European Agency for Safety and Health at Work

ISSN: 1831-9343

State of the art report on reproductive toxicants

Literature Review

European Risk Observatory Summary

Authors:

This report was compiled by the following researchers:

Klaus Kuhl, Kooperationsstelle Hamburg IFE, Germany

The main report was compiled by researchers from three institutes:

- Dr Ellen Schmitz-Felten and Klaus Kuhl (task leader), Kooperationsstelle Hamburg IFE, Germany;
- Dr Karin Sørig Hougaard, Det Nationale Forskningscenter for Arbejdsmiljø, Denmark;
- Dr Katarzyna Miranowicz-Dzierżawska, Centralny Instytut Ochrony Pracy: Państwowy Instytut Badawczy, Poland

The report was cross-checked by:

- Professor Dr György Ungváry, National Labour Office, Hungary;
- Dr Ferenc Kudász, National Labour Office, Hungary

Project management: Dr. Elke Schneider - European Agency for Health and Safety at Work (EU-OSHA)

This report was commissioned by the European Agency for Safety and Health at Work (EU-OSHA). Its contents, including any opinions and/or conclusions expressed, are those of the authors alone and do not necessarily reflect the views of EU-OSHA.

Cataloguing data can be found on the cover of this publication.

Luxembourg: Publications Office of the European Union, 2016

ISBN: 978-92-9496-224-9

doi:10.2802/87916

Table of contents

List of tables

1 Introduction

This document forms the summary of a comprehensive report that was commissioned by the European Agency for Safety and Health at Work (EU-OSHA) on reproductive and developmental health effects and workplace exposure in order to establish an evidence base for future activities in this area, including recommendations for policy, research, monitoring and practice. The identification of gaps in the knowledge should help to focus future research and develop improved prevention methods, while making the results more accessible for small and medium-sized enterprises (SMEs). Awareness, knowledge and understanding of reprotoxic risk is rather low, especially at a the company level.

The main target group of the report are occupational safety and health (OSH) researchers and policy makers, whereas the sections on prevention measures will be of special interest to company OSH practitioners.

The preliminary results were discussed at a workshop in Paris organised by EU-OSHA with the French Agency for Food, Environmental and Occupational Health and Safety (ANSES) to stimulate debate on workplace risks to reproductivity, and support a constructive dialogue between stakeholders on approaches to prevention. Approximately 60 participants from different EU Member States attended. The presentations and discussions are available on the EU-OSHA website and were incorporated into the main report (EU-OSHA, 2014).

The reproductive potential of the workforce can be affected by hazardous chemicals, pesticides and pharmaceuticals, as well as biological, physical and psychosocial factors. These risk factors may prevent workers from having children at all, or they may affect the offspring of workers, thus endangering the future of our society. Therefore, the problem of workplace risks to reproductivity deserves more attention than it currently receives.

Data on workers' exposure to risks are poor and incomplete. In France, data from the 2003 SUMER survey indicate that 180,000 of the country's 29.5 million workers were exposed to three reprotoxicants included in the survey: lead (and derivatives), dimethylformamide and cadmium (and derivatives) (Guignon and Sandret, 2005). According to a 2005 trade union survey of four sectors (chemicals, non-metal mineral products, metal work and food and drink) carried out in Madrid, workers were exposed to up to 31 products that are toxic to embryo development, 23 products that are toxic for reproduction and 40 potential endocrine disruptors (Rubio *et al*., 2005; Vogel, 2009).

A significant part of the workforce is, therefore, exposed to reprotoxicants and, in particular, to suspected endocrine disrupters. Reproductive effects deserve special attention from all stakeholders so that the overall well-being of everyone involved in occupational activities is maintained, not only for the current but also for future generations.

2 General overview

2.1 Scope of the report

Many workplace hazards affect reproduction, including organic and inorganic chemicals (e.g. solvents, pesticides, heavy metals and pharmaceuticals), as well as biological, physical, ergonomic and psychosocial factors. The main report investigates these factors and their effects from the OSH perspective, based largely on review papers.

The report does not only look at chemicals, although these are often the first that come to mind when thinking of reproductive hazards in the workplace. Workplace exposure to biological, physical, ergonomic and psychosocial factors is also taken into account. Some emerging risks, such as those caused by engineered nanomaterials and endocrine-disrupting compounds (EDCs), are also considered, as are combined effects. An overview table including examples of the different groups of substances, factors, conditions and related effects and endpoints is given in the main report.

The identification of all possible risk factors associated with reproductive and developmental health in the work environment was, however, beyond the scope of the report. Instead, examples of characteristic types of chemicals and other relevant factors are described, and typical issues that deserve attention from those involved in improving the work environment are presented.

For the past 20 years, there has been an increase in sickness absence among pregnant working women in many countries. Pregnancy complications and developmental problems are on the increase. A growing number of would-be parents are unable to conceive and seek treatment for infertility. For example, in Denmark it is estimated that 10-15 % of couples who wish to have a child do not conceive within one year. While the tendency for couples to wait until they are older before starting a family is a factor, some of these issues can be attributed to workplace hazards.

In OSH legislation, particular attention has been given to pregnancy and the effects on the unborn child. Although the focus of workplace prevention has largely been on women, especially expectant mothers, there are increasing concerns and research efforts relating to male fertility. Since 1993, there has been evidence of increases in certain malformations of male genitalia and testicular cancer. In a study among young Finnish men, Jørgensen and colleagues, for example, detected low and decreasing sperm counts in young Finns. In addition, younger Finns born around 1980 had 8-10 times higher incidences of testicular cancer than men born around 1950 (Jørgensen *et al*., 2011). One of the most likely explanations is that hormone-like substances, some of which occur in the work environment, have an impact on reproductive health before and after birth (Storgaard and Bonde, 2003).

There are also other more recently discovered factors affecting women, such as the altered entry into the menopausal transition, identified by Lawson and colleagues as an emerging issue (Lawson *et al*., 2006).

In addition to classic gene mutations leading to malformations, some recently described mechanisms for inheritance do not require changes in DNA, but may alter the expression of DNA and lead to inheritable changes that may be transmitted to the next generations. The term ‘epigenetics’ refers to such heritable changes in gene expression. Thus, transgenerational epigenetic inheritance has emerged as a new area of research for reproductive toxicity in the workplace. The focus is currently primarily on EDCs as the environmental agents causing transgenerationally inherited modifications (Rissman and Adli, 2014).

The report therefore includes a chapter on endocrine disruptors.

2.2 Definitions

Reproduction is a multistage process, involving the production of germ cells (gametogenesis), fertilisation, the implantation of the fertilised egg (zygote), embryonic and foetal development, childbirth and postnatal development until puberty. This process can be disrupted by a variety of endogenous (internal) and exogenous (external) factors. A number of agents and factors can affect the normal processes of reproduction and development in many ways, including:

- direct injury to the male and female reproductive cells, causing infertility or reduced fertility;
- induction of metabolic disorders in the mother’s body, causing changes in internal homeostasis and impaired maturation of the embryo;
- abnormal embryogenesis [1] and organogenesis [2] periods;
- a direct toxic effect on the foetus [3];
- factors affecting parturition (labour and delivery);
- factors affecting the early stages of a baby’s postnatal development;
- factors affects the later postnatal development of any offspring;
- transgenerational factors.

Technical terms are explained in the Glossary in Annex 9.1 of the main report.

[1] Human embryogenesis is a complex process that occurs during the first eight weeks after fertilization. Week 1 to Week 8 are considered the embryonic period of development.
[2] Organogenesis is the formation of organs and organ systems; by the end of the embryonic period, all organ systems are recognizable.
[3] Week 9 to week 37of a pregnancy or birth are considered the foetal period of development. The developing child is known as a foetus.

These factors can lead to the injury or death of reproductive cells, the intrauterine death of the embryo or foetus, developmental abnormalities, for example abnormal ossification (bone tissue formation), impaired physical development, functional impairment of systems and organs, or enzymatic deficiencies (Table 1).

Table 1: Processes and effects/endpoints

Processes affected	Effects/endpoints	Examples
Production of germ cells (gametogenesis) Libido	Direct injury to the male and female reproductive cells, causing infertility or reduced fertility Premature reproductive senescence (biological ageing)	• Menstrual dysfunction: irregular periods and stopping of menstrual cycles • Delayed conception • Erectile dysfunction and ejaculation difficulty • Reduced semen quality, low motile sperm count
Fertilisation, implantation of the fertilised egg Embryonic and foetal development	Induction of metabolic disorders in the mother's body, causing changes in internal homeostasis and impaired maturation of the embryo A direct toxic effect on the foetus Abnormal embryogenesis and organogenesis period	• Spontaneous abortions • Miscarriage in partners of exposed men or related birth defects • Masculinisation of female foetuses and feminisation of male foetuses • Congenital cryptorchidism (absence of one or both testes from the scrotum at birth) • Low birth weight
Childbirth and lactation	Initiation of preterm uterine contractions through elevated cortisol levels due to physical or psychological stressors Toxic effects from substances, including those mobilised from fatty tissues	• Preterm delivery • Exposure through breast milk
Postnatal development Development until puberty	Effects on the later postnatal development of the offspring	• Increased risk of childhood cancers • Increased propensity to develop allergies • Heart malformations, cardiovascular diseases • Testicular cancer • Diabetes, obesity • Neurodevelopmental effects
Transgenerational effects	Genetically based heritable effects	

Source: compiled by report authors and project manager.

The most detailed definitions of these effects are set out for chemical agents (see also section 4.2.).

During the setting of occupational exposure limits (OEL), setting the relevant committee at European level (Scientific Committee on Occupational Exposure Limits (SCOEL) uses the following definitions:

– Fertility includes the processes underlying male and female ability to initiate pregnancy. When evaluating effects on fertility, SCOEL includes

  'adverse effects on libido, sexual behaviour, spermatogenesis/oogenesis, any interference with hormonal activity or physiological parameters that affects the ability to fertilise, as well as adverse effects on fertilisation itself and the development of the fertilised ovum up to and including implantation'.

  (SCOEL, 2013, p. 24)

– Developmental toxicity covers in its widest sense any effect interfering with pregnancy and normal development, before as well as after birth. It includes embryotoxic/foetotoxic effects (such as reduced body weight, growth and developmental retardation, organ toxicity, death, abortion), structural defects (teratogenic effects), functional defects, peri- and postnatal defects and impaired postnatal mental or physical development up to and including normal pubertal development.

  (SCOEL, 2013, p.24)

Very similar definitions to those adopted by (SCOEL) are used in the Globally Harmonised System of Classification and Labelling as applied in the recent EU regulation on classification, labelling and packaging of substances and mixtures (CLP) (European Chemicals Agency, 2013). This addresses, for example, premature reproductive senescence, which is not specifically mentioned in the SCOEL definitions, but is probably included in the phrasing 'any interference with hormonal activity or physiological parameters that affects the ability to fertilise' (SCOEL, 2013).

Teratogenic effects (which cause human birth defects) constitute a health hazard for which a separate classification is no longer provided in the recent EU classification legislation (CLP Regulation 2008). Instead, they are seen as developmental toxicants, with developmental toxicity falling within the hazard class of reproductive toxicity. Teratogens are classified for reproductive toxicity in general and for developmental toxicity in particular.

Lactation has its own paragraph. Although adverse effects on or via lactation are included under reproductive toxicity, it is treated separately for classification purposes. By this means, a specific hazard warning about this effect can be provided for lactating mothers.

The known induction of genetically based heritable effects in offspring is addressed in the hazard class of germ cell mutagenicity. This hazard class primarily concerns substances that may cause mutations in the egg or sperm cells (germ cells) of women and men, respectively that can be transmitted to any progeny.

3 Legal situation

3.1 Basics

The EU regulatory framework covers, in principle, all types of workplace risks to reproductivity: physical, chemical, biological or organisational, either through general or specific provisions (e.g. directives for pregnant or breastfeeding women or young workers). Even directives not directly related to OSH, such as the directive on working time, may contribute to preventing risks to reproductive functions.

There are also EU policies and legislation that are not specifically occupational but that may have an effect on workers' exposure to toxicants, such as chemicals legislation (e.g. REACH) or environmental protection.

The European Framework Directive on Safety and Health at Work (Directive 89/391 EEC) sets out the employer's obligation to ensure the safety and health of workers in every aspect related to work and to conduct risk assessments and establish preventive measures (European Council, 1989) following a specific hierarchy:

1. elimination (including substitution): the removal of hazards from the workplace or the substantial reduction of them;
2. engineering controls: improved designs or modifications to plants, equipment, ventilation systems and processes that reduce exposure;
3. administrative controls: controls that alter the way work is done, including the timing of work, policies and other rules, and work practices such as standards and operating procedures (including training, housekeeping, equipment maintenance and personal hygiene practices);
4. personal protective equipment (PPE): equipment worn by individuals to reduce exposure, such as contact with chemicals or exposure to noise.

In situations in which there is not a clear way to control a hazard, or if legislation is not specific, companies should seek guidance from occupational health professionals, such as occupational hygienists or safety professionals. In any case, the Framework Directive and its key requirements still apply, that is, risk assessment, control measures applied in a specific hierarchy, provision of preventive services, information and training of workers, consultation of workers or their representatives, and health surveillance.

3.2 Specific legislation is scarce

Although the Framework Directive is very strict on the safety and health of workers, it does not specifically mention adverse reproductive and developmental factors. However, European legislators have seen the need for more specific directives to complement the general provisions including those that cover:

- chemical and biological agents;
- physical factors;
- psychosocial issues;
- vulnerable groups.

The main report presents chemicals legislation with an OSH focus (including the OEL setting), legislation with OSH relevance, such as REACH (including a comparison between OELs and derived no effect levels (DNELs)), and the harmonised classification (CLP). The report also discusses legislation on solvents, biocides, pesticides and regulations regarding EDCs.

However, there are hardly any specific regulations applying to workplace risks to reproductive function, the reproductive system and causing developmental effects. Below we summarise those pieces of legislation that have specific provisions and discuss the issues they do cover and the gaps identified in them.

3.3 Vulnerable workers

An important part of the specific legislation concerns vulnerable workers. The International Labour Organization (ILO) conventions and the directives on young workers, pregnant workers, workers who have recently given birth and women who are breastfeeding are described in the report.

3.4 Directive on pregnant workers, workers who have recently given birth and women who are breastfeeding

The EU directive on the protection of pregnant workers and workers who have recently given birth or who are breastfeeding (Council Directive 92/85/EEC) recognises a broad range of conditions that could present a risk for new and expectant mothers. It provides guidelines for assessing not only risks related to chemical agents but also physical and biological agents and ergonomic, physical and psychosocial factors. It contains specific provisions governing night work, maternity leave, antenatal examinations, employment rights and protection against discriminatory dismissal.

The workers in focus under no circumstances may be obliged to perform duties for which the assessment has revealed a risk of exposure to factors that would jeopardise their safety or health, or the safety or health of their offspring. Those agents, factors and working conditions are defined in Annex II of the directive. For example, Member States shall ensure that pregnant workers are not obliged to work night shifts when medically indicated (subject to submission of a medical certificate).

The directive should serve as a basis for a risk assessment of all activities that pregnant or breastfeeding workers may undertake, and related measures should be established to avoid these risks. Workers should be notified of the risk-assessment results and of the measures to be taken (e.g. adjustment of working conditions, transfer to another job or granting leave).

The European Community has published a guideline to support the implementation of the directive (European Commission, 2000). It has been suggested that the directive and the related guidance may need to be updated to reflect changes in workplace exposures and working practices. By way of example, risks from welding include only those related to non-ionising electromagnetic radiation and not to welding particles.

4 Reprotoxic chemicals

Reproductive and developmental risks can be recognised as such only if they have undergone appropriate investigation. For chemicals, there is at present a large discrepancy between the number of chemicals in use and the number of chemicals that have been evaluated for reproductive toxicity (Lawson *et al*., 2003). This might also explain the fact that up-to-date lists of reproductive toxicants, which are legally binding within the European Union, include only approximately 150 chemicals (including pesticides) classified as reproductive toxicants (category 1A: substances known to cause reproductive effects in humans; and category 1B: presumed human reproductive toxicants) from thousands of chemicals on the lists of classified substances [4] (Milieu and RPA, 2013). A list of reprotoxic substances and developmental toxicants is included in the main report. It covers a large variety of substances present in many industrial products, such as paints, adhesives or cleaning products, but also in products used in service sectors such as health care or hairdressing, where awareness of the associated risks may be low.

In the following sections, we explain how the reprotoxic properties and developmental effects of chemicals are assessed, and how this assessment is framed in specific legislation such as the chemicals regulations. To illustrate these properties, we present a selected number of examples where substances have been assessed for these effects and the evidence that is available. At the end of this chapter, conclusions are drawn on the state of knowledge and the gaps identified.

In the full report, more chemicals are discussed, but in this summary, some exemplary findings are presented that illustrate the wide range of chemical factors that may cause reproductive disorders and developmental health problems.

4.1 Registration, Evaluation, Authorisation and restriction of Chemicals (REACH)

The REACH regulation provides a framework for information on hazardous chemicals to be passed up and down supply chains. Under REACH, producers and those who market chemicals above a certain minimum amount need to register substances. The legislation takes a phased approach: the higher the

[4] Annex VI to Regulation 1272/2008 (CLP regulation) includes lists of harmonised classification and labelling for reprotoxic substances and certain other substances or groups of substances which are legally binding within the EU. The harmonised classification and labelling of hazardous substances is updated every year through an "Adaptation to Technical Progress (ATP)" by the European Commission. An excel table containing all updates to the harmonised classification and labelling of hazardous substance is available on the Website of the European Chemicals Agency.

amount of a chemical marketed or produced by a single registrant, the earlier the registration deadline and the stricter the requirements.

4.1.1 Testing requirements for chemicals

For chemicals marketed at quantities of 10 tonnes per year or more, standard animal tests on reproduction, covering male and female fertility and pre- and postnatal development in offspring, are required, which might include tests for developmental immunotoxicity and neurotoxicity. However, these tests can be adapted ('waived') by using a weight of evidence justification, by using tests that were performed with chemically related substances or by exposure-based adaptations.

Testing requirements are also regulated according to tonnage, i.e. the annual tonnage of each chemical produced or imported. Thus, the tonnage level supposedly reflects foreseen exposure. These tonnage rules do not require rigorous testing for reproductive toxicity until rather high levels are reached. The minimal testing requirements at each tonnage level may, however, be enhanced on a case-by-case basis if other mandatory tests give cause for concern (Piersma, 2013). More information on this can be found in a more recent publication on teratology testing under REACH (Barton, 2013) and in ECHA guidance (ECHA, 2015). Testing requirements are presented in detail in the main report, including the Organisation for Economic Co-operation and Development (OECD) test requirements and their application to the tonnage band in REACH. The main report also discusses the implications of new discoveries such as the transgenerational effect and the lack of exposure data. However, as regards reprotoxic effects of chemicals, only very few endpoints are included in the testing requirements

Substances of very high concern

Under REACH, a Member State or the European Chemicals Agency can also propose a substance to be identified as a substance of very high concern. A number of substances have been proposed to date by Member States because of reproductive endpoints. The listing of a substance as a substance of very high concern (SVHC) by the European Chemicals Agency (ECHA) is the first step in the procedure for restriction of one or all uses of a chemical. In these cases, the substances must no longer be used, except if they pass the authorisation process, meaning the risks can be adequately controlled (Article 60.2). However, authorisation can be granted for such substances only if it is shown that the socioeconomic benefits outweigh the risks, and there are no suitable alternative substances or technologies (Article 60.4) (European Commission, 2011). The first list of SVHCs was published on 28 October 2008 and the list has been updated many times (with the update on 20 June 2016 it includes a total 169 SVHCs), while there is also a list of SVHCs in articles. Once a substance has been listed, ECHA commissions a technical report, which analyses the available information on manufacture, imports, uses and releases of the substance, as well as possible alternatives. On the basis of this report, ECHA decides whether or not to prioritise the substance, in effect, whether or not to make a recommendation to the European Commission to add the substance to Annex XIV of the REACH Regulation, making its use subject to authorisation.

A lack of data and assessments of health effects leads to a lack of protection

While registration under REACH is expected to improve the knowledge of adverse effects of chemicals and the overall quality of the data set on hazardous substances; the tonnage banding approach is considered, problematic, as it results in a lack of data for chemicals produced in small quantities. In addition, regarding reprotoxic effects of chemicals, only a few endpoints of reproductive and developmental toxicity are included in the testing requirements. For many of the assumed reproductive effects, evaluation methods do not exist (effects on the male reproductive system, many effects (especially long-term effects) on the offspring, effects on immune function and metabolism, menopausal effects, earlier onset of puberty, transgenerational effects, etc.), which means that they will not be covered by the obligation for registrants to draw up exposure scenarios and any DNELs (a no-effect level under REACH), as systems are not in place to consider these effects. These limitations are not widely known, even among OSH professionals, which risks widespread underestimation of workplace risks to reproductivity.

Manufacturers and importers should therefore consider the precautionary[5] principle if data gaps have been identified or are suspected.

The candidate list for authorisation under REACH promotes efforts to reduce adverse effects of reprotoxins by limiting their use, but the process of developing the list is slow. After eight years, the list contains around 169 entries, of which only some are reprotoxic.

