Workplace risks affecting reproduction: from knowledge to action

Paris, 15 and16 January 2014

Introduction

The workshop was organised by the European Agency for Safety and Health at Work (EU-OSHA) on 15–16 January 2014, at the French Agency for Food, Environmental and Occupational Health and Safety (ANSES) premises in Paris, in cooperation with ANSES, with a view to presenting preliminary results of EU-OSHA research, stimulating debate on workplace risks to reproductivity and supporting a constructive dialogue between stakeholders. The research is part of a large-scale activity that the Agency is undertaking to address work-related diseases.

About 60 participants from various European Union (EU) Member States attended, including representatives of French national institutes, ministries and research organisations dealing with reproductive risks, the EU Directorate-General for Employment, Social Affairs and Inclusion (DG Employment) and the European Chemicals Agency (ECHA); attendees included workers, policy-makers, researchers, and representatives of authorities, NGOs, and EU-OSHA and its national focal points. Employers' representatives had to cancel at the last minute, but the point of view of this group was included in one of the presentations. The presentation of the results of the research commissioned by EU-OSHA was followed by presentations made by research bodies, inspection services and agencies, aiming to summarise the current knowledge and gaps in knowledge regarding workplace risks to reproductivity. Discussants from the European Trade Union Institute (ETUI), the Chemex group of the Senior Labour Inspectors Committee (SLIC), the Scientific Committee on Occupational Exposure Limits (SCOEL), the Advisory Committee on Safety and Health at Work's Working Party on Chemicals (WPC), and the World Health Organisation (WHO) were invited to present their points of view and aspects specific to their activities.

Main conclusions

Legislation and policies

- There is an EU regulatory framework covering occupational risks to reproductive functions. This legislation covers, in principle, all types of workplace risks to reproductivity, physical, chemical, biological or organisational, either through general or specific provisions (e.g. directives on pregnant, breastfeeding or young workers). Even directives not directly related to the subject, 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 may have an effect on workers' exposure, such as legislation on chemicals or environmental protection.
- It is important to review the legislation and its implementation to ensure equal protection for women and men, including those who plan to have children. New hazards should be specifically included where possible and the legislation needs to be sufficiently flexible to encompass other new hazards.
- At present, the debate on whether to introduce reprotoxicants into the EU Carcinogens and Mutagens Directive (Directive 2004/37/EC, CMD) is not closed, but frozen, because of contradictory points of view and the limited availability of supporting data. However, there is agreement that awareness-raising and specific guidance are urgently needed.

- In the USA, birth defects, spontaneous abortion and infertility are included in the occupational diseases list and are compensated. Updating of EU and other occupational diseases lists, including criteria for recognition and compensation, should be considered.
- Reproductive disorders, including those caused by work, should also be given priority in national health plans and plans for the prevention of non-communicable diseases, according to the WHO. Everybody should have access to reproductive health and planning.
- 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). The precautionary approach has to be highlighted.

Research, prevention measures, tools

- Precautions can be taken only if it is known that caution is necessary. For many chemicals and other non-chemical potentially adverse factors (whether physical, biological or organisational), very little knowledge exists about their impact on pregnancy, male and female reproductive function, and child health later in life.
- Studies need to give greater consideration to the time lag of potential effects; they should widen their scope beyond pregnancy, as, for example, functional disorders related to the immune, cardiovascular, metabolic and nervous systems are rarely investigated. Furthermore, effects on male and female reproduction, as well as transgenerational effects, are rarely investigated.
- A variety of data sources could be used to provide evidence of infertility or other reproductive health problems, such as the Danish Occupational Birth Register, which includes information on parents' occupations as well as information on births and children's contacts with the hospital system later in life.
- Studies should consider the real exposures of workers according to their occupations; for substances, this includes concentrations and mixtures that occur in workplace settings.
- More should be known about occupational and other exposures and their effects, how interventions should be targeted and how best to increase compliance with existing legislation.
- Including reproductive risks in risk assessment and widening the scope to cover both genders and transgenerational effects could also help address risks in early pregnancy and close the 'early pregnancy-gap' (i.e. not yet discovered and undeclared pregnancy, which are not covered by OSH legislation).
- Breastfeeding in the workplace is important and is not always sufficiently considered in debates on reprotoxic risks. Breastfeeding is considered in classification and labelling regulations for chemicals, as well as in the EU Pregnant Workers Directive (PWD). However, it is rarely addressed specifically in research or prevention. Greater awareness is needed about breastfeeding and its role in, on the one hand, transmitting hazardous substances to the offspring and, on the other hand, protecting the offspring from the effects of some exposures. More awareness is also needed with regard to ensuring that women are able to find a balance between work and the need to breastfeed. More research is also needed on the effects of different factors, such as exposure to chemicals, stress, shift work and night work, on the capacity to breastfeed.
- Many risks are hardly known among employers, workers and OSH professionals. Awareness raising and guidance are urgently needed. EU-OSHA research has clearly revealed that the issue of reprotoxic factors in the world of work is underestimated.
- Data gaps should be clearly indicated and guidance providing indications on measures to be taken in case of missing data offered. A precautionary approach should be adopted.
- It is important to engage health service providers – general practitioners, nurses, midwifes – and provide them with useful tools on how to consider occupational reproductive risks in delivering health measures. Because it is these professionals, in primary health care, to whom people will speak (even before occupational physicians) in case of a health problem that may be occupational in nature.

- Although limited, there are a number of tools available, including job–exposure matrices (JEMs), substitution databases and selected guidance documents. These, and experiences from countries with a longer history of implementing of specific measures, should be shared between Member States.
- An open call for tender for a study to develop proposals on a new database for occupational exposure was published last year by DG Employment. The database will be for all types of chemicals, but carcinogens and reprotoxicants could be prioritised.
- The basis for prevention (i.e. knowledge about reproductive and developmental risks) is insufficient. A higher priority should be given to reprotoxic risks, and knowledge should be developed and updated.

Chemical reprotoxicants

- There are a number of emerging issues that need to be addressed: exposure to nanoparticles, changes linked to work organisation, and process-generated substances such as those from combustion of diesel fuel and from welding. Pharmaceuticals are not regulated by REACH (the EU regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals) and therefore there is a lack of available data regarding hazards (specific test results are generally not published). Workers, however, may be exposed to anaesthetic gases, cytostatic drugs or disinfectants.
- REACH provides a framework for information on hazardous chemicals to be passed up and down supply chains. A number of health effects (end points), however, are not sufficiently covered by testing and assessment, for example regarding long-term effects on immune function and metabolism and transgenerational effects on both males and females.
- For chemicals marketed in 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 developmental immunotoxicity and neurotoxicity. However, those tests can be adapted ('waived') by using a weight of evidence justification, or by using tests that were performed with chemically related substances, or by exposure-based adaptations.
- No such information is required for chemicals marketed at lower tonnages, and specific caution is required for these chemicals. A first assessment of REACH registration records has also shown that there is room for improvement regarding information on the reprotoxicity of substances.
- Some countries have already implemented measures on reprotoxicants that go beyond the minimal requirements of the EU, and these have been shown to have beneficial effects on risk assessment and awareness, as well as helping implementation.
- Within the project on the extension of CMD, a model guidance document on working with reprotoxicants was developed. Other guidance documents on the use of REACH data are published by WPC and SLIC Chemex.
- As regards occupational exposure limits (OELs), for many chemicals there is a need to supplement the data, especially with epidemiological studies on humans that define the relationship between the level and duration of an occupational exposure and its health effects as well as testing/evaluation methods for critical end points. Lead, for example, is a well-known reprotoxicant, but its OEL is no longer state of the art and is currently under review, while a great number of workers are still exposed to lead and its compounds. ANSES is currently compiling an expert opinion about lead that it will share with SCOEL. The WPC is looking at mechanisms to improve OEL setting for non-threshold substances.
- Improved cooperation between SCOEL and ECHA and its risk assessment committee, and better access to registration data and 'grey literature' ([1]), would help create a better knowledge base for

([1]) 'Grey literature' has not been published in a conventional way, and can be difficult to identify and obtain through the usual routes. It includes a wide range of material such as government publications, reports, statistics, newsletters, fact sheets, working papers, technical reports, conference proceedings, policy documents and bibliographies. A wide range of organisations produce a significant amount of grey literature related to public health, health policy and epidemiology.

the consideration of reproductive effects in OEL setting. Data from safety testing of pharmaceuticals should be accessible for hazard and risk assessment of these products, although they do not fall under REACH.

