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Toward a multi-country monitoring system of reproductive health in the context of endocrine disrupting chemical exposure

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Background: Worrying trends regarding human reproductive endpoints (e.g. semen quality, reproductive cancers) have been reported and there is growing circumstantial evidence for a possible causal link between these trends and exposure to endocrine disrupting chemicals (EDCs). However, there is a striking lack of human data to fill the current knowledge gaps. To answer the crucial questions raised on human reproductive health, there is an urgent need for a reproductive surveillance system to be shared across countries. **Methods:** A multidisciplinary network named HUman Reproductive health and Global ENvironment Network (HURGENT) was created aiming at designing a European monitoring system for reproductive health indicators. Collaborative work allowed setting up the available knowledge to design such a system. Furthermore we conducted an overview of 23 potential indicators, based upon a weight of evidence (WoE) approach according to their potential relation with EDC exposure. **Results:** The framework and purposes of the surveillance system are settled as well as the approach to select suitable reproductive indicators. The indicators found with the highest scores according to the WoE approach are prostate and breast cancer incidence, sex ratio, endometriosis and uterine fibroid incidence, indicators related to the testicular dysgenesis syndrome, precocious puberty incidence and reproductive hormone levels. **Conclusion:** Not only sentinel health endpoints, but also diseases with high burdens in public health are highlighted as prior indicators in the context of EDC exposure. Our work can serve as a basis to construct, as soon as possible, the first multi-country reproductive monitoring system.

Introduction

Endocrine disrupting chemicals (EDCs), substances that interfere with endocrine functions, are ubiquitous in the environment and in mass-consumption products and food. The biological exposure of the general population to the most widely known EDCs such as dioxins, polychlorinated biphenyl (PCB), bisphenol A, phthalates or selected pesticides (synthetic pyrethroïds, organochlorines, organophosphates), is observed in all places and countries where human biomonitoring studies have been performed[1] and exposure to many of these chemicals can occur through multiple routes.

Reproductive effects of EDCs exposure have been suspected for a long time, based on human epidemiological studies, wild life observations and laboratory experiments. In humans, a decrease in sperm concentration was first reported in the 1990s, mainly in industrialized countries.[2,3] More recently, decreasing trends levels have been observed in Finland,[4] Spain[5] and France[6] but not in Sweden.[7] These studies and studies from Denmark,[8,9] Germany,[10] Japan[11] also revealed a high frequency of men with low semen quality. Geographical differences in semen quality were indeed reported in Europe[12–15] and USA.[16]

An increase in testicular cancer incidence has also been observed in almost all Western countries.[17] Interestingly, a West-East gradient was detected in Scandinavia similar to that observed for semen quality.[1,18] Increasing evidence support that impaired prenatal development of testicles leads not only to urogenital anomalies but also to the increased risk of testicular cancer and impaired semen quality in adulthood. These conditions may reflect a testicular dysgenesis syndrome (TDS) possibly caused by exogenous factors such as EDC exposure.[19] This hypothesis, suggested by comparisons between rates of reproductive disorders in Finland and Denmark was not refuted when comparison was extended to a larger number of countries.[20] As regards women, a secular decrease in age at onset of puberty has been observed in many countries,[21] and emerging evidence suggests increases in female reproductive diseases such as precocious puberty, endometriosis, premature ovarian failure and polycystic ovary syndrome.[1] The existence of an ovarian dysgenesis syndrome (ODS) has recently been proposed.[22]

At the same time, evidence for the impact of EDCs on human reproductive health has grown, especially concerning the effects of

developmental exposures.[1] Other data suggest the potential for transgenerational transmission of effects.[23]

These numerous and often consistent results suggest a significant impairment of human reproductive health overflowing fertility outcomes, that could, at least in part, be caused by EDC exposure.

