Santé publique France

SANTÉ ENVIRONNEMENT

2021, SEPTEMBER

METHODOLOGICAL REPORT

PEPS'PE STUDY. PRIORITIZATION OF HEALTH EFFECTS TO BE MONITORED AS PART OF THE MONITORING PROGRAM IN CONNECTION WITH ENDOCRINE DISRUPTORS FROM SANTÉ PUBLIQUE FRANCE.

Abstract

PEPS'PE study. Prioritization of health effects to be monitored as part of the monitoring program in connection with endocrine disruptors from Santé publique France. Methodological report

Santé publique France is planning to extend monitoring of health indicators related to endocrine disruptors (EDs) within the framework of the National Strategy on Endocrine Disruptors (SNPE), the National Health Environment Plan and the WHO recommendations, and also in response to the increasingly significant expectations that the public authorities and the general public have of the agency regarding EDs. For this reason, Santé Publique France has undertaken a project to prioritise the health effects associated with EDs, with the aim of setting the framework for the agency's surveillance programme on this topic.

Santé Publique France is proposing a method of prioritising the health effects to be monitored because of a suspected link with exposure to EDs. This method consists of ranking effects firstly according to the weight of the existing evidence, and secondly according to the epidemiological and societal value of implementing this surveillance. In order to evaluate these two criteria, Santé publique France is proposing a complementary method that combines available data from the literature and the opinions of experts and stakeholders in the field using the Delphi method.

This project fits into a rationale of health monitoring rather than taking an approach focused on a substance or exposure: it involves monitoring the evolution of a health indicator in the general population where there is a suspected link to exposure to EDs, instead of characterising the effect of an EDs product (or group of products) on health.

The Delphi method involves organising the consultation of a panel of experts to obtain a final and convergent opinion from the group. It will be organised around two questionnaires available online, one looking at the scientific component, and the other asking about the societal component. To complete these questionnaires, two groups of experts are formed, bringing together experts from the scientific field and also stakeholders in the field of EDs.

With a view to determining the agency's monitoring schedule, Santé publique France will then analyse whether it is feasible to monitor the effects that emerge as priority after the consultation.

The proposed methodology aims to seek the best compromise between a scientifically robust, workable and clear process for all. This report summarises the methodology suggested by Santé publique France to prioritise health indicators in the context of exposure to EDs.

KEY WORDS: ENDOCRINE DISRUPTORS, EPIDEMIOLOGICAL MONITORING, WEIGHT OF EVIDENCE, DELPHI METHOD, ENVIRONMENTAL EPIDEMIOLOGY

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Abbreviations

EC	European Commission
DSET	Environmental and Occupational Health Division
GSE	Groupe Santé Environnement; Environmental Health Group
WHO	World Health Organization
EDs	Endocrine disruptors
SNPE	Stratégie nationale sur les perturbateurs endocriniens; National strategy on endocrine disruptors

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INTRODUCTION

As part of the National Strategy on Endocrine Disruptors (SNPE) [1], the National Health Environment Plan 3 (PNSE 3) [2] and World Health Organization (WHO) recommendations [3], Santé Publique France has set up national epidemiological surveillance of reproductive health indicators in the context of endocrine disruptors (EDs) exposure [4]. However, the scientific literature is reporting more and more effects on functions other than reproductive function, such as neurodevelopmental disorders, metabolic disorders, immune function disorders and thyroid disorders [5], [6]. The general public have growing expectations of public authorities in this area.

In this context, Santé Publique France plans to extend the surveillance of health indicators related to EDs. Nevertheless, such monitoring requires resources and choices need to be made concerning what should or can be monitored. For this reason, Santé publique France has undertaken a project to prioritise the health effects to be monitored for their link with EDs to set the framework for the agency's surveillance programme on this topic, with priority indicators being identified that will then be placed under spatial-temporal surveillance on a sufficiently large scale (France as a whole with overseas departments and regions).

The objective of this project is to develop a **methodology for prioritising the health effects to be monitored due to a suspected link with exposure to endocrine disruptors**, by ranking them firstly according to the weight of the existing evidence of an effect of EDs, and secondly according to the epidemiological and societal value of implementing this surveillance. With a view to determining the agency's monitoring schedule, Santé publique France will then analyse whether it is feasible to monitor the effects that emerge as priority after the consultation.

