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Identification of risks of endocrine-disrupting chemicals: overview of existing practices and steps ahead

Report of a meeting in Bonn, Germany

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ABSTRACT

The meeting was organized by the WHO European Centre for Environment and Health of the WHO Regional Office for Europe, in cooperation with WHO headquarters. The main objective was to discuss methodologies for assessing the risk of endocrine-disrupting chemicals (EDCs) to human health and, in particular, experiences in assessing exposure to EDCs, health surveillance, and the design and performance of epidemiological studies, as well as of building the capacity necessary to address problems related to EDCs at the national and international levels. Next steps were agreed to facilitate activities aimed at identifying risks to human health from EDCs and supporting countries in implementing the relevant commitments made at the Third Session of the International Conference on Chemicals Management (ICCM), Nairobi, Kenya, 17-21 September 2012 and the Fifth European Ministerial Conference on Environment and Health in Parma, Italy, 10-12 March 2010.

KEYWORDS

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Abbreviations

BMI	body-mass index
BPA	bisphenol A
CEE	Central and Eastern Europe
CHICOS	Developing a Child Cohort Research Strategy for Europe
EDCs	endocrine-disrupting chemicals
ENRIECO	Environmental Health Risks in European Birth Cohorts
EU	European Union
GEOSS	Global Earth Observation System of Systems
GENASIS	Global Environmental Assessment Information System
GIS	geographic information system
GMP	Global Monitoring Plan
HBM	human biomonitoring
HEAL	Health and Environment Alliance
HELIX	The Human Early-Life Exposome
ICCM3	Third session of the International Conference on Chemicals Management
IOMC	Inter-Organization Programme for the Sound Management of Chemicals
NBP	National Biomonitoring Program
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute for Environmental Health Science
NGOs	nongovernmental organizations
OCPs	organochlorine pesticides
ODS	ovarian disgenesis syndrome
OH-PCBs	hydroxy-PCBs
PCBs	polychlorinated biphenyls
PCDDs	polychlorinated dibenzo-p-dioxins
PCDFs	polychlorinated dibenzofurans
PFNA	perfluorononanoic acid
POPs	persistent organic pollutants
RECETOX	Research Centre for Toxic Compounds in the Environment
SAICM	Strategic Approach to International Chemicals Management
SCRCs	The Stockholm Regional Centres for capacity building and technology
TDS	testicular disgenesis syndrome
T2D	type 2 diabetes
UNEP	United Nations Environment Programme
WHO-PCCD/F-TEQ	WHO scheme for the Toxicity Equivalents of Dioxins including PCDDs and PCDFs

Introduction

The meeting was organized by the WHO European Centre for Environment and Health of the WHO Regional Office for Europe, in cooperation with WHO headquarters. The aim of the meeting was to discuss: the current practices of, and the methodologies and tools used in, assessing the risks of endocrine-disrupting chemicals (EDCs) to human health; experiences in the assessment of environmental exposure to EDCs, the human biomonitoring (HBM) of EDCs, the surveillance of endocrine-system disorders at the international and national levels and the design of epidemiological studies; and needs in relation to capacity-building. The next steps necessary to facilitate EDC-related activities at the national level were also discussed. The programme of the meeting is outlined in Annex 1.

The meeting was attended by 32 leading international experts from 22 countries, including researchers, representatives of WHO collaborating centres, and observers from international and nongovernmental organizations (NGOs) (Annex 3).

Professor Dimosthenis Sarigiannis (Greece) was elected as Chairperson.

The Ministry for the Environment, Nature Conservation, Building and Nuclear Safety of Germany generously provided financial support for the meeting.

Background

EDCs represent an emerging issue on the global agenda in connection with the sound management of chemicals *(1)* and a priority for action in the area of environmental health in the WHO European Region *(2)*. The WHO/United Nations Environment Programme (UNEP) publication, *State of Science of Endocrine Disrupting Chemicals - 2012*, emphasized that, despite substantial progress made in recent times, there were still gaps in the knowledge about, and understanding of, the health risks of EDCs. The publication also stressed that progress made in understanding EDCs has been based mainly on information derived from studies in developed regions and that there is still a major lack of data from large parts of the world. Therefore, more research is necessary, involving developing countries and countries with economies in transition *(3)*.

To facilitate and coordinate action at the international level, the Inter-Organization Programme for the Sound Management of Chemicals (IOMC) developed the Workplan on endocrine-disrupting chemicals *(4)*. The WHO European Member States requested the WHO Regional Office for Europe to support them in assessing the health impacts of EDCs through information collection and sharing, networking, raising the awareness of health practitioners, and advice regarding epidemiological studies *(5)*. In response to this request, the Regional Office published the report, *Identification of risks from exposure to endocrine-disrupting chemicals at the country level (6)*, which provides information on activities being carried out in the area of EDCs in selected countries, the main results of epidemiological studies, and proposals of action that countries could consider as a first step towards the prevention of health risks from EDCs at the national level.

Scope and purpose

The meeting was organized to facilitate discussion on further activities aimed at identifying the risks to human health caused by EDCs and supporting the countries in their efforts to meet commitments made at the Third session of the International Conference on Chemicals Management, Nairobi, Kenya, 17-21 September 2012 (ICCM3) *(1)* and the Fifth European Ministerial Conference on Environment and Health, Parma, Italy, 10-12 March 2010 *(2)*.

The purpose of the meeting was, therefore, to:

1. review the current knowledge about, and experience and practice in, the assessment of human exposure to EDCs, and about existing health-outcome surveillance systems and epidemiological studies related to EDCs, and priorities for scientific research, capacity-building, resource mobilization and awareness raising;
2. discuss approaches to facilitating an exchange of science-based information, the dissemination of this information and networking on EDCs; and
3. compile expert advice on the facilitation of EDC-related activities at the country, regional and international levels.

Opening of the meeting

The meeting was opened by Dr Maria Neira, Director, Department for Public Health, Environmental and Social Determinants of Health, WHO headquarters. In welcoming the participants, Dr Neira stressed the importance of the meeting in promoting EDC-related activities worldwide. Over the last decade, WHO has been working in the international arena to promote the collection of information on EDCs that would provide a solid basis for decision-makers around the world. Dr Neira emphasized the value of the leadership of WHO collaborating centres and the deeper involvement of the health sector in chemicals management and activities related to EDCs.

The Head of the WHO European Centre for Environment and Health, Dr Elizabet Paunovic, outlined the priorities and challenges of the European Region in the area of environment and health. These include concerns about the impact of EDCs and harmful bio-accumulating chemicals on human health, which is exacerbated among vulnerable population groups. She specifically mentioned the existence of gaps between the developed and developing countries in the European Region in recognizing the necessity of addressing EDCs as a priority. However, there are common needs for support in this area among the countries of the Region, namely, in relation to promoting scientific research on the burden of disease, assessing risk and exposure, developing relevant tools and methodologies, conducting epidemiological studies at the national and regional levels, and meeting the commitments of the ICCM3 resolution *(1)* and the Parma Declaration *(2)*.

Background papers providing information about recent reviews and activities related to subtopics of the meeting were distributed to the participants prior to the meeting. These were briefly introduced at the beginning of each session.

During the meeting, the participants divided into working groups to discuss the topics from different perspectives. The results of these discussions were presented in plenary. The guiding questions for each working group are listed in Annex 2.

EDCs and public health

Dr Neira spoke about the relationship between EDCs and public health. Environmental factors are responsible for more than 25% of the global burden of communicable and noncommunicable diseases and injuries, the largest burden being found in the poorest countries. Chemicals-related hazards, including EDCs, are of concern along with poor water and sanitation, injuries, and indoor and outdoor air pollution. In the WHO publication, *Global Assessment of the State of the Science of Endocrine Disruptors* (2002), EDCs are defined as exogenous substances or mixtures that alter the function(s) of the endocrine system and consequently cause adverse health effects in an intact organism, or its progeny, or in (sub) populations *(7)*. Exposure to chemicals, and in particular to EDCs, is especially hazardous during certain periods of development and has a strong influence on health throughout the whole life course. Other WHO publications summarizing the existing scientific information on the health effects of EDCs and the knowledge gaps in this area are: *Endocrine disrupters and child health. Possible developmental early effects of endocrine disrupters on child health* (2012) *(8)*; *State of the science of endocrine disrupting chemicals - 2012* (2013) *(3)*; and *Identification of risks from exposure to endocrine-disrupting chemicals at the country level* (2014) *(6)*.

Stressing the need to create a solid basis for policy action on EDCs, Dr Neira identified additional steps to be taken to fill these knowledge gaps as follows: to strengthen knowledge about EDCs in mixtures and alone; to improve methods of testing that enable the identification of EDCs; to find the most effective ways of reducing exposure and, thereby, vulnerability to disease; to collect data from areas that have not been sufficiently surveyed; to create environments that promote and enable scientific progress, innovation, and disease prevention; and to promote research aimed at better understanding the cause of endocrine diseases.

In addition to knowledge enhancement, policy action at the global and local levels, such as spreading awareness about known EDCs, creating a detailed map of potential sources of exposure, providing substitutes for EDCs in products, eliminating occupational exposure to EDCs, developing government policies, and building capacity for action related to EDCs, will lead to the minimization and prevention of their negative health impact. In particular, the engagement of low- and middle-income countries is critical. Dr Neira stressed that the health sector, including WHO, should play a leading role in assessing exposure to EDCs and their risks to human health, strengthening the surveillance of endocrine-system disorders, and facilitating capacity-building and research, including epidemiological studies.