4.2 Occupational exposure limits for reprotoxic substances?

Occupational exposure limits (OELs) for hazardous substances provide important information for risk assessment and management. Regarding reprotoxicants, there are, however, limitations and gaps that need to be considered and addressed.

Definitions and establishment of occupational exposure limits

The EU Scientific Committee on Occupational Exposure Limits (SCOEL) has described the methodology that the committee applies when setting OELs and includes, in its considerations, effects on the offspring. The aim is

> 'to set limits for exposure via the airborne route such that exposure, even when repeated on a regular basis throughout a working life, will not lead to adverse effects on the health of exposed persons and/or their progeny at any time'
>
> (SCOEL, 2013, p. 8).

In principle, limit values should therefore be protective of an unborn child and future generations. Available published information on negative reproductive effects is considered by SCOEL for the derivation of occupational exposure limit values for chemicals in the workplace, but for many substances such data are insufficient or missing. SCOEL usually signals this lack of data in its documents.

Health-based OELs can be established in only those cases in which a review of the total available scientific data leads to the conclusion that it is possible to identify a clear threshold dose below which exposure to the substance in question is not expected to produce adverse effects (Bertazzi, 2010).

For substances for which there is no safe threshold (e.g. carcinogens) in many countries, recommended OELs are not determined, but it is recommended that, if they cannot be eliminated, they are maintained at the lowest possible concentrations. In others, such as Germany and the Netherlands, recommended exposure limits are set, based on the concept of acceptable risk, usually in the range of 10^{-2} to 10^{-5}, depending on whether the risk concerns the frequency of changes in health status during a year or over a lifetime (Czerczak, 2004). The 2014 EU-OSHA workshop in Paris identified a continuing discussion on whether or not to consider reprotoxic substances as threshold substances.

According to an EU-OSHA study on OELs for substances that are carcinogenic, mutagenic or toxic for reproduction (CMRs), there are different approaches to reproductive risks, OELs and pregnant workers' regulations. With the exception of common European OELs, each Member State establishes its own national OELs (EU-OSHA, 2009a).

Because of the complicated process for their establishment, OELs have been set for only a limited number of the substances currently used in the workplace. Many available data on humans support no estimation of dose–response or dose–effect relationships for occupational exposure to chemicals.

[5] The precautionary principle is detailed in Article 191 of the Treaty on the Functioning of the European Union (TFEU). It relates to an approach to risk management whereby if there is the possibility that a given policy or action might cause harm to the public or the environment and if there is still no scientific consensus on the issue, the policy or action in question should not be pursued. Once more scientific information becomes available, the situation should be reviewed. The EU's regulatory framework for chemicals (REACH) is based on the precautionary principle, as is its general regulation on food law ((Regulation (EC) N178/2002)). A Communication from the Commission on the precautionary principle (COM (2000) 1 final of 2 February 2000) informs interested parties how the Commission intends to apply the principle. In a wider sense, the precautionary principle (or precautionary approach) to risk management states that in case of threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically. The burden of proof that it is not harmful falls on those taking an action that may cause risk.

4.2.1 Lack of data and uncertainty factors

Occupational limit values are predicted from the contemporary state of knowledge. This makes sense, as limit values shall reflect expert evaluation based on scientific data. The available data are, however, frequently incomplete, and extrapolation of the results of animal experiments aimed at setting limits of concentrations that are safe for humans gives rise to multiple doubts (Gromiec and Czerczak, 2002). Many of the health effects described above (developmental and reproductive effects), so-called endpoints, are not included in the considerations in the standard process of setting values of chemicals because there are no testing/evaluation methods.

If toxicology studies are not requested by e.g. REACH, knowledge will not increase unless action is taken by other bodies (SCOEL, 2013). Academic institutions do carry out large well-designed prospective epidemiological studies to investigate effects at low exposure levels (e.g. financed by national research funding), but typically there is a long delay before the results feed into a re-evaluation of regulation (e.g. of occupational limit values). Updating legislation is in itself a slow process and represents a further delay between recognition of new data and implementation of worker protection. This is true even when new findings indicate adverse effects at much lower dose levels than previously anticipated. An example is the very small margin between effects levels and biological limit values for lead, which are only twice the numerical value of the approximate threshold for effect on male fertility, although many workers are still exposed to lead and its compounds. A more flexible approach to the re-evaluation of OELs is therefore needed that is able to act promptly upon new data that indicate adverse effects at lower exposure levels than previously observed.

Also, typically, the recommended exposure limit is derived from only one measurable toxic effect, which is considered the most sensitive of the observed changes, and is of relevance to the normal functioning of the body (Czerczak, 2004). Therefore, it is not certain that OELs are really set for reproductive endpoints.

The Working Party on Chemicals of the Advisory Committee for Safety and Health at Work is therefore looking at mechanisms to improve OEL setting for non-threshold substances. Repeated findings of adverse effects at exposure levels close to or below those of established OELs in well-designed studies could trigger re-evaluation or initiation of studies specifically designed to trigger this effect. This is especially important for reproductive and developmental toxicity that may not otherwise undergo testing.

Uncertainty factors and pregnancy, gametes (sperm and egg cells)

Lower uncertainty factors are generally accepted when health-based exposure limits are set for the occupational setting compared with limit values set for the environment and the population as a whole. This is based on the underlying (but sometimes questioned) assumption that the working population varies less in age and health than the general population. In addition, there is an unrealistic assumption regarding the levels of monitoring and control of exposure to chemicals in the workplace that chemical exposures are monitored and controlled at the workplace (Fairhurst, 1995). During pregnancy, however, a woman exposes her foetus to hazards in the workplace, thereby increasing the variation in age and also, perhaps, health status, in that foetuses in some instances are more sensitive than adults to chemical exposures. Toxic injury may also in some instances be reversible in adults, but a similar exposure might lead to permanent effects when it occurs during foetal development. One reason for this is that the developing foetus undergoes intense cellular division and differentiation, which is a very different environment to more static (i.e. adult) tissue (Larsen, 2001). This, to some degree, also applies to gametes (sperm and egg cells), as these are the precursors of conception. Moreover, exposures tend to be higher in the work place than in the general community. It has been suggested that sometimes workers ‘are the “canaries” or “sentinels”, first exhibiting the health effects which might be expected in a wider community exposure’ (McDiarmid and Gehle, 2006).

It may be concluded that even if a substance that is reprotoxic is subject to an OEL, this does not necessarily mean that it is protective for the reproductive effects (EU-OSHA, 2009a). More awareness of this fact should be raised among workers, and also among the general public.

4.3 Metals

Metals and metalloids are among the chemicals for which reproductive and developmental toxicity have been studied in epidemiological studies as well as in experimental animals, and several metals are classified as developmental toxicants (i.e. they present a risk to foetal development). It is beyond the scope of the report to describe the reproductive toxicity of all metals in workplace settings. Instead, lead and lead compounds are presented in more depth as illustrative examples of some relevant issues.

4.3.1 Lead as an example of a reproductive and developmental toxicant

Lead is one of the most studied and serious occupational hazards. Lead has been used in increasing amounts since World War II, in several European countries. Currently, the manufacture and recycling of batteries consumes by far the highest amount of lead, but exposure also occurs in, for example, construction and demolition, and smelting and handling of metal scrap. Lead appears in several different, including organic, forms, and exposure is mostly by inhalation of lead-containing dust. Once absorbed, lead accumulates in the body with half-lives in different tissues ranging from several days to several years. In the general population, blood lead levels are approximately 2-10 μg/dL, but blood lead levels above 60 μg/dL are not uncommon, particularly in exposed male workers. Lead transfers readily from the mother to the foetus.

In males, lead alters sperm properties and it decreases fertility at moderately high blood levels. SCOEL estimated a blood lead level threshold for effects on male fertility to be in the region of 40 μg/dL. The results from some recent epidemiological studies, however, indicate that lead affects male fertility at considerably lower blood lead levels, but epidemiological studies to clarify this finding have apparently not been initiated within the European Union.

Female fertility has been studied very little in relation to lead exposure. Lead deposits in women may be mobilised during pregnancy and expose the child during foetal development and lactation. The latter is especially worrying, as the nervous system is very sensitive to lead toxicity after birth.

The foetal nervous system is probably most at risk when blood lead levels in the mother increase as a result of occupational exposure. SCOEL concluded in 2002 that a definite threshold for effects on foetal development of the nervous system cannot be derived.

The European Commission has set a binding occupational exposure limit of 0.15 mg lead/m^3 calculated over a 40-hour working week, and a binding biological limit value of 70 μg lead/dL. It has been noted that this leaves no margin of uncertainty between the no-effect level and the (blood) occupational limit value and many European countries enforce lower biological limit values. The German MAK Commission for example distinguishes between workers in general (max. blood lead levels of 40 μg/dL) and women of childbearing age (i.e. less than 45 years of age) in particular (max. blood lead levels of 10 μg/dL) to minimise the potential risk to the foetus.

As was noted at the abovementioned EU-OSHA Paris workshop, the lead OEL is currently under review, and despite technological advancement many workers are still exposed to lead and its compounds (EU-OSHA, 2014).

4.4 Organic solvents

Organic solvents include a number of compounds of different chemical structure belonging to different chemical groups. For example, aromatic hydrocarbons are chemicals such as benzene, toluene and xylenes; the first is a constituent of fuels, the other two can be found in paints. Trichloroethylene, carbon tetrachloride and dichloromethane are chlorinated hydrocarbons, which are in declining use because of their toxic properties. Still widely used in industry are hydrocarbons, glycol ethers and acetone. The physical properties of these compounds, such as solubility in water and in lipids and their generally low evaporating temperatures, make it likely that they are absorbed into the body by inhalation and/or through the skin.

Some examples of effects described in the literature for these substances are outlined below.

Owing to the widespread use of solvents, the number of potentially exposed workers is relatively large. Solvents are mostly used in mixtures; therefore, studies often address, especially when they take an epidemiological approach by occupation, mixtures of solvents. While this makes it more difficult to trace the effects to specific substances, it is more representative of the actual workplace exposure.

Although complete data are not always available to assess the connection between exposure to specific solvents and reproductive abnormalities, there is a consensus that the compounds of this group of chemicals cause reproductive disorders in humans. Therefore, protective measures to reduce occupational exposure are necessary and **pregnant women are considered to require special protection from the effects of exposure to these substances**.

The report presents a table with recommendations regarding the classification of organic solvents with respect to effects on fertility, developmental toxicity and lactation, as established by the Health Council of the Netherlands (Health Council of the Netherlands, undated).

Organic solvents may have significant effects on male fertility.

The chemical 2-ethoxyethanol **disrupts male fertility** by causing a reduction in the number of sperm in the semen. There are several studies indicating that 2-methoxyethanol, methanol, styrene and xylene can cause different reproductive abnormalities in laboratory animals. A strong gonadotoxic agent is ethylene glycol methyl ether, which causes a reduction in the number of spermatocytes and testicular atrophy (wasting away).

In addition, a significant correlation was observed in these studies between occupational exposure to mixed organic solvents and time taken to conceive (time to pregnancy (TTP)).

Effects on female reproductive functions

The literature indicates that **menstrual cycle disorders** occur more frequently in populations of women exposed to toluene, xylene, styrene and formaldehyde. However, these results should be treated with caution, as the effects of exposure analysis did not always take possible confounding factors (e.g. stress, age, socioeconomic conditions, general health, nutrition, addictions, etc.) into account, nor the concentration levels of these substances in the workplace.

In women exposed to benzene and its homologues, as well as to styrene and trichloroethylene, an increased incidence of irregular and longer, often heavy and painful, menstrual bleeding was noted. Menstrual irregularities were also observed in women working in the refining and rubber industry. Chronic ethanol abuse is also considered toxic for reproduction.

Effects on the foetus

Research has also shown that ethylene glycol ethers (2-methoxyethanol and 2-ethoxyethanol) have **teratogenic effects in animals**. Intrauterine growth retardation is caused by butan-2-one, trichloroethylene, xylene and toluene.

A number of studies have shown that the risk of spontaneous abortions is higher in women exposed to organic solvents. These studies, however, did not analyse the type of solvent, or the type of industry that the exposed women were employed in, for example. Despite the lack of some detailed information on the exposure of workers, the studies concluded that there is a **causal relationship between exposure to organic solvents and the increased risk of spontaneous abortion in women**. There is also a **potential link between the exposure of men and the rate of miscarriages in their partners**.

Some studies also show that the frequency of birth defects in the offspring of women exposed to organic solvents during pregnancy (especially during the first trimester) is higher than in the population of newborns of women not exposed to such conditions. A **higher incidence of birth defects in newborns** was also found when the fathers were occupationally exposed to organic solvents used to dilute paint.

Another study showed that there was a significant correlation between spontaneous abortion and occupational exposure to organic solvent mixtures, and this correlation increased with rising levels of exposure to organic solvents.

Owing to the widespread use of solvents, the number of potentially exposed workers is relatively large. The physical properties of these compounds, such as solubility in water and lipids and the generally low

evaporating temperature, make it likely that they are absorbed into the body by inhalation and/or through the skin.

4.4.1 Glycol ethers

Glycol ethers are a group of solvents based on alkyl ethers of ethylene glycol commonly used in paints, inks, varnishes and cleaning agents. These solvents typically have a relatively high boiling point, together with the favourable solvent properties of low-molecular weight ethers and alcohols. Therefore, they evaporate slowly but can penetrate the skin fairly easily.

Some glycol ethers and their acetates have caused adverse reproductive and developmental effects in animal species exposed by different routes of administration. The compounds with the shortest chain lengths are the most toxic. Among manufacturing workers, exposure to ethylene glycol ethers has been related to an increased risk of **miscarriage, birth defects, subfertility and prolonged menstrual cycles** (Chapin and Sloane, 1997).

Several studies on various glycol ethers suggest the following effects:

- reduced fertility and elevated risk of spontaneous abortion for female workers; in addition, cases of genital defects in boys were associated with occupational exposure of the mother to 2-methoxyethyl acetate during pregnancy;
- reduced semen quality in shipyard painters, metal casters, chemical industry workers and semiconductor industry workers; later studies on less toxic glycol ethers showed low motile sperm count.

The exposure of female workers to these chemicals may occur in the semiconductor industry, but also in sectors in which paints, inks, varnishes and cleaning agents are used.

4.4.2 N-Methyl-2-pyrrolidone

This substance is a powerful solvent with broad solubility for resins and high chemical and thermal stability. It is completely soluble in water at all temperatures and is also soluble in most organic solvents. It has become a substitute for many chlorinated solvents.

N-Methyl-2-pyrrolidone has been found to **harm the developing foetus** when tested in pregnant animals and it is **toxic to the reproductive system of male and female test animals** (Hazard Evaluation System and Information System, 2006).

The chemical is used in a wide range of industrial applications, including process chemicals, engineering plastics, coatings, agricultural chemicals, electronics, paint stripping and cleaning, adhesives and pigment dispersions.

4.5 Epoxy resins

Epoxy resins are a class of reactive prepolymers that can be cross-linked (cured) either with themselves or with a wide range of co-reactants (i.e. hardeners). The most common and important classes are formed by reacting epichlorohydrin with bisphenol A (BPA) to form diglycidyl ethers of BPA.

Epoxy resins have many different uses. For example, resins that are cured through exposure to ultraviolet light are commonly used in fibre optics, optoelectronics and dentistry. Industrial applications use epoxy resins as glue and to make laminates, castings, fixtures and moulds. In the electronics industry, epoxy resins can be used to make insulators, transformers, generators and switchgear.

Studies suggest the following effects:

- **testicular abnormalities;**
- **erectile dysfunction and ejaculation difficulty;**
- **irregular periods and stopping of menstrual cycles.**

Female-specific effects may also be attributed to BPA (see section 4.10).

Workers are exposed during the preparation of the production and processing of resins.

4.6 Pesticides

Pesticides function as herbicides, insecticides, fungicides and fumigants. The most common chemical groups are organophosphates, carbamates and phenoxyherbicides.

Some pesticides (e.g. carbaryl, benomyl, ethylenthiourea, maneb, zineb and thiram) have demonstrated reproductive and/or developmental toxicity in experimental animals. **Many pesticides are suspected to be EDCs**, that is, chemicals that can lead to an increase in birth defects, sexual abnormalities and reproductive failure (for more on EDCs, see section 4.10). A mixture of organophosphorus pesticides has been found to harm male fertility and offspring development. This study showed that human sperm chromatin is sensitive to organophosphorus pesticide exposure and that such exposure may contribute to adverse reproductive outcomes (Sánchez-Peña *et al.,* 2004).

Lawson and colleagues mention a study (Cardinale and Pope, 2003) that showed additive adverse reproductive effects from anti-androgenic fungicides (Lawson *et al*., 2006).

Although in most studies risk factors could not be attributed to individual pesticides, the following effects were suggested:

- **interference with male reproductive functions;**
- negative reproductive effects among women such as **spontaneous abortions, congenital defects and pre-maturity, as well as infertility and delay in conception;**
- increased **risk of miscarriage or birth defects in partners of exposed men;**
- **impaired fertility** owing to a reduction in semen quality and possibly lower testosterone levels in exposed males;
- **impairment of foetal growth and development, miscarriages;**
- maternal occupational exposure to pesticides seems to **increase the risk of childhood leukaemia**. Pesticide exposure has also been **linked to other cancer types** (e.g. lymphomas, cancers of the brain and nervous system, Wilms' tumour and Ewing's sarcoma), but the increased risk may also be related to childhood exposure. Findings for paternal exposure are inconsistent.

The following sectors and professions may be affected: agriculture, greenhouse workers, pest controllers, chemical industry, production of pesticides and florists. In general, men and women working on or living near farms could also be affected.

4.7 Polychlorinated biphenyls, polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans

Polychlorinated biphenyls (PCBs) are compounds with a very wide range of applications used in many industries owing to their favourable physicochemical properties; they are also formed by the thermal decomposition of industrial waste in incinerators. Enclosed systems are used in the processes of heat exchange, as a component of lubricants, hydraulic fluids, and for the production of capacitors and transformers in the electrical industry. Exposure in open systems may occur when they are used as a component of plasticisers, printing inks, other inks, adhesives, dyes and pesticides.

Organochlorines are widespread pollutants. Concern over the adverse reproductive effects of these compounds arises from the accidental exposure of humans and from experimental studies. A number of studies in exposed populations indicate that **high concentrations of persistent organochlorines may adversely affect semen quality and cause testicular cancer in males, induce menstrual cycle abnormalities and spontaneous abortions in females, and cause prolonged conception time**

(time to pregnancy), reduced birth weight, skewed sex ratio [6], and altered age of sexual development. However, additional research is needed to fully elucidate the possible adverse effects of organochlorines on human reproductive health.

Developmental effects of long-term exposure were evaluated in eastern Slovakia in a region in which PCBs from a chemical plant contaminated the surrounding district: a **dose–response relationship between PCB exposure and developmental enamel defects of permanent teeth in children** was demonstrated (Jan *et al.*, 2007).

4.8 Pharmaceuticals

Some drugs have known adverse effects on the development of the foetus. Data on the effects of occupational exposure are, however, limited. Pharmaceutical factory workers may be exposed to drugs, and nurses, for example, to pentamidine or ribavirin (antimicrobial drugs), when administered to patients as an aerosol.

Diethylstilbestrol, a synthetic oestrogen formerly used as a medication to reduce the risk of pregnancy complications, is a known human reproductive hazard. Some sex hormones have induced masculinisation of female foetuses and feminisation of male foetuses in animal experiments. Azathioprine, cyclosporin A and some antiviral agents, such as acyclovir, ganciclovir and zidovudine, have also induced adverse reproductive effects (none specified) in animal experiments. Below, selected data on frequently used pharmaceuticals, which have undergone workplace measurements, are presented.

4.8.1 Anaesthetic gases

Anaesthetic agents are drugs that are used to block or suppress the sensation of pain in patients undergoing surgery.

In the work environment, concerns are mainly related to inhalational anaesthetic agents. Contemporary anaesthetic gases include isoflurane, sevoflurane and desflurane, and nitrous oxide. These are delivered to the (human or animal) patient by inhalation and may be released into the work atmosphere. This presents a risk of exposure to personnel, especially in rooms without ventilation or anaesthetic gas extraction (‘scavenging’) equipment, during mask anaesthesia and when disconnecting the gas circuits of patients.

Exposure occurs primarily in the health sector, dental clinics and veterinary surgeries. Workers are subject to much lower gas concentration exposures than the patients. Exposure may, however, last a whole working life.

Anaesthetic gases are pharmaceuticals, but exposure in the work environment is regulated by OSH legislation. The specific regulations and information requirements (such as the ones provided by exposure scenarios and safety data sheets) for chemicals do not apply to pharmaceuticals, and risks may therefore not be readily identifiable for workers. Also, most EU Member States lack OELs for airborne anaesthetic agents.

Several epidemiological studies have addressed the potential adverse effects of anaesthetic agents on reproduction. In some studies, occupational exposure is associated with increased risks of spontaneous abortion, malformations and increased time to achieve pregnancy, for example. It is difficult, however, to identify single agents as developmental toxicants, because workers are typically exposed to several anaesthetic gases. To evaluate the reproductive and developmental effects of specific anaesthetic gases, it is necessary to evaluate information obtained from animal studies. Many animal studies, however, have involved prolonged exposure to very high doses of gases and may, therefore, be more relevant for patients than for those exposed at work.