- The chemical-by-chemical approach to risk assessment appears insufficiently protective against the possibility of mixture effects and there is a need for changes in the current practice. Considering non-occupational exposure to substances with endocrine effects, limited room is left for workplace exposure to mixtures of endocrine disruptors, although these may be taken into account by SCOEL when setting OELs. Consequently, highly exposed women of reproductive age may not be sufficiently protected against the combined endocrine-disrupting effects of chemicals on the health of the unborn child.
- Exposure to reprotoxic risks may also be exported to third countries, for example through the export of electronic waste that may be processed by women and children in the destination countries. This should be prevented.
- Engineered nanoparticles present another challenge, as it is foreseen that increasing implementation of nanotechnology will considerably increase the likelihood of human exposure to a myriad of engineered nanoparticles, at work and from consumer products. No contributions are under way from launched research programmes within the EU, as none addresses effects on pregnancy and the unborn child. The present database on developmental toxicity of engineered nanoparticles is extremely poor and insufficient for even a preliminary hazard assessment for mother and fetus.
- There is an ongoing discussion about whether or not to consider reprotoxic substances to be threshold substances. Because of their potentially non-monotonic response, meaning the response may be greater at lower doses than at higher doses, and the fact that effects depend on the endocrine state of exposed persons, endocrine disruptors are considered by some to be non-threshold substances.
- Important health effects have been linked to exposure to EDCs, including damage to the reproductive system, cancer and metabolic diseases, as well as obesity and diabetes. Given the many, often delayed and irreversible, effects of EDCs, there is an urgent need to identify which substances and mixtures should be banned, which should be restricted, and how.
- Interpreting available information on additive and synergistic effects of exposures remains a challenge for employers, especially small businesses. Where there are some OELs in place, mixture effects can be considered. However, where the scientific data do not yet allow OELs to be defined, a precautionary approach needs to be applied and OSH research enhanced to provide better knowledge for taking preventive measures.
- A clear EU definition of endocrine disruptors is needed. EU policy on EDCs should take into account workplace exposures and workplace risks, as well as combined exposures.

Non-chemical reprotoxicants

- 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 much uncertainty. Proposed measures mainly concern pregnant women.
- Little is known about the effects of occupational exposure to biological risks on male reproductive functions.
- Regarding psychosocial risks, many studies apply unclear measures of stress and periods of exposure, and collect information only after the children are born (increased risk of bias).
- Regarding physical risks, a similar approach to that used for chemicals has been taken: research is closely related to pregnancy (e.g. abortion, preterm birth and fetal growth). These may not be the most sensitive end points. More research is needed, including the selection of the most sensitive end points (for example the nervous system function of the child).

- Risks to reproductivity should be addressed in EU-OSHA's Online interactive Risk Assessment tool (OiRA), for example by developing sub-modules for OiRA, so that they will be included by the sectoral social partners in their risk assessment tools.
- There are also studies on the effects of working hours, shifts and ergonomic issues on reproductive functions. A consideration of work organisation in companies is needed and should specifically address the situation of pregnant women. A legal approach should be considered.

To summarise the workshop, Dr Elke Schneider from EU-OSHA focused on four key areas: collecting evidence; tools and practice; working in synergy; and awareness-raising. The discussions were strongly focused on endocrine disruptors, because of the current policy debate on, for example, the definition of EDCs, but the other workplace risks (physical, biological, psychosocial and those due to combined exposures to several risk factors) need to be considered too, and are addressed in the Agency's report. Dr Schneider recalled the examples of laboratory, epidemiology and register evidence and the discussions on the need for a broader approach to reprotoxic effects, not focused only on women and pregnancy, as currently, but also addressing other risks, including effects on male workers. Dr Schneider mentioned the ongoing debates about whether or not to include reprotoxicants in the CMD, and the discussions on the threshold or non-threshold effects of EDCs and on the integration of combined exposures (including non-occupational exposure) in risk assessments. She also mentioned the usefulness of practical tools, such as JEMs and databases of good practice examples, or the use and limitatons of occupational exposure levels. She pointed out the general agreement of participants on the need to work in synergy with other policy areas.

Professor Lasfarges concluded on behalf of ANSES that the event had provided practical input for future cooperation and for policy options and actions. ANSES is in a unique position, as it addresses risks from several routes of exposure (food, air, environment, occupational), and makes recommendations for several policy fields and from different angles: policy, research, monitoring and practice. ANSES is also involved in the development of tools. At this workshop, ANSES supported EU-OSHA by bringing together national actors from the different policy fields for this important debate.

Raising awareness is important for all stakeholders and publishing EU-OSHA's forthcoming report on risks to reproductivity will contribute to this.

Further actions and recommendations

- EU policies, for example public health, environmental protection and chemicals policies, need to be integrated with OSH to enhance the prevention of reproductive risks.
- Legislation and its implementation should be improved to ensure equal protection for women and men, including those who plan to have children, and future generations.
- Communication with stakeholders and implementation of existing legislation should be improved.
- JEMs should be used more, to pinpoint areas of concern or jobs that need more awareness on reproductive risks. For example, a number of JEMs developed by and accessible through the French Institute for Public Health Surveillance (InVS), in French, provide information on exposures to different types of solvents and nanoparticles (engineered or not).
- Register data and public health information integrated with social security data should be used more to provide evidence of reproductive disorders.
- It is important to capitalise on participants' expertise and on the knowledge gathered in the report commissioned by EU-OSHA. Information will be made available to raise awareness and support further research as well as political and practical measures.

Day I: 15 January 2014 – Evidence and findings

The session started with the presentation of the report commissioned by EU-OSHA on workplace risks affecting reproduction. Further presentations were on the workplace relevance of EDCs, the health effects of exposure to EDC mixtures and the information requirements for reproductive toxicity under REACH.

Welcome and introduction to the workshop

Professor Gérard Lasfargues from ANSES welcomed the participants and mentioned the research done by ANSES and other French institution on EDCs and reprotoxicants. EDCs are included in the French strategy established in the framework of the National Environmental Health Plan. The objectives are to prioritise substances for risk assessment (including regulatory assessment) and management, to establish OELs, to recommend substitution and to improve knowledge. In France, ten projects on EDCs were conducted in the past two years. The research focused on bisphenol A (BPA) substitution, effects of low-level and combined EDC exposures, and new methods of classifying and prioritising EDCs. ANSES performed a risk assessment on BPA at the request of the French ministries for health and the environment and published a report on the results in 2013. The French National Research Programme for Occupational and Environmental Health issues calls for research proposals which are open to foreign teams (although submitted proposals must include a French partner). The relevant website is http://www.anses.fr/en/content/calls-research-projects.

Dr Elke Schneider from EU-OSHA presented the report on workplace risks affecting reproduction, which is part of a large-scale activity started by EU-OSHA on work-related diseases. The report on reprotoxicants will be published taking into account the discussions and observations made during the workshop.

EU-OSHA report: findings and recommendations

Karin Sørig Hougaard, National Research Centre for the Working Environment, Denmark, and

Klaus Kuhl from Kooperationsstelle Hamburg IFE, Hamburg, Germany

EU-OSHA commissioned a state-of-the-art report covering reprotoxicity and workplace exposures, based on the analysis of review papers and research studies, as well as relevant policy papers. The authors found that reproductive risks from chemicals play an important role in workplaces. However, various other factors can adversely affect both female and male workers as well as their offspring.

The research commissioned by EU-OSHA has clearly revealed that the issue of reprotoxic factors at work is underestimated. It is important to review the legislation and its implementation to ensure equal protection for women and men. This should include those who plan to have children and cover new hazards (such as nanoscale compounds). Knowledge on reproductive and developmental effects is very poor and consequently there is a lack of awareness. More research (on men and women) and specific prevention measures are needed.

Klaus Kuhl presented an overview of EDCs, biological, physical and organisational reproductive risks to workers, and prevention and policy issues.

Findings related to chemical reprotoxicants, particles, metals, pharmaceuticals and OELs were presented by Karin Sørig Hougaard.

Conclusions

- Emphasis should be placed on comprehensive risk assessment that covers people of both sexes of reproductive age, all developmental stages (including early pregnancy), long-term effects and all risk factors (including physical, biological and psychosocial factors). The precautionary approach has to be highlighted.

