HURGENT: toward a multi-country monitoring system of reproductive health in the context of EDC exposure

During the last decades, worrying trends regarding human reproductive endpoints (e.g. semen quality, reproductive cancers) have been reported and debated. In the meantime, evidences have considerably grown on the reproductive effects of endocrine disrupting chemicals (EDCs) and ubiquitous human exposure has been documented. Furthermore, the concept of the development of health endpoints strictly depend on socio-economic networks or newly collected easily in a cost/efficient way. This is an urgent need for a reproductive surveillance system to be shared across countries.

Methods
A multidisciplinary network named HURGENT (Human Reproductive Health and Global Environment Network) was created aiming at designing a European monitoring system for reproductive health indicators. Ten European and extra-european countries are represented: France, Denmark, United Kingdom, Ireland, Finland, Poland, USA, Hungary and Croatia. The network proposes the first steps of a strategy to design a multi-country monitoring system of reproductive health. Currently, we work already on setting up the available knowledge to design such a system. Furthermore we conducted an overview of 32 potential indicators, based on a weight of evidence (WoE) approach according to their potential relation with EDC exposures. The annex I of the report published by the European Commission for EDCs (1) was used to score WoE for linking an indicator or its variations to an endpoint mode of action from a mechanistic point of view, therefore focusing on health. The World Health Organization-United Nations Environment Program (WHO-UNEP) report (2) was used to estimate the WoE for the causal relationship with EDC exposures. It reflects a wider approach that used all available evidence obtained with biological, experimental, epidemiological and biological data, but only qualitative approvals of the WoE.

Results

Purposes of a reproductive health monitoring system
Considering all uncertainties and potential threats due to 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 participating countries;
- to compare the actual observations of temporal trends with the hypothesis of human reproductive health impact on a wider scale (global impairment);
- to observe 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, current 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 to identifying corrective measures (and their costs);
- to help anticipating and managing the ensuing resulting public health problems;
- to assess the impact of public health interventions in the future.

The bases to set a monitoring system: reproductive health 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. These indicators can be constructed using health or biological endpoints. Harmonized data would allow comparative analysis of indicators across various regions and countries and pooled analyses would provide results that are more robust.

Which methods/criteria to select suitable indicators?
We initially considered a wide range of indicators to avoid missing a potential useful endpoint. First, we addressed relevancy of endpoints, in order to then select among the relevant indicators those that had optimal feasibility. Regarding relevancy, it is interesting to make a focus on indicators of syndromes fitting the DORDO concept according to genetic or biological syndrome (DODS), that mirrors TDs in females [5].

Reproductive health indicators need to be relevant as regards the purposes of the monitoring system, in particular according to their sensitivity to environmental exposures such as EDCs exposure. In addition, they must be measurable, standardised, valid, and usable in time, in order to allow durable monitoring and comparisons. Eventually, they have to be measurable indicators. The indicators may be either already available in existing databases, either newly built using existing sources/networks or newly collected easily in a cost/efficient way. However other factors, such as changes shifts in diet and lifestyle [7-9] or occupational exposures [10-13], together with parallel 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 to reproductive outcomes), could contribute to the observed increase in reproductive disorders. It is therefore pertinent to take them into account in future analyses.

In summary, the relevancy criteria used to assess reproductive health indicators should include relevance to links with the general environment, comprising EDC exposure, and also public health and socio-economic factors.

| TABLE 1: OVERVIEW OF POTENTIAL INDICATORS |

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Population</th>
<th>Reference</th>
<th>Time-frame</th>
<th>Potential source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semen quality: Concentration</td>
<td>Adults</td>
<td>6.5</td>
<td>Likely</td>
<td>PCBs, phthalates, dioxins To be explored</td>
</tr>
<tr>
<td>Uterine fibroids</td>
<td>Adults</td>
<td>6.25</td>
<td>Sufficient</td>
<td>Dioxins and furans, PCBs, pesticides, treatments Health interview surveys</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>Adults</td>
<td>5.75</td>
<td>Plausible</td>
<td>Testimony, studies Health examination or health registers</td>
</tr>
<tr>
<td>Adult BMI</td>
<td>Adults</td>
<td>6.25</td>
<td>Likely</td>
<td>DDE, dioxin, pesticides Hospital/insurance data to be explored</td>
</tr>
<tr>
<td>Sonographic Macrosomia (TDS)</td>
<td>Newborns</td>
<td>7</td>
<td>Plausible</td>
<td>Dioxin and dibromochloropropane, phenylmethane, formulation of feed, practices, coding Clinical examination and health registers</td>
</tr>
<tr>
<td>Uterine fibroids</td>
<td>Adults</td>
<td>6.25</td>
<td>Likely</td>
<td>Dioxins and furans, PCBs To be explored</td>
</tr>
<tr>
<td>Testicular atrophy</td>
<td>Adults</td>
<td>6.25</td>
<td>Plausible</td>
<td>PBBs (5) (advance) Biomonitoring studies</td>
</tr>
<tr>
<td>Chronic(Environmental)ews</td>
<td>Cohort</td>
<td>N/A</td>
<td>N/A</td>
<td>Hospital/insurance data to be explored</td>
</tr>
<tr>
<td>Pregnancy (miscarriage)</td>
<td>Adults</td>
<td>N/A</td>
<td>Limited evidence</td>
<td>Hospital/insurance data to be explored</td>
</tr>
</tbody>
</table>

Conclusion
As regards the evidence for an underage mechanism of action and a causal link with EDC exposures, the indicators with the highest cumulated scores are prostate and breast cancer incidence, sex ratio in selected populations, endometriosis and uterine fibroids incidence, indicators related to TDS and precarious puberty incidence. Hormone levels are not documented for the WoE in the WHO-UNEP report, but they are evidently highly relevant.

Hence, 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 could help as a basis to construct, as soon as possible, the first multi-country reproductive monitoring system.

Reference List

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