasticized PVC may lead to additional oral intake of some phthalates (Koch and Angerer 2012).

Specific sources of phthalate exposure include enteric coated tablets/capsules (DEP, DnBP), PVC medical devices such as blood bags and tubing (DEHP). In medical patients metabolite levels in urine can be several-fold above the levels found in the general population (Koch and Angerer 2012).

Metabolism and elimination

Phthalates are rapidly metabolized in humans. In a first rapid step, the parent phthalate diester is cleaved into the respective monoester. This step can occur at various locations in the body (e.g. mouth, skin, stomach, intestines and blood). In a second step, the alkyl chain of the resulting monoester can be modified by various oxidation (Phase I) reactions. In a third step, both the hydrolytic monoester and the oxidized secondary metabolites can be conjugated with glucoronic acid (Phase II) and finally excreted in urine. The extent of oxidative modification increases with the alkyl chain length of the phthalate monoester. More than 95% of an oral dose of a phthalate is excreted (mainly via urine but also in faeces) as one of these metabolites within 24 hours after exposure (Latini 2005; Koch and Angerer 2012).

Oxidative metabolites are more water soluble than the corresponding hydrolytic monoesters, which, in turn, have decreased water solubility when the alkyl chain length increases. Therefore, short chain phthalates mostly metabolize only to their hydrolytic monoesters and not further. The urinary excretion of their monoesters represents approximately 70% of the oral dose. By contrast, long chain phthalates with eight or more carbons in the alkyl chain metabolize to their hydrolytic monoesters, which are extensively transformed to oxidative products. These secondary, oxidized metabolites are the main metabolites excreted in human urine. Only between 2 and 7% of the dose is excreted as the simple monoester for these long chain phthalates (Koch and Angerer 2012).

Reference values

Exposure to phthalates is interpreted based on the metabolite levels in urine. However, the metabolite pattern is different for the short chain phthalates compared to the long chain phthalates. Monoester metabolites are the preferred metabolites of the short chain phthalates such as DEP or DnBP/DiBP, while oxidized metabolites are the preferred metabolites for long chain phthalates such as DEHP or DiNP. Therefore, when only monoester metabolites such as MEP, MnBP and MEHP are interpreted with regard to exposure, similar MnBP and MEHP levels point to several-fold higher DEHP exposures (Koch and Angerer 2012).

Human biomonitoring values (HBM I) set for DEHP metabolites 5oxo- and 5OH-MEHP in urine are 500 µg/l for children (6-13 years), 300 µg/l for women of childbearing age, and 750 µg/l for males 14 years of age and older and remaining general population (Schulz et al. 2011).

Specimens for analysis

Most of the biomarkers used in modern phthalate biomonitoring are specific metabolites generated in the human body (secondary, oxidized metabolites) which are not prone to external phthalate contamination.

Blood and urine are the most common matrices for biomonitoring. In general, urine is the matrix of choice for non-persistent chemicals, such as phthalates, because urinary concentrations of these compounds or their metabolites are usually considerably higher than

blood concentrations. This is in contrast to persistent compounds where blood is the preferred matrix for biomonitoring. Still, blood is of interest and importance for non-persistent compounds such as phthalates when investigating distribution, elimination and metabolism (Koch and Angerer 2012).

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2.2.2 Organophosphate Pesticides (OPPs)

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Organophosphorus compounds or organophosphates (OPs) are synthetic compounds widely used in commercial agriculture to control pests. They are also used for household and other building pests, for head lice in humans and for a number of ecoparasites in domestic animals.

OP pesticide usage increased rapidly in the 1970’s, when the application of organochlorine pesticides was banned or restricted due to their persistence in the environment. OPPs are the most widely used pesticides worldwide and their metabolites are widespread across different populations (Aprea et al. 2000; Curl et al. 2003; Barr et al. 2004; Becker et al. 2006; Roca et al. 2014).

Chemistry

Organophosphorus compounds can be classified into several types according to their chemical structure, including phosphates, phosphonates, phosphinates and phosphorothioates, among others (Gupta 2005). The general chemical structure of an organophosphate comprises a central phosphorus atom (P) and the characteristic phosphoric (P=O) or thiophosphoric (P=S) bond.

There are various commercial OP pesticides with a variety of chemical, physical and biological properties. Most OPs have low solubility in water, high oil-water partition coefficient and low vapour pressure, among other properties (Kavvalakis and Tsatsakis 2012).

Examples of OPPs include malathion, parathion, dimethoate, chlorpyrifos and diazinon, among others (Figure 12).

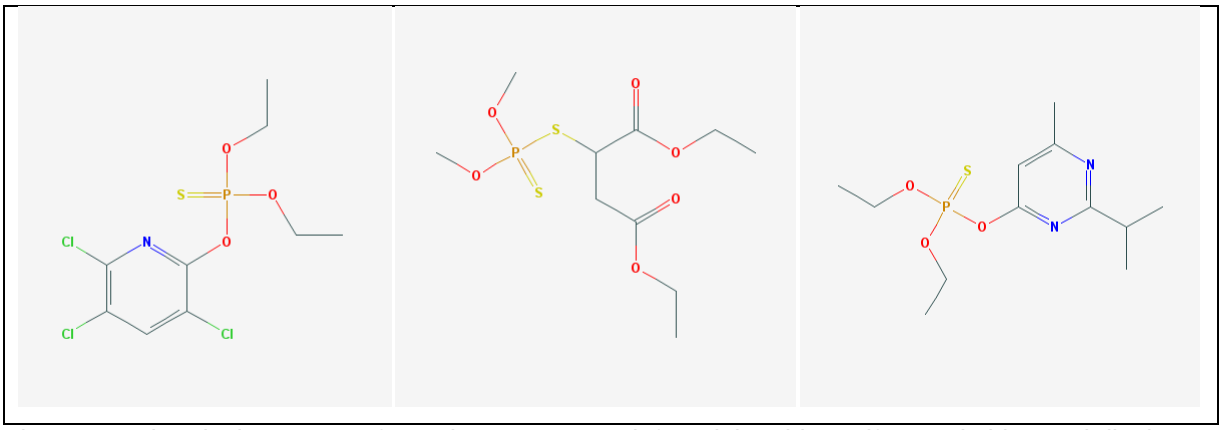

Figure 12: Chemical structure of certain OPPs. From left to right: chlorpyrifos, malathion and diazinon (NCBI 2014)

Effects on Biological Systems

OPPs exert their acute effects by inhibiting acetyl cholinesterase in the nervous system, resulting in respiratory, myocardial and neuromuscular transmission impairment. Acute exposure to organophosphates may cause vomiting, diarrhoea, abdominal pain and confusion, among other effects (Koureas et al. 2012). Chronic exposures to OP pesticides, even at low levels, are associated with neurologic effects, carcinogenesis, and endocrine and reproductive health alterations (Kang et al. 2004; Cakir and Sarikaya 2005; Giordano et al. 2007; Perry et al. 2011; Koureas et al. 2012). Specifically, prenatal and to a lesser extent postnatal exposure to OPPs may contribute to neurodevelopmental and behavioural deficits in preschool and school children (González-Alzaga et al. 2014; Zhang et al. 2014). At the population levels, few data exist. Vegetable growers may be at risk for acute adverse effects via the inhalation of chlorpyrifos and dicrotofos during pesticide application, mixing, loading, and spraying (Jaipieam et al. 2009).

Possible Exposure Routes

The main route of exposure to OP pesticides is through the consumption of contaminated food previously treated with these compounds and drinking water contaminated with agricultural run-off during spraying and industrial waste or discharge from seepage of buried toxic wastes (Maroni et al. 2000; Health Canada 2013; Roca et al. 2014). Humans can also be exposed to OPPs by dermal contact and inhalation of the vapours originated as a result of domestic use of these compounds and proximity to agricultural activities (Kavvalakis and Tsatsakis 2012; Health Canada 2013).

Absorption

OPPs can be incorporated into humans by several routes: they can be absorbed by the skin as well as by the respiratory system and the gastrointestinal tract. Some OPPs are very

lipophilic and they can be absorbed and then released from fat depots over a period of several days (Minton and Murray 1998).

Elimination

Organophosphate pesticides are degraded quickly by metabolic reactions. They are usually metabolised to the more reactive oxons which may bind to cholinesterase or be hydrolysed to a dialkylphosphate (DAP) and/or a hydroxylated organic moiety specific for each pesticide (Barr 2008). These metabolites and hydrolysis products are then excreted in the urine, either in free form or bound to sugars or sulphates. The intact pesticide may undergo hydrolysis prior to any conversion to the oxon form and a series of polar metabolites are then excreted (Kavvalakis and Tsatsakis 2012; Koureas et al. 2012). Specifically, six DAP metabolites are found in urine: and five specific metabolites are found in urine: dimethyl phosphate (DMP), diethyl phosphate (DEP), dimethyl thiophosphate (DMTP), dimethyl dithiophosphate (DMDTP), diethyl thiophosphate (DETP), and diethyl dithiophosphate (DEDTP) (Health Canada 2013). Specific metabolites of certain OPPs are also found in urine: 3,5,6-trichloropyridinol (TCPY) for chlorpyrifos, malathion dicarboxylic acid (MDA) for malathion, 2-isopropyl-4-methyl-6-hydroxypyrimidine (IMPY) for diazinon, 4-nitrophenol (PNP) for parathion and 2-diethylamino-6-methyl-4-pyrimidinol (DEAMPY) for pirimiphos methyl.

Reference values

The German Human Biomonitoring Commission has established reference values (RV_{95}) for general OPP metabolites (DAPs) in urine of both children 3-14 years of age and the general population (Schulz et al. 2011). Depending on the metabolite, these RV_{95} may vary in the range of 75-100 µg/l for children and 135-160 µg/l for adults in the case of DMP and DMTP, 10 µg/l for children in the case of DMDTP and DETP, and 30 µg/l for children and 16 µg/l for adults in the case of DEP (Schulz et al. 2011). The concentrations of DAPs in the urine of children and adults from several countries in Europe and North America are below the RV_{95} set by the German Commission (Aprea et al. 2000; Barr et al. 2004; Becker et al. 2006; InVS 2010; Health Canada 2013; Roca et al. 2014).

Specimens for analysis

OPPs can be measured in human plasma (Huen et al. 2012). However, human exposure to organophosphate pesticides is mainly biomonitored by measuring their metabolites in urine, both DAPs and specific metabolites (e.g. IMPY, TCPY and MDA, among others) (Barr 2008; InVS 2010; Health Canada 2013; Attfield et al. 2014; Roca et al. 2014). Median concentrations for DAPs in urine samples from the adult general population of France are in the range of 3.7 µg/g creatinine for DEP, 0.5-1.1 µg/g creatinine for DMDTP and DETP, and 6-8 µg/g creatinine for DMP and DMTP (InVS 2010). Alternative biological samples that are also used as a possible metabolite stores include amniotic fluid, meconium and hair (Bradman et al. 2003; Margariti and Tsatsakis 2009; Tsatsakis et al. 2009).

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2.2.3 Polycyclic Aromatic Hydrocarbon (PAHs) in food

WRITTEN BY DANAE COSTOPOULOU & LEONDIOS LEONDIADIS (NCSRD)

Polycyclic aromatic hydrocarbons (PAHs) are a class of environmentally persistent organic compounds which are mainly formed by incomplete combustion of organic molecules. They are usually found as mixtures of two or more compounds. Various toxic actions of PAHs to living organisms have been reported. Their toxicity has been evaluated by several authorities as the ATSDR, US EPA, IPCS, SCF and the Joint FAO/WHO Expert Committee on Food

Additives (JECFA). The following 16 PAHs have been defined of greatest concern with regard to potential exposure and adverse health effects (Table 5).

Table 5: Polycyclic aromatic hydrocarbons (PAHs) of greatest concern

benz[*a*]anthracene	chrysene	dibenzo[*a,l*]pyrene
benzo[*b*]fluoranthene	cyclopenta[*cd*]pyrene	indeno[1,2,3-*cd*]pyrene
benzo[*j*]fluoranthene	dibenz[*a,h*]anthracene	5-methylchrysene
benzo[*k*]fluoranthene	dibenzo[*a,e*]pyrene	benzo[c]fluorene
benzo[*ghi*]perylene	dibenzo[*a,h*]pyrene	
benzo[*a*]pyrene	dibenzo[*a,i*]pyrene	

Chemistry

PAHs constitute a large class of organic compounds that are composed of two or more fused aromatic rings, with a pair of carbon atoms shared between rings. They consist of carbon and hydrogen and do not contain heteroatoms. PAHs are solids with high melting and boiling points, low volatility at room temperature and very low aqueous solubility. They are highly lipophilic and soluble in organic solvents. Most of them can be photo-oxidized and degraded to simpler substances (EFSA 2008).

Molecular structure of four representative PAHs are presented in Figure 13.

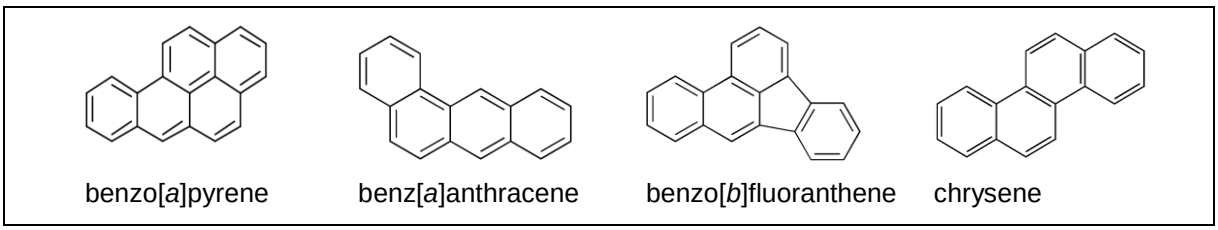

Figure 13: Molecular structure of four representative polycyclic aromatic hydrocarbons (PAHs)

Biological Systems Affected

The carcinogenicity of PAHs administered by inhalation, oral, or dermal routes has been assessed in a large number of studies. Researchers have reported increased incidences of skin, lung, bladder, liver, and stomach cancers, as well as injection-site sarcomas, in animals. In most studies, the site of tumour development was related to the route of administration, e.g. gastric tumours after oral administration, skin tumours after dermal application. However, tumours at sites other than the site of application were also observed. Increased incidences of lung, skin, and bladder cancers are associated with occupational exposure to PAHs. Epidemiologic reports of PAH-exposed workers have noted increased incidences of skin, lung, bladder, and gastrointestinal cancers, however these workers have been also exposed to other cancer-causing agents, therefore it is not clear that exposure to PAHs was the main cause of cancer incidence (Liu et al. 2008).

The mechanism of PAH-induced carcinogenesis is believed to be via the binding of PAH metabolites to DNA. PAH-induced carcinogenesis can result when a PAH-DNA adduct forms at a site critical to the regulation of cell differentiation or growth. Cells affected most significantly by acute PAH exposure appear to be those with rapid replicative turnover, such as those in bone marrow, skin, and lung tissue. Tissues with slower turnover rates, such as liver tissue, are less susceptible.

Embryotoxic (e.g. birth defects, decreased body weight), genotoxic (through reaction of PAHs metabolites with DNA) and immunotoxic effects (immunosuppression) of PAHs have also been reported (IARC 1983; ATSDR 2009).

Possible Exposure Routes

PAH exposure through air, water, soil, and food sources occurs on a regular basis for most people. Consumption of food is the major exposure route for non-smoking population. To ensure that PAHs in food products are kept at levels that they do not cause health concern, the EU has set maximum limits for benzo[a]pyrene and for the sum of benzo[a]pyrene, benz[a]anthracene, benzo[b]fluoranthene and chrysene in oils and fat, cocoa beans and derived products, smoked/heat treated meat, fish sprats, molluscs and their products, processed cereal-based foods and baby foods, infant and follow-on formulae and milk (EU 2011). The above PAHs have been found to be suitable indicators of total PAHs in food (EFSA 2008).

The US Occupational Safety and Health Administration (OSHA) has set Permissible Exposure Level for PAHs in the air in the workplace at 0.2 mg/m^3, and the US EPA has set Maximum Contaminant Level for PAHs in drinking water at 0.0001 mg/l for benz(a)anthracene, 0.0002 mg/l for benzo(a)pyrene, benzo(b)fluoranthene, benzo(k)fluoranthene and chrysene, 0.0003 mg/l for dibenz(a,h)anthracene and 0.0004 mg/l for indenol(1,2,3-c,d)pyrene.

For smokers and people exposed to passive smoking, contribution from smoking through the inhalation route may be significant. Ambient air is another possible source and also PAHs have been found in some drinking water supplies. For some people occupational exposure is also significant.

Absorption

PAHs are absorbed primarily through ingestion, and to a lesser extend through inhalation according to animal study data. In some cases, dermal contact has also been reported as possible exposure route.

After being absorbed, PAHs and/or metabolites are rapidly distributed to almost all organs and are able to cross the placental barrier and the blood-brain barrier. Highest levels have been found in the gastrointestinal tract and in lipid-rich tissues. They are metabolized primarily in the liver and kidneys. Higher absorption has been observed for lower molecular mass PAHs, whereas higher molecular mass PAHs are poorly absorbed (EFSA 2008).

Elimination

Because of their lipophilic nature, PAHs can accumulate in breast milk and adipose tissue. However, biliary and urinary excretion of PAHs is relatively efficient because of the wide distribution of enzymes that transform PAHs into polar metabolites.

PAHs are predominantly metabolized via cytochrome P450 enzymes in the liver. In addition to the liver and kidneys, metabolism of PAHs occurs in the adrenal glands, testes, thyroid, lungs, skin, sebaceous glands, and small intestines.

PAHs are transformed initially to epoxides, which are converted to dihydrodiol derivatives and phenols. Glucuronide and sulphate conjugates of these metabolites are excreted in the bile and subsequently eliminated through the faeces and in urine. Glutathione conjugates are further metabolized to mercapturic acids in the kidney and are excreted in the urine. The

hydroxylated metabolites of the PAHs are excreted in human urine both as free hydroxylated metabolites and as hydroxylated metabolites conjugated to glucuronic or sulfuric acids. A commonly measured urinary metabolite is 1-hydroxypyrene (EFSA 2008; Liu et al. 2008).

Reference values

Reference range levels of PAHs urinary monohydroxy metabolites have been reported for the US Population (Grainger et al. 2006).

Geometric mean values in ng/l for urine levels of PAHs metabolites in the US population are presented in Table 6. Detailed results i.e. percentiles, levels per age group, gender, race/ethnicity are provided in the study (Grainger et al. 2006).

Table 6: Geometric mean values in ng/l for urine levels of PAHs metabolites in the US population (Grainger et al. 2006)

Parent compound	Metabolite	Geometric mean
Fluorene	2-Hydroxyfluorene	441
	3- Hydroxyfluorene	171
Phenanthrene	1-Hydroxyphenanthrene	154
	2-Hydroxyphenanthrene	98.4
	3-Hydroxyphenanthrene	127
Fluoranthene	3-Hydroxyfluoranthene	13.4
Pyrene	1-Hydroxypyrene	79.8
Benzo[c]phenanthrene	1-Hydroxy Benzo[c]phenanthrene	NC
	2- Hydroxy Benzo[c]phenanthrene	NC
	3- Hydroxy Benzo[c]phenanthrene	NC
Chrysene	3-Hydroxychrysene	NC
	6-Hydroxychrysene	NC
Benz[a]anthracene	1-Hydroxybenz[a]anthracene	NC
	3-Hydroxybenz[a]anthracene	NC
NC: not calculated; the proportion of results below the LOD was too high to provide a valid result		

In Germany, for the non-smoking general population (aged 3-69 years) the Human Biomonitoring Commission of the German Federal Environment Agency has derived from the German environmental surveys a reference value of 0.5 mg/l (corresponding to 0.3 mg/g creatinine). For 1-hydroxypyrene in urine the commission has recommended the following upper margins of background exposures for adult non-smokers: 1-naphthol less than 30 µg/l, 2-naphthol less than 20 µg/l (Wilhelm et al. 2008).

Specimens for analysis

The most prominent biomarker of exposure to PAHs in humans is the level of one or more PAH metabolites is urine. 1-Hydroxypyrene, hydroxynaphtalenes and hydroxyphenanthrenes are the PAH metabolites most widely accepted as reliable biomarkers for internal PAH exposure because they are excreted in urine at a substantial extent, making possible then monitoring by analytical methods currently available (Kawanami et al. 2014).

Biomarkers of effect such as PAH-derived DNA adducts, DNA strand breaks and haemoglobin adducts in human white blood cells are currently under investigation (Grainger et al. 2006; Pratt et al. 2011).

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2.2.4 Bisphenol A (BPA)

WRITTEN BY JANJA SNOJ TRATNIK & MILENA HORVAT (JSI)

BPA is considered to be an endocrine disrupting chemical. It has potential to bind to oestrogen as well as androgen and thyroid receptors and to elicit significant responses. BPA is used primarily in the production of polycarbonate plastics, epoxy resins and thermal paper (Mørck 2012).

Chemistry

BPA is a plastic monomer, which at room temperature exists as a white solid. It is frequently used as a starting substance in epoxy-phenolic resins and as a monomer in the manufacture of polycarbonate (PC) plastics. Epoxy resins are used as an inner protective lining in canned

food and drinks and glass/bottle lids. PC is commonly used in plastic consumer products made for the handling of foods, such as baby bottles, reusable water bottles, plastic tableware or storage containers. Furthermore, BPA is used as an additive in other plastics, produced for example for dental sealants and children’s toys (Mørck 2012).

When polymers of BPA in plastic products are exposed to changes in heat or acidic condition during use – for example by microwave heating – the ester bond linking monomer of BPA can be hydrolysed. This results in the release of free BPA monomers that migrate into the food or liquid of the products or into the environment (Mørck 2012).

The industrial production volume is approximately 2.9 billion kilograms of BPA per year, which means that BPA is a chemical produced at one of the highest volumes in the world (Mørck 2012).

Biological Systems Affected

Owing to the ability of the BPA molecule to interact with and elicit responses through endogenous receptors it is defined as an endocrine disrupting chemical (EDC). Given that the normal functioning of endogenous hormonal systems is essential to the development and growth of the foetus and the reproductive organs in particular, it has been proposed that exposure to BPA may disrupt the development of the foetus and young child as a consequence of interaction of BPA with oestrogen, androgen and thyroid receptors (Mørck 2012).

Recent human studies indicate that BPA exposure in adults may be associated with reduced ovarian response and IVF (in vitro fertilization) success, reduced fertilization success and embryo quality, implantation failure, miscarriage, premature delivery, reduced male sexual function, reduced sperm quality, altered sex hormone concentrations, polycystic ovary syndrome (PCOS), altered thyroid hormone concentrations, blunted immune function, type-2 diabetes, cardiovascular disease (i.e. heart disease, hypertension, and cholesterol levels), altered liver function, obesity, albuminuria, oxidative stress and inflammation, and altered epigenetic markers and gene expression. Further, exposure to BPA during gestation could result in increased spontaneous abortion, abnormal gestation time, reduced birth weight, increased male genital abnormalities, and childhood obesity. Endocrine disrupting chemicals have long been known for their estrogenic properties and the ability to compete with endogenous steroid hormones binding to receptors. EDCs were found to disturb human male steroidogenesis, which alters reproductive hormones, a critical factor in spermatogenesis. Recent studies provide new insights about other mechanisms, such as oxidative stress, genetic susceptibility, and epigenetic effects, related to EDCs’ involvement with detrimental reproductive health outcomes (Jeng 2014). Particularly strong are the associations between early BPA exposure and altered behaviour and disrupted neurodevelopment in children, as well as increased probability of childhood wheeze and asthma. Many *in vitro* studies and *in vivo* animal studies have supported these proposed adverse health effects due to BPA exposures, at environmentally relevant doses (Rochester 2013).

The weight of evidence suggests that BPA increases cancer susceptibility through developmental reprogramming, potentially involving changes in target organ morphogenesis as a result of epigenetic alterations (epigenetic changes to DNA and morphogenetic mechanisms involving tissue interactions). However, due to the paucity of the current literature, it is premature to conclude that BPA is carcinogenic on its own (Keri et al. 2007).

Possible Exposure Routes

Several organizations concluded that oral exposures with food are the major source for bisphenol A exposure in all age groups of non-occupationally exposed human subjects (Dekant and Völkel 2008). The majority of BPA-leaching consumer products on the market are in direct contact with food, or designed for heating in microwave ovens or for food storage. Air and dust are also a potential source of human BPA exposure, as well as dermal contact with thermal paper – the type of paper used as a purchase receipts or fax paper (Mørck 2012).

Absorption

When absorbed into the body through the intestine, skin or lungs, BPA is rapidly absorbed through the gastrointestinal tract and efficiently conjugated with glucuronic acid into the conjugate BPA-glucuronide in the liver by first-pass metabolism. Only the free parent BPA is biologically active, and no evidence of oestrogenic activity of BPA-glucoronide has been reported (Mørck 2012).

Exposure to BPA from contaminated air or dust or through skin will escape the first-pass metabolism and may leave a greater part of the absorbed free BPA circulating in the blood (Mørck 2012).

Elimination

The rapid first-pass elimination (24h) of the biologically active BPA occurs when BPA is ingested. Metabolites are excreted in urine (Mørck 2012).

Reference values

The expected very low concentrations of bisphenol A due to rapid biotransformation and the very rapid excretion result in severe limitations in the use of reported blood levels of bisphenol A for exposure assessment (Dekant and Völkel 2008). In urine samples from several cohorts, bisphenol A (as glucuronide) was present in average concentrations in the range of 1-3 µg/l suggesting that daily human exposure to bisphenol A is below 6 µg per person (<0.1 µg/kg bw/day) for the majority of the population (Dekant and Völkel 2008).

Among few cross-sectional studies that have been conducted, findings reported by Takeuchi and Tsutsumi (2002) showed that there are gender differences in serum BPA concentrations, possibly due to differences in the androgen-related metabolism of BPA (Takeuchi and Tsutsumi 2002). Higher serum concentration of BPA was observed in men than in women as well as in women diagnosed with PCOS, compared with healthy women. There were significant positive correlations between serum BPA and testosterone concentrations in all subjects and likewise between serum BPA and testosterone concentrations in all female subjects, but not between serum BPA and other sex-related hormone concentrations in any group (Takeuchi and Tsutsumi 2002).

The German Human Biomonitoring Commission has derived reference values (RV_{95}) and TDI-based HBM I values for total BPA in urine. The RV95 values are 30 µg/l for 3-5 year olds, 15 µg/l for 6-14 year olds, and 7 µg/l for 20-29 year olds. The HBM I value for children is 1.5 mg/l and 2.5 mg/l for adults, respectively (HBM-UBA 2012). The Commission emphasized that the HBM values will require immediate adjustment should the current TDI of 0.05 mg/kg bw/day changed.

Specimens for analysis

Because BPA is transformed rapidly to BPA-glucoronide, this metabolite, often together with free BPA, it is measured in the majority of the biomonitoring studies investigating BPA exposure (Mørck 2012). Due to the rapid and complete excretion of orally administered bisphenol A, urine samples are considered as the appropriate body fluid for bisphenol A exposure assessment (Dekant and Völkel 2008). Other advantages with urine are the fact that it is easily retrieved and there are no ethical concerns related to invasive sampling. Studies have been conducted in many countries, and BPA is detected commonly in more than 60% of the samples (Mørck 2012).

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2.2.5 Parabens

WRITTEN BY JANJA SNOJ TRATNIK & MILENA HORVAT (JSI)

Parabens are preservatives used in a wide range of personal care and cosmetic products (including products for children), pharmaceuticals and in certain food products since the 1930s. They are used as preservatives because of their bactericidal and fungicidal properties. They are detected in waste water, rivers, soil and house dust. Although parabens are still widely considered to be safe, health concerns have been raised for endocrine disrupting effects at high exposure levels.

Chemistry

Parabens are esters of para-hydroxybenzoic acid with methylparaben, ethylparaben, propylparaben and butylparaben being most commonly used. Parabens and their salts are used for antimicrobial properties.

Biological Systems Affected

Parabens are known to cause allergic reactions including skin irritation and contact dermatitis on sensitive or already damaged skin (Kirchohof and de Gannes 2013). In addition, immediate IgE (immunoglobulin E) allergic reactions to parabens resulting in urticarial and bronchospasm have been observed (Kirchohof and de Gannes 2013).

Parabens are also known for their oestrogenic activity, which was validated *in vitro* and *in vivo* by several studies. Oestrogenicity appears to increase with side chain length (Boberg et al. 2010; Kirchohof and de Gannes 2013).

Moreover, parabens-containing antiperspirants have been suspected of increasing breast cancer incidence (Abbas 2010). Health risks were highlighted when several studies showed high concentrations of parabens in both healthy breast tissue and breast tumours. It has been hypothesized that the mimicking of oestrogen and high concentrations in breast tissue may promote breast cancer development (Harvey and Everett 2004; Kirchohof and de Gannes 2013).

Another source of controversy is the possible effect of parabens on the male reproductive system (Kirchohof and de Gannes 2013). This is due to the fact that exposure assessment is difficult because individuals are not routinely exposed to a single paraben, and most of the available paraben toxicity data are from single-exposure studies.

However, studies investigating the health effects of parabens are conflicting and there is insufficient amount of data suggesting serious consequences from paraben use and exposure to warrant drastic avoidance measures or government regulations (Kirchohof and de Gannes 2013).

Possible Exposure Routes

Among personal care products and cosmetics, many hand soaps, body lotions, lipsticks, toothpastes and sunscreens contain parabens in concentrations of up to 1%. Although commercially used parabens are of synthetic origin, some parabens are produced by living organisms, specifically by plants and microbes; among these are blueberries, carrots, olives and strawberries which principally contain methylparaben for its antimicrobial activity. Jam and other foodstuffs contain parabens in amount up to 0.1%. Concentrations of parabens in the environment are low (Kirchohof and de Gannes 2013).

Absorption and metabolism

Dermally applied parabens are taken up by skin and metabolized by hydrolysis catalysed by esterases or glucuronidation followed by hydrolysis. Uptake decreases with increasing chain length. Lipid solubilisers reduce percutaneous absorption, while penetration enhancers increase penetration (Abbas 2010; Boberg et al. 2010). Following oral exposure, parabens are metabolized by esterases in intestine and liver (Boberg et al. 2010). Sulfonations of the 4-hydroxygroup by sulfotransferase and formation of an amide from the carboxylic group by the amino acid transferase have also been found (Abbas 2010).

Elimination

Parabens are excreted in urine as glycine, glucoronide or sulphate conjugates of the parent compound or of the metabolite parahydroxybenzoic acid (PHBA). A large proportion of PHBA is excreted as p-hydroxyhippuric acid (PHHA, the glycine conjugate of PHBA). Excretion occurs mainly in urine and also in bile, and following oral exposure also in faeces (Boberg et al. 2010; Kirchohof and de Gannes 2013).

Reference values

Because data on human exposure to parabens are limited and the toxic effects of parabens in humans are mostly unknown, **no** reference values are available for parabens yet. Levels of parabens within human fluids and tissue are in general low. 95th percentile values reported for US population ≥6 years (NHANES 2005-2006) were the following: methylparabens 974 µg/l urine, propylparabens 299 µg/l urine, butylparabens 19.6 µg/l urine and ethylparabens 57.2 µg/l urine (n= 2548) (Calafat et al. 2010).

Specimens for analysis

Uptake of parabens in humans can be estimated by urinary measurements of free and conjugated paraben, and its metabolites, mainly free and conjugated p-hydroxybenzoic acid. As animals studies show, more than 90% of the administered paraben may be present as metabolites, and the same may apply to humans (Boberg et al. 2010). Ye et al (2006) detected methyl, ethyl, *n*-propyl, and butyl parabens in urine with high frequency, mostly in their conjugated form; suggesting that conjugated parabens could be valid biomarkers to assess human exposures to these compounds (Ye et al. 2006).

Data obtained from chronic administration studies indicate that parabens do not accumulate in the body, and serum concentrations of parabens quickly decline and remain low (Boberg et al. 2010).

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2.2.6 Pyrethroids

WRITTEN BY MERCÈ GARÍ & JOAN O. GRIMALT (CSIC)

Pyrethroids (PYR) are synthetic chemical insecticides widely used because of their relative safety for humans, high insecticidal potency at low dosages and rapid knock-down effects (WHO 2005). Although more than 1,000 pyrethroids have been synthesized, only a few are used in households, in mosquito control and in agriculture. In malaria-endemic zones, pyrethroid insecticides are used to impregnate mosquito nets and clothing for the prevention of malaria (Public Health Agency of Canada 2009; Feo et al. 2012).

Chemistry

Pyrethroids are synthetic forms of pyrethrins, which are natural insecticides derived from the extract of chrysanthemum flowers. There are two types of pyrethroids that differ in chemical structure and symptoms of exposure. Natural pyrethrins are esters of a cyclopropanecarboxylic acid and a cyclopentenolone alcohol. Structural modifications of these moieties have produced the diverse pyrethroids currently available. Examples of type I pyrethroids include allethrin, tetramethrin, permethrin and resmethrin (Figure 14, top part). Examples of type II pyrethroids include cyfluthrin, esfenvalerate and phenothrin (Figure 14, bottom part).

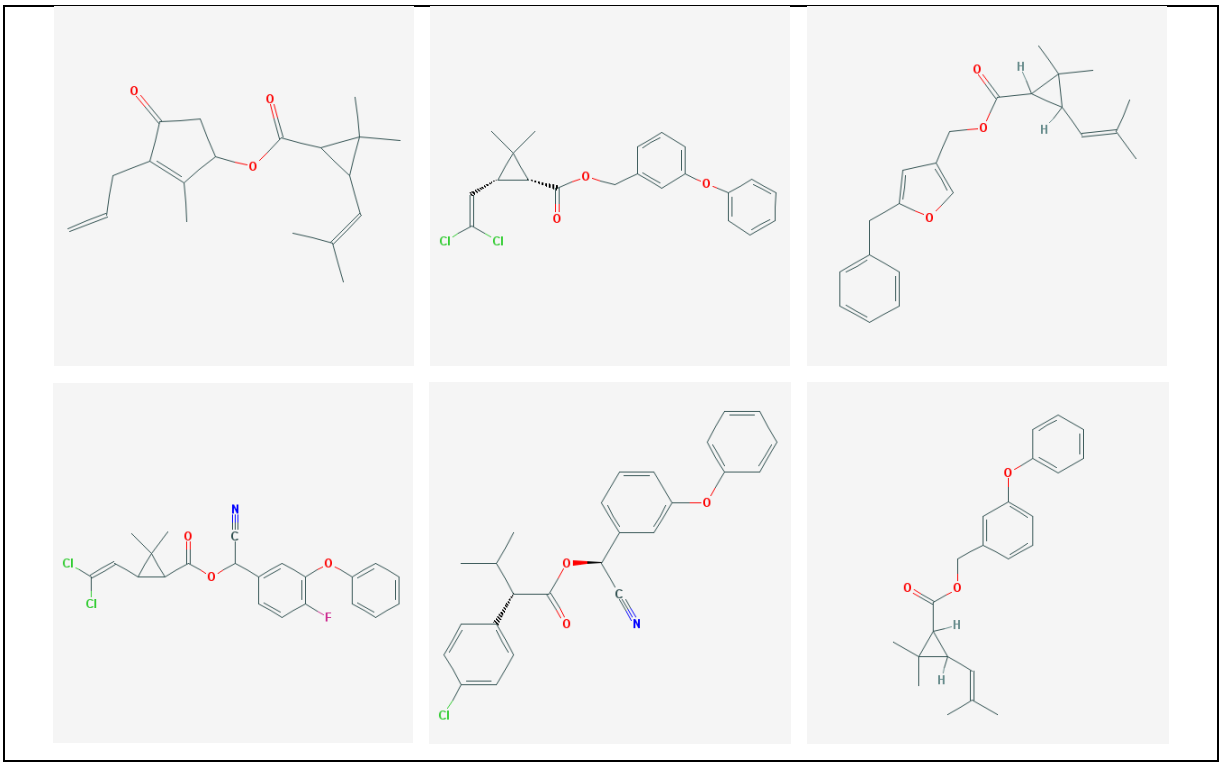

Figure 14: Chemical structure of certain pyrethroids. From left to right: (top) allethrin, permethrin and resmethrin as type I pyrethroids; (bottom) cyfluthrin, esfenvalerate and phenothrin as type II pyrethroids (NCBI 2014)

All pyrethroids can exist as at least four stereoisomers, each with different biological activity (Bradberry et al. 2005).

Biological Systems Affected

Pyrethroid insecticides are considered less toxic to humans compared to other classes of insecticides, and their health effects are still unclear. However, the US EPA has classified some pyrethroids as possible human carcinogens (class C, see Glossary) (US EPA 1997).

Accidental exposure to pyrethroids can lead to several symptoms such as local paraesthesia, nausea, vomiting and abdominal pain, among others (Bradberry et al. 2005). Pyrethroids can cross the placental barrier and are known to interfere with hormonal and neurological development, the immune system and other physiological functions (Muto et al. 1992; Bell et al. 2001; Hanke et al. 2003). At the population level, there are currently few studies

investigating the adverse health outcomes due to pyrethroids, and these are mainly related to male reproductive effects (e.g. sperm quality, sperm DNA damage and reproductive hormone disorders) (Koureas et al. 2012). Long-term exposure to pyrethroids can also lead to neurobehavioural and neurodevelopment effects (Shafer et al. 2005; Wolansky and Harrill 2008). Among workers, acute PYR-related illnesses have been observed (Hudson et al. 2014). The majority of cases were of low severity (85%) and 34% were work-related. Respiratory effects were the most common symptoms reported (48%).

Possible Exposure Routes

Pyrethroids are mainly found in air, but also in soil, food and water, because of their use in household insecticides, pet sprays and shampoos, as well as in agricultural applications. Therefore, pyrethroids are incorporated into humans through inhalation and dermal contact, and through ingestion of contaminated food (vegetables, fruits and crops that have been sprayed) and water. Newborns are exposed to pyrethroids through breastfeeding (Corcellas et al. 2012). Agricultural applicators and sprayers are occupationally-exposed to pyrethroids through inhalation and dermal contact of these compounds.

Absorption

Pyrethroids can be incorporated into humans through ingestion of contaminated food and water, and through inhalation and dermal contact (Colt et al. 2004; Lu et al. 2006; Hughes and Edwards 2010; Fortes et al. 2013). Once inside the body, they are rapidly metabolized through hydrolysis, oxidation and conjugation (Koureas et al. 2012). Recently, some studies point out the bioaccumulation of pyrethroids in humans (Corcellas et al. 2014).

Elimination

Pyrethroids are metabolized into carboxylic and phenoxybenzoic acids in the human body and then excreted mainly in the urine, but also in faeces and breath. Pyrethroid metabolites can be measured in blood and urine and concentrations are reflective of recent (the previous few days) exposure to the parent compound or the metabolite in the environment (Kühn et al. 1999; Starr et al. 2008). Pyrethroids are also found in breast milk, suggesting that these compounds may be excreted by women during lactation (Corcellas et al. 2012).

Reference values

Recently, the German Human Biomonitoring Commission has established reference values (RV_{95}) for pyrethroid metabolites in urine of both children 3-14 years of age and adults of 1-2 µg/l, depending on the metabolite (Schulz et al. 2011). Similarly, the Institute of Environment and Health (IEH) from the Cranfield University has established Reference Values (RV) for pyrethroid metabolites in urine of the general adult (>18 years) UK population of 0.7-4.3 µg/g creatinine, depending on the metabolite (IEH 2008). The concentrations of pyrethroid metabolites in the urine of children from several countries in Europe are below these RV_{95} set by the German Commission (Becker et al. 2006; Roca et al. 2014). Biomonitoring equivalent (BE) concentrations of some PYR metabolites in urine are in the range of 50-240 µg/l (Aylward et al. 2013).

Specimens for analysis

Human exposure to pyrethroids can be monitored by the analysis of blood and breast milk (Channa et al. 2012; Corcellas et al. 2012; Feo et al. 2012). Median concentrations of total

pyrethroids (ΣPYR) in breast milk are in the range of 4-8 ng/g lipid weight in samples from South America and Europe (Corcellas et al. 2012) and 150-500 ng/g lipid weight in samples from Africa (Bouwman et al. 2006; Feo et al. 2012).

Pyrethroid metabolites are also found in urine (Becker et al. 2006; Barr et al. 2010; InVS 2010; Roca et al. 2014). The most frequently measured general pyrethroid metabolite is 3-phenoxybenzoic acid (3PBA), which is a metabolite that is common to as many as 20 synthetic pyrethroids (Barr 2008). Median concentration (and percentile 95) of this metabolite in urine samples from a general adult population in France and from an infant population in Germany were 0.63 (3.5) µg/g creatinine and 0.29 (2.4) µg/g creatinine, respectively (Becker et al. 2008; InVS 2010). There are other more specific metabolites of PYR exposure, as follows: 4-fluoro-3-phenoxybenzoic acid (4F3PBA), which is a metabolite of cyfluthrin; cis-2,2-dibromo-2-dimethylvinyl-cyclo-propane carboxylic acid (DBCA), which is a metabolite of deltamethrin; and *cis* and *trans* isomers of 2,2-dichloro-2-dimethylvinyl-cyclopropane carboxylic acid (cis-DCCA and trans-DCCA), which are metabolites of permethrin, cypermethrin and cyfluthrin. P95 values of these metabolites in urine samples from a general adult population in France and from an infant population in Germany were in the range of 0.98-2.6 µg/g creatinine and 0.40-1.4 µg/g creatinine, respectively (Becker et al. 2008; InVS 2010).

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2.3 Toxic and potential toxic elements

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This chapter reviews some most relevant toxic and potentially toxic elements, their relevance to the human health, pathways of human exposure and appropriate biomarkers of exposure together with the health-based or population-based reference levels/intervals established.

The Priority list of Hazardous Substances (ATSDR 2013) includes five metals/metalloids that are listed in the top 20 chemicals of highest concern: **arsenic** (no. 1), **lead** (no. 2), **mercury** (no. 3), **cadmium** (no. 7) and **chromium** (no. 18). Chromium is considered essential element and is therefore required for normal body function. Other essential elements that have potential for toxicity include **copper**, **iron**, **manganese**, **selenium** and **zinc**. Risk assessments for essentiality versus toxicity for these elements have been performed by several organizations (Burtis et al. 2012) and due to their relevance in the HEALS project, basic facts are also included in this chapter.

Toxic elements are known to have adverse impacts on human health via various toxicological mechanisms, depending on the dose, chemical species, route of exposure and duration of exposure (acute vs. chronic). The doses at which adverse health effects take place are not well established for many of these chemicals. Infants and children are especially susceptible due to their increased exposures to the mixtures of chemicals, increased absorption rates and diminished ability to detoxify many exogenous compounds (Grandjean and Landrigan 2006). Elderly people are also more susceptible to toxicity than most adults are. There is growing evidence, that genetic predisposition plays important role

in manifestation of toxic effects. Lifestyle factors such as smoking and alcohol ingestion may influence toxicity indirectly. Cigarette smoke contains some toxic metals, and smoking also may have pulmonary effects. Alcohol ingestion may affect toxicity indirectly by altering diet and reducing the intake of essential elements (Burtis and Ashwood 1999). Moreover, toxic effects depend on the interaction between toxic and essential elements, particularly when the metabolism of a toxic element is similar to that of the essential element, e.g. absorption of toxic metals from the lung or gastrointestinal tract may be influenced by an essential metal (Burtis and Ashwood 1999). Essential element may also reduce bioavailability of a toxic metal/metalloid by sequestration, which is well demonstrated for selenium, interacting with both mercury and arsenic and thus protecting against their harmful effects.

The central nervous system is the target organ for elemental mercury vapour, methyl mercury, lead and manganese. The neurotoxicity of methyl mercury and lead is prominent especially during the developmental stage of nervous system (Blake 2004; Sanders et al. 2009), resulting in different neuropsychological dysfunctions, intellectual and behavior deficits. Accumulation of manganese in the brain causes a Parkinson-like neurodegenerative disorders. Among the most nephrotoxic elements recognized are cadmium, lead and inorganic mercury compounds (Nordberg et al. 2007; Skerfving and Berghdal 2007). Toxicity, absorption and metabolism of some elements are primarily dependant on the chemical species and or oxidation state. For example, inorganic arsenic is recognized as genotoxic and is a known human carcinogen; on the other hand, current dietary exposure to organic arsenic is unlikely to constitute a risk to health. Moreover, methyl mercury is much more toxic that elemental and inorganic mercury compounds. While Cr(III) is an essential form of chromium, Cr(VI) is a known carcinogen.

In contrast to toxic elements, having no known physiological function, essential elements are important for the development and maintenance of life functions, affecting all aspects of growth, health and reproduction, from the formation of cells, tissues, and organs to the initiation and development of host defence by the immune system in response to foreign microbes and viruses (Szefer and Nriagu 2007). Trace element deficiencies are estimated to result from poor diet and are reported for about 40% of the world’s population, especially in developing countries. However, when present in excess these same elements may result in endocrine, cardiovascular, skeletal, gastrointestinal, kidney, genetic, and ophthalmologic disorders in various individuals (Szefer and Nriagu 2007). The discovery of the central role of selenium deficiency in the aetiology of Keshan disease in China has greatly stimulated research on human selenium requirements and metabolism. Marginal states of zinc deficiency resulting in retardation of the growth of infants and of the preschool and schoolchildren have been identified in several countries. Cooper deficiency continues to be reported not only in infants and children undergoing rehabilitation but also in those reared under conditions of social deprivation.

The new analytical techniques based on inductively coupled plasma mass spectrometry (ICP-MS) allow for simultaneous determination of a number of toxic and essential elements and their species in biomarker tissues. Thus, the multielemental analysis may provide new insight and understanding of the role of toxic and essential elements in environmental wide association studies.

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2.3.1 Mercury (Hg)

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The toxic metal mercury (Hg) is commonly found in the environment and originates from natural as well as anthropogenic sources.

Chemistry

Mercury in the environment exists in several forms. These forms can be grouped under three headings: metallic mercury (also known as elemental mercury); inorganic mercury; and organic mercury. The most common natural forms of mercury found in the environment are metallic mercury, mercuric sulphide (cinnabar ore), mercuric chloride, and methyl mercury. Some microorganisms and natural processes can change mercury in the environment from one form to another (Horvat et al. 2012).

Metallic mercury is the elemental or pure form of mercury and is a heavy, shiny, silver-white metal that is a liquid at a room temperature. At a room temperature, some of the metallic mercury will evaporate and form mercury vapour. Mercury vapour is colourless and odourless (Horvat et al. 2012).

Many salts of divalent mercury (Hg^{2+}) are readily soluble in water, such as mercury sublimate ($HgCl_2$), and are thus highly toxic. In contrast, the water solubility of HgS (cinnabar) is extremely low, and, correspondingly, HgS is much less toxic than $HgCl_2$. The extremely high affinity of Hg^{2+} for sulfhydryl groups of amino acids such as cysteine and methionine in

enzymes explains its high toxicity. Monovalent mercury is found only in dimeric salts such as Hg_2Cl_2 (calomel), which is sparingly soluble in water and, again correspondingly, much less toxic than $HgCl_2$ (sublimate) (Horvat et al. 2012).

When mercury combines with carbon, the compounds formed are called ‘organic’ mercury compounds or organomercurials. There is potentially large number of organic mercury compounds; however, by far the most common organic mercury compound in the environment is monomethly mercury (known as methyl mercury or MeHg). MeHg is of particular concern because it can build up in certain edible freshwater and saltwater fish and marine mammals to levels that are many times higher than the levels in the surrounding water. In the past, the aryl organic mercury compound phenyl mercury was used in some commercial products. Ethyl mercury is used as a preservative in vaccines. Another organic mercury compound called dimethyl mercury is also used in small amounts as a reference standard for some chemical tests, dimethyl mercury is very harmful to humans and other animals (Horvat et al. 2012).

Biological Systems Affected

Target organs of mercury toxicity are kidneys and nervous system. The central nervous system is the most sensitive target for elemental mercury vapour and methyl mercury exposure. Prominent symptoms of mercury vapour exposure include tremors, emotional lability, insomnia, memory loss, neuromuscular changes, headaches, polyneuropathy and performance deficits in tests of cognitive function. Sensitive tests for psychomotor skills, tremor and peripheral nerve function revealed that adverse effects may be associated with very low exposures (WHO-IPCS 2003). According to the minimal effects found in the offsprings exposed prenatally to high levels of mercury vapour, the prenatal period may not be especially sensitive to the effects of vapour inhaled by the mother. Although vapour passes across placenta, much less accumulates in the foetal brain than in that of the mother (Clarkson 2002). However, children are seldom exposed to high levels of vapour, which occur mainly in occupational settings. There is no clear evidence up to date, that exposure to the small amounts of mercury vapour from dental amalgams may be harmful. No human studies as yet document any adverse effect of prenatal or early postnatal exposure to elemental mercury or mercury vapour (Davidson et al. 2004).

The neurotoxicity of methyl mercury is prominent especially during the developmental stage of nervous system. Prenatal exposure to methyl mercury interferes with the brain growth process adversely affecting the structural integrity of the nervous system (Rodier 1995; Blake 2004) and thus causing sub-clinical brain dysfunction at doses much lower than those affecting adult brain functions (Grandjean and Landrigan 2006). Fatalities and devastating neurological damage were observed in association with extremely high exposures to mercury (the Minamata disease), a milder syndrome was also identified in the Iraq outbreak, demonstrating a history of delayed achievements of developmental milestones; however chronic exposure to low-levels can lead to neuropsychological dysfunctions in the domains of language, attention, and memory, and to a lesser extent in visual-spatial and motor functions (Grandjean et al. 1997).

It was hypothesized that postnatal exposure to thimerosal from vaccines may be associated with autism spectrum disorders, however no direct test of this association has yet been reported (Davidson et al. 2004).

Damage to kidneys is the key end-point in exposure to inorganic mercury compounds. The most sensitive adverse effect observed following exposure to Hg^{2+} is the inflammation of

kidney. Developmental effects can occur as well, but our grasp is limited and reliable epidemiologic data are lacking (Davidson et al. 2004).

Distinct from the action of inorganic mercuric compounds, exposure to mercury vapour does not produce severe kidney damage. However, low-level chronic exposures (air concentration >50 µg/m^3) can cause decreased selectivity of the glomerular filter and diminished tubular re-absorptive function, which is evidenced by increased excretion of albumin and low-molecular weight proteins (Clarkson 2002).

Cardiovascular toxicity in humans has also been observed following ingestion of mercuric chloride and mercurous chloride; and statistically significant increases of blood pressure were found in volunteers with dental amalgams when compared with an age- and sex-matched control group without amalgam fillings (WHO-IPCS 2003). Furthermore, a statistically significant correlation was found between mercury exposure through fish consumption and cardiovascular disease even after correction for numerous cardiovascular risk factors. Increased blood pressure was observed also in 7-year old children from Faroes Islands prenatally exposed to low levels of methyl mercury (increase in blood pressure observed at the range of blood levels in the mother ranging from 1 to 10 µg Hg/l (reviewed by Clarkson 2002).

Possible Exposure Routes

People may be exposed to elemental or inorganic mercury from dental amalgam and through inhalation of ambient air during occupational activities where mercury and mercury compounds are produced (WHO-IPCS 2003). Occupational exposure have been reported from chlor-alkali plants, mercury mines, mercury-based small-scale gold and silver minings, refineries, thermometer factories, dental clinics with poor mercury handling practices, and production of mercury based chemicals. Furthermore small scale or artisanal mining, using gold-mercury amalgamation to extract gold from ore, is a significant source of exposure for the workers and nearby populations (ATSDR 1999; UNEP and WHO 2008). However, children are exposed to inorganic mercury compounds, elemental mercury or mercury vapour less commonly (Davidson et al. 2004).

The amalgams release mercury vapour that could be inhaled (Hg constitutes 50% of dental amalgam). Concentrations of mercury vapour in the air in the oral cavity were shown to exceed occupational health standards. However, the quantity of vapour was small because the volume of cavity was small. Levels of mercury vapour in the ambient are low and the intake from this source is negligible. Therefore, with the exception of certain occupational exposure, dental amalgam is the main source of human exposure to mercury vapour (Clarkson 2002).