[6] Number of male births relative to the number of female births.

In the following sections, isoflurane, sevoflurane and desflurane, and nitrous oxide are described as model compounds to illustrate some of the issues regarding inhalational anaesthetics in the work environment.

Reproductive toxicity of isoflurane, sevoflurane and desflurane

Isoflurane, sevoflurane and desflurane are closely related halogenated ethers. Isoflurane is the most potent of the three and the most studied. Anaesthesia occurs at dose levels above 12,000 parts per million (ppm). The toxicological data on sevoflurane and desflurane are poor.

When inhaled, fluranes distribute rapidly in the body and pass the placenta from the maternal to the foetal organism almost unimpeded. They are metabolised only a little and do not accumulate in body tissues. There is generally no knowledge of the potential mechanisms leading to their reproductive and developmental toxicity.

Occupational exposure has generally decreased in the past decades. At hospitals using modern systems for delivery of inhalational anaesthetics and for scavenging, exposure generally stays below 1-2 ppm. Some studies indicate however that exposures may be much higher at veterinary clinics.

Isoflurane has been shown to affect male fertility in rabbits but not in mice. The quality of the two available studies does not, however, allow for a hazard assessment for this effect. Studies investigating effects on female fertility were not identified for any of the three fluranes.

In pregnancy, exposure of laboratory animals to dose levels below 4,000 ppm has not been associated with overt effects on pregnancy or foetal development. Findings in rodents and non-human primates, however, indicate that the foetal nervous system is sensitive to isoflurane. At present, only anaesthetic dose levels have been investigated. No lower limit for this adverse effect has therefore been identified.

For breastfeeding, no studies were identified. As the fluranes are metabolised only a little and do not accumulate, no exposure through milk would be expected to occur as a result of maternal occupational exposure.

Reproductive toxicity of nitrous oxide

Nitrous oxide, or laughing gas, has been in use as an inhalational anaesthetic for more than 150 years. It is not very potent and may constitute as much as 70 % of the air that patients inhale. Occupational exposure regularly exceeds 50 ppm on an 8-hour time-weighted average and may show peaks in excess of 2,000 ppm. Nitrous oxide distributes rapidly in the body and quickly crosses the placenta.

In several animal studies, adverse effects have been reported, such as damage to testicular tissue and male-mediated developmental toxicity (i.e. developmental effects that arise in the offspring owing to exposure of the father before conception). These issues have, however, never been properly clarified.

In female rodents, nitrous oxide has been shown to interfere with the hormonal control of reproduction. At anaesthetic dose levels, it inhibits ovulation. Whether or not this also occurs at lower exposure levels has not been investigated.

Effects on pregnancy have been observed in some studies in laboratory animals at exposure levels at and above 1,000 ppm nitrous oxide, for 8 hours/day and over. Developmental neurotoxicity is an issue when exposure occurs in pregnancy. No studies have aimed to identify a no-effect level for this endpoint.

A lack of data precludes evaluation of effects during breastfeeding. Nitrous oxide leaves the body quickly and does not accumulate; therefore, exposure through breastfeeding would not be expected.

Conclusions

In conclusion, there is a general lack of knowledge as regards the reproductive and developmental toxicity of inhalational anaesthetics. Around the year 2000, isoflurane, nitrous oxide, enflurane and halothane were evaluated for reproductive and developmental toxicity by the Dutch Committee for Compounds Toxic to Reproduction (DECOS). DECOS recommended the classification of nitrous oxide as a substance of concern for effects on fertility and foetal development, and halothane of concern for developmental toxicity, according to EU Directive 93/21/EEC. For other compounds/types of effects, a lack of appropriate data precluded an assessment of classification.

Reported observations indicate that isoflurane, sevoflurane and desflurane, and nitrous oxide have the potential to affect male and female reproductive function. Furthermore, developmental neurotoxicity is an issue when exposure occurs in pregnancy. It is therefore recommended that these endpoints be assessed in appropriately designed studies, in order to identify the lower limits of effects.

4.8.2 Antineoplastic agents

Antineoplastic substances are also called cytostatics and are drugs used in chemotherapy.

The reproductive toxicity of antineoplastic drugs is known from clinical evidence of treated patients (they suppress cell proliferation). Effects on nurses, or among women working in pharmaceutical companies producing antineoplastic drugs, have been studied in many epidemiological studies, which found the following:

- effects on nurses or among women working in pharmaceutical companies producing them were spontaneous abortion and infertility;
- handling of antineoplastic agents in hospitals has been associated with menstrual dysfunction, subfertility, miscarriage, premature birth, low birth weight and birth defects in children;
- male fertility problems may be attributable to antineoplastic drugs.

Those affected include workers in hospital dispensaries, other hospital workers, and workers in medical practices or outpatient facilities. Workers can be exposed when cytostatic drugs are delivered, when medication vials are being unpacked and stored, during the preparation of cytostatic infusions for individual patients, during the in-house transport of inadequately packaged ready-to-use infusions and cytostatic waste products (e.g. between the dispensary and the ward), during the application of cytostatic drugs on the wards, when handling patients who are undergoing cytostatic therapy (sweat, vomit, secretions) or in cleaning activities.

4.9 Particulate matter

Particles of concern in the occupational setting include diesel exhaust particles (DEPs), engineered nanoparticles and particulates released during welding. These types of particles are also the focus of this report. Particles can also be found in environmental tobacco smoke and exhaust from gasoline engines, for example. Very small particles behave similarly to chemicals in a gas or vapour, and inhalation is the main route of exposure.

The most relevant characteristic of particles is their size and, in particular, their diameter. Traffic-generated particles are mostly referred to as fine (< 2.5 μm) and ultrafine particles (< 0.1 μm). Fine and ultrafine/nanosized particles deposit deep in the lung upon inhalation and are removed very slowly. Once in the lung, the particles may induce inflammation.

Particles may potentially affect reproduction and development in several ways. When inhaled, they may cause inflammation and oxidative stress in the airways and the resulting inflammatory mediators may harm reproduction and foetal development. Toxicity might also occur as a result of toxic compounds bound to the particles. Finally, if particles are released into the blood stream, direct effects on reproductive organs, the placenta or foetal development cannot be excluded.

4.9.1 Engineered nanoparticles

Nanoparticles are particles between 1 and 100 nanometres in size. Engineering of nanoparticles may result in new properties owing to the ability to design and control atomic structure, shape and surface coatings. Toxicity may, therefore, differ from that of the bulk material. However, regulation of engineered nanoparticles currently follows that of all other chemicals in the work environment (i.e. nanosized particles are regulated similarly to the bulk material). Thus, specific occupational exposure limits are not set for nanoparticles, even if the number of particles increases substantially as the particles become smaller.

Only the US National Institute for Occupational Safety and Health (NIOSH) has set an example by recommending two separate exposure limits. NIOSH recommends that fine TiO_2 particles be set at an exposure limit of 2.4 mg/m^3, and ultrafine TiO_2 be set at an exposure limit of 0.3 mg/m^3, at time-weighted average concentrations of up to 10 hours a day for a 40-hour working week (NIOSH, 2011).

Some nanomaterials have been in use for several years (e.g. the black pigment of carbon black), but new nanomaterials are being engineered at a fast pace. Until large-scale production is initiated, these are mainly manufactured and handled in the laboratory. In the workplace, workers can be exposed during manufacture, use (including research), transport, storage and waste treatment. Examples of trades in which exposure to ENPs might occur include the construction, automobile and textile industries, and in the production of paints and lacquers.

Most research into the developmental and reproductive toxicity of nanomaterials must be categorised as hypothesis generating. Despite the observed diversity in approach of the existing studies, whether administration is by inhalation or by the intravenous route, particles seem to distribute in organs with relevance for male and female fertility, although the amount may vary with route of exposure.

Male fertility has been investigated in a few mouse studies, and exposure through both the airways and subcutaneous injection affected sperm counts and male reproductive hormones.

Only one published study has investigated female fertility and reproductive function *in vivo* in mice. The route of ENP exposure had little relevance for the occupational setting and the dose was very high. Exposure affected female fertility as well as the balance of sex hormones.

For effects on and during pregnancy, it is mainly carbon black and titanium dioxide nanosized particles that have been assessed. Maternal gestational airway exposure does not seem to interfere with, for example, birth weight, litter size or gestation length, even if exposure was associated with lung inflammation in the mother. However, several other effects have been observed in offspring, including impaired fertility and change in hormone levels in males, altered immune function towards a more allergic phenotype and neurodevelopmental effects. Exposure has also been associated with significant changes in gene expression. At the time of writing, there was no information available on whether or not nanoparticles may be transmitted through lactation.

4.9.2 Welding particles

During welding, metals are joined, usually by melting a filler material that bonds the surfaces together upon cooling. Fumes are released during the process, and ultrafine particles constitute a major part of these fumes. Several different welding methods exist and new processes are introduced on a regular basis. Particle composition varies with the type of welding, but many are metal oxides. Welding is a common industrial process and up to 2 % of the EU workforce are estimated to be engaged in some sort of welding.

In contrast to ENPs, welding fumes and particles have been investigated in relation to reproductive and developmental toxicity in only epidemiological studies.

Effects on male fertility have mostly been studied in Denmark. Welding was found to adversely affect male reproductive potential over a range of different study designs, methods and endpoints, although not in all studies. No studies have been identified for effects on female fertility.

As for effects on the outcomes of pregnancy, some inconclusive data support the hypothesis that preconceptional exposure of the father might affect the outcome of pregnancy. Findings in one study of maternal gestational exposure indicate that working in welding may harm the intrauterine growth of the child. No studies are available for breastfeeding.

4.9.3 Diesel exhaust particles

Diesel exhaust particles (DEPs) and gases are released from diesel engines following combustion of diesel fuel, from both on-road and non-road engine exhaust. In occupational settings, levels may be much higher than in outdoor ambient air. Occupational exposure levels are highest for enclosed (underground) work sites, when heavy equipment is used. Intermediate levels are reported for working above ground in (semi-)enclosed areas, and the lowest levels are reported for enclosed areas separated from the source machinery or outside. Few countries have specific occupational exposure limits for DEPs.

DEPs often contain several different polycyclic aromatic hydrocarbons (PAHs). These substances are suspected to possess hormone-like properties, and this property has been confirmed in some animal studies of DEPs. It is highly debated whether it is the particles, associated compounds, exhaust gases or (maternal) lung inflammation that account for reproductive effects. Effects of fumes from pre-2006 diesel engines may differ significantly from those of post-2006 engines, because of improved engine technology and fuel formulations.

A few epidemiological studies indicate that working in heavy road traffic might affect male reproductive parameters. These findings are corroborated by findings of decreased semen quality and hormonal changes in male rodents exposed to diluted whole diesel exhaust, albeit at milligram DEP/m^3 exposure levels, rather than the microgram DEP/m^3 exposure levels in ambient air. Furthermore, exposure to ambient polluted air has been associated with male reproductive effects related to stability of the genetic material in sperm cells, i.e. fragmentation of the DNA (humans) and heritable germline mutations (animals). It should be noted, however, that epidemiological studies observe effects at ambient air exposure levels, which are rarely as high as the exposure levels reported in the work environment, meaning that effects may have been underestimated. Increased numbers of germline mutations have also been observed in mice after maternal inhalation of resuspended DEP during pregnancy, indicating that DEP may potentially induce germline mutations.

Female fertility has not been investigated in relation to particulate air pollution in humans. The only information available comes from a study in mice. Housing of female, sexually mature mice in heavy traffic pollution disturbed the foetal reproductive cycle and mice breeding under polluted conditions also took longer to become pregnant.

Exposure to air pollution during pregnancy was found to be associated with low birth weight, preterm birth and being born small for gestational age in a meta-analysis of more than 40 epidemiological studies.

Maternal exposure also seems to increase the propensity to develop allergic disease later in life in both animals and humans. DEP might be toxic to genetic material, as shown in humans as well as animals. The consequences for health later in life are largely unknown. DEP have, however, been shown to induce mutations in DNA from male mouse sperm cells, and these mutations were inherited by male offspring in the next generations (Ritz *et al*., 2011). DEP-associated PAHs may transfer to breast milk, but the consequences for the child of such lactational exposure have apparently not been studied.

4.10 Endocrine-disrupting compounds

Since 1993, researchers have presented evidence of an apparent increase in the prevalence of certain malformations of the male genitalia and testicular cancer. Male fertility may have been impaired in recent decades, but reliable data are still not available. One of the prevailing hypotheses points to hormone-like substances as possible causes of such effects (Storgaard and Bonde, 2003).

In June 2012, researchers indicated that increases/changes are clearly visible in the incidence statistics of the following effects from developed countries (EU conference proceedings, 2012):

- sperm/semen quality and count;
- cancers of the breast, testicles, prostate, thyroid;
- feminisation, anogenital distance reduction (as a measure of feminisation);
- diabetes, obesity;
- asthma;
- cardiovascular diseases;

- attention deficit hyperactivity disorder;
- autism;
- impact on intelligence quotient.

Birnbaum noted that these effects can sometimes be observed long after exposure has taken place, which would be especially true if the exposure occurred during growth and development (Birnbaum, 2012).

However, these findings are challenged by other researchers. So far, it has been demonstrated in animal studies that endocrine disruptors have clear adverse effects. There are, however, only few human studies, for example on the connection between congenital cryptorchidism (absence of one or both testes from the scrotum at birth) and levels of certain organochlorine pesticides in breast milk (Damgaard *et al*., 2006).

Epidemiological cross-sectional studies show some associations between exposure to hormone-like substances and effects in children. Endocrine disrupters are thought to influence boys' development. For example, there were 20 % more deformed children registered in 2005 than in the late 1990s in Denmark, and the increase is greater for malformations of the urinary organs in young children (National Board of Health, 2007). The increased focus might explain part of the observed increase. However, the incidence of male reproductive disorders and results from animal studies indicate that a wide range of chemicals with endocrine-disrupting properties are playing a part, even when levels of exposure to the chemicals are extremely low (Sharpe and Irvine, 2004). Decreases in anogenital distance among male infants have also been associated with prenatal phthalate exposure (Swan *et al*., 2005).

Toxicants that could cause endocrine disruption include a large number of xenobiotics used in various products, as well as naturally occurring toxicants produced by plants and fungi (Evans, 2011). The following are particularly interesting from the OSH perspective:

- plastics and related additives, such as BPA (Li *et al*., 2010);
- pesticides manufactured in chemical plants and used by farmers, farm workers, gardeners and greenhouse workers — about 105 substances can be listed, according to Mnif and colleagues, and of these, 46 % are insecticides, 21 % are herbicides and 31 % are fungicides; some were withdrawn from general use many years ago but are still found in the environment, potentially exposing workers (Mnif *et al*., 2011);
- heavy metals, which are another group of chemicals that are common at workplaces in the metallurgical and metal processing sectors (Iavicoli *et al*., 2009).

In 2009, Brouwers and colleagues developed a job-exposure matrix, which was first established by van Tongeren and colleagues in 2002. It was used to estimate the exposure to potential endocrine disruptors in several job categories in order to assist epidemiological research identify professions of concern (Brouwers *et al*., 2009). Chemicals with endocrine-disrupting properties (varying levels of evidence) were identified from the literature and classified into 10 chemical groups and further subgroups:

1. PAHs;
2. polychlorinated organic compounds;
3. pesticides;
4. phthalates;
5. organic solvents;
6. BPA;
7. alkylphenolic compounds;
8. brominated flame retardants;
9. metals;
10. miscellaneous (subgroups: benzophenones, parabens, siloxanes).

Phyto-oestrogens were not considered, because occupational exposure was expected to be negligible in comparison with other sources of exposure.

Three experts scored the probability of exposure to each chemical group and subgroup for 353 job titles as 'unlikely', 'possible' or 'probable', on the likelihood that the occupational exposure level would exceed background levels. Exposure to any chemical group was rated 'unlikely' for 238 professions (67 %), whereas the likelihood of exposure to one or several endocrine disruptors for 102 professions (29 %)

was classified as 'possible' (17 %) or probable (12 %). The unexposed professions were mainly managers, or science, technology, teaching, business and public services, administrative and secretarial, or sales and customer services professionals.

The exposed workers were predominantly skilled workers or process, plant and machine operators. PAHs, pesticides, phthalates, organic solvents, alkylphenolic compounds and metals were often linked with a specific job in the job-exposure matrix (JEM). The remaining chemical groups were found to involve very few occupations. The most commonly documented exposures were exhaust fumes (27 times), copper fumes (10 times) and lead fumes (7 times), and working with lead solder (5 times), metal cleaning and degreasing agents (7 times), pesticides for general agricultural purposes (13 times), adhesives (9 times) and coatings (5 times). It is important to note that no studies have been performed regarding the validity of this matrix. Such a study is greatly needed, but would require, according to Brouwers and colleagues, the collection and analysis of blood samples from potentially exposed workers and a reference population.

In recent years, apart from the studies by Brouwers *et al*. mentioned above, a number of studies focusing on occupational settings have been carried out. Mantovani and Baldi (2010) list several studies on exposure to EDCs, including:

- intensive agriculture work, especially greenhouse work;
- dioxin exposure in the steel industry;
- manufacturing of EDCs still in use (pesticides, phthalates, BPA, parabens, perfluorinated compounds, brominated flame retardants (BFRs));
- plastic (PVC) and rubber manufacturing related to phthalate internal exposure;
- polycarbonate plastic and epoxy resins manufacturing related to BPA internal exposure;
- office jobs and BFRs (household and upholstery dust).

A scenario of great concern, according to the authors, is the disposal of electronic waste (e-waste) in developing countries, which is associated with high exposure to dioxins, heavy metals and, above all, BFRs; nevertheless, BFR exposure was also reported in US facilities.

Hougaard and colleagues examined the possible association between employment in the plastics industry and infertility. Workers in this sector may be exposed to a large variety of different chemicals, such as monomers (ethylene, styrene, BPA, etc.), additives (phthalates, etc.), flame retardants, release agents and cleaners (organic solvents). Several are suspected to have endocrine-disrupting properties. During processing, additional agents, such as formaldehyde and cyclic hydrocarbons, may be generated. Economically active women and men in the Danish Occupational Hospitalisation Register were followed for hospital visits for infertility from 1995 to 2005 and the authors found an increased incidence of infertility treatment in female plastics workers (compared with all working Danish women), but not in male workers. They urged more specific studies of reproductive occupational health in the plastics industry (Hougaard *et al*., 2009).

BPA is produced in large amounts worldwide to manufacture polycarbonate plastics, the epoxy linings for most food and beverage cans, dental sealants and additives for other consumer products. Li and colleagues report that highly exposed workers in BPA manufacturing and epoxy resin manufacturing companies have significantly higher risks of male sexual dysfunction (Li *et al*., 2010). In France, restrictions on the use of BPA have been proposed (e.g. for their use in handling of thermal paper (cash register receipts, credit card receipts, etc.)), especially in an occupational environment (ANSES, 2014). The conclusions of the assessment show a potential risk to the unborn children of exposed pregnant women related to a change in the structure of the mammary gland in the unborn child that could promote subsequent tumour development.

In a review, Iavicoli and colleagues found reproductive and developmental abnormalities in workers exposed to cadmium, mercury, arsenic, manganese, zinc and iron (Iavicoli *et al*., 2009). Such exposure is likely in metallurgy and metalworking sectors, as well as in industries involving welding and soldering. Taskinen and colleagues describe workers' exposure to heavy metals and note that cadmium and other metallic ions may function as metallo-oestrogens and endocrine disruptors (Taskinen *et al*., 2011).

With regard to pesticides with endocrine-disrupting effects, Mnif and colleagues note in a review paper that residential proximity to agricultural activity may explain developmental abnormalities in

epidemiological studies of low birth weight, foetal death and childhood cancers. In addition, a higher prevalence of certain effects was found in areas with extensive farming and pesticide use, and in the sons of women working as gardeners (Mnif *et al*., 2011).

In summary, there is increasing evidence that endocrine disruptors are of concern in the occupational setting. In addition to the sectors mentioned above, it can be assumed that waste collection and processing occupations, as well as the maintenance and cleaning sectors, in European countries could be affected, because workers are exposed to heavy metals, organic solvents, paints and adhesives.

4.10.1 Specificities of endocrine disruptors

Although the results are disputed, several studies suggest that EDCs have non-monotonic responses, which means that the toxic effects may be greater at lower doses than at higher doses. Vandenberg and colleagues analysed hundreds of scientific publications and concluded that non-monotonic effects and low-dose effects are common in studies of hormones and EDCs. Thus, the effects of low doses cannot be predicted by the effects observed at high doses. They state that low doses cannot be ignored, as exposure to chemicals at levels found in the environment can have adverse effects on animals and humans (Vandenberg *et al*., 2012).

4.10.2 Mixtures of endocrine-disrupting compounds

Animal studies with concomitant exposure to several EDCs with similar modes of action have shown clear effects on early markers for endocrine-disrupting effects, such as anogenital distance, nuclear receptors and reproductive organ weight in male offspring (Hass *et al*., 2012).