- Studies need to give greater consideration to the time lag of potential effects; they should widen their scope beyond pregnancy, as, for example, functional disorders related to the immune, cardiovascular, metabolic and nervous systems are rarely investigated. Studies should also consider concentrations and mixtures that occur in workplace settings.
- A case has to be made for developmental and transgenerational effects, which have a longer latency than the currently studied effects. Research and policy do not address, or address very insufficiently, these issues, whether in relation to chemicals or other types of risk factors.
- Early pregnancy is not properly addressed by the regulations or in practice. This is mainly because most women are unaware of their pregnancy in the first 3–6 weeks and because preventive measures are generally taken after the pregnancy has been notified to the employer, instead of being taken after pregnancy is planned (or throughout the entire period during which the worker is of reproductive age). The early pregnancy gap is very important, because the fetus might be particularly sensitive early in pregnancy and the effects of exposure might be reversible in adults but irreversible in the fetus.
- Most research on workplace risks to reproductivity and developmental effects is from the field of chemicals. However, there is a clear discrepancy between the number of marketed chemicals and the proportion evaluated for effects on fertility and fetal development.
- Many metals are studied and classified as toxic to reproduction, but more research, as well as workplace measures, is needed, even for well-known metals. Lead is an example, as there is still workplace exposure, despite restrictions, and the EU binding biological limit is considerably higher than the threshold for male fertility effects set by SCOEL or by newer epidemiological studies. There are very few studies on the effects of lead on female reprotoxicity, and a definite threshold for effects on fetal development of the nervous system cannot be derived. Epidemiological studies are particularly important, since, for lead, animal models of fertility are of little use.
- EDCs are widely used and many sectors are affected (e.g. agriculture, plastics, waste management, maintenance, cleaning). Given the many, often delayed and irreversible, effects, there is an urgent need to clarify which substances and mixtures should be banned or restricted and how JEMs could be used to identify areas of concern needing further attention.
- Chemical agents for which information on reprotoxicity is missing include nanoparticles and process-generated particles that do not trigger testing under REACH. For particles, the end points that are sensitive to maternal exposure need to be identified, as these might not appear in conventional guidelines. The same is true for process-generated particles. In addition, process-generated particles (such as welding fumes or diesel emissions) are often not specifically regulated in the workplace (no OEL) and research on their reprotoxicity is limited.
- Reprotoxicity is rarely included in the setting of OELs, because most chemicals have not been studied. Furthermore, larger uncertainty factors are not applied to compensate for this lack of data.
- Interpreting available information on additive and synergistic effects of exposures remains a challenge for employers, especially small businesses. Where there are some OELs in place, mixture effects can be considered, based, for example, on methods applied in Denmark or Germany. However, where the scientific data do not yet allow OELs to be defined, a precautionary approach needs to be applied and OSH research should provide support for prevention.
- As a result of the requirements under REACH, a lot of additional information on the toxic effects of chemicals is being generated and probably many more derived no-effect levels (DNELs) ([2]) will be produced per year than OELs can be established. However, for many reproductive effects evaluation methods do not exist (effects on the male reproductive system, many effects on the offspring, menopausal effects, earlier onset of puberty, etc.), so they will not be covered, as there

([2]) The DNEL is the level of exposure to a substance above which humans should not be exposed. According to REACH, manufacturers and importers are required to calculate DNELs as part of their Chemical Safety Assessment for any chemical registered in quantities of 10 tonnes or more per year. At such tonnage, REACH requests that information should also cover effects on reproductive functions. DNELs are calculated from dose descriptors (such as no observed adverse effect level (NOAEL)/lowest observed adverse effect level (LOAEL) established using uncertainty factors related to extrapolations and the quality of data.

is no system in place to consider these effects. This needs to be addressed. Another problem that needs to be addressed is that DNEL values could be far below or above OELs.

- REACH does not cover process-generated particles, and nanoparticles are regulated as the parent material even if nanoscaling and engineering may alter biological activity considerably, and engineered nanoparticles may have different toxicity than the parent material. Research on the reprotoxicity of such particles is lacking.
- Furthermore, pharmaceuticals are not covered by REACH, even if they are produced to have biological activity. Therefore, there is a lack of available data regarding hazards (specific test results are generally not published). Anaesthetic gases, for example, are not evaluated for their effects on fertility, for developmental toxicity or for their effects on lactation. Moreover, most Member States have no OELs for such substances.
- Emergence of new knowledge on reprotoxicity does not automatically trigger a re-evaluation of the chemicals in question under REACH and the initiation of additional studies. The process should therefore be evaluated and amended to include a revision process of registration data based on new knowledge.
- Regarding combined exposures, some research has been carried out covering solvents, disinfectants, pesticides and EDC mixtures, and also on the combined effects of stress and chemicals, and chemicals and prolonged sitting. Much more research is needed.
- Regarding physical factors, there is research on the effects on reproductivity of ionising radiation, electric shock, electromagnetic fields, heat, cold, noise, ultrasound and vibration, mainly focused on pregnant workers. There are also studies on working hours, shifts and ergonomic issues.
- Biological agents are better studied in health-care units, but information and awareness are much needed in sectors such as meat processing and agriculture. In addition, little is known about the effects of biological agents on male reproductive functions or their long-term effects.
- Regarding psychosocial and organisational risks, many studies apply unclear measures of stress and periods of exposure, and collect information after the children are born (increased risk of bias). Research is closely related to pregnancy (e.g. on abortion, preterm birth and fetal growth). These may not be the most sensitive end points, on which research should focus (for example on the nervous system function of the child and its development). Improvement of work organisation in companies should also specifically address the situation of pregnant women. A legal approach should be considered.
- JEMs could be used better and applied to larger registers, containing developmental data or employment data that exist in some Member States. This could help identify areas of concern or jobs that need more awareness on reproductive risks.

Questions and Answers

Q1. Increased evidence that EDCs are of concern in the workplace was mentioned. What does this refer to? Is it increased exposure or increased potency?

A1. There are relevant studies dealing with occupational exposure. For example, one study found effects on workers in different professions dealing with pesticides. There is no clear conclusion to be drawn from all these studies, and we need to be cautious; however, there is also a need to act. The EU-OSHA forecast on emerging chemical risks (in 2009) pointed out that EDCs are of concern. The definition of emerging risks also covers issues that stakeholders are increasingly concerned about.

Q2. It is generally accepted now that many reprotoxicants are threshold substances. But is there not an overlap with EDCs, which may not have a threshold?

A2.There are studies showing that EDCs do not always follow the classic dose–response curve. It also depends on the exposed persons and their endocrine state (e.g. during maternity). So we still need to study this and take precautions.

Endocrine disruptors and their workplace relevance

Dolores Romano Mozo, Ecologistas en Acción, representative of the European Environmental Bureau on the ECHA committee for risk assessment (RAC) ([3])

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. Important health effects have been linked with exposure to EDCs, including damage to the reproductive system, cancer and metabolic diseases, as well as obesity and diabetes. Several health effects have been related to prenatal exposure to EDCs and, because of their toxicological properties, EDCs are considered non-threshold substances. EDCs have non-monotonic responses, meaning the response may be greater at lower doses than at higher doses, and the effects depend on the endocrine state of exposed persons. EDCs may be found in many products commonly used in workplaces, as solvents, pesticides and biocides, resins, adhesives, etc. The presentation reviewed information on worker exposure to EDCs and presented proposals to improve workers' protection.

Conclusions

There are studies showing a significant correlation between exposure to EDCs and increased occupational disease incidence. Preventive measures are needed and in order to be effective they need to consider the specificity of EDCs: non-monotonic dose–response curves, meaning the response may be greater at lower doses than at higher doses, with effects depending on hormonal balance, timing of exposure and state of development of the target tissue.

EDCs should be considered substances with no safe threshold; therefore, the priority must be to avoid worker exposure and guarantee in particular the protection of pregnant and lactating workers. There are several regulatory policy opportunities to improve workers' protection: the inclusion of EDCs in the CMD and in the pregnant Workers Directive, and the inclusion of specific measures to protect workers from the risks posed by EDCs in the EU Strategy on Endocrine Disrupters and the EU Strategy for Health and Safety at Work. Prevention measures that can already be implemented in workplaces include the identification of EDCs using databases such as RISCTOX and TEDX, the elimination or substitution of identified EDCs, with the aid of tools such as SUBSPORT, and the avoidance of the exposure of vulnerable groups.

Questions and answers

Q1. Why would including reprotoxicants in the CMD help? The CMD has not led to elimination of the use of carcinogens. Expanding legislation does not guarantee that Member States will properly implement it'.

A1. The CMD is more 'visible', for example for inspectors, and includes the obligation to substitute when technically feasible. The best course of action would be to include reprotoxicants and EDCs clearly in it, because if they do not have a threshold they should fall under the CMD.

Q2. Di(2-ethylhexyl) phthalate (DEHP) was authorised recently by ECHA. Is this a good idea?

A2. The authorisation granted is for a case where a closed system and other complex protective measures are used. Other uses of DEHP are currently being considered for authorisation by ECHA. However, RAC may not have all the data on the endocrine-disrupting effects of DEHP that it needs to take an informed decision.

Comment from RAC member: the DNEL for DEHP was established considering end points related to endocrine-disrupting mechanisms of action. When establishing the DNEL, no specific uncertainty factors were evaluated, because there is no such approach now in RAC. This matter will be discussed when discussing (more) substances that will be identified as EDCs under the substances of very high concern

([3]) The ECHA RAC prepares the opinions of ECHA on the risks of substances to human health and the environment in the REACH and CLP processes (harmonised classification, restriction, authorisation). The final decisions are taken by the European Commission.

(SVHC) ([4]) approach in accordance with REACH. Listing of EDCs as SVHC by ECHA is more recent than for other types of high-concern hazards. All currently available data were considered in establishing the DNEL, but there was no data available for low-dose effects.