This project fits into a rationale of health monitoring rather than taking an approach focused on a substance or exposure: it involves monitoring the evolution of a health indicator in the general population where there is a suspected link to exposure to EDs, instead of characterising the effect of an ED product (or group of products) on health.

It should be noted that in the field of environmental health few effects are specific to exposure to an environmental risk factor, and this is especially true of EDs. Furthermore, due to the specific characteristics of the mechanisms of action of EDs, there is still no commonly accepted method to assess the weight of evidence concerning the strength of the relationship between exposure to EDs and the occurrence of a health effect. In order to overcome these methodological challenges, Santé publique France is proposing a complementary method for prioritising the effects to be monitored that combines available data from the literature and the opinions of experts and stakeholders in the field using the Delphi method.

In this specific context and in accordance with the objectives and needs set out, the proposed methodology aims to seek the best compromise between a scientifically robust, workable and clear process for all. This report summarises the methodology suggested by Santé publique France to prioritise health indicators in the context of exposure to endocrine disruptors. A second report summarising the results and presenting the outcome of the prioritisation will be produced at a later date.

METHODOLOGY

The proposed methodology for prioritising the health indicators to be monitored for their link with ED is based on a review of data from the literature, the study of available methods specific to ED and consultation with experts on the subject. It is based on a classification of health indicators according to two prioritisation criteria:

(1) the weight of evidence
(2) the epidemiological and societal value of monitoring the health effect.

The method adopted follows these steps:

1. Current understanding of health effects suspected of being related to ED exposure,
2. Defining criteria for prioritisation and preparing questionnaires for the Delphi method,
3. Evaluating prioritisation criteria using data from the literature combined with collective expert appraisal using the Delphi method,
4. Combination of prioritisation criteria,
5. Feasibility of the agency monitoring the health effects categorised as priority,
6. Feedback to stakeholders and consultation.

1. Current understanding of health effects suspected of being related to EDs

In order to prioritise health effects related to endocrine disruptors, the first step was to identify as exhaustively as possible all the health effects suspected of being related to ED exposure. In 2012, two reports from the WHO and the European Commission prepared an initial assessment of the current understanding of diseases related to EDs [5, 6]. They served as the basis for establishing an initial list of suspected diseases, which we added to and validated using all new knowledge since 2012 through a narrative literature review.

Around fifty health effects have been identified, put into 11 categories of endocrine glands or biological functions affected by ED (Table 1). A detailed list of the health effects that fall under each of these categories, which will then be put in priority order, is given in Appendix 1.

Since the aim of this work involved prioritising and scheduling, an intentional choice was made to focus only on health effects. However, the possibility of identifying these effects through biological parameters that correspond to the mechanisms of action of EDs (epigenetic mechanisms, inflammatory mechanisms, etc.) and the question of biomarkers for an effect characterising exposure to EDs will be raised during the collective expert appraisal.

I TABLE 1 I

The 11 categories of health effects suspected to be related to endocrine disruptor exposure according to the literature review

Impaired reproductive health in women
Impaired reproductive health in men
Impaired reproductive health without sex distinction
Thyroid disorders
Paediatric neurodevelopmental disorders
Hormone-dependent cancers
Adrenal disorders
Bone disorders
Metabolic disorders
Immune function disorders
Skin and eye disorders

Source: Santé publique France

2. Definition of prioritisation criteria

Health effects will be prioritised by looking at two criteria that must be taken into account by Santé publique France as a national public health agency to address the problem of EDs:

1. **The weight of evidence** for an association between the occurrence of the health effect and exposure to EDs**,**

2. **The epidemiological and societal value of monitoring this effect.** This composite criterion takes into account the epidemiological value (severity, change in the incidence) and the societal concern of the stakeholders involved in the area.

2.1 Prioritisation criterion 1 "Weight of evidence"

The first prioritisation criterion defined is the weight of evidence for an association between the occurrence of the health effect and exposure to EDs. The weight of evidence is defined as "the formalised synthesis of lines of evidence, possibly of varying quality, in order to determine the level of plausibility of a hypothesis" [7].