Methods

In 5–6 December 2013, the French Institute for Public Health Surveillance (InVS) organized a European workshop to initiate exchanges within countries for monitoring reproductive disorders in a way that could allow shared temporal and spatial analyses in the context of EDC exposure. United Kingdom, Spain, Hungary, Netherlands, Poland and France, as well as representatives from the World Health Organization (WHO) and the European Commission were involved. A new scientific network, named HURGENT, meaning **Hu**man **R**eproductive health and **G**eneral **E**nvironment **N**e**T**work, was founded, aiming at designing a multi-country monitoring system for reproductive health indicators. Experts from three additional countries (USA, Israel, and Finland) joined the network later. Collaborating work during the workshop and follow-up call meetings and networking allowed setting a consensual framework and a strategy to select indicators.

Furthermore, we conducted an overview of potential indicators, with their potential link to EDC exposure. The list comprises the main indicators that have already been used in epidemiological studies. The annex 1 of the recent report published by the European Commission for regulatory aims[24] was used to score the weight of evidence (WoE) for linking the indicator or its variations to an endocrine mode of action from a mechanistic point of view, therefore focusing on the biological plausibility. In this report, for each health outcome, eight criteria have been reviewed. They were developed in 2002 through the International Program on Chemichal Safety (IPCS) for attribution of effects to endocrine disruption.[25] For example, the ability to isolate the response to endocrine sensitive tissues in an intact whole organism and the availability of dose–response observations are among criteria. For each indicator, we constructed an aggregated score, depending on whether each criterion was totally, mostly, partially or not met (results = 1.00,0.50,0.25,0.00). We added the 8 results, the aggregated score ranging from 0 to 8. The WHO-UNEP report[1] was used to estimate the WoE for the causal relationship with EDC exposure. It reflects a wider approach that used all available evidence obtained with biological, experimental, wildlife and epidemiological data, but only qualitative appraisals of the WoE (e.g. sufficient, likely, possible) were available at the end of each chapter. Eventually a combination of the two approaches of WoE allowed highlighting the most relevant indicators. For the few indicators that were not documented in these reports, a reference search selected the more recent reviews or articles which were relevant for their suspected link with EDCs, when available. The potential indicators are classified by gender under three headings: male, female and both genders; the latter section includes indicators that, theoretically, can be measured in both males and females, even if up to now data are more numerous for one gender.

Discussion on indicators is based on presentations and debates that occurred mainly during the workshop.

Results

Framework to monitor reproductive health

What is reproductive health?

According to the WHO, reproductive health addresses the reproductive processes, functions and system at all stages of life.[26] Therefore a framework to monitor reproductive health is not limited to fertility/fecundity outcomes (e.g. birth rate), which depends strongly on socio-economic issues, lifestyle and individual choices. Instead, it embraces reproductive organ attributes and pathologies such as cancers (e.g. testicular, breast or prostate cancer), as well as biological characteristics (e.g. level of reproductive hormones), developmental reproductive endpoints and inter-generational reproductive effects.

Purposes of a reproductive health monitoring system

Considering all uncertainties and potential threats about the evolution of reproductive health, the purposes of a human reproductive monitoring system at an international level would be:

- to quantify and compare reproductive health indicators within and among each participating country;
- to compare the actual observations of temporal trends with the hypothesis of reproductive health impairment at a wide scale;
- if observed temporal trends are consistent with the previous hypothesis, to appraise their scope and quantify them according to several characteristics, including the identification of susceptible populations;
- to provide data in support of, or against, existing causal hypotheses, e.g. role of EDC exposure, and/or to generate new hypotheses;
- to help estimating the health impacts and costs of EDC exposures and identifying corrective measures;
- to help anticipating and managing the ensued public health problems;
- to assess the impact of public health interventions in the future.

Strategy to select indicators

Monitoring reproductive health requires the selection of suitable epidemiological indicators that are simple or aggregated variables which then enable the estimation of temporal and geographical trends at the population level. Harmonized data would allow comparative analysis of indicators across various regions and countries and pooled analyses would provide more robust results. This strategy is in line with previous European programs such as REPROSTAT[27] or ECHIM,[28] which developed reproductive indicators for other purposes, especially in the area of sexual health or infectious diseases.