Effects of exposure to mixtures of endocrine disruptors during development

Ulla Hass, National Food Institute, Technical University of Denmark, Toxicology and Risk Assessment Division

Risk assessment of chemicals is generally based on a comparison of human exposure levels with an experimental no observed adverse effect level (NOAEL) ([5]). In most cases, this is done for one chemical at a time, but humans may be exposed daily to many different chemicals. This raises important questions: can combined exposure to EDCs induce severe effects, although the dose levels for the individual chemicals are around or below their NOAELs, and can these effects be predicted?

The Toxicology Division has designed large experimental mixture studies in rats to assess whether combination effects occur when chemicals with endocrine effects are combined at doses sufficiently low to be without observable effects when tested on their own.

For combinations of chemicals that interact with the same molecular endocrine target, there is clear evidence that mixture effects can arise at doses around, or below, NOAELs. In addition, the mixture effects can be predicted based on dose addition.

There is also good evidence that combinations of chemicals with diverse endocrine modes of action but similar effects induce mixture effects when each component is present at a dose equal to, or below, its NOAEL. We have, for example, investigated the effects of mixtures of a widely used plasticiser, di(2-ethylhexyl) phthalate (DEHP; two fungicides, vinclozolin and prochloraz; and a pharmaceutical, finasteride, on landmarks of male sexual development in the rat, including anogenital distance ([6]), retained nipples, sex organ weights, and malformations of genitalia. These chemicals were chosen because they disrupt androgen action with differing mechanisms of action. Surprisingly, the effect of combined exposures on malformations of the external sex organs was synergistic, and the observed responses were greater than would be predicted from the toxicities of the individual chemicals. For anogenital distance, retained nipples, and sex organ weights, the combined effects were dose additive. When the four chemicals were combined at doses equal to their NOAELs, significant reductions in anogenital distance were observed in male offspring.

The effects of mixtures of endocrine substances modelled based on human exposure were also studied. Thirteen chemicals for which data on *in vivo* endocrine-disrupting effects and information about human exposures were available were selected, including phthalates, pesticides, UV filters, BPA, parabens and paracetamol. The mixture ratio was chosen to reflect high-end human exposure, but not workplace exposure. The results suggest that highly exposed women of reproductive age may not be protected sufficiently against the combined effects of chemicals that affect the hormonal milieu required for normal sexual differentiation of fetuses.

Conclusions

- The chemical-by-chemical approach to risk assessment appears insufficiently protective against the possibility of mixture effects and there is a need for changes in the current practice.

([4]) An SVHC is a substance (or part of a group of chemicals) for which use within the European Union is subject to authorisation under REACH. Listing of a substance as an SVHC by ECHA is the first step in the procedure for restriction of its use. SVHC criteria include reprotoxicants and endocrine-disrupting effects.

([5]) The NOAEL in chemical toxicity studies is the highest dosage level at which chronic exposure to the substance shows no adverse effects (e.g., onset of sickness), usually calculated for laboratory animals. The NOAEL determined in non-human toxicity studies etc. is divided by uncertainty factors to convert it to a human NOAEL. When a NOAEL is unavailable, an uncertainty factor of 10 is often applied to a lowest-observed-adverse-effect level (LOAEL to estimate it.

([6]) Anogenital distance is the distance from the anus to the genitalia (the base of the penis or vagina). in rodent studies, this distance is shortened when the mother is exposed to chemicals that are anti-androgenic.

- In most cases the mixture effects were dose additive. Thus, cumulative risk assessment for endocrine disrupters is feasible and dose addition as an assessment method is recommended as a default.
- Severe mixture effects may occur at NOAELs for single endocrine disruptors, meaning that a mixture would have an effect when the substances taken on their own would not. Cumulative risk can be predicted by dose addition. The 'one chemical at a time' approach underestimates the risk.
- Highly exposed women may not be sufficiently protected in case of exposure to cumulated/synergistic risks.
- Considering non-occupational exposure, not much room is left for workplace exposure that will still be below the 'acceptable' level.
- There is a need for major changes to current risk assessment practice: the recommendation is to use dose addition as default, and allow each chemical to be used at only a fraction of the 'safe level', to allow for other exposures.
- Using molecular mechanisms of action as the only starting point for grouping endocrine disrupters into classes to be subjected to cumulative risk assessment appears insufficient, because mixture effects are seen also for substances with dissimilar mechanisms of action. Instead, grouping criteria should focus on common adverse health outcomes.
- More knowledge is needed on:
  - How broad grouping criteria should be, for example could they be based on a common type of effects, for example specific developmental toxicity effects? Substances whose physicochemical and/or toxicological and/or ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or 'category', of substances.
  - Human exposures. How many chemicals are relevant to combined exposure?

Questions and answers

Q1. Some articles say rodents are not appropriate to study effects on male reproductivity. What is your opinion?

A1. Some of these observations are correct, but sometimes the papers focus more on the differences and say less about the parts that are similar in rodent and humans. It is too early to dismiss animal studies based on the current evidence.

Q2. Why did you use NOAEL, which is more imprecise, instead of benchmark dose (BMD) ([7])?

A2. Benchmark doses are better, but the laboratory studied the substances before studying their mixture, and therefore the same NOAEL approach was used.

Information requirements for reproductive toxicity under REACH

Ulrike Reuter, European Chemicals Agency

The requirements for reproductive toxicity studies under REACH are dependent on the annual tonnage band of substances manufactured or imported:

([7]) BMD was originally proposed as an alternative to NOAEL and LOAEL for setting regulatory levels such as reference doses (RfDs), reference concentrations (RfCs) and acceptable daily intakes (ADIs). BMD is the dose of a substance that is expected to result in a pre-specified level of effect, the benchmark response level (BMR). It takes a general approach to characterising dose response, applicable to any toxicant and end point. A BMD is conceptually superior to a NOAEL for this purpose, because it is less determined by experimental design, because it is a precisely defined entity, and because its precision can be estimated (R. W. Setzer,C. A. Kimmel, 'Use of NOAEL, benchmark dose, and other models for human risk assessment of hormonally active substances', *Pure Appl. Chem.*, Vol. 75, Nos 11–12, pp. 2151–2158, 2003).

- 10 to 100 tonnes (REACH Annex VIII): a screening study for reproductive/developmental toxicity (OECD Guideline for testing of chemicals Test No. 421 ([8]), Reproduction/Developmental Toxicity Screening Test; or Test No. 422 ([9]), Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test).
- 100 to 1,000 tonnes (REACH Annex IX): a pre-natal developmental toxicity study in a first species (OECD Test No. 414) and a two-generation reproductive toxicity study (OECD Test No. 416) if the 28-day and 90-day study indicated adverse effects on reproductive organs or tissues.
- 1,000 tonnes or more (REACH Annex X): pre-natal developmental toxicity studies (OECD Test No. 414) in two species and a two-generation reproduction toxicity study (OECD Test No. 416).

Based on the NOAELs derived from these studies, the registrants need to derive DNELs for different populations, routes of human exposure, durations of exposure and types of effect by applying appropriate assessment factors to the NOAEL. For exposure assessment, the registrants have to determine exposure data and risk management measures for all identified exposure scenarios. Exposure data are usually generated by using an exposure model (for example the ECETOC targeted risk assessment (TRA) tool consists of three separate models for estimating exposures to workers, consumers and the environment that arise during a series of events ('exposure scenarios')) or by a more refined assessment using measured data. To demonstrate the safe handling and use of the substances, the registrants have to present risk characterisation ratios (RCRs; quotient of exposure level and DNEL), which need to be below 1.

REACH also allows the possibility of adapting ('waiving') the required studies, based either on argumentations specific to the end-point reproductive toxicity, listed in Annex IX/X, Section 8.7., Column 2, of REACH, or on general adaptation possibilities mentioned in Annex XI (e.g. weight of evidence, read-across ([10]) or exposure-based adaptations ([11])). When performing compliance checks, ECHA evaluates if the studies provided by the registrants comply with the REACH requirements and if the adaptations comply with the rules set out in the annexes.

There are other mechanisms of REACH that apply to substances classified as known reproductive toxicants. For such SVHCs, restriction and/or authorisation may apply. However, this issue is not addressed in this presentation.

Conclusions

For substances manufactured or imported in quantities starting from 10 tonnes per annum, REACH has specific requirements regarding reproductive toxicity studies. ECHA checks that these are met by sampling the compliance of dossiers. At the end of 2012, the number of active registrations was about 28,000, with more than 16,000 phase-in registrations above 1,000 tonnes. ECHA had performed more than 1,100 compliance checks by the end of 2013.

Questions and answers

Q1. How high is the proportion of dossiers where the registrants opted for waiving but when the dossier was checked this option was not supported by an argumentation compliant with REACH requirements?