Assessment of exposure to EDCs

Two information documents on the assessment of exposure to EDCs, *Exposure to endocrine-disrupting chemicals: overview of existing practice and step-by-step implementation at national level* and *Human biomonitoring of exposure to endocrine disruptors: current practices*, were prepared by leading experts, namely, the Research Centre for Toxic Compounds in the Environment (RECETOX) team headed by Professor Jana Klanova (Czech Republic) and Professor Dimosthenis Sarigiannis (Greece), respectively. Both documents include information on: existing practices and tools; linkage with the requirements of international agreements on chemicals; and exposure trends in the WHO European Region, as well as proposals for step-by-step implementation of national monitoring programmes.

In summarizing the information document, *Exposure to endocrine-disrupting chemicals: overview of existing practice and step-by-step implementation at national level*, the authors concluded that to establish a programme for monitoring EDCs is an extremely complex task because of the wide differences in the physicochemical properties, sources, pathways, and exposure routes of EDCs. Cut-off criteria to identify EDCs of primary concern, thresholds for the interpretation of monitoring results, and trigger values for actions aimed at reducing levels of EDCs should first be established. The existing programmes for monitoring exposure should be exploited. Monitoring needs to focus on relevant sources of human exposure and include food and other consumer products for which publicly available data are limited. The involvement of national and international authorities and stakeholders in the individual countries is crucial to the feasibility, cost-effectiveness, and sustainability of any programme on monitoring exposure.

According to the conclusion of the information document, *Human biomonitoring of exposure to endocrine disruptors: current practices*, which is based on experience in the WHO European Region, there are significant benefits to be gained from utilizing existing national biomonitoring programmes if they can be extended to cover emerging chemical risks, such as EDCs. For a HBM programme to be effective, there are several elements to which special attention should be paid, namely: the importance of considering population stratification and susceptible windows of exposure, as well as socioeconomic determinants, which should be longitudinal and applicable to both organic and inorganic EDCs and their metabolites; the need for the widespread spatial and temporal distribution of HBM in connection with which there should be special focus on areas with particular environmental contamination problems; and the need to consider toxicity-related data from in vivo, in vitro and high-throughput screening assays, as well as clinical phenotypic data, in parallel with measuring the biomarkers. In addition, it should be borne in mind that HBM has several limitations and should be supplemented by computational techniques for appropriate data interpretation, such as physiologically based biokinetic (PBBK) modelling.

Biomonitoring efforts in the United States of America were outlined in a presentation by Dr Mark Miller of the National Institute of Environmental Health Science (NIEHS). These biomonitoring programmes ranged in size and scope from the broad-based National Biomonitoring Program (NBP), providing information on exposure to more than 450 chemicals and nutritional status, and on individual investigator-initiated monitoring studies of specific population groups. The NBP's National Health and Nutrition Examination Survey

(NHANES) helps to determine the prevalence of chemical body burdens above a known toxicity level, as well as exposure trends over time and impact on human health. The indicators are measured in different matrices, such as human blood, urine, breast milk, and saliva. In the frame of the NBP, the United States Centers for Disease Control and Prevention (CDC) develop advanced laboratory methods, organize training sessions and assist laboratories in confirming their competence. NBP is a federal programme conducted at the state and local levels and involves multiple stakeholders - academia, NGOs, and industry. State-based biomonitoring programmes in California, New York, and Washington provide input to the NBP. A number of specific cohort studies are conducted across the United States to complement the overall understanding of population exposure (for example, the NIEHS Sister Study and Two Sisters Study, the Center for the Health Assessment of Mothers and Children in Salinas (CHAMACOS) longitudinal birth cohort). NIEHS also provides assistance in the implementation of biomonitoring surveys in other countries; the study of urinary concentrations of phenols and parabens among pregnant women in Puerto Rico is an example. The most important issues to address in developing HBM are: time of exposure and time of measurement; chemicals of concern (metabolites and/or "parent" compounds); and the approach that would be applicable – agnostic or lamppost. In addition, the clear formulation of programme objectives and expected outcomes will increase the effectiveness and usefulness of the HBM programme for policy decision-making.

The most sensitive window of human exposure to EDCs is early life (fetus and newborn). The assessment of early-life exposure is a complex task but very critical in evaluating the health effects of exposure to ECDs. Professor Reiko Kishi of the Hokkaido University Centre for Environment and Health, Japan, introduced the ongoing Hokkaido Study on Environment and Children's Health, a cohort study that started in 2002 with the aim of assessing early-life exposure to selected EDCs (polychlorinated biphenyls (PCBs), hydroxy-PCBs (OH-PCBs), dioxins, perfluoroalkyl acids (PFAAs), bisphenol A (BPA), and phthalates (MEHP). Consisting of two prospective birth cohorts, the Sapporo cohort (n = 514) and the Hokkaido large-scale cohort (n = 20,838), the study examines the effects of perinatal environmental factors on birth outcome and allergic diseases and developmental and neurobehavioral disorders in children up to 13 years of age, identifies high-risk groups classified by genetic susceptibility, and investigates the epigenetic effects of environmental chemicals. Chemicals concentration was measured in samples of maternal and cord blood, urine and house dust. A rapid pre-treatment procedure of blood samples to be analysed for PCBs, polychlorinated dibenzo-p-dioxins/ polychlorinated dibenzofurans (PCDDs/PCDFs) and OH-PCBs was developed. The main findings were that: the concentration of toxic equivalents of dioxins and other specific congeners of PCDF or PCDD affected birth weight, infants' neurodevelopment and immune function with significant gender differences with regard to effects; there was a negative correlation between levels of maternal PFCs and reduced birth weight; cord blood immunoglobulin E levels decreased significantly with high maternal perfluorooctanoic acid concentration; and perfluorononanoic acid and perfluorodecanoic acid levels increased among pregnant women between 2003 and 2011. It was found that lower prenatal exposure to perfluorotridecanoic acid may decrease the risk of developing eczema in early childhood that allows suggesting pathological immunosuppressive effects of prenatal PFC exposures. Both maternal PFCs and MEHP concentrations during pregnancy showed a negative association with Inhibin B and an insulin-like factor in cord blood. It was found that maternal genetic polymorphisms in aryl hydrocarbon receptors, cytochrome P450, family 1, subfamily A polypeptide 1, or glutathione S-transferases significantly modified the dioxin concentrations

in maternal blood that were probably caused by different dioxin accumulations in the bodies of individuals with these genotypes and could lead to different dioxin exposure levels. Future studies of the effects of EDCs and genetic polymorphisms (involving metabolism, neurodevelopment and immunoregulation) and their interaction on human health are necessary.

Another cohort study aimed at assessment of early-life exposure to selected EDCs performed at Chiba University under the scientific leadership of Professor Chisato Mori, showed that: umbilical-cord and cord blood are the media of choice for measuring fetal exposure to PCBs and organic compounds; parity should be taken into account in interpreting data as PCBs decrease with each consecutive baby; fetal exposure to several persistent chemicals can be estimated to some extent by measuring the maternal blood level; the levels of certain persistent organic compounds measured in the serum, maternal blood, umbilical-cord and cord blood are strongly correlated when the sources of chemical exposure are identical; there is clearly no difference between the body burdens from certain EDCs for men and nullipara; the levels of PCBs are higher in children under 3 years of age who had been breast fed than in children who had never been breast fed and in other age groups (0-19 years); the levels of PCBs in babies increase as the lactation period becomes longer; and the transplacental transfer of PCBs shows the same trends among PCB congeners. An ongoing hospital-based study in Chiba could serve as an example of designing a study of early-life exposure and risk assessment. It was stressed that the factors that needed to be considered in planning a survey are: the timing of assessment – early, mid-term and late pregnancy, delivery, 1- and 6-month-old newborns, children at ages 1, 2 and 6-8 years; matrices (fathers – saliva; mothers – blood, urine, faeces and breast milk; children – placenta, cord, cord blood, meconium, faeces, urine and teeth); development of a questionnaire and medical records for the collection of information; co-factors (exposure to chemicals, lifestyle, food, psychological and social factors); analysis parameters (epigenomic, biomarkers/indicators, intestinal microflora); and follow-up studies (low-birth-weight children; allergy and neurodevelopmental disorders; causes/co-factors). Biobanking and the economical costs of sample analysis should be also taken in account.