It is important to stress that this work is part of an approach focused on the population, rather than on substance or exposure: it is not a question of studying the effect of an ED product (or a group of products) on health; but of studying the occurrence of a health effect in the population because this health effect is suspected of being linked to exposure of the population to all ED products through all routes of exposure (inhalation, ingestion, transplacental or cutaneous).

This criterion of weight of evidence was first explored through a narrative review of the literature and will be dealt with primarily through consultation with experts using the Delphi method.

2.2 Prioritisation criterion 2 "Epidemiological and societal value of monitoring"

In order to assess whether there is value in the agency monitoring a health effect that has been identified as possibly related to EDs, both epidemiological and societal factors are taken into account.
Factors to assess the value of monitoring:

1. The **severity** of the health effect
2. Changes in the **incidence rate of** the health effect (known or suspected)

} Epidemiological value

3. **Whether society in France is concerned** about this health effect

} Societal value

The factor societal concern will be specifically assessed by all stakeholders in the field.

3. Consultation with experts and stakeholders using the Delphi method

3.1 Presentation of the Delphi method and rationale for using this method

There are several consensus methods for questioning experts/stakeholders, defined as a way to synthesise information and compare contradictory opinions with the aim of defining the degree of agreement within a group of selected individuals. This approach is useful in cases where professional opinion is not unanimous due to a lack of data from literature, a low level of evidence or contradictory data [8], and they make it possible to provide the public authorities with a basis for decision-making when neither regulation nor scientific certainty can be relied upon at present.

For the intended purpose, the Delphi method was selected. The Delphi method involves organising the consultation of a panel of experts in order to obtain a final, unique and convergent opinion from the group on specific issues. Each participant completes questionnaires and then reads through the opinions of others, and through this process can review their arguments and positions. All opinions remain anonymous and experts never interact directly with each other. The Delphi method therefore proceeds in stages: the responses are collected and summarised and then made available to the experts so that they can voice their opinions afresh. This process is repeated as many times as necessary, until consensus is reached and/or there is evidence of diverging opinions.

This method was chosen over the other expert consultation methods for the following reasons:

- Provides the public authorities with a basis for decision-making in cases when neither scientific certainty nor regulation can be relied on;
- Allows a large number of participants to be consulted remotely;
- Allows experts with different skills, backgrounds and areas of expertise to be consulted, which is essential in the area of EDs;
- Guarantees the participants' anonymity;
- Avoids the "personalities" effect (notoriety, charisma, leadership, etc.);
- Allows knowledge that is difficult to access (not published for example) to be voiced.

For this project, the aim of the Delphi method is to reach a consensus on the evaluation of the two prioritisation criteria for each of the health effects related to EDs identified by the literature review.

3.2 Questionnaires covering these criteria

Participants are consulted using the DELPHI method through questionnaires. To evaluate the two prioritisation criteria which draw on both scientific and societal factors, two questionnaires with different objectives were produced:

- **Questionnaire 1** is intended to evaluate criterion 1 (weight of evidence), but also part of criterion 2 on epidemiological value (severity and change in the incidence).
- **Questionnaire 2** has been designed to assess the level of concern in French society.

The development of the questionnaires is explained in the next part of this report, and the grids for questionnaire 1 and 2 are available in Appendices 4 and 5 respectively.

3.3 Selection of participants

The process of selecting participants is instrumental to the success of the Delphi consultation. It must be representative and consistent in terms of the type of stakeholders and areas of competence surveyed, and must also target a sufficiently large number of participants so that a consensus can be reached on the questions asked. For this project, the engagement and synergy of all stakeholders, as well as government, communities, economic actors, associations, health and education professionals and scientists are required.

To this end, Santé publique France identified a broad panel of stakeholders in advance with a view to asking them to take part in this study. Participants were separated into two groups to complete the two questionnaires. They were selected to complete either one of the questionnaires, but would not be able to complete both.

The first group formed was made up of experts in the scientific field (epidemiologists, toxicologists, academics, etc.) to answer questionnaire 1.

The second group formed was made up of the stakeholders in the field, excluding those participating in group 1 as scientists and any central government representatives or state operators, to complete questionnaire 2.