A1. REACH requires the generation of information on the intrinsic properties of substances through testing. In certain cases, the registrant is allowed to adapt or waive the standard information requirements. ECHA conducted either an overall compliance check (30 % of the cases) or a targeted

([8]) Organisation for Economic Co-operation and Development (OECD), Test No. 421: http://www.oecd-ilibrary.org/environment/test-no-421-reproduction-developmental-toxicity-screening-test_9789264070967-en
([9]) Organisation for Economic Co-operation and Development (OECD), Test No 422: http://www.oecd-ilibrary.org/content/book/9789264070981-en
([10]) Read-across is a technique for data gap filling where end point information from one chemical is used to predict the same end point for another chemical which is considered to be similar in some important aspect relating to that end point, such as mode of action, toxicokinetics, metabolism, etc. Read-across may be for a qualitative or quantitative result.
([11]) REACH requires the generation of information on the intrinsic properties of substances through testing and by other means: read-across from structurally related compounds and the use of QSARs, and by alternatives to animal testing such as *in vitro* methods. To avoid unnecessary animal testing, REACH provides for the option that information requirements may be adapted based on the justification that exposure is absent or not significant (exposure-based adaptation).

one (70 % of the cases). For compliance checks, ECHA selects dossiers either randomly or because there are particular concerns. Examples of such concerns are dossiers using a large number of adaptations; dossiers using many read-across approaches; or registrations of intermediates([12]); and substances with a reduced registration regime or substances that are totally exempted from the scope of the regulation . There is a significant proportion of registrations with waiving and read-across in the two-generation studies, but ECHA will focus on this in a specific project.

Q2. Looking at the practice of registrants testing and submitting the necessary data, and at the framework for doing this, is there any room for improvement ([13])?

A2. ECHA checked 5 % of the dossiers received for the 2010 registration deadline. Given that some end points are considered highly relevant for the safe use of chemicals, ECHA developed a strategy to focus on these and screened the whole database for specific parts of the dossiers, based on particular concerns. These can be, for example: substance identity issues; end points that are considered highly relevant to risk management and chemical safety; or chemicals that may in the near future be subject to substance evaluation. An IT tool is available to ECHA to pre-assess the dossiers selected for compliance checking so that problems are filtered, meaning that, after being identified as significant, they can be better addressed.

Reprotoxicants: an important issue for workers

Discussant: Tony Musu, European Trade Union Institute, member of the Working Party on Chemicals of the Advisory Committee on Health and Safety at Work

Abstract

The CMD is one of the two pieces of legislation that cover chemicals in the workplace. The CMD has been under revision since 2004. Recently, the debate was about whether or not to add OELs for selected substances to the (only) three already existing substances that have binding OELs in the CMD.

Another topic of debate is whether to extend the CMD to include substances hazardous to reproductivity. There are divergent opinions from employers' and workers' representatives. Employers consider that reprotoxicants are sufficiently covered by the Chemical Agents Directive (EU Directive 98/24/EC, CAD). Workers believe that the CMD needs to be extended to include reprotoxicants.

Knowledge on reprotoxicants is limited and there are problems in identifying reproductive effects for the substances on the market. According to REACH, requirements to provide reproductive toxicity data apply for substances produced or imported in the tonnage band over 10 tonnes per year. This leaves a lot of substances untested for which progress in toxicity studies concerning reproductivity is unlikely to occur.

The best measure to address reprotoxicity is to substitute. The CMD pushes for substitution and this is why reprotoxicants should be included in it. Some Member States included reprotoxic substances when they transposed the CMD into national legislation.

Including reprotoxicants in the CMD would be more consistent with REACH provisions that consider impairment of reproductivity one of the effects of very high concern. Because there is an overlap between reprotoxicants and EDCs, including the former in the CMD will be an additional incentive for the substitution of EDCs, too.

The inclusion of reprotoxicants in the CMD has been considered by the European Commission, which commissioned a study on the best approach. The results are inconclusive, which could be partially because of a lack of data. However, the study identified benefits in countries that had included reprotoxicants in national legislation when they transposed the CMD.

([12]) Article 3(15) defines an intermediate as 'a substance that is manufactured for and consumed in or used for chemical processing in order to be transformed into another substance'.

([13]) Over one-third of registered substances were covered by these dossier checks. In 69 % of the evaluated cases, the dossiers did not comply with REACH requirements. In these cases, ECHA issued a draft decision, requesting more information from the registrants.

Conclusions

Worker representatives are participating in debates regarding legislation and policies that cover substances posing risks to reproductive functions. Their general opinion is that reprotoxicants should be included in the CMD, providing better protection and increased coherence with REACH. Countries that have implemented this have already experienced benefits. Moreover, because some reprotoxicants are EDCs, EDCs might also be better addressed in workplaces following this approach.

Workplace risks to reproductive function

Discussant: Kären Clayton, Senior Labour Inspectors Committee, Chemex group

There is already a comprehensive EU regulatory framework covering substances that pose an occupational risk to reproductive functions. REACH provides a framework for information on hazardous chemicals to be passed up and down supply chains. The CAD covers all chemicals that may have any safety or health effect, including effects on reproductive functions. It requires employers to assess the risks and put preventive measures in place. The CMD includes some agents that are also reprotoxicants, besides being carcinogens and/or mutagens. The Pregnant Workers Directive requires employers to undertake a risk assessment that should include any specific risks to workers who are pregnant, have recently given birth or are breastfeeding. These risks can be from any process, working condition, or chemical, physical or biological agent.

Conclusions

Form a legal point of view, the current legislation offers an EU framework for occupational risks to reproductive functions. More should be known about occupational and other exposures and their effects, to help understand how interventions should be targeted and how best to increase compliance with existing legislation. We are still addressing historical problems (e.g. lead), and we need long-term commitment, as well as a mix of interventions and the involvement of different agencies.

Questions and answers

Q1. How are non-threshold reprotoxicants dealt with in the United Kingdom?

A1.The law says that, regardless of their type, a risk assessment on reprotoxicants has to be performed by the employer and measures taken according to the results of it and following the hierarchy of control, starting with elimination and substitution.

Day II: 16 January 2014 – Prevention policies and practices

The second day was dedicated to prevention policies and practices. Adrian Suarez from EU-OSHA made the link with a recent EU-OSHA workshop on research priorities, at which participants discussed the EU-OSHA report 'Priorities for occupational safety and health research in Europe: 2013–2020'. This report was published in 2013 and highlighted the need for further research on reprotoxic substances and endocrine disruptors. Considering the vast number of chemicals in use today and their broad range of applications, it is obvious that exposure to carcinogens, mutagens and reprotoxins (CMR) and sensitising substances occurs not only in the chemical industry, but also in various other occupations. There are significant occupational health concerns about the potential effects of exposure to toxic substances on reproductive outcomes. Worker exposure to reprotoxic agents and factors, such as epoxides, isocyanates, solvent mixtures, specific pharmaceuticals, EDCs, nanomaterials and stress will increase, and such exposures can harm individual workers or groups of workers. This is indicated by trends in the world of work, for example more complex mixtures of chemicals and other agents, increased used of plastics and composite materials owing to energy saving and faster production cycles, workers changing their place of work and their professional frequently, short contracts, etc. Exposure to reprotoxic substances is erroneously pigeonholed as a 'women's issue' even though it can have adverse effects on men, too. Some of the priorities that the report highlighted included:

- Further development of the methodology and use of JEMs as a means of identifying exposure to reprotoxic risks in the workplace.
- Reprotoxic studies in humans have mostly looked at effects closely related to the course of pregnancy, for example miscarriage, gestation length and birth weight. Additional research is needed on functional disorders related to, for example, the immune, cardiovascular and nervous systems.
- Development of reliable tools for quantitative risk assessment that will generate better quantitative data on potency/potential.
- The need to study the importance of physical and organisational factors (prolonged sitting, lack of access to rest and toilet facilities).
- Additional research is needed to update reproductive and developmental toxicity databases, which have limited information for many chemical exposures in the occupational setting.

Risk assessments of endocrine disruptors, prioritisation of chemicals for future studies and a substitution website were examples of research and practical tools addressing the most discussed type of reproductive risk factor: chemicals. The potential extension of the CMD to reprotoxicants was discussed, together with the results of the study contracted by the EU Commission ([14]). Chemical and other reproductive risks and how they are dealt with in Finland were also presented. A discussion of EU policy and guidance, as well as the WHO priorities and their relation to reproductive risks, concluded the session. Final questions and conclusions ended the workshop.

ANSES activities on endocrine disruptors

Jean-Nicolas Ormsby, ANSES, Paris, France

The mission of ANSES is to provide expertise on food, environmental and occupational health. Since 2009, ANSES has developed endocrine disruptors risk assessment projects at the request of the French health authorities. Though from the outset reproductive health has been the main focus of its activities, the scope of its endocrine disruptor projects has been broadened to take into account other end points. In addition, the various media (e.g. food, consumer goods, air, etc.) and routes of exposure are considered *a priori* before engaging in risk assessment. Several reports on BPA, other bisphenols and

([14]) Analysis at EU-level of health, socioeconomic and environmental impacts from a possible amendment to the Carcinogens and Mutagens Directive 2004/37/EC to extend the scope to include category 1A and 1B reprotoxic substances (SHEcan study), 2011. Available at: ec.europa.eu/social/BlobServlet?docId=10149&langId=en

BPA substitutes have been published ([15])([16])([17]). Ongoing and future endocrine disruptor projects include work on phenols, phthalates, and perfluorinated and polybrominated compounds.