Exposures to elemental mercury or inorganic mercury forms can also occur due to use of some skin-lightening creams and soaps, the presence of mercury in some traditional medicines, use of mercury in cultural practice, and due to various accidental mercury spills in homes, school or other locations. Moreover the use of mercuric compounds as fungicides in latex paint and to disinfect grain seeds can result in exposure to inorganic mercury, but such use is prohibited in many countries (UNEP and WHO 2008).

People are exposed to methyl mercury mainly through their diet, especially through the consumption of freshwater and marine fish and consumption of other animals that consume fish (such as marine mammals). The highest levels are found in fish that are apical predators of older age such as king mackerel, pike, shark, swordfish, walleye, barracuda, large tuna, scabbard, marlin and fish-consuming mammals such as seals and toothed whales (UNEP

2002; Miklavčič et al. 2011). Trimming, skinning off and cooking the mercury-contaminated fish does not reduce the mercury content of the fillet portion. However people that consume moderate amounts of variety of fish are not at risk (UNEP 2002). Based on the levels of methyl mercury in fish available on the Slovenian market and JECFA provisional tolerable weekly intake (PTWI) for methyl mercury, a 70 kg man can eat a portion (150 g) of fish on the top of food chain approximately once per week or approximately three portions (150 g) of fish lower on the food chain (Miklavčič et al. 2011).

Minor exposure to other forms of mercury may result from the use of thiomersal (ethylmercury thiosalicylate) as a preservative in some vaccines and other pharmaceuticals. However, the use of thiomersal in vaccine is being discontinued, or significantly reduced in many countries, especially in vaccines intended for children (UNEP and WHO 2008). Infants, immunized with these vaccines were/are exposed to small doses of this organic mercury compound (12.5-25.0 µg/dose), depending on the weight of the infant (Davidson et al. 2004). The predicted increase for the term infants based on methyl mercury is 2.2 µg Hg/l blood, which was the same as the observed increase (Clarkson 2002). However, smaller infants could have been exposed to a dose that was near or above the US EPA’s current permissible daily dose of 0.1 µg/kg/day (Davidson et al. 2004).

Absorption

Metallic mercury is highly lipophilic, and absorption of the inhaled vapour, followed by rapid diffusion across the alveolar membranes of the lungs into the blood, has been reported to be substantial. Exposure to 0.1-0.4 mg/m^3 elemental mercury vapour can result in approximately 70-80% of inhaled mercury vapour. Ingesting small amounts of metallic mercury such as contained in a standard thermometer does not produce symptoms of intoxication, because the absorption of ingested metallic mercury is negligible. Animal studies indicate, that the absorption of inorganic mercury such as mercuric chloride is approximately 10-30%. Rate of oral absorption of mercuric mercury compounds in rats is dependent on intestinal pH, compound dissociation, age and diet (Horvat et al. 2012).

Organic mercury compounds are more readily absorbed in the gastrointestinal tract than inorganic mercury compounds. About 95% of methyl mercury ingested is thought to be absorbed by the oral route. However absorption and bioavailability of methyl mercury may be affected by dietary components in food such as dietary fibre found in cereal products or selenium in fish (ATSDR 1999). Depending on the species of fish a low percentage of mercury in the fish is bio-accessible (less than 20%) in both simulated stomach and intestinal digestion. Low methyl mercury recovery could be attributed to the low ability of enzymes in in vitro method to release the mercury existing in each of the samples, perhaps due to the fact that mercury is complexed by selenium rather than a lack of bio-accessibility of methyl mercury itself. In fact, a recovery of 89% from in vitro enzymolysis of sample spiked with methyl mercury was obtained. Higher faecal extraction and lower tissue accumulation of mercury in rats from contaminated fish than from methyl mercury chloride added to fish has been demonstrated (Horvat et al. 2012).

Disposition of mercury after thimerosal injection is not very different from that expected from methyl mercury. The conversion in body tissues to inorganic mercury appears to be substantially faster from ethyl than from methyl mercury (Clarkson 2002).

Elimination

The main excretory pathways of metallic and inorganic mercury in humans are urine and faeces, with a half-life of approximately 1-2 months. In a study of a former chlor-alkali workers long term exposed to metallic mercury, the elimination of mercury in urine was well characterized by a one-compartment model, which estimated a half-life of 55 days. The tendency toward longer half lives in cases of shorter duration of exposure compared to long-term exposure was also observed. Therefore the excretion of mercury depends on the duration of exposure. Furthermore after an acute mercury exposure in humans, urinary excretions accounts for 13% of total body burden, while after long-term exposure urinary excretion increases to 58%. Elimination of metallic mercury also occurs through expired air. After human exposure of mercury vapour for less than an hour, excretion through expired air accounts for 7%. The half-life for this elimination pathway was estimated to be 14-25 hours. In a group of chlor-alkali workers, long-term exposed to metallic mercury, a two compartment model was used to estimate half-lives of whole blood and plasma. In whole blood the half-lives were 3.8 and 45 days for the fast and slow phase, respectively, while for the plasma the half-lives were 2 and 36 days for fast and slow phase, respectively (Horvat et al. 2012).

After an acute exposure to a high level of mercuric chloride, an elimination half-life in urine was estimated to be 25.9 days. The overall half-live of inorganic mercury from the body was estimated to be 60 days and it is eliminated with the same rate as from the kidneys, where most of the body burden is localized (ATSDR 1999; Horvat et al. 2012).

The predominant excretory route for methyl mercury, as well as for ethyl mercury, is the faecal pathway, with less than one-third of total mercury excretion occurring through the urine. In a study, that included four Japanese people, the extraction of methyl mercury into faeces was confirmed, but they found similar concentrations of methyl mercury in the urine compared to concentrations in faeces (Horvat et al. 2012). The residence time in the body is probably shorter for ethyl, but quantitative data are lacking (Clarkson 2002).

Animal studies showed that methyl mercury is secreted in the bile and can be reabsorbed in the intestine (Horvat et al. 2012). Clearance half-times are longer with methyl mercury than with inorganic compounds, however there is evidence that the half-life of ethyl mercury is shorter than that of methyl mercury (Davidson et al. 2004). The half-time in the blood is estimated to be 50 days (ATSDR 1999). Elimination of methyl mercury compounds generally follows first order kinetics because excretion because it is directly proportional to body burden and independent of the route of administration. Duration of exposure may affect the extraction process of mercury. A two-compartment model was establish for a single oral dose in monkeys, while following repeated dosing for two years a one-compartment model was considered a more reasonable fit for the data. Therefore the average steady-state blood levels of mercury after chronic-duration exposure should not be estimated on the basis of short-term exposure data (Horvat et al. 2012).

Reference values

Population-based reference values for mercury in urine and blood were established for German population in 1997-1999 (adults) and 2003-2006 (children). Mercury in urine of children 3-14 years of age without amalgam fillings was 0.4 µg/l and in urine of adults 18-69 years of age without amalgam fillings was 1.0 µg/l (n= 1,734 and 4,822, respectively). Mercury in blood of children was 1.0 µg/l and in blood of adults 2.3 µg/l (n= 1,552 and 4,645, respectively) (Wilhelm et al. 2004; Schulz et al. 2009). In a recent pilot study of European human biomonitoring (DEMOCOPHES), mercury was determined in hair of 1844 mothers

and their children aged 6-12 years and P95 values were 1.2 µg/g for mothers, 0.8 µg/g for children (Esteban et al. 2014).

Health-based values for total mercury in urine of children and adults are 5 µg/g creatinine (HBM I) and 20 µg/g creatinine (HBM II) or 7 and 25 µg/l urine, respectively (Schulz et al. 2011). For total mercury in blood the values are 5 µg/l (HBM I) and 15 µg/l (HBM II) (Schulz et al. 2011). Total mercury in hair of women in childbearing age derived from the US EPA Reference Dose is approximately 1 µg/g hair (US EPA 2001).

Specimens for analysis

In human biomonitoring programs and environmental studies, mercury is most frequently measured in hair. However, it is well known that Hg in hair is a good indicator for methyl mercury exposure through fish consumption, but this is not true for inorganic mercury to which general population is exposed mostly through amalgam fillings. In contrast to hair, which provides a simple, integrative, and non-invasive sample for estimating mid- to long-term average exposure (depending on the length of a hair sample), the presence of Hg in blood indicates recent or current exposure to both, organic and inorganic Hg, and does not give information on the historical exposure and seasonal (or other peak) variations (UNEP and WHO 2008). Inorganic Hg exposure is best indicated by urinary Hg. As inorganic Hg is slowly excreted from kidneys through urine, urinary Hg reflects not only recent exposure to inorganic Hg, but also exposure that occurred sometime in the past (Barregard 1993; Mason et al. 2001). In an occupationally non-exposed population, the number of amalgam surfaces was found to be the best predictor for urinary Hg (Langworth et al. 1992).

Two large well-designed and well-executed cohort studies, the Seychelles Child Development Study (SCDS) and the Faroe Islands study, provided an illustrative comparison between the two common biomarkers of prenatal methyl mercury exposure – hair and cord blood. The Faroese study, which used cord blood as a biomarker of exposure, reported adverse associations between prenatal MeHg exposure and a number of developmental endpoints; whereas in the SCDS, where maternal hair was used as a biomarker of exposure, only one endpoint showed adverse association with prenatal MeHg exposure. The Faroese researches reported that, using hair samples, associations with developmental outcomes were still present but weaker. Of course, other differences between the two studies were reported as well, which might at least partially explain the difference in outcome of the studies.

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2.3.2 Lead (Pb)

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Chemistry

Lead in organic compounds usually has the oxidation state II, but state IV also occurs. Lead is a soft, silvery grey metal. In the Earth’s crust it is present in various minerals such as sulphide, carbonate and sulphate. The metallurgy of lead consists of three separate operations: concentrating, smelting, and refining. Occupational exposure to lead occurs in a wide variety of settings during primary and secondary lead smelting, working in non-ferrous foundries, production of electric storage batteries, as well as sanding and scraping lead paint (Jakubowski 2012).

Biological Systems Affected

Lead is among the most nephrotoxic agents (Skerfving and Berghdal 2007). It can cause renal effects on vulnerable populations but it is uncertain whether it still poses health risk at the low exposure levels now prevailing in most industrialized countries (Chaumont et al. 2012). Chronic low-level exposure to lead is associated with increased urinary excretion of low molecular weight proteins and lysosomal enzymes (NAG, N-acetyl-beta-D-glucosaminidase); renal tubular dysfunction was found in association with sustained environmental exposure in childhood. Furthermore, epidemiologic studies have shown an association between blood lead levels and blood pressure, and hypertension is a cardinal feature of lead nephropathy (Loghman-Adham 1997). It interferes also with bone turnover and calcium metabolism (Goyer 1995).

Exposure of newborns to low levels of lead has demonstrated associations with decrements in central neurologic function during childhood (Landrigan and Todd 1994). Adverse health effects caused by lead exposure include intellectual and behaviour deficits in children, deficits in fine motor function, hand-eye coordination, and reaction time; and lowered performance in intelligence tests. The developmental effects of Pb occur during a critical time window, that is at <2 years of age (Sanders et al. 2009). Several findings consistently show no threshold levels especially for developmental toxicity in children (Schulz et al. 2011).

Possible Exposure Routes

Lead can be released into the atmosphere from natural and anthropogenic sources. The emission of lead during non-ferrous metal production and manufacturing, extensive use of lead in paints, or as an additive to gasoline took place on the global scale and can be considered as one of the biggest environmental disasters of anthropogenic origin. In the occupational settings, inhalation is still the most significant route of exposure to lead. In the general population dietary exposure is clearly the dominating source of overall lead exposure (Jakubowski 2012), other sources include ambient air, drinking water, soil, and dust (ATSDR 2007). For infants and young children, dust/soil may constitute a significant source of ingestion. Drinking water in houses containing lead pipes may contain Pb, especially if the water is acidic. Airborne Pb is a low-dose source of exposure in the general exposure (Landrigan and Todd 1994; ATSDR 2007). The initiation of unleaded gasoline usage in the beginning of 90s resulted in remarkably reduced Pb emissions, eliminating the major source of Pb pollution (Jakubowski 2012).

Absorption

Gastrointestinal absorption of ingested lead is influenced by physiological factors (e.g. age, fasting, nutritional calcium and iron status, pregnancy) and the physiochemical characteristics of particles (size, solubility and lead species). Studies on the uptakes of stable isotopes of lead in adults showed average absorption of 15-20%. In long-term metabolic studies, net absorption of dietary lead amounted to about 10%. In radiotracer experiments in fasting subjects, the absorption was 37-70%, depending on the study. Absorption of ingested soluble lead compounds appears to be higher in children than in adults and can be affected by nutritional iron status. A low iron intake and deficient iron status were associated with increased blood lead. An inverse relationship has been observed between dietary calcium intake and the blood lead concentration in children, suggesting that children who are calcium deficient may absorb more lead than calcium-replete children (Jakubowski 2012).

Deposition and absorption of inhaled lead-containing particles are influenced by their size and solubility. Particles larger than 5 microns are deposited on the lining fluid of trachea and bronchi; from there they are transferred by mucociliary transport into the pharynx and then swallowed, with possible absorption of lead from the gastrointestinal tract. Smaller particles can be deposited in the alveolar part of the lungs and almost completely absorbed (Jakubowski 2012).

Elimination

The half-life of lead in blood is approximately 30 days in adult male humans, but it varies depending on the level of exposure, sex and age. Lead is excreted primarily in urine, most likely by passive diffusion, and with faeces. Sweat, saliva, hair and nails, and breast milk are minor routes of excretion (Jakubowski 2012).

Reference values

Population-based reference values were established for German population in 1997-1999 (adults) and 2003-2006 (children). Reference values for lead in blood of 3-14 years old children was 35 µg/l, for women 70 µg/l and for men 90 µg/l (n= 1,560, 2,303 and 2,342, respectively) (Schulz et al. 2011).

In 1996, the German Human Biomonitoring Commission set health-based value HBM I at 100 µg/l for lead in blood of children aged ≤12 years and females of reproductive age. However, in 2009, the Commission concluded that any setting of an ‘effect threshold’ for blood lead levels would be arbitrary and therefore not justified and suspended the recommendation from the list (Wilhelm et al. 2010; Schulz et al. 2011).

Specimens for analysis

Most of the information on human exposure to lead, and the health effects resulting from it, is based on the lead in blood levels. Bergdahl and Skerfving (2008) have reviewed different biomarkers for lead exposure and data indicated that the best biomarker in some circumstances may be blood, but bone or teeth (for past exposures), faeces (for current gastrointestinal exposure), or urine (for organic Pb) are sometimes more useful. However, the authors concluded that almost all biomarkers lack systematic data on variation within and between individuals (Bergdahl and Skerfving 2008).

At steady-state, blood lead reflects a combination of recent lead exposure and that which occurred several years before. Lead in plasma or serum is present in very low concentration

– a ratio plasma/erythrocyte is 0.2-1%. Although there are indications that lead concentrations in plasma or serum could be alternative for biological monitoring, there are very few epidemiological studies in which plasma or serum lead levels have been used in exposure assessment (Jakubowski 2012).

Lead in urine reflects primarily the amount of lead absorbed recently. Urinary lead has been used in biological monitoring, but only to a limited extent. There is an association between lead in urine and blood, but the variation is too large to allow prediction of the individuals lead blood concentrations from the urinary lead concentration (Jakubowski 2012).

Hair has sometimes been used for biomonitoring of lead exposure, but because of the potential for external contamination, it is not a useful index of lead uptake into the body (Jakubowski 2012).

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2.3.3 Cadmium (Cd)

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Cadmium (Cd) is a toxic transition metal. It is typically found in ores with other metals, and is commercially produced as a by-product of zinc and lead smelting, which are sources of environmental cadmium. Cadmium ranks close to lead and mercury as one of the top toxic substances.

Chemistry

Pure cadmium is a soft, silver-white metal. Cadmium chloride and cadmium sulfate are soluble in water (ATSDR 2012).

Biological Systems Affected

Together with lead, cadmium is among the most nephrotoxic agents (Nordberg et al. 2007) and can cause renal effects on vulnerable populations but it is uncertain whether it still poses health risk at the low exposure levels now prevailing in most industrialized countries (Chaumont et al. 2012). Renal damage induced by cadmium affects primarily the cellular and functional integrity of the proximal tubules, the main site of the renal accumulation of the metal. This results in an increased excretion of calcium, amino acids, enzymes and proteins (low molecular weight proteins, such as retinol-binding protein (RBP), ß2-microglobulin (U-ß2M) and α1-microglobulin) (Bernard 2004). It interferes also with bone turnover and calcium metabolism (Goyer 1995).

Possible Exposure Routes

For non-smokers, food is generally the largest source of cadmium exposure. People who regularly consume shellfish and organ meats (kidney, liver) will have higher exposures (ATSDR 2012). Shellfish accumulate relatively high levels of cadmium (1-2 mg/kg), and animal liver and kidney can have levels higher than 50 µg Cd/kg. Many plants accumulate cadmium, for example cereal grains such as rice and wheat, and tobacco concentrate cadmium to levels of 10-150 µg Cd/kg (Liu et al. 2008). Cigarette smoking is a major non-occupational source of cadmium exposure, and smoking is thought to roughly double the life-time body burden of cadmium (Liu et al. 2008).

Absorption

The form of cadmium and the route of exposure can greatly affect the absorption and distribution of cadmium to various target sites, and therefore, the concentration at the target site and the severity of the observed effect. Gastrointestinal absorption of cadmium is limited to 5-10% of a given dose. Cadmium absorption can be increased by dietary deficiencies of calcium or iron and by diets low in protein. In the general population, women have higher blood cadmium levels than men, possibly due to increased oral cadmium absorption because of relatively low iron stores in women of childbearing age (Liu et al. 2008; ATSDR 2012). Cadmium does not readily cross the placenta. Breast milk is not a major source of early life exposure. About 50-75% of the retained cadmium is found in the liver and kidneys (Liu et al. 2008).

Elimination

Once absorbed, cadmium is very poorly excreted and only about 0.001% of the body burden is excreted per day. Both urinary and fecal excretory routes are operative (Liu et al. 2008). The biological half-life of cadmium in humans is not known exactly, but is probably in the range of 10-30 years (Liu et al. 2008).

Reference values

Blood cadmium levels in non-occupationally exposed, non-smokers are usually less than 1 µg/l. Reference values based on the German population are 1 µg/l in blood of non-smoking adults and <0.3 µg/l in blood of non-smoking children aged 3-14 years. Respective reference values in urine are 0.8 and 0.2 µg/l (Wilhelm et al. 2004; Schulz et al. 2009).

Health-based values for cadmium in urine are 1 µg/g creatinine (HBM I) and 4 µg/g creatinine (HBM II) for adults, and 0.5 µg/g creatinine (HBM I) and 2 µg/g creatinine (HBM II) for children, as set by the German Human Biomonitoring Commission in 2011 (Schulz et al. 2011).

Specimens for analysis

Blood cadmium primarily reflects recent exposure of 2-3 months and may also include a contribution from a long-term body burden. Cadmium measured in urine primarily reflects the total body burden of cadmium as a result of a much longer history of exposure (Berglund et al. 1994; ATSDR 2012; Adams and Newcomb 2014). Validity of a urinary cadmium as a reliable biomarker of the cadmium body burden was questioned by recent studies. Evidences exist however, that urinary cadmium is strongly influenced by a series of factors unlikely to be related to cadmium toxicity or accumulation (Chaumont et al. 2013). At low level environmental exposure to cadmium, associations were demonstrated between higher urinary or blood cadmium levels and an increased prevalence of various biomarkers of renal tubular damage (Järup et al. 1998; Alfvén et al. 2002; Noonan et al. 2002; Olsson et al. 2002). As described by Chaumont et al. (2011, 2012), renal tubular damage can lead to increased excretion of certain proteins, cadmium following the same glomerular filtration-tubular reabsorption pathway as proteins. Urinary cadmium would thus be a reflection of the functional integrity of the proximal tubule, rather than of the cadmium body burden, which was confirmed also at low environmental exposures (Chaumont et al. 2012).

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2.3.4 Arsenic (As)

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The toxic metalloid arsenic is, similarly as mercury, commonly found in the environment and originates from natural as well as anthropogenic sources.

Chemistry

Arsenic is a metalloid found in nature ubiquitously in a variety of inorganic and organic compounds. Arsenic can exist in the oxidation states -3, 0, +3 and +5, whereas in the environment, oxides of the oxidation state +3 (arsenites) and +5 (arsenates) are the most common compounds, the most stable form being As_2O_3 (arsenic trioxide). From both the biological and the toxicological point of view, arsenic compounds can be classified into three major groups: inorganic arsenic compounds, organic arsenic compounds, and arsine gas. Arsenic appears in nature primarily in the form of sulphides in association with sulphides of ores of silver, lead, copper, nickel, antimony, cobalt and iron. Trace amounts of arsenic are found in soils and other environmental media. In oxygenated soil, inorganic arsenic is present in the pentavalent form. Under reducing conditions, it is in the trivalent form. Leaching of arsenate is slow because of binding to hydrous oxides of iron and aluminium. Arsenic species can undergo transformations via biotic and abiotic processes. More than 25 different species of arsenic have been identified so far. Oxidation, reduction, adsorption, desorption, dissolution, precipitation and volatilization of arsenic occur commonly in the environment (Horvat et al. 2012).

Arsenic is mainly transported in the environment by water. In oxygenated water, arsenic usually occurs as arsenate, but under reducing conditions, for instance, in deep well-waters, arsenites predominate. In water, the methylation of inorganic arsenic to methyl- and dimethylarsenic acids (MA, DMA) is associated with biological activity. Some marine organisms have been shown to transform inorganic arsenic into more complex compounds, such as arsenobetaine (AsB), arsenocholine (AsC) and arsenosugars (AsS) and other compounds such as trimethylarsine oxide (TMAO) and tetramethylarsonium ion (TETRA) (Horvat et al. 2012).

In humans, arsenic binds to sulphhydryl group (primary mechanism of arsenic’s toxicity) on protein causing loss of protein activity. Arsenic can be incorporated instead of phosphate in different phosphate related biological reactions, because body treats arsenic (As^{5+}) like phosphate. For example, arsenic competes with phosphate for reaction with ADP (adenosine diphosphate) resulting in lower ATP (adenosine triphosphate) level (Burtis and Ashwood 1999).

Biological Systems Affected

Carcinogenicity is the most serious consequence of chronic arsenic exposure. The skin is a major target organ; chronic exposure to arsenic induces a series of characteristic changes in skin epithelium (hyperpigmentation, hyperkeratosis, warts, melanosis). Liver injury, characteristic of long-term arsenic exposure, manifests itself initially as jaundice, abdominal pain, and hepatomegaly. Arsenic and its inorganic compounds have long been known to be neurotoxic. Repeated exposure to low levels of inorganic arsenic can produce peripheral neuropathy. This neuropathy usually begins with sensory changes, such as numbness in the hands and feet but later may develop into a painful “pins and needles” sensation. Both

sensory and motor nerves can be affected, and muscle tenderness often develops, followed by weakness, progressing from proximal to distal muscle groups (Liu et al. 2008).

High levels of airborne arsenic and inorganic arsenic in drinking water have been shown to be associated with cardiovascular diseases. Peripheral vascular disease leading to gangrene of the extremities (known as Blackfoot disease) has been observed (Liu et al. 2008; Horvat et al. 2012).

As summarized by Tsuji et al. (2004), the most prevalent effects consistently reported at low doses with sub-chronic exposure involve skin changes. Other effects that have been reported both in children and adults with sub-chronic exposure include gastrointestinal disturbances, peripheral neuropathy, liver effects, and vascular and haematological disorders (Tsuji et al. 2004). Additional research is required to verify a link between inorganic arsenic exposure and diabetes. The hematologic consequences of chronic exposure to arsenic may include interference with haeme synthesis (Liu et al. 2008).

Tsuji et al. (2004) reported health effects of arsenic sub-chronic exposure and concluded that health effects in children are similar to those in older age groups. Children do not appear to be more sensitive at the same dose/body weight as adults, at low arsenic doses. Exposure studies in adults thus may also be relevant for deriving reference levels for children, although differences in dose-per-body-weight should be considered for estimating exposures to adults and children (Tsuji et al. 2004).

Possible Exposure Routes

General population is exposed to arsenic through food and water consumption and inhalation. Some other routes of exposure are associated with various uses of arsenic, such as the use of some pharmaceutical products containing arsenic. In the general environment, the oral route constitutes the main route of absorption of arsenic. In occupational exposures, arsenic is absorbed mainly through the lungs (Horvat et al. 2012).

Trace concentrations of arsenic are present in all foods. However, the most important source of non-occupational human exposure to arsenic is fish and other seafood (Hughes 2006; Horvat et al. 2012). In fish and shell fish the total amount of arsenic is normally the highest in all foods, but the amounts of inorganic arsenic are generally low (<1%). In fish and shellfish, arsenic is mostly present in non-toxic organic forms (mostly arsenobetain and arsenocholin), which are much less harmful to humans than inorganic arsenic. Other foodstuffs (meat, poultry, dairy products and cereals) contain higher proportions of inorganic arsenic although total arsenic concentrations in such foods are generally low. Freshwater fish contain much lower concentrations of arsenic than seawater fish (Horvat et al. 2012). Overall, organic arsenic appears to be the major form of dietary arsenic, while the most important medium for inorganic arsenic exposure is drinking water (Hughes 2006). The source of inorganic As in drinking water is primarily geologic (Nordstrom 2002). The concentration of arsenic in natural surface and groundwater is generally less than 10 µg/l, but it may exceed 1 mg/l in mining areas or where arsenic levels in soil are high. Groundwater is far more likely to contain high levels of arsenic than surface water. Drinking water may, therefore, contribute significantly to oral intake in regions where there are high arsenic concentrations in well-water or in mine drainage areas. Some geographical areas contain unusually high natural levels of arsenic in rock, and this can lead to unusually high levels of arsenic in soil or water (Horvat et al. 2012).

Absorption

The major routes of arsenic absorption in the general population are ingestion and inhalation. Human and animal data indicate that over 90% of the ingested dose of dissolved inorganic As(III) or As (V) is absorbed from the gastrointestinal tract. The small intestine is the major site of absorption. Organic arsenic compounds are also readily absorbed (75-85%). Absorption of less soluble forms, e.g. arsenic trioxide, is much lower. The bioavailability of arsenic in soil contaminated by smelter activities, following oral administration, is about 25% (Horvat et al. 2012).

Factors affecting the extent of absorption from the lungs include the chemical form of arsenic, particle size and solubility. Particles of more than 10 µm aerodynamic diameter are deposited predominantly in the upper airways (nasopharynx), particles of between 5 and 10 µm are deposited in the airways cleansed by mucociliary action, and particles with diameter less than 2 µm penetrate significantly into the alveoli. Airborne arsenic is usually in the form of arsenic trioxide. More than 23% of the particles in sample of arsenic-polluted air in occupational settings were reported to be larger than 5.5 µm (Horvat et al. 2012).

Elimination

Both methylated species, MA and DMA, bind less readily to tissues and are eliminated more rapidly than unmethylated form. Excretion takes place in urine but in lower amounts also through bile in the faeces. The high excretion in the urine (up to 80%) may vary with the dose and exposure duration. In general DMA(V) is the principal metabolite following long-term exposure, with lower levels of inorganic arsenic and MA. With increased amounts of ingested inorganic arsenic the proportions are changed in favour of inorganic arsenic. In the bile, arsenic is excreted via the formation of two arsenic-glutathione complexes, arsenic triglutathione and methylarsenic diglutathione, and most probably also in association with selenium (Horvat et al. 2012).

Most population groups studied so far have on average 10-30% inorganic As, 10-20% MA, and 60-70% DMA in their urine, but considerable inter-individual variation has been observed, which may be due to genetic polymorphism in biomethylation of arsenic, age, nutritional status and chronic renal insufficiency. The excretion of inorganic arsenic in breast milk is comparatively low (Horvat et al. 2012).

Reference values

The toxicity of arsenic is dependent on the form (inorganic/organic) and the oxidation state of arsenical compounds. The Committee on Toxicity of chemicals in food, consumer products and the environment (EFSA 2009) concluded that inorganic arsenic is genotoxic and a known human carcinogen and therefore exposure should be as low as is reasonably practicable (ALARP). On the other hand, current dietary exposure to organic arsenic is unlikely to constitute a risk to health.

Reference values based on the German population of children aged 3-14 years (2003-2006) and adults aged 18-69 years (1997-1999) are 14.0 µg/l urine and 18.9 µg/l urine, respectively (n= 1734 and 4741, respectively) (Wilhelm et al. 2004; Schulz et al. 2009). Reference value for children and adults who did not eat fish 48h prior to sample collection is 15.0 µg/l urine (Schulz et al. 2011).

Specimens for analysis

The most common biomarker of exposure for inorganic arsenic is the measurement of total urinary arsenic (Hughes 2006), while blood levels of arsenic do not appear to be a reliable indicator of chronic exposure to low levels of arsenic, due to the fast clearance of arsenic in blood (ATSDR 2007). Consumption of seafood before collection of urine sample can be clinically misleading.

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2.3.5 Copper (Cu)

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Copper is very abundant element in the earth's crust and occurs naturally in rock, soil, sediment, water, plants, and animals (Canadian Council of Ministers of the Environment 1999). It is an essential element required for the maintenance of health, needed in many

physiological processes counting cellular respiration, iron metabolism, antioxidant defence, connective tissue development, and neurotransmitter production (WHO 1998; Health Canada 2010).

Chemistry

Copper is ordinarily found in the form of various sulphide minerals (Health Canada 2010). Pure element is a reddish, lustrous, malleable and ductile metal, but many copper compounds have a blue-green colour (Canadian Council of Ministers of the Environment 1999). Copper is released from natural sources (volcanoes, decaying vegetation, and forest fires) or from anthropogenic sources (mining, farming, manufacturing operations, and combustion of fuels and other materials containing copper). Element and its alloys can be also used in cooking utensils, coins, antifouling paint, dental amalgams, plumbing fixtures and pipes, and architectural applications such as roofing, guttering, and flashing. To add, copper compounds are significant chemicals in the textile, petroleum refining, wood preservative, and agricultural industries (WHO 1998; Canadian Council of Ministers of the Environment 1999; ATSDR 2004; Health Canada 2010).

In biological system exists in +1 and +2 valence states. Copper is integral component of many metalloenzymes (ceruloplasmin cytochrome c oxidase, superoxide dismutase, dopamine-β-hydroxilase, ascorbate oxidase, lysyl oxidase, tyrosinase) (Burtis and Ashwood 1999).

Biological Systems Affected

High doses of copper can result in adverse effects, although toxic effects are not common in the general population (Health Canada 2010). The most adverse health effects of excess oral intake like gastrointestinal distress and nausea, vomiting, and abdominal pain have been reported soon after drinking solutions of copper sulphate or beverages stored in containers that readily release element. Ingestion of drinking water with >3 mg Cu per litter can produce gastrointestinal symptoms. Ingestion of large amounts of copper salts, usually copper sulphate, can produce hepatic necrosis and death (Liu et al. 2008). Hepatic element accumulation has been observed in a variety of paediatric liver diseases including Wilson disease (WD), Indian childhood cirrhosis (ICC), the non-Indian disease termed idiopathic copper toxicosis (ICT), and disorders associated with chronic cholestasis (Müller et al. 1998).

When it is inhaled, copper is a respiratory tract irritant. Metal fume fever has been associated with exposure to high concentrations of metal fumes, also copper, generally in an industrial setting. Eye irritation from exposure to copper dust has also been reported (WHO 1998; ATSDR 2004; Health Canada 2010). Epidemiological studies have not found any relation between copper exposure and cancer (WHO 1998; Liu et al. 2008).

Copper deficiency because of poor diet or malabsorption results in impaired iron absorption; various pathological conditions linked to the loss of cuproenzyme activity; and in infants in neutropenia, hypocromic anaemia, osteoporosis and various bone abnormalities, decreased pigmentation of skin, neurological abnormalities (late stage). Copper depletion contributes to an increased risk of coronary heart disease (Burtis and Ashwood 1999)

Possible Exposure Routes

The most commonly route, humans are exposed to copper is with food. Copper content of food is variable and can be affected by application to crops of copper-containing fertilizers and fungicidal sprays. Also the use of copper-containing cooking vessels contributes to total

intake. The metal is most plentiful in organ meats (liver, kidney), shellfish, nuts, whole grain cereals, bran and all cocoa-containing products. Lesser amounts are found in white meats, dairy products (cow’s milk) (Burtis et al. 2012). Low levels of copper in food and drinking water is likely to be beneficial as copper is an essential nutrient (Liu et al. 2008). Additional exposure may result from inhalation of dust particles (Health Canada 2013).

Absorption

Copper absorption occurs mainly in the small intestine and varies with dietary content of element. It is around 50% at low copper intakes (<1 mg Cu/day) and 20% at higher intakes (>5 mg Cu/day). Absorption is reduced by other dietary components such as zinc, iron and molybdenum, and is increased by amino acids and dietary sodium. Absorbed copper is transported to the liver in portal blood bound to albumin, where it is incorporated by hepatocytes into cuproenzymes and other proteins and then is exported in peripheral blood to tissue and organs. More than 90% of copper exported from liver to blood is in the form of glycoprotein ceruloplasmin (increased during pregnancy) and <10% is bound to albumin (Burtis et al. 2012).

The process of transport of copper across the basolateral membrane of enterocytes into the portal circulation is defective in Menkes’ Syndrome patients (Figure 15). It results in accumulation of element in the enterocytes and also in its deficiency in the body. Most of the absorption is normally taken up by the liver. In cases of copper overload, excess is excreted in the bile and this process is blocked in patients with Wilson disease, as is the delivery of copper to ceruloplasmin, the principal carrier in the blood. Other low molecular weight proteins such as Cu-metallothionein and Cu-histine are also proposed to be important sources of copper to tissues. The transport to the brain is blocked in patients with Menkes’ disease, followed by severe neurological abnormalities (Liu et al. 2008).

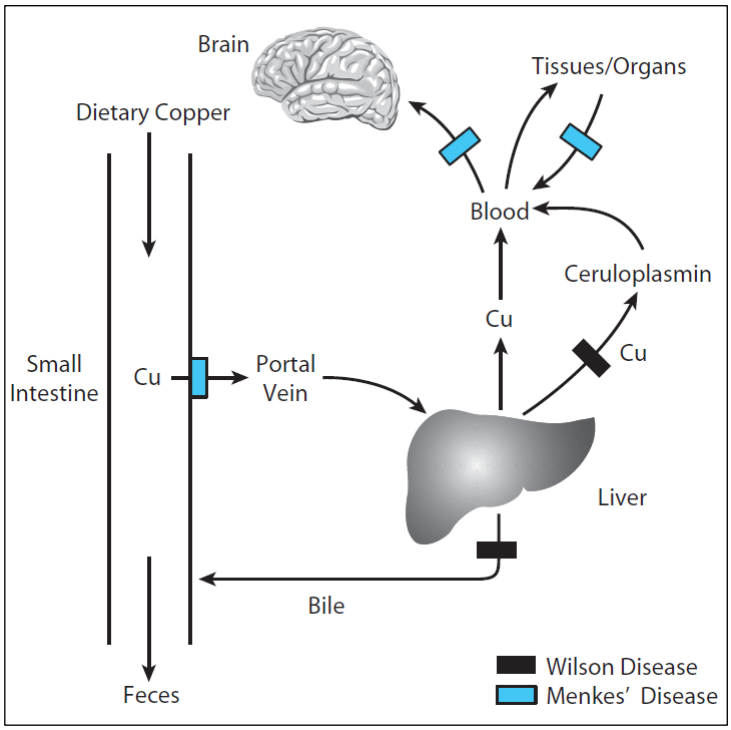

Figure 15: Pathways of copper (Cu) in the body and defects in Menkes’ and Wilson Diseases (Liu et al. 2008)

Elimination

Copper levels are controlled in human body mainly through control of excretion, although binding to hepatic metallothionein may act as a form of copper storage (Liu et al. 2008). The major excretory route is the bile, up to 70% of orally ingested element may be excreted in the faeces and normally 0.5% to 3.0% of daily intake is excreted in the urine (Health Canada 2010). Elimination of copper is biphasic with a biological half-life in the plasma of 2.5 and 69 days for the first and second phases, respectively (Health Canada 2010, 2013)

Reference values

Reference values for adults plasma copper are in the interval 70-140 µg/dl. Values in pregnant women are higher. Plasma copper <50 µg/dl in adults and <30 µg/dl in infants indicates probable depletion. Urine copper output is normally <60 µg/24h and values >200 µg/24h are found in Wilson’s disease (Burtis et al. 2012).

Levels for normal total erythrocyte copper are between 0.9-1.0 µg/ml of packed red cells. The values for copper, which were establish as normal, are: for serum in the range 0.64-1.56 µg/ml, ceruloplasmin 0.18-0.40 mg/ml, and hair in range 10-20 µg/g (WHO 1996).

Specimens for analysis

Exposure to copper can increase its concentrations in whole blood, serum, urine, hair and in the liver. Concentrations in serum are observed to decrease rapidly after exposure, indicating that they may only reflect recent exposures. Copper concentrations in hair and fingernails/toenails are also used to evaluate exposure, and may reflect exposure over longer periods of time (Health Canada 2010). The huge majority of serum copper is transported bound to ceruloplasmin; the rest is bound to albumin, transcuperin and copper-amino acid complexes. Twomey et all reported that their data seem to be in agreement with heterogeneity in the relationship between ceruloplasmin and total copper concentration (Twomey et al. 2005).

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2.3.6 Zinc (Zn)

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Zinc is one of the more common naturally occurring elements present in the Earth’s crust (Health Canada 2013). It is second to iron as the most abundant trace element in the body (Burtis et al. 2012). It is an essential element, as a constituent of many metalloenzymes.

Chemistry

Zinc is a metal which exists naturally in a +2 valence state in various inorganic and organic compounds. It is a lustrous, bluish white, relatively soft metal in pure state (Health Canada 2013). The most common zinc ore is sphalerite which often exists with the sulphides of other metallic elements (e.g. lead, copper, cadmium, and iron) (Health Canada 2013). It is also found as calamine in carbonate sediments; other forms of zinc are usually products of the oxidation of sphalerite (Health Canada 2010, 2013).

Zinc is an essential component of many metalloenzymes (carbonic anhydrase, alkaline phosphatase, RNA and DNA polymerase, thymidine kinase, carboxypeptidase and alcohol degydrogenase) therefore plays major role in protein synthesis and gene expression (Burtis and Ashwood 1999).

Biological Systems Affected

Exposure to high (more than twice the recommended daily intake) levels can affect human health. Acute effects of large doses of zinc can include stomach cramps, nausea, and vomiting (ATSDR 2005). Long-term exposure to high concentrations can cause "metal fume fever" which affects the lungs and the body's temperature control system (Health Canada 2010).

The clinical presentation of zinc deficiency disease is varied, nonspecific, and related to the degree and duration of depletion. Signs and symptoms include depressed growth with stunting; increased incidence in infection, possibly related to alternations in immune function;

diarrhoea; altered cognition; defects in carbohydrate use; reproductive teratogenesis; skin lesions; alopecia; eyesight defects and other adverse clinical outcomes (Burtis et al. 2012).

Possible Exposure Routes

Food is the main source of zinc in the general population. High-protein food as meat, fish and dairy products are good sources of available zinc (Burtis and Ashwood 1999). Increased exposure can occur from drinking water from pipes and fittings leaching zinc (Health Canada 2013). Acute zinc toxicity is normally the result of taking excess vitamin or mineral supplements or from drinking acidic beverages stored for long periods of time in galvanized containers (WHO 2014). Occupational exposure route can be through dusts and a fume of metallic zinc occurs in zinc mining and smelting (Liu et al. 2008).

Absorption

The net intestinal uptake of zinc is regulated by control of absorption efficiency in the face of variable dietary input and varies from 20 to 50% of the dietary content (Burtis et al. 2012). Uptake from the intestinal lumen includes passive diffusion and a carrier-mediated process through specific zinc transporters such as ZnT-1. Inner absorption of zinc can be reduced by dietary fibre, phytates, calcium and phosphorus, while amino acids, picolinic acid, and prostaglandin E2 can enhance zinc absorption (Liu et al. 2008). Absorbed zinc is transported to the liver by the portal circulation, where active incorporation into metalloenzymes and plasma proteins (albumin, α_2-macroglobulin) occurs. Blood plasma contains less than 1% of the total body content of zinc and about 80% of element in plasma is associated with albumin and most of the rest with α2-macroglobulin.The zinc content of erythrocytes is about 10 times that of plasma (Burtis et al. 2012).

Elimination

The primary route of excretion from the body is through the gastrointestinal tract; this excretion includes unabsorbed dietary zinc, a small amount from sloughing of intestinal epithelial cells, and zinc from biliary and pancreatic origin, so zinc is excreted in both urine and faeces. Under normal circumstances, a small amount of zinc may be lost daily in perspiration and in urine (Liu et al. 2008; Health Canada 2013).

Reference values

Serum zinc concentrations are generally 5-10% higher than in plasma because of osmotic fluid shifts from the blood cells when various anticoagulants are used. A reference interval for clinical guidance in serum is 80-120 µg/dl. Results <30 µg/dl suggest likely deficiency. Urine zinc excretion is in the range 0.2-1.3 mg/24h (Burtis et al. 2012).

Specimens for analysis

The concentration of zinc in plasma is not a sensitive indicator of zinc status and does not reflect the dose-response relationship between zinc levels in the body and effects at various target sites (Liu et al. 2008). Concentrations of zinc in serum and urine are believed to increase after exposure and serum zinc levels are commonly used as indicators of population zinc status (Hess et al. 2007). Hair and nail samples are also suggested to have potential value for longer-term exposure (Health Canada 2013). Determination of metallothionein in red blood cells and mitochondrial mRNA in circulating monocytes is a probable indicator of zinc deficiency in case of metallothionein decrease (Burtis et al. 2012).

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2.3.7 Selenium (Se)

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Selenium is a naturally occurring element that is widely distributed in rocks and soils. In humans and animals, it is an essential nutrient that plays a role in protecting tissues from oxidative damage as a component of glutathione peroxidase. It is also involved in synthesis and metabolism of thyroid hormones. Although selenium is an essential nutrient, exposure to high levels may cause adverse health effects.

Chemistry

Selenium is a non-metal element with atomic number 34 and an atomic mass of 78.96. Certain forms have metal-like properties. The chemical properties of selenium are similar to sulphur. Selenium combines with metals and many non-metals directly or in aqueous solution. The availability and the toxic potential of selenium compounds are related to their chemical forms and, most importantly, to solubility. Selenium occurs in nature and biological systems as selenate (Se^{6+}), selenite (Se^{4+}), selenide (Se^{2+}) and elemental selenium (Se^{0}). The type of selenium found may vary according to ambient conditions, such as pH and microbial activity (ATSDR 2003; Liu et al. 2008).

Elemental selenium (Se^{0}) is rarely found naturally, but it is stable in soils. Selenates (Se^{6+}) and selenites (Se^{4+}) are water soluble and can be found in water. Sodium selenate is among the most mobile forms of selenium because of its high solubility and inability to adsorb to soil

particles. More insoluble forms, such as elemental selenium, are less mobile; therefore, there is less risk for exposure. Because of greater bioavailability, water-soluble selenium compounds are probably more toxic than elemental selenium by any route. Selenium is found in nature complexed with multiple compounds. Plants can contain organic selenium primarily in the form of the amino acids, selenomethionine and selenocysteine, along with the dimethyl selenides (ATSDR 2003). Most of selenium in tissues is present in two forms: Selenocystein (21st amino acid) and selenomethionine (supplied with diet). Several type of selenium-containing proteins occur in the body, but it appears that only one type, which contains selenocystein, is specific for the element and is regulated physiologically. These specific selenocystein-containing proteins are referred to as *selenoproteins*, including an important antioxidative enzyme glutathione peroxidase and thioredoxin reductase (Burtis and Ashwood 1999; Reilly 2006).

Selenium has various bioinorganic interactions, which may affect the toxicity of selenium or other metals. For example, selenium forms insoluble complexes with various metals, thus increasing their biliary excretion. The methylation of selenium can influence other methylation reactions and can alter arsenic metabolism and toxicity. The mechanisms for these interactions are only partially understood, but their occurrence influences the determination of safe and toxic levels of selenium for the general population (ATSDR 2003; Liu et al. 2008).

Biological Systems Affected

Selenium is notable for its actions in antioxidant systems through involvement in over 20 selenoproteins. The most extensively documented deficiency of selenium in humans is Keshan disease (selenium-low areas of China and Eastern Siberia), characterized by various degrees of juvenile cardiomegaly and cardiac decompensation, that primarily affects children aged 2-10 years old, and to some extent women of child-bearing age (Liu et al. 2008; Navarro-Alarcon and Cabrera-Vique 2008). Glutation peroxidase activity and hair and serum selenium concentration are 30-40% lower than control levels (Burtis and Ashwood 1999). Kashin-Beck disease is an osteoarthropathy found in in certain areas of China and the former Soviet Union where combined deficiency of selenium and iodine occurs with elevated exposure to mycotoxin and fulvic acids. Selenium deficiency is a major contributing factor in this disease (Liu et al. 2008; Navarro-Alarcon and Cabrera-Vique 2008). In this disease, oxidative damage attacks cartilage leading to deformation of the bone structure. Kashin–Beck disease affects children aged 5-13 years (Navarro-Alarcon and Cabrera-Vique 2008).

Other potential effects of selenium deficiency include immune dysfunction, and susceptibility to cancer or infectious/inflammatory diseases (Liu et al. 2008). In females selenium deficiency results in infertility, abortions and retention of placenta. Newborns from Se-deficient mothers suffer from muscular weakness (Burtis and Ashwood 1999).

Chronic selenium toxicity (selenosis) can occur with environmental exposure when the intake exceeds the excretory capacity and is characterized by hair loss, fingernails changes and brittleness, gastrointestinal disturbances, skin rash, garlic breath and abnormal functioning of the nervous system (incl. numbness, paralysis and occasional hemiplegia). Other related toxic effects are a disruption of endocrine function, synthesis of thyroid hormones and growth hormones, and an insulin-like growth factor metabolism. Some epidemiologic data have linked low blood selenium levels and increased cancer risk in various populations. Increasing selenium content of forage crops has been shown to be beneficial in reducing cancer risk (ATSDR 2003; Liu et al. 2008; Navarro-Alarcon and Cabrera-Vique 2008).

Possible Exposure Routes

Foodstuff that provides the largest amounts of selenium in the diet is seafood (0.4-1.5 µg/g fresh weight), meat (0.1-0.4 µg/g), milk products (0.1-0.3 µg/g) and grains (0.1-0.8 µg/g). Some plants, such as alfalfa, yeasts, white grain and cruciferous species (e.g. mustard, cabbage, broccoli and cauliflower), are efficient accumulators of selenium (Liu et al. 2008). Selenium food content is influenced by geographical location, seasonal changes, protein content and food processing. Selenium content of plants is directly affected by the levels in the soil in which are grown, and selenium content of animal products reflects the levels in their consumed diet (Navarro-Alarcon and Cabrera-Vique 2008). Foods mainly contain organoselenium compounds; inorganic compounds of the element (such as sodium selenite) only enter the diet as supplements or contaminants (Finley 2006). Combustion of coal and other fossil fuels are the primary sources of airborne selenium compounds. Occupational exposure comes from selenium refining operations, metal smelting and milling operations, incineration of rubber tires and municipal waste (Liu et al. 2008).

Absorption

Orally administered selenite, selenate and selenomethione are readily absorbed, often greater than 80%; whereas elemental selenium and selenides are virtually insoluble and poorly absorbed. Because of their insolubility, these forms may be regarded as an inert selenium sink (ATSDR 2003; Liu et al. 2008).

Selenium accumulates in many tissues, with the highest accumulation in the liver and kidney. Selenium is transferred through the placenta to the foetus, and it also appears in milk. Levels in milk are dependent on dietary intake. Selenium in red blood cells is associated with glutathione peroxidase and is about three times more concentrated than in plasma (ATSDR 2003; Liu et al. 2008).

Elimination

Selenium is primarily eliminated in urine and faeces, with each route contributing approximately 50% of the total output. However, the proportion excreted via each route seems dependent on several factors, including the level of exposure, the time since exposure and the level of exercise. Lactating women and subjects depleted of selenium have decreased excretion of selenium in the urine and faeces (ATSDR 2003).

Reference values

Studies examining general populations have reported whole blood selenium levels between 60 µg/l and 300 µg/l, mean 122 µg/l. Mean plasma levels were 111 µg/l and mean urine levels around 30 µg/l (ATSDR 2003; Liu et al. 2008). In the NHANES III study (1988-1994), the mean selenium serum concentration for all ages and both sexes was estimated to be 125 µg/l (Niskar et al. 2003).

Reference intervals for selenium in serum are 16-71 µg/l (<2 year old children), 40-103 µg/l (2-4 year old children), 55-134 µg/l (4-16 year olds) and 63-160 µg/l (adults). In urine, reference interval for adults is 7-160 µg/l. Toxic concentration as measured in urine is >400 µg/l (Burtis et al. 2012).

Specimens for analysis

Selenium can be detected in the blood, faeces, urine, hair and nails of exposed individuals. Field studies have used primarily blood or urine levels to indicate the degree of selenium exposure. In developed countries, hair selenium concentrations are not necessarily indicative of dietary exposure to environmental selenium. Users of therapeutic dandruff shampoos containing selenium sulphide may have high levels of selenium in their hair because the externally deposited selenium adsorbs to hair. However, due to minimal levels of dermal absorption of selenium from shampoo, blood and urine levels are not significantly affected by selenium-containing shampoos (ATSDR 2003).

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2.3.8 Manganese (Mn)

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Manganese is the 12th most abundant element which occurs naturally in the Earth’s crust (ATSDR 2012). It is also found in low levels in water air, soil, and food. Manganese may be released into the air by iron and steel production plants, power plants, and coke ovens (US EPA 2013). Manganese is an essential metal; however in cases of excessive exposure it adversely affects central nervous system.

Chemistry

Manganese is a naturally-occurring metal that, in pure form, is silver-colour with no taste or smell (US EPA 2007). Of 11 oxidation states available chemically, manganese is present in biological system only in +2 or +3 valence state (Burtis et al. 2012). Element in the environment is always found combined with other elements in a variety of minerals (Health Canada 2013). Some compounds are: manganese dioxide (MnO_2), manganese tetraoxide

(Mn_3O_4), manganese salts (chloride, sulphate, carbonate, and nitrate), manganese silicate, and potassium permanganate ($KMnO_4$) (US EPA 2013). Organic manganese compounds do not occur in nature but are manufactured for specific uses (ATSDR 2012; Health Canada 2013). Manganese compounds are solids, small dust particles can become suspended in air. Element may dissolve in water (US EPA 2013).

Manganese is an essential metal required for many metabolic and cellular functions and as a cofactor for a number of enzymatic reactions (Liu et al. 2008). It is constituent of metalloenzymes and enzyme activator (hydrolases, kinases, decarboxylases and transferases). Important Mn-containing enzymes are arginase, pyruvate carboxilase and Mn-superoxide dismutase (Burtis and Ashwood 1999).

Biological Systems Affected

Exposure to manganese and its compounds at normal background levels is unlikely to have any adverse effect on human health. Excessive exposure, predominantly reported in adults exposed occupationally via inhalation, has been associated with adverse central nervous system effects. “Manganism” refers to a set of symptoms associated with relatively high exposure and includes muscle stiffness, lack of coordination, tremors, difficulties with breathing or swallowing, and other neuromuscular problems. Manganism has symptoms similar to Parkinson’s Disease (US EPA 2007). Exposure to moderately high levels of manganese in air may result in subtle neurological effects such as poorer fine motor skills (Health Canada 2010). In children, higher concentrations in hair or blood have been associated with learning disabilities and neuromuscular effects (US EPA 2007).

Overt manganese deficiency has not been documented in humans eating natural diets. Various unrelated medical conditions have been observed to be associated with lowered serum or whole blood manganese. These include osteoporosis, diabetes mellitus, and epilepsy. However, the clinical relevance of such observations is uncertain (Burtis et al. 2012).