Criteria/methods to select suitable indicators

Reproductive health indicators need to be relevant with regard to the purposes outlined below, with particular attention to their sensitivity to environmental exposures such as EDCs. They also have to be feasible: they must be measurable, standardized, valid and unchanged in time, to allow durable monitoring and comparisons. The indicators may be either already available in existing databases, newly built using existing sources/networks or newly collected in a cost efficient way.

A wide range of indicators were considered initially to avoid missing a potential useful endpoint. Relevancy was first addressed, in order to select among the relevant indicators those that had optimal feasibility. To address the question of global impairment of reproductive health, indicators that are biologically meaningful regarding such an overall idea are needed. The concept of TDS fits with this idea, as does the concept that mirrors TDS in females, namely ODS. More generally, indicators fitting the concept of the developmental origin of health and diseases (DOHaD)[29] could be particularly relevant, with possible windows of exposure in fetal, perinatal, pubertal or adult reproductive periods. If indicators of adverse changes in reproductive function/organs fit with a developmental hypothesis, this could be accumulative and result in a durable global impairment, provided that causal factors are still at work.

There are convincing experimental data in animals linking reproductive indicators with endocrine disruption and EDC exposure, but this issue is still debated in humans, for whom there is only association evidence.[1] Effects seen in animal studies may not be easily extrapolated to humans because of species differences and, as direct experiments in humans are impossible, there are inherent difficulties in proving causal relationships between human exposures and adverse reproductive health outcomes.

Nevertheless it is possible to use a WoE approach to identify, among a wide range of candidate indicators, those which are worth tracking while the causal evidence for human effects of EDCs exposure are sought for.

However other factors, such as changes in diet and lifestyle[30] or occupational exposures,[31] increases in the incidence of medical conditions that may influence reproductive health, such as obesity or diabetes (both also possibly linked to EDC exposure and reproductive outcomes), could contribute to the observed increase in reproductive disorders. It is therefore pertinent to take them into account in future analyses.

Also, the possible impairment of reproductive health is a public health concern because it impacts fecundity and hence may imply future changes in demography, socioeconomic consequences and growing needs for reproductive treatments. Moreover, there is growing evidence that changes in reproductive health may cause, or predispose to, other adverse health changes. Two recent studies showed a striking relationship between semen quality and mortality.[32,33] Finally, the health of the next generation could be affected if there are effects on the gametes. Hence the capacity of selected indicators of reproductive impairment (e.g. semen quality) to forecast public health consequences in the long range could be a valuable criterion.

Another aspect about relevancy is if valid indicators, collected through monitoring studies, could be used to launch etiological human studies later. Therefore it would be interesting to consider indicators best suited for both etiological studies and human health monitoring.

In summary, the relevancy criteria selected as reproductive health indicators should include those that link with the general environment, comprising EDC exposure, and also public health and research issues.

Overview of potential indicators

The overview of potential indicators, with their potential link to EDC exposure is proposed in Table 1.

As regards the WoE for an endocrine mechanism of action and a causal link with EDC exposure, the indicators found with the highest cumulative scores were prostate and breast cancer incidences, sex ratio, endometriosis and uterine fibroid incidence, indicators related to TDS, precocious puberty incidence and hormone levels.

Discussion

Male indicators

Prostate cancer incidence displays the highest cumulated score as regards the WoE. It has been linked to EDC exposure especially through pesticide use.[1] Monitoring trends of cancers is possible in several countries at a national level thanks to cancer registries when they cover the whole territory. Otherwise, analyzing spatial trends is not possible and alternative methods are needed.