Conclusions

The confidence level of the data in the endocrine disruptor risk assessment for BPA has been described as 'moderate' by the experts, but ANSES took its conclusions into consideration and recommended measures to reduce uncertainty and to improve awareness and prevention.

There are risks to the unborn child associated with exposure to BPA during pregnancy. The aggregate assessment for different exposures showed the predominance of dietary exposure. Nevertheless, the study of particular exposure scenarios during pregnancy identified specific risk situations associated with handling thermal paper and with drinking water from refillable polycarbonate containers.

The scenario relating to handling thermal paper additionally revealed risk situations involving other effects for the unborn child. These include effects on the brain, behaviour or metabolism, and could include triggering obesity or affecting the female reproductive system.

The available data are insufficient to conduct a risk assessment for other target groups (for example infants or adolescents)

Questions and answers

Q1. What is the meaning of the limited/moderate confidence levels that were mentioned?

A1. There were two levels: one was based on the weight of evidence of all data and articles, and was used to decide whether to consider them further; the second level was an expert elicitation later in the process, indicating which would be the appropriate level for the reliability of results. There were also uncertainties related to the availability and metabolism of BPA in rodents, compared with humans, for which there is not much data. The experts considered that the sample of 50 thermal papers included in the study was not representative enough and lowered the confidence level, while for food exposure the confidence level was higher.

Q2. Will ANSES establish a biological exposure limit for BPA?

A2. There is a lot of data, but it is hard to anticipate the intentions of the OELs committee/SCOEL.

Q3. In which sector will the occupational biomonitoring be done?

A3. There is an ongoing pilot study by the Institut national de Recherche et de Sécurité (INRS) on people manipulating thermal paper and a control group. There will be other studies, for example in supermarkets and in workplaces where paper rolls are made.

Q4. Is evidence sufficiently strong to recommend a ban or restriction on BPA?

A4. The Ministry of Ecology has requested ANSES to prepare a restriction proposal for BPA to be considered by ECHA.

Q5.Why is BPA used and does it have to be in thermal paper?

A5. It is used as revealer, but data from 2011 need to be updated to show how and how much it is currently used.

([15]) Opinion of the French Agency for Food, Environmental and Occupational Health & Safety 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, march 2013. Available at https://www.anses.fr/sites/default/files/documents/CHIM2009sa0331Ra-0EN.PDF

([16]) Press Kit. Presentation of reports on the health effects and uses of bisphenol A., September 2011. Available at https://www.anses.fr/en/documents/PRES2011CPA25EN.pdf

([17]) Bisphenol A. ANSES's Work on its uses and effects, and recommendations. Dedicated Webpage: https://www.anses.fr/en/content/bisphenol

Q6. Criteria for EDCs are still under discussion in the EU. From ANSES research, it seems clear that BPA is an endocrine disruptor. Would ANSES use this for the definition?

A6. The report does not say that BPA is an EDC; it says that there is toxicity for pregnant women. It is the job of the ministries, rather than ANSES, to give a definition for EDC. In parallel to the restriction proposal, it has been proposed that BPA be classified Repr. 1B ([18]).

Q7. Did the result translate into sectoral guidance for workplace prevention?

A7. ANSES recommended reducing exposure to BPA in the cases addressed in the research activities.

CMR substitution with a focus on reprotoxicants

Henri Bastos, ANSES, Paris, France

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 or 1B (EU classification) and to develop a tool to promote substitution.

This request fits into Action 4.9 of the first National Occupational Health Plan (2005–2009) by 'Promoting the principle of substitution of the most hazardous chemicals (CMR)'. Its main objective is to improve the process of substitution of CMR 1A and 1B substances. It is now a permanent activity of ANSES for which a website has been created: http://www.substitution-cmr.fr/. The information available in the portal was collected mainly through two surveys of companies on the use of CMRs and their substitutes, initiated in 2008 (23 priority CMR substances) and 2009 (56 CMR substances). The database is now continually updated, with examples coming from various sources.

Since 2009, ANSES has developed many collaborations, and in particular with the National Health Insurance Fund for Salaried Workers (CNAMTS), which allows ANSES to use the results of the national campaign on CMR risks to add specific examples of chemical substitution to its website.

Conclusions

At the end of 2013, more than 350 examples of alternatives were available on the website http://www.substitution-cmr.fr/ for over 100 CMR substances. These data were collected from 500 companies.

The website is not an 'all-inclusive tool'. Disclaimers make it clear that information must be carefully evaluated in the context of each enterprise and application. Of the 120 CMRs included at present in the substitution database, more than half are classified Repr. 1 (A, B) and Repr. 2. Updating is necessary to address recent changes to classification. The database could be extended to include plant protection products and biocides.

Questions and answers

Q1 The methodology used prioritised substances according to CLP hazards and exposure. Where does the information on exposure come from?

([18]) Presumed human reproductive toxicant. The classification is largely based on data from animal studies.

A1. 'Exposability', meaning the number of workers potentially exposed, rather than exposure, is based on a 2005 survey by INRS. In the framework of the inventory of CMR chemical agents produced by INRS in 2005, a worker 'potentially exposed' directly manipulates a CMR agent or is working in a workshop where it is used; the actual level of exposure is not prejudged. The prioritisation of substances was based on hazard, consumption and exposability criteria ([19]).

Q2. Do you rely on company information?

A2. Yes, we rely on industry assessments and safety data sheets, but a quick check is done.

Q3. Are you not duplicating the activities of SUBSPORT ([20])?

A3. We do not have the same point of view as SUBSPORT, but we collaborated, and it should be a shared approach.

Q4 Have you identified any illegal (unregistered) CMRs?

A4. It would be interesting to cross-check, but this was not done.

The Finnish policy on workplace reproductive risks and practical experience

Heikki Frilander, Finnish Institute for Occupational Health (FIOH), Finland

The aim of the Finnish legislation is to protect the reproductive health of both male and female workers, including the pregnant worker and her unborn child. Emphasis is put on improving the work environment, from the planning/constructing stages onwards. The employer is responsible for risk assessment and protective measures. The employer must use qualified expertise, such as occupational health services, in carrying out a risk analysis. Structural and technical solutions are the primary occupational safety measures when dealing with workplace reproductive risks. Legislation on special maternity leave was passed in 1991. In recent years, approximately 200 female workers annually have been granted special maternity leave, owing to chemical, biological or physical hazards. Women are increasingly involved in physically demanding jobs, but special maternity leave is generally taken for other reasons (biological or chemical factors), because legislation does not allow special maternity leave to be taken for the reason that a woman has a physically demanding job. The presentation addressed Finnish legislation and practical experiences.

Conclusions

Focus on prevention is an integral aspect of good workplace safety and health

Both female and male reproduction is considered in theory, but mostly female in practice.

There are still challenges regarding female workers, for example in the case of those in traditionally male-dominated, physically demanding professions.

The Finnish legislation (issued in 1991) listing hazards in workplaces to fetus, reproduction and heredity needs to be updated.

([19]) AFSSET (now ANSES) identified in 2007 a list of 82 substances in CMR category 1 or 2, primarily to assess their substitution. The SIRIS (Système d'Intégration des Risques par Interaction des Scores) tool supports decision-making based on the following criteria:

- EU CMR classification in the European Union (carcinogenic potential (classification C1–C3), mutagenic (classification M1–M3) and/or toxic for reproduction (classification R1–R3));
- annual consumption in France (according to the inventory of CMR substances developed by INRS in 2005); and
- the number of employees potentially exposed, or 'exposability' (according to the INRS inventory).
- The 82 substances were ranked in order of their SIRIS scores. Of these, 23 selected substances were studied.

A similar concept was used to develop a general method for identifying and prioritising substances of concern for priority actions in the framework of the second national Health and Environment Plan by INERIS and published in 2013.

([20]) SUBSPORT is a free-of-charge, multilingual platform for information exchange on alternative substances and technologies, as well as tools and guidance for substance evaluation and substitution management, set up with EU funding. See http://www.subsport.eu/.

Questions and answers

Q1. What proportion of pregnant women take special maternity leave each year'?

A1. The money spent on maternity leave is not much as a proportion of the social institutions budget (less than 1 %)

Q2. Could you give an example of women in a male-dominated profession? Why are ergonomics not considered?

A2. For example, in the emergency services, a pregnant woman who has to carry stretchers cannot get special maternity leave for this. What sometimes happens is that sick leave is used.

EU legislation and practical guidance on occupational reproductive risks

Alick Morris, DG Employment B3, Health and Safety

The presentation focused on:

- EU Treaty requirements on occupational safety and health;
- key OSH directives which are relevant to chemical risk management;
- the possible amendment of CMD to extend its scope to include reprotoxic chemicals;
- ongoing actions and options for future actions that could contribute to improving the risk management of reprotoxic chemicals in the workplace; and
- the need to work collaboratively with internal and external stakeholders at both the scientific and policy development levels.