The criteria for creating the groups of experts are given in Appendix 2.

4. Evaluation of prioritisation criteria using the Delphi consultation method

4.1 Evaluation of criterion 1 “weight of evidence”

Prioritisation criterion 1 "weight of evidence" will be assessed by the Delphi collective consultation. The evaluation of this criterion should lead to a consensus from the group that means that, for each of the health effects about which the participants will be asked, the weight of evidence can be classified into the four levels presented in Table 2.

I TABLE 2 I

Classification of the weight of evidence (WoE) for a link between the occurrence of the health effect surveyed and the exposure of the population to endocrine disruptors resulting from the Delphi consultation

Assessment of WoE level	**Strong**	**Moderate**	**Low**	**Undocumented**
Definition	Specific effects of exposure to EDs	Relatively specific effects of exposure to EDs	Less specific effects of exposure to EDs, where the proportion that can be attributed to EDs is not yet known	Effects that it is not worth monitoring (for the moment) for their relationship with EDs because there is currently no sufficient scientific data to justify this link

Given the methodological challenges inherent in studying the effects of EDs (dose-response is not necessarily monotonic, multiple mechanisms of action, etc.), the weight of evidence should be judged by the experts taking into account all the knowledge related to their area of expertise and sources of data that they are aware of (epidemiological studies, toxicology, biochemistry, cellular biology, animal studies of mechanisms and effects, exposure science, etc.).

Santé publique France also conducted a literature review to set out an initial ranking of health effects according to the weight of evidence when the data were available. The approach and results are presented in Appendix 3. However, this ranking remains prospective because it presents a number of limitations (no universal methodology for assessing the weight of evidence applicable to EDs; partial, old, or even contradictory scientific data, etc.). However, it is an initial basis for a proposal for ranking according to the weight of evidence, and will be useful both to compare with and validate the results of the collective expert appraisal, and if necessary, to supplement the information.

4.2 Evaluation of criterion 2 "epidemiological and societal value of monitoring"

Prioritisation criterion 2, "value of implementing epidemiological surveillance" will also be assessed by the Delphi collective consultation. The evaluation of this criterion should lead to a consensus from the group that means that, for each of the health effects about which the participants will be asked, the epidemiological and societal value can be classified into three levels: Strong / Moderate / Low.

To enable the group of participants to estimate the epidemiological value and societal value in a coordinated and unified manner, it will be broken down into three aspects. Each of the three aspects will be assigned a score following the Delphi consultation and, once combined, the scores will then classify the value as strong, moderate or low.

The three aspects used to assess the epidemiological and societal value are as follows:

- Epidemiological value: severity (1) and change in the incidence rate (2)
- Societal value: societal concern about this health effect in France (3).

4.2.1 Severity

In order to ask the Delphi participants about the severity of a health effect, we used the method developed by the Centre for Research, Studies and Documentation in Health Economics, which classifies disease by the degree of severity using two morbidity indicators: risk to life and physical disability [9]. The physical disability indicator was modified to a more global indicator of "quality of life", which is more suitable for the chronic effects of EDs. The severity of a health effect will therefore be assessed taking into account both the risk to life and health-related quality of life.

Risk to life
Risk to life risk is a fatal prognosis. It is similar to the notion of a severe condition that could lead to death in the short-term or be theoretically life-threatening in the longer term. The risk to life is classified into three categories: low, moderate and high risk to life.

Health-related quality of life
The WHO distinguishes six areas that shed light on quality of life [10]. For this project, in order to guide participants' assessment of the effect of a disease related to EDs on quality of life in a simple and easily understandable way, while being as robust as possible, three dimensions of health-related quality of life were chosen: physical, psychological and social functioning.

The effects will then be categorised by participants into three severity levels presented in Table 3.

I TABLE 3 I

Evaluation by Delphi consultation participants of the severity of a health effect, based on its impact on risk to life and quality of life

	High risk to life*	**Moderate risk to life**	**Low risk to life**
Very reduced quality of life*	Very severe	Very severe	Very severe
Reduced quality of life	Very severe	Severe	Severe
Minimal reduction in quality of life	Very severe	Severe	Mild

** Risk to life = life-threatening*
*** Quality of life = physical, psychological and social functioning*

It should be noted that some effects may have different levels of severity depending on the circumstances: age, sex, medical history, etc. For this project, participants will need to assess the level of severity of the health effect linked with EDs by considering the worst possible case.