Laboratory experiments with oestrogenic or anti-androgenic chemicals showed substantial mixture effects even though each individual chemical was present at ineffective doses (Silva *et al*., 2002; Hass *et al*., 2007; Metzdorff *et al*., 2007). Because workers may already have been exposed through the environment or food, only limited room is therefore left for workplace exposure to mixtures of endocrine disruptors, although the reproductive effects may have been taken into account by SCOEL when setting OELs for every substance. Consequently, highly exposed women of reproductive age may not be protected sufficiently against the combined endocrine-disrupting effects of chemicals on the health of the unborn child (Hass, at EU-OSHA, 2014).

The European Commission has examined the way in which exposure to multiple endocrine disruptors is currently addressed in EU legislation, noting that current legislation does not provide a comprehensive, integrated assessment of cumulative effects taking into account different routes of exposure and different product types. What is required is a framework that provides both for an assessment of the endocrine-disrupting potential of individual chemicals as well as the possibility to assess, when appropriate, the cumulative impact of identified combinations of substances on the endocrine system (European Commission, 2011).

4.11 Discussion

The discrepancy between the number of chemicals in workplaces and the number of chemicals that have been evaluated for reproductive toxicity is huge. This is the primary reason for the lack of knowledge on the potential adverse effects of chemicals on male and female fertility and on pregnancy. Currently, the testing of chemicals under REACH is triggered by considerations of volume produced or marketed. From the point of view of worker protection, reproductive toxicity assessments should also be applied to low-volume chemicals that are currently not subject to registration under REACH.

4.11.1 Methodological challenges

Knowledge on chemicals may emerge from epidemiological studies, animal studies and alternatives to animal studies (i.e. *in vitro* and *in silico* models). All three types of studies have their own advantages

and disadvantages for the identification of occupational factors with potential harmful effects on reproduction and pregnancy.

An exposure may be classified with certainty as harmful to human reproduction only if a causal relationship has been observed in an appropriate study in humans. However, epidemiological studies are not performed on a regular basis and they are not required under chemical regulation (e.g. REACH). Furthermore, it is mostly effects that are relatively close to the course of pregnancy that have been studied.

For most chemicals, knowledge of reproductive toxicity is therefore provided by experimental studies in animals. Interpretation must however acknowledge that testing has been performed in species different from humans, in a much smaller number of individuals and at dose levels exceeding those usually found in occupational settings.

Also, some relationships between dose and effect cannot be adequately studied in conventional experimental animal studies, because animals may be less sensitive than humans, as has been proposed for the effects of lead on male fertility, for example. Therefore, the relationship between dose and effect in animals cannot adequately serve as a basis for health-based OELs. This indicates the need for prospective epidemiological studies. However, by using only epidemiologic data, it can be very difficult to demonstrate a definitive cause-and-effect relationship. For humans exposed to EDCs, for example, when the xenobiotics have a weak hormonal activity, the endpoints are subtle or evident only after long exposure or later in life, and/or a number of different factors can have a causative role.

The most valid or most relevant conclusions are from retrospective studies of documented exposures to known agents. In conclusion, a combination of studies and data on exposure is warranted. Studies should consider concentrations and mixtures of chemicals that occur in workplace settings.

Existing tests for reproductive and developmental toxicity have a limited scope

There is also a lack of knowledge as regards the reproductive and developmental toxicity testing of chemicals, and testing routines have a limited scope. Although a wide range of endpoints are included in regulatory guidelines on reproductive toxicity, potentially important domains, such as the function of the nervous, cardiovascular, immune and endocrine systems, and hepatic and renal function are not typically examined in the tests. Effects that do not become evident until old age, induction and transfer to future generations of mutations in the germline, developmental toxicity owing to chemical exposures of the father (male-mediated developmental toxicity), epigenetic changes (see Glossary) and decreased stability of the sperm's DNA are not part of existing guidelines. Furthermore, although the weight and size of the body's organs are recorded in OECD animal testing guidelines, for example, the function of organ systems is rarely, if ever, assessed.

Existence of a test guideline does not guarantee its application either. Although test guidelines for developmental neurotoxicity were implemented by the US EPA and the OECD, only 15 industrial chemicals and solvents had been tested for developmental neurotoxicity as of 2008.

Furthermore, some types of toxicity may be multifactorial. Turning again to the example of lead, not only the stage of developmental exposure (e.g. prefertilisation, early/mid/late pregnancy), but also the duration of exposure and the genetic and nutritional background contribute.

Furthermore, unpredictable dose–effect relationships may be observed (e.g. for EDCs) and many different mechanisms are in play. Metal toxicity, for example, is characterised by a high degree of complexity and a multifactorial background. Several metals are essential components of normal cell and physiological functions, so both a lack of and an excess of exposure elicits adverse symptoms. Furthermore, toxicity might arise when one metal mimics another, as has been described for lead and calcium.

Issues of process-generated substances, such as those from diesel combustion and from welding, also need to be addressed, as REACH does not cover these substances, and therefore they are not addressed by testing routines.

Another methodological problem concerns nanomaterials; as particles supposedly exert effects through mechanisms involving oxidative stress, traditional methods of assessing reproductive effects, such as sperm counts, ought to be supplemented by assessments of other measures relating to sperm function, for example DNA fragmentation (for more on nanomaterials, see section 3.12).

There is a need for up-to-date exposure data

It is often the case that available data from epidemiological studies do not reflect contemporary exposure scenarios. This is, for example, the case for anaesthetics, where many studies were conducted before, or do not consider the introduction of, modern ventilation and scavenging systems. Studies are therefore performed at exposure levels that are much higher than those occurring in the present setting and may overestimate the risk of effects.

For diesel exhaust particles, past and recent studies primarily investigate the health effects of older diesel-engine technology and emissions. As new diesel technology and current fuel formulations differ considerably from pre-2006 technology, these older studies may have limited relevance for health effects.

4.11.2 OELs

It is evident from the report that the data on reproductive and developmental toxicity is limited for many chemical exposures in the occupational setting (e.g. nanoparticles, diesel particles and welding particles, and EDCs). Thus, relatively large uncertainty factors seem appropriate where the effects of the evaluated substances are serious and irreversible, e.g. malformations (Fairhurst, 1995).

Although the availability of data on the potential of various substances to produce adverse effects on aspects of the reproductive process is limited, the potential of each substance to cause reprotoxic effects should be considered, namely in respect of effects on male and female fertility and developmental toxicity as defined in section 2.2. of this summary.

Furthermore, some extra protection may be provided by the Member States. In Denmark, for example, for anaesthetic gases and organic solvents, as a rule, the risk to the foetus is regarded to be negligible if the air concentration is lower than one-tenth of the limit value.

A study comparing OELs and DNELs found that DNEL values could be far below, as well as far above, OEL values. These discrepancies may create confusion in terms of legal compliance, risk management and risk communication and need to be addressed, especially when discrepancies concern reproductive and developmental effects.

Improved cooperation between SCOEL, ECHA and its risk assessment committee, and better access to registration data and ‘grey literature’ would help create a better knowledge base for the consideration of reproductive effects in OEL settings and address these discrepancies

Findings indicating that there is no typical dose–response curve for some substances, such as endocrine disruptors, affect many of the traditional approaches and processes, the underlying concepts, such as linear dose–response relationships for OEL setting, but also the REACH approach (based on an effect-related DNEL). Because of this and the fact that effects depend on the endocrine state of exposed persons, EDCs are considered non-threshold substances by some stakeholders. This discussion needs to be resolved to be able to take decisions on OEL setting for EDCs and whether or not to set the same legislative requirements for them as for carcinogens and mutagens.

4.11.3 Endocrine-disrupting compounds

Important health effects have been associated with exposure to EDCs, including damage to the reproductive system, cancer and metabolic diseases, obesity and diabetes. There is also increasing evidence that endocrine disruptors are of concern in occupational settings. Low-dose effects, non-monotonic effects and transgenerational effects are a concern and need to be studied further.

Sectors in which workers encounter heavy metals, organic solvents, pesticides, plastics, paints, resins and adhesives may be affected. A JEM has proved able to identify areas of concern that need further attention. It could be improved, validated and applied in other sectors and occupations, and be tailored to national specificities.

Regulatory actions as regards OSH are still in their early stages. Given the many, often delayed and irreversible effects of reprotoxicity, there is an urgent need to decide which substances and mixtures should be banned, which should be restricted in use and what these restrictions should look like.

Endocrine disruptors — legal instruments

As regards EDCs, the EU strategy on endocrine disruption and the monitoring of the implementation are described in the main report. Chemical substances were screened and evaluated for their endocrine-disrupting effects and a preliminary priority list was established at the end of 2006. These lists have been followed up by several studies and reports.

According to REACH Article 57, substances with endocrine-disrupting properties may also be included in the List of Substances Subject to Authorisation (Annex XIV) provided that there is scientific evidence of the probable serious effects on human health or the environment, which gives rise to a level of concern equivalent to that of carcinogenic, mutagenic or toxic for reproduction (CMR) categories 1A or 1B (or substances of equivalent concern).

The European Commission´s recent definition of endocrine disruptors (European Commission, 2016) has drawn comments from a number of institutions. The French Agency for Food, Environmental and Occupational Health & Safety (ANSES), expressed regret that the current choice results in only 'known' EDs and not 'presumed' EDs being identified in the definition (ANSES, 2016). The EU proposal is based on the WHO/IPCS definition[7], taking into account the effects on humans and non-target organisms in the environment (WHO, 2002), which is essential for a comprehensive assessment of the effects of EDCs. Some non-governmental organisations (NGOs) have noted that the acknowledged WHO definition refers to factors 'causing adverse health effects' requiring a high level of proof. In their view, this will limit the impact of legal restrictions and would prefer a definition that refers to 'the probability of causing adverse effects' to reproduction.

Before the European Commission´s definition was released, some experts recommended the creation of a separate regulatory class for EDCs and the use of, as yet, non-validated, test methods in order to generate more data. They also requested the development of further guidance documents for the interpretation of test data (Kortenkamp *et al.*, 2011).

As mentioned above, the non-monotonic effects and potentially additive or multiplicative effects of endocrine disruptors present a particular challenge for the current legislative framework. A precautionary approach should therefore be considered. Furthermore, the EU policy on EDCs should take into account workplace exposures and workplace risks, as well as combined exposures.

4.11.4 Nanomaterials and other particles

Engineered nanoparticles present another challenge, as increasing use of nanotechnology is foreseen to considerably increase human exposure, both at work and from consumer products. No research programmes within the European Union address effects on pregnancy and foetuses, and the present database on the developmental toxicity of engineered nanoparticles is extremely poor and insufficient for even a preliminary hazard assessment for mother and foetus.

Published research on the reproductive and developmental toxicity of particles present a great diversity of study designs, for example with respect to particles and particle characteristics, model systems and animal species, dose levels, routes of exposure and endpoints. This diversity makes it difficult to deduce general rules for reproductive and developmental toxicity. It is also not known if chronic, low-dose exposure leads to an accumulation of particles that interferes with reproductive and developmental processes, even after termination of exposure. There is some evidence that nanosized and ultrafine

[7] Definition of an endocrine disruptor 2002, International Programme on Chemical Safety, a joint programme of various UN Agencies, including the World Health Organisation:
- *A potential endocrine disruptor is an exogenous substance or mixture that possesses properties that might lead to endocrine disruption in an intact organism or its progeny, or (sub)populations.*
- *An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations.*

particles may primarily affect the function of organ systems not traditionally assessed in guideline studies on developmental toxicity.

The determining characteristics of particle-related reproductive toxicity are not known. Surface area is likely to be an important determinant of lung inflammation after lung exposure to nanosized particles, but several other particle parameters are also believed to contribute to their toxicity (e.g. shape, surface chemistry, composition, solubility, charge, release of chemical components, etc.). Adding to the confusion are the myriad of measuring methods used to characterise these parameters, which hampers a comparison of studies. In addition, measuring these parameters is hindered by the highly specialised skills required, the fact that different instruments are needed for monitoring each parameter, as well as the considerable size of the instruments

At present, neither type of particle described in this report triggers toxicological testing in REACH. Furthermore, high-exposure particles such as diesel exhaust and welding fumes are 'process generated' and are therefore not covered by the formal testing system for industrial chemicals linked to REACH, as these are 'unintentionally generated in industrial and combustion processes'. There is a general need for clarification, namely that workers need to receive adequate protection at work.

It has been proposed to treat nanomaterials as distinct substances awaiting clarification, as the nanoscale makes all or only some types of particles display unique toxicological properties Under REACH, however, engineered nanoparticles are at present regulated in the same way as the corresponding bulk material. Test guidelines in support of REACH rely on conventional toxicological methods and these may not be appropriate for assessing the risks associated with nanoparticles. Even if REACH adopts specific rules for toxicity testing of engineered nanoparticles in the future, developmental toxicity will probably not be tested for, owing to the tonnage rules.

Overall, assessment of reproductive and developmental health effects of particles is urgently needed as a basis for regulation that adequately protects not only exposed workers but also their progeny. For maximum benefit for the work environment, research ought to prioritise lung/inhalation exposure.

4.11.5 Pharmaceuticals

There is a general lack of knowledge as regards the reproductive and developmental toxicity of pharmaceuticals and a lack of data for risk assessments of pharmaceutical agents in the work environment. For these agents, specific regulations apply regarding toxicological testing. Depending on the regulation in force at the time of marketing, many pharmaceuticals will have been tested for reproductive and developmental toxicity (i.e. animal test data are available in principle). They are, however, not easily accessible to risk assessors. One way to bypass lack of data for pharmaceuticals is therefore to open access to pharmaceutical toxicological data as well as to data for in vivo toxicity for the risk assessment processes of chemicals that may result in workplace exposures (for example through the pharmacovigilance system) (Gould *et al.*, 2013).

Pharmaceutical exposures in the workplace are regulated within the general framework of worker protection, although they do not form part of REACH. Pharmaceuticals do not, therefore, undergo mandatory labelling as other chemicals do, nor are they necessarily supplied with a safety data sheet, although pharmaceutical information is available for therapeutic use. Risks may therefore be difficult to identify for these exposures.

Given the fact that health professions are on the increase, there is an urgent need to address these issues in order to raise awareness among workers in the sector, and to organise health and safety protection for them. Many of them may also be subject to other conditions that increase their potential higher exposure, for example when working shifts or at patient's homes.

4.11.6 Multiple exposures are the norm

A significant problem, along with the identification of hazards and interpretation of data, may be the fact that mixtures of chemicals are more often used in industrial processes than single chemical substances. For mixtures, there is a possibility of chemical substances interacting with each other, and such mixtures can produce an effect different from those of each separate substance. This is rarely addressed.

Occupational exposures such as shift work, ergonomic factors, psychosocial strain (stress) and noise can also interact with these effects and may, for example, have an effect on the uptake of substances or on metabolisation and elimination. Very few combinations have been explored, but a few are presented in the report and briefly in this summary.

5 Reprotoxic risks: non-chemical factors

5.1 Biological agents

'Biological agent' is a term used to describe micro-organisms that can cause illness or injury to human health. Biological agents include bacteria, viruses, chlamydia, fungi and parasites (or parts thereof or products they generate), and their metabolites, parasitic worms and plants. They can enter the body by inhalation, ingestion or absorption through the skin, eyes, mucous membranes or wounds (bites from animals, needle injuries, etc.) (EU-OSHA, 2010).

Some biological agents may have the potential to cause ill health and are classified, according to their infection risk level in Directive 90/679/EC, into four risk groups.

Workers can be exposed to biological agents either directly, through working with them (e.g. in a research laboratory), or indirectly (e.g. healthcare workers, farmers, workers in waste-sorting plants) (EU-OSHA, 2010). Infectious agents may impair fertility (in men and women) or cause adverse effects during pregnancy. Examples of exposures associated with increased risk of birth defects include exposures to infectious agents, such as cytomegalovirus, rubella (German measles) and toxoplasmosis, which may also be workplace hazards for healthcare workers, teachers, childcare workers or animal workers (Drozdowsky and Whittaker, 1999).

Biological agents that adversely affect reproduction include bacteria, viruses and fungi. Some of these are sexually transmitted and not relevant for workplaces, but others can be associated with occupations. Table 2 lists the most relevant infections associated with occupations.

Table 2: Biological agents that present reproductive hazards to workers

Agent	Observed effect	Potentially exposed workers
Cytomegalovirus	Birth defects, low birth weight, developmental disorders	Healthcare workers, workers in contact with infants and children
Hepatitis B virus	Low birth weight	Healthcare workers, social workers, police, emergency workers, tattooists, body piercers
Human immunodeficiency virus	Low birth weight, childhood cancer	Healthcare workers, social workers, emergency workers, tattooists, body piercers
Human parvovirus B19	Miscarriage	Healthcare workers, workers in contact with infants and children
Rubella (German measles)	Birth defects, low birth weight	Healthcare workers, workers in contact with infants and children
Toxoplasmosis	Miscarriage, birth defects, Developmental disorders	Animal care workers, veterinarians, cattery workers, street cleaners and park cleaners (grounds maintenance staff)

Agent	Observed effect	Potentially exposed workers
Varicella-zoster virus (chickenpox)	Birth defects, low birth weight	Healthcare workers, workers in contact with infants and children
Brucella	Miscarriage	Slaughterhouse workers, veterinarians, hunters, laboratory workers, long-distance transport drivers and workers who travel into endemic areas
Epstein–Barr virus	May be related to testicular cancer in the offspring	Dentists, healthcare workers
Mumps virus	Sterility (men), miscarriage	Teachers, childcare workers, healthcare workers, social workers
Coxiella burnetii (Q fever)	Premature birth, foetal or newborn death	Farmers, laboratory workers, sheep and dairy workers, veterinarians
Coxsackie virus	Meningitis, sepsis	Teachers, childcare workers, healthcare workers
Group B streptococcus	Meningitis, sepsis	Healthcare workers
Listeriosis	Miscarriage or stillbirth, low birth weight baby	Laboratory workers, health care workers

Source: Compiled by the authors (taken from (NIOSH, 1999) and supplemented).

Infections can be transmitted in different ways. Exposure can be through:

- ingestion when eating and drinking contaminated food products;
- contact with contaminated material (e.g. hands, surfaces and body fluids);
- inhalation when breathing in contaminated air (droplets);
- percutaneous inoculation (needle and syringe, cuts or abrasions from contaminated items and animal bites).

Some professions are at particular risk of developing work-related infections, because the workers are exposed to persons with a higher prevalence of infectious diseases or to infectious animals or materials. Examples of occupations associated with a risk of infectious diseases are:

- health care, with direct patient contact;
- social workers, nursing homes, schools, childcare and prisons;
- emergency services (ambulance/fire/police/rescue) and first aid;
- laboratory work, with exposure to infective material or production of biological materials;
- working with animals or animal products (risk of zoonotic infections);
- refuse collection or sewage plants;
- ground-breaking or earthmoving;
- local authority services (street cleaning, park maintenance, refuse disposal, public lavatory maintenance);
- hairdressing and beautician, tattooing, ear and body piercing;
- work that requires travelling, including into areas of endemic disease (an area currently listed as high risk for Brucellosis is, among others, the Mediterranean Basin (transport, offshore work, etc.)) (CDC, 2012, US Office of Technological Assessment, 1985).

Healthcare personnel are particularly exposed to infectious agents that may produce 'teratogenic effects in their offspring, be passed to and infect their offspring' or induce abortion. Biological agents of particular relevance regarding reproduction are rubella, cytomegalovirus and hepatitis B. Some infectious agents may also infect and impair male reproductive function (e.g. mumps, orchitis) (Office of Technological Assessment, 1985).

5.2 Physical factors

5.2.1 Radiation

There is the potential for higher exposure to ionising radiation for dentists and dental assistants, medical/technical radiography personnel, nuclear medicine specialists and radiologists, laboratory workers handling radioisotopes, specialised researchers, nuclear power plant personnel and manufacturers of products such as luminous dials and fire alarms. Other jobs potentially affected by radiation exposure are quality controllers (e.g. pipe maintenance), manufacturers of sterilised (medical) products, maintenance workers, and workers involved in cleaning and waste management. The adverse effects of ionising radiation exposure on the father, mother or developing foetus are related to the amount of energy delivered to target tissues. Cell death, mutations in DNA or chromosomal damage may result from exposure and can lead to cancer. Safe occupational exposure thresholds cannot be established, and exposure limits have been promulgated to reduce the likelihood of cancer (Suruda, 1998).

The European Euratom Directive (European Council, 1996) defines the following dose limits for workers exposed to ionising radiation:

- effective dose of 100 mSv over a period of five consecutive years, must not exceed 50 mSv in one year;
- young workers (under 18 years) may not be exposed to ionising radiation at work;
- pregnant women and breastfeeding mothers may not be assigned to work involving a significant risk of bodily radioactive contamination as soon as they inform the company of their condition;
- effective dose of 6 mSv/year for apprentices and students aged between 16 and 18 years, who, in the course of their studies, are obliged to use ionising radiation sources;
- for air crew who may be subjected to more than 1 mSv annually, special measures apply, among which are the conditions that, for pregnant women, there must be a guarantee that the foetus will not receive a dose that exceeds 1 mSv during the remainder of the pregnancy.

5.2.2 Electric shock and lightning strikes

Researchers have described several foetal effects for pregnant women who experienced electric shocks and recommended that any work that could expose a pregnant woman to electric shock must be avoided. If an electric shock occurs, the foetal status should be checked immediately (Peters *et al*., 2007).