In presenting the instruments available for sharing information on EDCs, Professor Jana Klanova, RECETOX, Czech Republic, said that monitoring human exposure to environmental EDCs is challenging and requires the cooperation of national and international authorities, as well as various stakeholders, including academia. Existing requirements and instruments, such as multilateral environmental agreements, could serve as a basis for planning the assessment of exposure to EDCs. For example, the Global Monitoring Plan (GMP) is a tool for monitoring the implementation of the Stockholm Convention on Persistent Organic Pollutants *(9)* and sets an example of how to collect and provide open access to global data on air pollution and the contamination of breast milk with persistent organic pollutants (POPs). The GMP portal is incorporated in the Global Earth Observation System of Systems (GEOSS) and included in its revised 10-year Implementation Plan. GMP data on air pollution can be sorted by sampling methods (active and passive), compounds, and years. Information on breast-milk contamination is stratified and presented by spatial distribution, parameters, and survey round. The Global Environmental Assessment Information System (GENASIS), created jointly by RECETOX and the Institute of Biostatistics and Analysis of the Masaryk University, Brno, Czech Republic, supports automated data analyses, interactive risk assessment case studies, geographic information

system (GIS) visualization and space-time modelling. The WHO Data Browser presents data from the WHO-UNEP coordinated Survey of Human Milk for POPs. Thus, GMP, GEOSS and GENASIS serve for the collection, analysis, storage and sharing of POPs exposure data and could be used as a basis for the development of an EDCs monitoring system. Professor Klanova mentioned the Stockholm Convention Regional Centres (SCRCs) for capacity building and technology, which are found worldwide, as a possible source of assistance in building regional capacity to address EDCs. In Brno, Czech Republic, the SCRC for capacity building and technology in Central and Eastern Europe (the CEE region), which is a joint project of these countries, has been running an International Summer School of Environmental Chemistry and Ecotoxicology since 2005. This training programme is open to environmental assessment and management professionals from developing countries; to date, 425 have been trained.

Summary of working-group discussions on exposure assessment

Lists of questions for the working groups discussing exposure assessment were framed around the following issues: (1) the contribution of existing programmes to identifying exposure to EDCs; (2) limitations and gaps in existing programmes; (3) necessary action and priorities at the national level; (4) proper harmonization of methods and tools; (5) expert advice to facilitate assessment of exposure to EDCs on various scales, (6) needs for capacity-building (Annex 2).

Working group on environmental exposure and exposure to chemicals in consumer products

(Chair: Dr Katerina Sebkova (Czech Republic); Rapporteur: Ms Suzanna Andonova (The former Yugoslav Republic of Macedonia))

The overall outcome of the discussions was as follows.

- The existing programmes cover only a few EDCs, there is a lack of comparability and harmonization among them, and exposure data (particularly for consumer products) are missing or insufficient; programmes for monitoring chemical exposure exist that can be expanded to include other chemicals with EDC-potentiality;
- For a comprehensive assessment of exposure, EDCs in water, air, food and soil should be monitored; consumer products are priority targets as very little information exists about compounds in these.
- EDCs and their metabolites (planned for inclusion in an exposure monitoring programme) can be grouped and should be prioritized based on physicochemical properties, potential for causing adverse effects, levels of consumption, volumes of production and use, data availability, and identifiable hotspots; appropriate data inventories are useful for prioritizing target chemicals.
- It is important to reach a certain level of harmonization among monitoring programmes to enable the comparison of exposure and the identification of hotspots.
- Quality assurance/quality control in collecting and analysing samples and banking specimens is highly important; integrated surveillance and environmental sample banks are also necessary for monitoring EDCs in the environmental media, as well as in consumer products.

- The step-by-step approach introduced in the GMP can also be applied to the monitoring of EDCs.
- There are huge gaps in exposure monitoring among countries due to lack of capacity, human resources, and legislative support; countries in Africa, especially, have limited monitoring capacity.
- The SCRCs for capacity building and transfer of technology, which have locations worldwide, could be utilized in building capacity for EDCs monitoring. The Centres could provide expertise, analyse samples and manage databases.

Working-group on HBM
(Chair: Professor Martin van den Berg (Netherlands); Rapporteur: Dr Lucija Perharic (Slovenia))

The group started the discussion by emphasizing the significant value of HBM in identifying risks of exposure to EDCs and opportunities for the implementation of HBM at the national level. The overall outcome of the discussion was as follows.

- HBM is essential from a public-health viewpoint and relevant for the assessment of short-term, low-level exposure to raise awareness and drive political decisions. Each country would benefit from implementing its own HBM even if only to assess the exposure of a small population group. Unfortunately, very few countries around the world have HBM programmes, either national or local.
- Currently, some information on levels of EDCs is being collected through epidemiological studies; this should be taken into account in planning the implementation of HBM programmes at the national level.
- In planning HBM programmes, it is most important to consider: identification of the priority chemicals and which of them to include in the programme; the exposure pathways for the future analysis of sources of chemicals; inclusion of chemicals with short half-life - not only those with long half-life (e.g., POPs); selection of appropriate biological matrices; and the cost-effectiveness of studies.
- Country-level HBM can enable assessment of the influence of exposure determinants (e.g. lifestyles) that may be country-specific.
- The information generated from HBM should be communicated to the public as well as to policy-makers.
- Although harmonizing HBM programmes is a very complex issue, even at the regional level, a certain level of harmonization is necessary to enable further investigation into current knowledge. Once the countries develop basic HBM data pools and harmonize their data, at least to a certain level, it will be possible to use the data to identify hotspots at the regional level. This could be another way of using HBM to move forward.

Surveillance of endocrine-system disorders

The information document, *Surveillance of endocrine system disorders: health statistic and surveys*, prepared by Professor Valentina Drozd (Belarus), provided a review of existing statistical data on endocrine-system disorders at the national, regional and international levels and weighed their potential use in assessing the health effects of exposure to EDCs. It also included information about the trends of endocrine diseases in the European Region, the

biomarkers of disorders related to EDCs, and the surveillance of relevant health determinants. There is a number of health surveillance programmes, activities and databases that could provide data on diseases potentially linked to exposure to EDCs. However, these data are not systematic. With respect to endocrine diseases and metabolic disorders, there has been no comprehensive survey or compilation of data that could serve as a unified source of information on diseases related to EDCs and their surveillance. Population-based surveillance systems for the real-time capture of sentinel health endpoints should be developed, and the existing data sources (for example, cancer and malformation registers, hospital statistics data) and newly developed databases (for example, endpoints registers related to EDCs) are essential to this end. A precondition for doing so is the development of validated, sensitive, and cost-effective biomarkers of effects, as well as recommendations on the use of newer molecular and imaging technologies to assess causal associations between exposure and effect. National protocols for the surveillance of endocrine-system disorders should also be developed and agreed internationally to ensure sustainability of the surveillance system.

Dr Joëlle Le Moal, French Institute for Public Health Surveillance (InVS), St-Maurice, France, spoke about the testicular dysgenesis syndrome (TDS) and the ovarian dysgenesis syndrome (ODS). She mentioned that these syndromes have been identified as reproductive-health disorders that are possibly related to exposure to EDCs. TDS includes urogenital malformations, cryptorchidism, hypospadias, poor semen quality, poor testosterone levels, and testicular cancer. ODS encompasses earlier age at puberty, ovulatory troubles, genitourinary malformations, uterine fibroids, polycystic ovary syndrome, endometriosis, reproductive cancers, and reduced fecundity. A series of French studies analysed the national temporal trends and spatial distributions of TDS indicators (semen quality, testicular cancer, cryptorchidism and hypospadias), utilizing existing databases, such as the Fécondation In Vitro National Database (which recorded data on reproductive-technology-assisted attempts from 1989 to 2005), and hospital data. Findings from the analysis include: (a) a decline in semen quality among the general population, which was proven through a 17-year follow-up study; (b) the observation that the decline was seen in almost all regions of France consistently with a change in environmental exposure; (c) a 2.5%/year increase in the rate of surgically treated testis cancer between 1998 and 2008; and (d) increases of 1.8%/year and 1.2%/year in the rates of surgically treated cryptorchidism and hypospadias, respectively, between 1998 and 2008. These results, observed at the level of a large country, are especially consistent with the hypothesis of an increasing incidence of TDS related to growing ubiquitous exposures to EDCs and, whatever the causes, they constitute a serious public health warning. Dr Le Moal mentioned that, although the results were limited by differences in medical practice, coding, and rough proxy for environmental exposures and timing, the French cases showed that it was feasible and helpful to monitor reproductive-health indicators using the existing databases. Considering the increasing public concern about the deterioration of the reproductive-health status in several European countries, and the growing evidence about its relation to EDCs exposure, she stressed that reproductive disorders need to be monitored at the international level to answer the question of a possible global impairment and to analyse the temporal and geographical variations in indicators of reproductive health. Monitoring is also essential to guide and evaluate health policies and interventions. For this purpose, the French Institute for Public Health Surveillance organized the European workshop, “Human reproduction disorders and exposure to endocrine disrupting-chemicals: which reproductive health monitoring systems for the future?", which took place in Paris, France, on 5-6 December 2013. It led to the creation of a new scientific network, Human

Reproduction and General Environment Network, the aim of which is to design a multicountry monitoring system; currently, 11 countries (9 European countries, Israel and USA) are participating. Dr Le Moal displayed the identified milestones for this project, including the inventory and review of potential indicators and existing databases, and the method of selecting the most suitable indicators. Financial support, visibility and the involvement of environmental health surveillance and existing health databases in each country would be necessary to go ahead.

The surveillance of endocrine-system disorders associated with EDCs is necessary for quantifying the disease burden attributable EDCs. Dr Leonardo Trasande, New York University School of Medicine, USA, shared his research on this topic. He described work dating back to the philosopher, Adam Smith (18th century), and documented by Nobel prize winner (2001), George Akerlof, showing that uncertainties in information on health risk negatively influence the price of goods on the market, leading to an undervaluation of goods that may actually be free of environmental contaminants. Environmental chemicals also produce externalities, in that costs are borne by people who do not sell or buy the goods being produced. This phenomenon results in the overproduction of goods because the price at which goods are sold is lower than the societal price. That being said, the lack of information about toxicity and its impact on health, the latency of epidemiological studies, many potential confounders of outcomes, and uncertainty about dose-response relationships, thresholds and subclinical effects have complicated efforts to determine the cost of EDCs to society. Dr Trasande noted that the situation is different for well-investigated chemicals; for example, the economic costs of lead exposure and methylmercury exposure are estimated with more confidence. In the absence of estimates of the disease and disability burden caused by exposure to EDCs, the costs of alternatives can be incorrectly perceived to outweigh concerns about health consequences.