Possible Exposure Routes

Food is the main source of manganese for the general population (ATSDR 2012). Manganese is found in trace amounts in all plant and animal tissues. Grain products contribute approximately 37% of manganese intake in the adult diet (IOM 2001). Concentrations in food levels from approximately 0.03 mg/kg in milk to approximately 43.9 mg/kg in wheat flour (Health Canada 2010). The average daily intake from food levels from 1 to 5 mg/day (US EPA 2013). Occupational exposures to high concentrations of manganese may occur in a number of settings, including manganese dioxide mines and smelters. Significant exposure may also occur in factories making manganese steel alloys, electrical coils, batteries, glass, welding rods, and during production of potassium permanganate ($KMnO_4$) (Liu et al. 2008). People who work in that factories are most likely to be exposed through inhalation to higher than normal levels of manganese (US EPA 2013).

Absorption

Manganese and its compounds may enter the body by either inhalation, ingestion of water or food, or by dermal contact with manganese or products containing manganese. The main routes of absorption for manganese are the gastrointestinal tracts and respiratory (Health Canada 2010). Ingested manganese is absorbed from small intestine by mechanisms that may have common pathway to that of iron. Absorption is increased at low dietary intakes and

is decreased at higher intakes, with tracer studies suggesting absorption efficiencies of 2-15% (Burtis et al. 2012). Diets high in iron, calcium, magnesium, phosphates, oxalate and tannins from tea can reduce absorption of manganese. Absorbed manganese is transported in portal blood (Burtis et al. 2012). Inhaled manganese particles enter systemic circulation directly, making the manganese available for distribution to and accumulation in the body's tissues, including the brain (Health Canada 2010). Inside the plasma, manganese is largely bound to gamma globulin and albumin, with a small fraction bound to transferrin. Element concentrates in mitochondria, so that tissues rich in these organelles, like pancreas, liver, kidneys, bones, and intestines, have the highest concentrations of manganese. It quickly crosses the blood–brain barrier and accumulates in specific brain regions (Burtis and Ashwood 1999; Crossgrove and Zheng 2004; Liu et al. 2008) 25% of total body stores of manganese are in skeleton (Burtis and Ashwood 1999).

Elimination

Manganese is eliminated in the bile and reabsorbed in the intestine and further on, biliary excretion is the main excretory pathway, and once manganese reaches the intestines, a large fraction of the element is ultimately excreted in the faeces. Urinary excretion of manganese is low and has been found to be relatively resistant to small changes in dietary manganese intake (Davis 1992; Malecki et al. 1996; Liu et al. 2008; Health Canada 2010).

Reference values

The normal range of manganese concentrations according to the ATSDR (2000) is approximately 4 to 14 µg/l in whole blood, 0.15 to 2.65 µg/l in serum, and 0.97 to 1.07 µg/l in urine (Health Canada 2010). Reference interval for serum manganese is 0.5-1.3 µg/l, for whole blood 5-15 µg/l and in urine 0.5-9.8 µg/l (Burtis et al. 2012).

Specimens for analysis

The manganese can be measured in blood, urine, hair, or faeces (US EPA 2013). The concentrations in blood and urine can be used to evaluate exposure to manganese and the concentration in whole blood is preferred rather than in plasma or serum since slight haemolysis of samples can have a significant effect on plasma or serum manganese concentrations (IOM 2001). Concentrations in blood tend to show the overall body burden, while concentrations in urine are more usually used to measure levels following an acute exposure as it is only responsive to significant fluctuations in manganese intake (IOM 2001). Excess manganese is usually removed from the body within a few days, making it difficult to measure past exposure to manganese (Health Canada 2010; US EPA 2013).

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2.3.9 Chromium (Cr)

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Chromium is a naturally appearing element found in rocks as part of the mineral crocoite (lead chromate), soil, plants and animals in volcanic dust and gases. Hexavalent chromium (Cr^{6+}) is a by-product of various industrial processes and is a human carcinogen and produces a variety of toxic effects (ATSDR 2000; Liu et al. 2008). Trivalent chromium (Cr^{3+}) is an essential trace element and is the most stable form in biological systems. Chromium is commercially available as a part of many multivitamins or alone in tablet and capsule forms (Tulasi and Rao 2014).

Chemistry

Chromium is a transition metal and occurs in the environment primarily in two valence states, trivalent Cr^{3+} and hexavalent chromium Cr^{6+}, each having markedly different properties. Trivalent Cr^{3+} has no redox or acid-based properties, hexavalent Cr^{6+} is a strong oxidant that can cause tissue damage, although toxic Cr^{6+} is normally reduced to Cr^{3+} during contact with foodstuffs and gastric contents. The Cr^{3+} compounds are sparingly soluble in water and can be found in water bodies as soluble Cr^{3+} complexes, while the Cr^{6+} compounds are easily soluble in water (US EPA 2000; ATSDR 2012; Burtis et al. 2012).

Biological Systems Affected

Chromium is toxic to kidney, liver, nervous system and blood (Soetan et al. 2010). Toxic effects were attributed principally to airborne Cr^{6+} compounds in industrial settings. It is a recognized carcinogen, and industrial exposure to fumes and dusts containing this metal is associated with increased incidence of lung cancer, dermatitis, and skin ulcers. Respiratory tract is the major target organ of Cr^{6+} toxicity, it can cause chronic ulceration and perforation of the nasal septum, as well as chronic ulceration of other skin surfaces (ATSDR 2000). Cr^{6+} raises allergic contact dermatitis among earlier sensitized individuals, which is a type-IV allergic reaction inducing skin erythema, pruritus, oedema, papule, and scars. The prevalence of chromium sensitivity is less than 1% of the general population. Occupational exposure to chromium can be a reason for asthma. Ingestion of high doses of Cr^{6+} compounds can cause acute renal failure characterized by proteinuria, haematuria, and anuria, but kidney damage from lower-level chronic exposure is equivocal (ATSDR 2000; Liu et al. 2008).

Cr^{3+} is an essential trace element in humans; its species are relatively nontoxic in part because of their poor intestinal absorption and rapid excretion in urine. Only a few cases of clinical chromium deficiency have been reported, all patients having similar presentations, with previously stable patients developing insulin-resistant glucose intolerance, weight loss, and in some cases neurologic deficits (Burtis et al. 2012). A role for chromium in lipid metabolism and chromium deficiency in the development of atherosclerosis is evident from animal and human studies (ATSDR 2000). Chromium depletion has long been thought to be associated with increased cardiovascular risk, however, additional large-scale studies are necessary to confirm the effects of chromium on risk factors for cardiovascular disease (Burtis et al. 2012).

Possible Exposure Routes

The level of chromium in air and water is generally low, however contaminated well water may contain Cr^{6+}. Environmental health risks arise from soil contamination by Cr^{6+} waste disposal sites from leather tanning and dyestuff industries. The average daily intake from air, water, and food is estimated from 0.2 to 0.4 µg, 2.0 µg, and 60 µg, respectively. In the US population, dietary intake for adults was estimated to vary from 20 to 30 µg/day. Processed meats and wholegrain products are the best source of chromium; relatively good sources are also green beans, broccoli and some spices. Levels in food may vary also because of contamination caused by contact with stainless steel during food processing, storage and cooking. Dermal exposure to chromium can occur during the use of consumer products that contain chromium, such as wood treated with copper dichromate or leather tanned with chromic sulphate, but just a small amount of it enters the human body (Burtis and Ashwood 1999; ATSDR 2000, 2012; US EPA 2000; Burtis et al. 2012).

The occupational exposure to chromium may be two orders of magnitude higher than exposure to the general population. It can appear from chromate production, stainless-steel production, chrome plating, and working in tanning industries. Also people who live in the neighbourhood of chromium waste disposal sites or chromium manufacturing and processing plants and those who smoke tobacco have a greater probability of elevated chromium exposure than the general population. These exposures are principally mixed Cr^{6+} and Cr^{3+} (US EPA 2000; ATSDR 2012; Burtis et al. 2012).

Absorption

Intestinal absorption of Cr^{3+} is low, ranging from 0.4 to 2.5%. Absorption of Cr^{6+} compounds is higher (2-10%). Absorption is increased marginally by ascorbic acid, amino acids, oxalate and other dietary factors. Cr^{6+} promptly crosses cell membranes on carriers for sulphate and phosphate, whereas the less insoluble Cr^{3+} compounds are absorbed via passive diffusion and phagocytosis. Absorption of inhaled chromium compounds takes place in the lung through transfer across alveolar cell membranes. Dermal absorption is dependent on the chemical form, the vehicle, and the integrity of the skin. Once in the blood, Cr^{6+} is taken up by erythrocytes, whereas Cr^{3+} is only loosely associated with erythrocytes. After absorption, Cr^{3+} binds to β-globulin fractions of serum proteins, specifically to transferrin with an affinity similar to that of iron. Chromium concentrates in human liver, spleen, other soft tissues and bone. The highest levels are in liver, spleen, and kidney. Particles containing chromium may be retained in the lungs for years (Burtis and Ashwood 1999; Liu et al. 2008; Burtis et al. 2012).

Elimination

In the human body Cr^{6+} is changed to Cr^{3+}. Absorbed chromium is excreted normally in urine; the half-life for excretion of chromium is about 35-40 hours (ATSDR 2000). Most of the chromium leaves the body in the urine within a week, although some can remain in cells for several years or longer (ATSDR 2000; Liu et al. 2008). Paradoxically, urine output appears to be relatively increased at low dietary amounts. Faecal output mainly consists of unabsorbed dietary chromium (Burtis et al. 2012).

Reference values

Very low values are now considered as normal for serum 0.1-2 µg/l and for urine <0.2 µg/l. Detection of deficiency by direct analysis is thus difficult. Reference interval for whole blood is 0.7-28.0 µg/l, in serum 0.1-0.2, in red blood cells 20-36 µg/l, and in urine 0.1-2.0 µg/day (Burtis et al. 2012).

Specimens for analysis

Chromium can be measured in the hair, urine, serum, red blood cells, and whole blood. Because Cr^{3+} is an essential nutrient, low levels of chromium are normally found in body tissues and urine. Estimation of chromium exposure is useful for people exposed to high levels, which are indicated by chromium in urine and red blood cells. Since the body changes Cr^{6+} to Cr^{3+}, the form of chromium that humans were exposed to cannot be determined from levels in urine. Chromium levels in the red blood cells are indicative for recent exposure (up to 120 days) to Cr^{6+} (ATSDR 2012).

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2.3.10 Iron (Fe)

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Iron is an abundant transition metal. One of the first sources of iron was from fallen meteorites and the name may derive from the Ethruscan word aisar which means “the gods” (Liu et al. 2008). Iron is a mineral which is naturally present in many foods, added to some food products, and available as a dietary supplement (Ross et al. 2014).

Chemistry

In biological systems, iron mostly exists as the ferrous +2 and ferric +3 forms (Liu et al. 2008). It is an essential metal in a number of biochemical pathways required for neuronal function that include mitochondrial enzymes and various neurotransmitters (Burtis and Ashwood 1999). It is also essential for erythropoiesis and an important component of haemoglobin (2.5 g Fe; 0.34% by weight), myoglobin (content of Fe 130 mg), haeme enzymes, metalloflavoprotein enzymes. Iron is necessary for growth, development, normal cellular functioning, and synthesis of some hormones and connective tissue (Ross et al. 2012; NIH 2014). Transport from one organ to another is accomplished by apotransferin (Burtis and Ashwood 1999).

Biological Systems Affected

Medical considerations are significant in terms of iron deficiency, accidental acute exposures, and chronic overload because of idiopathic hemochromatosis or as a consequence of excess dietary iron or frequent blood transfusions (IOM 2001; Papanikolaou and Pantopoulos 2005; Liu et al. 2008).

Iron deficiency is one of the most prevalent disorders of humans, particularly in children, young women and old people (Burtis et al. 2012). The primary causes of deficiency include low intake of bioavailable iron, increased element requirements as a result of rapid growth, pregnancy, menstruation, excess blood loss and impaired absorption of iron. Deficiency can exist with or without anaemia. Some functional changes may occur in the absence of anaemia, but the most functional deficits appear to occur with the development of anaemia. Even mild and moderate forms of iron deficiency anaemia can be associated with functional impairments affecting cognitive development, immunity mechanisms, and work capacity. Iron deficiency during pregnancy is associated with a variety of adverse outcomes for both mother and infant, including increased risk of sepsis, maternal mortality, perinatal mortality,

and low birth weight. Iron deficiency and anaemia also reduce learning ability and are associated with increased rates of morbidity (Abbaspour et al. 2014).

Moreover, low iron cause higher uptake of lead and cadmium, it affects the uptake of other possible toxic elements (Burtis and Ashwood 1999).

The most common cause of acute toxicity is from accidental ingestion of iron containing dietary supplements and it most usually occurs in children. Alarming toxicity occurs after the ingestion of more than 0.5 g of iron or 2.5 g of ferrous sulphate and toxicity occurs about 1–6 hours after ingestion. Symptoms contain abdominal pain, diarrhoea, and vomiting. Especially concern is pallor or cyanosis, metabolic acidosis, and cardiac collapse. Death can occur in severely poisoned children within 24 hours. Inhalation of iron oxide fumes or dust may cause pneumoconiosis in occupational settings (Doherty et al. 2004).

Chronic iron toxicity from iron overload in adults is a relatively usual problem. Raising body iron may play a role in the development of cardiovascular disease and it is suspected that iron may act as a catalyst to produce free radical damage resulting in artherosclerosis and ischemic heart disease (Liu et al. 2008). Inhalation of iron oxide fumes or dust by workers in hematic mines (mainly Fe_2O_3), steel workers, and welders can produce siderosis (non-fibrotic), and in some cases silicosis (fibrotic) in the lung, with increases in total body iron (Doherty et al. 2004). Liver iron overload from hereditary hemochromatosis is associated with a high risk for hepatocellular carcinoma, also with other malignancies (Papanikolaou and Pantopoulos 2005; Liu et al. 2008).

Possible Exposure Routes

Exposure routes are through ingestion from food and inhalation of iron oxide fume or dust (Liu et al. 2008). Chronic transfusion is usually the sole cause of iron overload (Burtis et al. 2012).

Absorption

The fraction of iron absorbed from the amount ingested is typically low, but may range from 5 to 35% depending on circumstances and type of iron. Absorption occurs by the enterocytes by divalent metal transporter 1, a member of the solute carrier group of membrane transport proteins. This takes place predominantly in the duodenum and upper jejunum. It is then transferred across the duodenal mucosa into the blood (controlled by ferroportin) where it is transported by transferrin to the cells or the bone marrow for erythropoiesis. The physical state of iron entering the duodenum greatly influences its absorption. A number of dietary factors influence iron absorption. Ascorbate and citrate increase iron uptake in part by acting as weak chelators to help to solubilize the metal in the duodenum (Abbaspour et al. 2014).

In case of autosomal recessive disorder (Hereditary hemochromatosis) there is abnormal absorption of iron from the intestinal tract (Liu et al. 2008).

Elimination

Apart from iron losses due to menstruation, other bleeding or pregnancy, iron is highly conserved and not readily lost from the body. There are some obligatory loss of iron from the body that results from the physiologic exfoliation of cells from epithelial surfaces, including the skin, genitourinary tract, and gastrointestinal tract. However, these losses are estimated to be very limited (≈1 mg/day). Iron losses through bleeding can be substantial and

excessive menstrual blood loss is the most common cause of iron deficiency in women (Abbaspour et al. 2014).

Desferrioxamine is the chelator of choice for the treatment of acute iron intoxication and chronic iron overload and also iron chelates have been suggested for the treatment of cancers with iron overload (Liu et al. 2008).

Reference values

Reference intervals for serum iron differ by as much as 35% between commercial methods. Therefore, a generic reference interval is not valid. From a practical standpoint, if an automated commercial method is used, a laboratory should independently define its own reference interval (Burtis et al. 2012).

Specimens for analysis

Iron can be measured in blood, urine, or sweat; although these last two do not appear to be very important (Liu et al. 2008).

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2.4 Volatile Organic Compounds (VOCs)

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Volatile organic compounds (VOCs) are a large group of chemicals with a high relevance for indoor and outdoor air quality (Sarigiannis et al. 2011; US EPA 2012a). Some of them have short- or long-term effects, some are carcinogenic, others cause non-carcinogenic health effects (Sarigiannis et al. 2011; US EPA 2012b). Mixtures of VOCs are also health relevant what was examined in PBPK models, as summarized by Sarigiannis and Hansen (2012). The results were dose-response relationships based on health effects due to the internal dose of the mixture instead of the environmental concentration.

The VOCs benzene, toluene and xylene are summarized as BTX. All of them are compounds of petrol (WHO 2011). Recently, a health risk assessment of BTX in service stations was conducted resulting in an enhanced health risk (Edokpolo et al. 2014). Toluene and xylene are the most widely used solvents (IEH 2008). Benzene has a high relevance because it is a serious health hazard in environmental and occupational medicine with comprehensive carcinogenic and non-carcinogenic health effects (Angerer et al. 2007; Bahadar et al. 2014). The three mentioned VOCs are described in detail in the subchapters 2.4.1, 2.4.2 and 2.4.3, while VOCs in general are introductory described below.

Chemistry

Organic compounds are chemical compounds that contain carbon. Excluded from this definition are carbon mono-/dioxide, carbonic acid, metallic carbides/carbonates and ammonium carbonate (US EPA 2012a). VOCs are defined as “organic chemical compounds whose composition makes it possible for them to evaporate under normal indoor atmospheric conditions of temperature and pressure” (US EPA 2012a). The EU defines VOCs in accordance to their boiling point (lower or equal to 250°C under an atmospheric pressure of 101.3 kilopascal, kPa) (US EPA 2012a). The WHO distinguishes between very volatile organic compounds (VVOCs; boiling point: 0-100°C; e.g. propane), VOCs (boiling point: 50-260°C; e.g. formaldehyde) and semi volatile organic compounds (SVOCs; boiling point: 240-400°C; e.g. pesticides) (WHO 1989; US EPA 2012a).

Several substances belong to the group of VOCs. Exemplary substance groups are alkanes, cycloalkanes, isoalkanes, aromatics, chlorinated hydrocarbons, terpenes, alcohols, carbonyls, aldehydes, phenols and glycols (Gratza 2001). More general, “especially aromatic, halogenated and aliphatic hydrocarbons” are VOCs (Angerer et al. 2007). The VOCs benzene, toluene, xylene and styrene – summarized as BTXS – as well as terpenes are most commonly found (Sarigiannis et al. 2011).

VOCs evaporate under normal atmospheric conditions (US EPA 2012a). VOCs emit as gases from solids or liquids (US EPA 2012b).

Biological Systems Affected

While some VOCs are highly toxic, others are not known to cause health effects (US EPA 2012b). VOCs are the cause of several unspecific health effects like headache or fatigue (Angerer et al. 2007). Furthermore, “conjunctival irritation, nose and throat discomfort, allergic skin reaction, dyspnoea, declines in serum cholinesterase levels, nausea, emesis, epistaxis” and dizziness are typical symptoms of VOC exposures (US EPA 2012b). VOCs are assumed to cause typical symptoms of the sick-building syndrome (e.g. dry mucous

membranes) (Nowak 2010). Damages to liver, kidney or the central nervous system are possible (US EPA 2012b).

Some VOCs cause cancers in animals (e.g. methylene chloride, perchloroethylene) and humans (e.g. benzene, see chapter 2.4.1) (US EPA 2012b).

In some cases, the metabolites are more toxic than the VOCs themselves. Examples are glycol ethers (a component of several consumer products like water based varnishes) and their metabolite carboxylic acids (Angerer et al. 2007).

Possible Exposure Routes

VOCs are air pollutants. The exposure occurs by breathing contaminated air (NIH 2012). The concentration of VOCs is mostly (up to ten times) higher indoor in comparison to outdoor. Thousands of products emit VOCs (US EPA 2012b). Possible sources in indoor air are building materials, furnishings, detergents and especially tobacco smoke (Nowak 2010). Staying in a newly renovated residence can lead to high VOC exposures (Angerer et al. 2007). High air pollution due to VOCs can persist long after using the emitting product (US EPA 2012b).

In outdoor air, VOCs are emitted due to production processes or the use of products and materials containing VOCs (US EPA 2012a). Other sources are burning fuel like gasoline, wood, coal or natural gas (NIH 2012). Several VOCs are components of automotive exhaust and industrial emissions (Sexton et al. 2004).

In the non-occupational setting children are at higher risk in comparison to adults, because they are more susceptible and might have a higher exposure due to a greater intake per unit body weight (Sexton et al. 2004).

Absorption

VOC absorption is possible from “air, water, soil, dust, food, beverages and consumer products” (Sexton et al. 2004, p. 347). In the liver, VOCs are transformed. Some VOCs are converted to water soluble non-volatile compounds which are easily excretable (de Lacy Costello et al. 2014).

Elimination

The biggest part of the internal VOC dose is eliminated within hours, but another part takes much longer time for excretion. Repeated exposures may also lead to a bioaccumulation of VOCs. The half-life of VOCs in blood, muscle tissues and adipose tissues takes hours, days and months, respectively (Sexton et al. 2004).

Specimens for analysis

A recent review identified 1840 VOCs which can be detected in breath, salvia, blood, milk, skin secretions, urine and faeces. Less than one percent, namely “acetaldehyde, 2-propanone (acetone), benzaldehyde, 1-butanol, 2-butanone, hexanal, heptanal, octanal, pentanol, benzene, styrene and toluene” are measurable in all mentioned matrices (de Lacy Costello et al. 2014, p. 4). By contrast, formaldehyde was just measured in exhaled breath and skin secretions; furan in urine, exhaled breath and milk. It is notable, that VOCs are more often detected in faeces than in urine. Although it is assumed that more compounds do exist in urine, they might be available in very low (not detectable) concentrations, while the concentrations in faeces is higher (de Lacy Costello et al. 2014).

The previous exposure to VOCs can be determined examining exhaled breath. This is called “volatilome” in the framework of the exposome (Amann et al. 2014). Breath analysis has advantages because of the non-invasive procedure, the unlimited access and the possibility for real-time measurement (de Lacy Costello et al. 2014).

Metabolites of VOCs can be measured in urine, while aromatic- and halogenated-hydroxycarbons themselves are measurable in blood (Angerer et al. 2007). Blood samples allow a sensitive measurement of VOCs. However, metabolites of VOCs have a longer half-life than VOCs themselves, why their measurement in urine samples has advantages. An example is carboxylic acids, the metabolite of glycol ethers (Angerer et al. 2007). Table 7 lists exemplarily some VOCs and their metabolites measurable in urine.

Table 7: Exemplary biomarkers of volatile organic compounds (VOCs; for benzene, toluene and xylene see chapters 2.4.1, 2.4.2, 2.4.3)

VOC	**Biomarker of exposure / metabolite analysable in urine**	**Reference**
Acrylamide	N-Acetyl-S-(2-carbamoylethyl)-L-cysteine (AAMA), N-Acetyl-S-(2-carbamoyl-2-hydroxyethyl)-L-cysteine (GAMA)	(CDC 2012, 2014)
Cyanide	2-Aminothiazoline-4-carboxylic acid (ATCA)	
Ethylbenzene	Phenylglyoxylic acid*	(CDC 2014)
	Mandelic-acid (MA)	(Angerer et al. 2007)
Glycol ethers	Carboxylic acids (e.g. phenoxic acetic, methoxypropionic acid)	
	2-Methoxy acetic acid	(HBM-UBA 2014)
Styrene	Phenylglyoxylic acid*	(CDC 2014)
	MA	(Angerer et al. 2007)
Phenoxyethanol	Phenylglyoxylic acid (PGA) (HBM-UBA 2014)	
Methoxypropanol	Phenoxy acetic acid, Methoxy propionic acid	
Further biomarkers of VOC exposure are listed in CDC’s Laboratory Procedure Manual (CDC 2012) * Metabolite of ethylbenzene and styrene (CDC 2014)		

Some studies has even used “glass bleads rolled on to the skin followed by heat to desorb the VOCs”, as summarized by de Lacy Costello et al. (2014).

There is a research need to determine when VOCs are detectable in some but not in other matrices. It is assumed, that compounds detectable in blood but not in urine were transformed by the kidneys or bladder (de Lacy Costello et al. 2014).

Internal VOC concentrations are elevated in smokers in comparison to non-smokers, what was shown by several studies. The most non-occupationally exposed people have VOC concentrations in the range of parts-per-trillion to part-per-billion (Sexton et al. 2004). Table 8 summarizes latest reference values for some VOCs.

Table 8: Reference values of some volatile organic compounds (VOCs)

VOC	Biomarker of exposure in specimen	Reference values	Population		Reference
Acrylamide	N-Acetyl-S-(2-carbamoyl-2-hydroxyethyl)-L-cysteine in urine	P95: 138 µg/l; P95: 78.3 µg/g creatinine	US population, 2011/2012	Smokers (n= 889)	NHANES (CDC 2014)
		P95: 41.5 µg/l; P95: 37.3 µg/g creatinine		Non-smokers (n= 1307-1308)	
	N-Acetyl-S-(2-carbamoylethyl)-L-cysteine in urine	P95: 507 µg/l; P95: 337 µg/g creatinine		Smokers (n= 889)	
		P95: 157 µg/l; P95: 118 µg/g creatinine		Non-smokers (n= 1307-1308)	
Cyanide	2-Aminothiazoline-4-carboxylic acid in urine	P95: 608 µg/l; P95: 514 µg/g creatinine		Smokers (n= 889)	
		P95: 433 µg/l; P95: 418 µg/g creatinine		Non-smokers (n= 1307-1308)	
Ethylbenzene	Ethylbenzene in blood	P95: 0.140 ng/ml	US population, 2005/2006, n= 3119		
	Ethylbenzene in urine	P95: 75 to 289 ng/l^{-1}	Primary school children, Italy (cities: Poggibonsi, Treviglio, Valenza, n= 107-139)		(Minoia et al. 1996)
	Phenylglyoxylic acid* in urine	P95: 1140 µg/l; P95: 782 µg/g creatinine	US population, 2011/ 2012, smokers (n= 889)		NHANES (CDC 2014)
		P95: 566 µg/l; P95: 394 µg/g creatinine	US population, 2011/ 2012, non-smokers (n= 1308, 1307)		
Glycol ethers	MAA in urine	P95: 0,3 mg MAA/l	General population, Germany		(HBM-UBA 2014)
PCP	PCP in blood	GM: 0.38-0.63 µg/l	Students in Germany (cities: Greifswald, Halle/ Saale, Münster, Ulm, n= 104-128), 2010		(UBA 2014)
	PCP in 24h urine collection	GM: 0.05-0.09 µg/l			
	PCP in plasma	Mean: <5 µg/l	Not exposed population		(Scholz 2001)
	PCP in serum	P95: 25 µg/l			
	PCP in urine	P95: <10 µ6/l			
PER	PER in blood	P95: <1 µg/l	General population, Germany		(Gratza and Kevekordes 2001)
Styrene	Mandelic acid in urine	P95: 1200 µg/l; P95: 882 µg/g creatinine	US population, 2011/2012	Smokers (n= 889)	NHANES (CDC 2014)
		P95: 465 µg/l; P95: 361 µg/g creatinine		Non-smokers (n= 1308, 1307)	
	N-Acetyl-S-(phenyl-2-hydroxyethyl)-L-cysteine in urine	P95: 6.26 µg/l; P95: 4.64 µg/g creatinine		Smokers (n= 889)	
		P95: 1.87 µg/l; P95: 2.61 µg/g creatinine		Non-smokers (n= 1308, 1307)	
	Phenylglyoxylic acid* in urine	P95: 1140 µg/l; P95: 782 µg/g creatinine		Smokers (n= 889)	
		P95: 566 µg/l; P95: 394 µg/g creatinine		Non-smokers (n= 1308, 1307)	
	Styrene in blood	P95: 0.135 ng/ml	US population, 2005/2006 (n= 2808)		NHANES (CDC 2014)

Abbreviations: GM (geometric mean), MAA (2-Methoxy acetic acid), P95 (95th percentile), PCP

(Pentachlorophenol), PER (Perchlorethylene), US (United States) * Metabolite of ethylbenzene and styrene (CDC 2014)

Threshold values (especially HBM values and BEs) are presented in Table 9 for some VOCs. A more comprehensive list of BEs and reference values (from NHANES) for VOCs are contained in Aylward et al. (2013).

Table 9: Threshold values for some volatile organic compounds (VOCs)

VOC	**Biomarker in specimen**	**HBM values (reference)**	**BE (reference)**	**Other threshold values (reference)**
2-Ethoxy-ethanol*	Ethoxyacetic acid in urine	/	/	BAT: 50 mg/l (DFG 2014)
Ethylbenzene	Ethylbenzene in whole blood	/	BE: 1 µg/l (Aylward et al. 2010, 2013)	/
2-Butoxy-ethanol**	Butoxyacetic acid in urine	/	/	BAT: 100 mg/l (DFG 2014); BAT: 200 mg/l (after hydrolysis) (DFG 2014)
Glycol ethers	MAA in urine	HBM I: 0.4 mg MAA/g creatinine, HBM II: 1.6 mg MAA/g creatinine (HBM-UBA 2014)	/	/
PCP	PCP in urine	HBM I: 25 µg/l; 20 µg/g creatinine HBM II: 40 µg/l; 30 µg/g creatinine (HBM-UBA 1997)	/	/ EKA (after hydrolysis) (DFG 2014), see Table 10
	PCP in serum	HBM I: 40 µg/l HBM II: 70 µg/l (HBM-UBA 1997)		/
	PCP in plasma/ serum	/		EKA (DFG 2014), see Table 10
Styrene	Styrene in whole blood	/	BE: 3 µg/l (Aylward et al. 2010, 2013)	/
	Styrene in urine	/	/	BAT: 600 mg/g creatinine (DFG 2014)

Abbreviations: BAT (Biological Tolerance Value; see Glossary for further descriptions), EKA (exposure equivalents for carcinogenic substances), HBM values (human biomonitoring values [HBM I and HBM II] of the Human Biomonitoring Commission of the German Federal Environment Agency; see Glossary for further descriptions), MAA (2-Methoxy acetic acid), PCP (Pentachlorophenol)
* Ethylene glycol monoethyl ether
** Ethylene glycol monobutyl ether

Table 10: EKA (exposure equivalents for carcinogenic substances) for pentachlorphenol (adapted from DFG 2014, p. 245)

Air pentachlorphenol mg/m^3	Sampling time: not fixed	
	Urine pentachlorphenol (after hydrolysis) µg/l	Serum/plasma pentachlorphenol µg/l
0.001	6*	17
0.005	300	1000
0.10	600	1700
*value obtained by extrapolation		

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2.4.1 Benzene (C_6H_6)

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Chemistry

The chemical benzene occurs naturally and is emitted into the environment as well by human activity (WHO-IPCS 1993). Benzene is a highly volatile organic compound (WHO 2000) and belongs to the group of the aromatic hydrocarbons. It consists of six carbon and six hydrogen atoms (chemical formula: C_6H_6, see Figure 16). At 20°C room temperature benzene is liquid but vaporises at 80.1°C. It is colourless and has a characteristic aromatic smell, and it is easily flammable (WHO-IPCS 1993). Benzene is not persistent in water or soil but transported by air (WHO 2010).

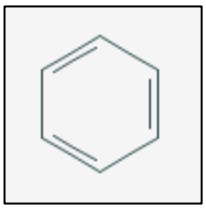

Figure 16: Chemical formula of benzene (NCBI 2014)

Biological Systems Affected

Benzene crosses the placenta (WHO-IPCS 1993). It damages the bone marrow and causes aplastic anaemia and pancytopenia (Nowak 2010).

Benzene is “carcinogenic to humans (Group 1)” (see Glossary) (IARC 2012, p. 285). Acute myeloid leukaemia (AML) is a verified health outcome of benzene exposure. Benzene can cause other leukaemia's, lymphomas and myelomas (acute lymphocytic leukaemia (ALL), chronic lymphocytic leukaemia (CLL), multiple myeloma (MM), and Non-Hodgkin Lymphoma (NHL)), but the evidence is limited. Benzene is associated with childhood leukaemia. The evidence of multiple genotoxic effects (chromosomal changes) due to benzene is strong (IARC 2012).

Several “non-cancerous health effects with functional aberration of vital systems in the body like reproductive, immune, nervous, endocrine, cardiovascular, and respiratory” are associated with benzene. Additionally, there is a need to follow up interactions with “endocrine disturbances with particular reference to non-allergic asthma, diabetes, breast and lung cancers” (Bahadar et al. 2014. p. 83).

Acute toxic effects of benzene can follow high exposures like in the occupational setting (WHO 2010). Acute symptoms are fatigue, weakness, sleeplessness, vertigo, nausea, headaches, paleness, loss of weight, eyes flicker, palpitations during physical activities, mucosal bleeding and enforced menstrual bleeding. Skin contact leads to degreasing and if longer lasting and repetitive to a kind of dry dermatitis (Böse-O'Reilly 2001).

Some of the health effects are caused by the metabolites of benzene (ATSDR 2007).

Possible Exposure Routes

Benzene emits from natural and anthropogenic sources (WHO-IPCS 1993). It is an organic air pollutant, so the main exposure of the general population is due to inhalation (WHO 2010). Benzene is a natural part of petroleum. Using petrol releases benzene what is the main pathway for environmental contamination (WHO-IPCS 1993). Especially in regions with poor monitorings of the content of benzene in petrochemicals, chronic diseases have become a health burden of major concern (Bahadar et al. 2014).

Examples of further anthropogenic benzene emitting processes are coking of coal or producing other aromatic compounds like xylene and toluene (see chapters 2.4.2 and 2.4.3). It is used as industrial solvent which can result in high benzene air concentrations in the occupational and environmental setting (WHO-IPCS 1993).

In ambient and indoor air benzene can be found (WHO-IPCS 1993). Benzene is an important chemical for indoor air quality while it is measurable in almost all indoors (Sarigiannis et al. 2011). Paints, adhesives and other interior materials can enhance the benzene concentration but the most important factor of indoor benzene emission is cigarette smoke (WHO-IPCS 1993). Accumulation of benzene indoors is an important exposure pathway of the general population due to the long everyday duration staying in internal spaces like office, home or in vehicles (WHO 2010). The indoor concentration of benzene in Europe is the highest in the South. A reason could be the higher temperatures and associated higher volatilizations (Sarigiannis et al. 2011).

There is a small exposure pathway due benzene contamination of food and/or water (WHO-IPCS 1993).

Absorption

Inhalation is the primary route of benzene absorption while dermal and oral exposure is of lesser importance. Around 50% is inhalative absorbed by an exposure to around 160 to 320 mg/m^3 (WHO-IPCS 1993).

In the biological system, benzene enters the bloodstream, travels throughout the body and can briefly be stored in fat and bone marrow (ATSDR 2007). VOCs are mostly converted to its metabolites in the liver to enter the bloodstream (de Lacy Costello et al. 2014).

Elimination

The biggest part of not metabolized benzene is eliminated by exhalation (US EPA 2002). The conversion of benzene to its metabolites occurs in liver and bone marrow (ATSDR 2007). Metabolic products following benzene exposure are especially excreted in urine (WHO-IPCS 1993) within 2 days after exposure (ATSDR 2007).

Specimens for analysis

Benzene has been detected in faeces, urine, exhaled breath, skin secretion, breast milk, blood and saliva (de Lacy Costello et al. 2014). The examination of bone marrow can also be used to detect benzene exposure (and its health effects) (ATSDR 2007).

The detection of benzene in blood is a sensitive and specific biomarker with a high relevance to the concentration in target tissues. Due to its short half-life (Hays et al. 2012), especially recent exposures can be measured in blood. However, blood analysis is not useful if the exposure with benzene was low (ATSDR 2007). The detection of benzene in blood is

suitable to determine the exposure of the general population as well as industrial exposures (Arnold et al. 2013). Biomarkers like DNA and protein adducts in blood are no suitable to detect benzene exposures (Arnold et al. 2013).

Benzene can be measured in urine what is a specific biomarker but not directly relevant to the concentration in target tissues (Hays et al. 2012). Benzene in urine is suitable to detect industrial exposures and exposures of the general population (Arnold et al. 2013). Metabolites of benzene are also measurable in urine (Angerer et al. 2007; ATSDR 2007). Urinary phenol levels were measured historically but the procedure includes several limitations (WHO 2010). It is only useful shortly after a benzene exposure of at least 10 ppm (parts per million) in air. Moreover, phenol is non-specific to benzene exposure (Hays et al. 2012) while the concentration in urine can be increased due to other factors like diet or due to the exposure to other aromatic compounds (ATSDR 2007). Better indicators to identify benzene exposures are the metabolites muconic acid and S-phenyl mercapturic acid (S-PMA) in urine (ATSDR 2007), however, trans-, trans-muconic acid (ttMA) (as well as the metabolite hydroquinone) is also non-specific to benzene exposures (Hays et al. 2012). S-PMA in urine is the most specific metabolite of benzene and useful to determine exposures of the general and occupational population. Other biomarkers (ttMA, phenol, hydroquinone, catechol) have other sources than benzene (Arnold et al. 2013). S-PMA has a half-life of around 9 to 13 hours and can be used as sensitive biomarker for high and low benzene exposures (IEH 2008) of the general and occupational concentration (Arnold et al. 2013). The correlation with environmental benzene exposures is well (IEH 2008).

The metabolites phenol, catechol, and hydroquinone are also found in bone marrow (WHO-IPCS 1993).

Benzene in exhaled air is a specific biomarker, too (Hays et al. 2012). It can be used to determine industrial exposures and exposures of the general population (Arnold et al. 2013).

Reference values

Latest reference values (particularly P95) of benzene and the most specific metabolite S-PMA (Arnold et al. 2013, see above) as determined in big surveys or summarized in reviews are given in Table 11. Other small surveys have focused on benzene (and other VOCs) and metabolites and present reference values based on small sample sizes (n= <200), specific subgroups (e.g., school children, blood donors) or which are not up to date (>20 years old) (Brugnone et al. 1989, 1992; Mannino et al. 1995; Minoia et al. 1996; Perbellini et al. 2003; Mochalski et al. 2013). These values are not presented in Table 11 unless there are no values available which do fulfil the criteria mentioned in the first sentence.

Reference values of other metabolites than S-PMA, which are less appropriate to detect benzene exposures, are available but not presented here. See Arnold et al. (2013) (catechol, hydroquinone, phenol) and CDC (2014) (N-Acetyl-S-(phenyl)-L-cysteine, ttMA) for details.

Table 11: Recent reference values for benzene and S-PMA

Biomarker in specimen	**Reference value, population, year, sample size (reference)**
Benzene in exhaled air	Range of central tendency[1]: 3-32 ng/l, non-smoking general populations, 14-73 ng/l, smokers, range of several studies (Arnold et al. 2013)
Benzene in blood	P95: 0.310 ng/ml, US population (NHANES), 2005/2006, n= 3091 (CDC 2014)
	Range of central tendency[1]: 50-200 ng/l, non-smoking general population, 100-500 ng/l, smoking general population, range of several studies (Arnold et al. 2013)
Benzene in urine	P95: 311.5 ng/l, non-smoking, non-occupationally exposed subjects, random sample of the general population, Italy, n= 86 (Campagna et al. 2014)
	Range of central tendency[1]: 0.10-0.25 µg/l, non-smoking general population, 0.20-0.80 µg/l, smoking general population, range of several studies (Arnold et al. 2013)
S-PMA in urine	P95: 38.0 nmol/l; 7.0 µg/g cr., general adult (>18 years), UK population, n= 355 (IEH 2008)
	Range of central tendency[3]: 0.5-9 µg/l; 0.3-8.9 µg/g cr., non-smoking general populations, 0.76-18 µg/l; 0.3-9.9 µg/g cr., non-occupationally exposed smokers, range of several studies from countries in Asia and Europe (Arnold et al. 2013)
Abbreviations: cr. (creatinine), P95 (95th percentile), S-PMA (S-phenyl mercapturic acid) [1]Examples of the central tendency are mean, median and geometric mean (Arnold et al. 2013)	

Based on the carcinogenic properties of benzene, there is no safe level of exposure (WHO 2000). Table 12 shows exposure limit values for benzene and its metabolites.

Table 12: Exposure limit values for benzene and S-PMA

Biomarker in specimen	**HBM values**	**BE (reference)**	**Other exposure limit values (reference)**
Benzene in blood	/	BE: between 0.04 and 1.29 µg/l (depending on the underlying non-cancer risk assessment[1]) (Hays et al. 2012)	/
Benzene in urine	/	BE: between 0.05 and 1.42 µg/l (depending on the underlying non-cancer risk assessment[1]) (Hays et al. 2012)	EKA: see Table 13 (DFG 2014)
S-PMA in urine	/	/	BEI: 25 µg/g creatinine (Arnold et al. 2013)
[1]The following non-cancer risk assessments were considered: US EPA Chronic RfC (Reference Concentration), TCEQ ReV (Texas Commission of Environmental Quality, Reference Value), CA REL (California, Reference Exposure Level), ATSDR chronic inhalation MRL (Minimal Risk Level) (Hays et al. 2012). Abbreviations: BE (biomonitoring equivalent), BEI (biological exposure index; see Glossary for further descriptions), EKA (exposure equivalents for carcinogenic substances), HBM values (human biomonitoring values [HBM I and HBM II] of the Human Biomonitoring Commission of the German Federal Environment Agency; see Glossary for further descriptions)			

It is not possible to derive BAT values for carcinogenic substances like benzene. Thus, the exposure equivalents for carcinogenic substances (EKA; see Glossary for definition) are analysed. The EKA for benzene in air and S-PMA in urine is given in Table 13. Based on insufficient data, there is no EKA for benzene in blood. EKA for ttMA is also available (DFG 2014) but not presented here.

Table 13: EKA (exposure equivalents for carcinogenic substances) for benzene (adapted from DFG 2014, p. 241)

Air Benzene		Sampling time: end of exposure or end of shift
ml/m^3	mg/m^3	S-PMA in urine (µg/g creatinine)
0.3	1.0	10
0.6	*2.0*	*25*
0.9	3.0	40
1.0	3.3	45
2	6.5	90
4	13	180
6	19.5	270
printed in italics: Equivalent Values according to ERB (Exposure-Risk-Relationships for carcinogenic substances; Expositions-Risiko-Beziehung für krebserzeugende Stoffe)		

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2.4.2 Toluene (C_7H_8)

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Chemistry

Toluene (chemical structure: C_7H_8, Figure 17) is a clear liquid at room temperature with a characteristic odour. It is a volatile organic compound with a vapour pressure of 28.4 mmHg (millimetres of mercury) at 25°C. Toluene evaporates fast from surface water and soil. Toluene remains longer in underground water. Toluene can contaminate fish, plants and animals (ATSDR 2000). A synonym of toluene is methylbenzene (WHO-IPCS 1986).

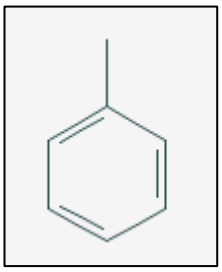

Figure 17: Chemical Structure of toluene (NCBI 2014)

Toluene is used in gasoline (as mixture with benzene and xylene, BTX), as a solvent and for the production of benzene and TNT (trinitrotoluene) for example. Beside industrial use, it occurs naturally in crude oil and can be found in the tolu tree. It is used in industry as a solvent. Toluene is used for paints and varnishing, for fingernail polish, adhesives as well as in the rubber and leather industries (ATSDR 2000).

Biological Systems Affected

Toluene may acutely affect the brain resulting in headache, sleepiness, or avoiding clear thinking. A chronic low exposure (e.g. at the workplace) may result in “tiredness, confusion, weakness, drunken-type actions, memory loss, nausea and loss of appetite” (ATSDR 2000, p. 5). Loss of hearing or colour vision is also a negative outcome due to long term exposure. It is assumed that the effects fade after exposure stops. It is unknown whether permanent effects due to low levels of exposure are possible. However, effects like problems with “speech, vision, or hearing”, “loss of muscle control, loss of memory, poor balance and decreased mental ability” following high exposures appear likely to be permanent (ATSDR 2000). A chronic occupational skin contact to toluene may cause nonallergic contact dermatitis (IARC 1999).

Repeated high acute exposures to toluene might even cause death following a state of dizziness and/or unconsciousness. High levels of toluene can damage the kidneys and liver. A toluene exposure in combination with alcohol enhances the risk of adverse liver effects. Additionally, an effect on hearing can be increased by a toluene exposure with simultaneous intake of some medicines (e.g. aspirin; see chapter 3.7.4) (ATSDR 2000).

Although there were reproductive effects observed in humans and animals exposed to toluene (IARC 1999), there is no clear evidence if reproductive effects (e.g. spontaneous abortions) are associated with toluene (ATSDR 2000).

Occupational exposures to toluene might cause increased chromosomal aberrations, micronuclei and DNA strand breaks (IARC 1999).

Toluene is not classified as carcinogen from IARC (categorized in Group 3, see Glossary) (IARC 1999). The US EPA came to the result, that toluene is “not classifiable as to its human carcinogenicity” (ATSDR 2000).

Metabolites of toluene are less harmful (ATSDR 2000).

Possible Exposure Routes

Exposure is possible through air, food and water, consumer products, or within an occupational setting. Using toluene containing products pollutes the air. Spills from material containing toluene, like petroleum or solvents, can contaminate water and soil. Automobile exhaust and paints are relevant sources of toluene exposures. Cigarette smoke contains small amounts of toluene (ATSDR 2000).

Absorption

The human body can absorb toluene over the lung or skin. It quickly reaches the blood stream. Within the human body, toluene is metabolized to less harmful substances (ATSDR 2000).

Elimination

A large amount (>75%) of absorbed toluene is excreted from the human body within 12 hours. Either by exhaling toluene contaminated air or via urine (ATSDR 2000). The amount of exhaled unchanged toluene is between 25 and 40%. The residual toluene is metabolized and excreted (de Lacy Costello et al. 2014).

90% of the absorbed toluene is initially converted to benzyl alcohol and excreted as hippurate, what is the main metabolite (IARC 1999). The bioconversion from toluene to benzyl alcohol occurs in the liver (de Lacy Costello et al. 2014). Other metabolites are *ortho*- and *para*-cresol, what is the result of around 3 and 5% of the absorbed toluene (IARC 1999).

Hippurate excreted in urine is a poor biomarker of toluene exposure, if the concentration is 200 ppm (760 mg/m^3) or lower. *Ortho*-cresol is also not reliable for low exposures. A better indicator might be the toluene concentration in exhaled air (IARC 1999).

Specimens for analysis

Toluene has been detected in faeces, urine, exhaled breath, skin secretion, breast milk, blood and saliva (de Lacy Costello et al. 2014). The exposure can be assessed in blood within 12 hours after exposure (ATSDR 2000). Toluene in blood is a sensitive and specific biomarker of exposure with a high relevance to the concentration in target tissues. Toluene in urine is a specific biomarker but not directly relevant to the concentration in target tissues. Toluene in exhaled air is also a specific biomarker but the reproduction of results is difficult (Aylward et al. 2008).

The breakdown products are not solely a result of toluene metabolism but come also from the metabolism of other chemicals (ATSDR 2000). The metabolites hippuric acid, *ortho*- (*o*-) cresol, *S*-*p*-Toluylmercapturic acid and *S*-Benzylmercapturic acid are potential biomarkers of exposure to toluene analysable in urine. Hippuric acid is not specific to toluene exposure and has no direct relevance to the concentration in target tissues (Aylward et al. 2008), but it is described as the usual biomarker to determine toluene (Siqueira and Paiva 2002). However, the appropriateness for low exposures is not given (Konjin et al. 2013). The metabolite *o*-cresol is non-specific for environmental exposures and has also no direct relevance to the

concentration in target tissues. *S-p*-Toluylmercapturic acid and *S*-Benzylmercapturic acid are specific biomarkers. However, the relevance to the concentration in target tissues is limited and the analytical sensitivity is insufficient (Aylward et al. 2008).

Reference values

Latest reference values (particularly P95) for toluene and hippuric acid (as the common biomarker (Siqueira and Paiva 2002), see above) are summarized in Table 14. Reference values for other metabolites (e.g. for N-Acetyl-S-(benzyl)-L-cysteine in urine (CDC 2014)), based on small sample sizes (n= <200) (Mochalski et al. 2013), specific subgroups (e.g. school children) (Sexton et al. 2004) or which are not up to date (>20 years old) (Wang et al. 1993; Ashley et al. 1994) are available but not presented here unless there are no values available which do fulfil the criteria mentioned.

Table 14: Reference values for toluene and metabolites

Biomarker in specimen	**Reference value, population, year, sample size (reference)**
Toluene in exhaled air	Range: 0.3-8.6 ppb, mean: 1.42 ppb, healthy volunteers, Austria, n= 28 (Mochalski et al. 2013)
Toluene in blood	<1 µg/l, non-smoker (Scholz 2001)
	<2 µg/l, smoker (Scholz 2001)
	P95: 0.814 ng/ml, US population, 2005/2006, n= 3,050 (CDC 2014)
	Range: 0.023-4.880 ng/ml, mean: 0.442 ng/ml, median: 0.234 ng/ml, adults (20-59 years old), USA, 1999-2000, n= 351 (Jia et al. 2012)
Toluene in urine	P95: 481-1361 ng/l^{-1}, primary school children, Italy (cities: Poggibonsi, Treviglio, Valenza), n= 107-147 (Minoia et al. 1996)
Hippuric acid in urine	P95: 0.36 g/g creatinine, nonoccupational exposed population, Brazil, n= 115 (Siqueira and Paiva 2002)
Abbreviations: ppb (parts per billion), P95 (95th percentile)	

Table 15 shows threshold values available for toluene and hippuric acid. Threshold values are also available for other metabolites of toluene (e.g. BAT, BEI and BLW for cresol (ACGIH 1999; DFG 2014)) but not presented here.

Table 15: Threshold values for toluene and metabolites

Biomarker in specimen	**HBM values**	**BE (reference)**	**Other threshold values (reference)**
Toluene in blood	/	BE: between 3 and 50 µg/l^{-1} (depending on the underlying non-cancer risk assessment[1]) (Aylward et al. 2008)	BAT: 600 µg/l (DFG 2014)
			BEI: 0.05 mg/l ((ATSDR 2000), original source (no free access): (ACGIH 1999))
Hippuric acid in urine	/	/	BEI: 1.6 g/g creatinine ((ATSDR 2000), original source (no free access): (ACGIH 1999))
[1]The following health-based exposure guidelines and toxicity values were considered: US EPA Chronic RfC (Reference Concentration), Health Canada chronic inhalation TDI (tolerable daily intake), WHO air quality guideline. ATSDR chronic inhalation MRL (Minimal Risk Level), ATSDR acute MRL (Aylward et al. 2008). Abbreviations: BAT (Biological Tolerance Value; see Glossary for further descriptions), BEI (biological exposure index; see Glossary for further descriptions), HBM values (human biomonitoring values [HBM I and HBM II] of the Human Biomonitoring Commission of the German Federal Environment Agency; see Glossary for further descriptions)			

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2.4.3 Xylene (C_6H_{10})

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Chemistry

Xylene is industrially used as solvent, thinner and cleaning agent. It is used for printing and varnishing, as well as in the rubber and leather industry. Additionally, it is used in coatings of fabrics and its isomers are used to produce plastics. It can be found in petroleum, coal tar and especially as an industrial synthesis product from petroleum (ATSDR 2007). Xylene is a component of crude oil and contained in tobacco smoke (WHO-IPCS 1997).

Synonyms of xylene are xylol as well as dimethyl benzene (ATSDR 2007), which is used by the IUPAC (WHO 2003). The chemical formula of xylene is C_8H_{10}, see Figure 18. It has three isomers, meta- (*m*-), ortho- (*o*-) and para- (*p*-) xylene, depending on the variation of the methyl groups on the benzene ring. Xylene is an easily flammable colourless liquid which evaporates quickly and smells sweet (ATSDR 2007).