5.2.3 Electromagnetic fields

Higher exposure to electromagnetic fields (EMFs) may occur for welders, electricians, electric train operators and magnetic resonance imaging machine operators, and for workers in electroplating companies, aluminium refineries and relay stations. Research on reproductive outcomes has concentrated mainly on visual display terminal use. According to Kay, there is no conclusive evidence that exposure leads to any related problems for male or female workers (Kay, 1998). This also holds true for physiotherapists, who are exposed to shortwave and microwave diathermy. In one study, Cromie and colleagues concluded that physiotherapists are unlikely to have an increased risk of negative reproductive outcomes as a result of their exposure to electrophysical agents (Cromie *et al*., 2002). However, avoiding strong magnetic fields is advised, and the International Commission on Non-Ionising Radiation Protection has recommended exposure limits (Kay, 1998), as outlined in Table 3.

Table 3: Exposure limits to electromagnetic fields

Occupational exposure	Electric field	Magnetic field
Whole working day	10 kV/m	5,000 mG
Short term	30 kV/m	50,000 mG

Source: Kay, 1998.

In order to minimise exposure, the following measures are recommended (Kay, 1998):

- find out where major EMF sources are located in the work area;
- increase the distance between worker and EMF source;
- reduce the time spent near EMF sources;
- use equipment with low EMF emissions.

Jensen and colleagues concluded in 2006 that occupational and environmental exposure, and toxicants such as heat and ionising radiation, have known or suspected deleterious effects on male reproductive function, strongly supported by well-designed epidemiological studies. However, they recognise that the low-frequency electromagnetic radiation to which welders are exposed is not a likely cause of negative effects (Jensen *et al*., 2006).

In a more recent review paper, Peters and colleagues recommended that pregnant women may continue working with visual display terminals. However, ergonomic conditions, working hours and work-related stress should be carefully considered (Peters *et al*., 2007). The authors proposed similar recommendations for mobile phone use and for working with other sources of electromagnetic radiation.

5.2.4 Noise

Some scientists believe that intensive noise exposure should be considered a possible risk factor for prematurity and low birth weight. There is biological and epidemiological evidence to suggest that sound exposure above 85 dBA may be hazardous in late pregnancy. This level coincides with the mandatory OEL for all workers (Greenberg *et al*., 1998).

Hougaard and Lund reviewed several studies and concluded that low-frequency noise (< 500 Hz) reaches the foetus almost unhindered, whereas maternal tissues and fluids surrounding the foetus reduce the noise of higher frequencies. The noise environment in the womb is therefore dominated by low-frequency sounds. Animal studies with sheep likely to be relevant for humans have shown that intense sound pressure levels can damage the foetal hearing organ and cause hearing loss in offspring. These results are summarised below.

A few studies have focused on exposure to noise at work during pregnancy and children's hearing after birth. The studies reported a correlation between exposure of the pregnant woman to noise > 85 dB and hearing impairment in children. The quality of the studies is not optimal, but, the results from these human studies are consistent with findings in animals. They therefore support the hypothesis that foetal hearing may be damaged by loud noises in the environment. Furthermore, results from several animal species also indicate that the hearing organ may exhibit an increased sensitivity to noise during development compared with the fully developed organ. Therefore, the foetal hearing organ may be harmed by noise at lower levels than that of an adult. It is also important to note that, in humans, the hearing organ develops during the latter half of pregnancy (Hougaard and Lund, 2004). Hearing protection for the mother cannot prevent damage to foetal hearing, so engineering or organisational controls are needed.

In the same review, the authors noted that indirect effects of noise exposure during pregnancy are assumed to arise as a result of noise-induced maternal stress. The susceptibility of human pregnancy

to noise exposure in the work environment has been examined in several epidemiological studies. The examined endpoints include miscarriage, premature birth, reduced birth weight and birth defects. Although some studies have methodological limitations, the results indicate that noise in the working environment of around 85 dBA Leq (8 h) can negatively affect birth weight.

5.2.5 Ultrasound

Significant gonadal or foetal exposure to diagnostic ultrasound is unlikely if the worker's trunk is not in contact with a conducting medium. However, ultrasonic devices may generate adverse effects at very high intensity and it is, therefore, important to follow safety guidelines when using such devices (e.g. in the healthcare sector) (Greenberg *et al*., 1998).

5.2.6 Vibration

Data on the relationship between vibration and reproductive outcomes are limited. However, occupational vibration exposure should be limited for all workers according to regulations, regardless of whether or not they are of reproductive age. For pregnant workers, whole body vibration is to be avoided, especially at the resonance frequency of the spine and uterus (Greenberg *et al*., 1998).

5.2.7 Cold

According to some studies, there seem to be no adverse effects for males, non-pregnant females and pregnant females. However, these findings do not exclude the possibility of adverse effects if a mother suffers hypothermia during middle and late pregnancy. Therefore, prevention of cold exposure should follow the relevant good work practices (Mitchell and DeHart, 1998).

5.2.8 Heat

Very high temperatures over longer periods may cause teratogenic effects. Extreme core temperature elevations should be avoided for both sexes (Mitchell and DeHart, 1998).

Heat is a potential contributor to male infertility. In a questionnaire study conducted by De Fleurian *et al*., excess heat and extended sitting periods were associated with impaired sperm motility (De Fleurian *et al.*, 2009). Some professions involve high outdoor temperatures and prolonged sitting, e.g. agriculture. Summer heat may affect sperm count, motility and sperm morphology (Levine *et al*., 1990). The incidence of pathospermia was investigated as early as the 1970s among occupational drivers compared with other professionals and it has been found to increase in proportion to the number of years of driving. The deterioration of spermiogenesis was mild among car drivers, but was severe in agricultural/industrial hard machinery and farm equipment drivers. There was a higher incidence of impaired fertility in drivers than in other professionals (Sas and Szöllösi, 1979).

5.2.9 Working hours and shifts

Long working hours and shift work can affect reproduction, although the mechanisms are poorly understood (Hage, 1998a). Hage pragmatically suggested that recommendations on work duration, intensity and shift patterns for pregnant workers should be made carefully on a case-by-case basis (Hage, 1998a).

Working in changing and irregular periods is generally assumed to have a negative influence on the body's natural circadian rhythm, sleep and health. Most of the body's biological functions, such as heart rate, temperature and hormone regulation, vary in accordance with certain patterns during the day. The human circadian rhythm is controlled by the 'internal biological clock' in combination with 'external time givers' such as night/day, work and social life. The body's biological clock will seek to adapt to the external time givers after displacement during working hours (Danish Labour Inspection, 2003). Shift

work results in the disruption of normal circadian rhythms and thus changes to the normal hormone balance (Reinberg and Smolensky, 1992).

Shift workers have a high incidence of symptoms such as irritability, restlessness, anxiety and nervousness, and they are more tired and lack energy (Danish Labour Inspection, 2003). These are very similar to the classic symptoms of stress, and, as such, can affect the course of pregnancy. Desynchronisation of the body's biological rhythms may also affect reproduction and pregnancy. Shift work affects the body's sex hormones, which may potentially affect fertility (Zhu *et al*., 2003). Direct effects on foetal development during pregnancy can occur in two ways: firstly, the desynchronisation of the mother's biological rhythms can affect the foetus's own ability to synchronise the body's biological rhythms; and, secondly, the synchronisation of the mother's biological rhythms blurs the essential time markers in otherwise strictly coordinated developmental processes (Hougaard, 2003).

The significance of shift work has primarily been investigated for infertility, spontaneous abortion, premature birth and reduced birth weight in relation to the time of birth ('small for gestational age'). In a meta-analysis of results from six studies involving a total of almost 10,000 pregnant women, statistically significant associations between shift/night work and premature birth were found. The authors concluded that there is only a low risk of preterm delivery, low birth weight or babies being 'small for gestational age'. Little evidence was found on pre-eclampsia (hypertension in pregnancy) (Bonzini *et al*., 2011).

On the other hand, although the risk of workplace factors causing premature birth may seem low, premature birth in general is difficult to prevent. Therefore, factors in the work environment are important because they can be changed, therefore reducing the incidence of this pregnancy complication. Following a meta-analysis based on 160,988 women in 29 studies to evaluate the association of physically demanding work, prolonged standing, long working hours, shift work, and cumulative work fatigue score with preterm birth, Mozurkewich et al. calculated that, in prevention terms, one premature birth can be prevented for every 23-171 pregnant women who abstain from shift work or night work during pregnancy (Mozurkewich *et al*., 2000). Several studies suggest that it is primarily fixed night-time work that poses a problem for pregnant women.

It should be noted that in some European countries expectant or breastfeeding mothers are prohibited from shift work or working overtime, whereas in other countries (e.g. the United Kingdom) this is allowed; however, if a specific work risk has been identified or a medical certificate is produced, the employer must offer suitable alternatives to the woman, and if that is not possible, must suspend her from work on paid leave.

5.2.10 Ergonomic exposure

A 1997 review of six studies investigating the reproductive health of cleaners identified an increased risk of spontaneous abortion, preterm delivery, low-weight babies and high blood pressure during pregnancy in cleaners. The risk factors identified were prolonged standing, carrying heavy loads and high abdominal pressure from bending and stooping. One of the studies reviewed also found an association between low reproductive capacity (fecundity) and heavy cleaning work in combination with unfavourable working hours (Krüger *et al*., 1997).

There are few data on the effects on males and females; the available data mainly relate to pregnant women. The evidence of adverse effects is mixed. Nesbitt discusses the effects of ergonomic exposure on workers, subdividing this aspect into heavy work, lifting/pushing/pulling/bending, prolonged standing, prolonged sitting and repetitive upper-extremity use in pregnancy (Nesbitt, 1998). There is clear evidence that heavy lifting during pregnancy can lead to spontaneous abortion, whereas studies on the effects of prolonged standing show some degree of correlation. According to Nesbitt, prolonged standing probably has the most significant effect on pregnancy of any single ergonomic risk factor. A more recent study focused on daycare workers (Riipinen *et al*., 2010).

Hjollund and colleagues suggest that heavy lifting at the time of implantation can be a factor for increased risk of subsequent spontaneous abortion (Hjollund *et al*., 2000b). They urged further research to determine whether or not this represents a problem in the working environment. In any case, they regard the issue as serious, because the described effect takes place at a time when a worker is unable to know that she is pregnant and therefore unable to observe precautions.

Du Plessis and Agarwal published a review article in 2011, noting that prolonged sitting, whether for office workers or drivers, leads to increased scrotal temperature, reduced semen quality and increased time to conceive (Du Plessis and Agarwal, 2011).

Workers who ride a bicycle as part of their job may be at risk for genital numbness or more serious sexual and/or reproductive health problems from pressure in the groin (perineum) from the traditional bicycle saddle. NIOSH researchers have investigated potential health effects of prolonged bicycling in police bicycle patrol units, including the possibility that some bicycle saddles exert excessive pressure on the urogenital area of cyclists, restricting blood flow to the genitals, and resulting in adverse effects on sexual function. NIOSH studies have also demonstrated the effectiveness of no-nose bicycle saddles in mitigating these effects. While most workers in jobs that involve bicycling are men, recent evidence suggests that no-nose bicycle saddles may also benefit women (NIOSH, 2009).

5.3 Psychosocial factors

Stress can be caused by a variety of factors, such as an abusive environment and high demands. It can be defined in several ways. The Karasek model hypothesises that the highest level of stress is found in jobs characterised by high demands in combination with low control (Karasek and Theorell, 1990). Another model, which may be more relevant to female workers, developed by Johannes Siegrist in the early 1990s, assumes that an imbalance between the effort expended at work and rewards received can result in a stress response. Stress in pregnant women is thought to affect unborn children via changes in maternal physiology or via behaviour. Stressed people produce more stress hormones, and stress modifies the pregnant woman's hormonal environment. Stress hormones may be transmitted from mother to foetus, and the cortisol-like hormones affect development. Stress hormones also affect physiology, and stress reduces blood flow to the placenta. This may have implications for the exchange of nutrients between mother and foetus and, hence, foetal well-being. The mother's immune system is also sensitive to stress, and increased susceptibility to infections may also have negative consequences for the foetus (Wergeland *et al*., 1996; Hougaard, 2004).

The **effect of stress on male reproductive function has been under-studied**. In a Polish study, work-related stress was assessed by the Subjective Work Characteristics Questionnaire and was found to **affect some semen parameters** (Jurewicz, *et al*., 2010). Stressful life events have also been shown to interfere with semen quality (Gollenberg *et al*., 2010). Both studies were cross-sectional (i.e. they assessed exposure and effect at the same time). This makes it difficult to infer cause and effect. Two Danish pre-studies collected data on stress before the start of the main studies, and investigated occupational and general stress with regard to several male reproductive parameters, including time to conceive. The authors concluded that the effects of stress on semen quality are small or non-existent (Hjollund *et al*., 2004a; Hjollund *et al*., 2004b).

Female fertility has also been under-studied in relation to stress at work, or in general. One well-planned study did not find an overall increase in the risk of prolonged conception time. However, when only couples without suspected reduced fertility were included, **women with high-strain jobs conceived at a slower pace**. General psychological distress was found to influence time taken to conceive among women with the longest menstrual cycles (Hjollund *et al*., 1999). The menstrual cycle was not found to change considerably as a result of general stress (Sanders and Bruce, 1999). Finally, information may also be retrieved from studies of the influence of stress on *in vitro* fertilisation. Several studies offered no indication that emotional distress or stressful life events compromised the chances of conceiving (Boivin *et al*., 2011).

Although results from studies during preconception and conception do not provide a clear picture, results from studies in both humans and experimental animals provide evidence that stress during pregnancy may affect foetal development, with undesired consequences for the pregnancy, as well as for the child after birth. Well-conducted epidemiological studies provide reasonable grounds for assuming that prenatal stress can affect birth weight negatively. Stress during pregnancy has also been associated with increased risks of stillbirth and premature birth (Lobel, 1994; Paarlberg *et al*., 1995; Wisborg *et al*., 2008). Generally, there is good evidence that moderate prenatal stress is associated with changes in behaviour and cognitive function in children (Talge *et al*., 2007).

In another study, stress at work was moderately associated with **preterm delivery and low birth weight.** Furthermore, although job strain alone was often not associated with spontaneous abortion, there were some indications of an interaction between an adverse psychosocial environment and other risk factors (e.g. smoking, older age at pregnancy, etc.) (Mutambudzi *et al*., 2011). It is, therefore, plausible that psychosocial stress at work can affect pregnancy and development.

To further determine whether or not stress at work affects reproductive endpoints, sound epidemiological studies need to be conducted. Many epidemiological studies apply unclear measures of stress and periods of exposure, and collect information after the children are born. The latter factor, in particular, increases the risk of bias. Most investigated endpoints are relatively close to pregnancy (e.g. abortion, preterm birth and foetal growth). These may, however, not be the most sensitive endpoints (Mutambudzi *et al*., 2011). Sensitive endpoints could be, for example, the nervous system function of the child. Gulati and Ray demand a fresh approach that considers the stress pathways that are activated by particular stressors, to determine how these pathways affect the secretion and actions of various hormones and neuromodulators (Gulati and Ray, 2011).

6 Combined exposure

In occupational settings, workers may be exposed to not only single agents, but also to any combination of agents. Workers may also be exposed through different routes simultaneously (e.g. inhalation and dermal absorption or ingestion). Common combinations include solvent mixtures, noise and ototoxic substances, pesticides mixtures, cleaners and disinfectants, any agents/substances (including biological agents) occurring in health care, nanomaterials occurring in a large variety of technical products (paints, glues, cleaners, health care), welding fumes in combination with radiation, noise, heat and awkward postures, and, finally, stress.

This is a large field, with many methodological challenges, and so far there have been very few reviews or studies. The following paragraphs give a short overview of what has been analysed so far.

Some consideration was already given to mixtures of chemicals, such as endocrine disruptors, in Chapter 3.

6.1 Solvent mixtures

The studies mentioned above have established a significant correlation between spontaneous abortion and time to pregnancy and occupational exposure to organic solvent mixtures. Furthermore, a study showed that shift workers were significantly more likely to suffer spontaneous abortion than non-shift workers. A **synergistic effect** on spontaneous abortion was identified **between shift working and occupational exposure to organic solvent mixtures** (Attarchi *et al*., 2012).

Vulimiri and colleagues noted, in a 2012 review article on specific single solvents and gases,that most exposure comes from complex mixtures of substances. They conclude that it is important to gather more information on both individual chemicals and mixtures of chemicals (Vulimiri *et al*., 2012).

Lawson and colleagues mention a study (Brown-Woodman *et al*., 1994) that detected additive adverse reproductive effects from solvent mixtures (Lawson *et al*., 2006).

6.2 Stress and chemicals

Both stress and chemicals can affect foetal development. What happens if both types of effects occur simultaneously during pregnancy has not been investigated in epidemiological studies. A review of nearly 40 animal studies showed that stress can increase the effects of chemical exposure when the chemical exposure is so high that it in itself induced effects in the offspring, or the mother was strongly affected (Hougaard, 2005, 2010). The number of studies is, however, limited, and most used very high doses of chemicals (Rider *et al*., 2009; Taskinen *et al*., 1999).

6.3 Chemicals and prolonged sitting

A study in 2009 on the effects of working postures, in association with exposure to traffic pollutants, on male motorway workers concluded that there is a possible interaction between chemical exposure and a prolonged seated position at work. Those workers who were exposed to the fuel combustion gas nitrogen dioxide had a significantly lower sperm total motility than unexposed workers, and the same effect was observed in workers with a forced seated working posture. The effects were especially strong when chemical and postural risk factors were associated (Boggia *et al*., 2009).

6.4 Management and prevention

Researchers have concluded that 'interpreting available information on additive and synergistic effects of exposures remains a challenge for employers, especially small businesses' (Lawson *et al*., 2006). Studies should consider combinations of risk factors that occur in workplace settings. Where there are some OELs in place for combinations of chemicals, for example, mixture effects can be considered; for example applying SCOEL's guideline on risk assessments for exposure to mixtures of chemical substances which may have similar modes (mechanisms) of action (IGHRC, undated).

7 Prevention

The main report outlines the guiding principles of prevention: sound OSH management and a comprehensive programme of risk assessment. It explains the hierarchy of measures, stressing the importance of elimination and substitution and the importance of carefully examining the choice of prevention measures (e.g. noise protection for pregnant women will not protect the foetus). Training has an important role, as it can be a personal measure (e.g. introducing and practising ergonomic postures) or a collective, company-wide measure (e.g. introducing a new exhaust system would require training to ensure its correct handling). The report presents an overview table of all types of measures, covering chemicals, non-chemicals, emerging factors and psychosocial conditions, as well as combined exposures, in which examples for each measure are given and tools and guidelines are referred to. A few examples from Member States are also presented.

7.1 Member State examples

A range of approaches is found across the EU, with Austria, the Czech Republic, Germany, Finland, France and the Netherlands having included reprotoxic substances in their national legislation at the same level as carcinogens and mutagens when implementing Directive 2004/37/EC. A further 18 Member States cover only carcinogens and mutagens. Two countries cover only some reprotoxic substances (category 1A and 1B) (Milieu and RPA, 2013).

The following sections provide some interesting examples of policy initiatives at Member State level, but are not exhaustive.

7.1.1 Austria

The foetus is particularly sensitive to chemically induced malformations during the first weeks of pregnancy, when a female pregnant worker might not realise that she is pregnant. The current legislation therefore leaves a prevention gap, which was defined here as the 'early pregnancy gap'. The guideline published by the European Commission for the implementation of the Pregnant Workers Directive mentions this problem without providing a satisfactory solution. Austria has partly addressed this situation: employers must undertake a related risk assessment as part of the overall risk assessment regardless of a pregnancy as soon as they employ a female worker, which means that they can apply a predefined policy without delay if a pregnancy occurs and then tailor measures specifically for the pregnant worker in question. Similar approaches apply to risk assessment for young workers where Austria applies a protective approach foreseeing prohibitions of some tasks and exposures, with the

exception of workers who are in vocational training and need to perform these tasks in the frame of apprenticeship for example.

This approach can be considered as an important step towards a proactive approach that would take account of reproductive risks for both genders and that would have to be applied when considering counselling of workers who wish to have children. This example could be followed in other Member States, and considerations regarding reproductive risks introduced into principles of health surveillance and the activities of occupational physicians at workplaces.

7.1.2 Denmark

In Denmark, more than 30 % of all house painters are female. To enable female painters to work during pregnancy without excessive risk to the unborn child, the Danish Painters' Occupational Health Service has evaluated all products used with a view of identifying chemicals of concern. Together with Occupational Health Clinics, they prepared criteria for classifying paints into three risk classes, to indicate whether or not the pregnant painters can use the paints. The evaluation considers the extent of exposure to the chemical substances during work with water-based paints and the risk of reproductive damage. Before working with epoxy resins and isocyanates, Danish chemicals law stipulates that workers must complete special training, developed by social organisations and approved by the labour inspectorate. Denmark has also established very specific guidelines on ergonomics for pregnant women.

This national example highlights the need for avoiding preconceptions about who is exposed in specific tasks and occupations and for taking into account the specific needs of vulnerable groups and both genders when carrying out risk assessment for reproductive and developmental risks. Ergonomic considerations would also have to be taken into account for young workers at these workplaces.