Dr Trasande stressed that new approaches should be explored to assess the economic burden of EDCs. As an example, he demonstrated the approach used to assess costs related to bisphenol A (BPA) replacement based on existing information on obesity and cardiovascular diseases. The total economic benefits of BPA replacement are assessed at US$ 1736 million (base-case scenario) or from US$ 889 million to US$ 13 801 million (sensitivity analysis) *(10)*. This work exemplifies the type of newer economic models that are needed to account for uncertainty in disease causation, so that trade-offs involved in decisions, such as whether to remove BPA from food uses, can be weighed more carefully in spite of incomplete understanding of the health consequences. These newer approaches will be especially important in informing regulations on EDCs. Information on the costs of their ongoing use, however incomplete, is needed because of the broad public health effects of these chemicals. Dr Trasande also commented that the true economic health cost of BPA is probably much higher, as his study only examined two of the health impacts to which BPA has been linked. The Intergovernmental Panel on Climate Change has documented rigorous methods to deal with these uncertainties, and consensus methods have been developed to evaluate strength of evidence, including the WHO grading of recommendations assessment, development and evaluation system and the Danish Environmental Protection Agency's approach to evaluating toxicological evidence. Dr Trasande stated that uncertainty in health outcomes should not preclude the estimation of potential economic benefits associated with prevention, which could be substantial. Such data could be highly informative in the EU, where laws on pesticides (2009) and biocides (2011) *(11,12)* mandate phasing out pesticides and biocides

with endocrine-disrupting properties that may be harmful to health and the environment. Policy discussions that completely incorporate probable as well as certain health costs of EDCs will be critical, as the EU discussions set scientific and policy precedents for other national policies and for a global approach to the regulation of these chemicals under agreements, such as the Strategic Approach to International Chemicals Management (SAICM).

The implementation of an effective surveillance system for thyroid diseases, both carcinogenic and noncancerous, in relation to environmental hazards was demonstrated by Professor Dimitry Bazyka, National Research Center for Radiation Medicine, Kyiv, Ukraine, who spoke about the experience gained in Ukraine in the aftermath of the Chernobyl nuclear catastrophe in 1986. Cancer registration started in Ukraine in 1932 and a cancer registry was created in 1996. The cancer statistics in the country are formed from information collected by 46 institutions specializing in oncology. Aggregated information on the pathology of non-cancerous thyroid diseases is also sent by endocrinology dispensaries and departments at the local level to the regional and central levels (Ministry of Health). After the catastrophe, substantial changes were made to improve the functionality of the surveillance system for thyroid diseases, including: the introduction of direct thyroid-dose measurements; the inclusion of endocrinologists in health-survey teams; the reorientation of the Institute of Endocrinology and Metabolism to the study of exposed-children's health; the creation of scientific and clinical departments dealing with radiation endocrinology for children and adults in the Research Centre for Radiation Medicine; the introduction of a separate field for reporting thyroid cancer in annual statistical reports instead of registering it under "other-forms"; a change in age intervals for reporting on population groups - from (0-29, 30-39, 40-49 and further with 10-year intervals) to (0-1, 1-4, 5-9, 10-14 and further with 5-year intervals). The register allows linkage between health disorders and exposure because the thyroid-diseases surveillance system, which operates at three levels (district, region, country), includes data on exposed individuals, exposure dose (radiation dose), and annual health status.

In addition to the general system described above, the State Chernobyl Registry was established for the clustering of exposed groups according to dose. These groups included: (1) people who were involved in the cleaning-up operations; (2) people who were evacuated from the exclusion zone in 1986; (3) residents of the monitored territories; and (4) children of parents in groups 1-3. Collecting the data within the frame of the surveillance system makes it possible to reveal the regions with the highest incidence rates, the dynamics of thyroid-cancer incidence, and the level of, and the average annual increase in, thyroid-cancer incidence in relation to exposure dose. In concluding, Professor Bazyka stated that the Ukrainian thyroid-disease surveillance system has demonstrated its usefulness for long-term follow-up and for revealing the environmental hazards that affect the thyroid gland. In addition to routine surveillance, scientific studies are conducted to assess the combined health effect of hormonal status and exposure to environmental hazards.

Summary of working-group discussions on endocrine-system disorders

Working group on surveillance of endocrine-system disorders

(Chair: Professor Rosella Elisei (Italy); Rapporteur: Professor Djuro Macut (Serbia))

A list of questions was framed around the following issues: the existing health-statistics system and its use in the surveillance of diseases potentially related to EDCs; main gaps in information on health disorders; priority action required to monitor disorders potentially related to EDCs at the national level; the harmonization of tools and methods for the collection of relevant information; recommendations on national action and capacity-building in relation to the surveillance of endocrine disorders.

The overall outcomes of the discussion were as follows.

- Health surveillance information on the potential effects of exposure to EDCs contributes to the collection of evidence, development of evidence-based risk-reduction measures and facilitates their implementation. This information should be available to decision-makers and interested professional groups and the collection of standardized data on health endpoints should be included in relevant research studies.
- Currently, there are no health-surveillance programmes that are fully applicable to monitoring health outcomes related to exposure to EDCs; the existing health statistics are partly applicable in this respect.
- Only small-scale etiological surveys have been carried out so far; however, some observations have been made as part of cohort and other studies.
- With the exception of a few countries, no registries of diseases that could be potentially related to EDCs are available at the present.
- The lack of data on human exposure represents the main difficulty in assessing health outcomes related to exposure to EDCs.
- There is an urgent need to define appropriate health indicators for monitoring outcomes related to EDCs, such as, congenital abnormalities or disorders of the reproductive system.
- The following action is necessary to promote the collection of knowledge and information:
  - to carry out a review of current approaches to and practices of assessing exposure to potential EDCs and their effects, the results of which could be disseminated through medical/scientific journals (under the auspices of WHO);
  - to promote the exchange of knowledge and information at the country, regional and global levels;
  - to suggest simple clinical tools for diagnosing health outcomes related to EDCs;
  - to develop a strategy for collaboration among various multidisciplinary groups, such as endocrinologists, environmental specialists, pediatricians and gynecologists.
- To facilitate capacity-building in the field of EDCs, consideration could be given to involving WHO collaborating centers, other partner institutions and professional organizations (societies), collaborating with community organizations and NGOs, and training medical professionals. WHO assistance could be provided where the necessary systems and/or capacity might be lacking.

Methodologies for and planning of epidemiological studies to assess the effects of EDCs

The information document, *Epidemiological studies of endocrine disruptors' health effects: methodologies, tools and databases*, developed by Dr Oleg Sergeyev, Chapaevsk Medical

Association, Russian Federation, includes an analysis of the specific characteristics of EDCs and their effects, the sensitive windows of exposure (windows of susceptibility) and the vulnerable population groups to which special attention should be paid in planning epidemiological studies related to EDCs. Different types of epidemiological studies were discussed in relation to their applicability for assessing risks related to EDCs. Examples of cohort studies with a focus on large birth cohorts were listed. A step-by-step approach to planning epidemiological studies was proposed based on an analysis of the existing information and demonstrated by case studies.

The information document concludes that, despite the fact that epidemiological studies of the impact of EDCs on human health are challenging because of the specific characteristics of this group of chemicals and health endpoints, if they are designed appropriately, they provide the most relevant information. Based on an analysis of the existing practices, it is possible to conclude that all known types of epidemiological studies are applicable for the assessment of the impact of EDCs at the national and multicountry levels. For example, conducting ecological and cross-sectional studies could be the first step to obtaining pilot results in a relatively short period of time, at a reduced cost, and involving more participants. Prospective cohort studies are more relevant for investigation of the relationship between exposure to EDCs and their endpoints, especially when focusing on sensitive windows of exposure and vulnerable population groups. Longitudinal cohort studies are preferable for investigation of the causality of exposure to EDCs in relation to health. In order to facilitate epidemiological studies in developing countries, there should be political commitment at the national level to, and financial support at the national and international levels for, the development of relevant programmes and capacity-building. Multilateral and bilateral projects with the involvement of developing countries and countries with economies in transition could be the first step in designing the most effective epidemiological surveys for the collection of evidence.