The indicators of TDS, including anogenital distance (AGD), also display high WoE scores. As regards semen quality, the need to monitor this indicator has been recognized for some time, in the general population or in a sample unselected by fertility.[6,35] In any method, it needs to be studied in the same population over time. Sperm concentration is probably the most reliable endpoint for epidemiological analysis because it has been measured for a long time and mostly in the same way. Furthermore, assessment of semen volume is very easy and, if standardized methods are used, reliable assessment of total sperm counts (i.e. semen volume x sperm concentration) can also be provided.

Testis cancer (specifically, testicular germ cell tumors) displays a lower score because there is no satisfying animal model for this cancer, which seems quite human specific. It is appropriate to study epidemiologically because it affects young men, with unmistakable clinical features and the cancer registry data are highly reliable, as well as hospital data because it is systematically treated by surgery. Comparatively, urogenital congenital anomalies, cryptorchidism (undescended testis) and hypospadias (urethral malformation) seem less easy to monitor because of differences and evolutions in medical practices. Their prevalence can be approached using hospital data[36] or prospective cohort studies. Cryptorchidism is not recorded in birth defects registers, but in most cases hypospadias is, and the European Surveillance of Congenital Anomalies (EUROCAT) has a special focus on it.

Female indicators

Breast cancer incidence displays the highest cumulated score in this part. Indeed, according to the WHO-UNEP report, there is sufficient evidence linking breast cancer with dioxins, furans, and PCBs exposure. The cumulated score is also high for endometriosis and uterine fibroids incidence. Endometriosis is very difficult to define but, in the future, a non-invasive marker could be developed. Uterine fibroids and polycystic ovarian syndrome (PCOS) are also not well defined, although a consensus for PCOS is available now, but was not in earlier years. Age of menopause could be interesting to measure in the general population, since menopause is regarded as representing the duration of female reproductive health. To use age of menopause as a reliable indicator for the future, data on past individual treatments would need to be collected in order to exclude the women who are hormonally treated before the menopause. Premature ovarian failure (POF) would be a more measurable indicator since diagnosis is standardized.[37] According to WHO estimates, more than 1% of women exhibit ovarian failure earlier than the age of 40 years.[38]

Common male and female indicators

Anogenital distance (AGD)

Most concern about adverse effects of endocrine disruption is centered on effects in fetal life within a specific time-window. A key example is masculinization of the male fetus by androgens, which essentially involves modifying the 'set-up programme', which is to become a female. Experimental studies in rats have established that this occurs within a short time-period termed 'The Masculinisation Programming Window' (MPW). Any deficiency in androgen levels/action within the MPW results in smaller adult reproductive organ size (testes, penis, prostate, seminal vesicles) and increased risk of reproductive abnormalities (cryptorchidism, hypospadias, poor sperm production/subfertility), whereas reduced androgen exposure in the fetal period after the MPW has no discernible long-term effect on these anomalies.[39] In humans, the MPW is estimated to be within 8–14 weeks' gestation,[39] but proof of its existence and importance cannot be evaluated directly. But it was demonstrated in rat studies that AGD, which is normally 50–100% longer in males than in females, is also programmed by androgen action in the MPW, and is thought to provide a life-long read-out of the level of androgen exposure level specifically during the MPW.[40] Thus, measurement of AGD in an adult male may provide a means of 'looking back in time' and discerning the level of androgen exposure during the MPW for that individual.[34]

In humans, the same sex difference in AGD length between normal males and females (50–100% longer in males) is found as in rats.[34] Moreover, penis length is positively correlated with AGD in