7.1.3 Germany

The Federal Committee on Hazardous Substances (Ausschuss für Gefahrstoffe) has issued several technical rules (equivalent to codes of practice) approved by the Ministry of Labour and Social Affairs that provide guidance on how to fulfil the obligations of the law. These rules give clear guidance to companies on specific exposures and occupations. The report presents the rules relating to reprotoxic substances in a table. Some are also available in English and one is available in French. The rule on substitution is noteworthy: it explains in detail all necessary steps that a company must take in order to identify a workable solution.

The technical rules do not yet cover nanomaterials, but they do include substances with reprotoxic effects. They allow companies to make risk assessments and establish preventive measures that consider these substances. There is, so far, however, no rule or comprehensive guidance available for companies looking into the issue of reprotoxicity as a whole.

7.1.4 Finland

Finland has had a list of reprotoxic substances in its national legislation since the 1980s and legislation on special maternity leave was passed in 1991. In accordance with the Occupational Safety and Health Act, an employer is obliged to observe the impacts and risks of occupational conditions on reproductivity. In four sections, reproductive health risks are explicitly addressed.

State Council and Ministry of Labour resolutions address both male and female workers, covering reprotoxic factors that are chemical (e.g. ethylene oxide, manganese), biological (e.g. herpes viruses, listeria bacteria) and physical (e.g. ionising radiation). Further guidance has been published by the Finnish Institute for Occupational Health (FIOH). FIOH and the Nordic Institute for Advanced Training in Occupational Health also provide training courses for relevant target groups.

The Social Security Institution in Finland compiles annual statistics on workers who were granted special maternity leave because of exposure to workplace reprotoxins. In recent years, approximately 200

female workers annually have been granted special maternity leave owing to chemical, biological and physical hazards. However, women are increasingly involved in physically demanding jobs, but special maternity leave is granted mainly for other reasons (biological or chemical) because legislation does not explicitly allow leave for physically demanding jobs (EU-OSHA, 2014).

The national report on the state of OSH listed the five most important reprotoxicants as follows: solvents, viruses, lead, ionising radiation and night-shift work. Given that they are reprotoxic to both males and females, ethoxyethanol, ethoxyethyl acetate, methoxyethanol and methoxyethyl acetate have been largely voluntarily replaced in industry with safer alternatives.

7.1.5 France

Following the 2001 implementation of legislation regarding CMR substances, initiatives in France have developed campaigns (e.g. a labour inspection campaign), guidelines, awareness-raising tools, voluntary agreements and a web-based substitution platform.

Conventions were set up between the Ministry of Labour and three industrial federations: metallurgy, chemistry and paints/inks/adhesives. The industrial federations took steps to ensure better implementation of legislation on workers' exposure to CMRs. These steps include the dissemination of information and training, mainly targeted at SMEs. Most federations renewed the conventions in 2011.

In 2006, ANSES was asked by the French Ministry of Labour to carry out a study on the effectiveness of substitution of chemicals classified as CMR category 1A and 1B (EU classification), and to develop a tool to promote substitution (see http://www.substitution-cmr.fr/). The information available in the portal has been mainly collected through two surveys among companies on the use of CMR and their substitutions, initiated in 2008 (23 priority CMR substances) and 2009 (56 CMR substances). The database is now permanently enriched with examples from different sources.

8 Conclusions and recommendations

The report presents the state-of-the-art OSH research in the field of reprotoxicity. However, identification of all possible reproductive and developmental issues potentially affected by the workplace environment was outside the scope of this report. Instead, examples of the characteristic types of chemicals and other exposures that affect men and women at work are described. This is followed by the identification of typical issues that deserve attention from those involved in improving the work environment so that it is healthy not only for workers themselves, but also for their progeny. Some issues are of a general nature, whereas others primarily relate to specific exposures.

Worker exposure to reprotoxic agents and factors, such as epoxides, isocyanates, solvent mixtures, paints, specific pharmaceuticals, EDCs, nanomaterials, physical agents and stress, are expected to increase over time. This is related to a number of trends in the world of work, including the use of more complex mixtures of chemicals and other agents, and the increased use of plastics and composite materials owing to energy saving and faster production cycles. Workers are also increasingly changing their place of work and their professions, having long commutes to workplaces and short contracts, all of which makes monitoring of their exposures more difficult and complex, as their exposures also frequently change. Although the shift in employment from industrial and manufacturing sectors to the service sector may be associated with a reduction in exposure to some occupational risks, the comparative lack of awareness in the service sector regarding workplace risks and especially those related to dangerous substances, is a concern.

The findings of research presented in the main report clearly reveal that the challenge of reprotoxic factors in the workplace is underestimated. This is the case with exposure to suspected endocrine disrupters has been underestimated, mainly because the majority of chemicals interfere to some degree with hormonal regulation. In addition, particulate exposures are common in the work setting and little regulated, except through crude occupational exposure limits.

The debate over whether or not to introduce reprotoxicants into the Carcinogens and Mutagens Directive has not yet been resolved, owing to differing points of view and the limited availability of supporting data. However, there is agreement that awareness raising and specific guidance are urgently needed.

Although a significant part of the workforce is exposed to workplace risks to reproductivity, many of the adverse factors are under-researched or not considered important. This issue deserves attention as reprotoxicity has an impact on the immediate and long-term future of society.

Increasing awareness is needed at all societal levels so that rather than being seen as a disruption to business, pregnancies are recognised for their importance to society, including as the basis for a sustainable labour force. Furthermore, not improving the work environment to accommodate safe working conditions for reproductive and gestational health, whether by subconscious psychosocial pressure or by various agents and factors, will undermine the future of the companies and, eventually, society as a whole.

8.1 Legal frame

8.1.1 Women and chemicals focus

Legislation on reprotoxicity focuses mainly on women, in particular pregnant and breastfeeding women, but it should not overlook the fact that the substances, agents, factors and conditions toxic to reproduction may affect the reproductive health of both sexes. Current law also protects, to a certain extent, young male (and female) workers, but the male reproductive age is considered to range, on average, from 15 to 60 years old. It is therefore important to review the legislation and its implementation to ensure equal protection for women and men, including those who plan to have children.

As there are no specific regulations for couples wishing to conceive, existing policy in fact ignores that men and women might be exposed to reproductive toxicants while attempting to conceive, as well as the time lapse from conception to awareness of pregnancy. One of the main conclusions from the assessment of existing legislation is therefore that legislation and guidance should focus on a comprehensive risk assessment and risk management approach that covers both sexes, all developmental stages, long-term effects and all risk factors (including physical, biological and psychosocial factors).

Another important consideration is that women may work in stereotypically ‘male occupations’, meaning that assumptions on which gender may be exposed to particular risk factors should therefore be avoided. Not all welders or painters are male, and not all horticulture and agricultural workers are female, for example. There are increasing numbers of female public transport drivers exposed to diesel exhaust fumes. In addition, exposure may vary, for example, pesticide exposure may vary over time for agricultural or greenhouse workers; this needs to be considered. One example presented in the report is that of female painters in Denmark, that is, 30 % of all painters in Denmark, and the specific measures designed to protect them from harm.

Legislation is also very much focused on chemical substances, but it barely addresses other reproductive factors such as physical, biological and psychosocial risks specifically. However, even in chemicals-related legislation, specific aspects, such as the non-monotonic and potentially multiplicative effects of endocrine disrupters or the particular aspects linked to fine particle toxicology would need to be addressed. These properties of the substances in question challenge the current legislative approaches such as the setting of occupational limit values or the definition of risk management measures based on DNELs, which are based on the assumption that there is a linear relationship between the level of exposure and the effect. The inclusion of reprotoxicants into the Directive on the Protection of Workers from Risks Related to Exposure to Carcinogens or Mutagens at Work has been proposed, in order that they are included in stricter national worker protection legislation. This would the hierarchy of control measures, starting with substitution, and draw attention to the nature of risks to workers, as well as obliging employers to take specific action when using such substances.

Because of the many knowledge gaps, the need to take a precautionary approach has to be highlighted. A positive example is Council Directive 92/85/EEC which recognises a broad range of chemical, physical and biological agents, work processes and working conditions that could present a risk for new and expectant mothers. In 1992, the European Commission has published guidance to support the

implementation of the directive, but the directive and related guidance are widely regarded as needing an update.

8.1.2 Wider impact of changes on the Pregnant Workers Directive

A European Commission report of 15 March 1999 on the implementation of the Directive (European Commission, 1999) highlighted specific problems with implementation that led to infringement proceedings, e.g. the outright ban by several Member States on night work for pregnant workers and the lack of any compulsory maternity leave, which are now resolved. The report identified other areas of concern, such as differences over which type of workers fell within the scope of the directive, the difficulty in squaring health and safety considerations with women's entitlement to non-discriminatory treatment, and the right to return to their job.

The Directive grants maternity leave, and stipulates that women must not be dismissed from work because of their pregnancy and maternity leave for the period from the beginning of their pregnancy to the end of the period of leave from work. An initiative to amend the directive (European Commission, 2008) was dismissed in 2015. It proposed to extend maternity leave, to grant additional leave in the event of premature childbirth, children hospitalised at birth, the birth of children with disabilities and multiple births. On returning to work, workers could also have requested a re-examination of their working hours in order to better reconcile professional and family life.

The tendency to make greater use of temporary contracts undermines the protection of pregnant women against dismissal. These contracts may terminate employment regardless of pregnancy, thus rendering important aspects of maternity law inapplicable. This also promotes the tendency among women workers not to report their pregnancy until it becomes apparent to employers and co-workers, thereby hindering effective risk prevention.

Although the Directive is exemplary in considering many factors (chemical agents, and biological, physical and psychosocial factors), it does not cover males and females of reproductive age. The directive also leaves out the 'early pregnancy gap', the time a woman may not yet be aware that she is pregnant, during which the provisions of the directive may not be applied. This can be a crucial period for the foetus.

8.1.3 The early pregnancy gap

As noted above, the foetus is particularly sensitive to chemical induction of malformations during the first 3-8 weeks of pregnancy, when the organs are formed. To prevent malformations, preventive measures are of crucial importance. However, during the initial 4-6 weeks of pregnancy, a woman might not realise that she is pregnant, and she is therefore unable to inform her employer of her condition, in which case the preventive measures outlined in Directive 92/85/EEC are not applied. One study estimated that approximately one-quarter of women were not aware of their pregnancy one month after fertilisation (i.e. at the time when many women realise that they are missing their period). At eight weeks pregnant, almost one in ten women still did not experience symptoms (Sayle *et al*., 2002). Even when recognised, hazards and risks for the pregnancy may still not be assessed until the woman reaches 6-8 weeks of pregnancy. At this time, the opportunity for prevention of most types of malformations is missed. The current legislation is therefore ineffective with regard to prevention of early injury.

Once a woman's pregnancy is confirmed and the employer has been informed, the latter is obliged to assess risks and remove, avoid or reduce risks for the pregnant woman and unborn child.

Austria has partly addressed this situation: employers must undertake a related assessment regardless of a pregnancy. This is also warranted when young workers may be working in an enterprise. This can surely serve as a good example.

In this respect, the report mentions the Finnish legislation in which an emphasis is put on improving the work environment when planning or constructing workplaces.

8.1.4 Other challenges

Chemicals with a potential for bio-accumulation might present special cases, as these may be mobilised during pregnancy, even if the pregnant woman herself avoids exposure (McDiarmid and Gehle, 2006). For example, high stores of lead in the bone from past exposure may be mobilised during pregnancy and expose the foetus. This also needs to be considered in a related risk assessment to prevent the exposure leading to accumulation in the first place.

8.1.5 Breastfeeding

At the abovementioned EU-OSHA workshop in Paris, the World Health Organization (WHO) noted that breastfeeding is an important issue and is not always sufficiently considered in debates on reprotoxicants (EU-OSHA, 2014).

Breastfeeding is considered in classification and labelling regulations for chemicals, as well as in the Pregnant Workers Directive. However, it is rarely addressed in OSH-related research or prevention. The role of breastfeeding in transmitting hazardous substances to the offspring, on the one hand, and in protecting the offspring from the effects of some exposures, on the other hand, needs more research, as does the ability of women to find a balance between work and the need to breastfeed. More research is also needed on the effect of different factors on the capacity to breastfeed, such as exposure to chemicals, stress, shift work or night work.

8.2 Limited knowledge on exposures and effects

Knowledge of the potential impairment of reproductive function owing to exposure in the work environment is very limited. For many chemical and non-chemical potential risk factors (whether physical, biological or organisational), very little knowledge exists as to their impact on pregnancy, male and female reproductive function, and child health later in life.

Our knowledge of the harmful effects of chemical substances comes mostly from animal studies. One reason is that in population studies it may be difficult to identify a single chemical in the working environment, for example, as multiple exposures are the norm rather than the exception.

Major chemical exposures in the work environment that do not automatically trigger testing (e.g. within REACH) or where relevant models do not resolve important controversies (such as process-generated particles, nano-sized engineered particles, chemicals for which animal models are inadequate for risk assessment, shift work, ergonomic factors and psychosocial strain (stress)) ought to be investigated by relevant study designs to provide data for adequate risk assessment.

In other instances, the nature of exposure may not allow for studies in animals, at least not to a degree where they may serve as a basis for regulation. This applies to the effects of work stress and heavy lifting on human pregnancy outcomes, for example. For both of these factors, prospective epidemiological studies may be necessary. As well-designed studies come at a high cost, many controversies may remain unresolved for a longer period of time.

Occupational regulations require that several non-chemical exposures be evaluated when a female worker becomes pregnant, for example shift work, ergonomic factors, psychosocial strain (stress), noise and biological agents. These exposures are, however, mainly investigated by universities and governmental research groups as a result of academic interest, which limits the scope of such assessments and the funds available for this type of research. They are not necessarily targeted at those areas where the impact is highest or where the need for prevention is most urgent. The approach to the investigation may also be driven by research questions rather than by problems occurring in the workplace (observational studies). Also, exposure assessment for these factors is very limited.

In addition, studies in humans have mostly looked at effects closely related to the course of pregnancy, for example abortion, gestation length and birth weight. Functional disorders related to the immune, cardiovascular and nervous systems, for example, are rarely investigated. Investigations should therefore consider wider coverage in terms of gender, generations and the time span covered.

All possible channels and data sources (e.g. data from infertility treatment or hospital discharge data) should be used to spot reproductive harm, as well as to identify relevant exposures, for example by linking effects data with data from the occupational histories (social security records, employer documentation, health and exposure surveillance) of workers and previous (parent) generations. One example is the Danish Occupational Birth Register, which includes information on parents' occupations as well as on birth and children's contact with the hospital system later in life. The ultimate aim should be to identify at-risk occupational groups among men and women.

Regarding exposure assessment, the job-exposure matrices (JEMs), as described in Chapter 3, seem to be a promising tool to identify exposure risks in the working environment. The methodology and use of these instruments should be further developed. For example, a number of JEMs that were developed by and are accessible through the French Institute for Public Health Surveillance (InVS) provide information (in French) on exposure to different types of solvents and nanoparticles (engineered or not).

8.3 Occupational diseases

Regarding occupational diseases (ODs), it can be said that the EU list of occupational diseases does not refer to any reproductive disorders caused by any of the risk factors identified in this review. The report notes that in France and a number of other countries, it is possible to recognise a disease as an OD not only in accordance with the national list of diseases but also in accordance with the complementary system, in which the victim has to prove the link between the illness and their job. It was also noted that in the USA, the list of ODs has a chapter on reproductive issues, including infertility, birth defects and spontaneous abortion. The ILO list of ODs does not explicitly include reproductive ODs but it does include a general clause allowing for any other diseases that can be demonstrated to be occupational. Health providers should be made more aware about this possibility, because they are the first point of call for victims initiating a claim (EU-OSHA, 2014). The update of EU and other occupational diseases lists, including criteria for recognition and compensation, should be considered.

A much larger variety of data sources could be used to provide evidence of reproductive effects, such as the Danish Occupational Birth Register mentioned above, that includes information on parents' occupations as well as information on birth and children's contacts with the hospital system later in life, in combination with other disease register data and the abovementioned job-exposure matrices.

8.4 Long-term effects

Factors toxic to reproduction should be given higher priority because of their health effects for workers as well as for future generations. The developmental effects of reprotoxicity may only appear after a long time (especially in the development of offspring), so estimations of the correlation of levels of parental exposure with reprotoxic effects could be difficult and require the implementation of appropriate research methods. Equally, these effects should be addressed by the current legislation, starting with regulations on testing and information requirements for chemicals, legislation that sets use conditions and not least worker protection requirements. More awareness at all levels — company, enforcement and policy — is needed. New hazards should be included and any new legislation should be sufficiently flexible to encompass these.

Table 4: Summary of conclusions on testing and evaluation of negative reproductive and developmental effects

Issue	Recommendation
Few chemicals evaluated for reproductive toxicity Only relatively few chemicals have been tested for their effect on reproduction and pregnancy in animals; this needs to be increased considerably	Systematically increase the number of chemicals tested for reproductive effects. Include effects previously not considered.

Issue	Recommendation
	Manufacturers and importers should consider the precautionary principle where data gaps have been identified or are suspected.
Process-related chemicals not under testing routines of chemicals legislation, e.g. welding fumes, diesel exhaust	Develop methods to assess them, build on existing knowledge from studies of fine particulate matter. Conduct epidemiological studies.
For most chemicals, knowledge of reproductive toxicity is provided by experimental studies in animals. Epidemiological studies are performed relatively infrequently and they do not form part of the requirements for regulations on chemicals (e.g. REACH). This is true even if suspicion arises that marketed chemicals might be harmful to reproduction	Animal studies should also consider investigating chemical concentrations that occur in workplace settings. Develop epidemiological studies, especially prospective population studies and use them in a complementary way. Consider setting up complementary data collection systems on emerging risks and alert systems, based on job-exposure profiles. Design testing procedures and legal mechanisms that are triggered automatically when suspicion arises about a possible adverse effect on reproductive functions, related hormonal mechanisms and development.
Some outcomes cannot be assessed by animal studies, e.g. effects of work stress and heavy lifting on pregnancy outcomes	Develop epidemiological studies and proper study settings. Consider combined exposures of several stressors.
Mainly effects on pregnancy studied, for example abortion, gestation length and birth weight Long-term effects not studied	Develop further and apply methods to assess effects on male fertility, epigenetic effects and other long-term effects on the progeny. Dedicate resources to other effects relevant to female workers, such as early onset of puberty or the menopause. Studies should consider the time lapse between the adverse action of a hazardous factor and the assessment of potential effects.
Developmental studies lacking Potentially important domains, such as the function of the cardiovascular and immune systems, neuroendocrine axis and hepatic and renal function, not examined in the tests Effects that do not become evident until old age not assessed Harm to the nervous system and related cognitive deficits, for example, might not become apparent	Develop cohort studies over long time spans. More prospective studies are needed that assess effects over a longer period of time. Human studies should consider the time lapse between the adverse action of a hazardous factor and the assessment of potential effects. Consider including data on parental (maternal and paternal) occupations and exposure when assessing reproductive health effects.

Issue	Recommendation
until a child's learning abilities are evaluated by professionals	Use data from a variety of sources, e.g. malformations registers, hospital registers, in combination, using for example data warehouse approaches.[8] Use new methodologies such as data mining.[9] Dedicate resources to targeted research in epigenetics.
Epigenetic effects not assessed	Develop methodologies to assess epigenetic effects, including basic research and research in specific occupations. Consider longer time spans for epidemiologic studies. The scope of the investigated endpoints should be widened and cover, for example, functions of the cardiovascular and immune systems, the neuroendocrine axis and hepatic and renal functions.
Mechanisms such as oxidative stress caused by nanoparticles currently not covered by testing methods	Develop adequate testing routines and alternative methods.
Studies lack information on exposures	Consider including parental exposure and exposure histories. Develop job-exposure matrices and study routines for specific occupations based on exposure profiles. Adapt exposure studies to new technologies, for example when considering emissions by diesel engines or from nanomaterials, and consider technological developments Ensure emerging sectors such as waste management or health professions are covered, and within the sectors consider the range of different professions (e.g. nurses vs. home care).

[8] In computing, a data warehouse, is a system used for reporting and data analysis. Data warehouses are central repositories of integrated data from one or more disparate sources.

[9] Data mining is an interdisciplinary subfield of computer science, the computational process of discovering patterns in large data sets involving methods at the intersection of artificial intelligence, machine learning, statistics, and database systems.

8.5 Non-chemical reprotoxicants

8.5.1 Biological agents

The hazard of biological agents in health care has long been recognised and studied. It is, however, necessary to link known biological risks to workplaces and activities, and to integrate this knowledge into prevention measures, especially for pregnant women in other at-risk professions (e.g. the meat processing and agriculture industries).

Little is known about the effect of biological agents at workplaces on male fertility and reproduction. Further research is needed into this, and it is necessary to raise awareness of the fact that male reproduction may also be impaired by biological agents, especially as men are increasingly moving into professions that are traditionally female dominated. One example may be the risk of infection by mumps in adult men in nursery wards and primary schools. For some of the traditionally exposed professions, such as agriculture or animal breeding, there is more information now on non-infectious work-related diseases, such as respiratory disorders, caused by biological agents, but little is known about reproductive and developmental effects in these professions. Equally, as more workers travel for work or migrate to other countries for work, the reproductive effects of potential infections and other diseases should also be explored further.