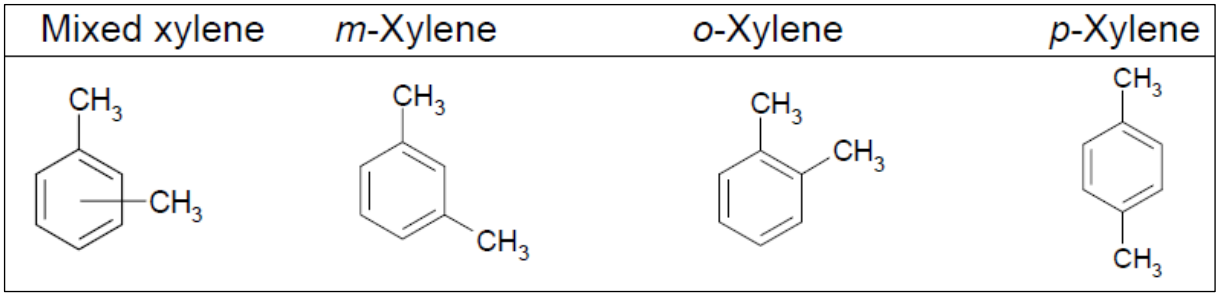

Figure 18: Chemical formula of xylene (ATSDR 2007, p. 186)

Based on its fast evaporation, xylene is mostly present in air as vapour (e.g. emitted during production or application). However, in its liquid form it can also enter soil and water, but it vaporizes quickly. In the air it is decomposed to more harmless chemicals within a few days. However, xylene can stay in groundwater for months before it is broken down. In plants and animals just small amounts of xylene are detectable (ATSDR 2007).

Biological Systems Affected

Low xylene concentrations are considered to have a low toxicity (IEH 2008). There are no health effects following the background concentration of xylene in air. The health effects described are mostly observed in occupational medicine (and animal) studies (ATSDR 2007).

The three isomers of xylene have similar health effects. High short-term exposures to xylene may result in “irritation of skin, eyes, nose and throat; difficulty in breathing; impaired function of the lungs; delayed response to a visual stimulus; impaired memory; stomach discomfort; and

possible changes in the liver and kidneys” (ATSDR 2007, p. 5). The central nervous system may be affected following short- or long-term exposures. Headaches, problems with the coordination of muscles, as well as dizziness, confusion or problems with the sense of balance are possible. Death is a possible consequence of exposures to very high xylene concentrations (ATSDR 2007).

IARC and US EPA concluded that xylene is not classifiable as human carcinogen because of an insufficient data base (ATSDR 2007).

Possible Exposure Routes

99.1% of xylene is found in air. The remaining percentage is distributed in water (0.7%), soil (0.1%), sediment (0.1%) and a very low amount can be found in fish (<0.1%) (ECETOC 1986; WHO 2003).

The main sources of xylene exposure are its industrial use as solvent and the emission of xylene from automobile exhaust. Besides occupational exposures to xylene, a contamination is also possible at hazardous waste sites. The main exposure route is inhalation. Inhalation of xylene vapour may occur when using consumer products like gasoline, paint or varnish, but also cigarettes. The indoor air xylene concentration might be higher than the outdoor air concentration (ATSDR 2007).

Absorption

The lungs absorb 50 to 75% of inhaled xylene. Xylene absorption following eating contaminated food or drinking contaminated water occurs fast and complete. A direct skin contact with liquid xylene results in a rapid absorption. However, the absorption of xylene vapour by skin is poor. Xylene enters the blood stream soon after absorption. It binds to serum proteins in the blood and accumulates in body fat. All isomers of xylene are metabolized by the same enzymes (ATSDR 2007).

Elimination

In the liver, xylene is transformed and becomes more water soluble. It is excreted via kidney and urine. Seconds after inhaling xylene, some parts are eliminated by exhalation. The largest amount of xylene is eliminated within 18 hours after exposure. Nevertheless, 4 to 10% of the absorbed xylene accumulates in fat (ATSDR 2007).

After oxidation of xylene, methylbenzoic acid isomers are initially formed. In combination with glycine, the predominant metabolite – an isomer (*o-, m-* or *p-*) of methylhippuric acid (MHA) – is excreted in the urine (WHO-IPCS 1997; ATSDR 2007). Additionally, the metabolites methylbenzyl alcohol and glucuronic acid occur and can be found in urine after xylene exposure (ATSDR 2007).

Specimens for analysis

Xylene (unidentified isomer) was detected in urine, breast milk and blood. (*p-, m-, o-*) Xylene can be measured in faeces, exhaled breath, breast milk, blood (ATSDR 2007; de Lacy Costello et al. 2014) and body tissue (ATSDR 2007). Solely *p-* and *o*-xylene can also be measured in saliva; *p*-xylene is additionally detectable in skin secretion (de Lacy Costello et al. 2014). Urine can be used to measure xylene and its metabolites a few hours after exposure. The *m-* and *p-*isomers are difficult to separate; this is why their concentrations are mostly reported as a sum concentration (ATSDR 2007).

The metabolite (*o-, m-* or *p-*) MHA is used to assess low occupational or environmental concentrations (IEH 2008). MHA is specific biomarker for recent xylene exposures while a distinction between short-term, intermediate and chronic-duration exposures is not possible (ATSDR 2007).

Reference values

Latest reference values (particularly P95) of xylene and MHA are presented in Table 16. Reference values for other metabolites (e.g. N-Acetyl-S-(dimethylphenyl)-L-cysteine (CDC 2014)), based on small sample sizes (n= <200) (Sexton et al. 2004; Mochalski et al. 2013) or specific subgroups (e.g., school children) (Sexton et al. 2004) or which are not up to date (>20 years old) (Ashley et al. 1994) or do not present P95 (Jia et al. 2012) are available but not presented here unless no value fulfilling the mentioned criteria is available.

Table 16: Reference values of xylene

Biomarkers in specimen	**Reference value, population, year, sample size (reference)**
(*o-*, *m-*, *p-*) xylene in urine	P95: 230-909 ng/l^{-1}, primary school children, Italy (cities: Poggibonsi, Treviglio, Valenza) n= 96-144 (Minoia et al. 1996)
Xylene in blood	P95: <1 µg/l, non-smoker (Scholz 2001)
	P95: <2 µg/l, smoker (Scholz 2001)
o-xylene in blood	P95: 0.110 ng/ml, US population, 2005/2006, n= 3,153 (CDC 2014)
m-, *p*-xylene in blood	P95: 0.410 ng/ml, US population, 2005/2006, n= 3,153 (CDC 2014)
MHA in urine	P95: 440.0 µmol/l, 94.7 mg/g creatinine, general adult (>18 years) UK population, n= 360 (IEH 2008)
2-MHA in urine	P95: 408 µg/l, 382 µg/g creatinine, smokers, n= 889, 170 µg/l, 156 µg/g creatinine, non-smokers, n= 1307-1308, US population, 2011/2012 (CDC 2014)
3- and 4-MHA in urine	P95: 2850 µg/l, 2260 µg/g creatinine, smokers, n= 889, 1,330 µg/l, 1,060 µg/g creatinine, non-smokers, n= 1,307-1,308, US population, 2011/2012 (CDC 2014)
Abbreviations: LOD (limit of detection), MHA (methylhippuric acid), P95 (95th percentile)	

Table 17 shows exposure limit values available for xylene and MHA.

Table 17: Exposure limit values for xylene and methylhippuric acid

Biomarker in specimen	**HBM values (reference)**	**BE (reference)**	**Other exposure limit values (reference)**
Xylene in blood	/	BE: 0.3 µg/l whole blood (Aylward et al. 2010, 2013)	BAT: 1.5 mg/l (DFG 2014)
Methylhippuric (toluric) acid (all isomers) in urine	/	/	BAT: 2,000 mg/l (DFG 2014)
Abbreviations: BAT (Biological Tolerance Value; see Glossary for further descriptions), BEI (biological exposure index; see Glossary for further descriptions)			

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2.5 Pharmaceuticals in the environment

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Pharmaceuticals are key ingredients to public health and to quality of life. They are designed to stimulate a physiological response in humans, animals, bacteria or other organisms. During the

past decade, concern has grown about the adverse effects, the use and disposal of pharmaceuticals might potentially have on human and ecological health. Research has shown that after passing through wastewater treatment, pharmaceuticals, amongst other compounds, are released directly into the environment, mainly in soil, potable and effluent water and air.

Recent studies of pharmaceuticals and other chemicals of emerging environmental concern have demonstrated that the manner in which we handle and dispose of our waste can concentrate these chemicals in the environment.

Pharmaceuticals and personal care products comprise a remarkably diverse array of unique chemical substances, most of which are purchased for use directly by, or for, consumers and medical and agricultural practices The chemicals encompassed in this diverse group include all chemicals used for humans, domestic animals, or agricultural crops that: (i) treat disease (e.g. antibiotics), (ii) alter or improve physiological, cosmetic, or emotional function, appearance, or status, (iii) prevent disease (e.g. vaccines) or maintain health, (iv) help in the diagnosis or monitoring of health or disease (e.g. X-ray contrast media, radiopharmaceuticals), or (v) serve to formulate the active ingredient into a commercial product (e.g., excipients and delivery vehicles) (Kummerer K. 2010).

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2.5.1 Antibiotics

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Antibiotics are among the most important groups of pharmaceuticals used. Antimicrobial drugs can be used for prevention or treatment of disease caused by microorganisms such as bacteria and fungi. Antibiotics that are sufficiently nontoxic to the host are used as chemotherapeutic agents in the treatment of infectious diseases of humans, animals and plants.

The classic definition of an antibiotic is a compound produced by a microorganism that inhibits the growth of another microorganism. Over the years, this definition has been expanded to include synthetic and semi-synthetic products. Antibiotics are grouped based on chemical structure or the mechanism of inhibition of microorganisms.

Antibiotics are used extensively in human and veterinary medicine as well as in aquaculture for the purpose of preventing or treating microbial infections, while in livestock farming they are also used to promote the growth of animals. Some antibiotics are also used in growing fruit and in bee keeping.
Estimated total antibiotic market consumption world-wide lies between 100,000 and 200,000 tons (Kummerer 2003).

Data on human consumption of antibiotics are available for Europe by the European Centre for Disease Prevention and Control (ECDC 2012) and for the United States by the Center for Disease Dynamics, Economics and Policy (CDDEP 2014). A study on antibiotic consumption from 2000 to 2010 in 71 countries (including Brazil, Russia, India, China, and South Africa) has been recently published (Van Boeckel et al. 2014)

The amount of antimicrobials use in food animals is not known precisely. It is estimated that about half of the total amount of antimicrobials produced globally is used in food animals (WHO 2002).

Up to 95% of the administered dose of human or veterinary drugs can be excreted unmetabolised and discharged into wastewater. Antibiotics are also released into the environment by discharged expired drugs and hospital effluents. Recent studies have clearly shown that elimination in sewage treatment plants (STPs) is often incomplete, with efficiencies ranging between 3 and 90%, depending on the compound, for a variety of polar drugs; therefore they are released into natural waters. More than 30 antibiotics have been found in the sewage influent and effluent samples in surface, ground and drinking waters (Milić et al. 2013).

Chemistry

Antibiotics are a diverse group of chemicals that can be divided into subgroups such as β-lactams, quinolones, tetracyclines, macrolides, sulfonamides and others. The active compounds of antibiotics are often complex molecules which may possess different functionalities. Under environmental conditions, these molecules can be neutral, cationic, anionic or zwitterionic. Because of the different functionalities within one molecule, their physicochemical and biological properties may change with pH levels.

Biological Systems Affected

There is still no significant evidence about the systematic uptake and input of low antibiotic doses and their impact on humans and the environment (Milić et al. 2013). Allergies in sensitive individuals and reduced effectiveness of antibiotics against infections are potential risks for human health. More specifically, the widespread use of antibiotics results in the generation of antibiotic concentration gradients in humans, livestock and the environment. Thus, bacteria are frequently exposed to non-lethal concentrations of drugs, and recent evidence suggests that this is likely to have an important role in the evolution of antibiotic resistance (Kantiani et al. 2010; Andersson and Hughes 2014). In a recently published study an hypothesis is presented that low dose antibiotics in humans may be related to obesity due to the disruption of intestinal microbial population and its impact on body metabolism and energy balance (Riley et al. 2013).

Other adverse effects that have been reported from therapeutic use of antibiotics should also be examined for possible association with low levels of antibiotics in humans.

Absorption

After oral administration, the antibiotic is released in the small intestine and absorbed into the bloodstream. Antibiotics absorption is affected by their molecular weight, ionization and solubility.

Elimination

Most antibiotics are excreted kidneys or eliminated by the liver.

Possible Exposure Routes

Antibiotics for prevention or treatment of disease in humans are administered by oral, parenteral, and topical routes.

Additional human exposure to low levels of antibiotics may occur through food consumption and drinking water. More specifically, exposure can occur through consumption of food products of animal origin like meat, milk and eggs, consumption of aquaculture products and honey because of antibiotic use in food animal husbandry, aquaculture and apiculture. Exposure can

also occur through consumption of food products of plant origin, since antibiotics have been shown to accumulate in plant tissue form manure-amended soil (Riley et al. 2013).

The European Union (EU 2009) has set maximum levels for certain antibiotics in food products of animal origin (Commission Regulation 37/2010 and its amendments 758/2010 and 759/2010). Moreover, the EU prohibits the use of CAP as a veterinary drug for food producing animals.

Specimens for analysis

Human levels of antibiotics can be assessed by analyzing blood serum/plasma and urine. Special attention should be paid to study participants selection, to exclude those who have received antibiotics for therapeutic or prophylactic purposes.

Due to the fact that antimicrobial agents residues have increasingly entered our food chain and the environment over the last 20 years, mass exposure of humans to low levels of antibiotics occurs and severe threats to human health are associated with this exposure (evolution of resistant bacteria, perhaps obesity). Thus, inclusion of levels of antibiotics in humans in the “exposome” study would be very important.

Reference values

Ciprofloxacin, for example, was found in concentrations of between 0.7 and 124.5 µg/l in hospital effluent. Ampicillin was found in concentrations of between 20 and 80 µg/l in the effluent of a large German hospital. Antibiotic concentrations calculated and measured in hospital effluents are of the same order of magnitude as the minimum inhibitory concentrations for susceptible pathogenic bacteria. The dilution of hospital effluents by municipal sewage will lower the concentration of antibiotics only moderately, because municipal waste water also contains antibiotic substances and disinfectants from households, veterinary sources and to a minor extent from livestock. Antibiotics have been detected in the µg/l range in municipal sewage, in the effluent of STPs, in surface water and in ground water. These included quinolones such as ciprofloxacin, sulphonamides, roxythromycin, dehydrated erythromycin and others. If antibiotics are used in animal husbandry, they pass into the soil from manure. Tetracyclines have been detected in concentrations of up to 0.2 µg per kg in soil whereas others have been found in the sediment under fish farms (Kummerer 2003).

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2.5.2 Chemotherapy

WRITTEN BY ESTER HEATH AND TINA KOSJEK (JSI)

One major class of pharmaceuticals overlooked in the environment, yet of high importance due to their cytotoxicity, genotoxicity, mutagenicity and teratogenicity, are anticancer drugs also known as antineoplastics and cytostatics.

Chemistry

Cytostatic drugs are used to fight cancer – a disease of uncontrolled multiplication of the body’s own cells and spread of abnormal forms within the body. Chemotherapy, together with surgical excision and irradiation, is one of the three main approaches to treat established cancer. These drugs work by preventing the growth and proliferation of cancer cells. The Anatomical Therapeutic Classification (ATC) system groups cytostatics into Class L – Antineoplastic and Immunomodulating Agents according to their chemical structures and therapeutic properties and divides them into five classes: L01A alkylating agents; L01B antimetabolites; L01C plant alkaloids and other natural products; L01D cytotoxic antibiotics and related substances; and L01X other antineoplastic agents. Cytostatics differ widely in their chemical structures and accordingly in their physicochemical parameters, which in turn determines their absorption, elimination and fate in the environment. This variety in chemical structure indicates that they can hardly be addressed under the same common denominator. Detailed structures of the most common cytostatics and their physic-chemical parameters are shown and described in detail in Kosjek and Heath (2011).

Biological Systems Affected

Exposure to cytostatics can, due to their genotoxicity even at very low doses, induce mutations with delayed effects resulting in cancers and other chronic diseases, reproductive effects, heritable diseases, and also neurodegenerative effects (Filipič et al. 2013). Cytostatics have the potential to harm a broad variety of species including microorganisms, plants, animals and humans due to their interference with the function of DNA and genetic material, which is common in all organisms. Such adverse effects that impact reproduction and population fitness may in principle, also be expected to occur in aquatic organisms at environmental concentrations and through continuous exposure. The awareness of these drugs possible adverse effects has also been recognised by REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) legislation that classifies those chemicals with carcinogenic,

mutagenic and reproductive toxicity (CMRs) as priority pollutants regardless production quantities.

Humans

Humans can be exposed to cytostatics during occupational or environmental exposure (see subchapter “Possible Exposure Routes”).

Aquatic organisms

Studies have shown that aquatic organisms living in waters polluted with genotoxic contaminants are affected i.e. DNA damage, micronuclei, and mutations. Despite this, only a few studies have addressed the effects of genotoxic contamination on the ecosystem. There is evidence to show that exposure to mutagens in water or soil can enhance the frequency of heritable recessive lethal mutations, and the accumulation of such mutations can contribute to the decline of small populations (García-Dorado 2003).

The latest research outcomes obtained within the EU FP7 (Seventh Framework Programme for Research) project CytoThreat (CytoThreat 2011; Filipič et al. 2013) show that data on the acute toxicity of cytostatics to aquatic organisms are irrelevant for predicting adverse effects during chronic exposure in the aquatic environment. Chronic exposure assays associated with the detection of genotoxic effects showed differences in susceptibility of aquatic organisms from different trophic levels (algae, cyanobacteria and higher plants as producers, crustacean and mussel as primary consumers and vertebrate as secondary consumers) to the toxic and genotoxic effects of the tested cytostatic drugs. These results indicate that data from long term *in vivo* tests focusing on specific effects like genotoxic and reprotoxic are needed to determine the significance of the presence of these drugs in the environment. However, CytoThreat results show that certain cytostatics including 5-fluorouracil exerted toxic and genotoxic effects at concentrations close to predicted environmental concentrations and those found in hospital wastewaters. This indicates that certain cytostatics may pose a threat to aquatic organisms indicating the need for further investigation of their ecotoxicological properties as well as an investigation of the occurrence of cytostatic drugs in the environment (Filipič et al. 2013).

Possible Exposure Routes

Occupational exposure

Main routes of occupational exposure, which is much less intensive than therapeutic exposure, are *via* inhalation of aerosolized particles and transcutaneous absorption. Various manipulations in the preparation and administration of cytotoxic drugs could lead to exposure by these routes. Aerosolization might occur when one breaks open an ampule, withdraws solution form a vial, and injects liquid into a powder or during manufacturing process. Transcutaneous absorption could occur following spills on the skin.

Centres for Disease Control and Prevention, USA Government, USA list effects of occupational exposure, e.g. acute and chronic effects and effects on fertility and reproductive outcomes (CDC 2014):

- Various acute toxic effects of antineoplastic agents are well documented in patients treated with high doses and include nausea, rashes, hair loss, liver and kidney damage, hearing loss, cardiac and hematapoetic toxicities…. Workers handling antineoplastic agents have also reported some of these effects.
- Only a limited number of studies have examined chronic health effects related to the occupational exposure to antineoplastic drugs, but effects on fertility and reproductive health

have been seen in number of studies, mainly in female nurses. On the other side, chronic effects in patients treated with these agents are well documented. Epidemiological studies showed very clearly that prolonged exposure to low, non-therapeutic doses of cytostatic during occupational exposure induced genotoxic effects in humans, whereas patients treated with alkylated cytostatics developed secondary cancers and cumulative increase in mutant frequency in peripheral lymphocytes has been reported (Crauste-Manciet et al. 2005).

Based on the existing data the authors (CDC 2014) conclude that there is limited evidence in the literature concerning occupational cancer related to antineoplastic agents and further research is needed before any firm conclusions can be made.

Environmental exposure

Cytostatic compounds are present in wastewaters from hospital sewage plants, or in case of out-patient treatment in municipal wastewater treatment plants (WWTP), or resulting from improper disposal. Once released to the environment, they may potentially end up in drinking water where they could have a negative impact on human health.

Environmental cytostatic concentrations are expected to be lower than occupational exposure levels. Exposure may occur through drinking water, particularly when surface water is recycled and reused. It may also occur through recreational activities in contaminated water. The general consensus of the scientific community is that it is impossible to consume a sufficient quantity of drinking water in order to receive a therapeutic dose of a pharmaceutical. For example to receive a therapeutic dose of the common antidepressant fluoxetine a person would have to drink 37,000 to 62,500 litre of water (Mendoza et al. 2014; Warnes 2014). To our knowledge, cytostatics are found in much lower concentrations and are less widespread compared to other groups of pharmaceuticals and the amount of drinking water that would need to be consumed would be considerably higher. However, increased probability of adverse health effects due to DNA damage (CytoThreat 2011) at continuous low level exposure (chronic) to genotoxins has to be taken into account.

Absorption and other parameters influencing fate and behaviour of cytostatics

The parameters determining the fate and distribution of cytostatics can to some extent be predicted from their chemical structures (Table 1 in Kosjek and Heath 2011) and physico-chemical properties including the dissociation constant (pK_a), bioconcentration factor (BCF), octanol-water partition coefficient (K_{ow}), organic carbon partition coefficient (K_{oc}), atmospheric OH rate, solubility, Henry’s coefficient (K_H) and vapour pressure (Table 2 in Kosjek and Heath 2011).

Dissociation

pK_a is an equilibrium constant that describes the degree of dissociation of a compound at a particular pH. Given an average environmental pH of 7 and according to the pK_a values listed in Table 2 in Kosjek and Heath (2011), only selected compounds (e.g. chlorambucil, melphalan and methotrexate) are likely to be dissociated, which will increase their aqueous mobility and affect ultimately their environmental fate. However, it is possible for a wider pH range (5-9) to be present in the environment.

Sorption

This is a key factor controlling input, transport, and the transformation of pharmaceuticals in the aquatic environment. The mechanism and magnitude of sorption is defined by a compound’s chemical structure. Generally, according to the literature data, most of cytostatics

(cyclophosphamide, ifosfamide, 5-fluorouracil and capecitabine) have negligible sorption onto sludge, while some (methotrexate, vinblastine and in general all anthracyclines) show sorption potential. For details see Kosjek and Heath (2011).

Solubility

Solubility of cytostatic compounds is generally higher than the actual concentrations in aqueous environment (Kosjek and Heath 2011), implying that solubility does not limit their occurrence in aqueous matrices.

Biodegradability

Most cytostatics have low biodegradability, while some, e.g. cytarabine containing sugar moieties, have higher biodegradation rate reported (Table 3 in Kosjek and Heath 2011).

Stability towards photolysis

Literature on direct photolysis of cytostatics shows a dearth of data. However studies on indirect photolysis of selected cytostatics with OH radicals (AOP) indicate great potential of this removal mechanism for cytostatic compounds (Table 3 in Kosjek and Heath 2011).

Volatility

Because of the low values for the Henry’s coefficient (K_H) and vapour pressure (Table 2 in Kosjek and Heath 2011), the fraction removed by volatilization is considered negligible.

Elimination

Generally, not all the administered drugs are metabolised and the metabolism rates depends greatly on mode of application. The majority of cytostatic medicines are intravenous and are administered in either a clinic or a hospital. Other ways of administration include intramuscular, intraosseous, intralesional, topical, or oral. The trend in cytostatic administration is shifting towards increasing oral administration executed at home or external ambulatory infusion pumps (e.g. for 7 days) installed at the health-care facility but taken home for the time of treatment.

Absorption of the active ingredient may vary from 0-100% from gastrointestinal tract, 100% when administered intravenously and can be rather low when applied locally (on healthy skin). Metabolism leads to biotransformation into more hydrophilic metabolites that are usually excreted from body by urine. In addition, metabolism and elimination depends greatly on compounds structure. For example, typical metabolism rates for 5-FU (5-fluorouracil) and CAP (capecitabine) are 0.85 and 0.70, respectively. The remainder, a mixture of parent compounds and metabolites, are excreted from the body and typically enter the sewerage system eventually reaching surface waters.

We should stress that in addition to the parent cytostatic compounds, it is also important to consider their metabolites and environmental transformation products, which are often the actual cytostatic compounds. These also have the potential to contribute to the total biotoxic and mutagenic potential.

Reference values

Not available.

Specimens for analysis

The main excretory pathways of cytostatic drugs in humans are urine and faeces.

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2.6 Smoking

WRITTEN BY KINGA POLAŃSKA (NIOM), DANIJELA ŠTIMAC AND ZDRAVKO ŠPIRIĆ (OIKON)

The tobacco epidemic is one of the biggest public health threats. According to the most recent data, nearly 20% of the world’s population smoke cigarettes; including about 800 million men and 200 million women. In addition, about 40% of children and a third of non-smoking adults are exposed to second-hand smoke (SHS) (Eriksen et al. 2012).

In 2011, tobacco use killed about 6 million people a year with 80% of these deaths occurring in low- and middle-income countries (Eriksen et al. 2012). More than five million of those deaths are the result of direct tobacco use. Based on existing data, up to half of all lifetime smokers will ultimately die of a disease caused by smoking including: cancers, heart attacks, stroke, chronic obstructive pulmonary disease (COPD) and many others (IARC 2004; Eriksen et al. 2012; WHO 2013). It is also estimated that about 600,000 individuals die annually from exposure to SHS with majority of deaths occurring among women and children. SHS exposure contributes to a range of diseases, including heart diseases and cancers. It is also a risk factor for adverse pregnancy outcomes, children’s health and development (Eriksen et al. 2012).

Taking into account the level of exposure and its health consequences, all effort is taken in a form of policy measures and public health interventions to stop the diseases, deaths and economic damages caused by tobacco use. Despite such activities, the prevalence of smoking is still high, with increasing prevalence among women and young girls in some countries.

Unless urgent action is taken, the annual death toll could rise to more than eight million by 2030 (Eriksen et al. 2012).

Chemistry

Chemical composition of tobacco smoke, although influenced by the specific manner in which individuals smoke, is primarily determined by the type of tobacco (IARC 2004). It is also influenced by the design of the smoking device or product and, for cigarettes, by the presence or absence of filters, and by other factors including ventilation, paper porosity and types of additives. As a result, concentrations of individual chemicals in smoke vary.

Over 4,000 compounds have been identified in tobacco smoke, of which at least 250 are known to be harmful and more than 50 are known to cause cancer (IARC 2004, 2012). Classes of compounds include neutral gases, carbon and nitrogen oxides, amides, imides, lactams, carboxylic acids, lactones, esters, aldehydes, ketones, alcohols, phenols, amines, N-nitrosamines, N-heterocyclics, aliphatic hydrocarbons, monocyclic and polycyclic aromatic hydrocarbons (PAHs), nitriles, anhydrides, carbohydrates, ethers, nitro compounds and metals (Rodgman and Perfetti 2009). The addictive properties of tobacco smoke are attributed to nicotine (Hukkanen et al. 2005). There are over 50 carcinogens in tobacco smoke that have been evaluated by the IARC Monographs programme as having sufficient evidence for carcinogenicity in either laboratory animals or humans. Sixteen of these chemicals (benzo[*a*]pyrene (BaP), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), *N'*-nitrosonornicotine (NNN), 2-naphthylamine, 4-aminobiphenyl, formaldehyde, 1,3-butadiene, benzene, vinyl chloride, ethylene oxide, arsenic, beryllium, nickel compounds, chromium VI, cadmium, and polonium-210) are classified as carcinogenic to humans (Group 1, see Glossary) (IARC 2004, 2012).
Composition of mainstream (MS) and sidestream smoke (SS) is qualitatively similar but quantitatively different. As an example SS:MS ratios are: nicotine, 7.1; carbon monoxide, 4.8; ammonia, 455; formaldehyde, 18.6; benzo[a]pyrene, 16.0; NNN, 0.43; NNK, 0.40 (Jenkins et al. 2000; IARC 2004, 2012).

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2.6.1 Active Tobacco Smoking

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Definition

Smoking is a practice in which a substance is burned and the resulting smoke breathed in to be tasted or inhaled. Smoked forms of tobacco include various kinds of cigarettes (manufactured, hand-rolled, filtered, un-filtered and flavoured), cigars and pipes. While cigarette smoking, particularly manufactured cigarettes, is by far the main form of tobacco smoked globally, in some countries other forms of smoked tobacco are dominant (IARC 2004, 2012; Eriksen et al. 2012).

Distribution of active smoking in the world

Over one billion people smoke tobacco in the world. In developed countries, the overall percentage of smokers has decreased, but the percentage is still increasing in developing countries and among women (Eriksen et al. 2012). In most populations, 20 to 66% of men smoke. Even though the share of women who smoke is increasing, this percentage is generally lower than among men. In 2010, WHO reported that in the 28 EU countries smoking prevalence of daily or any current smoking was 41.4% in men and 27.8% in women and (in all the WHO European region, 47.3% in men and 24.1% in women).

Active smoking compounds

The burning of tobacco generates over 4000 compounds, of which at least 250 are known to be harmful and more than 50 are known to cause cancer. The smoke can be separated into gas and particulate phases. Among the gaseous phase components are carbon monoxide, carbon dioxide, nitrogen oxides, ammonia, volatile nitrosamines, hydrogen cyanide, volatile sulfur containing compounds, volatile hydrocarbons, alcohols and aldehydes and ketones. Nicotine is the most abundant of the volatile alkaloids in the tobacco leaf. The actual content of nicotine in tobacco can vary from 0.2% to 5%. The composition of the smoke delivered to the smoker depends on the composition of tobacco and how densely it is packed, the length of the column of tobacco, the characteristics of the filter and the paper, the temperature at which the tobacco is burned.

Biological systems affected and health effects

All current tobacco products expose smokers to carcinogens (IARC 2004, 2012; US Department of Health and Human Services 2014). Tar is the compound in tobacco that remains after the moisture and nicotine are subtracted and consists of polycyclic aromatic hydrocarbons, which are carcinogens. Some of tobacco compounds inhibit ciliary movement in the lungs. Non-volatile nitrosamines and aromatic amines play an etiologic role in bladder cancer. Diverse effects of nicotine occur as a result of both stimulant and depressant actions on various central and peripheral nervous system pathways. This drug can increase the heart rate by excitation of the sympathetic nervous system, or by paralyzing the parasympathetic nervous system. Nicotine affects the medulla in the brain to increase heart rate. Nicotine causes a discharge of epinephrine from the adrenal medulla, which causes an increase in heart rate and raises blood pressure. Other smoke compounds increase the risk of acute thrombosis of narrowed vessels and increase the degree of atherosclerosis in the blood vessels (CDC 2010).

The cancers considered to be causally related to tobacco smoking include lung (with almost 80% of male and nearly 50% of female lung cancer deaths caused by tobacco), oral and nasal cavity cancer, pharynx, larynx, oesophagus, stomach, pancreas, liver, kidney, urinary bladder, cervix cancers and myeloid leukaemia (IARC 2004, 2012). Results from epidemiological studies have also shown a small overall association between smoking and breast cancer incidence.

Active smoking also causes long-term risk of no-cancer health problems such as: coronary heart disease (CHD), stroke, aortic aneurysm, and peripheral artery disease (PAD), emphysema, COPD, kidney diseases, diabetes and higher mortality rate. For majority of the above associations dose-response relationship has been established, which means that the risk increases along with the duration and intensity of smoking. Additionally, the studies indicate that the risk decreases after smoking cessation.

In the case of CHD, stroke, aortic aneurysm, and PAD, the risk associated with active smoking is seen both as an increased risk of acute thrombosis of narrowed vessels and as an increased degree of atherosclerosis in the blood vessels involved (CDC 2010). Risks are not reduced by smoking cigarettes with lower machine-measured yields of tar and nicotine. In the long term, lung tissue is damaged in case of tobacco use leading to emphysema and lung function deterioration. Smoking is at the origin of metaplasia of secretory cells in the airways and thus of chronic bronchitis. A recent meta-analysis showed a modest association between smoking and asthma and allergic diseases among adults, children and adolescents (Saulyte et al. 2014). However, additional studies with detailed measurement of exposure and better case definition are needed to further explore the role of smoking in allergic diseases.

The available data indicate that smoking is a significant risk factor for Alzheimer’s disease and dementia. However, active smoking is a preventive factor for Parkinson’s disease (Cataldo et al. 2010; Tanaka et al. 2010). Smoking is thought to cause dementia by the same biological mechanisms as its contribution to coronary artery disease, cerebrovascular disease, and stroke, namely by increasing total plasma homocysteine, which is a known risk factor for stroke, cognitive impairment, Alzheimer's, and other dementias, by accelerating atherosclerosis in heart and brain, which deprives your brain cells of oxygen and important nutrients. Arterial stiffness is associated with the buildup of beta-amyloid plaque in your brain, which is a hallmark of Alzheimer's disease and through oxidative stress, excitotoxicity, neural death, and inflammation that may directly or indirectly be related to brain changes seen in people with Alzheimer's

Smoking during pregnancy is associated with various adverse effects on pregnancy and foetal development. It carries a lot of serious complications such as spontaneous abortion, placental abruption and reduced birth weight of the newborn (Samet and Yoon 2010; US Department of Health and Human Services 2014). Children of smoking mothers have an increased risk of premature birth, low birth weight, sudden infant death syndrome, asthma as well as other respiratory diseases and neurodevelopmental outcomes during infancy (Clifford et al. 2012; US Department of Health and Human Services 2014).

Specimens for analysis

A number of markers have been used as biochemical indicators of tobacco consumption, including: nicotine, cotinine, thiocyanate (SCN), carbon monoxide (CO) levels (SRNT Subcommittee on Biochemical Verification 2002; IARC 2012) and some others less used. Nicotine, although highly specific for tobacco use (in the absence of nicotine replacement therapy, NRT), taking into account its short half-life (2 hours), technical difficulties and costs of analysis is not recommended for general use. Cotinine, the major metabolite of nicotine, is highly specific and sensitive for tobacco use. In addition, fairy long half-life (17 hours for general

population and shorter half-life for pregnant women) and moderate costs of analysis make it a good biomarker for tobacco smoking and cessation (when NRT is not employed). Cotinine can be measured in blood, cord blood, saliva and urine (with the following cut-off points for biomarker values to distinguish tobacco use vs. no tobacco use: plasma and saliva: cotinine 15 ng/ml, urinary cotinine 50 ng/ml). The advantage of saliva and urine over blood is that the first two are not invasive and do not require venepuncture. A current state-of-the-art method for determination of cotinine in biological material is liquid chromatography with mass spectrometry (LC-MS/MS) and atmospheric pressure or electrospray ionization. Measuring CO in expired air (cut-off: 8-10 ppm to distinguish tobacco use vs. no tobacco use) is the cheapest and most easily performed method for determining smoking status. CO is reasonably specific for detecting heavy cigarette smoking but is of marginal utility for light smoking because of endogenous and environmental sources. SCN is not recommended as a biomarker for tobacco use because of inadequate sensitivity and specificity. Among other biomarkers, anabaisne and anatabine, although useful for determining tobacco use, are relatively expensive.

Except for biomarkers of tobacco smoking, the standardized questionnaire can give assessment of smoking status, smoking history and amount of tobacco smoked, which is especially important, taking into account the costs of analysis in the case of large studies.

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2.6.2 Second-hand Smoke (SHS)

WRITTEN BY KINGA POLAŃSKA (NIOM)

Second-hand smoke (SHS), also known as environmental tobacco smoke (ETS), is a general term for any smoke that non-smokers are exposed to. SHS smoke comprises the sidestream smoke (SS) which is released from the burning tip of a cigarette between puffs and the mainstream smoke (MS) exhaled by the smoker. Side-stream smoke accounts for 85% of the ETS in a smoky room and it contains more carcinogens (cancer causing substances) than the mainstream smoke. In most developed countries (as a consequence of regulation measures banning or restricting smoking in workplaces and public places) home environment is the primary source of SHS exposure. Over 40% of children have at least one smoking parent. So far, according to the WHO over 1 billion people, or 16% of the world's population, are protected by comprehensive national smoke-free laws.

Health effects

Second-hand smoke causes more than 600,000 premature deaths per year. Children accounted for almost 30% of the deaths attributable to SHS (CDC 2006; Eriksen et al. 2012).
According to multiple cohort, case-control, and meta-analytical studies, in adults, SHS increases the risk of cardiovascular diseases by 25-30%. Physiologic and basic science research suggest that the mechanisms by which SHS affects the cardiovascular system are multiple and include increased thrombogenesis and low-density lipoprotein oxidation, decreased exercise tolerance, dysfunctional flow-mediated vasodilatation, and activation of inflammatory pathways with concomitant oxidative damage and impaired vascular repair. As a result, chronic exposure promotes atherogenesis and the development of cardiovascular disease, increasing the risk of an acute coronary syndrome (ACS) (Dunbar et al. 2013). Over the last 10-15 years, there has been a significant and reciprocal decline in the incidence of emergency admissions for ACS by an average 17% with the implementation of state-wide and nationwide public smoke-free legislation across the United States and Europe, respectively.

The existing evidence firmly establishes that exposure to second-hand tobacco smoke is causally associated with lung cancer risk in both men and women (with the increased lung cancer by 20-30%) (IARC 2012). Passive exposure of pregnant women adversely affects the developing foetus in a similar way as described in the case of active smoking but at lower magnitude. Postnatal SHS is putting the children at a higher risk of a sudden infant death syndrome, acute respiratory infections, ear problems and more severe asthma. In addition, such exposure is associated with poor academic achievement and neurocognitive performance in children and adolescents. Furthermore, SHS exposure was associated with an increased risk of neurodevelopmental delay.

Specimen for analysis

There are several ways to assess SHS exposure and they are either based on questionnaire data or on measurements. Questionnaires can be addressed to the non-smoking people asking them about their exposure to SHS or to the smoking people to state the number of smokers in the household and/or the number of cigarettes smoked. Questionnaire data can be interpreted

using measurement data that link reported exposure to a range of concentrations either in the indoor air, documented by ambient or by personal monitoring or as internal exposure by biomonitoring (cotinine level in biological sample).

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2.6.3 Third-hand Smoke (THS)

WRITTEN BY KINGA POLAŃSKA (NIOM)

Another threat to human health is represented by third-hand smoking (THS) that consists of pollutants that remain on surfaces and in dust after tobacco has been smoked and which are re-emitted into the gas-phase, or react with other compounds in the environment to form secondary pollutants that can linger on surfaces and furnishings long after these products have been extinguished (Becquemin et al. 2010). THS constitutes a high potential risk for infants and children that are more prone to the risks related to THS exposure than adults because they typically spend more time indoors and have age-specific behaviours that may expose them to potential health hazards from THS (Ferrante et al. 2013). THS consists of gasses and particulate matter, including carcinogens and heavy metals such as arsenic, lead and cyanide. Ozone and related atmospheric oxidants react with nicotine smoke or smoke coming from the second-hand smoke, releasing the smallest particles with high risk of asthma (Jung et al. 2012). In addition, residual nicotine that persists in high concentrations on the interior surfaces, including clothing, is forming in the reaction with nitric acid carcinogenic compounds of specific nitrosamines. A study found that exposure to thirdhand smoke is genotoxic to human cell lines (Hang et al. 2013).

Efforts towards reducing exposure to tobacco smoke coming from the passive and indirect smoking should be placed at a high priority throughout the European Union. Further investigations are necessary to study the health effects of THS relevant to different exposure pathways and profiles. It would be also very important to evaluate how THS may affect lung development through *in utero* exposure during prenatal life.

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2.6.4 Smokeless tobacco

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The term smokeless tobacco implies the use of unburned tobacco in the finished products. Over 25 distinct types of smokeless tobacco products are used worldwide. Those include both commercialized and local or homegrown products available for oral or nasal use. Products intended for oral use are sucked, chewed (dipped), gargled or applied to the gums or teeth, while fine tobacco mixtures are usually inhaled into the nostrils. Snus is a moist powder tobacco product that is placed under the upper lip for extended periods. Although used similarly to American dipping tobacco, snus does not typically result in the need for spitting and, unlike naswar, snus is steam-pasteurized. Global patterns of smokeless tobacco use vary widely. The countries with a high prevalence (≥10%) represent about 25% of the global adult population (example of prevalence of smokeless tobacco use: Bangladesh (men, 26%; women, 28%), India (men, 33%; women 11-18%), Nepal (men, 31%), Madagascar (men 23%; women, 20%), Mauritania (women, 28%), Norway (men, 17.0%; women, 5.0%), Sweden (men, 26%), Uzbekistan (men, 22.5%) (IARC 2012)).

Smokeless tobacco products contain many of the toxins and carcinogens found in cigarettes (Eriksen et al. 2012; IARC 2012). In 17 brands of moist snuff from the USA, the nicotine content ranged from 0.47 to 3.43%.The nicotine content of Swedish snus ranges from 0.5-1.7%. Carcinogens that have been identified in smokeless tobacco include tobacco-specific N-nitrosamine (NNK, NNN), N-nitrosamino acids, volatile N-nitrosamines, PAHs (benzo[a]pyrene, benz[a]anthracene, chrysene, benzofluoranthenes, and dibenz[a,h]anthracene), formaldehyde, acetaldehyde, acrolein and crotonaldehyde.

The exposure to smokeless tobacco can results in the same diseases as caused by active smoking. Systematic review of the association between smokeless tobacco and cancer in Europe (62 studies) and North America (18 Studies) indicated statistically significant smoking-adjusted association for oropharyngeal cancer (1.4; 1.04–1.8, n=19) and prostate cancer (1.3, 1.1–1.6, n=4). The oropharyngeal association disappeared for estimates published since 1990 (1.0, 0.8 –1.2, n=14), for Scandinavia (0.97, 0.7–1.4, n=7), and for alcohol-adjusted estimates (1.1, 0.8–1.4, n=10) (Lee and Hamling 2009). Of 142,205 smoking-related male US cancer deaths in 2005, 104,737 are smoking-attributable. Smokeless tobacco-attributable deaths would be 1,102 (1.1%) if as many used smokeless tobacco as had smoked, and 2,081 (2.0%) if everyone used smokeless tobacco. In addition, smokeless tobacco use increases periodontal disease, tooth loss, and precancerous mouth lesions (Eriksen et al. 2012; IARC 2012).

Research addressing smokeless tobacco is limited. Monitoring and surveillance systems are scarce, and significant research gaps exist in identifying ingredients, additives and toxicities of smokeless tobacco products. Little is known about product pricing, substitution of smokeless tobacco for smoked tobacco, and youth susceptibility to smokeless tobacco use. Policies to control smokeless tobacco are underdeveloped. The integration of smokeless tobacco control measures into a wider framework of tobacco control can help to curb its use.

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3 Stressors – partially/no Biomarkers of Exposures

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In the last chapter pollutants were listed, for which biomarkers of exposure are available. But there are many pollutants and other stressors for which biomarkers exist, but they are difficult to assess, esp. in the framework of exposome studies. Sometimes stressors lead to specific effects, e.g. asbestos exposure to mesothelioma, but unless there is a tissue biopsy, the asbestos fibres cannot be found. For other stressors no biomarkers of exposure exist, even though they can be well analysed in the environment. An example is ozone, frequently measured in outdoor air; yet there is currently no method to measure ozone in the lung, or blood stream. Chapter 3 will focus on these stressors with partial or no existence of biomarkers of exposure. For an exposome approach it is essential to take these stressors equally into account compared to the measurable biomarkers of exposure.

3.1 Air pollution

WRITTEN BY ANDREW POVEY (UM)

Air pollution can be defined as the contamination of air (either indoor or outdoor) by chemical, physical or biological agents and it can therefore be a complex mixture of these different contaminants. Common sources of air pollution are both man-made (e.g. cars and buses, industry) and natural (e.g. forest fires). Air pollution can have a number of health effects including respiratory and cardiovascular diseases that can be fatal. Pollutants of public health concern include particulate matter (PM; chapter 3.1.1), ozone (chapter 3.1.5) and nitrogen oxides (NO_x; chapter 3.1.4).

3.1.1 Particulate Matter ($PM_{2.5}$, PM_{10})

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Chemistry

Airborne particulate matter (PM) consists of a mixture of solid and liquid particles, suspended in the air, which physical and chemical characteristics can vary with source. Particles can either be directly emitted into the air from natural or anthropogenic sources (primary PM) or be formed within the atmosphere as a result of chemical reactions of gaseous precursors such as nitrogen oxides and sulphur that lead to the formation of substances of low volatility that condense to from secondary PM (Kelly and Fussell 2012).

PM varies in size from a few nanometres to about 100 µm in diameter. PM is traditionally subdivided by their aerodynamic equivalent diameter into fractions that are either ≤10 µm (PM_{10}), ≤2.5 µm ($PM_{2.5}$) or ≤0.1 µm (Ultrafine particles, UFP, also called nanoparticles). A diameter between 2.5 and 10 µm ($PM_{2.5–10}$) has been defined as “coarse” and less than 2.5 µm, as “fine”. Hence PM_{10} contains ultrafine, fine and coarse fractions (Anderson et al. 2012). PM size largely determines their behaviour within the atmosphere and also within the human respiratory tract. The greatest numbers of particles are UFPs but these UFPs contribute little to particle mass. UFPs arise largely from fresh automobile and combustion emissions and as secondary particles produced by gas-to-particle conversion processes. They are inherently unstable with a lifetime of minutes to hours and can grow into larger particles through coagulation and condensation. Geographically they are not distributed (~100s metres) widely

from their source. Fine PM arise from all combustion sources (e.g. coal, oil, gas) and from the coagulation and condensation of smaller particles. Their lifetime is of the order of days to weeks and hence can be distributed more widely from their source (>1,000 km). Coarse particles arise from primary sources such as agriculture, or road dust but also secondary sources. Their lifetime is of the order of hours to days and can distribute 10-100 km from their source (Brook 2008).
The chemical composition of PM can also vary widely and will depend upon their origin. A wide range of different chemical components have been identified including sulphates, nitrates, ammonia, elemental carbon, metals, organic carbon e.g. volatile organic compounds and polycyclic aromatic hydrocarbons (Ghio et al. 2012; Kelly and Fussell 2012). In addition, biological components such as allergens and microbial compounds can be found in PM (Ghio et al. 2012).

Biological Systems Affected and related health effects

Inhalable PM can induce both short-term and long-term health effects including respiratory and cardiovascular morbidity, such as aggravation of asthma, respiratory symptoms and mortality from cardiovascular and respiratory diseases and from lung cancer (Anderson et al. 2012). The World Health Organization estimates that PM contributes to approximately 800,000 premature deaths each year (WHO 2002). The most serious health problems arise in susceptible groups with pre-existing lung or heart disease, as well as elderly people (e.g. cardiovascular and respiratory morbidity and mortality and children (e.g. respiratory effects) (Sacks et al. 2011; Anderson et al. 2012).
Fine PM have been considered as the main culprit of the adverse effects of PM air pollution on human health (Brook et al. 2010) but coarse fractions may also contribute (Brunekreef and Forsberg 2005). UFPs are also increasingly seen as a mediator of PM induced health effects, but the distribution and dispersion of UFPs can differ from that of other PM suggesting a complex interaction between different PMs and induced health effects. PM composition is considered to be a determinant of their capacity for oxidant generation and both organics such as PAHs and metals and inorganic salts are currently seen as being responsible for health effects (Valavanidis et al. 2008).
Sparse data have shown that PM can affect other systems than the cardiopulmonary organs. Gestational exposure to ambient urban PM_{10}, especially during late pregnancy, contributed to lower vitamin D levels in offspring, which could affect the child's risk of developing diseases later in life (Baïz et al. 2012). Two birth cohort studies have linked fine particle ($PM_{2.5}$) exposures with altered lymphocyte immunophenotypic distributions in cord blood (Hertz-Picciotto et al. 2008; Baïz et al. 2011) and possible changes in cord serum immunoglobulin E levels (Baïz et al. 2011). This study also underscored the tight connection between the development of the immune system and that of the central nervous system, and the plausibility that disruption of critical events in immune development may play a role in neurobehavioural disorders. Exposure to PM2.5, and PM10 during pregnancy and during the first year of life was associated with autism and other neurological outcomes (Volk et al. 2013).

Possible Exposure Routes

PMs are emitted from both natural (e.g. wind-blown dust, volcanic ash, soil particles, forest fires) and man-made sources (e.g. fossil fuel combustion in vehicles and power plants, industrial processes and activities, cigarette smoking (Brook 2008; WHO 2013). Levels and the physical and chemical composition of PM will vary in time and space but human exposure is unavoidable. Airborne PM is principally inhaled but can also be absorbed through the skin or retina. However,

more recent data suggest that PM could attain the brain through a systemic inflammatory response and oxidative stress. The brain is particularly vulnerable to oxidative stress, due to its high consumption of oxygen, low level of antioxidants, high levels of polyunsaturated fatty acids and elevated iron content (particularly in the substantia nigra).

Absorption

Size is the principal determinant of how far PM penetrates the respiratory system and in general the smaller the particles the more able they are able to penetrate into the deeper regions of the respiratory tract. Typically PM ≥10 µm are deposited in the nose or throat and cannot reach the lower tissues of the respiratory tract whereas coarse PM will deposit primarily in the primary bronchi and fine PM will penetrate to the alveoli and terminal bronchioles (Kelly and Fussell 2012). The surface areas of the various regions of the respiratory tract differ greatly, so that in terms of dose per unit area, the nasal region is frequently the most heavily affected (Oberdorster 2005). Particle deposition may also be heavy in certain exposed regions such as the spur junction at the division of the airway to the lobes of the lung (Borm et al. 2004). In the alveolar region, where the lungs are most permeable, both UFP and fine particles have high deposition efficiencies of 30 to 60% (between 20 and 40 nm) and 20 to 30% (between 1 and 3 µm) of the inhaled particles respectively (ICRP 1994). PM retained in the lung may translocate and reach other target organs such as the heart and this translocation is most effective for smaller particles. In animal models, PM ≤50 nm were detected in the brain and remote organs, PM ≤1 µm in the blood and ≤10 µm in the lung (Nakane 2012). The dose within organs other than the lung is likely to be considerably lower than that in the lung but may be retained for long periods of time.
Animal studies suggest that PM may access the brain either through the nasal pathway or through the circulation. Fine particles in the central nervous system have been associated with increased brain inflammation in several studies. In one study, levels of several pro-inflammatory cytokines, including whole-brain IL-6 (Interleukin 6) and TNF α (tumour necrosis factor-alpha), among others were elevated in the brains of mice exposed to high levels of particulate matter compared to controls (Campbell et al. 2005). Furthermore, a study of Mexico city residents, showed higher levels of neuroinflammation of the olfactory bulb (as indicated by higher levels of cyclooxygenase-2 (COX 2) and Interleukin-1 beta (IL1β)) and higher concentrations of metals associated with PM (including manganese, nickel and chromium) among inhabitants of urban areas (Calderón-Garcidueñas et al. 2013). A study using autopsies of brains from children and young adults in Mexico City, Mexico found elevation of indices on neuroinflammation and oxidative stress in the brains of participants exposed to high levels of particulate matter (Calderón-Garcidueas et al. 2012; Calderón-Garcidueñas et al. 2013). Higher levels of inflammatory factors in the brain have been linked with increased risk of Parkinson disease (PD) in several studies (Bowler et al. 2006; Finkelstein and Jerrett 2007; Guilarte 2010; Willis et al. 2010; Calderón-Garcidueñas et al. 2013). Exposure to particulate air pollution was also related to cognitive decline in women (Weuve et al. 2012).

Elimination

Lipid or water soluble PM components will be dissolved, diluted and may undergo metabolic transformation before ultimately being excreted. The remaining insoluble PM fraction may accumulate leading to high doses within individual cells in the lungs and other organs. The residence times of these particles in the lungs is limited by clearance mechanisms such as mucociliary clearance which can clear PM larger than about 6 µm from the lungs within 1 to 2 days. However, heavy metals fractions persist even 2 months. UFP can penetrate across

membranes and hence are less likely to be cleared in a similar fashion but they can be eliminated at a much slower rate by uptake by phagocytic or epithelial cells (Geiser et al. 2005).

Reference values

The EU air quality standards for PM_{10} are 50 µg per m^3 over 24 hours and 40 µg/m^3 over a one year period and for $PM_{2.5}$ 25 µg/m^3 over one year (EC 2014).