Table 1 Overview of potential indicators

Indicators	Measurement	Population	Weight of evidence for attributing effects/ variations to an endocrine disruption mode of action (total rank = 8) (1) (Kortenkamp et al. 2012)	Weight of evidence for the causal relation with EDCs exposure (Bergman et al. 2012)	Main suspected EDCs (Bergman et al. 2012; Kortenkamp et al. 2012)	Main data to be controlled	Potential sources
Male only							
Semen quality: Concentration Total count Morphology Motility	 Million spz/ml Million spz % normal sperm % motile sperm	Adults	6.5 (Declining male reproductive health)	Possible (TDS)	Pesticides, fungicides, PBDE and phthalates	Age Abstinence delay Measurement methods	Health examination surveys Nationwide ART data bases Donor data bases
Cryptorchidism	Prevalence	Children	6.5 (Declining male reproductive health)	Possible (TDS)	Pesticides, fungicides, PBDE, phthalates, DES	Shift in medical practices, coding	Hospital data Prospective cohort studies
Hypospadias	Prevalence	Children	6.5 (Declining male reproductive health)	Possible (TDS)	Pesticides, fungicides, PBDE and phthalates, DES	Shift in medical practices, coding	Birth defect Registers Hospital data Prospective cohort studies
Testis cancer	Incidence	Adults	2.25	Possible (TDS) (but animal data lacking)	Pesticides, fungicides, PBDE and phthalates	Age	Cancer registers Hospital data
Prostate cancer	Incidence	Adults	7	Sufficient	Pesticides (occupational exposure), Arsenic, PCBs	Age	Cancer registers Hospital/Insurance data
Female only							
Endometriosis	Incidence	Adults	6.5	Likely	PCBs, phthalates, dioxins	To be explored	Hospital/insurance data to be explored
Uterine fibroids	Incidence	Adults	6.25	Likely	PCBs, phthalates, dioxins	To be explored	Hospital/insurance data to be explored
Polycystic ovarian syndrome (PCOS)	Incidence	Adults	4.75	Plausible but insufficient	BPA	To be explored	Hospital/insurance data to be explored
Premature ovarian failure (POF)	Incidence	Adults< 40	N/A	N/A	2-Bromopromane (occupational exposure) (42)	To be explored	Hospital/insurance data to be explored
Breast cancer	Incidence	Adults	6.25	Sufficient	Dioxins and furans, PCBs, organic solvants	Age, surveillance biases	Cancer registers Hospital/insurancedata
Ovarian cancer	Incidence	Adults	NA	Limited evidence	Triazine pesticides	Age	Cancer registers Hospital/insurance data
Endometrial cancer	Incidence	Adults	NA	Limited evidence	DDT	Age	Cancer registers Hospital/insurance data
Age at menopause	Mean age	Adults	N/A	Insufficient	DDE, dioxin, pesticides	Treatments	Health interview surveys
Preterm birth	Incidence	Newborn	7 (adverse pregnancy outcomes)	Limited evidence	Organochlorine and organophosphate pesticides, metals	Medical condition	Perinatal data bases/medical birth registers

(continued)

Table 1 Continued

Indicators	Measurement	Population	Weight of evidence for attributing effects/ variations to an endocrine disruption mode of action (total rank = 8) (1) (Kortenkamp et al. 2012)	Weight of evidence for the causal relation with EDCs exposure (Bergman et al. 2012)	Main suspected EDCs (Bergman et al. 2012; Kortenkamp et al. 2012)	Main data to be controlled	Potential sources
Common male and female							
Hormone levels: Anti-Müllerian hormone (AMH) Testosterone, Inhibin B . . .	Serum or urine levels	Adults Children	N/A Theoretically 8	N/A	N/A	Measurement methods, sex dependent cofounders, health, nutrition . . .	Biomonitoring studies
Anogenital distance (AGD)	Clinic in mm	Newborns, children or adults	6.5 (Declining male reproductive health)	Possible (TDS)	Pesticides, fungicides, PBDE and phthalates	Measurement methods	Health examination surveys
2D/4D ratio(43,44)	Radiography, or direct measurements	Adults	N/A	N/A	Pesticides, phthalates	Measurement methods	Health examination surveys
Precocious puberty	Incidence	<8 years old (girls) <9 years old (boys)	5.5 (female)	Plausible (female)	PBBs, cosmetics or hair care with estrogens	Medical practices, obesity, ethnicity	Hospital/insurance data
Age of puberty (e.g. ageat menarche for girlsand voice changes in boys)	Mean age in years, clinic definition	Teenagers	N/A	Plausible (female)	Lead (45,46) (delay) PBBs (47) (advance)	Nutrition, ethnicity, socio-economic factors	Health studies
Time to pregnancy	Interview, month	Couples desiring a child	5.75 (female sub fecundity)	N/A	PFOAs PFOs	Socio-economic factors	Health studies
Infertility	% >12 months of unsuccessful trial	Couples desiring a child	5.75 (female subfecundity)	Likely but insufficient (female infertility)	N/A	Couple's age, previous fertility	Health studies
Sex ratio	Counts, Demography	Newborns	7 (adverse pregnancy outcomes)	Sufficient (in selected populations)	Dioxin and dibromochloro propane	Community customs	Demographic data, Perinatal data bases/ medical birth registers
Natural dizygotic twin ratio (48)	Counts, Demography	Newborns	N/A	N/A	N/A	ART treatments	To be explored