A review of epidemiological studies aimed at revealing the link between exposure to POPs and type 2-diabetes (T2D), conducted by an international team in the Republic of Korea, was presented by Professor Duk-Hee Lee, School of Medicine, Kyungpook National University, Daegu, Republic of Korea. The review was designed taking into account: characteristics of the pattern of exposure to POPs in the general population (low-dose mixtures); non-monotonic dose‑response relationship; endocrine-disrupting mechanisms; glutathione and mitochondrial dysfunction mechanisms; innate limitations of human studies; outcomes of experimental studies on animals; the complex interaction of metabolic systems; and the current trends and geographical distribution of diseases. The team found a link between the activity of the chemicals-detoxification enzyme (gamma-glutamyl transpeptidase) and T2D in Korean men, which led them to investigate chemicals, especially POPs, as a new risk factor of T2D. Chemical prioritization was carried out based on an assessment of their characteristics, such as, exposure through the food chain, lipophilic nature, detoxification by glutathione conjugation, diabetogenic abilities in in-vitro experiments, and the findings of assessments of occupational exposure. A number of cofounders were considered in evaluating the association between POPs and T2D (age, race, sex, poverty income ratio, BMI, and waist circumference). NHANES biological monitoring data on POPs and several prospective studies were utilized in the review to reveal links between POPs mixture and T2D that led to the conclusion that focusing on POPs mixture is more reasonable than assessing individual components. To support the findings of the population-based study, evidence from experimental studies was included in the data analysis. The hypothesis on

POPs mixture and T2D can lead to a new scientific paradigm that lipophilic chemicals stored in adipose tissue and moving with serum lipids may play a more fundamental role in the pathogenesis of T2D than obesity itself even though obesity can worsen the association between POPs and T2D. The team considered that large prospective studies with serial measurement of a broad range of POPs, adiposity and clinically relevant biomarkers are still needed to reveal the complicated interrelationship among POPs, obesity and the development of T2D.

Exposure to EDCs at critical periods in early life (pregnancy and childhood) needs to be studied to obtain a better understanding of lifetime influence and promote the development of preventive programmes. Dr Maribel Casas Sanahuja of the Centre for Research in Environmental Epidemiology, Barcelona, Spain, who represented the scientific team studying birth cohorts at the EU level, said that studies on birth cohorts can contribute to knowledge about the health effects of EDCs through: examination of the early determinants of health and the effects of single/multiple exposure(s) to EDCs on multiple outcomes; provision of information on many confounders; and elucidation of the temporal relationship between exposure to EDCs and health outcomes. During the last few decades, a lot of data has been collected through cohort studies. The scientific consortia, Environmental Health Risks in European Birth Cohorts (ENRIECO) and Developing a Child Cohort Research Strategy for Europe (CHICOS), have developed recommendations on the conduct of birth-cohort surveys based on an inventory and the review and pooling of existing cohort data in Europe, and an evaluation of contribution to policy. They cover methodology, collaboration on existing data, and areas of interest for future work. For example, for the group, “other chemical exposures (brominated flame retardants, perfluorinated chemicals (PFCs), phthalates, phenols)”, it was concluded that HBM is the state-of-the-art method of estimating total dose and that repeated measurements are necessary for non-persistent compounds. In the team’s opinion, active dialogue and partnership among scientists would be essential for selecting new emerging contaminants and prioritizing measurements in birth-cohort studies. CHICOS and ENRIECO reviewed the data available in the cohorts, including those on outcomes (perinatal outcomes, asthma, allergies, obesity and metabolic health, cognition and behaviour development, accidents and injuries, infectious diseases, childhood cancers) and determinants (social/cultural inequalities, nutrition and physical activity, lifestyle exposures, environmental exposures, and genetics). They concluded that combining, pooling and comparing data is possible and can bring about scientific progress for translation into European policy on child health (and healthy aging), that different studies complement each other, and that considerable progress has been made in standardizing the data of a wide variety of cohorts. There is, however, still much to be done. It was noted that collaborative analysis requires adequate funding. A new EU-funded project, the Human Early-Life Exposome (HELIX) (2013-2017), aims to combine all of the environmental hazards to which mothers and children are exposed, and link these to the health, growth and development of children. HELIX will exploit novel tools and methods of characterizing early-life exposure to a wide range of environmental hazards (remote sensing/GIS-based spatial methods, “omics”-based approaches, exposure biomarkers, exposure devices and models, statistical tools for combined exposures, novel study designs, and burden-of-disease methodologies) in order to characterize early-life exposure to a wide range of environmental hazards and integrate and link them with data on major child-health outcomes (growth and obesity, neurodevelopment, immune-system outcomes).

The results of an international longitudinal cohort study on EDCs in a contaminated site in the Russian Federation were presented by Dr Oleg Sergeyev, Chapaevsk Medical Association, Russian Federation. In accordance with government strategies at the federal and local levels, consecutive and analytical epidemiological studies were started 20 years ago in Chapaevsk (where organochlorine pesticide was formerly produced) and are still ongoing. Several components were included in the study design: assessment of environmental exposure to dioxins and pesticides; HBM of levels of dioxins and pesticides in blood and breast-milk; and evaluation of outcomes with a focus on cancer and reproduction. The main findings were much higher serum levels of pollutants in workers in the plant than in the population, depending on the distance from the plant. The cancer-mortality rate was higher than expected, especially for lung cancer and cancer of the urinary organs in men and breast and cervical cancer in women. A study of the semen quality in workers revealed altered semen morphology in 92% of the examined workers.

A retrospective case-control study revealed a strong association between the prevalence of breast cancer and the consumption of locally produced pork and fish. In a pilot cross-sectional study in 1998, it was estimated that Chapaevsk boys were thinner than boys in other parts of the Russian Federation and in the United States, that they reached puberty and sexual maturity later, and that there was a higher frequency of cryptorchidism and varicocele among them. Subsequently, 516 Chapaevsk families (mother-boy pairs and all 8-9 year-old boys) were enrolled in a longitudinal cohort study in 2003 to investigate: exposure to dioxins, PCBs, lead and organochlorine pesticides (OCPs) at the perinatal, early-life and peripubertal stages; indexes for pubertal development, including onset, tempo and timing (sexual maturity), somatic growth and body composition, level of reproductive hormones, and semen quality. As estimated, the serum concentration of β-hexachlorocyclohexane and other OCPs in the Chapaevsk boys was several-fold higher than in similar age populations in other industrialized countries. Dr Sergeyev presented associations between prepubertal increase of lead level in the blood, lower height and lower levels of serum IGF-1, and between prepubertal increase in serum level of OCPs and dioxins and reduced BMI and lower height. Prepubertal levels and maternal level of serum dioxins, as well as prepubertal level of serum HCB, were associated with the later pubertal onset. After the implementation of remediation and social programmes, the means of 2005 WHO-PCDD/F-TEQ declined (by 3.8 times in the decade of remediation activity).

Summary of working-group discussions on planning epidemiological studies

Working groups discussed the appropriate planning and design of epidemiological studies as a function of the objectives, as well as scientific gaps relating to EDCs.

Working group on epidemiological studies in the relevant policy context

(Chair: Dr Maribel Casas Sanahuja (Spain); Rapporteur; Dr Barbora Jarosova (Czech Republic))

To ensure that epidemiological studies form a firm scientific basis for policy development, the following should be recognized.

- It is important, right from the start of planning an epidemiological study, to involve a wide range of professionals and stakeholders to ensure that the interests of all groups are taken into consideration.
- Epidemiological studies need to focus on priority chemicals, real-life exposure scenarios, the most vulnerable population groups (such as, pregnant women, newborns, children), and endpoints that have a strong health, social and economic impact on society. Chemicals of concern and endpoints influencing health should be identified at the national and/or regional levels, as well as their exposure scenarios and the resulting health issues.
- It may be of benefit to consider including in the studies a wider range of exposure sources and information about affected populations and the determinants of endocrine-system disorders, if possible.
- The results of epidemiological studies should be shared among interested stakeholders and translated into economic-impact language using a cost-effectiveness approach.
- It is important to try to keep the studies consistent.

To facilitate epidemiological studies on EDCs at the national level, it would be necessary to address the availability of:

- information on how to determine the lists of chemicals (criteria for prioritizing EDCs), exposure and effect biomarkers, and health endpoints;
- analytical tools for and methods to investigate relevant biomarkers;
- recommendations on surveillance of disorders, endpoints and biomarkers related to EDCs for use in conducting epidemiological studies at the national level.

To fill possible gaps, it was suggested that:

- countries without capacity be included in regional studies (at least for small pool surveys) as even short-term studies with limited resources can provide valuable information for policy decision-making;
- groups focusing on different aspects of EDCs and information gaps related to EDCs, be formed (under WHO umbrella);
- practical recommendations be developed, applicable at the national level;
- consideration be given to developing legislation that would involve industry in financing the assessment of exposure to EDCs on health.

A certain level of harmonization among epidemiological studies on the effects of EDCs was deemed necessary, particularly with respect to study tools and methods. Some components are, however, difficult to harmonize, such as, the design of short-term studies, the selection of criteria, and the definition of confounding factors that should be considered in the study.

Working group on the planning and design of epidemiological studies
(Chair:Dr Katerina Sebkova (Czech Republic); Rapporteur: Dr Mark Miller (USA)

The following factors should be taken into consideration in designing epidemiological studies to investigate links between chemical exposure and endocrine-system disorders (possibly through reviews of existing information):

- chemicals of concern and target endpoints (health outcomes);
- exposure pathways;

- biomarkers of exposure and effect;
- vulnerable populations;
- risk factors and confounders;
- budget.

It was concluded that the following types of epidemiological studies could be effective (in the context of evidence gathering and policy-making) in the short and long terms.

- For short-term approaches, descriptive studies using national health statistics or existing biomarkers data (borrowed from other studies) and cross-sectional studies could be considered. These types of studies can be utilized for raising awareness and identifying issues of concern.
- For mid-term approaches, case-control studies could be conducted.
- For long-term approaches, prospective cohort studies could be recommended.