8.5.2 Physical risks

Regarding physical factors, there is research on the reproductive effects of ionising radiation, electric shock, electromagnetic fields, heat, cold, noise, ultrasound and vibration. However, most research focuses on pregnant women, with wide uncertainty in the findings. Proposed measures mainly concern pregnant women.

As with chemicals, research is closely related to pregnancy problems (e.g. abortion, preterm birth and foetal growth). These may not be the most sensitive endpoints. More research is needed, including in the selection of the most sensitive endpoints (e.g. the nervous system function of the child).

8.5.3 Psychosocial risks

To determine whether stress at work affects reproductive endpoints, sound epidemiological studies are needed. Many epidemiological studies apply unclear measures of stress and periods of exposure, and collect information after children are born. This, in particular, increases the risk of bias. As in the other fields, most investigated endpoints are relatively close to pregnancy. Some scientists demand a fresh approach that considers the stress pathways that are activated by particular stressors, and determines how these pathways affect the secretion and actions of various hormones and neuromodulators.

Studies on the effects of working hours, shifts and ergonomic issues on reproductive functions have shown that there are effects of physical workload and shift or night work on pregnancy outcomes. A consideration of work organisation in companies is therefore needed and should specifically address the situation of pregnant women.

8.6 Prevention

8.6.1 Awareness raising

Pregnant workers, workers who have recently given birth and breastfeeding workers are reasonably well covered by prevention measures and guidance, but when it comes to other workers and conditions, much remains to be done, especially considering the range of reprotoxic agents. The main knowledge gap within prevention is the very poor understanding of reprotoxicity (i.e. knowledge on reproductive and developmental toxicity). In addition, many risks are little understood by employers, workers or OSH professionals. These risks include diverse factors such as frequently used chemicals, biological agents, noise below 500 Hz, prolonged sitting for men, heat and stress.

The trend to work far from a base or at clients' premises also contributes to making exposure assessment difficult and risks being underestimated or not realised. The increasing diversification of

working relationships will remain a major challenge for the communication of such wide-ranging risks as reproductive and developmental factors at workplaces and their interaction.

The cultural norms in some sectors (e.g. road transport, construction and several service sectors) and the current economic climate may also have to be taken into account when designing awareness-raising activities. Behaviour-oriented measures that aim to improve the safety culture, including methods such as peer observation and peer discussion, could be a useful vehicle for awareness raising and the introduction of a real preventive approach. They need, however, preconditions such as example setting by managers and supervisors, a no-blame culture and valuing feedback proposals. A truly participative approach should be considered in issues as sensitive as risks to reproduction.

Furthermore, reproduction and the ability to procreate may be perceived as a personal matter by all actors, including employers and authorities. However, all concerned parties need to be informed of the risks and the current legislative shortcomings and these hurdles will have to be overcome to achieve solutions. Plans on how to establish comprehensive prevention measures, how interventions should be targeted and how to increase compliance with legislation should be developed.

Some countries have already implemented measures on reprotoxicants that go beyond the minimal requirements of the European Union Directives, which have been shown to have beneficial effects on risk assessment and awareness, as well as on helping implementation. These could serve as good practice examples.

The above tasks can be successfully conducted only if all stakeholders, including social partners and the actors in compensation and recognition of disease, view this as a joint challenge, and if the labour inspectorates support the projects. France has conducted campaigns involving social partners and labour inspectorates and this can serve as a good practice example.

8.6.2 Guidelines are urgently needed

There is also an urgent need to establish more guidelines for companies, labour inspectorates and accident/health insurance organisations. Employers and workers should be informed on what to do in case of missing data, unclear results, etc. Importantly, they should be informed of when and how to apply the precautionary principle.

The European Commission developed model guidance on working with reprotoxicants within the project on the extension of the Carcinogens and Mutagens Directive. Another important guideline was issued by the Commission to support the application of Council Directive 92/85/EEC, but it is considered to be due for revision.

A few examples of guidelines for the assessment of reproductive and developmental risk factors are also available, and they stress the importance of counselling and information, as well as the consultation of workers, which is important to ensure that preventive measures are put in place efficiently. Although caution needs to be applied where personal data are concerned, such counselling can give an opportunity to explore any possible risk factors to workers at their workplaces, while at the same time raising awareness in a mutual learning approach, for example if occupational physicians were involved.

Health service providers (general practitioners, nurses, midwives) should also be provided with tools to assess occupational reproductive risks. These should be consulted by occupational physicians in case of a health problem that may be of an occupational nature (pre-conceptual guidance).

Tools, guidance instruments and experience in applying these should be shared between Member States (an exemplary case in Finland places an emphasis on improving the work environment when planning/constructing workplaces).The development of guidance documents and tools should be accompanied by training courses, in order to assist companies in the risk assessment and in the implementation of preventive measures. Finland has established some courses that could serve as examples.

Table 5 provides a number of recommendations for prevention that emerge from the analysis.

Table 5: Recommendations for prevention

Findings	Recommendations
Very few examples of guidance available.	Develop guidelines to support enterprises in raising awareness and identifying reproductive and developmental risks. Ideally it should be sector specific, cover all factors, such as chemicals, biological agents, physical and psychosocial agents, and ensure that the issue of reprotoxicity is comprehensively addressed. Develop guidelines for labour inspectors and engage in a dialogue with stakeholders to elucidate how to legally approach issues related to endocrine disruption and new and emerging risks. Ensure prevention rapidly follows up on research findings. Review the guidelines for pregnant workers that accompany the EU directive Collect good practice cases addressing reproductive risks, to ensure experience is shared.
Reproductive risks not included in tools for workplace risk assessment.	Complement existing tools to include a focus on reproductive and developmental risk.
Lack of knowledge on reproductive risks.	Apply a precautionary approach where there are data gaps and mixture effects are expected. Follow up any unusual results from health surveillance or concerns that may arise among workers. Ensure employers are informed about the presence of nanomaterials or endocrine-disrupting properties of chemicals, e.g. through safety data sheets.
OELs do not cover reproductive risks.	Make sure that workers understand the limitations of the OELs for the substances they work with. Ensure that OELs for endocrine disruptors are reassessed. Ensure that more research is conducted on particle and EDC effects at workplaces.
Men and women may be exposed in non-traditional professions.	Avoid assumptions of who are exposed and design guidance for a diverse working population. Address risks in a gender-sensitive way (e.g. infectious diseases may harm male fertility in education, and women exposed to heavy physical work in traditionally male professions).

Findings	Recommendations
Only risks to pregnant women and the unborn child are (partly) addressed.	Raise awareness of reproductive risks to all workers. Consider counselling of workers. Promote tools and measures that support elimination of the risk (and substitution of chemicals). Ensure protective measures related to breastfeeding are implemented and effects of workplace risks on breastfeeding are further elucidated.
Early pregnancy gap	Raise awareness of reproductive risks and early effects in pregnancy. Explain the early pregnancy gap and ensure that women workers are aware of their rights and can report their pregnancy in a non-blame, non-discriminatory culture.
Health services do not have guidance on how to assess risks and identify potential occupational health effects.	Develop guidance to support OSH services. Develop guidance for counselling to workers and identification of workplace-related occupational health effects.

8.6.3 Precautionary approach

Various problems described in this report do not allow for clear limit values to be set or considered in the risk assessment, nor for a clear assessment of the risks at all levels, whether to reproductive function, the parents or the child, and the introduction of preventive measures. In occupational settings, workers may be exposed not only to single agents, factors or conditions, but also to any combinations of these through different routes simultaneously (e.g. inhalation and dermal absorption or ingestion). Assessing potential risks of all exposures remains a challenge for employers, especially small businesses. Additionally, there are emerging risks (e.g. from nanomaterials and EDCs) where the scientific approach is still being discussed, and the various mixture effects would also need to be considered. Where the scientific data do not yet allow the defining of protective levels of exposure, a precautionary approach needs to be applied. This approach must also consider the 'early pregnancy gap'.

8.7 Final remarks

It has been widely recognised that EU policies need to be coordinated to improve the prevention of reproductive risks, for example public health, environmental protection and chemicals policies. The WHO, for example, demands that reproductive disorders, including those caused by work, should be given priority in the national health plans and plans on the prevention of non-communicable diseases.

Legislation and its implementation should be coherent to ensure equal protection for women and men, including those who plan to have children, as well as for future generations. Women and men should be reassured that having children is something that is welcomed within society and within enterprises, notwithstanding pressure in times of economic crisis. Risk assessments should include both male and female aspects of reproduction, and should be based on the possibility that any woman of reproductive age may become pregnant without her knowledge. Workplace organisation and working conditions should also allow for the specific requirements of pregnant women and young mothers. Factors harmful

to reproduction should be given higher priority because of their health effects for workers as well as future generations. In all areas (chemicals, non-chemicals, mixtures, emerging factors), there are large gaps in scientific toxicological data. Much more effort is needed to close these gaps.

Finally, the 2014 EU-OSHA workshop in Paris underlined that exposure to reprotoxic risks may be exported to third countries, for example through the export of electronic waste that is then processed by workers including women and children in the destination countries. This should be prevented.

9 References

ANSES — French Agency for Food, Environmental and Occupational Health & Safety, Opinion on the assessment of the risks associated with bisphenol A for human health, and on toxicological data and data on the use of bisphenols S, F, M, B, AP, AF and BADGE, 2014. Available at https://www.anses.fr/en/content/bisphenol-anses-demonstrates-potential-health-risks-and-confirms-need-reduce-exposure

ANSES – French Agency for Food, Environmental and Occupational Health & Safety, Opinion on 'the definition of scientific criteria for defining endocrine disruptors', 2016. Available at https://www.anses.fr/en/system/files/SUBCHIM2016SA0133EN.pdf

Attarchi, M.S., Ashouri, M., Labbafinejad, Y. & Mohammadi, S., 'Assessment of time to pregnancy and spontaneous abortion status following occupational exposure to organic solvents mixture', *International Archives of Occupational and Environmental Health*, Vol. 85, No 3, 2012, pp. 295-303.

Birnbaum, L., 'Endocrine disruption', presentation at European Commission conference *Endocrine Disruptors: Current challenges in science and policy Brussels*, June 2012. Available at http://ec.europa.eu/environment/chemicals/endocrine/pdf/endocrine_presentations.zip

Boggia, B., Carbone, U., Farinaro, E., *et al*., 'Effects of working posture and exposure to traffic pollutants on sperm quality', *Journal of Endocrinology Investigation*, Vol. 32, No 5, 2009, pp. 430-434.

Boivin, J., Griffiths, E. & Venetis, C.A., 'Emotional distress in infertile women and failure of assisted reproductive technologies: meta-analysis of prospective psychosocial studies', *British Medical Journal*, 342, 2011, d223.

Brouwers, M.M., van Tongeren, M., Hirst, A., Bretveld, R.W. & Roeleveld, N., 'Occupational exposure to potential endocrine disruptors: further development of a job exposure matrix', *Occupational and Environmental Medicine*, Vol. 66, 2009, pp. 607-614.

Brown-Woodman, P.D., Webster, W.S., Picker, K. & Huq, F., 'In vitro assessment of individual and interactive effects of aromatic hydrocarbons on embryonic development of the rat', *Reproductive Toxicology*, Vol. 8, 1994, pp. 121-135.

Chapin, R.E. & Sloane, R.A., 'Reproductive assessment by continuous breeding evolving study design and summaries of ninety studies', *Environmental Health Perspectives*, Vol. 105, Suppl. 1, 1997, pp. 199−395.

Conference Proceedings, EU Conference on endocrine disruptors: Current challenges in science and policy, Brussels June 2012. Retrieved 28 August 2012, from: http://ec.europa.eu/environment/chemicals/index.htm.

Cullinan, P., Acquilla, S. & Dhara, V., 'Long term morbidity in survivors of the 1984 Bhopal gas leak', *National Medical Journal of India*, Vol. 9, 1996, pp. 5-10.

Czerczak S., 'Zasady ustalania wartości najwyższych dopuszczalnych stężeń chemicznych czynników szkodliwych w środowisku pracy' [Rules for determining the maximum permissible concentrations of harmful chemical agents in the workplace], *Podstawy i Metody Oceny Środowiska Pracy*, Vol. 4, No 42, 2004, pp. 5-18.

De Fleurian, G., Perrin, J., Ecochard, R., Dantony, E., Lanteaume, A., Achard, V., Grillo, J.M., Guichaoua, M.R., Botta, A. & Sari-Minodier, I., Occupational exposures obtained by questionnaire in clinical practice and their association with semen quality, *Journal of Andrology* 30, 2009. pp.566-79. doi: 10.2164/jandrol.108.005918. Epub 2009 Feb 19.

Drozdowsky, S.L. & Whittaker, S.G, 'Workplace hazards to reproduction and development: a resource for workers, employers, health care providers, and health & safety personnel', *Safety and Health Assessment and Research for Prevention SHARP*, technical report No. 21-3-1999, 1999, pp. 1-7.

Du Plessis, S.S. & Agarwal, A., 'Environmental insults on spermatogenesis', in Racowsky, C., Schlegel, P.N., Fauser, B.C. and Carrell, D.T., *Biennial reviews of infertility*, Vol. 2, Springer, 2011, pp. 133-154.

ECHA – European Chemicals Agency, Guidance on the application of the CLP Criteria. Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures. ECHA-12-G-14-EN, version 4.0, 2013b.

ECHA – European Chemicals Agency, Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7a: Endpoint specific guidance, version 4.1, 2015.

EU-OSHA – European Agency for Safety and Health at Work, Exploratory survey of occupational exposure limits for carcinogens, mutagens and reprotoxic substances at EU Member State levels, Luxembourg, Office for Official Publications of the European Communities, 2009a. Available at: https://osha.europa.eu/en/publications/reports/548OELs

EU-OSHA — European Agency for Safety and Health at Work, *Risk assessment for biological agents*. E-fact 53, 2010, pp. 1-14. Available at: https://osha.europa.eu/es/tools-and-publications/publications/e-facts/efact53/view

EU-OSHA – European Agency for Safety and Health at Work, Workplace risks affecting reproduction: from knowledge to action, seminar online summary of workshop held in Paris, January 2014. Retrieved 21 July 2014 from: https://osha.europa.eu/en/seminars/workplace-risks-affecting-reproduction-from-knowledge-to-action

European Commission, Report from the Commission on the implementation of Council Directive 92/85/EEC of 19 October 1992 on the introduction of measures to encourage improvements in the health and safety at work of pregnant workers and workers who have recently given birth or are breastfeeding, COM/99/ 0100 final, Brussels, 1999.

European Commission, Communication from the Commission on the guidelines on the assessment of the chemical, physical and biological agents and industrial processes considered hazardous for the safety or health of pregnant workers and workers who have recently given birth or are breastfeeding (Council Directive 92/85/EEC), Communication from the Commission, COM(2000) 466 final/2, Brussels, 2000.

European Commission, 2008, Proposal for a Directive of the European Parliament and of the Council of 3 October 2008 amending Council Directive 92/85/EEC on the introduction of measures to encourage improvements in the safety and health at work of pregnant workers and workers who have recently given birth or who are breastfeeding COM (2008) 637 final, 2008/0193 (COD). Available at http://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:52008PC0637

European Commission, 'Commission recommendation of 18 October on the definition of nanomaterial (2011/696/EU)', *Official Journal of the European Union,* L 275, 2011, pp. 38-40.

European Commission, 2011, Fourth Report on the implementation of the 'Community Strategy for Endocrine disrupters' a range of substances suspected of interfering with the hormone systems of humans and wildlife (COM (1999) 706), Commission Staff Working Paper, SEC(2011) 1001 final, 10.08.2011.

European Commission, Press release 15.06.2016, *Commission presents scientific criteria to identify endocrine disruptors in the pesticides and biocides areas*. Available at http://europa.eu/rapid/press-release_IP-16-2152_en.htm

European Commission, 2016. Executive summary of the impact assessment SWD(2016) 212 final; Communication from the Commission to the European Parliament and the Council. COM(2016) 350 final. Available at http://ec.europa.eu/health/endocrine_disruptors/policy/index_en.htm

European Council, Council Directive 92/85/EEC of 19 October 1992 on the introduction of measures to encourage improvements in the safety and health at work of pregnant workers and workers who have recently given birth or are breastfeeding (tenth individual Directive within the meaning of Article 16 (1) of Directive 89/391/EEC).

European Council, 1996, Council Directive 96/29/Euratom of 13 May 1996 laying down basic safety standards for the protection of the health of workers and the general public against the dangers arising from ionizing radiation.

Evans, T.J., 'Endocrine disruptors', in Gupta, R.C. (ed.), *Reproductive and developmental toxicity*, Elsevier Inc., London, Burlington, MA, San Diego, CA , 2011, pp. 874-875.

Fairhurst, S., 'The uncertainty factor in the setting of occupational exposure standards', *Annals of Occupational Hygiene,* Vol. 39, 1995, pp. 375-385.

Feveile, H., Schmidt, L., Hannerz, H. & Hougaard, K.S., 'Industrial differences in female fertility treatment rates – a new approach to assess differences related to occupation?', *Scandinavian Journal of Public Health*, Vol. 39, No 2, 2011, pp. 164-171. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21239478

Gould, J.C., Kasichayanula, S., Shepperly, D.C. & Boulton D.W., 'Use of low-dose clinical pharmacodynamic and pharmacokinetic data to establish an occupational exposure limit for dapagliflozin, a potent inhibitor of the renal sodium glucose co-transporter 2', Regulatory Toxicology and Pharmacology, 2013, pii: S0273-2300(13)00104-9.

Greenberg, G.N., Cohen, B.A., Frazier, L.M. & DeHart, R.L., 'Noise, ultrasound, and vibration', in Frazier, L.M. & Hage, M.L. (eds), *Reproductive hazards of the workplace*, John Wiley and Sons, Inc., New York, 1998, pp. 401-414.

Gromiec, J.P. & Czerczak, S., 'Kryteria Oceny Narażenia na Substancje Chemiczne w Polsce i na Świecie – Procedury Ustalania i Stosowania [Polish and worldwide criteria for assessing exposure to chemicals: procedures and applications]', *Medycyna Pracy*, Vol. 53, No 1, 2002, pp. 53-59.

Guignon, N. & Sandret, N., 'Les expositions aux produits mutagènes et reprotoxiques', *DARES – Premières Synthèses Informations*, No. 32.1, 2005.

Gulati, K. & Ray, A. 'Stress: its impact on reproductive and developmental toxicity', Gupta, R.C. (Ed.), *Reproductive and Developmental Toxicity*, Elsevier Inc., London, Burlington, MA, San Diego, CA, 2011, pp. 825-834

Hage, M.L., 'Disinfectants', in Frazier, L.M. & Hage, M.L. (eds), *Reproductive hazards of the workplace*, John Wiley and Sons, Inc., New York, 1998, pp. 257-275.

Hage, M.L., 'Working hours, shift rotation, and shift duration', Frazier, L.M., Hage, M.L. (eds), *Reproductive hazards of the workplace*, John Wiley and Sons, Inc., New York. 1998, pp. 506-512.

Hass, U., & Filinska, M., 'Effekter på hjernens udvikling og funktion efter udsættelse for kemiske stoffer med hormonlignende virkninger [Effects on brain development and function after exposure to chemicals with hormone-like effects]', *Miljø og Sundhed*, vol. 23, 2003, pp. 12-19.

Hass, U., Herrmann, S.S., Jacobsen. P.R., Jensen, B.H., Petersen, A., Poulsen, M.E., Taxvig, C., Vinggaard, A.M., Boberg, J., Christiansen, S., Clemmensen, L.H. & Axelstad, M., 'Adverse effects on sexual development in rat offspring after low dose exposure to a mixture of endocrine disrupting pesticides', *Reproductive Toxicology*, Vol. 34, No 2, 2012, pp. 261-274.

Hass, U., Scholze, M., Christiansen, S., Dalgaard, M., Vinggaard, A.M., Axelstad, M., Metzdorff, S.B. & Kortenkamp, A., 'Combined exposure to anti-androgens exacerbates disruption of sexual differentiation in the rat', *Environmental Health Perspectives*, Vol. 115, Suppl. 1, 2007, pp. 122-128.

Health Council of the Netherlands, 'Advisory reports on healthy working conditions', undated. Retrieved 29 July 2014 from: http://www.gezondheidsraad.nl/en/search/results/evaluation%20of%20effects%20on%20reproduction

Hjollund, N.H., Kold, J.T., Bonde, J.P., Henriksen, T.B., Kolstad, H.A., Andersson, A.M., Ernst, E., Giwercman, A., Skakkebaek, N.E. & Olsen, J., 'Job strain and time to pregnancy', *Scandinavian Journal of Work, Environment and Health*, Vol. 24, 1998, pp. 344-350.

Hjollund, N.H., Jensen, T.K., Bonde, J.P., Henriksen, T.B., Andersson, A.M., Kolstad, H.A., Ernst, E., Giwercman, A., Skakkebaek, N.E. & Olsen, J., 'Distress and reduced fertility: a follow-up study of first-pregnancy planners', *Fertility and Sterility*, Vol. 72, 1999, pp. 47-53.