(1) The rank is based on the eight 2002-IPCS criteria.[25] For each criterion, the grade is 1 when the criterion is met, 0.5 when mostly met, 0.25 when partly met and 0 otherwise. The rank sums the grades for each eight criteria.

babies and adult men. Hypospadias and cryptorchidism are both associated with reduced AGD in humans,[41] as they are in rats.[39] Other studies show a positive relationship between AGD and sperm count and fertility, as men who are childless have a shorter AGD than men who have fathered children.[34]

The usefulness of AGD measurement in humans, whether at birth, during puberty or in adulthood, remains to be fully explored and population-based reference values are needed.

Puberty

The cumulative score for precocious puberty incidence appears relatively high. This pathology is clinically well defined: development of secondary sexual characteristics before 8 years in girls and 9 years in boys. As regards the indicator ''age of puberty'', it is easy to approach in women, using age at menarche. Age of puberty in boys requires clinical examination.

Sex ratio

The number of boys divided by the number of girls born, or sex ratio, is a potential indicator with a high score. However if the WoE for biological plausibility is high, the WHO-UNEP report concludes that sufficient evidence for EDC impact is only available for selected populations, and is mainly accidental (e.g. the Seveso accident) or related to occupational exposures.

Reproductive hormones

Hormone levels are not documented for the WoE in the WHO-UNEP report, but they are evidently highly relevant. There are potential indicators of great interest in the general population because they could directly reflect endocrine disruption and their levels are quantifiable.

At the population level, assessment of hormone levels in blood would probably be the more appropriate medium. For males, the recommended hormones (and their calculated derivatives) could be testosterone, luteinising hormone (LH), sex-hormone binding globulin-bound (SHBG), INSL3 and probably follicle stimulating hormone (FSH), and Inhibin B. For females, AMH (anti müllerian hormone) is the only hormone that can give an idea of ovarian reserves, since there is no oocyte quality marker. AMH might also be of interest in newborns males and young children. Blood sampling and measurements have to be done under standardized conditions to allow comparisons.

Conclusion

Not only sentinel health endpoints, but also diseases with high burdens in public health are highlighted as prior indicators in the context of EDC exposure. Our work can serve as a basis to construct, as soon as possible, the first multi-country reproductive monitoring system.

The next steps would consist of making positive choices and validation of indicators. Feasibility issues will be addressed including measurement and collecting methods, existing database exploitation, possible adaptations for existing databases, or de novo data collection. In depth knowledge of the existing databases in the participating countries and multidisciplinary collaborations will be required.

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Key points

- Whether or not global impairment of reproductive health is currently happening is a crucial issue for public health.
- Only epidemiologic surveillance at a wide scale will enable this question to be answered convincingly.
- Not only fecundity outcomes, but reproductive cancers and disorders are part of the reproductive health.
- If there is a global impairment, we need to know to what extent EDCs might be causally involved and, if not, what other factors should be investigated.
- Monitoring reproductive health is essential for quantifying the disease burden attributable to EDCs and other factors, guiding public health interventions and their assessment in the future.

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