Specimens for analysis

There are various ways of assessing personal exposure to PM (e.g. mass, number and composition of PM (e.g. Karanasiou et al. 2014)) but there are no specific biomarkers for PM exposure but markers of PM exposure can range from measurements of specific PM components, their metabolites and their reaction with cellular macromolecules such as DNA or protein or other effects on cellular processes. These can be measured in body fluids or within target and non-target tissues (Lewtas 2007) but their usefulness can be exposure and time specific. For example, serum oxidative stress markers (oxidized low-density lipoprotein (Ox-LDL), low-density lipoprotein receptor-1 (LOX-1), thiobarbituric acid reactive substances (TBARS), malondialdehyde (MDA)) but not inflammatory markers (C-reactive protein (CRP), IL-6) may be useful in determining an effect following acute exposures of the lung to PM (Elvidge et al. 2013). Oxidative DNA damage can be increased in the lung and other internal organs following pulmonary and gastrointestinal tract exposure (Møller et al. 2013).

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3.1.2 Polycyclic Aromatic Hydrocarbon (PAHs) in air

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Polycyclic aromatic hydrocarbon (PAHs) and their derivatives are produced by the incomplete combustion of organic material arising, partly, from natural combustion such as forest and volcanic eruption, but with the majority due to anthropogenic emissions. The PAH concentration varies significantly in various rural and urban environments and is mainly influenced by vehicular and domestic emissions (Ravindra et al. 2007).

Chemistry

PAHs compounds are a class of complex organic chemicals, which include carbon and hydrogen with a fused ring structure containing at least 2 benzene rings. Low-molecular-weight PAHs (two and three rings) occur in the atmosphere predominantly in the vapour phase, whereas multi-ringed PAHs (five rings or more) are largely bound to particles. Intermediate-molecular-weight PAHs (four rings) are partitioned between the vapour and particulate phases, depending on the atmospheric temperature. Particle-bound PAHs are considered to be very hazardous to human health. Benzo[*a*]pyrene (B[*a*]P) is often used as a marker for total exposure to carcinogenic PAHs, as the contribution of B[*a*]P to the total carcinogenic potential is high.

PAHs have a relatively low solubility in water (e.g. solubility in water of B[*a*]P at 25 ºC is 3.8 µg/l) but are highly lipophilic (e.g. B[*a*]P log K_{ow} = 6.04) and are soluble in most organic solvents. Once adsorbed on to soil, PAHs have low mobility (e.g. B[*a*]P log K_{oc} = 6.6–6.8). Therefore, once released into the environment and owing to their low aqueous solubility, elevated octanol-water and organic carbon coefficients as well and high melting and boiling points, PAHs have a tendency to be associated with particulate matter, soils and sediments (WHO 2000; Ravindra et al. 2008).

Molecular structure of four representative PAHs are presented in Figure 19.

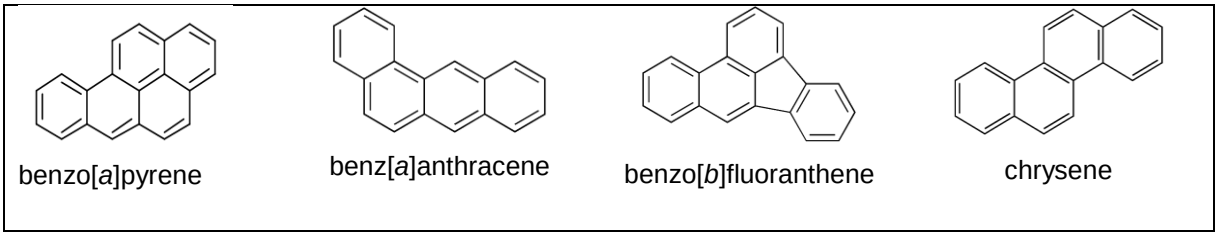

Figure 19: Molecular structure of four representative polycyclic aromatic hydrocarbons (PAHs) (US EPA 2012)

Table 18 lists the priority PAHs, emission sources and phase distribution (ATSDR 2009). Except for benzo[j]fluoranthene in Table 18, the other compounds are also known as 16 priority US EPA PAHs.

Table 18: ATSDR/US EPA priority PAHs (polycyclic aromatic hydrocarbons) and their phase distribution (Ravindra et al. 2007, p. 2898)

PAHs	Particle/gas phase distribution
Acenaphthene	Gas phase
Acenaphthylene	Gas phase
Anthracene	Particle gas phase
Phenanthrene	Particle gas phase
Pyrene	Particle gas phase
Benz[a]anthracene	Particle phase
Chrysene	Particle phase
Benzo[b]fluoranthene	Particle phase
Benzo[j]fluorantheneb	Particle phase
Benzo[k]fluoranthene	Particle phase
Benzo[a]pyrene	Particle phase
Benzo[e]pyrene	Particle phase
Fluoranthene	Particle gas phase
Fluorine	Gas phase
Dibenz[a,h]anthracene	Particle phase
Benzo[ghi]perylene	Particle phase
Indeno[1,2,3-c,d]pyrene	Particle phase

Formation of PAHS

PAHs may be synthesized from saturated hydrocarbons under oxygen-deficient conditions. Pyrosynthesis and pyrolysis are two main mechanisms that can explain the formation of PAHs. Low hydrocarbons form PAHs by pyrosynthesis. When the temperature exceeds 500°C, carbon-hydrogen and carbon-carbon bond are broken to form free radicals. These radicals combine to acetylene which further condenses with aromatic ring structures, which are resistant to thermal degradation. The tendency of hydrocarbons to form PAH structure by pyrosynthesis varies in the order aromatics > cycloolefins > olefins > parafins (Manahan 1994). Pyrosynthesis is the major contributing mechanism to the PAH emissions from the combustion of pulverized coal and tire crumbs. However, survivability of parent PAHs may be a minor mechanism at very high equivalent ratios.

Sources of PAHs

PAHs usually occur in complex mixtures rather than single compounds. These pollutants are mostly formed during the incomplete combustion and pyrolysis of fossil fuels or wood, and from the release of petroleum products (Manahan 1994). Other sources of PAHs include petroleum spills, oil seepage, and diagenesis of organic matter in anoxic sediments. PAHs are also found in coal tar, crude oil, creosote, and roofing tar and a few are used in medicine or to make dyes, plastics, and pesticides. PAHs produced for commercial use, include naphthalene, fluorene, anthracene, phenanthrene, fluoranthene, and pyrene (Franck and Stadelhofer 2011). These pure PAHs usually exit as colourless, white or pale yellow-green solids. In general, there are five major emission sources of PAHs**.**

Domestic emissions are predominantly associated with the burning of coal, oil, gas, garbage, or other organic substances like tobacco or char broiled meat (Smith 1987). Furthermore, wood combustion also constitutes an important factor (WHO 2002).

Mobile sources include the emission from vehicles such as aircraft, shipping, railways, automobiles, off-road vehicles, and machinery. The emission of PAHs from these sources is a function of engine type, load and age, fuel type and quality (e.g. aromaticity), PAH accumulation in lubricant oil, lubricant oil combustion, and driving mode, including cold starting and emission control.

The most important **industrial** sources of PAHs include primary aluminium production, coke production, creosote and wood preservation, waste incineration, cement manufacture, petrochemical and related industries, bitumen and asphalt industries, rubber tire manufacturing, and commercial heat/power production (Ravindra et al. 2007).

Agricultural sources include the stubble burning, open burning of moorland heather for regeneration purposes, and open burning of brushwood and straw. All of these activities involve the burning of organic materials under sub-optimum combustion conditions (Freeman and Cattell 1990; Godoi et al. 2004).

Natural sources of PAHs contain terrestrial sources and cosmic origin sources. Terrestrial sources of PAHs include the non-anthropogenic burning of forests, woodland, and moorland due to lightning strikes (Baumard et al. 1999). Among the cosmic source of PAHs are carbonaceous chondrites, which originate in the main asteroid belt and are not associated with life (Clemett et al. 1993; Sagan et al. 1993; Halasinski et al. 2005).

Atmospheric transport, seasonal trends, residence time, and reactions

The transport, deposition, and chemical transformation of these compounds depends on their gas/particle phase partitioning (Harner and Bidleman 1998). The gas/particle partitioning of PAHs depends on the molecular weight of the compounds, temperature, humidity, and precipitation (Subramanyam et al. 1994; Lee et al. 2005). Baek et al. (1991) also noticed that (i) vapor pressure of the PAHs, (ii) ambient temperature, (iii) PAH concentration/amount, and (iv) type of fine particles present in the atmosphere, can influence partitioning. While reviewing levels and seasonal trends of particulate PAHs in some major cities of the world, Ravindra et al. found comparatively higher concentrations occurring during the winter season. The higher concentrations in winter are most likely due to (a) reduced vertical dispersion due to inversion; (b) lower mixing layer and less intensive atmospheric reactions; (c) enhanced sorption to particles at lower temperature, and (d) increased emissions from domestic heating and power plants during winter with low temperature (Lee et al. 2005; Ravindra et al. 2006; Vasilakos et al. 2007).

Organic substances brought to the atmosphere by evaporation from the earth’s surface or emissions from human activities may be subsequently transported by air masses over long distances. Water in clouds becomes saturated with these substances and precipitation contaminates surface water and land, sometimes far away from the emission sources (Rogge 1993). Removal of PAHs from the atmosphere can be accomplished by dry or wet deposition of particles and vapours. The dry or wet deposition of PAHs from the atmosphere prevails in the removal of particulate compounds and depends on their physico-chemical properties, its vapour-to-particle partitioning and meteorological parameters. In general, PAHs present in the gas phase dissolve within clouds and into raindrops (Golomb et al. 2001; Offenberg and Baker 2002), whereas PAHs bound to particles are washed out from the atmosphere by precipitation (Ravindra et al. 2008).

It was found that dry deposition dominates in the case of the PAHs which are hydrophobic and may be easily bound to particles suspended in air (Golomb et al. 1997). Up to 70% of B[a]P in wet precipitation was found adsorbed on aerosol particles o0.3 mm (Kiss et al. 1997), while naphthalene, due to its solubility in water (31.7 mg/l), is present in the precipitation predominantly as a solute (Manoli and Samara 1999). Although most combustion-derived (pyrogenic) PAHs are deposited close to their source, atmospheric transport can carry significant amount of these compounds to remote locations, and may be found in high-altitude lake sediments, deep sea sediments, and arctic ice and snow. Combustion related PAHs tend to be associated with fine mode vehicle emissions. The concentration of PAHs may vary due to meteorological conditions but high concentrations with high temperature and high solar intensity are considered favourable to photochemical and/or chemical reaction in the atmosphere (Harrison et al. 1996). Photochemical transformations are also considered significant processes for the removal of atmospheric PAHs. Studies suggest that PAHs in the vapour phase are more susceptible to such reactions than particulate phase (Valerio and Lazzarotto 1985; Kamens et al. 1988; Wild and Jones 1995). PAHs in air also exhibit thermal oxidation and can react with a number of atmospheric chemicals to produce derivatives.

Routes of Exposure

Humans are exposed to PAHs through several routes, namely inhalation of air and re-suspended soil and dust, consumption of food and water, and dermal contact with soil and dust. All these sources are relevant to global human exposure. However, while soil contact generally occurs outdoors and food and water consumption is usually indoors, inhalation leads to exposure both indoors and outdoors. Yet people spent 80-93% of their time indoors, and hence indoor air would be the most relevant source contributing to the inhalation route. For smokers and people exposed to passive smoking, contribution from smoking through the inhalation route may be significant (WHO 2010).

The Occupational Safety and Health Administration (OSHA) have set a limit of 0.2 mg of PAHs per m^3 of air. The National Institute for Occupational Safety and Health (NIOSH) recommends that the average workplace air levels for coal tar products not exceed 0.1 mg/m^3 for a 10 hour workday, within a 40-hour workweek (WHO 2010). The concentrations of low-molecular-weight PAHs (two and three rings) are usually higher indoors than outdoors, whereas those of high-molecular-weight PAHs (four rings and larger) are normally higher outdoors than indoors, suggesting that the indoor concentrations of the high-molecular-weight PAHs are dominated by outdoor sources (Naumova et al. 2002).

Absorption

The major route of exposure to PAHs in the outdoor or indoor environment is through the lungs and respiratory tract after inhalation of PAH-containing aerosols and particles. Data on the fate of PAHs in lungs are mainly based on animal and in vitro studies. After deposition in the airways, the structure of the PAH and the dimensions and the chemical nature of the particles define the fate of the PAH. PAHs may dissolve from particles, the remainder in particles may be eliminated by bronchial mucociliary clearance of particles (to be swallowed), or the PAH in particles may remain in the lungs for a longer time. B[*a*]P is rapidly absorbed in the lungs from solutions. After intratracheal instillation of radiolabelled B[*a*]P in rats, the peak concentration in the liver was attained in 10 minutes. The B[*a*]P-associated radioactivity was cleared from lungs with elimination half-lives of 5 and 116 minutes, respectively (WHO 2010).

Excretion

The faeces are the main route of excretion of high-molecular-weight PAHs and their metabolites. Biliary secretion and enterohepatic circulation are significant and increase the concentrations of metabolites and parent compounds in the gastrointestinal tract. PAHs in bile are nearly completely present as metabolites. Less than 1% was detected as B[*a*]P in bile after intravenous administration of B[*a*]P to mice. Urine is the other main excretion route. Some 4-12% of B[*a*]P was excreted in urine in rats compared with 60% of pyrene as metabolites. The role of urine as an excretion route is compound-specific; for large-molecule PAHs, it is a minor route (Kotin et al. 1959; Viau et al. 1999).

Specimens for analysis

See chapter 2.2.3

Reference values

See chapter 2.2.3

Health Hazard information

In the environment, individuals are most likely to be exposed to PAH vapours or PAHs that are attached to dust or other particles in the air (Lewtas 2007). Exposure to PAHs can results in cell mutation (Ravindra et al. 2006).The carcinogenicity classifications verified by the US EPA Carcinogenicity Risk Assessment Endeavor Work Group (US EPA 1994) show that B[a]A, B[b]F, B[k]F, B[a]P, Chr, D[ah]A and Ind are considered to be probable human carcinogens, whereas other PAHs such as AcPy, Ant, B[ghi]P, Flut, fluorene, PA and Pyr are not classified as promoters of the same health risk.

Acute Effects

- Acute animal tests in rats have shown benzo[a]pyrene to have high acute toxicity from oral exposure.

Chronic Effects (Non-cancer)

- Skin exposures to mixtures of carcinogenic PAHs cause skin disorders in humans and animals, and adverse skin effects have been noted in humans and animals following application of solutions containing benzo[a]pyrene.
- An epidemiological study of workers exposed by inhalation to benzo[a]pyrene and other particulate matter reported some respiratory effects. The role of benzo[a]pyrene in this association, however, is unclear.

- Animal studies have reported effects on the blood and liver from oral exposure to benzo[a]pyrene and a slight hypersensitivity response from dermal exposure to benzo[a]pyrene.

Reproductive/Developmental Effects

- No information is available on the reproductive or developmental effects of PAHs in humans.
- Animal studies have indicated that benzo[a]pyrene, via oral exposure, induces reproductive toxicity, including a reduced incidence of pregnancy and decreased fertility. Developmental effects, such as a reduced viability of litters and reduced mean pup weight, have also been noted from oral exposure to benzo[a]pyrene in animals.

Cancer Risk

- Epidemiologic studies have reported an increase in lung cancer in humans exposed to coke oven emission, roofing tar emissions, and cigarette smoke.
- Animal studies have reported respiratory tract tumours from inhalation exposure to benzo(*a*)pyrene and forestomach tumours, leukaemia, and lung tumours from oral exposure to benzo[a]pyrene.
- US EPA has classified seven PAHs (benzo[*a*]pyrene, benz[a]anthracene, chrysene, benzo[b]fluoranthene, benzo[k]fluoranthene, dibenz[a,h]anthracene, and indeno[1,2,3-cd]pyrene) as Group B2, probable human carcinogens.
- US EPA uses mathematical models, based on animal studies to estimate the probability of a person developing cancer from ingesting water containing a specified concentration of a chemical. US EPA has calculated an oral cancer slope factor of 7.3 $(mg/kg/d)^{-1}$ for benzo[a]pyrene.

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3.1.3 Bioaerosols

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Bioaerosols are airborne particles that are composed of, or derived from viruses, bacteria, fungi, animal or plant materials (Douwes et al. 2003). Mould is used to define fungal species (typically ascomycota, deuteromycota, and zygomycota) found in household dust and observed as visible multicellular filaments (Pettigrew et al. 2010). Non-viable bioaerosols (such as those containing pollen) cannot multiply (as they are not alive) whereas viable bioaerosols (containing for example bacteria) are living organisms that can multiply in appropriate conditions (such as a damp home environment).

Chemistry

Bioaerosols consist of pathogenic and/or non-pathogenic microorganisms (such as bacteria, viruses, and fungi), their biological active components (e.g. endotoxins, β(1→3)-glucans, microbial volatile organic compounds (MVOCs) and mycotoxins), plant fragments (e.g. pollen)

and animal-derived materials (e.g. hair, allergens, dander) (Douwes et al. 2003; Korpi et al. 2009; Oppliger 2014). Hence each bioaerosol sample is likely to be unique due to differences in the abundance and type of microorganisms, plant and animal derived materials and other bioactive components (Oppliger 2014). Examples of bioaerosols are shown in Table 19 (Goyer et al. 2001).

Table 19: Mould and bacterial composition of certain bioaerosols (Goyer et al. 2001)

Home/workplaces	**Dominant moulds and bacteria**
Bakeries	*Penicillium, Aspergillus, Cladosporium*
Farms	*Aspergillus, Penicillium, Absidia, Rhizomucor, Fusarium, Wallemia, Curvularia*
House dust	*Alternaria, Aspergillus, Mucor, Trichoderma,Penicillium*
Household waste (composting)	*Aspergillus, Alternaria, Paecilomyces, Penicillium,Trichoderma, Actynomyces*
Offices (ventilation systems/ humidifiers)	*Aspergillus, Alternaria, Cladosporium, Acremonium,Aureobasidium, Rhodotorula, Mucor, Penicillium, Legionella, Pseudomonas*

In indoor air, bioaerosols can consist not only of pollen and spores of plants (coming mainly from outdoors), bacterial, fungi (coming from outdoors or indoors) but also microbes and allergens spread between humans or animals (WHO 2009).

Biological Systems Affected and related health effects

Bioaerosol exposure can result in a number of health effects including infectious and respiratory diseases and cancer (Douwes et al. 2003; Samadi et al. 2013). Infectious diseases result from exposure to pathogenic microorganisms such as amongst the most known Legionnaires disease and Legionellae. Respiratory diseases include both non-allergic (e.g. chronic bronchitis or chronic airflow obstruction) and allergic (e.g. allergic asthma or rhinitis). These symptoms result from airway inflammation caused by specific toxins, pro-inflammatory agents or allergens (from plants, microorganisms, insects and animals) (Douwes et al. 2003). People who are sensitised or who have an existing respiratory condition, such as asthma or allergies, are more likely to suffer adverse effects from bioaerosols (NAS 2004; NTP 2013). Exposure to mould can cause both cutaneous and systemic infections, allergic bronchopulmonary aspergillosis, allergic fungal rhinosinusitis, hypersensitivity pneumonitis, rhinitis and asthma (Pettigrew et al. 2010; Heinrich 2011; Hulin et al. 2012). Moulds are also at the origin of non-allergic asthma and rhinitis through microbial volatile organic compounds (Korpi et al. 2009). Mycotoxins are low-molecular-weight, non-volatile, secondary metabolites produced by fungi that can cause a range of acute and chronic ill-health including nausea, vomiting, renal toxicity, hepatotoxicity and cancer (Pettigrew et al. 2010). Lastly, epidemiological studies suggest an association between bioaerosols and sick building syndrome, and toxicological studies have provided some evidence supporting biological plausibility. This could be due to a nonspecific inflammatory response to bioaerosols, modified by psychosocial factors such as stress (Laumbach and Kipen 2005).

Possible Exposure Routes

Inhalation is considered the primary way that people are exposed to bioaerosols though exposure can also occur through the skin (e.g. mould) or through food contamination (e.g. mycotoxins) (Marin et al. 2013; NTP 2013). Bioaerosols are ubiquitous being found in both home and work environments with their size distribution varying depending upon their source (Goyer et al. 2001; Thomas 2013; Oppliger 2014). Levels can be high in certain industries (e.g. agriculture, waste management, textile and wood industries) and are associated with known occupational diseases (e.g. farmer’s lung in agriculture) (Oppliger 2014). In the home environment, dampness and inadequate ventilation can lead to microbial growth and bioaerosol formation (WHO 2009).

Absorption/Elimination

Absorption of particles within the lung has been described elsewhere (chapter 3.1.1 on Particulate Matter) and bioaerosol size will also determine their site of deposition within the lung. Clearance mechanisms will depend upon site of deposition e.g. phagocytic with the lung or mucociliary escalators within the nose or trachea (Thomas 2013). Specific chemicals (e.g. mycotoxins), once absorbed through the lung or gut can undergo metabolism that are potentially more toxic (e.g. DNA damaging) and/or more easily eliminated from the body (Turner et al. 2012).

Reference values

There are few exposure limits proposed for bioaerosols. This includes an occupational exposure limit for endotoxins of 90 endotoxin units/m^3, based on acute respiratory effects and a lowest observed effect level of 100,000 spores/m^3 for non-pathogenic and non-mycotoxin producing fungal species based on inflammatory respiratory effects (Eduard et al. 2012).

Specimens for analysis

Given bioaerosol heterogeneity, there is no one specific method or approach that is applicable for all exposures (Caruana 2011; Eduard et al. 2012) and a variety of methods have been used in epidemiological studies (e.g. for mould exposure as described in Heinrich (2011) and Hulin et al. (2012)). In general, exposure can be assessed by capturing the bioaerosols and then analysing the resulting sample (Caruana 2011). Bioaerosol samplers range from impaction devices (impactors and impingers) to cyclones and inhalable dust cassettes: size fractionation of bioaerosols can also be carried out using impactor devices (Eduard et al. 2012). A variety of different techniques have been described to assay the sample including cell culture, molecular based analysis or recognition (via detection of DNA, protein or other specific chemicals), and physical detection (e.g. microscopy: Caruana (2011)). The cellular effects of samples (e.g. cytokine release) can also be assayed (Oppliger 2014). Cell culture methods are widely used but may underestimate the total number of microorganisms present (as many cannot be cultured) and also do not quantify dead cells that may retain their allergenic or toxic properties (Oppliger 2014). Microbial organisms and/or their by-products can be detected in blood and tissues and such approaches are widely used for diagnostic purposes (e.g. Beirão and Araujo 2013) and are beyond the scope of this review. Biomarkers of MVOCs and mycotoxin exposure have been described (Korpi et al. 2009; Turner et al. 2012).

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3.1.4 Nitrogen oxides (NO_x)

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Chemistry

There are seven oxides of nitrogen that may be present in ambient air (Table 20) but the sum of NO and NO_2 is generally referred to as NO_x. N_2O, NO and NO_2 are the most abundant nitrogen oxides in the air.

Table 20: Type and some properties of Nitrogen oxides present in ambient air (WHO-IPCS 1997)

Oxide	Name	Boiling Point (°C)	Properties
NO	Nitric oxide	-151.8	Colourless gas, slightly water soluble
NO_2	Nitrogen dioxide	21.2	White solid/reacts with water to give nitrous acid (HNO_2) and nitric acid (HNO_3)
NO_3	Nitrate	-	-
N_2O	Nitrous oxide	-88.5	Colourless gas, water soluble
N_2O_3	Dinitrogen trioxide	47 (decomposes)	Deep blue solid/ reacts with water to give HNO_2
N_2O_4	Dinitrogen tetroxide	21.2	Reacts with water to give HNO_2 and HNO_3
N_2O_5	Dinitrogen pentoxide	3.24 (decomposes)	Reddish-brown gas, reacts with water to give HNO_2

Biological Systems Affected

Nitrogen oxides (NO_2, N_2O_4, N_2O_3 and N_2O_5) are irritating to the eyes, skin, mucous membranes, the upper respiratory tract and lungs even at low concentrations. Short-term NO_2 exposure is associated with increased airway responsiveness, often accompanied by respiratory symptoms, particularly in children and asthmatics (US EPA 2008). Gas cooking has been related to asthma and impaired respiratory health in women and children. A recent meta-analyse showed increased risks of hypertensive disorders in pregnancy for NO_x and NO_2 (Alim et al. 2014; Kile et al. 2014; Pedersen et al. 2014). Long-term exposure also results in respiratory health effects and has been associated with cardiovascular disease and adverse perinatal effects especially in susceptible subgroups (Cal/EPA 2007). NO_2 exposure has been associated with all-cause mortality (Cesaroni et al. 2013).

Possible Exposure Routes

The primary route of exposure to nitrogen oxides is by inhalation, but exposure by any route can cause systemic effects. N_2O, NO, and NO_2 are the most abundant nitrogen oxides in the air but the types and concentration of NO_x can vary greatly with location time of day and season. The main sources of NO_x emissions are combustion processes though there are natural sources of NO_x including microbial activity in soils, lightning, and wildfires (US EPA 2008). Fossil fuel power stations, motor vehicles and domestic combustion appliances emit NO_x, mostly in the form of NO and to a lesser extent NO_2. NO is converted to NO_2 in the atmosphere (WHO-IPCS 1997). N_2O is a greenhouse gas emitted as a trace component of some combustion sources and has biogenic sources including plants and yeasts (US EPA 1999).

Absorption

NO_2 and NO is almost completely absorbed in the respiratory tract following inhalation (70-90%) (Ewetz 1993; WHO 2005). Inhaled NO_2 is partly dissolved in the mucous of the upper airways and can be removed by the nasopharynx. Modelling indicates that NO_2 deposition will be highest at the junction of the conducting airways and the gas exchange region of the lungs. NO_2 or its reaction products can remain in the lung for prolonged periods though it (or its products) can also be detected in extra-pulmonary sites (WHO 2005).

Elimination

Once absorbed in the lung, NO_x can react with water to form nitrous and/or nitric acids or with other extra-cellular constituents including anti-oxidants. These can remain in the lung or are taken up, translocated via the bloodstream and other body fluids and excreted *via* the urine. These reaction products are a significant contributor to NO_x induced toxicity. NO is biotransformed within the body by a number of different routes to form a variety of metabolites including nitrite and nitrate, S-nitroso proteins and S-nitrosothiols which act as a store for NO (Kelm 1999). NO is an important endogenous second messenger within several organ systems.

Reference values

The current WHO guideline values are 40 µg/m^3 (annual mean) and 200 µg/m^3 (1-hour mean).

Specimens for analysis

NO_2 can be measured in outdoor air, indoor air and personal air by passive samplers (Varshney and Singh 2003; Yu et al. 2008) but not directly in body fluids but the products of NO_x interactions with cellular components, and the effects of such exposure have been detected (Halatek et al. 2005). NO in exhaled breath is a marker for lung diseases and is a potential marker of ambient air pollution (Berhane et al. 2014).

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3.1.5 Ozone (O_3)

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Chemistry

Ozone (O_3) is a highly reactive, though poorly water soluble, gas at physiological temperature (boiling point -112°C). Ozone at ground level is one of the major constituents of photochemical smog and arises from the reaction of oxygen with O(3P) ground state oxygen, that is produced by ultraviolet radiation (UV) induced decomposition of NO_2 (see Figure 20). Oxidation of volatile organic compounds (VOC) leads to free-radicals that combine with NO to form NO_2. These precursor compounds (VOC and nitrogen oxides (NO_x)) can arise from both anthropogenic and natural emissions (US EPA 2013).

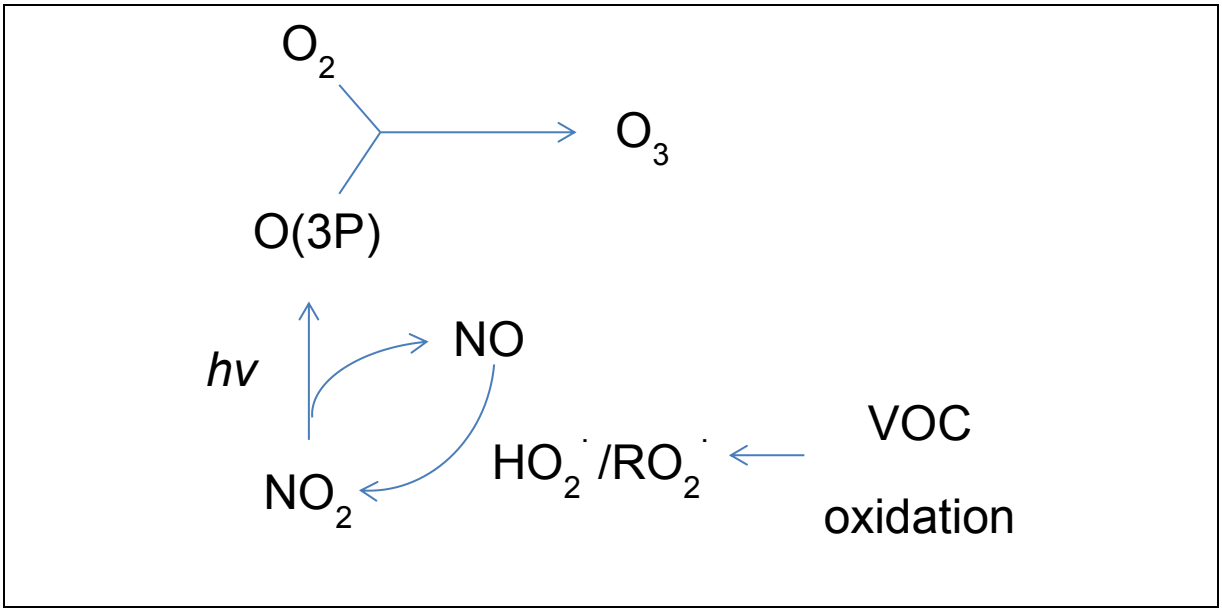

Figure 20: Formation of ozone by reaction of oxygen with a ground state oxygen atom.

Biological Systems AAffected

Short-term O_3 exposure causes respiratory morbidity including respiratory symptoms, lung inflammation and airway hyperresponsiveness, and is likely to cause cardiovascular effects and increased total mortality whilst there is more limited evidence for central nervous system effects. Longer-term ozone exposure is likely to cause respiratory effects including lung function declines, increases in inflammation and the development of asthma but evidence is more limited for cardiovascular, reproductive, developmental, and central nervous effects and increased total mortality (US EPA 2013). Recent data suggest that exposure to outdoor ozone increases the risk of pregnancy-induced hypertensive disorders (Pedersen et al. 2014). Higher associations between ozone exposure and health outcomes were observed with unemployment or lower occupational status and weak evidence of sensitivity for racial/ethnic minorities and persons with low education, in poverty, or without central air conditioning. Findings show that some populations, especially the elderly, are particularly sensitive to short-term ozone exposure (Bell et al. 2014).

Possible Exposure Routes

The main exposure of the general population occurs by inhalation, particularly of outdoor air where concentrations are highest but also through indoor air due to air transfer. O_3 is used in a wide variety of industrial processes (e.g., as disinfectant in the production of drinking water) and is an incidental by-product of other activities (e.g., electric arc welding) (HSE 2014).

Absorption

Inhalation is the primary route of O_3 exposure. In humans, at rest, total ozone uptake in the entire respiratory tract is 80-95% efficient. About half of the ozone that is absorbed from the airstream will be removed by the upper respiratory tract and most of the remainder in the lungs. The amount of O_3 that is absorbed is affected by the shape and size of the respiratory tract, and the route of breathing (nose or mouth), as well as how quickly and deeply a person is breathing (US EPA 2013).

Elimination

O_3 is unlikely to penetrate far beyond the lung’s extracellular lining fluid and the epithelial cell layer as it will react with the lining fluid and cellular constituents including anti-oxidants, proteins, lipids and fatty acids. These reactions result in the formation of secondary oxidation products that can initiate numerous cellular responses not only within the respiratory system but elsewhere in organ systems (US EPA 2013). Pulmonary cancer initiation and promotion has been linked to a series of biochemical pathways of oxidative stress, DNA oxidative damage, macrophage stimulation, telomere shortening, modulation of gene expression and activation of transcription factors with important role in carcinogenesis (Valavanidis et al. 2013).

Reference values

In the EU the air quality standard is 120 micrograms per cubic metre (µg/m^3) based on a maximum daily 8 hour mean (EC 2014).

Specimens for analysis

Sensitive and accurate methods are available to measure the levels of ozone in ambient air, but no methods have been developed to determine the dose of ozone that reaches tissues in the respiratory tract. The reaction products of ozone with cellular constituents can be measured in blood, urine or other fluids but no specific markers for ozone exposure are currently available. Oxidation products measured in blood, plasma or urine do not appear to be appropriate markers of ozone exposure (Kadiiska et al. 2013).

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3.2 Water

WRITTEN BY MERCÈ GARÍ & JOAN O. GRIMALT (CSIC)

Water is essential to sustain life. The availability and access to safe drinking-water is necessary to humans, and it is required for all usual domestic purposes, including drinking, food preparation and personal hygiene. Water of high quality is required for certain purposes, such as food production and pharmaceutical and medical uses (WHO 2011).

Unintentional chemical pollutants (including radionuclides) and microbial hazards found in drinking-water may pose a risk to the human health (WHO 2011). Therefore, water treatment is of unquestionable importance in the supply of safe drinking-water. Depending on the type of treatment (e.g. filtration, sedimentation, absorption, disinfection) pathogenic microorganisms are destructed, and small particles and organic or inorganic compounds are removed from the water.

Microbial hazards

Microbial hazards such as pathogenic bacteria, viruses and parasites (e.g. protozoa and helminths) are the most common and widespread health risk associated with drinking-water. Human health effects caused by waterborne transmission vary in severity from mild gastroenteritis to severe and sometimes fatal diarrhoea, dysentery, cholera, hepatitis and typhoid fever, among other diseases, and this is still a challenge in developing countries. In our environment, however, many disinfection treatments are used to eliminate microbiological contamination of drinking-water. Chlorine-based chemicals are the most common products in use due to the versatility, effectiveness, low cost and retentive power of chlorine (Judd 2000). However, chlorination and related disinfection treatments (e.g. bromine-based disinfectants, ozone) have some disadvantages such as the formation of undesired disinfection by-products (DBPs) by reaction with organic matter, which can pose a risk to human health (Richardson et al. 2007; Zwiener et al. 2007). Notwithstanding, the risks associated with exposure to DBPs are small compared to an inadequate disinfection of the water for daily use, including drinking, bathing and swimming in pools (WHO 2011).

Chemical pollution

Chemical contamination of drinking-water is associated with chronic effects, generally medium to long term, such as cancer, neurological and reproductive effects, which require longer exposures and are more difficult to assess. There are a broad range of chemical pollutants in drinking-water, including metals, nitrates, pesticides and herbicides, radioactive isotopes, as well as the aforementioned DBPs (Richardson et al. 2007; Richardson and Ternes 2014). In developed countries, water quality is generally poor due to chemical pollution, and it raises concerns in public health (WHO 2011). For instance, several studies have recently determined pharmaceuticals and illicit drugs in urban groundwaters and wastewaters, but at concentrations in the order of nanograms per litre (ng/l) that are significantly below than those which could pose a threat to the human health (Postigo and Richardson 2014). In fact, humans should drink more than a hundred litre of water to achive a concentration of milligram per litre (mg/l), which could lead with adverse health effects. Therefore, the effects of some of these pollutants, although they are detected in drinking-water, are irrelevant for the human health.

In 1998, the EU approved the Drinking Water Directive on the quality of water intended for human consumption (Council Directive 98/83/EC). The Directive established the essential quality standards at EU level through the regular monitoring of 48 microbiological, chemical and indicator parameters (EU 1998).

This chapter investigates the exposure and health effects of certain chemical pollutants, specifically those originated in the disinfection process of water: disinfection by-products (DBPs, chapter 3.2.1) and more specifically, trihalomethanes (THMs), the most common DBP found in drinking-water (chapter 3.2.2).

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3.2.1 Disinfection by-products (DBPs)

WRITTEN BY MERCÈ GARÍ & JOAN O. GRIMALT (CSIC)

Disinfection by-products (DBPs) result from reactions between organic and inorganic matter in water with chemical treatment agents during the water disinfection process (Richardson et al. 2007). Water disinfectants are highly reactive compounds, and chlorine is one of the most commonly used for water disinfection. Different disinfectants produce different types of DBPs. Although more than 600 DBPs have been reported in the literature, only a small number has been assessed either in quantitative occurrence or health-effects studies (Richardson et al. 2007).

The most common DBPs are trihalomethanes (THMs; see chapter 3.2.2) and haloacetic acids (HAAs) (Villanueva et al. 2003). Other DBPs include haloacetonitriles, haloketones, halofuranones (such as mutagen X or MX), chlorite, chlorate and bromate, among others (Richardson et al. 2007). Chlorite and chlorate can be formed from hypochlorite (liquid bleach) or chlorine dioxide (Adam and Gordon 1995). Bromate is primarily the result of disinfection with ozone – the reaction of ozone with bromide ions in water produces bromate.

Chemistry

THMs (see chapter 3.2.2) are organic compounds with three halogen molecules (Figure 21). They are fully described in the following section (chapter 3.2.2).

HAAs are carboxylic acids in which halogen atoms takes the place of hydrogen atoms in an acetic acid molecule (Figure 21). The most common HAAs are monochloroacetic acid (MCAA), dichloroacetic acid (DCAA), trichloroacetic acid (TCAA), monobromoacetic acid (MBAA) and dibromoacetic acid (DBAA); these compounds are usually referred as HAA_5.

Chlorite, chlorate and bromate are easily dissolved in water and fairly stable (Figure 21).

3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX) has both an open and closed form, and several of these analogues have been found in drinking-water (Richardson et al. 2007).

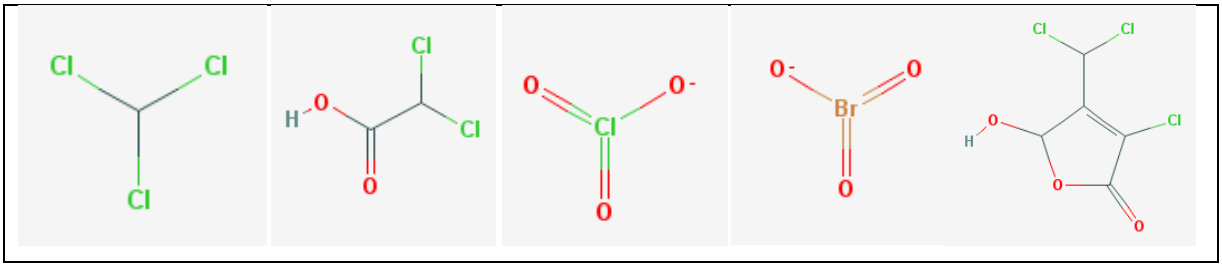

Figure 21: Chemical structure of certain disinfection by-products (DBPs). From left to right: chloroform (a trihalomethane, THM), dichloroacetic acid (an haloacetic acid, HAA), chlorate, bromate and mutagen X (MX) (NCBI 2014)

Effects on Biological Systems

Chronic exposure to DBPs in drinking-water has been associated with cancer, specifically an increased risk of bladder cancer (Villanueva et al. 2007). Chloroform, bromodichloromethane (both THMs), dichloroacetic acid (HAA), bromate and MX have been classified by the IARC as possible carcinogenic to humans (group 2B; see Glossary). MX is a potent mutagen in bacteria and in cells in vitro (Richardson et al. 2007). Chlorite is not considered to be carcinogenic to humans, but it is associated with haemolytic anaemia and allergic dermatitis (WHO 2005). At high concentrations, certain HAAs (e.g. dichloroacetic acid and trichloroacetic acid) can cause severe skin and eye irritation. Trichloramine and other volatile chemicals in swimming pools are respiratory irritants. In fact, pool attendance has been associated with asthma and other respiratory effects, as well as short-term changes in respiratory biomarkers (Font-Ribera et al. 2009, 2010b). Moreover, genotoxic effects have been found in swimmers exposed to DBPs in indoor swimming pools (Kogevinas et al. 2010).

Possible Exposure Routes

DBPs are found in drinking water from public water supplies. Humans are mainly exposed to DBPs through the ingestion of drinking water (WHO 2004), but also through inhalation and dermal contact during domestic activities such as bathing, showering, washing dishes and doing laundry (Font-Ribera et al. 2010a). DBPs are also found in disinfected swimming pools, where swimmers are additionally exposed to them by both inhalation and dermal contact (Lourencetti et al. 2012). Chlorite and chlorate may occur in foodstuff as a result of their use in certain food processing and packaging, as well as in other uses (WHO 2005).

Absorption

DBPs are incorporated into humans mainly by ingestion of drinking water. DBPs are rapidly absorbed in the intestinal tract. DBPs may also be inhaled and absorbed through the skin. HAAs, unlike THMs, are non-volatile compounds, hence having low dermal absorption.

Elimination

Excretion of chloroform, the main THM, occurs primarily via the lungs. For HAAs, the primary pathway involves dechlorination and oxidation, and the metabolites are then excreted in the urine. Chlorite is primarily excreted in the urine, but also in the faeces.

Reference values

Based on US EPA, the maximum allowable levels for total THMs in drinking-water is 80 µg/l; for HAA_5, 60 µg/l; for bromate, 10 µg/l; and for chlorite, 1 mg/l. Based on the WHO, guideline values for DBPs in drinking-water is 300 µg/l for chloroform, 100 µg/l for bromoform and DBCM (dibromochloromethane), 60 µg/l for BDCM (bromodichloromethane), 20 µg/l for MCA acid, 50 µg/l for DCA acid, 200 µg/l for TCA acid, 700 µg/l for chlorite and chlorate, and 10 µg/l for bromate (WHO 2011). Biomonitoring equivalents (BEs) for THMs in blood are as follows: 230 pg/ml for chloroform, 80 pg/ml for BDCM, 20 pg/ml for DBCM, and 130 pg/ml for bromoform (Aylward et al. 2013).

Specimens for analysis

Human biomonitoring of DBPs include several matrices, such as blood and exhaled breath (Kogevinas et al. 2010; Riederer et al. 2014). Blood total THM levels in the general population of the US are in the range of 18 pg/ml (LaKind et al. 2010; Riederer et al. 2014). Indirect monitoring of DBPs includes the analysis of tap water from public supplies, water from swimming pools and indoor air at home or in swimming pools (Font-Ribera et al. 2010b; Kogevinas et al. 2010).

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3.2.2 Trihalomethanes (THM)

WRITTEN BY MERCÈ GARÍ & JOAN O. GRIMALT (CSIC)

Trihalomethanes (THMs) are formed as a by-product predominantly when chlorine is used to disinfect water for drinking or in swimming pools. Chloroform is the most representative THM (Figure 22).

Chemistry

THMs are organic compounds that contain one single atom of carbon attached to three halogen molecules (e.g. chlorine, bromine or a mixture of both of them). THMs are volatile substances that can vaporise from water to environmental air depending on many variables (e.g. vapour pressure, water solubility). The main THMs are chloroform, bromoform, dichlorobromomethane and dibromochloromethane (Figure 22).

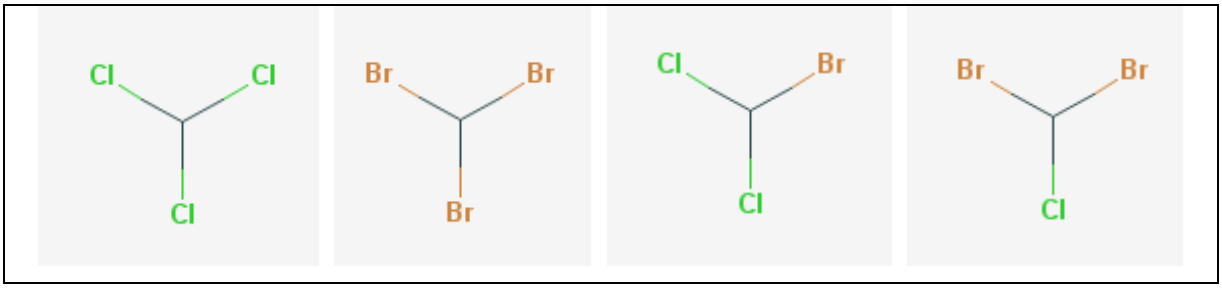

Figure 22: Chemical structure of certain THMs. From left to right: chloroform, dichlorobromomethane, dibromochloromethane and bromoform (NCBI 2014)

Effects on Biological Systems

THMs are carcinogenic and genotoxic compounds in experimental models (Richardson et al. 2007). Chloroform and bromodichloromethane have been classified by the IARC as possibly carcinogenic to humans (group 2B; see Glossary). Human ingestion of THMs has been associated with bladder cancer (Villanueva et al. 2006; Hamidin et al. 2008), colon cancer (Hamidin et al. 2008) and adverse outcomes on respiratory function and asthma (Nickmilder and Bernard 2007; Font-Ribera et al. 2009). In fact, chlorinated swimming pool attendance of children and adolescents is related to asthma, allergy and other respiratory diseases (Bernard et al. 2007, 2009), probably due to exposure to THMs. Prenatal exposure to THMs is associated with adverse reproductive outcomes such as small for gestational age, intrauterine growth retardation and preterm delivery (Nieuwenhuijsen et al. 2002, 2009; Aggazzotti et al. 2004).

Possible Exposure Routes

THMs are found in drinking water from public water supplies. Humans are mainly exposed to these compounds through the ingestion of drinking water (WHO 2004). THMs are volatile at room temperature and can be detected in ambient air during domestic activities such as bathing, showering, washing dishes and laundry (Backer et al.; Gordon et al. 2006; Font-Ribera et al. 2010a). Humans are then exposed to these compounds by dermal contact and inhalation. THMs are also found in chlorine and bromine disinfected swimming pools. Swimmers are additionally exposed to these compounds by both inhalation and dermal contact (Lourencetti et al. 2012). THMs have been detected in several foodstuffs (e.g. decaffeinated coffee, olive oil, pork; (Bauer 1981)) and in soft drinks (e.g. Cola; (Abdel-Rahman 1982; Entz et al. 1982; Wallace et al. 1984)).

Absorption

THMs are incorporated into humans through ingestion, inhalation and dermal contact (WHO 2004). Once ingested, THM are absorbed in the intestinal tract. Inhalation of THMs can occur at home (e.g. showering, bathing) or swimming in swimming pools (Font-Ribera et al. 2010a). Depending on the type of activity and level of effort in the case of swimmers, the concentration of THMs inhaled may be variable (Font-Ribera et al. 2010b). Absorption of THM through the skin depends on a range of factors, including the period of contact with the water, the temperature of the water and the concentrations of the compounds (WHO 2004). Chloroform distributes throughout the whole body, mainly in fatty tissue, blood, liver, kidney, lungs and nervous system.

Elimination

THMs are eliminated in the expired air, and also in urine and faeces (WHO 2004). In fact, THMs are detected in exhaled breath, in urine and faeces (Lourencetti et al. 2010).

Reference values

In the EU, the limit value for THMs in drinking water is 100 µg/l. The WHO TDI (tolerable daily intake) for chloroform, bromoform and dibromochloromethane is 15 µg/l, 21.4 µg/l and 17.9 µg/l, respectively (WHO 2004). Biomonitoring equivalents (BEs) for THMs in blood, as mentioned in chapter 3.2.1 (disinfection by-product, DBPs), are as follows: 230 pg/ml for chloroform, 80 pg/ml for BDCM, 20 pg/ml for DBCM, and 130 pg/ml for bromoform (Aylward et al. 2013).

Specimens for analysis

THMs are detected as parent compounds. Human biomonitoring of THMs include several matrices, such as blood and exhaled breath (Aggazzotti et al. 1998; Font-Ribera et al. 2010b; Kogevinas et al. 2010; Lourencetti et al. 2010). In a study conducted in 2010 based on 49 adult swimmers, mean concentrations of total THM in exhaled breath before and after swimming in an indoor chlorinated pool for 40 minutes were 1.2 µg/m^3 and 7.9 µg/m^3, respectively (Font-Ribera et al. 2010b; Kogevinas et al. 2010). Indirect monitoring of THMs includes the analysis of tap water from public supplies, water from swimming pools and indoor air at home or in swimming pools (EC 1997; Font-Ribera et al. 2009, 2010a; Lourencetti et al. 2012). Concentrations of THMs in drinking-water from several countries in Europe can vary in a range of <1 to 200 µg/l (EC 1997). In the aforementioned study conducted in a swimming pool, mean concentrations of total THM in pool air and water were 74.1 µg/m^3 and 45.4 µg/l, respectively (Font-Ribera et al. 2010b; Kogevinas et al. 2010).

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3.3 Noise

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Noise is each vibration transmitted through an elastic solid or a liquid or a gas, with frequencies in the approximate range of 20 to 20,000 hertz, capable of being detected by human organs of hearing. Loudness of sound is assessed in decibel (dB). The weakest sound heard is 0 dB, the loudest sound possible is 194 dB.

According to the European Environment Agency (www.eea.eu), in the EU 27 countries, about 100 million persons are exposed to road traffic noise above 55 dB (L_{DEN}, the Day Evening Night Sound Level). Exposure to railway noise affects 16 million individuals, aircraft noise 4 million and industry noise 1 million persons.

It is estimated that DALYs (disability-adjusted life years) lost from environmental noise are 61,000 years for ischaemic heart disease, 45,000 years for cognitive impairment of children, 903,000 years for sleep disturbance, 22,000 years for tinnitus and 654,000 years for annoyance in the European Union Member States and other western European countries (WHO 2011).

Health effects of noise

Although the proportion of people reporting to be exposed to noise exposure is substantial, health effects of noise have been investigated only recently. Experimental and observational data have shown that elevated noise can cause both auditory and non-auditory health effects (Röösli 2013). Hearing impairment and loss initially restricted to occupational settings where they are highly prevalent are nowadays increasing also at the population level due to excessive social noise exposure to music concerts, fireworks, traffic, jet engines, etc.. Non-auditory health effects include objective noise-induced effects as hypertension and ischemic heart disease as well as subjective effects as annoyance. In terms of objective health effects, there is some evidence of an association among environmental noise exposure and blood hypertension and ischemic heart disease (Stansfeld and Crombie 2011). Evidence is less consistent for other cardiovascular diseases and for cognitive effects. Experimental studies addressing the impact of acute exposure to noise showed negative effects on speech perception and listening comprehension. These effects are more pronounced in children as compared to adults. Children with language or attention disorders are still more impaired than age-matched controls. Noise-

induced disruption was also found for non-auditory tasks like serial recall of visually presented lists and reading. The impact of chronic exposure to noise was examined in quasi-experimental studies. Indoor noise and reverberation in classroom settings were found to be associated with poorer performance of the children in verbal tasks. Regarding chronic exposure to aircraft noise, studies consistently found that high exposure is associated with lower reading performance (Klatte et al. 2013). The association between metabolic syndrome and noise has rarely been investigated so far. Recently an association between road traffic noise and diabetes was observed in a large Danish cohort study (Sorensen et al. 2013). A 10 dB higher level of average road traffic noise at diagnosis and during the 5 years preceding diagnosis was associated with an increased risk of incident diabetes, with incidence rate ratios (IRR) of 1.08 (95% CI: 1.02, 1.14) and 1.11 (95% CI: 1.05, 1.18), respectively, after adjusting for potential confounders including age, body mass index, waist circumference, education, air pollution (nitrogen oxides), and lifestyle characteristics. In addition changes in the immune system and birth defects have been attributed to noise exposure (Passchier-Vermeer and Passchier 2000). However, in a recent review, chronic noise exposure during pregnancy was not associated with birth weight, preterm birth, congenital anomalies, perinatal and neonatal death based on 6 cohort, 4 case-control, and 2 cross-sectional studies (highest evidence level 2+ (Hohmann et al. 2013). There was some evidence supporting an association of chronic noise exposure with increased systolic blood pressure and stress hormone levels in urine and saliva in children evaluating 2 cohort and 15 cross-sectional studies (highest evidence level 2). Noise-related annoyance has been shown to be responsible for sleep disturbance, stress-related symptoms, and even poor well-being (Passchier-Vermeer and Passchier 2000). Recent data have brought up moderate evidence that the presence of vegetation can generally reduce the negative perception of noise (supported with an electroencephalogram test in one of the experimental studies; consistent with the data from two epidemiological studies; one experiment found no effect and one was inconclusive about the positive effect) (Dzhambov and Dimitrova 2014).

Some studies showed that associations between noise level and cardiovascular outcomes were stronger with respect to noise exposure at night (Maschke 2003; Jarup et al. 2008).