The main knowledge gaps to be addressed urgently to assist countries identify the health effects of EDCs relate to developing*:*

- recommendations on the health endpoints considered most important and informative for studying variations between countries and/or regions;
- methodologies for assessing the economic benefits of interventions to reduce exposure to EDCs, across countries and time trends (necessary for raising the awareness of the general public, scientists, and policy-makers of the related health risks).

Working group on future studies, the multicausal nature of diseases related to EDCs- and early-life exposure
(Chair: Dr Leonardo Trasande (USA); Rapporteur: Ms Lisette van Vliet (Belgium))

The best ways to ensure that the multicausal nature of diseases related to EDCs is properly addressed are to:

- establish close links among professionals in toxicology, epidemiology, clinical medicine, public health, bioinformatics, system biology, and –omics;
- study specific endpoints and biomarkers, for example hormones levels (if possible), or specific gene alterations, and to cover the majority of confounders;
- conduct descriptive studies on specific health outcomes that are not difficult to diagnose, along with hormonal assays.

To address the specific characteristics of epidemiological studies aimed at assessing the effects of early-life exposure, the following should be kept in mind.

- In designing the study, it is important to start with developing a list of selected chemicals, taking the budgetary limitations for, and financial burden of, sample analysis into consideration.
- Birth-cohort design can be the choice for studies to characterize the effects of early-life exposure; for studies involving rare diseases, case-control or nested case-control would be appropriate.
- Sample banking (of, for example, blood, cord blood, urine, placenta, etc.) is very important and worth the investment for future studies with improved analytical techniques and newly defined biomarkers.

- In addition to the concept of windows of susceptibility, the results of birth-cohort studies should be taken into consideration.
- Socioeconomic factors need to be considered as health determinants.
- Preconception exposure is likely to be very important although most studies start sample collection at the pregnancy stage.
- The meta-analysis of existing cohort studies worldwide could be a supplementary approach to identifying issues and developing hypotheses for designing new cohort studies.

The following were identified as areas to be addressed in future studies in order to fill the main knowledge gaps.

- The development of biomarkers of effect relating to exposure to EDCs and an EDCs toxicity-screening framework, which could reduce fishing expeditions involving many chemicals.
- Investigation into the biological plausibility and mode of extrapolating toxicological data from animal studies to human health, as well as the uncertainties connected with doing so, and the transgenetic effects of exposure to EDCs through epigenetics mechanisms, intergenerational effects, etc.

Capacity-building to strengthen activities in the area of endocrine disruptors

Within the context of EDCs management, capacity-building includes a wide range of activities, including - but not limited to - the development and implementation of methodologies, tools and instruments to enhance analytical capacity, the education and training of professionals in relevant areas, and the construction of channels of networking and information exchange. In the information document, *Review of current practices at national and regional levels for capacities building for identifying exposures to and managing risks from endocrine disruptors*, developed by Dr Nida Besbelli, two areas of capacity-building are addressed: training and information sharing (including networking). International and national examples are given, which could be considered in connection with capacity-building at the national level.

The information document states that, although much has been done at the international level, training programmes are not given priority and there are gaps in information exchange. Experience in running collaborative projects on EDCs is very limited. At the international level, there is still the need for a clearing house dedicated specially to EDCs, a website for information exchange, a network of scientists on different topics, including, but not limited to, monitoring, exposure assessment, and the provision of advice and assistance to countries on scientific and administrative issues. At the national level, it is of the utmost importance to build human capacity in all the relevant sectors, for example, by including relevant topics related to EDCs in the curricula of training programmes and higher-education courses, and in seminars/congresses involving professionals. Professional associations and NGOs could play an important role in activities related to EDCs.

The implementation of sound chemical management through the promotion of international approaches, the involvement of industry and civil society, and the provision of assistance to

governments in the development of a national regulatory and administrative framework is essential. Dr Desiree Montecillo Narvaez, UNEP Chemicals Branch, presented UNEP's position and described ongoing activities to combat the increasing risk posed by chemicals, which is due to the growing number of individual chemicals and mixtures available, product complexity, and the shifting of production and consumption to developing countries and countries with economies in transition. The prevention of risks from EDCs was recognized as an emerging issue at the ICCM3 *(1)* where countries agreed to raise awareness about these risks and support each other in providing up-to-date information and expert advice and in conducting research. Despite strong evidence of the harmful effects of EDCs on wild-life, including reproduction impairment, thyroid disorders, and damage to the metabolic and immune systems, there are still gaps in knowledge about the impact of EDCs on many species and about mechanisms of action; in addition, little is known about the effects of chemicals other than POPs. An investigation of the disorders and diseases found in wildlife may have similar results to those related to humans; long-term studies are critical to understanding trends over time. To raise awareness about EDCs, UNEP organized a series of regional workshops for countries of Central and Eastern Europe, the Group of Latin American and Caribbean Countries in the United Nations and countries of Africa in 2013, and in countries of Asia in 2014. To meet requests from the countries, UNEP included in its Programme of Work for 2014-2015 a project entitled, "Information and expert advice on risks from endocrine disrupting chemicals", the main outcome of which is evidence-based advice from a network of experts on ways of reducing risks to the environment caused by EDCs. As a next step, UNEP is planning a stakeholder consultation to discuss plans for dealing with the environmental aspects of EDCs, developing a resource-mobilization plan and a repository of data on EDCs, disseminating information about environmental exposure and impact (UNEP webpage related to EDCs), and creating a UNEP advisory group on the environmental exposure and impact of EDCs.

Building the capacity of professional society NGOs, such as the Endocrine Society, and involving them will provide significant input to the collection and dissemination of knowledge about EDCs. Professor Djuro Macut (Serbia), Endocrine Society Global Task Force presented the activities of the Society and its position on EDCs.

The Endocrine Society is a global organization with more than 17 000 members in 120 countries, its main purpose being to collect and disseminate new knowledge on endocrine-system disorders through meetings and publications. The trends of diseases of the endocrine system are worrisome, which is why EDCs are in the focus of the Society's scientific discussions to agree urgent actions to influence the situation. In order to draw the attention of health-care professionals to the problem of EDCs, a forum was organized at each of the Endocrine Society's 87th and 91st annual meetings (ENDO 2005 and ENDO 2009, respectively) where EDCs were included as a special working area. The Endocrine Society issued a Scientific Statement in 2009 *(13)* and a Statement of Principles in 2012 *(14)*. The Society supports communication with media outlets to provide background information on the science of endocrinology and communicates with high-level policy-makers, for example, in the US Congress, the US Environmental Protection Agency, the US Food and Drug Administration, the National Institute for Environmental Health Science, the National Academy of Sciences, the European Parliament and the European Commission. It also collaborates on ongoing issues within the framework of global processes, such as SAICM.

The main messages of the Endocrine Society regarding EDCs are that they interfere with hormone action and can cause life-long effects, they are ubiquitous and standard risk assessment protocols are insufficient, and that endocrine experts must be included in designing protocols and interpreting results. To enhance endocrine research aimed at regulatory decisions on EDCs, the Society will continue to work at increasing the level of knowledge of endocrinologists, primary health care physicians, paediatricians, gynaecologists and urologists, among others, about the long-term health consequences of exposure to EDCs, paying specific attention to developmental, metabolic and reproductive endocrinology.

As part of the continuing education programme for health professionals with university degrees working in the Brazilian national health system, the Ministry of Health of Brazil organized an open, distance-learning training course. Professor Carmen Asmus Froes, Federal University of Rio de Janeiro, Brazil, explained that the course was developed and supported by the Open University of the Health System of Brazil, which has a wide network across the country. The University has a repository of open educational resources for health, a collaborative network of educational institutions, and an information system on health workers. Education offered includes: post-graduate qualification programmes on health-care management; environmental health specialization; courses in family health, maternal and child health, care of the elderly, pharmaceuticals services, and epidemiology; educational modules for primary care; and qualification programmes on home care, mental health and policies. A wide range of educational resources are available, including multimedia, video and audio materials, and equipment for producing Power Point presentations, images, animations and text-based lectures. More than 65 000 students have benefited from the courses, 4000 of which took part in the Environmental Health Programme, which encompasses courses on: environmental health surveillance, risk assessment, disasters, health and development, and the quality of drinking water.

At the regional level, the University organizes courses within the Environmental Health Programme in the frame of technical cooperation with other countries in Latin America (the Plurinational State of Bolivia, Chile, Colombia, Ecuador, Guyana, Paraguay, Peru and the Bolivarian Republic of Venezuela) with the support of the WHO Regional Office for the Americas/the Pan American Health Organization. Open-distance courses create educational opportunities for health professionals, students and the community at the national and international levels; they are easily accessible and do not require a lot of resources. They could be useful for raising the awareness of the health sector about EDCs.