Because of the concerns that real or potential exposure of workers to reprotoxicants in the workplace cause, the European Commission decided to explore the possibilities of integrating such concerns into a policy framework while simultaneously taking steps to have a guidance document drafted that could help workers, employers and policy-makers take the right steps to minimise such effects.

Therefore, a study report was commissioned from a contractor ('Report to analyse at EU level the health, socioeconomic and environmental impacts from a possible amendment to the Carcinogens and Mutagens Directive 2004/37/EC to extend the scope to include category 1A and 1B reprotoxic substances'); alternative options would have to be explored alongside the one in the title of the report ([21]). The aim was to evaluate the individual and collective benefits of a possible extension to the scope of the directive. The consultants took into consideration inputs by the CWP set up under the Advisory Committee on Safety and Health at Work (ACSH).

The contractors had a difficult task, having to reflect different point of views. Some opinions highlighted an increase in legislative coherence and in employers' responsibilities. On the other hand, possible negative effects for specific enterprises or workers, such as difficulties for SMEs or regarding young workers, could be entailed by the extension. All these had to be quantified and evaluated. The study report did not manage to collect sufficiently robust data for a final conclusion to be reached. One consensus emerged, however: a higher priority should be given to reprotoxicants, and knowledge on these substances should be developed and updated. For example, the lead OEL is no longer state of the art, while a considerable number of people are still exposed to lead and its compounds.

There are also EU policies and legislation that are not specifically occupational, but may have an effect on workers' exposure. All these have to be coherent and, where possible, synergistic. Policy and legislation on chemicals, such as REACH and CLP; the activities of other DGs, such as those for the environment or enterprises; and the work of SCOEL and RAC can contribute to preventing occupational exposure to reprotoxic substances.

([21]) The final report has been prepared by Milieu Ltd and Risk and Policy Analysts Ltd (RPA) for DG Employment, Social Affairs and Inclusion under Service Contract VC/2010/0400. The point of view does not necessary represent the official position of DG Employment.

Conclusions

DG Employment commissioned a report ('Report to analyse the health, socioeconomic and environmental impacts from a possible amendment to the Carcinogens and Mutagens Directive 2004/37/EC to extend the scope to include category 1A and 1B reprotoxic substances'), which was finalised in 2013.

- The EU Treaty promotes employment and better working conditions. Various pieces of legislation contribute to achieving this. Even directives not directly related to the subject, such as the directive on working time, may contribute to preventing risks to reproductive functions. The Framework Directive and its approximately 25 daughter directives (including the CAD, the CMD, the Pregnant Workers Directive and the Young Workers Directive) are a package that should be read collectively. Legislation should evolve, and EU and Member State legal approaches should complement each other. Some countries have already implemented measures on reprotoxicants that go beyond the minimal requirements of the EU, and this is compliant with the Treaty.
- There are many ongoing activities at EU level that, directly or indirectly, may have an effect on achieving better protection of workers who are or may be exposed to reprotoxicants.
- A higher priority should be given to reprotoxicants and knowledge on these substances should be developed and updated. Reprotoxicants are clearly an important issue, as reflected by the recent opinion of ACSH.
- At the scientific level, work is ongoing to prioritise and evaluate substances. At the policy level, DG Employment discusses the problems with external stakeholders in the framework of the tripartite advisory committee, including the Working Party on Chemicals, as well as internally, mainly via the inter-service steering group on the amendment of the CMD.
- The existing OEL for lead is currently under review.
- ANSES is currently preparing a background document on lead, with a specific focus on reprotoxic effects, that will be made available to the SCOEL for its ongoing work on updating the OEL.
- An open call for tender for a study to develop a new database on occupational exposure to a range of priority chemicals was published last year and it is expected that a contractor will be appointed in the near future. The database will be for all types of chemicals, but carcinogens and reprotoxicants could be prioritised.
- WPC is considering a number of possible ways to improve limit setting for non-threshold chemicals.
- The entire EU OSH legislative *acquis* is currently under review and this provides a further opportunity to consider how best to manage the potential risks that may arise from occupational exposure to reprotoxic chemicals.

Questions and answers

Q1. The evaluation for nano-scale titanium dioxide (TiO2) was mentioned; will the developmental effects of nanomaterials be evaluated along with all other effects (which does not always happen)?

A1. The Joint Research Centre of the Commission services (DG JRC), which provides scientific support to SCOEL, is currently reviewing information on nano-TiO2 and it could be contacted for details on the current state of play regarding this work.

The Scientific Committee on Occupational Exposure Limit Values

Discussant: Professor Len Levy, SCOEL

The Scientific Committee on Occupational Exposure Limits was set up by a Commission Decision (Decision 95/320/EC ([22])) with a mandate to advise the European Commission on occupational exposure limits for chemicals in the workplace.

It does this through scientific recommendations to the Commission, which are used to underpin regulatory proposals on OEL values for chemicals in the workplace. Draft recommendations from SCOEL undergo a six-month stakeholder consultation to allow all interested parties to submit health-based scientific comments and further data.

The Committee is composed of a maximum of 21 members, selected on the basis of their proven scientific expertise and experience, with a balanced geographical distribution and appointed by the Commission. They are experts in chemistry, toxicology, epidemiology, occupational medicine and industrial hygiene, and able to critically review available information and recommended exposure limits where possible; they have general competence in setting OELs.

All SCOEL members act as independent scientific experts, not as representatives of their own governments.

SCOEL is not involved in the classification of chemical substances but provides information on existing EU harmonised classification data in the SCOEL/SUM documentation on the chemicals it reviews, and these are published on the SCOEL website ([23]).

Any available published information on reproductive effects from human or toxicological studies will be taken into account when recommending OEL values, but it is recognised that there is a paucity of information in this area for many occupationally used substances. Although no extra uncertainty factors are used in recommending OEL values for the absence of such data, the lack of data is usually noted in the SCOEL/SUM documentation, so that national risk assessors and risk managers can take this into account.

The philosophy of SCOEL in the area of reproductive health outcomes is encapsulated in their Key Documentation: Methodology for the Derivation of Occupational Exposure Limits (Version 7, June 2012). This can also be found on the SCOEL website.

'The objective of OEL setting is to prevent adverse health in occupationally exposed persons and in their progeny. Thus, the potential of each substance to produce adverse effects on various aspects of the reproductive process needs to be considered, even though the availability of relevant data in this field of toxicology is limited for quite a number of substances.'

After the workshop, Mr Levy provided a guideline for risk assessments for exposure to mixtures of chemical substances which may have similar modes (mechanisms) of action (the Interdepartmental Group on Health Risks from Chemicals, *Chemical Mixtures: a Framework for Assessing Risks to Human Health*, undated).

Conclusions

The methodology for derivation of OELVs includes reproductive effects on exposed persons and their progeny. Available published information on negative reproductive effects is considered by SCOEL, but for many substances such data are insufficient or missing. SCOEL usually notifies this lack of data in its documents.

([22]) The Commission Decision was replaced in March 2013 by Decision 2014/113/EU, which aligns the functioning of SCOEL with the Commission's rules on expert groups.
([23]) http://ec.europa.eu/social/main.jsp?catId=148&langId=en&intPageId=684

Reprotoxic substances in the context of the revision of the CMD: viewpoint from Advisory Committee for Safety and Health's Working Party on Chemicals and from France

Discussant Mathieu Lassus, designated chairman of the Advisory Committee for Safety and Health's Working Party Chemicals, contrasted the views of various stakeholders represented in the WPC.

The Advisory Committee on Safety and Health at Work has set up a Working Party on Chemicals. Its remit is to consider issues and developments concerning the use of chemicals in the workplace, to actively engage with and support the activities of SCOEL, develop activities within the framework of the CAD and CMD, deal with occupational safety and health issues arising from the 'inter-relationship' between EU OSH requirements and other EU legislation and initiatives, and monitor developments on the use of chemicals in the workplace, in particular emergent risks such as endocrine disrupters and nanomaterials.

The WPC expressed its opinion in May 2013 on whether or not the CMD should be extended to reprotoxic substances (Doc 727/13).