Tinnitus is defined as the sensation of sound in the absence of an external sound source. Tinnitus caused by excessive noise exposure has long been described; 50% to 90% of patients with chronic noise trauma report tinnitus. In some people, tinnitus can cause sleep disturbance, cognitive effects, anxiety, psychological distress, depression, communication problems, frustration, irritability, tension, inability to work, reduced efficiency and restricted participation in social life.

Possible mechanisms

In the case of auditory effects, experimental studies have shown that noise-induced hair-cells and nerves damage involved in hearing loss may depend on oxidative stress (Basner et al. 2014). Direct physiological responses and psychological stress responses are involved in non-auditory effects. Acute exposure to noise has been associated with excitement of the autonomic nervous and endocrine systems which cause the release of stress hormones (including catecholamines and glucocorticoids). Chronic exposure to noise has been shown to engender an imbalance in the organism homoeostasis (its ability to keep the conditions inside it the same despite any changes in the conditions around it), which affects the metabolism and the cardiovascular system. Studies of the combined effects of noise and air pollution by showing independent statistical effects of these two stressors support the hypothesis of different underlying mechanisms namely cognitive and autonomic stress response *vs.* inflammatory processes, respectively.

Noise sources

There is a wide array of potentially troublesome noise sources that can exist in even the most benign lab environments. There are natural sources of noise which are native to the environment and man-made sources. Some noise sources are hard to characterize as belonging to either category. Natural sources include seismic movement, building sway, wind, ocean waves, solar events and Earth’s magnetic field. Man-made sources include umps and other machinery, foot traffic, vehicle traffic, moving parts within instrument, construction, mining operations, human voices, pumps and other machinery, machines, radio communication, noise floor constraints, construction and industry, community sources (neighbours, radio, television, bars and restaurants); and social and leisure sources (portable music players, fireworks, toys, rock concerts, firearms, snowmobiles, etc..

Assessing noise

“Europe is acting to fight noise pollution. The Environmental Noise Directive (2002/49/EC) requires EU Member States to determine the exposure to environmental noise through strategic noise mapping and elaborate action plans to reduce noise pollution. Since June 2007, EU countries are obliged to produce strategic noise maps for all major roads, railways, airports and agglomerations, on a five-year basis. These noise maps are used by national competent authorities to identify priorities for action planning and by the European Commission to globally assess noise exposure across the EU. This information also serves o inform the general public about the levels of noise to which they are exposed, and about actions undertaken to reduce noise pollution to a level not harmful to public health and th e environment” (Kephalopoulos et al. 2012, p. 11).

“A common approach for assessing noise levels in Europe is an important prerequisite for improving the effectiveness of implementing the Environmental Noise Directive. This will help in obtaining consistent and comparable figures on the number of people exposed to noise levels in and across EU Member States. To achieve this, Article 6.2 of the Directive foresees the development of a harmonised methodological framework for noise assessment. In 2009, the European Commission decided to develop CNOSSOSEU (Common NOise aSSessment MethOdS) for noise mapping of road traffic, railway traffic, aircraft and industrial noise” (Kephalopoulos et al. 2012, p. 11).

Noise Indicators

“The long-term average noise indicator specified in European Directive 2002/49/EC is the day-evening-night indicator, L_{den}, defined by:

$$L_{DEN}=10 \times \lg \left\{ \frac{12}{24} 10^{L_{day}/10} + \frac{4}{24} 10^{(L_{evening}+5)/10} + \frac{8}{24} 10^{(L_{night}+10)/10} \right\}$$

where:

L_{day} (respectively $L_{evening}$ and L_{night}) is the A - weighted long - term average sound level, as defined in ISO 1996 - 2: 2007, determined over all the day (respectively evening and night) periods of a year, and obtained on the basis of $L_{eq,T}$ […]. The day is 12 hours, the evening four hours and the night eight hours, and a year is a relevant year as regards the emission of sound and an average year as regards the meteorological circumstances. Day, evening and night periods may be defined slightly differently at national level. The parameters used in the various formulations are usually defined locally in the respective sections. A few general parameters are

common to the formulations and they are summarised in the following two tables” (Kephalopoulos et al. 2012, p. 27).

Table 21: Noise parameters (Kephalopoulos et al. 2012, p. 28)

L_p	Instantaneous sound pressure level	[dB] (re. 2 10^{-5} Pa)
$L_{Aeq,LT}$	Global long-term sound level L_{Aeq} due to all sources and image sources at point R	[dB] (re. 2 10^{-5} Pa)
L_w	‘in situ’ sound power point of level of a point source (moving or steady)	[dB] (re. 10^{-12} W)
$L_{w,i,dir}$	Directional ‘in situ’ sound power level for the *i*-th frequency band	[dB] (re. 10^{-12} W)
$L_{w'}$	Average ‘in situ’ sound power level per metre	[dB] (re. 10^{-12} W)

Table 22: Other physical parameters (Kephalopoulos et al. 2012, p. 28)

p	r.m.s of the instantaneous sound pressure	[Pa]
p_0	Reference sound pressure =2.10-5 Pa	[Pa]
W_0	Reference sound power= 10-12 W	[Watt]

Noise from different sources can be measured or described in different ways. In addition, the sounds and noises people hear are not steady. Apart from variation in tones, the magnitude or the sound pressure level of a sound or noise changes with time. The n-percent exceeded level, L_n, is the sound pressure level exceeded for n percent of the time. In other words, for n percent of the time, the fluctuating sound pressure levels are higher than the L_n level. L_n can be obtained by analyzing a given noise by statistical means. The commonly used value of n for the n-percent exceeded level, L_n, is 10, 50, and 90. L_{10} is the level exceeded for 10% of the time. For 10% of the time, the sound or noise has a sound pressure level above L_{10}. For the rest of the time, the sound or noise has a sound pressure level at or below L_{10}. These higher sound pressure levels are probably due to sporadic or intermittent events. L_{50} is the level exceeded for 50% of the time. It is statistically the mid-point of the noise readings. It represents the median of the fluctuating noise levels. L_{90} is the level exceeded for 90% of the time. For 90% of the time, the noise level is above this level. It is generally considered to be representing the background or ambient level of a noise environment. For a varying sound, L_{10} is greater than L_{50} which in turn is greater than L_{90}. L_{eq} has been introduced as a descriptor of the constant noise level which, under a given situation and time period, contains the sas a descriptor oame acoustic energy as the actual time-varying noise level. As L_{eq} measures the energy content of a noise over a period of time, noise with different characteristics, such as fluctuating (e.g. from traffic) or impulsive noise (e.g. from hammering) as described in the next section, can give the same L_{eq} Level.

Assessment of exposure to noise at the population level requires consideration of many factors, including (http://www.euro.who.int/__data/assets/pdf_file/0008/136466/e94888.pdf).

- measured exposure or calculated/predicted exposure
- choice of noise indicator
- population distribution
- time-activity patterns of the exposed population
- combined exposures to multiple sources of noise.

The exposure of the population of interest to the noise source can be obtained by measurement or by using models that calculate noise exposure based on information about the source and on information about sound propagation conditions from source to receiver

There are many methods and tools to assess traffic noise. One of the commonly adopted methods for the assessment of road traffic noise is based on the procedures given in the UK Department of Transport document "The Calculation of Road Traffic Noise (CRTN)".

The assessment method gives corrections to adjust the reference noise level for traffic flow (such as traffic volume and speed), road surface correction, distance, ground effect (soft or hard), barrier and reflection effects etc.

The road traffic noise is presented in terms of noise levels exceeded for 10% of the one-hour period for the hour having the peak traffic flow. The symbol is L_{10} (1hour) and the unit is dB(A). The assessment point is taken to be at 1 m from the external facade. This approach follows the CRTN and is commonly adopted in other international environmental noise standards. Studies elsewhere have shown that environmental noise assessed outside people's home, correlate well with people's response to the noise. Furthermore the setting of environmental standards at fa cade can avoid complications due to reflection from furniture and walls of the room.

Reference values

The WHO recommended daytime sound level of 55 dB ($L_{Aeq\ 16h}$, the average level of sound pressure within 16 hours using an A-filter for frequency weighting) and night time recommendation of 45 dB ($L_{Aeq\ 8h}$). The level at which sustained exposure may result in hearing loss is 90-95 dB. Ear pain begins at 125 dB and even short-term exposure at 140 dB can cause permanent damage. However, even sound levels as low as 40 dB(A) (about as loud as a refrigerator or library) can generate noise complaints and the lower threshold for noise producing sleep disturbance is 45 dB(A) or lower.

Specimens for analysis

There are no specific markers for noise exposure in the case of non-auditory effects. However, reactions at the organism level can be assessed in terms of effect (immune system, cardiac response).

Unmet needs

Further studies are required to explore gender differences, the effects of day and night time exposure, and exposure modifying factors.

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3.4 Nanoparticles (NPs) and Ultrafine Particles (UFPs)

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A nanoparticle (NPs) also called ultrafine particle (UFPs) is a small object, between 1 and 100 nanometres (1 nanometre= 10^{-9} meter) (<0.1 micrometres or microns) in size that behaves as a whole unit with respect to its transport and properties. Although NPs and UFPs are synonymous, the term NPs is generally reserved to nanoparticles that are manufactured. However, in the present text, the NPs and UFPs terms are reported as presented in the papers of reference.

NPs can present as an aerosol (mostly solid or liquid phase in air), a suspension (mostly solid in liquids) or an emulsion (two liquid phases). There exist different types of NPs: inorganic NPs like magnetic (supermagnetic iron oxide) nanoparticles, metallic (gold or silver) nanoparticles, nanoshells (dielectic silica core in a thin gold shell), ceramic (silica, titanium, aluminium) NPs and organic NPs like those from lipids, proteins, polysaccharides among others. The principal parameters of NPs are their shape (including aspect ratios where appropriate), size, and the morphological sub-structure of the substance they are formed with. NPs have a long history as they were already used in the ninth century in Mesopotamia. However, NPs research has developed only in the past decades. Two are the directions of NPs research: health impact and potential applications in biomedical, optical and electronic fields. Only health impact is dealt with in this report.

Chemistry

The composition of a specific NP can be very complex, depending on what interactions it has had with other chemicals or particles and on its lifetime (http://ec.europa.eu/health/scientific_committees/opinions_layman/en/nanotechnologies/l-3/3-nanoparticle-properties.htm). NPs have different ways of interacting with each other. They can

remain free or group together depending on the attractive or repulsive interaction forces between them. These interactions remain difficult to characterize. Nanoparticles suspended in gas tend to stick to each other more readily than in liquids. The chemical processes taking place on the surfaces of nanoparticles are very complicated and remain largely unknown. Of note, in the presence of certain chemicals, properties of the substances forming the nanoparticles may be modified. It has been observed that at the nanoscale, materials behave very differently compared to larger scales (Zhang 2014).

Biological Systems Affected and health effects

NPs/UFPs are of great concern to human health because of their small size and high catalytic properties. In literature, it is hypothesized that a chronic exposure to their high number concentrations and their vast surface area, transporting various toxicants, injure tissues or cells and induce inflammation including neuroinflammation.

At the molecular level, UFPs influence signalling cascades, the actin-cytoskeleton pathway, immunoregulation, reactive oxygen species generation to trigger histaminic response, mast cell activation, and pro-inflammatory changes. Mutagenic and carcinogenic effects are also expected based on complementary evidence on the carcinogenic potential of diesel exhaust in humans (Roy et al. 2014). The molecular changes are considered to be the subclinical effects that manifest disease exacerbations or the predisposition of subjects to pathologies after exposure to UFPs. Experimental research and animal experiments documented inflammatory reactions to nanoparticles within the alveoli and other parts of the respiratory system (Andujar et al. 2011). Both *in vivo* and *in vitro* studies consistently found biological effects of nanoparticles on the respiratory system, including oxidative stress generation, proinflammatory and prothrombotic effects, pulmonary fibrosis (an increase of connective tissue in the lung) and emphysema, and DNA damage after an exposure to nanoparticles.

In terms of health effects, UFPs in urban ambient have been found to be toxic to the respiratory, cardiovascular, and nervous systems (Kumar et al. 2013). UFP exposures have been associated with increased cardiovascular mortality and morbidity, while ongoing research supports adverse systemic and cardiovascular health effects after NP exposures (Shannahan et al. 2012). Adverse cardiovascular health effects include alterations in heart rate variability, hypertension, thrombosis, arrhythmias, increased myocardial infarction, and atherosclerosis through a variety of mediators and mechanisms. Human epidemiological studies and controlled animal studies have also shown that exposure to air pollution may lead to neurotoxicity that may contribute to the etiology of neurodevelopmental disorders, including autistic spectrum disorders (Costa et al. 2014).

Possible Exposure Routes

Human inhalation exposures to manufactured nanoparticles and airborne ultrafine particles continues to increase in both occupational and environmental settings.NPs may get released into the environment in high amounts. Studies on the number concentrations of particles of aerodiamtre <0.1 microns show tens of thousand times greater levels in urban aerosol than in nonurban aerosol. NPs can enter inside of an organism and attain several systems and organs through various routes such as dermal, oral and respiratory tract. Scientists could prove that nanoparticles/ultrafine particles reach the blood system via the alveoli after being inhaled. It was also shown in experiments that nanoparticles can enter the body through the skin as well as the olfactory epithelium, from where they travel along nerve fibers directly into the central nervous

system (Aschner 2009). It is the innate immune system (complement system and scavenger receptors) that indirectly and directly recognize NPs as foreign (Roy et al. 2014).

Absorption

Little is known about the behaviour of NPs/UfPs in the environment and their interaction with the biological systems. After entering the systemic circulation via the different routes of exposure NPs/UFPs are distributed to the various organ systems including blood cells, liver, spleen, kidney, testis, thymus, heart, lung and brain. NPs/UFPs are deposited deep in the tissues, translocate, and skip the innate clearance mechanisms. After retention for a long time, these can infiltrate into the interstitium and permeate cells. Once there, immediately after being exposed to body fluids, NPs interact with a heterogeneous mixture of proteins and numerous different cell types that modify the nanoparticle surface and affect their bioavailability (Prantner and Scholler 2014).

Mechanisms of NPs toxicity include injury of epithelial tissue, inflammation and oxidative stress response and depend on the physicochemical parameters of the NPs (Roy et al. 2014). In vitro and animal studies have shown that NPs are capable of activating proinflammatory cytokines, chemokines and adhesion molecules with recruitment of inflammatory cells. These changes may impact the homeostasis of the immune system and the consequent immune system derangement can lead to increases in the incidence of autoimmune, allergic and even neoplastic diseases.

In the case of cardiovascular diseases, UFPs and NPs, as well as their soluble components, are known to systemically translocate from the lung (Shannahan et al. 2012). Translocated particles could mediate cardiovascular toxicity through direct interactions with the vasculature, blood, and heart. Recent study suggests that sensory nerve stimulation within the lung may also contribute to UFP- and NP-induced acute cardiovascular alterations. Activation of sensory nerves, such as C-fibers, within the lung may result in altered cardiac rhythm and function. Release of pulmonary-derived mediators into systemic circulation has also been proposed to facilitate cardiovascular effects. Pulmonary-derived mediators include proinflammatory cytokines, oxidatively modified macromolecules, vasoactive proteins, and prothrombotic factors contributing to the subsequent prothrombotic, atherogenic, and inflammatory effects after exposure (Shannahan et al. 2012).

The genotoxicity of some nanomaterials, e.g., metal oxides like ZnO, TiO2, CuO and carbon based materials has commonly been related to oxidative stress, and subsequent inflammation (Rittinghausen et al. 2013).

Human epidemiological studies and controlled animal studies have also shown that exposure to air pollution may lead to neurotoxicity (Costa et al. 2014). In addition, air pollution exposure has been associated with increased expression of markers of neurodegenerative disease pathologies.

Elimination

Elimination time is important to be known in view of risk assessment associated with NPs. The primary organs responsible for nanoparticle bioelimination are kidney, liver, and spleen. In an animal study of rats exposed to a 28-day oral exposure to silver NP, silver was cleared from most organs after 8 weeks postdosing, but remarkably not from the brain and testis (Van Der Zande et al. 2012). Still in rats, gold nanoparticles administrated through intravenous injections were identified in almost all Kupffer cells one day after the injection, but the fraction of gold-loaded cells gradually decreased to about one fifth after 6 months. Transmission electron

microscopic analysis showed that over time an increasing part of the total amount of gold NPs in the liver was contained in fewer macrophages accumulated in growing clusters (Sadauskas et al. 2009).

Reference values

There are no reference values for NPs. However, exposure to NPs is indirectly limited by references values for $PM_{2.5}$ and PM_{10} that contain NPs. An understanding of the immunotoxic effects of manufactured or engineered nanoparticles would help in the development of safety guidelines by authorities to promote nanotechnology for applications without hazard.

Specimens for analysis

There are no specific markers for NPs exposure. However, as previously described for larger PMs, markers of NPs exposure can range from measurements of specific NPs components, their metabolites, their reaction with cellular macromolecules such as DNA or protein or other effects on cellular processes taken in various biospecimens.

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3.5 DNA-damaging agents

Human DNA (deoxyribonucleic acid) can be damaged as a result of exogenous exposures (e.g. occupation, lifestyle and chemotherapy), endogenous cellular and physiological processes (e.g. metabolism of dietary substrates, inflammation). This damage includes single and double strand breaks and covalent modifications of the four nucleobases and phosphates. Cell death and gene mutations are but two of the consequences of DNA damage but not all damage has a biological effect. In addition, cell specific factors (e.g. DNA repair) will help to determine the consequences of DNA damage. DNA damage can increase cancer risk and associations between DNA damage and other diseases, such as infertility, neurodegenerative and cardiovascular ill-health, have been described. As an example, of the issues involved in assessing exposure, there will be a section on the alkylating agents (chapter 3.5.4).

3.5.1 Ultraviolet (UV)

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Chemistry

Ultraviolet (UV) radiation is part of the non-ionizing region of the electromagnetic spectrum emitted by the sun. It is arbitrarily divided into the following three bands: UVA 315-400 nm, UVB 280-315 nm, UVC 100-280 nm (IARC 2009), though these bands can vary slightly. As sunlight passes through the atmosphere, all UVC and approximately 90% of UVB radiation is absorbed, particularly, by ozone. UVA radiation is less affected by the atmosphere so that UV radiation reaching the Earth’s surface is largely composed of UVA with a small UVB component (Lucas et al. 2006).

Biological Systems Effected

Small amounts of UV are essential for the production of vitamin D in people and can have beneficial effects for rickets, osteoporosis and osteomalacia. Acute excessive exposure will lead to sunburn and photokeratitis and conjunctivitis whereas prolonged human exposure may result in immune effects (e.g. activation of latent virus infection), and can affect the eyes (e.g. Cortical cataract, Pterygium) and skin (e.g. solar keratosis) (Lucas et al. 2006). UV radiation is classified as carcinogenic to humans causing malignant melanoma and other skin and eye tumours (WHO-IPCS 1994; Lucas et al. 2006; IARC 2009).

Possible Exposure Routes

Exposure to UV occurs from both natural and artificial sources. For most people, the sun is the major source of UV exposure though for some people, artificial sources, such as the use of artificial tanning devices and high intensity sources used in industry such as welding arcs, may contribute significantly to exposure (NRPB 2002). It is also used in the treatment of certain diseases such as psoriasis. In almost all circumstances humans are exposed simultaneously to UVB and UVA, and UVB and UVA exposures vary more or less in parallel.

Absorption

UV can be absorbed, reflected or scattered by the human skin so that the actual exposure received by skin layers will be lower than that original exposure (WHO-IPCS 1994). The longer the wavelength the deeper the penetration but the shorter the wavelength the greater the

biological effect e.g. UVB is more effective in inducing erythema than UVA (Birch-Machin et al. 2013). While UVB is fully absorbed by the cornea, UVA passes through to the lens. Among adults only 1 per cent or less of incoming UV radiation reaches the retina because of the filter function of cornea and lens.

Elimination

UV is strongly absorbed by proteins and DNA and the primary products are generally reactive species or free radicals which form extremely quickly but which can produce effects that can last for hours, days or even years.

Reference values

Exposure limits for occupationally exposed workers have been described (ICNIRP 2010).

Specimens for analysis

Whilst personal UV exposure has largely been measured in epidemiological studies by recall of exposure, other methods of exposure assessment include personal dosimetry of UV radiation can be achieved through polysulphone film badges (NRPB 2002; Worswick et al. 2008). UVA and UVB can both contribute to DNA damage and cause oxidative stress. Mitochondrial DNA damage in human skin (Birch-Machin et al. 2013) and urinary levels of thymine dimers (Liljendahl et al. 2013) have been used as markers of UV exposure.

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3.5.2 Radon (Rn)

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Chemistry

Radon (Rn) is a radioactive gas found in nature. It has no colour, odour or taste and is chemically inert. It is a decay product of uranium and thorium which are found in most soils and granite.

The three naturally occurring radon isotopes ^{222}Rn ($T_{1/2}$=3.8 days), ^{220}Rn ($T_{1/2}$=55.8 sec) and ^{219}Rn ($T_{1/2}$=3.98 sec) are formed on the alpha decay of their radium isotopes ^{226}Ra, ^{224}Ra and ^{223}Ra, respectively. All radon isotopes are noble gases, occurring as nonpolar, monomatic molecules, and are inert for practical purposes (Ishimori et al. 2013).

A principle characteristic of radon that gives it more radiological significance than earlier members of the uranium (and thorium) decay chains it the fact that it is a noble gas. As such, once it is formed in radium-bearing material, a radon atom is relatively free to move. Radon can reach air or water to which humans have access, provided that transport is sufficiently rapid to be completed before the radon decays (Nazaroff and Nero 1988; US EPA 2014).

Radon atoms located within the soil grains are unlikely to become available for release to the atmosphere, owing to their very low diffusion coefficients in solids. However, if they are located in the interstitial space between grains, they may diffuse to the surface. Therefore, releases of radon from the residue repository to the atmosphere take place by the following series of processes:

- Emanation-radon atoms formed from the decay of radium escape from grains (mainly because of recoil) into the interstitial space between the grains.
- Transport-diffusion and adjective flow cause the movement of the emanated radon atoms through the residue of soil profile to the ground surface.
- Exhalation-radon atoms that have been transported to the ground surface and then exhaled to the atmosphere (Ishimori et al. 2013).

Biological Systems Affected

The majority of sources of natural radiation are harmless to humans in the ambient environment. However, radon, a large component of the natural radiation that human are exposed to (greater than sixty percent of total radiation), can pose a threat to the public health when radon gas accumulates in poorly ventilated residential and occupational settings. In buildings with high radon levels, the main mechanism of entry of radon is flow of soil gas through cracks in the floor (mainly in cellars and ground floor). In addition, certain building materials can act as significant sources of indoor radon (lightweight concrete with alum shale, phosphogypsum and Italian tuff) (UNSCEAR 2006).

Concentrations of radon in the outdoor environment are affected not only by the magnitude of release rate from the ground to the atmosphere but also by atmospheric mixing phenomena (UNSCEAR 2006). It is important to stress that natural radon releases from soil are higher in some areas in Europe (sites with high radon exhalation over large surrounding areas) and lower in the isolated islands or coastal regions (Dubois 2005; UNSCEAR 2006).

The biggest problem is not radon by itself, but its decay products. What particularly distinguishes the decay products from ^{222}Rn is their chemical activity: the decay products can attach to airborne particles, to indoor (macroscopic) surfaces, and to the human respiratory tract, where they can deposit either directly or after attachment to airborne particles. In addition, the detailed behaviour and health significance of the decay products is greatly influenced by their half-lives and decay modes. The alpha decays imparting the radiation dose of greatest significance are those of the polonium (Po) isotopes ^{218}Po and ^{214}Po (Nazaroff and Nero 1988; WHO 2009; US EPA 2014).

Possible Exposure Routes

The primary route of exposure to radon and its progeny is inhalation. Charged radon particles can easily bind to available aerosolized particles such as dust and other particulates. Once bound to aerosolized particles, the charged progeny can easily be transported throughout the environment via wind action, and more importantly, can be inhaled by respiring animals and humans. The radon progeny can be inhaled either as free particles or particles that are attached to dust. Because they are ionized, the progeny preferentially attach to the respiratory epithelium – particularly the bronchi – the site of most lung cancers. Most of the radon gas inhaled will be exhaled (due to the relatively long half-life of radon gas) before it can decay and deposit a significant radiation dose to the lung tissue (Nazaroff and Nero 1988; WHO 2009; Ishimori et al. 2013; US EPA 2014).

It is estimated that there are about 21,000 lung cancer deaths in the USA (US EPA 2014) and about 20,000 in EU (Dubois 2005) caused by radon.

The second possible route of exposure to radon is oral ingestion, particularly from dissolution of radon in drinking water. Drinking water containing radon can present a risk of developing internal organ cancers, primarily stomach cancer. However this risk is much smaller than the risk of developing lung cancer from radon released to air from tap water. EPA estimates that radon in drinking water causes about 168 cancer deaths per year, of which only 11% are caused by stomach cancer and 89% from breathing radon from water (US EPA 2014).

Absorption

The radon progeny deposit on the mucus lining of the respiratory tract through impaction, sedimentation and diffusion. The radon daughters act as soluble substances and are released from the dust particles after they undergo solvation. The depth at which a radon progeny can incorporate into the respiratory tract is related to the size of the aerosolized particle it is attached to. The total respiratory radon progeny deposition is 18-51% of the inhaled amount. The larynx and trachea deposition is approximately 22% of the inhaled amount

Oral ingestion of water with dissolved radon gas in it can release charged radon daughters which attach to the stomach lining when the stomach contents are agitated. If the radon is in the uncharged gaseous phase, it can be absorbed into the blood stream through the stomach or intestinal walls and distributed throughout the body. The majority of radon absorption following ingestion in water occurs in the stomach and small intestine, and only 1% to 3% of the ingested radon remains to enter the large intestine.

Once radon has entered the blood stream it is distributed among the organs according to the blood flow to them and the relative solubility of radon in the organs as compared to the blood. Radon dissolved in blood that enters the lung will equilibrate with air in the gas-exchange region and be removed from the body. Greater than 90% of the absorbed dose is eliminated by exhalation in less than one hour (WHO 2009; US EPA 2014).

Elimination

The radon progeny are eventually cleared from the respiratory tract through mucociliary action or engulfment by macrophages, but because of their short half-life, the progeny can release alpha particles before being removed.

Since radon is highly fat soluble and actively transported through the body on the coattails of lymphocytes, common organs of destinations are the liver (5%), kidney (1.6%), lungs (90% - primarily for elimination), and other adipose tissue stores. Once the dissolved gas decays and becomes charged, it can bind and decay further within various body tissues, and emit harmful, mutagenic and cytotoxic, alpha particles.

Long-lived radon progeny have been detected in excreted urine.

The absorption of radon following ingestion of a meal high in fat is delayed (deals with the high solubility of radon in fat) (Nazaroff and Nero 1988; US EPA 2014).

Reference values

The concentrations of ^{222}Rn in typical soil ranges from 4 to 40 kilobecquerel per cubic metre (kBq/m^3), several orders of magnitude higher than ^{222}Rn concentrations in the outdoor atmosphere (10 to 100 becquerel per cubic metre (Bq/m^3)). Worldwide indoor concentrations of ^{222}Rn range from 9 to 184 Bq/m^3. In Croatia average concentrations in indoor air is 35 ± 18 Bq/m^3 with the range from 20 to 92 Bq/m^3 (UNSCEAR 2006, 2011).

In the new BSS (Basic Safety Standards), European Commission suggested reference level for indoor radon concentrations for workplaces to <300 Bq/m^3 (European Council 2014).

Specimens for analysis

Biomarkers of exposure to radon and its progeny include the presence of radon progeny in several human tissues and fluids, including: lung, bone, teeth, hair, urine, and blood. Although the presence of radon progeny in these tissues and fluids indicate exposure to radon, exposure to uranium or radium may also result in the presence of these decay products.

Biomarkers of radon or radon progeny exposure may be present after any exposure duration (acute, intermediate, and chronic). Because of the relatively short half-lives of most radon progeny, with respect to a human lifetime, the time at which the biological sample is taken relevant to time of exposure may be important. However, for the longer lived progeny the time factor is less critical (Nazaroff and Nero 1988).

Radiation-induced changes in the supramolecular organization of the membranes, including the plasma membrane as well as different cell organelle membranes, can play a significant role in the development of radiation effects (UNSCEAR 2006). Although several potential biomarkers of radon exposure have been studied, at this time chromosome aberrations appear to be the most promising (UNSCEAR 2006; Robertson et al. 2013).

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3.5.3 Electromagnetic Fields

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Non-ionising electromagnetic fields (EMF) of all frequencies represent one of the most common and fastest growing environmental influences. All populations are now exposed to EMF, and the levels and duration of exposure are expected to continue to increase as technology advances.

Chemistry

Electromagnetic fields are classified into ionizing and non-ionizing, according to their frequency (measured in Hertz, Hz), since the ability of an electromagnetic wave to ionize an atom or molecule depends on its frequency. The electromagnetic spectrum extends from static field to cosmic rays. Non ionizing electromagnetic fields are classified according to their frequency in static, extremely low frequency (ELF), intermediate frequency (IF) and radiofrequency (RF) fields.

Static Fields

Static fields do not vary with time and therefore have a frequency of 0 Hz. Sources of static magnetic fields (SMF) can be found in occupational settings, e.g. metal (aluminium) industries, welding processes and certain underground and train systems, but the main source of humans, either as staff or patients, to static magnetic fields is from magnetic resonance imaging (MRI). During MRI a main magnet is used to generate a primary static field. Clinical imaging systems typically have field strengths up to 3T (1T = 10,000 Gauss, for reference the Earth’s magnetic field ≈ 0.5 Gauss) while spectroscopic systems, currently only used for research applications, are available with field strengths as high as 17.5T (McRobbie et al. 2007). The number of people with implanted metallic devices such as pacemakers that can be affected by static magnetic fields is growing.

Extremely Low Frequency (ELF)

The main source of extremely low frequencies (up to 50/60 Hz) is alternating current (AC) carried in power lines, wiring and household appliances. Besides power lines and household appliances, important sources of extremely low frequency fields include power plants and substations, welding machines, induction heaters and railway, tramway and subway systems. Medical applications of ELF fields include bioimpedance measurement, pain treatment and bone growth stimulation (SCENIHR 2007).

Intermediate Frequency (IF)

Intermediate Frequency electromagnetic fields extend from 300 Hz to 100 kHz. Examples of sources of IF are some anti-theft devices operated at the exits of shops, induction hotplates, computer and television screens which use cathode ray tubes, compact fluorescent lamps, as well as some radio transmitters (SCENIHR 2007).

Radio Frequency (RF)

RF electromagnetic fields extend from 3 kHz to 300 GHz. The main source of RF since the late 1990s are from the use of mobile communication such as mobile phones (ICNIRP 1998). Other RF sources are mobile phone base stations, broadcasting antennas (AM and FM), new digital TV technology and civil and military radar systems. Sources include other wireless applications, like cordless phones or WLAN systems, operate with lower output power than mobile phones levels (SCENIHR 2007). During MRI examinations, patients also get exposed to RF superimposed upon the main static field (McRobbie et al. 2007).

Possible Exposure Routes

The public is exposed to electromagnetic fields generated by an increasing variety of electrical and electronic devices and installations. The rapid increase in mobile telecommunications and the growing range of personal, domestic, commercial and medical equipment have considerably increased the number of sources of EMF exposure and are significantly changing the level, type and pattern of everyday exposure of the public.

Biological Systems Affected

The potential adverse health effects of ELF applications such as power lines and power plants have received much attention over the last twenty some years, especially in relation to childhood leukaemia. Despite differences in study design and setting, results of many studies are sufficiently consistent to believe that an increased risk of leukaemia does indeed exist in children with high exposure (Belpomme et al. 2007; Hartwig et al. 2009). In particular, several studies have shown that there is an association between childhood leukaemia and proximity of home address at birth to high voltage power lines, and the apparent risk extends to a greater distance than would have been expected from previous studies (Draper et al. 2005).

However, over the last ten years most clinical studies on EMF have been directed at mobile phone-related health effects and examine potential carcinogenic effects and effect on cardiovascular and endocrine systems. A wide range of behavioral tests have been used to examine cognitive function and attention in humans yet no consensus arises (Ghosn et al. 2013).

There is epidemiologic evidence suggesting a link between exposure to RF from prolonged heavy cell phone usage and the development of an ipsilateral brain tumour. Daily prolonged use of mobile phones associated with a long-term use of it for ≥10 years give some increased risk of

brain tumours (Hardell et al. 2007) although confounding cannot be excluded. Results indicate that using a cell phone for ≥10 years approximately doubles the risk of being diagnosed with a brain tumour on the same ("ipsilateral") side of the head as that preferred for cell phone use (Khurana et al. 2009). Effects such as glioma, meningioma or non-CNS cancers caused by long-term and heavy use require further investigation (Baan et al. 2011). Based on the most recent cohort and incidence time trend studies, it appears that the evidence for glioma became weaker while the possibility of an association with acoustic neuroma remains open (SCENIHR 2013).

For breast cancer and cardiovascular disease, recent research has indicated that an association with ELF is unlikely (EC 2008). No consistent relationship has been demonstrated between ELF fields and a) cerebral circulation (Ghosn et al. 2012). There are studies in which protein expression changes have been observed as a cause of a long term EMF radiation. These changes may be related to brain plasticity alterations, indicative of oxidative stress in the nervous system or involved in apoptosis and might potentially explain human health hazards, such as headaches, sleep disturbance, fatigue, memory deficits and tumour risk (Fragopoulou et al. 2012; Pelletier et al. 2013). In addition, idiopathic environmental intolerance attributed to electromagnetic fields (‘electromagnetic hypersensitivity’) describes a series of medically unexplained and subjective symptoms reported as a result of exposure to electrical devices. Depending on the area, it is reported by 1-10% of the general population, but to date there is no medically accepted mechanism through which these may occur while double-blind provocation studies to date have also failed to provide evidence of a causal association (Rubin et al. 2010).

It should also be noted that the available literature suggests that EMF exposure may modify the effects of chemicals or other physical agents (SCENIHR 2013). However, the reports on combined effects lack consistency and are not linked to specific experimental conditions. Further research is needed in order to clarify any relevance of combined exposures to human cancer risk under real life exposure conditions, and to explore the potentially beneficial (protective) effects of such exposures.

Reference values

The Council Recommendation of 12 July 1999 (European Council 1999) on the limitation of exposure of the general public to electromagnetic fields (0 Hz to 300 GHz) fixes basic restrictions and reference levels for the exposure of the general public to electromagnetic fields (EMFs). Specifically assessment was provided for radio frequency (RF) (100 kHz <f ≤ 300 GHz), intermediate frequency (IF) (300 Hz <f≤ 100 kHz), extremely low frequency (ELF) (0 <f≤ 300 Hz) and static fields (0 Hz). The European Commission relies on the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) to review periodically new information that may influence the assessment of risks to human health in this area and to provide regular updates on the scientific evidence base to the Commission. SCENIHR published its opinions on March 2007 (SCENIHR 2007), January 2009 (SCENIHR 2009a), July 2009 (SCENIHR 2009b) and a preliminary opinion on November 2013 (SCENIHR 2013). While these opinions do not yet identify any scientific rationale that could justify a modification of the Council Recommendation, they give particular attention to issues affected by important gaps in knowledge in previous opinions and make recommendations for additional research on this issue.

Specimens for analysis

EMF may influence cellular activities through ion channel, enzymatic alteration and structural changes in macromolecules. It had been proposed that electric fields affect charge distribution

at interfaces but penetrate into the interior by polarizing the interface and forming an electric double layer with mobile charges in a protein or DNA (Behari and Paulraj 2007). In general, we are far from having identified robust biomarkers of exposure to EMF or early biomarkers of effect. During medical examination, a method that has proven useful is to use stress associated findings for diagnosis and follow-up and to evaluate them synoptically. Basic diagnostic tests should be carried out as a first step, followed by measurements of EMF exposure as a second step. Only then can specific diagnostic tests be considered.

Putative yet non-specific biomarkers that have been proposed by the EMF Working Group of the Austrian Medical Association (ÖAK) as diagnostic markers of electro-hypersensitivity (EHS) include i) blood sugar levels (levels in EHS individuals increase after 30 minutes of EMF exposure), ii) Electro-Encephalographical (EEG) Analysis (EHS persons are expected to show large expressiveness in alpha-rhythm parietal-occipital areas), iii) Heart Rate Variability (HRV) tests (with EHS individuals experiencing rapid changes in heart rate variability when exposed to cordless phones and Wi-Fi routers) and iv) hormone analysis (EMF exposure has been found to disrupt the production of hormones such as melatonin and adrenaline in EHS individuals) (ÖAK 2012). Furthermore, biomarkers such as melatonin (ii) Ca^{2+} (iii) Ornithine decarboxylase (ODC), (iv) protein kinase, (v) Na^{+}–K^{+} ATPase have been suggested as conceivable indicators of cell growth and development (Behari and Paulraj 2007). It has to be underlined that the above are non-specific markers and thus cannot be used as effective markers of exposure or effect associated with exposure to EMF in the context of HEALS. Much stronger evidence on specificity of these markers is needed to adopt them for environment and health association studies.

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3.5.4 Alkylating Agents (AAs)

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Alkylating agents are DNA damaging agents that can be toxic, carcinogenic, mutagenic and teratogenic. Human exposure is unavoidable and can occur through exogenous sources (e.g. cigarette smoke) or normal endogenous processes but the extent of this exposure and their association with human disease requires further clarification.

Chemistry

Alkylating agents (AAs) are a diverse set of organic compounds that alkylate both cellular nucleophiles and nucleophilic sites within cellular macromolecules such as DNA and proteins. AAs can be classified broadly into monofunctional and bi- or polyfunctional AAs depending upon the number of reactive alkyl groups present (Lawley 1976).

N-nitroso compounds (NOCs) are AAs that have a nitrosyl group bound a nitrogen atom (Figure 23) and can be classified as nitrosamines which have alkyl or aryl groups as R_1 and R_2 and nitrosamides where R_1 is an alkyl or aryl group and R_2 is an acyl group. Nitrosamines are generally stable compounds that only slowly decompose in aqueous acid solutions whereas nitrosamides are much less stable in aqueous acids and unstable in basic solutions (WHO-IPCS 1978).

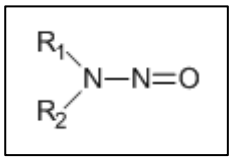

Figure 23: General structure of N-nitroso compounds

NOC physical properties vary widely depending on R1 and R2. Dimethylnitrosamine is an oily liquid miscible in polar solvents whereas others are solids that can be practically insoluble in water (WHO-IPCS 1978).

AAs can undergo substitution reactions with nucleophiles either in a unimolecular fashion (S_n1) or bimolecularly (S_n2). S_n1 type alkylating agents alkylate both oxygens and nitrogens in nucleic acids whereas S_n2 alkylating agents mainly alkylate nitrogens (Lawley 1976): 12 different alkyl adducts may be formed are of varying biological potency with O^6-alkylguanines being considered the most potent (Margison et al. 2002).

Biological Systems Affected

AAs are invariably toxic, mutagenic carcinogenic and teratogenic (Lawley 1976). NOC show pronounced organotrophism which can vary with dose and route of administration (Lijinsky 1992).

Possible Exposure Routes

Humans are exposed throughout their life to AAs from both exogenous and endogenous sources. AAs, such as the tobacco-specific nitrosamines (TSNAs) are found in cigarette smoke. TSNAs are predominantly formed during tobacco curing but some formation can occur during smoking (IARC 2004). Humans can be exposed by the use of smokeless tobacco products or by inhaling tobacco smoke during active smoking and, to a much lower level, by passive smoking (IARC 2007; CDC 2013). NOCs are present in the rubber and type manufacturing

industries and in metal and grinding shops and can be present in industries concerned with the production and use of amines (Tricker et al. 1989). Certain foodstuffs may contain preformed NOCs (EPIC 2014) or promote NOC formation endogenously (Lunn et al. 2007). AAs may be formed endogenously through the nitrosation of, for example amines, amino acids and bile acids (Tricker 1997). NOC are usually formed unintentionally when amines and nitrosating agents come together and the yield of nitrosamine depends upon the amine, basicity, steric requirements, the nitrosating species and medium (WHO-IPCS 1978). NOC formation may also be catalysed by bacterial strains (Tricker 1997). It has been suggested that endogenous exposure to AAs exceeds that from exogenous sources (Tricker 1997) but the full extent of endogenous formation has never been fully characterised. AAs are also used in chemotherapy and the five major classes are nitrogen mustards, nitrosoureas, alkyl sulfonates, triazines and ethylenimines. Health care workers handling and administering these drugs can be exposed especially if not wearing personal protective equipment (PPE) (OSHA 1999).

Absorption

There is relatively little quantitative data on AA absorption. NOC are rapidly absorbed from the gastrointestinal tract and their biological half-time appears to be less than 24 h. NOC can be absorbed through the skin with rates depending upon the physical properties of the compound: for example dimethylnitrosamine can rapidly penetrate the skin but the amount actually available for penetration is low due to its volatility (Brain et al. 1995) whereas *N*-nitrosodiethanolamine (NDELA) is more poorly absorbed with ~2-5% of NDELA recovered in urine within 20h after skin application (Edwards et al. 1979).

Elimination

After absorption, NOC are distributed throughout the body but non-volatile metabolites may accumulate in certain organs and tissues. NOC may be excreted unchanged through the urine or faeces or even exhaled but the majority of the absorbed compound undergoes extensive metabolism that can yield an electrophile that reacts with cellular nucleophiles (WHO-IPCS 1978; Rostkowska et al. 1998).

Reference values

Urinary levels of 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol, a metabolite of the tobacco-specific nitrosamine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), are about 50-150 times higher in smokers than non-smokers. Levels vary with gender and racial/ethnic differences with higher levels (adjusted geometric mean in females: 353 pg/ml, 95% confidence interval (CI): 324-384 pg/ml; adjusted geometric mean in non-Hispanic whites: 336 pg/ml, 95% CI: 298-379 pg/ml) (CDC 2013).

Other NOC have been detected in the urine and faeces of different populations. Excretion of apparent total N-nitroso compounds in healthy adults has been estimated to be 1.3 between 1.6 and 3.2 micromole per day (µmol/day) in urine and faeces respectively. Endogenous nitrosation has been assessed by determination of urinary *N*-nitrosoproline levels after proline administration (Tricker 1997).

DNA adducts arising from AA exposure have been detected in a variety of human tissues (De Bont and van Larebeke 2004). For example N7-methyldeoxyguanosine is present at varying levels in ~90% of human DNAs whatever the source (Lees et al. 2007; Stocks et al. 2010).

Specimens for analysis

NOC and NOC metabolites can be detected in urine and faeces (Tricker 1997). The reaction products of AAs with DNA or proteins can be detected in human tissues (De Bont and van Larebeke 2004; Goel et al. 2013).

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3.6 Occupational Hazards

WRITTEN BY NADINE STECKLING & STEPHAN BÖSE-O'REILLY (KUM-LMU)

Occupational hazards are important factors of morbidity and mortality and influence population health all over the world (Driscoll and Fingerhut 2008). A broad range of occupational-induced health effects can be identified. The reason is the usually repetitive exposure with or without additional environmental risks or genetic factors. Nevertheless, in some occupational groups, the healthy worker effect (the good health condition of a worker) may hide the enhanced occupational health risk (Sokas and Sprince 2008). Beside traditional occupational diseases like pneumoconiosis, new hazards appear in the frame of rapid globalization and technological and social changes which have occurred in the occupational environment. For example, the prevalence of mental and musculoskeletal disorders is rising (ILO 2013).

The most common occupational diseases in Europe were surveyed by EuroStat for the reference year 2001. Data of 68 entities of recognized occupational diseases in Austria, Belgium, Denmark, Finland, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden, and United Kingdom were collected. In 2001, 31,945 new cases of occupational diseases were documented in the mentioned states. The top ten documented occupational diseases were wrist tenosynovitis, epicondylitis of the elbow, contact dermatitis, noise-induced hearing loss, Raynaud's syndrome/vibration white-finger, carpal tunnel syndrome, mesothelioma, asthma, asbestosis, and coal worker's pneumoconiosis. Most occupational diseases are caused by physical agents (e.g. due to noise, overstraining, vibration; see chapter 3.6.1), inhalation of substances (e.g. asbestos, silica, dust), or substance caused skin diseases (Karjalainen and Niederlaender 2004).

Occupational diseases and fatalities have a very high potential to be prevented. Understanding the causing mechanisms helps to avoid health burden due to work (Driscoll and Fingerhut 2008). The European Agency for Safety and Health at Work (EU-OSHA) has defined priorities for research needs in the area of occupational safety and health (OSH) in Europe for the years 2013 to 2020. This priority list is prepared in harmony with the Europe 2020 strategy and the

Horizon 2020 programme (EU-OSHA 2014). The key topics, which countries in the EU are facing, are highlighted:

- “demographic change – sustainable work for healthier and longer working lives;
- globalisation and the changing world of work;
- OSH research for safe new technologies;
- new or increasing occupational exposures to chemical and biological agents” (EU-OSHA 2014).

Occupational hazards can be distinguished in physical, chemical, biological, mechanical, and psychosocial risk factors (Nowak 2010). This structure is used in the following chapters.

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3.6.1 Physical Occupational Hazards

WRITTEN BY NADINE STECKLING & STEPHAN BÖSE-O’REILLY (KUM-LMU)

Physical hazards are hazards which transfer energy in different forms like noise (see chapter 3.3), vibration, pressure, temperature extremes, ionizing and non-ionizing radiation (see chapter 3.5). Mechanical hazards could either be subsumed under physical hazards or considered separately (Levy et al. 2011). In this report, mechanical hazards are content of chapter 3.6.2.

Physical occupational stressors

Typical physical stressors in the occupational setting are noise and vibration (Sokas and Sprince 2008; EC 2009). Additionally, electricity (Stout et al. 2008), extreme temperatures, hyper- and hypobaric atmospheres (Sokas and Sprince 2008) and ionizing and non-ionizing radiation (e.g. heat or ultraviolet radiation (EC 2009)) may affect workers health (Sokas and Sprince 2008).

Occupational subgroups at risk

Noise, can be continuous or a unique event, is present in almost all occupational activities, but in some cases – like the processing of specific materials as well as in mining, construction, or transportation – the noise levels are particularly high (Concha-Barrientos et al. 2004). Vibration during work can be a hazard affecting the entire body or specific body parts separately. Workers using power tools or working with forklifts or off-road vehicles are subgroups at risk. Employees possibly exposed to radiation are for example workers in nuclear power plants, medical workers (using x-rays), or airline crews. Heat as an occupational risk factor is present in some industries where the workplace is outside with high ambient temperatures, in very hot rooms or working with hot objects. Workers can be exposed to cold stress if they are employed in a cold storage e.g. in food industries or if they work outside in cold weather conditions. Open-water divers do also have an increased risk of cold stress. Pressure above or below atmospheric pressure in the workers' surroundings is associated with health risks in certain occupations. Affected by atmospheric high pressure are people who work underwater while a low environmental pressure is present in aircrafts (Levy et al. 2011).

Biological Systems Effected

Noise is a risk factor for causing hearing loss and/or tinnitus. Additionally, noise is associated with hypertension and ischemic heart disease, sleep disorders and annoyance. Vibration causes musculoskeletal disorders like low-back pain (Levy et al. 2011). VWF (Vibration-induced White Finger) is the most common health effect of hand-arm vibration. Other effects such as changes in tendons, muscles, bones, joints are known as hand-arm vibration syndrome (HAVS). Whole body vibration can cause fatigue, insomnia, headache and shakiness (Government of Alberta 2011). Bursitis or other musculoskeletal diseases due to physical stress or overstraining can be a result (EC 2009). Exposure to ionizing radiation, either electromagnetic radiation (e.g. x-rays or gamma radiation) or particle radiation (e.g. alpha or beta radiation), can cause tissue damage and cancer at high levels (Guidotti 2011). Leukaemia, skin cancer or bone and articular cartilage cancer are possible outcomes (Driscoll et al. 2004). Very high doses of ionizing radiation, which were observed in on-site workers and emergency workers during the Chernobyl accident in 1986 (highest absorbed dose of radiation in human body observed in connection with the Chernobyl accident: 20 gray, Gy), can be fatal (IAEA 2006). Nonionizing radiation consists of electromagnetic radiation and can cause physical changes in cells. Ultraviolet radiation is the most common form and causes sunburn and prolonged exposure over time causes cataracts and skin cancer (Guidotti 2011). Hypothermia and hyperthermia can be followed by several symptoms. Heat may result in irritability and problems with thinking, as well as cramps or even heat strokes. Extreme coldness may cause disorientation, coordination problems, a decreased pulse, or skin effects (like heat rush or heat hives). In the worst case, occupational exposures to extreme temperatures can be followed by death (Levy et al. 2011). Conditions in the workplace may expose the worker to unusually high or low pressures. Examples of health outcomes are decompression sickness and high altitude sickness (Guidotti 2011).

Possibilities to survey

Physical stressors can be measured in specific units (e.g. hertz for the frequency of vibration) (Levy et al. 2011). Personal dosimetry (Worswick et al. 2008) or urinary thymine dimers (Liljendahl et al. 2013) are biomarkers for radiation (see chapter 3.5.1). The noise level can be measured in decibel (dB(A); see chapter 3.3). High or low temperatures as acute risk factors can be identified by changing body temperatures. A rise of the body temperature of 1.5 °C is

critical, as well as a temperature below 35°C. In the medical history, all jobs should be listed to find possible causes of diseases (Nowak 2010). For identifying occupational hazards, a Job-Exposure-Matrix (JEM) can be used to survey the job history (Pearce and Douwes 2008).

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3.6.2 Mechanical Occupational Hazards

WRITTEN BY NADINE STECKLING & STEPHAN BÖSE-O'REILLY (LMU)

(Bio-)Mechanical exposures are very common in the occupational setting (Sokas and Sprince 2008). Mechanical hazards are considered separately and not subsumed under physical hazards (Levy et al. 2011) within this report.

Mechanical occupational stressors

Continuous or repeating mechanical stress may cause occupational diseases. Effects can be a result of work posture, force, frequent workloads (Sokas and Sprince 2008), heavy lifting or forceful movements (Levy et al. 2011), repetitive movements of the hands and forearms as well as the use of hand tools such as picks, hammers or shovels (Tadesse et al. 2002).

Occupational subgroups at risk

Workers frequently using (computer) keyboards (e.g. for data-entry) or hand tools like knifes (e.g. in the meat production) are at risk for mechanical occupational hazards. An ergonomic workplace can reduce the risk of mechanical hazards. Other subgroups are workers performing unaccustomed or highly repetitive work like machine operators. Other mechanical risks are traffic accidents especially for bus or truck drivers (Levy et al. 2011).

Biological Systems Affected

The carpal tunnel syndrome, back pain and other musculoskeletal disorders are frequent results of mechanical work-related hazards. Mostly affected are the neck, the low back and the upper extremities, while the evidence of disorders of hip and knee is rising. Inflammations are common (Levy et al. 2011). Road accidents or accidents related to machinery or tools may lead to mechanical occupational injuries (Stout et al. 2008). In industries where repetitive movements of the hands and forearms are common, the tendon sheaths and musculocutaneous junctions become inflamed. Workers using hand tools such as picks, hammers, shovels or who habitually kneel at their work may suffer from "beat" condition of the hand, knee or elbow. Beat hand is a subcutaneous cellulites, which occurs among miners and stoker caused by infection of tissues devitalized by constant bruising (Tadesse et al. 2002).

Possibilities to survey

The work history should be surveyed to identify occupational mechanical hazards as causes of related diseases (Levy et al. 2011). The medical history will reveal the specific hazards if it includes a detailed job history (Nowak 2010) and Job-Exposure-Matrices can be used to identify specific exposures (Pearce and Douwes 2008).

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3.6.3 Chemical Occupational Hazards

WRITTEN BY NADINE STECKLING & STEPHAN BÖSE-O'REILLY (LMU)

Occupational chemical stressors include toxic metals (see chapter 2.3), toxic organic substances (see chapter 2.1 and 2.2), organic solvents, inorganic gases, volatile organic compounds (see chapter 2.4), beyond others. Commercially, around 80,000 chemicals are used and every year around 1,000 are added (Levy et al. 2011). The most important chemicals are described elsewhere in this report. This chapter will only give an overview of chemical occupational hazards.