Hjollund, N.H., Bonde, J.P., Henriksen, T.B., Giwercman, A. & Olsen, J., 'Job strain and male fertility', *Epidemiology*, Vol. 15, 2004a, pp. 114-117.

Hjollund, N.H., Bonde, J.P., Henriksen, T.B., Giwercman, A. & Olsen, J., 'Reproductive effects of male psychologic stress', *Epidemiology*, Vol. 15, 2004b, pp. 21-27.

Hjollund, N.H., Bonde, J.P., Jensen, T.K., Henriksen, T.B., Andersson, A.M., Kolstad, H.A., Ernst, E., Giwercman, A., Skakkebaek, N.E., & Olsen. J., 'Male-mediated spontaneous abortion among spouses of stainless steel welders', *Scandinavian Journal of Work, Environment and Health*, Vol. 26, 2000a, pp. 187-192.

Hougaard, K.S., 'Effekter af stress i fostertilværelsen [Effects of stress on foetal stage]', *Miljø og Sundhed*, Suppl. 4, 2004, pp. 14-24.

Hougaard, K.S., *Neurobehavioral Teratology of maternal stress in combination with chemical exposure in rats*, PhD thesis, Institute of Occupational Health, 2003, Copenhagen

Hougaard, K.S., *Reproduction Injuries and pregnancy complications — Note to Working Environment Authority,* strategy project 2010, unpublished, 2005

Hougaard, K.S., *Reproduction Injuries and pregnancy complications — Update to note to Working Environment Authority strategy project*, unpublished, 2010

Hougaard, K.S. & Lund, S.P., Helbredseffekter af støj i arbejdsmiljøet [Health effects of noise in the working environment], AMI Documentation 13, Copenhagen, 2004.

Hougaard, K.S., Jackson, P., Jensen, K.A., Sloth, J.J., Loschner, K., Larsen, E.H., Birkedal, R.K., Vibenholt, A., Boisen, A.M., Wallin, H. & Vogel, U., 'Effects of prenatal exposure to surface-coated nanosized titanium dioxide (UV-Titan). A study in mice', *Particle and Fibre Toxicology,* Vol. 7, No 16, 2010, p. 16.

Hougaard, K.S., Hannerz, H., Feveile, H. & Bonde, J.P., 'Increased incidence of infertility treatment among women working in the plastics industry', *Reproductive Toxicology,* Vol. 27, 2009, pp. 186-189.

Iavicoli, I., Fontana, I. & Bergamaschi, A., 'The effects of metals as endocrine disruptors', *Journal of Toxicology and Environmental Health*, Part B: Critical Reviews, Vol. 12, No 3, 2009, pp. 206-223.

IGHRC – Interdepartmental Group on Health Risks from Chemicals, *Chemical mixtures: a framework for assessing risks to human health*, undated. Available at: http://ieh.cranfield.ac.uk/ighrc/publications1.html

Jensen, T.K., Bonde, J.P. & Joffe, M., 'The influence of occupational exposure on male reproductive function', *Occupational Medicine (London),* Vol. 56, No 8, 2006, pp. 544-553.

Jørgensen, N., Vierula, M., Jacobsen, R., Pukkala, E., Perheentupa, A., Virtanen, H.E., Skakkebæk, N.E. & Toppari, J., 'Recent adverse trends in semen quality and testis cancer incidence among Finnish men', *International Journal of Andrology*, Vol. 34, 2011, pp. e37–e48.

Karasek, R. & Theorell, T., Healthy work: stress productivity and the reconstruction of working life, Basic Books, New York, 1990.

Kay, H.H., 'Electromagnetic fields', in Frazier, L.M. & Hage, M.L. (eds), *Reproductive hazards of the workplace*, John Wiley and Sons, Inc., New York, 1998, pp. 391-400.

Kortenkamp, A., Martin, O., Faust, M., Evans, R., McKinlay, R., Orton, F. & Rosivatz, E., *State of the art assessment of endocrine disruptors*, 2011. Available at: http://ec.europa.eu/environment/chemicals/endocrine/pdf/sota_edc_final_report.pdf

Krüger, D., Louhevaara, V., Nielsen, J. & Schneider, T., 'Risk assessment and preventive strategies in professional cleaning', *Werkstattberichte Wissenschaft + Technik*, Wirtschaftsverlag NW, No 13, Hamburg, 1997.

Larsen, P.B., 'Børn og ufødtes udsættelse og følsomhed over for kemiske stoffer [Exposure of children and the unborn and sensitivity to chemicals]'', *Miljø og Sundhed,* Vol. 17, 2001, pp. 8-11.

Lawson, C.C., Grajewski, B., Daston, G.P., Frazier, L.M., Lynch, D., McDiarmid, M., Murono, E., Perreault, S.D., Robbins, W.A., Ryan, M.A., Shelby, M. & Whelan, E.A., 'Workgroup report: implementing a national occupational reproductive research agenda – decade one and beyond', *Environmental Health Perspectives*, Vol. 114, No 3, 2006, pp. 435-441.

Lawson, C.C., Schnorr, T.M., Daston, G.P., Grajewski, B., Marcus, M., McDiarmid, M., Murono, E., Perreault, S.D., Schrader, S.M. & Shelby, M., 'An occupational reproductive research agenda for the third millennium', *Environmental Health Perspectives,* Vol. 111, No 4, 2003, pp. 584-592.

Levine, R.J., Mathew, R.M., Chenault, C.B., Brown, M.H., Hurtt, M.E., Bentley, K.S., Mohr, K.L. & Working, P.K., Differences in the quality of semen in outdoor workers during summer and winter, *New England Journal of Medicine* 323, 1990, pp.12-16.

Li, D., Zhou, Z., Qing, D., He, Y., Wu, T., Miao, M., Wang, J., Wenig, X., Ferber, J.R., Herrinton, L.J., Zhu, Q., Gao, E., Checkoway, H. & Yuan, W., 'Occupational exposure to bisphenol A (BPA) and the risk of self-reported male sexual dysfunction', *Human Reproduction,* Vol. 25, 2010, pp. 519-527.

Lobel, M., 'Conceptualizations, measurement, and effects of prenatal maternal stress on birth outcomes', *Journal of Behavioral Medicine*, Vol. 17, 1994, pp. 225-272.

Mantovani, A. & Baldi, F., 'Emerging aspects – endocrine disrupters aggregate exposure in living environment and workplace', 2010. Retrieved 12 August 2015 from: http://www.iss.it/binary/inte/cont/ENG.pdf

Metzdorff, S.B., Dalgaard, M., Christiansen, S., Axelstad, M., Hass, U., Kiersgaard, M.K., Scholze, M., Kortenkamp, A. & Vinggaard, A.M., 'Dysgenesis and histological changes of genitals and perturbations of gene expression in male rats after in utero exposure to antiandrogen mixtures', *Toxicological Sciences*, Vol. 98, No 1, 2007, pp. 87-98.

Milieu Ltd & Risk and Policy Analysts Ltd (RPA), Final Report, Analysis at EU-level of health, socioeconomic and environmental impacts in connection with possible amendment to Directive 2004/37/EC (carcinogens and mutagens at work) to extend the scope to include category 1A and 1B reprotoxic substances, funded by the European Commission and the DG EMPL as a Study Service Contract, 2013.

Mnif, W., Hassine, A.I.H., Bouaziz, A., Bartegi, A., Thomas, O. & Roig, B., 'Effect of endocrine disruptor pesticides: a review', *International Journal of Environmental Research and Public Health,* Vol. 8, 2011, pp. 2265-2303.

Mozurkewich, E.L., Luke, B., Avni, M. & Wolf, F.M., 'Working conditions and adverse pregnancy outcome: a meta-analysis', *Obstetrics & Gynecology*, Vol. 95, 2000, pp. 623-635.

Mutambudzi, M., Meyer, J.D., Warren, N. & Reisine, S., 'Effects of psychosocial characteristics of work on pregnancy outcomes: a critical review', *Women Health*, Vol. 51, 2011, pp. 279-297.

National Board of Health (Sundhedsstyrelsen), Malformation Register 1994-2006 – New figures from the Health Protection Agency, Denmark, 2007, 11 (13), pp. 1-13.

Nesbitt, T., 'Ergonomic exposures', in Frazier, L.M. & Hage, M.L. (eds), *Reproductive hazards of the workplace*, John Wiley and Sons, Inc., New York, 1998, pp. 431-464.

NIOSH – National Institute for Occupational Safety and Health (USA), *The effect of workplace hazards on female reproductive health*, DHSS (NIOSH) Publication No 99-104, 1999, p. 5. Available at: http://www.cdc.gov/niosh/docs/99-104/pdfs/99-104.pdf

NIOSH – National Institute for Occupational Safety and Health (USA), *Current intelligence bulletin 63: occupational exposure to titanium dioxide*, NIOSH Publication No 2011-160, 2011. Available at: http://www.cdc.gov/niosh/docs/2011-160/pdfs/2011-160.pdf,

NIOSH – National Institute for Occupational Safety and Health (USA), Workplace Solutions. No-nose Saddles for Preventing Genital Numbness and Sexual Dysfunction from Occupational Bicycling. Available at http://www.cdc.gov/niosh/docs/wp-solutions/2009-131/pdfs/2009-131.pdf

Office of Technology Assessment, *Reproductive health hazards in the workplace*, OTA-BA-266, US Congress, US Government Printing Office, Washington DC, December 1985.

Paarlberg, K.M., Vingerhoets, A.J., Passchier, J., Dekker, G.A. & Van Geijn, H.P., 'Psychosocial factors and pregnancy outcome: a review with emphasis on methodological issues', *Journal of Psychosomatic Research*, Vol. 39, 1995, pp. 563-595.

Peters, P., Miller, R.K. & McElhatton, P.R., 'Occupational, industrial, and environmental agents', in Schaefer, C., Peters, P. & Miller, R.K. (eds), *Drugs during pregnancy and lactation*, Academic Press, 2007.

Rider, C.V., Wilson, V.S., Howdeshell, K.L., Hotchkiss, A.K., Furr, J.R., Lambright, C.R. & Grey Jr., L.E., 'Cumulative effects of in utero administration of mixtures of "antiandrogens" on male rat reproductive development', *Toxicology and Pathology*, Vol. 37, No 1, 2009, pp. 100-113.

Riipinen, A., Sallmén, M., Taskinen, H., Koskinen, A. & Lindbohm, M.L., 'Pregnancy outcomes among daycare employees in Finland', *Scandinavian Journal of Work, Environment and Health*, Vol. 36, No 3, 2010, pp. 222-230.

Rissman, E.F. & Adli, M., Minireview: transgenerational epigenetic inheritance: focus on endocrine disrupting compounds, *Endocrinology*, Vol. 155, No 8, 2014, pp. 2770-2780.

Ritz, C., Ruminski, W., Hougaard, K.S., Wallin, H., Vogel, U. & Yauk, C.L., 'Germline mutation rates in mice following in utero exposure to diesel exhaust particles by maternal inhalation', *Mutation Research,* Vol. 712, 2011, pp. 55-58.

Rubio, A.A.C., Valdés, J.M.R., Lareo, A.C., Merino, R.G. & Cencillo, F.R., 'Riesgo quimico laboral: Elementos para un diagnostico en Espana', *Revista Española de Salud Pública*, Vol. 79, 2005, pp. 283-295.

Sánchez-Peña L.C., Reyes B.E, López-Carrillo L., Recio R., Morán-Martínez J., Cebrián M.E. & Quintanilla-Vega B., 'Organophosphorous pesticide exposure alters sperm chromatin structure in Mexican agricultural workers', *Toxicology and Applied Pharmacology*, Vol. 196, No 1, 2004, pp. 108-113.

Sanders, K.A. & Bruce, N.W., 'Psychosocial stress and the menstrual cycle'. *Journal of Biosocial Science*, Vol. 31, 1999, pp. 393-402.

Sas, M. & Szöllösi, J., 'Impaired spermiogenesis as a common finding among professional drivers', *Archives of Andrology*, Vol. 3,1979, pp.57-60.

SCOEL – Scientific Committee on Occupational Exposure Limits, *Methodology for the derivation of occupational exposure limits: key documentation (version 7),* European Commission, Brussels, 2013, pp. 1-39.

Sharpe, R.M. & Irvine, D.S., 'How strong is the evidence of a link between environmental chemicals and adverse effects on human reproductive health?', *British Medical Journal*, 2004, 328 (7437), pp. 447-451.

Silva, E., Rajapakse, N. & Kortenkamp, A., 'Something from "nothing" – eight weak estrogenic chemicals combined at concentrations below NOECs produce significant mixture effects', *Environmental Science and Technology*, Vol. 36, No 8, 2002, pp. 1751-1756. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11993873

Storgaard, L. & Bonde, J.P, 'Endocrine disrupters and semen quality', *Environment and Health*, Vol. 21, 2003, pp. 9-15.

Suruda, A.J., 'Radiation', in Frazier, L.M. & Hage, M.L. (eds), *Reproductive hazards of the workplace*, John Wiley and Sons, Inc., New York, 1998, pp. 367-390.

Swan, S.H., Main, K.M., Liu, F., Stewart, S.L., Kruse, R.L., Calafat, A.M., Mao, C.S., Redmon, J.B., Ternand, C.L., Sullivan, S. & Teague, J.L., 'Decrease in anogenital distance among male infant with prenatal phthalate exposure', *Environmental Health Perspectives*, Vol. 113, No 8, 2005, pp. 1056-1061.

Talge, N.M., Neal, C. & Glover, V., 'Antenatal maternal stress and long-term effects on child neurodevelopment: how and why?', *Journal of Child Psychology and Psychiatry*, Vol. 48, 2007, pp. 245-261.

Taskinen, H.K., Kyyrönen, P., Sallmen, M., Virtanen, S.V., Liukkonen, T.A., Huida, O., Lindbohm, M.L. & Anttila, A., 'Reduced fertility among female wood workers exposed to formaldehyde', *American Journal of Industrial Medicine*, Vol. 36, No 1, 1999, pp. 206-212.

Taskinen, H., Lindbohm, M.-L. & Sallmén, M., 'Occupational exposure to chemicals and reproductive health', Gupta, R.C. (Ed.), *Reproductive and Developmental Toxicity*, Elsevier Inc., London, Burlington, MA, San Diego, CA, 2011, pp. 949-955.

Vandenberg, L.N., Colborn, T., Hayes, T.B., Heindel, J.J., Jacobs, Jr., D.R., Lee, D.-H., Shioda, T., Soto, A.M., vom Saal, F.S., Welshons, W.V., Zoeller, R.T. & Myers, J.P., 'Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses', *Endocrine Reviews*, June 2012, 33(3), pp. 378-455.

Vogel, L., *Reproductive hazards, prevention and equality*, lecture at a seminar on chemical substances at work: facing up to the challenges, 2009. Retrieved 12 November 2016 from: https://osha.europa.eu/en/tools-and-publications/seminars/chemical-substances-at-work-facing-up-to-the-challenges

Vulimiri, S.V., Pratt, M.M., Kulkarni, S., Beedanagari, S. & Mahadevan, B., 'Reproductive and developmental toxicology: toxic solvents and gases', in Gupta, R.C. (ed.), *Reproductive and developmental toxicity,* Elsevier Inc., 2011, pp. 303-315.

Wergeland, E., Strand, K. & Bjerkedal, T., 'Smoking in pregnancy: a way to cope with excessive workload', *Scandinavian Journal of Primary Health Care*, Vol. 14, 1996, pp. 21-28.

Wisborg, K., Barklin, A., Hedegaard, M. & Henriksen, T.B., 'Psychological stress during pregnancy and stillbirth: prospective study', *British journal of obstetrics and gynaecology*, Vol. 115, 2008, pp. 882-885.

WHO, World Health Organization, International Programme on Chemical Safety, 'Global assessment of the state-of-the-science of endocrine disruptors', Damstra, T., Barlow, S., Bergman, A., Kavlock, R., Van Der Kraak, G. (eds.), 2002. Available at http://www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/

10 Further reading

Feveile, H., Schmidt, L., Hannerz, H. & Hougaard, K.S., 'Industrial differences in female fertility treatment rates – a new approach to assess differences related to occupation?', Scandinavian Journal of Public Health, Vol. 39, No 2, 2011, pp. 164-171.

11 Annexes

11.1 Glossary

Anogenital distance: The distance from the anus to the genitalia, the base of the penis or vagina. It is considered medically significant for a number of reasons, in both humans and animals. It is regulated by dihydrotestosterone, which can be disrupted by endocrine disrupters.

Confounding factor: A variable that is related to both the exposure and the outcome being studied. Not considering confounding factors may lead to mis-estimations.

Congenital: Present at birth.

DNA: Deoxyribonucleic acid, a molecule that encodes the genetic instructions used in the development and functioning of all known living organisms and many viruses.

Endpoint: The particular biological response being measured.

Embryo/foetus: The embryonic stage begins at about 3 weeks and extends to about 8 or 9 weeks; the foetal stage extends from 8 weeks until birth. .

Epidemiology: The study of the distribution of diseases and their precursors in human populations.

Epigenetic changes: Changes in gene expression caused by certain base pairs in DNA, or ribonucleic acid (RNA), being 'turned off' or 'turned on' again, through chemical reactions.

Oestrogen: Any natural or artificial substance that induces oestrogenic activity; more specifically the oestrogenic hormones oestradiol and oestrone produced by the ovary; the female sex hormones.

Gamete: A mature male or female germ cell (spermatozoon or ovum).

Gametogenesis: Production of germ cells (the male and female reproductive cells, sperm or egg).

Gestation: Period of intrauterine development from conception to birth.

Gonadotoxic: Toxic to the sex organs.

Infertility: Inability to produce live-born children.

Intrauterine growth retardation: Poor growth of a baby while in the uterus.

In vitro: Outside the living organism an in an artificial environment.

In vivo: Within the living organism.

Implantation: Process whereby a fertilised ovum burrows into the lining of the uterus on its arrival there, and attaches itself firmly. Successful implantation is essential to the future development of the embryo/foetus and is sometimes considered the true moment of conception.

Metabolic disorder: Inborn errors of metabolism (set of life-sustaining chemical transformations within the cells).

Parturition: Labour and delivery.

Postpartum or postnatal period: The period beginning immediately after the birth of a child and extending for approximately 6 weeks.

Potency: In the field of pharmacology, potency is a measure of drug activity expressed in terms of the amount required to produce an effect of given intensity. A highly potent drug (e.g. morphine, alprazolam or chlorpromazine) evokes a larger response at low concentrations, whereas a drug of lower potency (ibuprofen, acetylsalicylic acid) evokes a small response at low concentrations.

Teratogen/teratogenesis: An agent that interferes with embryonic or foetal development. A chemical or physical agent that causes physical defects in offspring.

Testosterone: A hormone secreted by the testes that stimulates the development of masculine characteristics.

Reproductive health hazard: A chemical, physical or biological agent that causes reproductive impairment in adults and developmental impairment or death in the embryo/foetus or child (Hage).

Senescence: Biological ageing.

Xenobiotic: A foreign chemical substance found within an organism that is not normally naturally produced by or expected to be present within that organism.

11.2 List of abbreviations

BPA: bisphenol A

CLP: classification, labelling and packaging of substances and mixtures

CMR: carcinogenic, mutagenic or toxic for reproduction

DEP: diesel exhaust particle

DNA: deoxyribonucleic acid

DNEL: Derived no-effect level

EDC: endocrine-disrupting compound, also endocrine-disrupting chemical

ENP: engineered nanoparticle

EU-OSHA: European Agency for Safety and Health at Work

FIOH: Finnish Institute for Occupational Health

ILO: International Labour Organization

JEM: job-exposure matrix

NIOSH: National Institute for Occupational Safety and Health (USA)

NMP: N-methyl-2-pyrrolidone

OD: occupational disease

OECD: Organisation for Economic Co-operation and Development

OEL: occupational exposure limit

OSH: occupational safety and health

PAH: polyaromatic hydrocarbons

PCB: polychlorinated biphenyl

PPE: Personal Protective Equipment

ppm: parts per million

REACH: Registration, Evaluation, Authorisation and restriction of CHemicals

SCOEL: Scientific Committee on Occupational Exposure Limits

SME: small and medium-sized enterprise

11.3 Additional material provided in the annex of the report

- Substances classified as toxic to reproduction according to European Regulation (EC) No 1272/2008 (CLP) (consolidated version, dated 1 December 2013).
- List of chemical agents with occupational exposure limit values (OELVs), which are marked with note ‘reprotoxicity’ according to the CLP regulation.
- The Polish OELs for substances with ‘Ft’ notation.
- List of substances toxic for reproduction included in the candidate list (per 23 July 2014).

TE-RO-16-004-EN-N

The European Agency for Safety and Health at Work (EU-OSHA) contributes to making Europe a safer, healthier and more productive place to work. The Agency researches, develops, and distributes reliable, balanced, and impartial safety and health information and organises pan-European awareness raising campaigns. Set up by the European Union in 1994 and based in Bilbao, Spain, the Agency brings together representatives from the European Commission, Member State governments, employers' and workers' organisations, as well as leading experts in each of the EU Member States and beyond.

European Agency for Safety and Health at Work

Santiago de Compostela 12, 5th floor

48003 Bilbao, Spain

Tel. +34 944358400

Fax +34 944358401

E-mail: information@osha.europa.eu

http://osha.europa.eu

Publications Office