The contributions of civil society organizations (NGOs) to national and international action in the area of EDCs are valuable. In her presentation on the health costs of EDCs, Ms Lisette van Viet, Health and Environment Alliance (HEAL), Belgium, stressed that, through their wide network at the regional and international levels, NGOs provide expertise, raise the awareness of the public, decision-makers and health professionals, identify stakeholders' information needs, and educate vulnerable population groups. For example, HEAL has more than 70 members in 30 different countries working at creating synergies and advocating for better policies (including those on EDCs) at the EU and global levels. To promote a decision on EDCs at the EU level, HEAL prepared the report, *Health costs in the EU: how much is related to EDCs*? *(15)*, and released a policy statement that outlines the organization's position on EDCs. An assessment of incidence data (breast cancer, obesity, prostate cancer, infertility, diabetes, attention deficit hyperactivity disorder/autism) led to an estimation of the

total cost of EDC-related diseases, amounting to €636–637.1 billion per year (all causes). A more realistic assessment (based on 5% of disease burden) would be €31 billion/year in EU-28, although more scientific work is necessary to authenticate it. Ms van Viet considered that even this assessment could drive decisions on reducing exposure, preventing diseases, avoiding health-care costs and improving productivity. She mentioned several examples of regulatory and other governmental measures implemented in the EU, namely: a ban on the use of EDCs in the production of soothers (Austria) and food contact materials (Belgium, France); a national toxic-free strategy (Sweden); EU laws on pesticides and biocides (bans related to EDCs are forthcoming); classification of EDCs (BPA), listing of phthalates, OCPs, 4-nonyl phenol as substances of very high concern, authorization processes and restrictions (BPA in cash register receipts) under the EU Registration, Evaluation, Authorisation and Restriction of Chemicals.

Conclusions

Conclusions and recommendations were summarized by the Secretariat in consultation with the chair of the meeting and agreed with the meeting participants by written procedure subsequent to the meeting.

Exposure assessment

Monitoring the environmental exposure of humans to EDCs requires the participation of many disciplines and stakeholders and cooperation between programmes; existing commitments and instruments include multilateral environmental agreements.

The existing monitoring programmes could serve as a basis for planning the monitoring of EDCs exposure; however, some gaps have been identified, such as the lack of coverage of target chemicals, the lack of comparability of data and harmonization between programmes, and poorly addressed exposure sources, such as consumer products.

Considering the potential exposure routes of EDCs, all environmental media, including air, water, soil and food, should be monitored, with food and consumer products as priorities.

HBM is essential from a public-health point of view; it is also relevant for exposure assessment in the short and long terms, for persistent and short-life compounds, and for raising awareness and driving policy decisions.

The early life (prenatal period and infancy) of a human is the most sensitive window of exposure to EDCs; therefore, the assessment of early-life exposure should be considered as a top priority in planning national HBM.

Countrywide HBM programmes are justified when EDCs are identified in the environment and among the population on a regular basis. More focused surveys can provide reliable data for introducing risk-reduction measures in countries with limited resources. Every country would benefit from HBM even if only a small population group were assessed.

There is a huge gap among countries in the monitoring of exposure to EDCs as a result of differences in capacity and human resources.

Surveillance of endocrine-system disorders

Considering the public's concerns about the increasing rates of endocrine-system disorders, health outcomes linked with exposure to EDCs need to be monitored. However, there are no health-surveillance programmes that are fully applicable to the present. The lack of human exposure data and knowledge on the effects of human exposure to EDCs represents one of the main complications to setting up a programme for the surveillance of health outcomes related to EDCs.

Existing health statistics can serve for monitoring diseases relating to exposure to EDCs with some supplementary action, for example, to develop a consensus list of indicators, biomarkers and reporting protocols.

There are examples of surveillance systems for monitoring reproductive and thyroid disorders that have proved themselves useful in revealing the link between health and environmental exposure to EDCs and following up in the long term.

The development of a surveillance system for health outcomes related to EDCs at the regional and international levels (in addition to national surveillance systems) would allow the comparison of relevant health trends and determinants.

Epidemiological studies

Epidemiological studies are necessary for identifying and assessing the risks of adverse health impact and gathering evidence for implementing effective and efficient measures to reduce the risk. In designing an epidemiological study, special attention needs to be paid - when prioritizing the target chemicals - to reflecting real-life exposure scenarios and identifying the most vulnerable population groups (pregnant women, newborns, children, etc.) and the health endpoints that have the strongest impact on health, society and the economy.

There are huge differences among the countries as regards technical, personal and financial resources and capacity. Depending on the status and needs of the countries, the following designs of epidemiological studies can be considered: for a short-term approach, descriptive studies, using national health statistics or existing biomarkers data (borrowing from other studies) and cross-sectional studies with possible long-term follow-up; for a mid-term approach, case-control studies; and for a long-term approach, prospective cohort studies.

Birth-cohort studies can contribute to the knowledge base on the health effects of EDCs through: examination of the early determinants of health and the effects of single/multiple exposure(s) to EDCs on multiple outcomes; the provision of information on many confounders; and clarification of the temporal relationship between exposure to EDCs and health outcomes.

Active dialogue and partnerships among scientists (in the areas of toxicology, epidemiology, clinical medicine, public health, bioinformatics, system biology, and –omics) and stakeholders are essential for planning epidemiological studies at the national level.

Capacity-building

There is an urgent need to build capacity (including analytical capacity) in all the relevant professional groups, especially in developing countries and countries with economies in transition, to facilitate activities related to EDCs at the national and international levels.

Involving and building the capacity of professional groups and NGOs would contribute significantly to the collection of information and the dissemination of knowledge about EDCs, and to providing expertise, raising the awareness of the public, decision-makers, and health professionals, identifying the information needs of stakeholders, and scoping vulnerable population groups (women of child-bearing age, pregnant women, newborns, children).

Existing resources should be utilized to form the basis for building capacity for action related to EDCs.

Recommendations

Development of a monitoring and surveillance programme

EDCs and potential EDCs should be included in existing national programmes for monitoring environmental pollutants in various media.

A step-by-step approach is recommended for the development and implementation of programme for monitoring EDCs.

At the planning stage, an initial assessment, based on an inventory of existing data, would be useful for: defining the purposes and tasks of the programme; identifying priority chemicals (based on physicochemical properties, potential for causing adverse effects, level of consumption, volume of production and use); deciding the exposure windows to be assessed (early life, puberty, etc); choosing appropriate methodology and analytical methods; and creating a biobank and database.

A certain level of harmonization among programmes for monitoring EDCs is required to compare exposure level and identify hotspots.

Health-surveillance systems to meet the needs of assessing the impact of exposure to EDCs in the general population and the burden of disease, as well as the impact of risk reduction measures in the long run, should be created in all countries and at the international level, and a harmonized list of indicators and protocols should be developed for this purpose.

The information generated from the exposure assessment should be shared with the public as well as policy-makers;

Planning epidemiological studies

The following factors should be taken into consideration in designing epidemiological studies to investigate links between chemical exposure and endocrine-system disorders: priority chemicals and mixtures; the wider range of exposure sources; vulnerable populations; real-life exposure scenarios; determinants/confounders of endocrine-system disorders, including socioeconomic factors; specific influential health endpoints and biomarkers, for example hormones levels; genetic and epigenetic markers; and cost of studies.

Sample banking (of, for example, blood, cord blood, urine, breast milk, placenta, etc.) is very important and worth investing in for future studies using better analytical techniques and newly defined biomarkers.

Finding evidence from experimental studies and the meta-analysis of existing cohort studies worldwide could be a supplementary approach to identifying issues and developing hypotheses for designing new studies. Investigations of disorders and diseases found in wildlife may be similar to those of disorders and diseases in humans, and longitudinal studies may be critical to understanding trends over time.

The results of epidemiological studies should be shared among groups and translated into economic impact, using a cost-effectiveness approach.

It is important to ensure that the studies are consistent and to recognize the effort required to do so.

A certain level of harmonization among epidemiological studies is necessary, particularly with respect to the tools and methods used in studies at the national and regional levels.

Capacity-building

The capacities of WHO Collaborating Centres, the Stockholm Convention Regional Centres for capacity-building and transfer of technology, and other relevant regional centers should be utilized for the monitoring and surveillance of EDCs; a range of possible functions, including expertise in the development and harmonization of methodologies and the creation of databases, can be explored.

To facilitate capacity-building, it is necessary to involve professional organizations (such as societies and academia), collaborate with community organizations and NGOs, and focus on the training of medical professionals and medical students.

The health sector needs to play a leading role in assessing exposure to EDCs and the related risk to human health, strengthening the surveillance of endocrine-system disorders, and facilitating research, including epidemiological studies.

Gaps in scientific knowledge

Gaps that should be addressed in the short and long term were identified in connection with:

- development of criteria for prioritizing EDCs, exposure and effect biomarkers and health endpoints, and for making recommendations on the surveillance of disorders, endpoints and biomarkers related to EDCs that would be useful for conducting epidemiological studies at the national level;
- improvement of the toxicity screening framework, to better identify and assess chemicals with endocrine-disrupting properties to prevent their hazardous (or adverse) effects and, where indicated, to stop or prevent marketing;
- investigation into biological plausibility and mode of action, uncertainties related to the extrapolation of toxicological data from animal studies to human health, the transgenetic effects of exposure to EDCs through epigenetics mechanisms, intergenerational effects, etc.;
- development of methodologies to assess the economic benefits of interventions for reducing exposure to EDCs, across nations and time trends;
- improvement in the identification of endocrine-active chemicals in environmental media and consumer products;
- development of analytical tools for investigating environmental and clinical biomarkers and methods of conducting epidemiological studies at the national level;
- strengthening understanding of the impact on health of single-substance EDCs and mixtures of EDCs ;
- finding the most effective ways of reducing hazardous exposures and, thereby, vulnerability to disease;
- gathering data from regions that are currently not well surveyed;
- creating environments that promote and enable scientific advances, innovation, and disease prevention;
- promoting research for a better understanding of the cause of endocrine diseases.