Chemical Occupational stressors

In the occupational setting, exposures to natural or synthetic chemicals are possible (Sokas and Sprince 2008). A worker can be exposed to chemical agents like arsenic, bromine, cadmium, formaldehyde, lead, mercury, organic acids, and many more. Occupational chemical exposure can also occur due to exposure with dust, particulate matter, oils, by-products of the distillation of coal, or in underground mines (EC 2009). The rise of man-made materials like “plastics, synthetic fibres, solvents, fertilizers, and pharmaceutical products” may be hazardous to producers and users (Tadesse et al. 2002). Occupational exposure to lead is possible due to lead based paints for example (Angerer et al. 2007)

Occupational subgroups at risk

Subgroups at risk are people who are exposed to chemicals while working e.g. farmers (pesticides), craftsmen (varnishes, paints), laboratory technicians (solvents) or people working in industry were chemicals are used (e.g. lead-acid production, plastic or synthetic products industry) (Levy et al. 2011).

Biological Systems Affected

The absorbed chemicals may induce damages to specific organs, genetic damage, reproductive effects, or they can cause cancer (Sokas and Sprince 2008). Common occupational carcinogens are for example “arsenic, asbestos, beryllium, cadmium, chromium, diesel exhaust, nickel”, and silica which cause cancer of the trachea, bronchus, or lung. Leukaemia can be a result of exposure to benzene or ethylene oxide. Exposures to asbestos may cause malignant mesothelioma. The three mentioned types of cancer are the most documented forms of cancer

in occupational settings. Other kinds of cancer are e.g. bladder cancer caused by exposure to e.g. aromatic amines, liver cancer due to exposures with vinyl chloride, nasal cavity and middle ear cancer caused by hardwood dust, chromium VI or nickel compounds as well as arsenic induced skin cancer (Driscoll et al. 2004).

Besides lung cancer, silica causes silicosis (Driscoll et al. 2004). Furthermore, pneumoconiosis can be caused by exposure to asbestos; in other cases it has been characterized as result of working with coal (ILO 2013). Silicosis, asbestosis, allergic rhinitis or asthmas may be a result of an inhalative exposure (EC 2009).

The physical state of a chemical compound is important in determining its toxicity to man and the environment. The effects of chemical agents are asphyxiation, systemic intoxication, pneumoconiosis, carcinogens and irritation. Among all chemical agents in work place the most notorious and most in contact with the skin or respiratory system that deserve attention are solvents. Exposure to solvents occurs throughout life. For example, organic solvent vapour inhaled by a mother could reach the foetus (Tadesse et al. 2002).

Reference values

Several assessment values for human biomonitoring are available. However, enough data for determining such values are mostly just available for a limited number of chemicals (Angerer et al. 2011). An example of an occupational reference value is the BAR (biological workplace reference values; “Biologischer Arbeitsplatz Referenzwerte”), established by the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission). Examples of occupational threshold values are the BAT (biological tolerance values, “Biologische Arbeitsstoff-Toleranzwerte”) and BLW values (biological guideline values, “Biologische Leitwerte”), also determined by the German MAK Commission, the BEI value (biological exposure indices) from the American Conference of Governmental Industrial Hygienists (ACGIH) (Angerer et al. 2011). The Scientific Committee on Occupational Exposure Limits (SCOEL) gives recommendations for occupational exposure limits (OEL) on the level of the European Union. Biological Limit Values (BLV) and Biological Guidance Values (BGV) are those assessing concentrations in biological material (EC 2013)

The definitions of the mentioned values are given in the glossary of this report. The values for single chemicals are given in several publications (ACGIH 1999; Drexler and Göen 2012; DFG 2014).

Possibilities to survey

A structured monitoring and health surveillance of workers is not common and just done by around fifty percent of all countries over the world (ILO 2013). The long latency period, e.g. of occupational caused cancers complicate the recognition of work-related diseases (ILO 2013).

Chemical exposure in occupational settings are commonly distinctly higher in comparison to environmental exposures (Pearce and Douwes 2008). Exposure to chemicals can be monitored, e.g., analysing the chemical or its metabolites in urine or blood (see chapter 2) (Nowak 2010). If individual exposure measurement is no option, a detailed medical and job history is important (Nowak 2010) and a Job-Exposure-Matrix (JEM) can be used to identify occupational exposures based on the work history (Pearce and Douwes 2008).

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3.6.4 Biological Occupational Hazards

WRITTEN BY NADINE STECKLING & STEPHAN BÖSE-O'REILLY (LMU)

Exposures to living organisms are described as biological hazards (Sokas and Sprince 2008). Biological occupational agents can be in distinguished “allergenic and/or toxic agents forming bioaerosols, and agents causing zoonosis and other infectious diseases” (Dutkiewicz et al. 2011).

Biological occupational stressors

Occupational diseases are possible following exposures to “viruses, bacteria, fungi, rickettsia, Chlamydia, protozoa, helminthes, and […] prions” (Sokas and Sprince 2008). Common bioaerosols occurring in the agricultural environment are bacteria, fungi and metabolites of fungi (mycotoxins and volatile organic compounds (VOCs)) as well as particles of plant and animal origin (Dutkiewicz et al. 2011). These can be communicable or non-communicable (Sokas and Sprince 2008). Common biological agents are human immunodeficiency virus (HIV), hepatitis B and C viruses and tubercle bacillus (Levy et al. 2011) as well as zoonotic agents causing tick-borne diseases (e.g., Lyme borreliosis) (Dutkiewicz et al. 2011). Hepatitis is much more common in the occupational setting in comparison to HIV (Nowak 2010). Additionally, agents causing non-vector borne diseases like “hantavirus diseases, avian and swine influenza, Q fever, leptospirosis, staphylococcal diseases caused by the methicillin-resistant *Staphylococcus aureus* (MRSA) strains and diseases caused by parasitic protozoa“ can be important biological occupational hazards. The exposure to bacteria causing legionellosis is also possible in the occupational setting (Dutkiewicz et al. 2011).

Occupational subgroups at risk

Occupational subgroups at risk are those who work with people or animals and those who work (and maybe live) in big groups (Sokas and Sprince 2008). Health care workers can be exposed to biological hazards due to contact with “blood, tissues, saliva, mucous, urine and faeces”. Working with animals enhances the risk to be exposed to animal diseases or infections (Safe Work Australia 2011). Additionally, people who have frequent business journeys are at risk for an enhanced contact to unusual pathogens. Workers moving soil (Sokas and Sprince 2008), working in a laboratory or having contact with dust, food, rubbish, wastewater or sewerage do also have a high risk to biological exposures due to work (Safe Work Australia 2011). Infections due to biological occupational agents can occur by transmission through air, food, water or as result of direct contact (e.g. needle stick injuries) (Levy et al. 2011).

Biological Systems Affected

Infections following occupational contact to biological agents during work are the outcome (Levy et al. 2011).

Possibilities to survey

The biological agent or corresponding antibodies can be surveyed in blood (Levy et al. 2011). An occupational exposure can be surveyed by requesting the job history (Nowak 2010). A Job-Exposure-Matrix (JEM) can give information about possible exposures of jobs (Pearce and Douwes 2008). Important are employment information like the occupation and industry, the employment conditions and the size of the workplace. Furthermore, the exposure of workers to

different hazards and available hazard control systems should be taken into account (Safe Work Australia 2011).

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3.6.5 Psychological Occupational Hazards

The European Agency for Safety and Health at Work (EU-OSHA) recently conducted a literature review to summarize the costs of work-related psychosocial effects. Based on an estimate of 2002 from the European Commission it is assumed that every year 20 billion €uro are lost due to work-related stress in 15 European Member States[1]. Further annual 617 billion €uro are attributable to work-related depression in Europe. The most of these work-related costs are paid by the society due to the public health care systems in Europe. However, many organisations pay the costs of the absence of their staff, of a lower productivity due to the presence of ill staff as well as of a higher staff turnover rate (EU-OSHA 2014).

Stress in general without the connection to work is also content of chapter 3.7.8 in this report.

Stressors and occupational subgroups at risk

Stressors can be related to the organization or demand of work as well as to the low control at the job or insufficient reward systems. Traumatic events (direct or indirect), harassment, unemployment or the threat of losing the job are important factors in the development of psychological effects (Sokas and Sprince 2008). A long working day, excessive workload, low payment and lacking social support are further work-related risk factors for psychosocial

[1] EU-15: Belgium, Denmark, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, United Kingdom, Austria, Finland, Sweden. List of Country Abbreviations in the European System of Social Indicators. Access: http://www.gesis.org/fileadmin/upload/dienstleistung/daten/soz_indikatoren/eusi/Abbreviations.pdf [2014-11-17].

diseases (EU-OSHA 2014). At risk for work-related stress are individual workers, which abilities and knowledge do not match with job demands. It becomes a risk factor for worker’s health and safety when “work exceeding the worker’s capacity, resources and ability to cope is prolonged” (ILO 2014). For example, stressors of nurses can be time pressure, understaffing or contact with difficult or seriously ill patients (CDC 2008).

Biological Systems Affected

Occupational stress may be the cause for psychological reactions like irritability or dissatisfaction. Furthermore, behavioural effects (e.g. problems with sleep) and physical health effects like headache, stomach upset or a changing blood pressure are possible (CDC 2008). Besides mental health effects (e.g. depression), cardiovascular effects like coronary heart disease (CHD) comprise an approved result of psychological exposures at the workplace (Sokas and Sprince 2008; EU-OSHA 2014). Another important stress-related health outcome at work are musculoskeletal disorders like lower back pain, pain in the limbs, back and muscles as well as stress-related injuries (EU-OSHA 2014).

Latest research activities found an association between psychosocial work stress, low job control or high job strain and diabetes mellitus type II in women. This effect was not observed in men. Nevertheless, a possible gender effect regarding the exposure to psychosocial hazard exposure needs to be analysed in future studies (EU-OSHA 2014).

Possibilities to survey

Several instruments (questionnaires and observational instruments) are available to measure psychosocial factors in the work environment (Tabanelli et al. 2008). Job stress surveys or specific scales are developed (Levy et al. 2011). Medical history, interviews and employee surveys may give indications to possible psychological exposures during work (Nowak 2010). Specific psychological exposures can be identified by using Job-Exposure-Matrices (JEM) (Pearce and Douwes 2008).

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3.7 Cultural Factors

WRITTEN BY ZDRAVKO ŠPIRIĆ & DANIJELA ŠTIMAC (OIKON)

Cultural factors have significant influence on health status and development of disease. These include the extent of inequality allowed between the most affluent and disadvantaged people in society and the adoption of behaviours likely to promote health or destroy health. Behaviours such as physical inactivity, unhealthy diet, cigarette smoking, alcohol over-consumption and drug abuse are established risk factors for the development of the chronic diseases and have generally been shown to currently be more prevalent among the disadvantaged socioeconomic groups, particularly in the most affluent countries (Dow and Rehkopf 2010).

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3.7.1 Socioeconomic Status (SES)

WRITTEN BY ZDRAVKO ŠPIRIĆ & DANIJELA ŠTIMAC (OIKON)

Socioeconomic status (SES) is one of the most important determinants of health. Differences in morbidity and mortality between socioeconomic groups constitute one of the most consistent findings of epidemiologic research. The WHO Commission on the Social Determinants of Health (CSDH) concluded in 2008 that the social conditions in which an individual is born, grows, lives, works, and ages are the single most important determinants of health status. The stressors that humans typically face in the modern, developed world originate largely from social and interpersonal interactions, rather than from physical stressors (McKittrick et al. 2009).

Chief measures of SES include education, income and affiliation to the labour market however measures of material assets, in particular home ownership and car ownership, also have been found to be strongly related to health. Persons with insecure jobs were at an increased risk of poor health (see chapter 3.6.5).

Differences in the availability or affordability of or access to healthy foods or places to exercise, healthcare services and health information, and differences in health related behaviours between socioeconomic groups have all been proposed as potential explanations for the social patterning of main death causes and main burden of diseases (McKittrick et al. 2009).

Definition

The complex, integrated and overlapping social structures and economic systems that are responsible for most health inequities. These social structures and economic systems include the social environment, physical environment, health services, and structural and societal factors. Social determinants of health shaped are by the distribution of money, power, and resources throughout local communities, nations, and the world (Evans and Kantrowitz 2002).

Biological Systems Affected

Socioeconomic status has influence on all biological systems, especially cardiovascular, nervous, metabolic, alimentary and endocrine. Animal studies have shown an impaired response to stress in subordinate animals (Blanchard et al. 1993). Social stress leads to heightened activation, and, in some cases, impaired regulation and responsiveness of the HPA axis and dysregulation of androgen secretion (McKittrick et al. 2009). Chronic social stress has been shown to result in changes in chemical neurotransmission and neuronal structure; many of these changes occur within neural pathways that have been implicated in a variety of human affective disorders (McKittrick et al. 2009).

A graded association of lower SES with increased incidence of many illnesses including diabetes and coronary heart disease has been shown (Marmot 2013).

Influence on other stressors of interest

Health behaviours (physical activity, dietary habits, smoking, alcohol consumption and drug abuse) are strong predictors of mortality and are also patterned by SES (Guo et al. 2007; Hiscock et al. 2012; Nandi et al. 2014). Social subordination has been found to increase consumption of high calorific foods in rhesus monkeys which may then further act as a metabolic stressor that synergizes with the psychosocial stress of subordination to further increase the consumption of these diets (Arce et al. 2010). In humans, health behaviours have been found to mediate the relationship between SES and elevated levels of C-reactive protein a marker for inflammation, hypertension and heart disease (Brummett et al. 2013). However the extent that health behaviours contribute to SES related inequalities in health may depend on cultural factors such as the level of polarization between rich and poor and government redistribution of resources (Dow and Rehkopf 2010).

There is also geographical patterning of SES. Persons with low SES may be have insufficient wealth to avoid locations to live and work with high levels of air and water pollutants and noise (Sexton and Adgate 1999; Evans and Kantrowitz 2002). Occupational hazards may be concentrated among workers with low SES (Clougherty et al. 2010). Low SES groups may also make unhealthy lifestyle choices, such as sunbed use, leading to increased exposure to UV (Bentzen et al. 2013).

Subgroups at risk

Groups vulnerable to low SES include ethnic minorities, the elderly and the young, women and single parents (Committee on Pediatric Research 2000; Hiscock et al. 2012) at least partly due to cultural beliefs and stigma. Inequalities in ability to deal with household financial problems will become increasingly important mental health issues as the population ages. Additionally chronic illnesses and disabilities generally heighten vulnerability to low SES (Schuring et al. 2013); this possibility of reverse causation needs to be taken into account in studies.

Possibilities to analyse

Censuses, surveys and national data registers can provide data on SES of population, using a variety of measures at an individual (e.g. personal occupation, household (e.g. Family Affluence Scale (FAS)) or neighbourhood scale (e.g. Carstairs, Index of Multiple Deprivation, IMD). Such sources often include measures of medical conditions, mental health and wellbeing including self-report, health service records and a few surveys such as national health surveys may include biological samples (Brummett et al. 2013).

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3.7.2 Alcohol Consumption

WRITTEN BY ZDRAVKO ŠPIRIĆ & DANIJELA ŠTIMAC (OIKON)

Alcohol affects every organ in the body. A central nervous system depressant is rapidly absorbed from the stomach and small intestine into the bloodstream. Alcohol metabolized in the liver by enzymes; however, the liver can only metabolize a small amount of alcohol at a time, leaving the excess alcohol to circulate throughout the body. The intensity of the effect of alcohol on the body is directly related to the amount consumed. Individual reactions to alcohol vary, and are influenced by many factors: age, gender, race or ethnicity, physical condition (weight, fitness level, etc.), amount of food consumed before drinking, how quickly the alcohol was consumed, use of drugs or prescription medicines, family history of alcohol problems.

Definition

Ethyl alcohol, or ethanol, is an intoxicating ingredient found in beer, wine, and liquor. Alcohol is produced by the fermentation of yeast, sugars, and starches. Alcohol abuse is a pattern of drinking that result in harm to one’s health, interpersonal relationships, or ability to work. Manifestations of alcohol abuse include the following: failure to fulfil major responsibilities at work, school, or home, drinking in dangerous situations, such as drinking while driving or operating machinery, legal problems related to alcohol, such as being arrested for drinking while driving or for physically hurting someone while drunk, continued drinking despite ongoing relationship problems that are caused or worsened by drinking, long-term alcohol abuse can turn into alcohol dependence, dependency on alcohol, also known as alcohol addiction and alcoholism, is a chronic disease (Bonnie and O’Connell 2004). “The signs and symptoms of alcohol dependence include – a strong craving for alcohol, continued use despite repeated physical, psychological, or interpersonal problems, the inability to limit drinking” (CDC 2014).

Biological Systems Affected

Excessive drinking both in the form of heavy drinking or binge drinking, is associated with numerous health problems, including chronic diseases such as liver cirrhosis (damage to liver cells); pancreatitis (inflammation of the pancreas); various cancers, including liver, mouth, throat, larynx (the voice box), and esophagus; high blood pressure; and psychological disorders, unintentional injuries, such as motor-vehicle traffic crashes, falls, drowning, burns and firearm injuries, violence, such as child maltreatment, homicide, and suicide, harm to a developing foetus if a woman drinks while pregnant, such as fatal alcohol spectrum disorders, sudden infant death syndrome (SIDS), alcohol abuse or dependence (Hingson et al. 2000). Although several hypotheses have been postulated for alcoholic cardiomyopathy and for the low-dose beneficial cardiovascular effects, the precise mechanisms and mediators remain largely undefined.

Influence of the confounder to other stressors of interest

Studies of epidemiologic and treatment populations indicate that the majority of substance-abusing women have one or more types of comorbid mental disorders, with depression being the most common and the most elevated compared with substance-abusing men, but antisocial personality being extremely high compared with samples of non-substance-abusing women.

Lower SES is correlated with higher rate of dinking problems, smoking and drug abuse (Grant et al. 2009).

Possibilities to analyse the confounder

Population-based, cross-sectional study, using structured questionnaire on health behaviour and health status, hospital records from hospitals databases about mental disorders caused by alcohol abuse F10 (ICD-X rev), blood analysis to determine the alcohol content (BAC).

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3.7.3 Drug Consumption

WRITTEN BY ZDRAVKO ŠPIRIĆ & DANIJELA ŠTIMAC (OIKON)

Drug addiction is a brain disease. Although initial drug use might be voluntary, drugs of abuse have been shown to alter gene expression and brain circuitry, which in turn affect human behaviour. Once addiction develops, these brain changes interfere with an individual’s ability to make voluntary decisions, leading to compulsive drug craving, seeking and use. The impact of addiction can be far reaching. Cardiovascular disease, stroke, cancer, HIV/AIDS, hepatitis, and lung disease can all be affected by drug abuse. Some of these effects occur when drugs are used at high doses or after prolonged use; however, some may occur after just one use (Moore and Werch 2005).

Definition

A drug is, in the broadest of terms, a chemical substance that has known biological effects on humans or other animals. Foods are generally excluded from this definition, in spite of their physiological effects on animal species. Recreational drugs are chemical substances that affect the central nervous system, such as opioids or hallucinogens (Chappel et al. 1985). They may be used for effects on perception, consciousness, personality, and behaviour. Many recreational drugs are also used in medicine. Some drugs can cause addiction and habituation and all drugs have side effects. Many drugs are illegal for recreational purposes and international treaties such as the Single Convention on Narcotic Drugs exist for the purpose of legally prohibiting certain substances (Hingson et al. 2006). In the modern medical profession, the three most used diagnostic tools in the world, the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM), World Health Organization's International Statistical Classification of Diseases and Cross Racial Identity Scale (ICRIS), Medical

organization Related Health Problems (ICD), no longer recognize 'drug abuse' as a current medical diagnosis. Instead, DSM has adopted substance abuse as a blanket term to include drug abuse and other things. ICD refrains from using either substance abuse or drug abuse, instead using the term "harmful use" to cover physical or psychological harm to the user from use. Physical dependence, abuse of, and withdrawal from drugs and other miscellaneous substances is outlined in the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association 1994). Compulsive and repetitive use may result in tolerance to the effect of the drug and withdrawal symptoms when use is reduced or stopped. These, along with substance abuse are considered substance use disorders.

Biological Systems Affected

Drug abuse not only weakens the immune system but is also linked to risky behaviours like needle sharing and unsafe sex. The combination greatly increases the likelihood of acquiring HIV/AIDS, hepatitis and many other infectious diseases. Researchers have found a connection between the abuse of most drugs and adverse cardiovascular effects, ranging from abnormal heart rate to heart attacks. Injection drug use can also lead to cardiovascular problems such as collapsed veins and bacterial infections of the blood vessels and heart valves. Drug abuse can lead to a variety of respiratory problems. Smoking cigarettes, for example, has been shown to cause bronchitis, emphysema and lung cancer. Marijuana smoke may also cause respiratory problems. The use of some drugs may also cause breathing to slow, block air from entering the lungs or exacerbate asthma symptoms (Nutt et al. 2007). Among other adverse effects, many drugs of abuse have been known to cause nausea and vomiting soon after use. Cocaine use can also cause abdominal pain. Steroid use during childhood or adolescence, resulting in artificially high sex hormone levels, can signal the bones to stop growing earlier than they normally would have, leading to short stature. Other drugs may also cause severe muscle cramping and overall muscle weakness. Some drugs (heroin, inhalants 3,4-Methylenedioxy-N-Methylamphetamine (MDMA), phencyclidine (PCP)) may cause kidney damage or failure, either directly or indirectly from dangerous increases in body temperature and muscle breakdown. Chronic use of some drugs, such as heroin, inhalants and steroids, may lead to significant damage to the liver. All drugs of abuse act in the brain to produce their euphoric effects; however, some of them also have severe negative consequences in the brain such as seizures, stroke, and widespread brain damage that can influence all aspects of daily life. Drug use can also cause brain changes that lead to problems with memory, attention and decision-making. Chronic use of some drugs of abuse can cause long-lasting changes in the brain, which may lead to paranoia, depression, aggression, and hallucinations. Steroid abuse disrupts the normal production of hormones in the body, causing both reversible and irreversible changes. These changes include infertility and testicle shrinkage in men as well as masculinization in women. In addition to the effects various drugs of abuse may have on specific organs of the body, many drugs produce global body changes such as dramatic changes in appetite and increases in body temperature, which may impact a variety of health conditions. Withdrawal from drug use also may lead to numerous adverse health effects, including restlessness, mood swings, fatigue, changes in appetite, muscle and bone pain, insomnia, cold flashes, diarrhoea, and vomiting.

Influence of the confounder to other stressors of interest

Substance abuse (SA), which includes the consumption of alcohol, cigarette smoking, the consumption of drugs and other behaviours, is a significant public health issue in the world today. SA is often associated with detrimental consequences and creates certain difficulties for not only the individuals who misuse the substances but also their parents, families, school,

peers, and society as a whole (Barrett et al. 2008). Today, it is generally accepted that the earlier a child begins to use substances, the greater the chance that the child will become addicted. In contrast, those who reach the age of 21 without smoking, consuming illegal drugs or binge drinking are likely to never engage in these behaviours. Therefore, it is particularly important to find any possible protective factors or risk factors for SA among adolescents. The importance of physical activity is well known. Physical activity helps to reduce the risk of a number of critical health problems, including obesity, heart disease, stroke, colon cancer, diabetes and osteoporosis. Additionally, participation in physical activity and sports among young people has been shown to promote social well-being, physical and mental health, academic achievement, self-discipline, and socialization. It is also hypothesized that participation in sports and physical exercise will reduce the tendency of young people to abuse substance (McCabe et al. 2009).

Possibilities to analyse the confounder

National registers of substance abuse, cross-sectional analysis using retrospective testing using an extensive self-administered questionnaire. The questionnaire should include questions involving topics such as sociodemographic variables, scholastic variables, sport factors, and substance abuse data (smoking habits, drugs consumption and alcohol consumption using the AUDIT questionnaire). Descriptive statistics, frequencies, analyses of the differences and correlational analyses should be performed (Antai-Otong 2008).

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3.7.4 Pharmaceutical Consumption

WRITTEN BY JOAQUIM ROVIRA & MARTA SCHUHMACHER (URV)

According to the target organ or system the pharmaceutical are classified as follows (WHO 2012):

- **Alimentary tract and metabolism**. Include, among others, drugs for acid related disorders, drugs for gastrointestinal disorders, constipations, antidiarrhoeals, antiinflammatory, antiobesity, digestives, antinauseants, vitamins, minerals and stomatological preparations.
- **Blood and blood forming organs.** This category includes antithrombotic agents antihemorrhagics, antianemic preparations, blood substitutes and perfusion solutions and other haematological agents.
- **Cardiovascular system.** Includes cardiac therapy drugs, antihypertensives, diuretics, peripheral vasodilators, vasoprotectives, beta blocking agents, calcium channels blockers, agents acting on the renin-angiotensin system and lipid modifying agents.
- **Dermatologicals.** This category includes antifungals, emollients and protective, treatment for wounds and ulcers, antipuritics, antipsoriatics, antibiotics, corticoids, antiseptics and disinfectants and antiacne preparations.
- **Genito-urinary system and sex hormones.** Urological, gynaecological antiinfectives and antiseptics, sex hormones and modulators of genital system.
- **Systemic hormonal preparations, excluding sex hormones and insulin.** This category includes thyroid therapy, pancreatic hormones, calcium homeostasis drugs, pituitary and hypothalamic hormones and analogues and corticoids.
- **Antiinfectives for systemic use.** Covers antibacterials, antimycotics, antimycobacterials, antivirals, immunoglobulins and vaccines
- **Antineoplastic and immunomodulating agents.** Category formed by antineoplastic agents, endocrine therapy drugs, immunostimulants and immunosuppressants.
- **Musculo-skeletal system.** Formed by antiinflammatory and antirheumatic products, topical products for joint and muscular pain, muscle relaxants, antigout preparations and drugs for bone diseases.
- **Nervous system.** Includes anaesthesic, analgesics, antiepileptics, anti-parkinson drugs, psycholeptics, psycoanaleptics and other nervous system drugs.
- **Antiparasitic products, insecticides and repellents.** This category covers antiprotozoals, anthelmintics and hectoparasiticides.
- **Respiratory system.** This category covers nasal, throat, cough and cold preparations, drugs for obstructive airways diseases, antihistamines for systemic use and other respiratory systems products.
- **Sensory organs.** Ophtalmological and ontological preparations.
- **Various** such as contrast media and diagnostic and therapeutic radiopharmaceuticals, allergens.

Biological Systems Affected

Depending on the pharmaceutical specific target and the dose, it will affect a specific biological target or system. Nevertheless, in liver most of the substances, including pharmaceutical products, are metabolized and altered, therefore the liver is vulnerable to injury from many pharmaceutical products. Drugs with well know hepatotoxicity are among others antidepressants, antibiotics, anti-inflammatory products, muscle relaxants, oestrogens, anabolic steroids and oral antidiabetic agents (Riley III and Bhatti 2001; Liss and Lewis 2009). A combination of total bilirubin and alanine aminotransferase as biomarker has high sensitivity and specificity for liver injury (Antoine et al. 2013).

Drug-induced renal damage can be acute or chronic, prerenal, intrarenal (vascular, tubular, glomerular or interstitial) or postrenal. Increasing serum creatinine and blood urea and electrolyte and acid base abnormalities are signals of kidney toxicity (Choudhury and Ahmed 2006). A review (Coca et al. 2008) concluded that serum cystatin C, urine interleukin-18 (IL-18)

and urine kidney injury molecule-1 (KIM-1) performed best for the differential diagnosis of kidney injury (Choudhury and Ahmed 2006). Drugs that can cause kidney damage are antibiotics, anticoagulants, antihypertensives, antivirals, chemotherapeutics, diuretics, immunosuppressants and radiocontrast agents.

Subgroups at risk

All population are exposed to pharmaceuticals through direct consumption but also through an indirect pathway (environmental exposure through drinking water or food) (Arnold et al. 2013; Li 2014). It is noteworthy that genome variability (including variation in the coding sequence and/or in regulatory regions of genes) explains a great deal of interindividual variation in drug pharmacokinetics and pharmacodynamics (drug absorption, metabolisation, transportation, response and toxicity of drugs) (Rezić and Steffan 2007; Ma and Lu 2011; Pinto and Eileen Dolan 2011; Evans and Mcleod 2014). Others factors that explains interindividual variations on effectiveness and side effects of drugs are environmental factors (such as tobacco, alcohol, environmental chemicals and diet) and physiological factors (such as sex, age, pregnancy, disease state, physical activity, circadian rhythm and malnutrition) (Ma and Lu 2011). Foetus, infants, pregnant women and elderly are special risk groups. In addition, chronic and/or cocktail drug consumers are population subgroups specially exposed to this confounder.

Influence on other stressors of interest

Individual approach is needed to determine the influence of reported drug consumption to levels of exposure biomarker. For example, an individual medicated with diuretics will show lower biomarker urine levels due a dilution effect. Other example is that some pharmaceutical consumption, could damage liver and consequently rise serum hepatic enzymes (Riley III and Bhatti 2001; Liss and Lewis 2009) and confound with the effects of other pollutant or stressor. Due the large amount of pharmaceutical categories it is not possible assess the influence of pharmaceutical consumption to the others stressor of interest, as a whole.

Possibilities to analyse

Pharmaceutical consumption can be evaluated using consumption questionnaire, medical history and/or analysing the specific drug or metabolites in the body (blood, saliva, urine).

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3.7.5 Nutritional Status

WRITTEN BY JOAQUIM ROVIRA & MARTA SCHUHMACHER (URV)

Nutritional status of an individual is a result of many interrelated factors. These factors are classified as follows (Jenab et al. 2009):

- **Food intake factors:** These factors include the quantity but also the quality of macro and micronutrients content.
- **Internal factors:** Physiological parameters and individual characteristics are included in this category. Metabolism, age, gender, hormonal status, and health status of the individual are some of these factors.
- **External factors or lifestyle factors:** Includes all external parameters that could modify the nutritional status such as the climatic conditions, physical activity, among others.

Nutritional status classification spread from severe obesity to severe malnutrition. The prevalence of obesity was around 20% and 10% population in 2010 for adult and children, respectively, the triple than 25 years ago (Mladovsky et al. 2009). Moreover, malnutrition in Europe is estimated in 5% of population (Ljungqvist et al. 2010) being more affected elderly subpopulation and chronic patients. Nutritional status of individuals are assessed by the following methods or a combination of them (Gibson 2005):

- **Anthropometric methods:** Include the measure of several body composition parameters such as, body weight and height, and proportions of lean mass and fats
- **Clinical methods:** Clinical history revision and clinical examination are the main tools.
- **Dietary evaluation methods:** Several dietary questionnaires are the main tools for the dietary evaluation. EPIC-Norfolk and Food4Me online tool are both useful food frequency questionnaire, first one is validated questionnaire and the second have good agreement with the first one (Forster et al. 2014; Mulligan et al. 2014).
- **Biochemical methods:** Dietary biomarkers assess objectively dietary consumption and nutritional status. The type of sample used (e.g., blood, hair, adipose tissue) is a main determinant of time. Biomarkers can be classified as following according with the time that the biomarker integrate (Potischman 2003):

- Short-term (reflecting intake over past hours/days).
- Medium-term (reflecting intake over weeks/months).
- Long-term markers (reflecting intake over months/years).

Nutritional status biomarkers most frequently used are (CDC, 2012):

- Water and fat-soluble vitamins (B, C, A, E, and D vitamins and carotenoids).
- Essential trace elements indicators (such as zinc, iron and iodine).
- Isoflavones and ligands.
- Hormones:
  - Leptin serum levels, as a signal of satiety, are related to amount of body fat.
  - Cortisol, adrenal hormone, is elevated in response to low energy availability. It’s sensitive to stress.
  - Ghrelin, secreted in stomach is a hunger signal and inversely related to body fat.
  - T_3 thyroid hormone reflects of metabolic rate and decrease with energy restriction.
  - Insulin or C-peptide (by-product of insulin production) in urine gives integrated measure of insulin production.
- Hepatic serum proteins (albumin, transthyretin, transferrin, retinol binding protein). Markers of protein/calorie malnutrition.
- Nitrogen in urine: as a protein intake measure.

Biological Systems Affected

Nutritional status of an individual affects almost all his biological systems, especially for extreme cases, severe obesity or severe malnutrition. In one hand, malnutrition leads to a tissue depletion of micro and macronutrients (Emery 2005). Blood mineral, transferrin, and albumin are reduced and, in a severe cases, fat tissue and or muscle were wasted (Emery 2005). Dehydration is also associated to sever malnutrition. On the other hand, metabolic syndrome is a state of chronic low grade inflammation as a consequence of complex interplay between genetic and environmental factors (high energy diet, lifestyle habits, among others) (Kaur 2014). Alterations of this syndrome are among others insulin resistance, hyperglycaemia, hypertension, vasoconstriction, elevated lipoprotein synthesis and gluconeogenesis, dyslipemia, oxidative stress, proinflammatory state, and hypercoagulable state (Dugan and Fernandez 2014; Kaur 2014).

However, not only, the extreme cases can modify the normal biological function; inadequate consumption of one food category (for excess or defect) can alter also biological parameters in human body. A high fatty diet intake increase liver enzymes (liver damage) in blood (Marchesini et al. 2001).

Subgroups at risk

All individuals with some important alterations in nutritional status, malnutrition or obesity are subgroups at risk because the biological parameters are altered.

The entire population of the world is susceptible to be exposed to this confounder. Ingestion of high amounts of a food category could lead to an exposure to a nutrient or pollutant (i.e. high amount of fish and seafood consumption could lead to a high Hg exposure). On the other hand, the low ingestion of some food categories could represent adverse effects for health (low ingestion of fruits and vegetable lead to vitamins scarcity).

Influence on other stressors of interest

Nutritional status act as a confounder to other stressors of interest in HEALS.

Weight loss (fat tissue mobilisation) produces an increase in blood concentration of organic pollutants, such as polychlorinated biphenyls (PCBs), hexachlorobenzene (HCB), polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), among other (Chevrier et al. 2000; Kim et al. 2008).

Nutritional status also includes hydration and it could modify internal levels of biomarkers of exposure.

Some studies (Kelly 2007; Vardavas et al. 2011) conclude that nutritional status may protect from air pollution and smoking. High intakes of dietary antioxidants can reduce the magnitude of lung function decrements in subjects exposed to air pollution (Kelly 2007).

Possibilities to analyse

As discussed above, it is possible to analyse the nutritional status/dietary intake. Anthropometric, clinical, biochemical, and dietary evaluation methods are usually used to evaluate nutritional and dietary intake.

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3.7.6 Physical Activity

WRITTEN BY JOAQUIM ROVIRA & MARTA SCHUHMACHER (URV)

Physical activity is defined as an energy dependent movement of the body produced by skeletal muscles. Physical inactivity, consequence of a sedentary lifestyle, has been identified as the fourth leading risk factor for global mortality (WHO 2010). According with a study (Hallal et al. 2012) the 34.8% of European adult population is physically inactive.

Physical activity improves physical fitness (cardiorespiratory fitness and muscular strength), reduces body fatness, prevents obesity, enhances bone health, reduces depression symptoms, and protects against cardiovascular and metabolic (diabetes) diseases (WHO 2010).

Time duration, the intensity of the physical effort, as well as the fitness of the subject may alter biological parameter such as biomarkers.

Parameters that influence the amount of extracellular release and clearance from blood of several biomarkers are:

- Biological characteristics of the molecule (biomarker).
- Fitness of subject.
- Type, intensity and duration of exercise.
- Recovery time after physical activity.

Biological Systems Affected

According to a recent review (Sanchis-Gomar and Lippi 2014) the biological parameters and system affected by physical activity are listed below.

- Plasma volume: Some physical activity, especially transient exercise in warm and low humidity environment, induced dehydration or hypohydration. It can produce a reduction in plasma volume, and consequently haemoconcentration (Lippi et al. 2006; Brun et al. 2007). In trained subjects, plasma volume is higher than untrained subjects (haemoconcentration). The larger blood volume after long-term endurance training is mostly due to an increase of plasma volume (plasma expansion) and erythrocyte volume (Lippi et al. 2006; Brun et al. 2007).

- Increased basal metabolism: Exercise increases basal energy demands and, therefore, basal metabolism (Lippi et al. 2006).
- Increases in cellular damage: Physical exercise causes an increased generation of reactive oxygen species (ROS), and magnifies oxidative stress in muscle and other organs, resulting in cell damage (Urso and Clarkson 2003; Rousseau et al. 2006; Karolkiewicz et al. 2009).
- Tissue damage biomarkers: Endurance or strenuous physical activity elevates temporally the levels of muscular and cardiac biomarkers. These biomarkers are cardiac troponins, natriuretic peptides, neutrophil gelatinase associated lipocalin alanine aminotransferase, creatine kinase, aspartate aminotransferase, lactate dehydrogenase among others (Romagnoli et al. 2014).
- Iron metabolism alterations: Iron deficiency is a common problem among athletes. Altered iron metabolism in athletes is due to an increase in the iron regulatory hormone hepcidin, up regulated by exercise-induced increases of the inflammatory cytokine interleukin-6 (Sim et al. 2014).
- Renal function markers: During physical activity blood flux in kidney decreases dramatically. After physical activity, temporal high levels of serum protein directly related to the intensity and duration of exercise are reported in athletes. Professional athletes shown lower levels of serum creatinine concentration than healthy sedentary individuals (Sanchis-Gomar and Lippi 2014).
- Inflammation and infection biomarkers: Exhaustive physical activity increases the concentration of C-reactive protein (CRP) (Ledue and Rifai 2003). Interleukin 6 (IL-6), a key element in inflammatory processes, is also increased by the physical activity (Margeli et al. 2005).
- Hormones: Cortisol and endorphin increase during high intensity short duration exercise, and lower intensity long duration physical activity. Testosterone increases with high-intensity exercise, but may decrease if the exercise is very prolonged (Viru 1992; Martínez et al. 2010).

The biological parameters and system affected by physical inactivity and sedentary lifestyle are listed below (Tremblay et al. 2010).

- Overweight and obesity: There are several correlations between sedentary lifestyle and overweight and obesity, but not all sedentary behaviours have been associated with obesity (Shields and Tremblay 2008).
- Metabolic dysfunction, characterized by increased plasma triglyceride levels, decrease in high density lipoprotein (HDL), cholesterol and decrease in insulin sensitivity. Physical inactivity is a risk factor for type 2 diabetes.
- Bones: reduction in bone mineral density. Reduction in bone mass is mediated by changes in the balance between bone resorption and deposition. Markers of bone resorption, including urinary calcium and type I collagen cross-linked N-telopeptides, are reported to increase
- Vascular system: increase in blood pressure and decrease in arterial diameter.

Subgroups at risk

As was commented above, biomarkers altered by physical activity depends, among other factors, on the type, duration, and intensity of physical activity and on the fitness of the subjects. Subjects exposed to physical activity, as a confounder are all who do sport punctual, continuous, or at professional level, regardless of the fitness.

Influence on other stressors of interest

Biomarkers levels could be altered by physical activity of subjects. Accordingly with (Sanchis-Gomar and Lippi 2014), modification results of the biomarkers could be:

- A physiological adaptation to regular exercise
- Change occurred during and/or following regular or punctual exercise.

Physical activity influences the exposure to other stressors of interest. Exposure can be altered due to various aspects such as:

- Physiological parameters. As commented before physical activity modifies metabolism, release and clearance in body compartments, inhalation rates among others physiological parameters. For example, the increase inhalation rate during physical activity may lead to an increase of air pollutants especially in polluted areas such as urban environments.
- Lifestyle habits: The subjects who regularly practice physical activity may have healthier lifestyle (diet, smoking among others) than other individuals with sedentary lifestyle.
- Co-exposure to other substances. A subgroup of athletes may be exposed to stressors such as steroids.

Possibilities to analyse

Global physical activity and International Physical Activity questionnaires (GPAQ and IPAQ) (Craig et al. 2003; Bull et al. 2009) will be useful in order to obtain information regarding activity and inactivity levels of that act as confounder to other stressors of interest in HEALS.

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3.7.7 Consumer Products

WRITTEN BY JOAQUIM ROVIRA & MARTA SCHUHMACHER (URV)

There is large quantity of consumer products in the market, with a high number of different chemical substances in their formulations, being used daily. Personal care products (PCP), is only one group of consumers products and include among others, cosmetics, insect repellents, fragrances, synthetic musk, shampoos, soaps, hair spray, toothpastes, deodorants, and sunscreens (Ortiz de García et al. 2013; Odukudu et al. 2014). In addition to PCP, there are other consumer items widely used for population that must be taken into account (paints, textiles, clothes, cleaning agents, pesticides, toys, automobile materials, furniture, plastic items such as lunch box and bottles). These consumer products contain a mixture chemical compounds which are among others, flame retardants (organophosphate and halogenated flame retardants), volatile organic compounds (VOCs) (formaldehyde, benzene, acetone, among others), preservatives (bisphenol A), phenols (alkylphenols and chlorophenols), parabens, toxic metals (As, Cr, Hg, Pb, among others), UV filters, pesticides, phthalates, perfluorinated compounds (PFC), nanomaterials, and (Sarigiannis and Hansen 2012)(Sarigiannis et al. 2011; Yusa et al. 2012; Odukudu et al. 2014).

Due the high variety and uses of the consumer products, exposure to chemical mixtures contained in them is through all possible routes. Dermal absorption is an important route in the case of direct application of PCP in the skin (Yusa et al. 2012). Also a direct exposure to these

compounds through inhalation and ingestion of vapours, particles and dust during the use are possible (Yusa et al. 2012). Finally, an indirect exposure is described through dietary ingestion of chemicals due a migration from consumer product to food and/or water (Hoekstra and Simoneau 2013; Ustun et al. 2014).

Biological Systems Affected

Several compounds mentioned above are endocrine disruptors (EDs). EDs are compounds that interfere with the normal functioning of human endocrine system. A plasticiser, such as bisphenol A, interferes with thyroxin and cortisol hormone, and phthalates and nonylphenol, also plasticisers, are disruptors for estrogenic hormones (Tijani et al. 2013). Bisphenol A can cause damage to reproductive organs, thyroid gland, and brain tissues during foetal development, and there is a link between exposure and cancer development in humans (Chouhan et al. 2014). Perinatal exposure to EDs appears to be associated with the occurrence of autism spectrum and attention deficit hyperactivity (De Cock et al. 2012).

Subgroups at risk

Due the spread use of consumer products, almost whole population is exposed to these stressors. The greatest impacts of endocrine disruptors, in large quantities in consumer products, are in foetus, newborn, child, and pregnant women. These are the subpopulations at risk.

Influence on other stressors of interest

The use of PCP such as, hair spray or nail paints will modify the contents of biomarkers in human matrices (nails and hair). Consumption of consumer products could be an important exposure pathway of several stressors such as metals and endocrine disruptors (Odukudu et al. 2014; Serrano et al. 2014). Some studies show that exposure to phthalates, commonly use as plasticizers in plastics, but also in cosmetics, are associated with a risk of develop asthma and allergies (Jaakkola and Knight 2008).

Possibilities to analyse

Analytical determination of endocrine disruptors and chemicals of concern contained in consumer products in biological samples are reported in several publications (Faniband et al. 2014). Also performing use frequency and life style questionnaires regarding these products will be very helpfully to elaborate an exposure profile. However, due the complexity to analyse all the activities, consumer products, and chemicals containing in them, the use of biomarkers of exposure to the chemicals contained in consumer products seems to be a more reasonable way to assess the exposure to this confounder.

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3.7.8 Stress

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Three broad approaches to assess the role of stress as a risk factor for development of disease or as a confounding factor can be distinguished. The environmental one focuses on assessment of environmental events or experiences that are objectively measured with substantial adaptive demands (assessment of natural disasters, stressful life events or daily events). The psychological approach focuses on individuals' subjective evaluations of their abilities to cope with the demands posed by specific events or experiences and their affective response to that evaluation (e.g. demand of work; see chapter 3.6.5). The third, biological approach, focuses on activation of specific physiological systems that have been repeatedly shown to be modulated by both psychologically and physically demanding conditions (response of sympatheic-adrenal medullary system and *hypothalamic-pituitary-adrenal axis)* (Cohen 2000).

Definition

Psychological stress is a generic term that includes a wide range of different types of exposures which can be acute – resulting from external disasters or disease/death of a family member, as well as chronic – such as occupational stress (see chapter 3.6.5) or daily hassles. A different issue is istress in pregnancy or during postpartum period (e.g. stress, anxiety and post-partal depression) (Nast et al. 2013).

Stress is a multidimensional concept. It results from a perceived imbalance between psychological stress (acute or chronic) and individual resources such as personality, social support and lifestyle and socio-economic conditions. This imbalance may lead to a heightened stress perception and the increased risk of maladaptive cognitive, emotional and behavioural responses (Nast et al. 2013).

Biological Systems Affected

Stress affects human health through complex psycho-physiological mechanisms. Negative health effects of stress depend on its duration and/or magnitude – the stronger the stress and/or the more prolonged exposure, the higher the probability of health problems. Several outcomes are associated with stress including problems with sleep, headache, stomach upset, or a change in blood pressure as well as depression, asthma and cardiovascular effects. A wide range of different outcomes have also been shown to be associated with prenatal stress including congenital malformations, lower birth weight or shorter gestational age (Lazinski et al. 2008). In additon, prenatal exposure to stress can be associated with neurodevelopmental as well as psychopathological outcomes in the offspring (including decreased cognitive, language and motor abilities and emotional or behavioural problems) (Lazinski et al. 2008; Kingston et al. 2012). The impact of post-partal depression on maternal and child health outcomes, such as: maternal-infant interaction and infant temperament as well as child neurodevelopmental delay, has also been reported (Kingston et al. 2012). Stress factors have been related to immune system and aging (Bauer et al. 2009). Psychosocial stress during pre- and early postnatal life may increase the vulnerability of infants to the effects of immunotoxicants or immune-mediated diseases, with long-term consequences. Neural-immune interactions may provide an indirect route through which immunotoxicants affect the developing immune system (Bellinger et al. 2008). Exposure to psychosocial job stress (high job demands, low job control, high job strain, job dissatisfaction, high effort-reward imbalance, overcommitment, burnout, unemployment, organizational downsizing, economic recession) had a measurable impact on immune parameters (reduced NK cell activity, NK and T cell subsets, CD4+/CD8+ ratio and increased inflammatory markers) (Nakata 2012). The evidence supports that psychosocial job stresses are related to disrupted immune responses but further research is needed to demonstrate cause-effect relationships.

Influence on other stressors of interest

Psychological stress may influence the exposure to other factors of interest. Somebody with a higher level of psychological stress may have an inferior lifestyle including diet, smoking, alcohol consumption, drug abuse, lack of physical activity. People with lower levels of SES report more stressful life events, although these studies have focused on lower versus higher SES and not on determining a gradient. Psychological stress has a nice graded relation with both education and income as do negative affect measures (Cohen 2000).

Subgroups at risk

At risk to be exposed to stress are occupational groups (ILO 2014) (see chapter 3.6.5), disable people and people in specific life situations (e.g. pregnancy, postpartum women).

Possibilities to analyse

Although a broad range of instruments is available to assess psychological stress, there is no measure that is appropriate for all the aspects of stress (e.g. occupational stress, anxiety, depression, daily hassles, life events, socio-environmental stressors) and for all populations

(children, adolescents, adults, pregnant and post-partal women). The exact stress measure that one may choose depends on the question that is being posed (Nast et al. 2013).

A rule from a methodological perspective is, that the more objective the measure, the more reliable are the results. Thus, cortisol levels for measurement of prenatal stress would be of greatest value. On the other hand, in large scale studies, researchers had to meet half way between organizational possibilities and the best methodological solution and chose standardized self-administered psychological methods. Questionnaires/scales are usually validated and their psychometric value is proven but the core challenge is the choice of a proper tool (Kingston et al. 2012).

Instruments used to measure psychosocial factors in work environment are described in chapter 3.6.5.

Among many instruments to assess anxiety, the State-trait Anxiety Inventory (STA) is the most frequently used scale (Spielberger et al. 1983). This self-report inventory measures two types of anxiety – state anxiety, or anxiety about an event, trait anxiety or anxiety level as a personal characteristic.

The gold standard for a research diagnosis of depression is the Structural Clinical Interview (SCID), a clinical interview that uses the Diagnostic and Statistical Manual of Mental Disorders criteria for illness. However, epidemiological studies often use Composite International Diagnostic Interview (CIDI) or the Diagnostic Interview Schedule (DIS) or self-report questionnaires that measure symptoms and mood rather than illness and disorder (Kessler et al. 2004).

The Perceived Stress Scale (PSS) is identified as an adequate instrument to measure disturbances by daily hassles (Cohen et al. 1983). The PSS is a measure of extent to which situations are regarded as unpredictable, uncontrollable and burdensome.

Life events as stress factors are frequently measured by Social Readjustment Rating Scale or its adaptation (Holmes and Rahe 1967).

Specific socio-environmental stressors can be related to experience of physical or psychological violence or can be related to family quality and communication. This is frequently assessed by the APGAR (Adaptation, Partnership, Growth, Affection, Resolve) Family Scale (Smilkstein et al. 1982; Smilkstein 1993).

The Prenatal Distress Questionnaire is identified as the best currently available instrument for the assessment of stress related to pregnancy and parenting (Alderdice et al. 2013).

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4 Conclusions for HEALS

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The traditional way to assess the effects of stressors is to measure a specific stressor as a biomarker of exposure, e.g. a chemical substance such as lead in a human specimen such as blood. Next step is to look for an adverse health effect using either an epidemiological or a toxicological approach, in the case of lead negative health effects such as anaemia, loss of IQ etc. Usually the biomarker of exposure is analysed at the same time as the effect, in this example lead in blood and IQ level. This classical way of environmental health research has enabled to identify a long list of serious stressors and relevant diseases. But the real world is by far more complex than this simplified old approach assumed. A typical problem is the latency period between the exposure especially to carcinogen substances and the development of diseases. Occupational asbestos exposure seized decades ago, but the peak of asbestos related cancers is still to come. There is no way to measure nowadays the biomarker of an exposure 20-50 years ago. So indirect assumptions such as level, duration and frequency of asbestos fibre exposure are needed to assess a possible causal relationship between lung cancer and asbestos exposure earlier in life. In the case of loss of IQ due to lead exposure it is even more difficult, did the maternal lead burden prenatally cause the loss of IQ and the measured level of lead in blood of the infant is just an indicator of still leaving in a lead contaminated surrounding? Or is it a real time effect and lead was causing the effect on IQ during the postnatal period. The developmental origin of health and disease (DOHaD) is a nice concept, expanding from stressors such as deprivation from nutrition in early life causing metabolic disorders in late life to environmental contaminants such endocrine disrupting chemicals (EDCs). Some of the most suspicious EDCs can be detected as biomarkers of exposure either directly or indirectly via their specific metabolites, phthalates are just an example for these EDCs. Another important EDC, BPA is measurable in human specimens, but due to a very short biological half-life the measured level cannot reveal the accumulated exposure over time. E.g. a newborn is being bottle fed with formula milk – the plastic bottle releasing BPA into the milk. A single spot assessment of BPA in urine will depend on the time gap between exposure to BPA released into the milk and the collection of urine with a plastic urine bag, not to mention the contamination of the collection bag itself with BPA. So it is necessary to consider single spot assessment of biomarkers of exposure versus multiple time assessments.

In this report many different stressors are listed, many of them are chemical stressors. But the number of chemicals humans are exposed to is by far greater than any report could make a list of. In a recent report from the NHANES study in the US EDCs were analysed in serum from 2nd trimester pregnant women. Over 500 different EDCs were detected. Only for a very limited number of chemicals analytical methods are known to measure the chemical or relevant metabolites in human specimens. Even for many high volume chemicals there is no biomarker of exposure available. Industry can develop, produce, market, trade and apply chemicals without having to deal with a possible effect on human health. Different to pharmaceuticals chemicals have not been tested before involuntary application to pregnant women, infants, adolescents and other populations at risk. The precautionary principle still needs to be taken by far more serious and the new European REACH approach cannot assess the multitude of existing chemicals within short time. So there is a huge gap of knowledge between the exposure to existing chemicals, estimated for humans to range between 10.000 and 100.00 substances and the availability to analyse the respective biomarkers of exposure.