- From the Workers Interest Group: the CMD should be extended to include reprotoxicants. This would harmonise the provisions of the CMD and REACH, which includes these substances in the SVHCs. It would also increase the synergies between REACH and CMD. Six Member States have already extended the scope of the CMD when implementing it, to cover reprotoxic substances. The European Parliament, in its resolution of 15 December 2011 on the mid-term review of the European strategy 2007–2012 on health and safety at work ([24]), also called for an extension of the CMD to include reprotoxicants.
- From the Employers Interest Group: the CMD should not include reprotoxicants, as it was conceived to deal with non-threshold substances, while most reprotoxicants are considered to have a threshold mechanism of action. Reprotoxicants should be considered under the CAD, which provides a framework that is sufficient to deal with reprotoxicants.
- The Governments Interest Group (GIG) has been neutral on this point. The point of view of France within the group was that a global CMR approach is possible. France adopted it in 2001 when transposing the CMD and could share its experiences. With such a regulatory scheme, there is less gender discrimination when considering effects on males/females, and it contributes to a global risk prevention approach for workers and the general population. This scheme is still coherent with the national and EU classification under CLP and also with the approach of REACH, and the biocides, cosmetics and pharmaceuticals regulations.
- The analysis in the report commissioned by DG Employment noted some benefits for the countries that had included reprotoxicants in their transposition of CMD (e.g. France, Germany). The report could not substantiate a decision on 'the most appropriate approach at EU level' at the time of writing. Awareness raising and guidance appeared to be the most cost-effective measures.

Conclusions

The debate on the extension of the CMD is still ongoing, since at present it is not possible to decide on the most appropriate approach because of the divergent views on the concept, scope and purpose of the CAD and the CMD, including on how to regulate substances for which a threshold for effects can be established.

Consensus was reached on the importance of effective workers' protection and guidance and the need to put into practice the general principles of prevention.

There is no need simply to wait for legislative changes; meanwhile, other measures can be taken, such as identifying priority reprotoxicants, providing non-binding guidance and raising awareness, and setting

([24]) European Parliament resolution of 15 December 2011 on the mid-term review of the European strategy 2007-2012 on health and safety at work (2011/2147(INI)), http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+TA+P7-TA-2011-0589+0+DOC+XML+V0//EN#def_1_27

OELs or renewing IOELVs/BOELs([25]) if appropriate (e.g. for lead and compounds). Moreover, there is a strategy on EDCs in progress in the EU, and also in some Member States.

WHO perspective on reproductive hazards at work

Discussant Ivan Ivanov, World Health Organisation (WHO), Geneva, Switzerland

The World Health Organisation (WHO) is a specialised agency of the United Nations.

There are several WHO priorities relevant for this workshop.

- One priority is protecting and promoting health throughout the entire course of a life. It is important to consider every stage of exposure and the specific vulnerabilities along the course of a life.
- Another priority is work on non-communicable diseases. In 2011, for the first time since a session on HIV, a special session of the General UN Assembly was held on a disease-related topic, this time on non-communicable diseases. The UN registered 16 million deaths linked to non-communicable diseases, some of them related to occupational exposure.
- Universal health coverage is also a WHO priority: everybody should have access to reproductive health and planning. The WHO is working with Member States to reform health systems and make them people-centred: delivering health services where people live and work, according to the specific health needs of people. This includes taking into account work history in providing (reproductive) health services. All this requires good collaboration between the health, labour and environmental sectors.
- We must always remember practical implementation. In addition to regulations, national plans are needed. There are various national plans currently running, and recently several Member States developed action plans for non-communicable diseases.
- It is important to engage health service providers – general practitioners, nurses, midwives – and provide them with useful tools on how to consider occupational reproductive risks in delivering health measures. It is these professionals, in primary health care, that people will speak to, even before occupational physicians, in case of a health problem that may be occupational in nature.
- Breastfeeding is an important issue for our species. It should be considered in relation to reprotoxicity in two ways: its role in, on the one hand, transmitting hazardous substances to the offspring and, on the other hand, protecting the offspring from the effects of some exposures'. Breastfeeding in the workplace is important and is not always sufficiently considered in debates on reprotoxicants.
- In the USA, birth defects, spontaneous abortion and infertility are occupational diseases and are compensated. Recognition and compensation should be available in the EU.
- Non-EU aspects are important for the WHO, as an international body, and they should be considered at EU level, too. There are concerns on the reprotoxicant content of waste electrical and electronic equipment that is sent to Africa and China, where it is processed by women and children without any protection. We should export our knowledge on reprotoxicant risk prevention to these areas, too.

([25])Indicative or binding occupational limit values

Final questions and answers and proposals

Q1. Does SCOEL have an agreement with ECHA to allow access to relevant information?

A1. Steps are being taken for a closer collaboration between SCOEL and ECHA: a representative of ECHA's risk assessment committee will participate regularly in SCOEL meetings. There is a lot of data generated by REACH, and it is important to agree, with ECHA, on how SCOEL can access information and what type of information is available. Information could be tracked on the ECHA website and ECHA or the owner of the data could be contacted. Data that is not on the ECHA website is generally missing from the dossiers. Experts on reprotoxicity could also be contacted, because even open research literature is not always easy to track, or SCOEL may consult such an expert.

Q2. Does SCOEL take into consideration background exposure when setting OELs?

A2. It is hard to consider all factors; there are occupational studies that are considered. It is, however, important that combined exposures in private life and in the workplace are considered. The biological limit values take into account all exposures.

Q3. In France, it is possible to recognise a disease as an occupational disease (OD) not only according to the national list of diseases but also through the complementary system, in which the victim has to prove the link between the illness and his or her work. How is this done in other countries?

A3. In the USA, the list of occupational diseases has a chapter on reproductive diseases, including infertility, birth defects and spontaneous abortion. The International Labour Organisation list of occupational diseases does not explicitly include reproductive occupational diseases, but it includes a general clause allowing for any other diseases that can be demonstrated to be occupational. Health providers should know about this, because they are the first who help victims initiate a claim.

ANNEX: Questions for discussion

Research

- Do we need more prospective (epidemiological) studies that look at effects during a longer period of time, and how can that be achieved?
- Do we need studies in humans that do look not only at effects closely related to the course of pregnancy (abortion, gestation length and birth weight) but also at other effects, such as hormonal effects in men, or transgenerational effects and functional disorders related to, for example, the immune, cardiovascular and nervous systems, and how can that be achieved?
- Should animal studies also consider concentrations that occur in workplace settings?
- Do we need specific study designs for major chemical exposures in the work environment that do not automatically trigger testing, for example within REACH, or where relevant models do not resolve important controversies (such as process-generated particles, engineered nanoparticles, chemicals for which animal models are inadequate for risk assessment, shift work, ergonomic factors, and psychosocial strain (stress))?
- Should the scope of the investigated end points be widened and cover , for example, functions of the cardiovascular and immune systems, the neuroendocrine axis, and hepatic and renal functions?

Definition

- In relation to research, testing or prevention, should the definition be revised to include the many effects, especially effects on the offspring/transgenerational effects?
- Should the definition of ECDs refer for legal purposes to 'the probability of causing adverse effects'?

Evidence, exposure

- How to design more systematic exposure assessment programmes and routines?
- How can JEMs be further developed to aid prevention? How can the development of such matrices be supported (e.g. by exchange of information on exposure data, e.g. from exposure databases)?
- Is there a need for open access to pharmaceutical toxicological data for risk assessments?
- Are endocrine disruptors of concern also in the occupational setting? Does research need to be broadened and intensified in this respect?
- Is there too much focus on chemicals and do we need to widen the scope?
- Do we need more research on the effect of biological agents in workplaces, particularly but not exclusively in relation to male fertility and reproduction, and how could this be achieved?
- Is there a need for more sound epidemiological studies regarding stress at work affecting reproductive end points (most investigated end points are, time-wise, relatively close to pregnancy, e.g. abortion, preterm birth and fetal growth, which may not be the most sensitive end points)?
- Do we need more studies on physical exposures and combined exposures, and how can this be achieved?

Legal issues, OELs

- Do compensation schemes in Member States cover the various effects of reprotoxicants? For example, how is compensation managed in the case of a child that is born damaged because of the parental occupational exposure?

- Should legislation and its application in practice (e.g. regarding OELs) be reviewed to ensure more equal protection for women and men, including those who plan to have children, as well as the inclusion of new hazards into law (such as nanoscale compounds)?
- Importance of the early pregnancy-gap in legislation: how can it be closed?
- Should reproductive toxicity assessment be applied also for low-volume chemicals which are not subject to registration under REACH, and how can this be done?
- What would a comprehensive risk assessment that covers both sexes, all developmental stages, long-term effects and all risk factors (including physical, biological and psychosocial factors) look like? How can the development be organised?
- Should there be a separate regulatory class for EDCs?
- Should the use of not (yet) validated test methods be encouraged in order to stimulate the generation of more data, and how could that be achieved?
- How could further guidance documents for the interpretation of test data be developed?
- Should pregnancy and gametes be specifically considered when setting OELs? In what way?
- How should the OELs/DNELs problem be addressed?

Policy

- Do we need more awareness-raising measures, and how could this be organised?
- Do we need more guidelines, and how could this be achieved? Who are the main actors?
- How can SMEs be supported to prevent workplace risks to reproductivity?

Prevention

- Could OiRA be used to improve risk assessment in this area? If so, how?
- Should EDCs and nanomaterials be indicated in SDSs, and how could this be achieved?

Final

- What are the conclusions for research?
- What are the conclusions for regulation?
- What are the conclusions for prevention?
- What are the gaps and needs?