Uncertainty about health outcomes should not preclude the estimation of potential economic benefits associated with prevention, which can be large. However, information gaps in estimating the burden of disease and disability caused by exposure to EDCs and potential EDCs should be the focus of risk and impact assessment. New approaches should be explored to assess the economic burden of EDCs.

In addition to routine surveillance, scientific studies should be carried out to assess the combined effect of hormonal status and exposure to environmental hazards, as well as related health outcomes.

Next steps

It was agreed that the next steps (in the short term) should be to:

- strengthen collaboration between stakeholders at the national and international levels;
- review current approaches and practices relating to exposure to and effects of EDCs, and provide advice on the implementation of exposure monitoring, surveillance of endocrine-

system disorders, and planning and performance of epidemiological studies to assess the health risks and impact of potential EDCs at the national level, and disseminate this information through medical/scientific journals;

- involve professional organizations (such as societies and academia), collaborate with community organizations and NGOs, and focus on the training of medical professionals and medical students;
- utilize the capacities of WHO Collaborating Centres, the Stockholm Convention Regional Centres for capacity-building and transfer of technology, and other relevant regional centers for the monitoring and surveillance of EDCs and development of relevant protocols and tools;
- strengthen the health-sector role in chemicals management at the national level.

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Annex 1

Programme

Monday, 7 July 2014

08:30 – 09:00 Registration

09:00 – 09:40 Opening of the meeting
Dr Maria Neira, WHO headquarters
Dr Elizabet Paunovic, WHO European Centre for Environment and Health

Introduction of participants

Purpose and expected outcomes of the meeting
Dr Irina Zastenskaya, WHO European Centre for Environment and Health

Election of Chair and Rapporteur

Adoption of the agenda

09:40 – 10:20 ***Session 1. Endocrine-disrupting chemicals (EDCs) and public health***

Keynote: Endocrine-disrupting chemicals and public health
Dr Maria Neira, WHO headquarters

Discussion

10:20 – 10:50 Coffee break

10:50 – 12:30 ***Session 2. Assessment of exposure to endocrine disruptors***

Introduction of the information papers
Secretariat

National programme for monitoring of hazardous substances exposure: challenges and advantages for EDCs, body burden assessment, prioritization of chemicals
Dr Mark Miller, National Institute of Environmental Health Science, USA

Early life exposure assessment: challenges and methodologies
– based on the Hokkaido Birth Cohort Study
Professor Reiko Kishi, Hokkaido University Centre for Environmental and Health Science, Japan

Cooperation in environmental pollutants exposure assessment: available instruments for sharing information on EDCs
Professor Jana Klanova, Research Centre for Toxic Compounds, Czech Republic

Discussion

12:30 – 13:30 Lunch

13:30 – 15:00 ***Session 3. Surveillance of endocrine-system disorders***

Introduction of the information paper
Secretariat

Human reproductive health: the urgent need for monitoring at international level in the context of EDCs exposure
Dr Joelle Le Moal, French Institute for Public Health Surveillance, France

Quantifying disease burden attributable to EDCs
Dr Leonardo Trasande, New York University School of Medicine, USA

Thyroid disorders and environmental hazards: experience of implementation of surveillance programme in Ukraine
Professor Dimitry Bazyka, National Research Center for Radiation Medicine, National Academy of Medical Sciences of Ukraine

Discussion

15:10 – 15:30 Coffee break

15:30 – 17:00 Discussion in working groups

17:00 – 17:30 Working groups' reports

17:45 – 18:00 Closure of the day

Tuesday, 8 July 2014

9:00 – 10:30 ***Session 4. Methodologies and planning of epidemiological studies on endocrine-disrupting chemicals effects - assessment***

Introduction of the information paper
Secretariat

Can persistent organic pollutants explain the current epidemic of type 2 diabetes?
Professor Duk-Hee Lee, School of Medicine, Kyungpook National University, South Korea

European birth cohorts for environmental health research
Dr Maribel Casas Sanahuja, Center for Research in Environmental Epidemiology, Spain

Longitudinal cohort study of EDCs in the contaminated site
Dr Oleg Sergeyev, Chapaevsk Medical Association, Russian Federation

10:30 – 11:00 Coffee

11:00 – 12:30 Discussion in working groups

12:30 – 13:30 Lunch

13:30 – 14:00 Working groups' reports

14:00 – 15:00 ***Session 5. Needs for capacity-building to strengthen endocrine-disruptors-related activities***

Introduction of the information paper
Secretariat

UNEP activities on EDCs
Dr Desiree Montecillo Narvaez, UNEP Chemicals Branch, Switzerland

Awareness-raising and networking of health care professionals
Professor Djuro Macut, Endocrine Society's Global Task Force on EDCs, Serbia

15:00 – 15:15 Coffee

15:15 – 16:00 ***Session 5. Needs for capacities building to strengthen endocrine-disruptors-related activities (cont'd)***

Open and distance learning. Possibilities in training of health professionals. A Brazilian experience
Professor Carmen Asmus Froes, Federal University of Rio de Janeiro, Brazil

Health costs from EDCs – towards estimate in EU
Ms Lisette van Vliet, Health and Environment Alliance, Belgium

Discussion

16:00 – 16:30 Follow-up activity

Closure of the meeting

Annex 2

Topics of working-group discussions

Working Group 1. Environmental exposure and exposure to chemicals in consumer products

1. Do existing monitoring programmes (international agreements, routine environment pollution, food and consumer product safety monitoring at national level) provide data for assessment of exposure to EDCs? Are data collected within existing programmes in different countries comparable?
2. What are the main gaps?
3. What actions are required at national level to facilitate EDCs exposure assessment? Prioritize actions, please, if possible.
4. Should tools and methods of exposure assessment be harmonized and at what level?
5. What recommendation/suggestions to facilitate EDCs exposure assessment at national/regional/international level can be provided?
6. What capacities are necessary and need to be built at national/regional level?

Working Group 2. Exposure assessment (HBM)

1. Is it necessary to conduct HBM for EDCs exposure? For what purposes?
   Are EDCs adequately addressed in existing HBM programmes and, if not, what are the main gaps?
2. What actions are required at the national level to facilitate EDCs exposure assessment? Prioritize actions, please, if possible.
3. Should tools and methods of exposure assessment (HBM) be harmonized and at what level? What recommendation/suggestions can be provided to facilitate EDCs exposure assessment at national/regional/international level?
4. What capacities are necessary and need to be built at national/ regional level?

Working Group 3. Surveillance of endocrine-system disorders

1. Do existing health surveillance programmes/instruments provide the necessary data to monitor EDCs-related diseases and disorders? What kind of databases can be utilized to get information on EDCs-related disorders?
2. What are the main gaps?
3. What actions are required at national level to monitor EDCs-related disorders? Prioritize actions, please, if possible.
4. Should tools and methods of monitoring EDCs-related disorders be harmonized and at what level?
5. What recommendation/suggestions can be provided to facilitate the monitoring of EDCs-related disorders at national/regional/international level?
6. What capacities are necessary and need to be built at national/ regional level?

Working Group 4. Epidemiological studies in the relevant policy context

1. What is needed to ensure that epidemiological studies are firm scientific bases for policy development?

2. What are the main gaps in knowledge to facilitate epidemiological studies on EDCs at national level?
3. Should approaches to epidemiological studies to reveal EDCs effects be harmonized and at what level?

Working Group 5. Planning of epidemiological studies and studies design

1. What specific factors should be taken into consideration in designing epidemiological studies to reveal links between EDCs exposure and endocrine-system disorders?
2. What types of epidemiological studies can be effective (in the context of evidence and policy making) in the short and long terms?
3. What are the main gaps in knowledge that that should be addressed urgently to assist countries to identify health effects of EDCs?

Working Group 6. Future studies, multicausal nature of EDCs-related diseases, and early-life exposure

1. What are the main gaps in knowledge that should be addressed in future studies?
2. How to ensure that the multicausal nature of EDCs-related diseases is properly addressed?
3. What are the specific characteristics of epidemiological studies aimed to assess early-life exposure effects? What can be recommended?

Annex 3
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The WHO Regional Office for Europe

The World Health Organization (WHO) is a specialized agency of the United Nations created in 1948 with the primary responsibility for international health matters and public health. The WHO Regional Office for Europe is one of six regional offices throughout the world, each with its own programme geared to the particular health conditions of the countries it serves.

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The meeting was organized by the WHO European Centre for Environment and Health of the WHO Regional Office for Europe, in cooperation with WHO headquarters. The main objective was to discuss methodologies for assessing the risk of endocrine-disrupting chemicals (EDCs) to human health and, in particular, experiences in assessing exposure to EDCs, health surveillance, and the design and performance of epidemiological studies, as well as of building the capacity necessary to address problems related to EDCs at the national and international levels. Next steps were agreed to facilitate activities aimed at identifying risks to human health from EDCs and supporting countries in implementing the relevant commitments made at the Third Session of the International Conference on Chemicals Management (ICCM), Nairobi, Kenya, 17-21 September 2012 and the Fifth European Ministerial Conference on Environment and Health in Parma, Italy, 10-12 March 2010.

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