As was listed in great detail for some of this stressors, excellent biomarkers of exposure are available. Some examples are lead in blood and lead in bones; mercury in urine, blood, hair or elsewhere, PCBs in blood or breast milk etc. etc. At the same time some very important stressors have no measurable biomarkers of exposure et al., e.g. air pollutants such as PM2.5 or ozone. Whole groups of stressors, such as nanoparticles or UV light do not leave any measurable substances in accessible body specimens. Some stressors cannot be measured directly but there metabolites can be analysed, e.g. formaldehyde. But these metabolites are not substance specific and could be a result of other metabolic pathways.

Physical, chemical, biological, social and psychological stressors influence the health and can contribute to the pathogenesis of diseases. Life starts before conception - the effects of stressors on the genes of the previous generations are extremely important. More and more research results prove that gene alteration and modification can be related to many of the listed stressors. But it is impossible to assess biomarkers of exposure for these transgenerational effects.

More and more it is realised that the origin of many diseases originates from stressors during prenatal and early years of life. Especially birth cohorts are useful tools to identify relevant stressors. But what is the best time of sampling - 1st, 2nd or 3rd trimester of pregnancy? The answer depends on the critical window of susceptibility of the negative health effect. Should urine, blood or even amniotic fluid be taken? How invasive is still safe and ethical? What is better, cord blood or placenta? How many times can an infant be hurt and how much hair or blood can technically be taken?

Having giving all these limitations for applying biomarkers of exposure, why still bother to collect specimens analyse them? Because so far still the best way to identify stressors that do play a role in pathogenesis of diseases is to look for stressors and analyse their biomarkers of exposure. The HEALS approach is a unique opportunity to develop methods to overcome some of this restrictions by looking into interactions of chemicals and stressors. Genetic and environmental triggers contribute to disease endpoints. E.g. asthma in childhood has a strong genetic influence, either parent having an atopic disease or even asthma increases the likelihood of asthma for a child. However, prenatal factors such as smoking parent(s) and indoor and outdoor air pollution are needed for the occurrence of the disease. Medication in early childhood, e.g. antibiotics or paracetamol are possibly triggering factors, whereas VOCs, moulds, or lack of physical activity etc.. are established risk factors. Social factors, housing conditions, air quality in school, nutrition, medication, all are also important factors (see Figure 24). So the interaction of different stressors is of importance. The HEALS concept takes these different critical windows of susceptibility and the different stressors into account modelling potential disease outcomes.

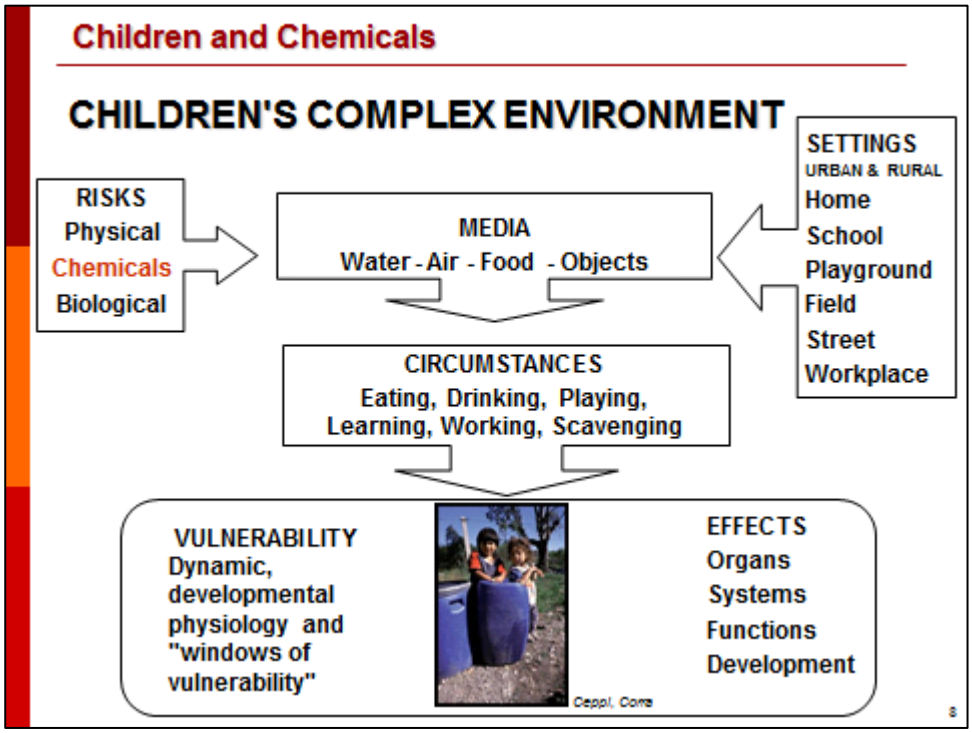

Figure 24: Children’s complex environment. From WHO training module “Chemicals” for Health Care Providers

The external exposome is derived using environmental, social, occupational and dietary data and model fusion using efficient algorithms for mining existing environmental monitoring datasets and ubiquitous sensing using geo-localized sensors and mobile phones. A key innovation is the development and optimization of the necessary software apps for data integration and the coupling of these datasets with agent-based modelling incorporating the socio-economic determinants of population exposure to health stressors. Exposomic analysis is focusing on critical stages in human life extrapolating to the whole lifespan using Bayesian statistical modelling to construct the integrated individual exposome. The internal and external exposome data above is used to derive environment-wide associations between exposure and health. Novel mathematical and computational tools are used to explore the association between different environmental, genetic and epigenetic determinants and identified biological perturbations and, eventually, disease phenotypes. In addition, using the HEALS methodology, a plausible pathway towards establishing causality in the observed associations between environmental stressors and health status is tread.

Table 23: Summary of biomarkers of exposure and their reference and exposure limit values

Chapter	Stressor	Specimen	Biomarker of exposure	Reference value, population, year, sample size (reference)	Exposure limit values		
					HBM value (reference)	BE (reference)	Other exposure limit values (reference)
2.1.1	PCBs	S	ΣPCBs	Range of central tendency: 170-550 ng/g lipid (general adult populations from Europe) (Garí et al. 2014); P95: 720 ng/g lipid (general adult population from France) (InVS 2010).	/	/	/
		B		/	RV_{95} in children and adults: 1 µg/l and 1.1-7.8 µg/l, respectively (Schulz et al. 2011).	Critical concentrations threshold: 700 ng/g lipid (in plasma) for pregnant women, women of childbearing age, breastfeeding women and children under 3 years of age and 1800 ng/g lipid (in plasma) for other adults (ANSES 2013; Aylward et al. 2013).	/
		M		/	RV_{95} in human breast milk: 0.5 mg/kg fat (Schulz et al. 2011).	/	/
2.1.2	OCPs	S	4,4’-DDE	Range of central tendency: 100-800 ng/g lipid (general adult populations from Europe) (Garí et al. 2014); P95: 730 ng/g lipid (general adult population from France) (InVS 2010).	/	/	/

		B		/	RV_{95} in children and adults: 0.7-1.4 µg/l and 1.5-31 µg/l, respectively (Schulz et al. 2011).	/	/
		M	ΣDDTs	/	RV_{95} in human breast milk: 0.5 mg/kg fat (Schulz et al. 2011).	/	/
		S	DDT+DDE	/	/	BE: 5000 ng/g lipid (Aylward et al. 2013).	/
		S	HCB	Range of central tendency: 10-200 ng/g lipid (general adult populations from Europe) (Garí et al. 2014); P95: 73 ng/g lipid (general adult population from France) (InVS 2010).	/	BE: 47 ng/g lipid (Aylward et al. 2013).	/
		B		/	RV_{95} in children and adults: 0.3 µg/l and 0.4-5.8 µg/l, respectively (Schulz et al. 2011).	/	/
		M		/	RV_{95} in human breast milk: 0.06 mg/kg fat (Schulz et al. 2011).	/	/
		S	β-HCH	Range of central tendency: 10-100 ng/g lipid (general adult populations from Europe) (Garí et al. 2014); P95: 190 ng/g lipid (general adult population from France) (InVS 2010).	/	/	/
		B		/	RV_{95} in adults: 0.3-0.9 µg/l (Schulz et al. 2011).	/	/

		M		/	RV_{95} in human breast milk: 0.07 mg/kg fat (Schulz et al. 2011).	/	/
2.1.3	PBDEs	S	ΣPBDEs	Range of central tendency: 2-15 ng/g lipid (general adult populations from Europe); P90: 35 ng/g lipid (general adult population from Catalonia, Spain) (Garí and Grimalt 2013).	/	/	/
			BDE-99	Range of central tendency: 0.16-2.4 ng/g lipid (general adult populations from Europe); P90: 5.2 ng/g lipid (general adult population from Catalonia, Spain) (Garí and Grimalt 2013).	/	BE: 520 ng/g lipid (Aylward et al. 2013).	/
2.2.1	Phthalates	U	5oxo- and 5OH-MEHP	/	HBM I: 500 µg/l for children (6-13 years); 300 µg/l for women of childbearing age; 750 µg/l for males ≥14 years and remaining general population (Schulz et al. 2011)	/	/
2.2.2	OPPs	U	DMP and DMTP (DAPs)	Range of central tendency: 6-8 µg/g creatinine, and P95: 49-59 µg/g creatinine (general adult population from France) (InVS 2010).	RV_{95} in children and adults: 75-100 µg/l and 135-160 µg/l, respectively (Schulz et al. 2011).	/	/
			DMDTP and DETP (DAPs)	Range of central tendency: 0.5-1.1 µg/g creatinine, and P95: 6.5-7 µg/g creatinine (general adult population from France) (InVS 2010).	RV_{95} in children: 10 µg/l (Schulz et al. 2011).	/	/
			DEP (DAP)	Range of central tendency: 3.7 µg/g creatinine, and	RV_{95} in children and	/	/

				P95: 15.9 µg/g creatinine (general adult population from France) (InVS 2010).	adults: 30 µg/l and 16 µg/l, respectively (Schulz et al. 2011).		
2.2.4	BPA	U	Total BPA	P95 (reference value): 30 µg/l for 3-5 year olds, 15 µg/l for 6-14 year olds, and 7 µg/l for 20-29 year olds (HBM-UBA 2012)	HBM I: 1.5 mg/l for children; 2.5 mg/l for adults (HBM-UBA 2012)	/	/
2.2.5	Parabens	U	Methyl parabens	P95: 974 µg/l, US general population ≥6 years, NHANES (2005-2006), n=2548 (Calafat et al. 2010)	/	/	/
			Propyl parabens	P95: 299 µg/l, US general population ≥6 years, NHANES (2005-2006), n=2548 (Calafat et al. 2010)	/	/	/
			Butyl parabens	P95: 19.6 µg/l, US general population ≥6 years, NHANES (2005-2006), n=2548 (Calafat et al. 2010)	/	/	/
			Ethyl parabens	P95: 57.2 µg/l, US general population ≥6 years, NHANES (2005-2006), n=2548 (Calafat et al. 2010)	/	/	/
2.2.6	PYR	M	ΣPYR	Range of central tendency: 4-8 ng/g lipid weight (women from Spain) (Corcellas et al. 2012).	/	/	/
		U	3PBA (PYR metabolite)	Range of central tendency: 0.63 µg/g creatinine, and P95: 3.5 µg/g creatinine (general adult population from France) (InVS 2010).	RV: 4.3 µg/g creatinine (IEH 2008).	/	/
				Range of central tendency: 0.29 µg/l, and P95: 2.4 µg/l (children population from Germany) (Becker et al. 2008).	RV_{95} in children and adults: 2 µg/l (Schulz et al. 2011).	/	/
			4F3PBA, DBCA, cis-DCCA and trans-DCCA (PYR	P95: 0.98-2.6 µg/g creatinine (general adult population from France) (InVS 2010); Range of central tendency: 0.05-0.14 µg/g creatinine, and P95: 0.40-1.4 µg/g creatinine (children population from Germany) (Becker et al. 2008).	RV_{95} in children and adults: 1-2 µg/l (Schulz et al. 2011). RV in adults: 0.7-1.8 µg/g creatinine (IEH 2008).	BE: 50-240 µg/l (Aylward et al. 2013).	/

			metabolites)				
2.3.1	Mercury	H	Mercury	P95: 1.2 µg/g for mothers, 0.8 µg/g for children, European population (17 countries) (2012), n=1844 mother-child pairs (DEMOCOPHES Pilot Study) (Esteban et al. 2014)	/	/	RfD-based value: 1 µg/g, for women of childbearing age (US EPA 2001)
		B	Mercury	P95: 1.0 µg/l, children aged 3-14 years, German population (2003-2006), n=1552 (Schulz et al. 2009) P95: 2.3 µg/l, adults 18-69 years, German population (1997-99), n=4645, (Wilhelm et al. 2004)	HBM I: 5 µg/g creatinine HBM II: 15 µg/g creatinine (Schulz et al. 2011)	/	/
		U	Mercury	P95: 0.4 µg/l children 3-14 years without amalgam fillings, German population (2003-2006), n=1734 (Schulz et al. 2009) P95: 1.0 µg/l, adults 18-69 years without amalgam fillings, German population (1997-99), n=4822 (Wilhelm et al. 2004)	HBM I: 5 µg/g creatinine HBM II: 20 µg/g creatinine (Schulz et al. 2011)	/	/
2.3.2	Lead	B	Lead	P95 (reference value): 35 µg/l for children, 70 µg/l for women and 90 µg/l for men, German population (1997-99, 2003-2006), n=1560; 2303; 2342, respectively (Wilhelm et al. 2004; Schulz et al. 2009, 2011)	*suspended*	/	/
2.3.3	Cadmium	U	Cadmium	P95: 0.2 µg/l for non-smoking children 3-14 years, German population, n=1667 (Schulz et al. 2009) P95: 0.8 µg/l for non-smoking adults, German population (1997-99), n=4645 (Wilhelm et al. 2004)	HBM I adults: 1 µg/g creatinine; children: 0.5 µg/g creatinine HBM II adults: 4 µg/g creatinine; children: 2	/	/

					µg/g creatinine		
		B	Cadmium	P95 (reference value): <0.3 µg/l, non-smoking children 3-14 years, German population (2003-2006), n=1498 (Schulz et al. 2009) P95 reference value): 1 µg/l, non-smoking adults, German population (1997-99), n=3061 (Wilhelm et al. 2004)	/	/	/
2.3.4	Arsenic	U	Arsenic	P95: 18.9 µg/l, adults 18-69 years, German population (1997-99), n=4741 (Wilhelm et al. 2004) P95: 14.0 µg/l, children 3-14 years, German population (2003-2006), n=1734 (Schulz et al. 2009) *15.0 µg/l: for children and adults who did not eat fish 48 h prior to sample collection (Schulz et al. 2011)	ALARP		
2.3.5	Copper	B	P-Copper	Reference interval for clinical guidance: 70-140 µg/dl, adults (Burtis et al. 2012) *<50 µg/dl in adults and <30 µg/dl in infants indicates probable depletion.	/	/	/
2.3.6	Zinc	B	S-Zinc	Reference interval for clinical guidance: 80-120 µg/dl (Burtis et al. 2012) *Results <30 µg/dl suggest likely deficiency.	/	/	/
2.3.7	Selenium	B	Selenium	Reference interval: 60 µg/l and 300 µg/l, general population (ATSDR 2003; Liu et al. 2008)	/	/	/
		B	S-Selenium	Reference interval for clinical guidance: 16-71 µg/l (<2 year old children), 40-103 µg/l (2-4 year old children), 55-134 µg/l (4-16 year olds), and 63-160 µg/l/l (adults) (Burtis et al. 2012)	/	/	/
2.3.8	gane	B	Manganese	Reference interval for clinical guidance: 5-15 µg/l (Burtis et al. 2012)	/	/	/
		B	S-	Reference interval for clinical guidance: 0.5-1.3 µg/l	/	/	/

			Manganese	(Burtis et al. 2012)			
		U	Manganese	Reference interval for clinical guidance: 0.5-9.8 µg/l (Burtis et al. 2012)	/	/	/
2.3.9	Chromium	B	Chromium	Reference interval for clinical guidance: 0.7-28.0 µg/l (Burtis et al. 2012)	/	/	/
		B	S-Chromium	Reference interval for clinical guidance: 0.1-0.2 µg/l (Burtis et al. 2012)	/	/	/
		U	Chromium	<0.2 µg/l (Burtis et al. 2012)	/	/	/
2.3.10	Iron			*generic reference interval is not valid*			
2.4.1	Benzene	A	Benzene	Range of central tendency[2]: 3-32 ng/l, non-smoking general populations, 14-73 ng/l, smokers, range of several studies (Arnold et al. 2013)	/	/	/
		B	Benzene	Range of central tendency[1]: 50-200 ng/l, non-smoking general population, 100-500 ng/l, smoking general population, range of several studies (Arnold et al. 2013)	/	BE[3]: between 0.04 and 1.29 µg/l (Hays et al. 2012)	/
		U	Benzene	P95: 311.5 ng/l, non-smoking, non-occupationally exposed subjects, random sample of the general population, Italy, n= 86 (Campagna et al. 2014) Range of central tendency[1]: 0.10-0.25 µg/l, non-smoking general population, 0.20-0.80 µg/l, smoking general population, range of several studies (Arnold	/	BE[3]: between 0.05 and 1.42 µg/l (Hays et al. 2012)	EKA: see chapter 2.4.1 (DFG 2014)

[2] Examples of the central tendency are mean, median and geometric mean (Arnold et al. 2013).
[3] The range of the BE is based on the underlying non-cancer risk assessment. The following non-cancer risk assessments were considered: US EPA Chronic RfC (Reference Concentration), TCEQ ReV (Texas Commission of Environmental Quality, Reference Value), CA REL (California, Reference Exposure Level), ATSDR chronic inhalation MRL (Minimal Risk Level) (Hays et al. 2012).

				et al. 2013)			
		U	S-PMA	P95: 38.0 nmol/l; 7.0 µg/g cr, general adult (>18 years), UK population, n= 355 (IEH 2008) Range of central tendency[3]: 0.5-9 µg/l, 0.3-8.9 µg/g cr, non-smoking general populations, 0.76-18 µg/l, 0.3-9.9 µg/g cr, non-occupationally exposed smokers, range of several studies from countries in Asia and Europe (Arnold et al. 2013)	/	/	BEI: 25 µg/g creatinine (Arnold et al. 2013)
2.4.2	Toluene	A	Toluene	Range: 0.3-8.6 ppb, mean: 1.42 ppb, healthy volunteers, Austria, n= 28 (Mochalski et al. 2013)	/	/	/
		B	Toluene	P95: 0.814 ng/ml, US population, 2005/2006, n= 3050 (CDC 2014)	/	BE[4]: between 3 and 50 µg/l^{-1} (Aylward et al. 2008)	BAT: 600 µg/l (DFG 2014) BEI: 0.05 mg/l (ATSDR 2000)[5]
		U	Toluene	P95: 481-1361 ng/l^{-1}, primary school children, Italy (cities: Poggibonsi, Treviglio, Valenza), n= 107-147 (Minoia et al. 1996)	/	/	
		U	Hippuric acid	P95: 0.36 g/g creatinine, nonoccupational exposed population, Brazil, n= 115 (Siqueira and Paiva 2002)	/	/	BEI: 1.6 g/g creatinine (ATSDR 2000)Errore. II

[4] The range of the BE is based on the underlying non-cancer risk assessment. The following health-based exposure guidelines and toxicity values were considered: US EPA Chronic RfC (Reference Concentration), Health Canada chronic inhalation TDI (tolerable daily intake), WHO air quality guideline. ATSDR chronic inhalation MRL (Minimal Risk Level), ATSDR acute MRL (Aylward et al. 2008).

[5] Original source (no free access): (ACGIH 1999).

							segnalibro non è definito.
2.4.3	Xylene	B	*o*-xylene	P95: 0.110 ng/ml, US population, 2005/2006, n= 3153 (CDC 2014)	/	BE: 0.3 µg/l whole blood (Aylward et al. 2010, 2013)	BAT: 1.5 mg/l (DFG 2014)
		B	*m-, p-* xylene	P95: 0.410 ng/ml, US population, 2005/2006, n= 3153 (CDC 2014)	/	/	/
		U	*o-, m-, p-* xylene	P95: 230-909 ng/l^{-1}, primary school children, Italy (cities: Poggibonsi, Treviglio, Valenza) n= 96-144 (Minoia et al. 1996)	/	/	/
		U	MHA	P95: 440.0 µmol/l, 94.7 mg/g creatinine, general adult (>18 years) UK population, n= 360 (IEH 2008)	/	/	BAT: 2,000 mg/l, methylhippuric (toluric) acid (all isomers) (DFG 2014)
		U	2-MHA	P95: 408 µg/l, 382 µg/g creatinine, smokers, n= 889, 170 µg/l, 156 µg/g creatinine, non-smokers, n= 1307-1308, US population, 2011/2012 (CDC 2014)	/	/	/
		U	3- and 4-MHA	P95: 2850 µg/l, 2260 µg/g creatinine, smokers, n= 889, 1330 µg/l, 1060 µg/g creatinine, non-smokers, n= 1307-1308, US population, 2011/2012 (CDC 2014)	/	/	/
3.2.1	DBPs	B	THMs (chloroform, BDCM, DBCM, bromoform	Range of central tendency: 18 pg/ml (general population from the US) (LaKind et al. 2010; Riederer et al. 2014).	/	BE: 230 pg/ml for chloroform; 80 pg/ml for BDCM; 20 pg/ml for DBCM; 130 pg/ml for bromoform (Aylward et	/

			)			al. 2013).	
3.2.2	THMs	A	THMs	Range of central tendency: 1.2 µg/m^3 and 7.9 µg/m^3 (adult swimmers before and after swimming in an indoor chlorinated pool for 40 minutes, respectively) (Font-Ribera et al. 2010; Kogevinas et al. 2010).	/	/	/

Abbreviations: A (exhaled air), B (blood), BAT (Biological Tolerance Value; see Glossary for further descriptions), BE (biomonitoring equivalent), F (faeces), H (hair), HBM values (human biomonitoring values [HBM I and HBM II] of the Human Biomonitoring Commission of the German Federal Environment Agency; see Glossary for further descriptions), M (breast milk), MHA (methylhippuric acid), P (plasma), ppb (parts per billion), P90 (90th percentile), P95 (95th percentile), RV (Reference Value), RV_{95} (Reference Value based on 95th percentile), S (serum), S-PMA (S-phenyl mercapturic acid), U (urine)

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Abbreviations

3PBA	3-Phenoxybenzoic Acid
4F3PBA	4-Fluoro-3-Phenoxybenzoic Acid
5-FU	5-Fluorouracil
°C	Degree Celsius
α1M	α1-Microglobulin
ß2M	ß2-Microglobulin
µg	Microgram
µmol	Micromole
AA	Alkylating Agent
AAMA	N-Acetyl-S-(2-carbamoylethyl)-L-cysteine
AC	Alternating Current
ACGIH	American Conference of Industrial Hygienists
ACS	Acute Coronary Syndrome
ADME	Accumulation, Distribution, Metabolism and Excretion
ADP	Adenosine Diphosphate
AhR	Aryl hydrocarbon Receptor
AI	Adequate Intake
Al	Aluminium
AIDS	Acquired Immune Deficienay Syndrome
ALARP	As low as is reasonably practicable
ALL	Acute Lymphocytic Leukaemia
AM	Amplitude Modulation
AMAP	Arctic Monitoring and Assessment Programme
AML	Acute Myeloid Leukemia
ANSES	French Agency for Food, Environmental and Occupational Health and Safety
APGAR	Adaptation, Partnership, Growth, Affection, Resolve
As	Arsenic
As_2O_3	Arsenic Trioxide
AsB	Arsenobetaine
AsC	Arsenocholine
AsS	Arsenosugars
ATC	Anatomical Therapeutic Classification
ATCA	2-Aminothiazoline-4-carboxylic Acid
ATP	Adenosine Triphosphate
ATSDR	Agency for Toxic Substances and Disease Registry
B	Boron
Ba	Barium

BAC	Blood Acohol Content
B[*a*]P	Benzo[*a*]pyrene
BAT	Biological Tolerance Value (Biologische Arbeitsstoff-Toleranzwerte)
BBzP	Butyl Benzyl Phthalate
BCF	Bioconcentration Factor
BDCM	Bromodichloromethane
BDE	Brominated Diphenyl Ether
BE	Biomonitoring Equivalent
BEI	Biological Exposure Index
BFR	Brominated Flame Retardant
BGV	Biological Guidance Values
BLW	Biological Guideline Values (Biologische Leitwerte)
BPA	Bisphenol A
BSS	Basic Safety Standards
BTX	Benzene, Toluene and Xylene
BTXS	Benzene, Toluene, Xylene and Styrene
Bq	Becquerel
bw	Body weight
C_6H_6	Benzene
C_7H_8	Toluene
C_8H_{10}	Xylene
Ca	Calcium
Cal/EPA	California Environmental Protection Agency
CAP	Capecitabine
CA REL	California, Reference Exposure Level
Cd	Cadmium
CDC	Centers for Disease Control and Prevention
CDDEP	Center for Disease Dynamics, Economics & Policy
CHD	Coronary Heart Disease
CI	Confidence Interval
CIDI	Composite International Diagnostic Interview
CLL	Chronic Lymphocytic Leukaemia
CMR	Carcinogenic, Mutagenic and Reprotoxic
CNOSSOSEU	Common Noise assessment Methods
CNS	Central Nervous System
CO	Carbon Monoxide
COPD	Chronic Obstructive Pulmonary Disease
COX-2	Cyclooxygenase-2
cr.	Creatinine

Cr	Chromium
Cr^{3+}	Trivalent Chromium
Cr^{6+}	Hexavalent Chromium
CRP	C-reactive Protein
CRTN	Calculation of Road Traffic Noise
Cs	Caesium
CSDH	Commission on the Social Determinants of Health
Cu	Copper
DALY	Disability-Adjusted Life Year
DAP	Dialkylphosphate
dB	Decibel
dB(A)	Decibel
DBAA	Dibromoacetic Acid
DBCA	2,2-Dibromo-2-Dimethylvinyl-Cyclo-Propane Carboxylic Acid
DBCM	Dibromochloromethane
DBP	Disinfection By-product
DCA acid	Dichloroacetic Acid
DCAA	Dichloroacetic Acid
DCCA	2,2-Dichloro-2-Dimethylvinyl-Cyclopropane Carboxylic Acid
DDD	Dichlorodiphenyldichloroethane
DDE	Dichlorodiphenyldichloroethylene
DDT	Dichlorodiphenyltrichloroethane
DEAMPY	2-Diethylamino-6-Methyl-4-Pyrimidinol
Deca-BDE	Decabromodiphenyl Ether
DEDTP	Diethyldithiophosphate
DEHP	Di(2-ethylhexyl) Phthalate
DEP	Diethyl Phthalate
DEP	Diethylphosphate
DER	Deoxyribonucleic Acid
DETP	Diethylthiophosphate
DFG	German Research Foundation (Deutsche Forschungsgemeinschaft)
DiBP	Di-iso-butyl Phthalate
DiDP	Di-iso-decyl Phthalate
DiNP	Di-iso-nonyl Phthalate
DIS	Diagnostic Interview Schedule
dl	Decilitre
DL	Dioxin-like
DMA	Dimethylarsenic Acid
DMDTP	Dimethyldithiophosphate
DMP	Dimethyl phthalate

DMP	Dimethylphosphate
DMTP	Dimethylthiophosphate
DNA	Deoxyribonucleic Acid
DnBP	Di-n-butyl Phthalate
DNEL	Derived No-Effect Level
DOHaD	Developmental Origin of Health and Disease
DPHP	Di(propylheptyl) Phthalate
DRI	Dietary Reference Intake
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders (fourth edition; text revision)
EAR	Estimated Average Requirement
EBFRIP	European Brominated Flame Retardant Industry Panel
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
ECETOC	European Chemical Industry Ecology & Toxicology Centre
ED	Endocrine Disruptor
EDC	Endocrine Disrupting Chemical
EDR	Exposure-Dose-Response
EEG	Electro-Encephalographical
EFSA	European Food Safety Authority
EHS	Electro-hypersensitivity
EKA	Exposure equivalent for carcinogenic substances (Expositionsäquivalente für krebserzeugende Arbeitsstoffe)
ELF	Extremely Low Frequency
EMF	Electromagnetic Fields
EPIC	European Prospective Investigation of Cancer
ERB	Exposure-Risk-Relationships for carcinogenic substances (Expositions-Risiko-Beziehung für krebserzeugende Stoffe)
ETS	Environmental Tobacco Smoke
EU	European Union
EU-OSHA	European Agency for Safety and Health at Work
EWAS	Environment-wide Association Studies
FAS	Familly Affluence Scale
Fe	Iron
FEDESA	European Federation of Animal Health
FEP	Free Erythrocyte Protoporphyrin
FID	Flame Ionization Detection
FM	Frequency Modulation
FP7	Seventh Framework Programme for Research
FTOH	Fluorotelomer Alcohol

g	Gram
G6PD	Glucose-6-phosphate dehydrogenase
GABA	γ-Aminobutyric acid
GAMA	N-Acetyl-S-(2-carbamoyl-2-hydroxyethyl)-L-cysteine
GC	Gas Chromatography
GHz	Gigahertz
GM	Geometric Mean
GPAQ	Global Physical Activity Questionnaire
Gy	Gray (unit of absorbed dose of radiation)
h	Hours
HAA	Haloacetic Acid
HAVS	Hand-arm Vibration Syndrome
HBM	Human Biomonitoring
HBM I	Human biomonitoring value I of the Human Biomonitoring Commission of the German Federal Environment Agency
HBM II	Human biomonitoring value II of the Human Biomonitoring Commission of the German Federal Environment Agency
HCB	Hexachlorobenzene
HCH	Hexachlorocyclohexane
HDL	High Density Lipoprotein
HEALS	Health and Environment-wide Associations based on Large population Surveys
Hg	Mercury
Hg^{2+}	Divalent Mercury
$HgCl_2$	Mercury Sublimate
HgS	Cinnabar
HIV	Human Immunodeficiency Virus
HNO_2	Nitrous Acid
HNO_3	Nitric Acid
HRV	Heart Rate Variability
HSE	Health and Safety Executive
Hz	Hertz
IAEA	International Atomic Energy Agency
IARC	International Agency for Research on Cancer
ICC	Indian Childhood Cirrhosis
ICD	International Classification of Diseases
ICNIRP	International Commission on Non-Ionizing Radiation Protection
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
ICRIS	International Statistical Classification of Diseases and Cross Racial Identity Scale
ICRP	International Commission on Radiological Protection
ICT	Idiopathic Copper Toxicosis

IEH	Institute of Environment and Health
IF	Intermediate Frequency
IgE	Immunoglobulin E
IL1β	Interleukin-1 beta
IL-6	Interleukin 6
IL-18	interleukin-18
ILO	International Labour Organization
IMD	Index of Multiple Deprivation
IMPY	2-Isopropyl-4-Methyl-6-Hydroxypyrimidine
InVS	French Institute for Public Health Surveillance
IOELV	Indicative Occupational Exposure Limit Values
IOM	Institute of Medicine
IPAQ	International Physical Activity Questionnaire
IPCS	International Programme on Chemical Safety
IQ	Intelligence Quotient
IRR	Incidence Rate Ratios
IUPAC	International Union of Pure and Applied Chemistry
IVF	In Vitro Fertilization
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JEM	Job-Exposure-Matrices
kBq	Kilobecquerel
kg	Kilogram
K_H	Henry’s Coefficient
kHz	Kilohertz
KIM-1	Kidney Injury Molecule-1
km	Kilometre
$KMnO_4$	Potassium Permanganate
K_{oc}	Organic Carbon Partition Coefficient
K_{ow}	Octanol-water Partition Coefficient
kPa	Kilopascal
l	Litre
LC-MS	Liquid Chromatography with Mass Spectrometry
L_{DEN}	Day Evening Night Sound Level
LOAEL	Lowest Observed Adverse Effect Level
LOX-1	Low-Density Lipoprotein Receptor-1
M	Months
m^3	Cubic Metre
MA	Mandelic-acid
MA	Methylarsenic Acid
MAK	Maximum Workplace Concentration

MAK Commission	German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area
MAA	2-Methoxy Acetic Acid
MBAA	Monobromoacetic Acid
MCA acid	Monochloroacetic acid
MCAA	Monochloroacetic Acid
MDA	Malathion Dicarboxylic Acid
MDA	Malondialdehyde
MDMA	3,4-Methylenedioxy-N-Methylamphetamine
MeHg	Methyl Mercury
mg	Milligram
Mg	Magnesium
MHA	Methylhippuric Acid
ml	Millilitre
MM	Multiple Myeloma
mmHg	Milimetres of Mercury
Mn	Manganese
Mn_3O_4	Manganese Tetraoxide
MnO_2	Manganese Dioxide
MRI	Magnetic Resonance Imaging
MRL	Minimal Risk Level
mRNA	Messenger Ribonucleic Acid
MRSA	Methicillin-resistant *Staphylococcus aureus*
MS	Mainstream Smoke
MVOS	Microbial Volatile Organic Compounds
MX	Mutagen X
m-	*Meta-*
N_2O	Nitrous Oxide
N_2O_3	Dinitrogen Trioxide
N_2O_4	Dinitrogen Tetroxide
N_2O_5	Dinitrogen Pentoxide
NAG	N-acetyl-beta-D-glucosaminidase
NAS	National Academy of Sciences
NC	Not Calculated
NCBI	National Center for Biotechnology Information
NDELA	*N*-nitrosodiethanolamine
ng	Nanogram
NHANES	National Health and Nutrition Examination Survey
NHL	Non-Hodgkin Lymphoma
NIH	National Institutes of Health

NIOSH	National Institute for Occupational Safety and Health
nm	Nanometre
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	*N′*-nitrosonornicotine
no.	Number
NO	Nitric Oxide
NO_2	Nitric Dioxide
NO_3	Nitrate
NOAEL	No Observed Adverse Effect Level
NOC	*N*-nitroso Compound
NO_x	Nitrogen oxides
NP	Nanoparticle
NRT	Nicotine Replacement Therapy
NTP	National Toxicology Program
O_3	Ozone
o-	*Ortho-*
ÖAK	Austrian Medical Association
OC	Organochlorine
OCP	Organochlorine Pesticide
ODC	Ornithine Decarboxylase
OEL	Occupational Exposure Limits
OP	Organophosphate
OPP	Organophosphate Pesticide
OSH	Occupational Safety and Health
OSHA	Occupational Safety and Health Administration
Ox-LDL	Oxidized Low-Density Lipoprotein
P	Phosphorus
p.	Page
P95	95th percentile
PAD	Peripheral Artery Disease
PAH	Polycyclic Aromatic Hydrocarbon
Pb	Lead
PBDE	Polybromdiphenyl Ether
PBPK	Physiologically based Pharmacokinetic
PC	Polycarbonate
PCB	Polychlorobiphenyl
PCDD	Polychlorinated Dibenzo-p-Dioxins (Dioxins)
PCDF	Polychlorinated Dibenzofurans (Furans)
PCOS	Polycystic Ovary Syndrome
PCP	Pentachlorphenol

PCP	Phencyclidine
PCP	Personal Care Products
Pd	Palladium
PD	Parkinson Disease
PER	Perchlorethylene
PFBS	Perfluorobutanesulfonic Acid
PFC	Perfluorinated Compounds
PFOA	Perfluorooctanoic Acid
PFO	Perfluorooctanoate
PFOS	Perfluorooctanesulfonic Acid
pg	Picogram
PGA	Phenylglyoxylic Acid
PHBA	Parahydroxybenzoic Acid
PHHA	P-hydroxyhippuric Acid
PID	Photoionization Detection
pK_a	Dissociation Constant
PM	Particulate Matter
PNP	Para-Nitrophenol
Po	Polonium
POP	Persistent Organic Pollutant
PPARa	Peroxisome Proliferator-Activated Receptor Alpha
ppb	Parts per Billion
PPE	Personal Protective Equipment
ppm	Parts per Million
PSS	Perceived Stress Scale
Pt	Platinum
PTMI	Provisional Tolerable Monthly Intake
PTWI	Provisional Tolerable Weekly Intake
PVC	Polyvinyl Chloride
PYR	Pyrethroid
p-	*Para-*
RBP	Retinol-Binding Protein
RDA	Recommended Dietary Allowance
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RF	Radiofrequency
RfC	Reference Concentration
RfD	Reference Dose
Rn	Radon
RNA	Ribonucleic Acid

ROS	Reactive Oxygen Species
RV	Refrence Value
RV_{95}	Refrence Value of the German Human Biomonitoring Commission (95th percentile; see also P95)
SA	Substance Abuse
SCDS	Seychelles Child Development Study
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SCF	Scientific Committee on Food
SCID	Structural Clinical Interview
SCN	Thiocyanate
SCOEL	Scientific Committee on Occupational Exposure Limits
Se	Selenium
Se^{0}	Elemental Selenium
Se^{2+}	Selenide
Se^{4+}	Selenite
Se^{6+}	Selenate
SES	Socioeconomic Status
SHS	Second-hand Smoke
SIDS	Sudden Infant Death Syndrome
SMF	Static Magnetic Fields
S-PMA	S-phenylmercapturic Acid
Sr	Strontium
SRNT	Society for Research on Nicotine and Tobacco
SS	Sidestream Smoke
STA	State-trait Anxiety Inventory
STEL	Short-term Exposure Limit
STP	Sewage Treatment Plants
SVOC	Semi Volatile Organic Compound
TBARS	Thiobarbituric Acid Reactive Substances
TCA acid	Trichloroacetic Acid
TCAA	Trichloroacetic Acid
TCDD	Tetrachlorodibenzo-p-Dioxin
TCEQ ReV	Texas Commission of Environmental Quality, Reference Value
TCPY	3,5,6-Trichloropyridinol
TDI	Tolerable Daily Intake
TEACH	Toxicity and Exposure Assessment for Children’s Health
TEF	Toxic Equivalency Factor
TEQ	Toxic Equivalency
TETRA	Tetramethylarsonium Ion
THM	Trihalomethane

THS	Third-hand Smoking
Tl	Thallium
TMAO	Trimethylarsine Oxide
TNF α	Tumor necrosis factor-alpha
TNT	Trinitrotoluene
TSNA	Tobaco-specific Nitrosamine
ttMA	Trans-, Trans-muconic Acid
TV	Television
TWA	Time Weighted Average
TWI	Tolerable Weekly Intake
U	Uranium
UBA	German Federal Environment Agency (Umweltbundesamt)
UN	United Nations
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation
US	United States
US EPA	United States Environment Protection Agency
US FDA	United States Food and Drug Administration
US OSHA	United States Department of Labor, Occupational Safety & Health Administration
USA	United States of America
UFP	Ultrafine Particle
UK	United Kingdom
UL	Tolerable Upper Intake Level
UV	Ultraviolet
V	Vanadium
VOC	Volatile Organic Compound
VVOC	Very Volatile Organic Compound
VWF	Vibration-induced White Finger
WD	Wilson Disease
Wi-Fi	Wireless Fidelity
WHO	World Health Organization
WLAN	Wireless Local Area Network
WWTP	Wastewater Treatment Plants
y	Years
Zn	Zinc
γ-HCH	Lindane

Glossary

ADI: Acceptable Daily Intake

The ADI is the “estimated maximum amount of an agent, expressed on a body mass basis, to which individuals in a (sub)population may be exposed daily over their lifetimes without appreciable health risk”. Related term: Tolerable Daily Intake (TDI) (WHO-IPCS 2004, p. 10)

AGÖF Guidance Values (AGÖF [Arbeitsgemeinschaft ökologischer Forschungsinstitute e.V.] Orientierungswerte)

The AGÖF Guidance Values are used “to assist in the assessment of indoor air measurements”. The “statistically derived attention values were determined for indoor air”. “It is this guidance value that indicates the threshold, above which the indoor air concentration of a compound must be considered a problem based on statistical significance or toxicological knowledge.” (AGÖF 2013, p.1f)

BAR: Biologischer Arbeitsplatz Referenzwert (biological reference value for workplace substances)

BAR “describe the background level of a substance which is present concurrently at a particular time in a reference population of persons of working age who are not occupationally exposed to this substance. The BAR are based on the 95th percentile without regarding effects on health. It must be taken into account that the reference level of the background exposure can be influenced by such factors as age, sex, social status, residential environment, life style and geographical region. The reference level for a substance or its metabolite in biological material is derived with the help of the measured level in a random sample from a defined population group. Occupational exposure can be assessed by comparing biomonitoring values in occupationally exposed persons with the BAR” (DFG 2014, p. 249).

“These BAR values are similar to the reference values of the German HBM Commission. They are statistical descriptions of the background exposure to a chemical substance in a reference population of persons who are not occupationally exposed to the substances. They are based on the 95th percentile. The difference between a BAR value and a reference value [RV95] is that a BAR value is derived from persons of working age with the aim to assess occupational exposure, whereas reference values [RV95] are derived from groups of the general population with the aim to assess environmental exposures” (Angerer et al. 2011, p. 350)”.

BAT: Biologische Arbeitsstoff-Toleranzwerte (biological tolerance value)

The BAT is a health-related value (Drexler and Göen 2012) and evaluates “the risk to an individual’s health which results from exposure to a substance at the workplace” (DFG 2014). “The BAT value describes the occupational-medical and toxicological derived concentration for a substance, its metabolites or an effect parameter in the corresponding biological material at which the health of an employee generally is not adversely affected even when

the person is repeatedly exposed during long periods. BAT values are based on a relationship between external and systemic exposure or between the systemic exposure and the resulting effect of the substance. The derivation of the BAT value is based on the average of systemic exposures” (DFG 2014).

BE: Biomonitoring Equivalent

“Biomonitoring Equivalents (BEs) are defined as the concentration or range of concentrations of a chemical or its metabolite in a biological medium (blood, urine, or other medium) that is consistent with an existing health-based exposure guideline such as a reference dose (RfD) or tolerable daily intake (TDI)” (Hays et al. 2012).

BEI: Biological Exposure Indices

The biological exposure indices (BEI) are reference values developed and recommended by the ACGIH (American Conference of Industrial Hygienists). “The BEI are reference values intended as guidelines for the evaluation of potential health hazards in the practice of industrial hygiene”. The value is used to prevent injurious exposures (Morgan 1997). “The BEI are intended for use in biological monitoring where the goal is the determination of the worker's internal, or biologically effective, dose of a chemical. The determinant may be the parent compound itself, metabolite(s), or a characteristic reversible biochemical change induced upon absorption. The index values represent the level of the determinant most likely to be observed in specimens collected from a worker with an internal dose equivalent to that arising solely from inhalation exposure at the TLV concentration. Thus, most of the BEI are closely linked to the corresponding TLV and are based on preventing the same health effect addressed by the TLV. This does not imply, however, that airborne concentrations and biological levels must always be correlated in exposed workers, since routes of absorption in addition to inhalation are possible” (Morgan 1997, p. 106).

BGV: Biological Guidance Values

“Where toxicological data cannot support a health-based BLV, a biological guidance value (BGV) might be established. This value represents the upper concentration of the substance or a metabolite of the substance in any appropriate biological medium corresponding to a certain percentile (generally 90 or 95 percentile) in a defined reference population. If background levels cannot be detected, the BGV may be equivalent to the detection limit of the biomonitoring method, which then is to be specified in the document. A value exceeding the BGV might help to identify the need for an expert consideration of the working conditions. Unlike BLVs, BGVs are not health-based and therefore do not set a limit between absence or presence of adverse health effects” (EC 2013, p. 36).

BGW: Biologische Grenzwerte (biological limit values)

BGW are legal limit values determined in the German Ordinance on Hazardous Substances (Gefahrstoffverordnung; GefStoffV). They are determined by the Committee on Hazardous Substances (Ausschuss für Gefahrstoffe, AGS) of the Federal Institute for Occupational Safety and Health (Bundesanstalt für Arbeitsschutz und Arbeitsmedizin, BAuA). BGW are mainly based on BAT values (Drexler and Göen 2012).

BLV: Biological Limit Values

“Biological Limit Values (BLVs) are reference values for the evaluation of potential health risks in the practice of occupational health. They are established on the basis of currently available scientific data. Exposure concentrations equivalent to the BLV generally do not affect the health of the employee adversely, when they are attained regularly under workplace conditions (8 hours/day, 5 days/week), except in cases of hypersensitivity” (EC 2013, p. 31).

BLW: Biologischer Leitwert

The BLW evaluates “the risk to an individual’s health which results from exposure to a substance at the workplace” (DFG 2014). BLW “is the amount of a chemical substance or its metabolites or the deviation from the norm of biological parameters induced by the substance in exposed humans which serves as an indicator for necessary protective measures. BLWs are assigned only for hazardous materials for which the available toxicological or occupational-medical data are insufficient for the establishment of BAT values (i. e. for carcinogenic substances and suspected carcinogens in the categories 1 to 3 and for non-carcinogens for which the toxicological data are inadequate). BLW values are generally established on the assumption that persons are exposed at work for at most 8 hours daily and 40 hours weekly during their working lives. The BLW is based on occupational-medical information as to the effects of handling the hazardous material together with toxicological data. Since observance of the BLW does not exclude a risk of adverse effects on health, it is necessary to extend our knowledge of the relationships between exposure to the substance, the systemic dose and the resulting risks for health so that BAT values may be derived. The BLW values are intended to advance this aim by providing a basis for biomonitoring of exposed persons by the physician. By continual improvement of the industrial situation, occupational hygiene and the protective aspects of work planning, concentrations as far as possible below the BLW should be attained” (DFG 2014).

EKA: Expositionsäquivalente für krebserzeugende Arbeitsstoffe (Exposure equivalent for carcinogenic substances)

EKA describes “the relationships between the concentration of the carcinogen in the workplace air and that of the substance or its metabolites in biological material”. This is done for the “occupational medical detection and quantification of the individual exposure to the substances. Concentrations of a substance or its metabolites in biological material which are higher than those known to correspond to the concentration of the substance in the workplace air are indicative of additional exposure by other routes, usually percutaneous” (DFG 2014, p. 240f).

HBM I and HBM II: Human Biomonitoring Values

“The HBM I value corresponds to the concentration of a substance in human biological material below which adverse health effects are not expected, and HBM II value corresponds to the concentration of a substance in human biological material above which there is an

increased risk for adverse health effects in susceptible individuals of the general population” (UBA 2014).

Human carcinogens determined by IARC

The International Agency for Research on Cancer (IARC) evaluates the carcinogenity of agents, mixtures or exposure circumstances on the basis of evidence from experimental and human studies (IARC 1999). The categorization is defined as follows:

“Group 1 — The agent (mixture) is carcinogenic to humans. The exposure circumstance entails exposures that are carcinogenic to humans. This category is used when there is sufficient evidence of carcinogenicity in humans. Exceptionally, an agent (mixture) may be placed in this category when evidence of carcinogenicity in humans is less than sufficient but there is sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent (mixture) acts through a relevant mechanism of carcinogenicity” (IARC 1999).

“Group 2 — This category includes agents, mixtures and exposure circumstances for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost sufficient, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents, mixtures and exposure circumstances are assigned to either group 2A (probably carcinogenic to humans) or group 2B (possibly carcinogenic to humans) on the basis of epidemiological and experimental evidence of carcinogenicity and other relevant data” (IARC 1999).

“Group 2A — The agent (mixture) is probably carcinogenic to humans. The exposure circumstance entails exposures that are probably carcinogenic to humans. This category is used when there is limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals. In some cases, an agent (mixture) may be classified in this category when there is inadequate evidence of carcinogenicity in humans, sufficient evidence of carcinogenicity in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent, mixture or exposure circumstance may be classified in this category solely on the basis of limited evidence of carcinogenicity in humans” (IARC 1999).

“Group 2B — The agent (mixture) is possibly carcinogenic to humans. The exposure circumstance entails exposures that are possibly carcinogenic to humans. This category is used for agents, mixtures and exposure circumstances for which there is limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals. It may also be used when there is inadequate evidence of carcinogenicity in humans but there is sufficient evidence of carcinogenicity in experimental animals. In some instances, an agent, mixture or exposure circumstance for which there is inadequate evidence of carcinogenicity in humans but limited evidence of carcinogenicity in experimental animals together with supporting evidence from other relevant data may be placed in this group” (IARC 1999).

“Group 3 — The agent (mixture or exposure circumstance) is not classifiable as to its carcinogenicity to humans. This category is used most commonly for agents, mixtures and exposure circumstances for which the evidence of carcinogenicity is inadequate in humans and inadequate or limited in experimental animals. Exceptionally, agents (mixtures) for which the evidence of carcinogenicity is inadequate in humans but sufficient in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans. Agents, mixtures and exposure circumstances that do not fall into any other group are also placed in this category” (IARC 1999).

“Group 4 — The agent (mixture) is probably not carcinogenic to humans. This category is used for agents or mixtures for which there is evidence suggesting lack of carcinogenicity in humans and in experimental animals. In some instances, agents or mixtures for which there is inadequate evidence of carcinogenicity in humans but evidence suggesting lack of carcinogenicity in experimental animals,

consistently and strongly supported by a broad range of other relevant data, may be classified in this group” (IARC 1999).

LOAEL: Lowest-observed-adverse-effect-level

“The lowest exposure level at which there are biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group” (US EPA 2014).

MAK: Maximum Workplace Concentration (maximale Arbeitsplatz-Konzentration)

“The MAK value (“maximale Arbeitsplatz-Konzentration”: maximum workplace concentration) is defined as the maximum concentration of a chemical substance (as gas, vapour or particulate matter) in the workplace air which generally does not have known adverse effects on the health of the employee nor cause unreasonable annoyance (e. g. by a nauseous odour) even when the person is repeatedly exposed during long periods, usually for 8 hours daily but assuming on average a 40-hour working week.” (DFG 2014)

NOAEL: No-observed-adverse-effect-level

“The highest exposure level at which there are no biologically significant increases in the frequency or severity of adverse effect between the exposed population and its appropriate control; some effects may be produced at this level, but they are not considered adverse or precursors of adverse effects” (US EPA 2014).

REL: Recommended Exposure Limit

REL are “time-weighted average (TWA) concentrations for up to a 10-hour workday during a 40-hour workweek” determined by the National Institute for Occupational Safety and Health (NIOSH) (ATSDR 2000).

RfC: Reference Concentration

Reference Concentration (RfC) is “an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m3 or ppm.” (ATSDR 2000).

RfD: Oral Reference Dose

“The RfD is an estimate […] of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime.” “It is expressed in units of milligrams per kilograms per day (mg/kg/day)” (US EPA 2002, p. 1).

RV_{95}: Reference Value

“Reference values are statistically derived values that indicate the upper margin of background exposure to a given pollutant in a given population at a given time. They may be used to assess the exposure of individuals or population groups in relation to the ubiquitous background exposure. Since environmental conditions are changing, reference values are continuously checked and updated if new information becomes available” (Schulz et al. 2007). The reference value of the German HBM Commission is based on the 95% confidence interval of the 95th population percentile of the concentration level of the respective parameter in the matrix obtained from the reference population. The reference value is derived by rounding off the 95th population percentile within the 95% confidence interval. Since the term “reference value” may be used more generally for different purposes, in 2011 the Commission introduced the abbreviation RV_{95} to avoid ambiguity (Schulz et al. 2011).

TDI: Tolerable Daily Intake

“Analogous to Acceptable daily intake. The term “tolerable” is used for agents that are not deliberately added, such as contaminants in food” (WHO-IPCS 2004). The calculation of the tolerable daily intake (TDI) is presented in Formula 1.

$$\text{TDI} = \frac{\text{NOAEL or LOAEL or BMDL}}{\text{UF and/or CSAF}}$$

where

NOAEL: no-observed-adverse-effect-level
LAOEL: lowest-observed-adverse-effect-level
BMDL: lower confidence limit on the benchmark dose
UF: uncertainty factor
CSAF: chemical-specific adjustment factor

Formula 1: Tolerable Daily Intake (WHO 2011)

TLV: Threshold Limit Values

The threshold limit values (TLV) are reference values for inhalation exposure developed and recommended by the ACGHI. They defined as follows: Threshold Limit Values (TLV) “represent conditions under which nearly all workers may be exposed repeatedly over a working lifetime without adverse health effects” (Morgan 1997).

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