4.2.2 Change in the incidence rate

The incidence rate is defined as the number of new cases of a pathology observed over a given period. A condition may, regardless of its level of severity, have an increased incidence and thus represent a public health issue over the long term.

The Delphi consultation participants will therefore be consulted on their knowledge about the change in the incidence rates of each of the health effects related to EDs in France or internationally over the last 20 years. Delphi consultation participants will need to classify the incidence rate into three levels: Increasing / Stable / Decreasing.

4.2.3 Societal concern

Santé publique France also wishes to take into account the level of societal concern when evaluating prioritisation criterion 2. This component will be a questionnaire targeted specifically at relevant stakeholders, in order to ask about their expectations and interests regarding the monitoring of each of the health effects related to EDs.

The societal concern will be estimated by stakeholders based on several complementary factors: their perception of the level of concern in the general population, the level of information and prevention, the level of scientific data available, the severity of the effect and the value of monitoring for each stakeholder interviewed.

Delphi participants will have to decide on the extent to which they agree with a list of statements. The statements to be evaluated by the participants are presented in Table 4.

I TABLE 4 I

List of statements for assessing societal concern submitted to the consultation with stakeholders

Statement 1	The French population is concerned about the occurrence of this health effect in the general population
Statement 2	The public should have more information about this health effect
Statement 3	There should be greater prevention of this health effect
Statement 4*	There is insufficient scientific literature and knowledge on this health effect nationally and internationally
Statement 5	The consequences of this effect on human health are severe, that is, this effect impairs daily quality of life and/or leads to a risk of death in the short or long term
Statement 6	You and your organisation are interested in the implementation of epidemiological surveillance of this health effect in France

** Proposition 4 will not be included in the scoring, and will be used for information purposes to compare the perceived level of scientific knowledge between the two questionnaires*

Stakeholders will have to estimate the extent to which they agree with each of the six statements using scale of agreement shown in Table 5, and each degree of agreement awarded equates to a quantitative score. The six scores obtained for each of the statements will be added together (except proposal n°4, see table 4), and the sum, from 0 to 15 points, will be used to assess the level of societal concern as shown in Table 6.

I TABLE 5 I

Scale of agreement that the Delphi consultation participants use to rate the 5 statements so that the level of societal concern can be estimated, and the corresponding scores

Degree of Agreement	Totally disagree	Somewhat disagree	Somewhat agree	Totally agree
Corresponding score	0	1	2	3

I TABLE 6 I

Evaluation of the level of societal concern by the Delphi consultation participants based on the sum of the 5 scores obtained

Sum of 6 scores	Score between 11 & 15	Score between 5 & 10	Score between 0 & 4
Societal concern	Strong	Moderate	Low

4.2.4 Final evaluation of criterion 2

Once the three aspects of prioritisation criterion 2 have been evaluated and a consensus has been reached by the group, a score of 1 to 3 will be assigned (see Table 7) in order to obtain an overall score so that criterion 2 can be estimated from all perspectives (see Table 8)[1].

I TABLE 7 I

Qualitative evaluation of the three aspects of prioritisation criterion 2 "epidemiological and societal interest" resulting from the Delphi consultation and corresponding score

Prioritisation criterion 2 "epidemiological and societal value"									
	Severity			**Change in the incidence rate**			**Societal concern**		
Qualitative evaluation	Very severe	Severe	Mild (or no response)	Increasing	Stable	Decreasing (or no response)	Strong	Moderate	Low (or no response)
Points	3	2	1	3	2	1	3	2	1

I TABLE 8 I

Final evaluation of prioritisation criterion 2 "epidemiological and societal value" on the basis of the score obtained during the Delphi consultation

Sum of the points obtained (severity, change in the incidence rate, societal concern)	8 or 9 points	5, 6 or 7 points	3 or 4 points
Final evaluation of prioritisation criterion 2 "Epidemiological and societal value of implementing surveillance"	**Strong**	**Moderate**	**Low**

[1] As a reminder, societal concern is an integral part that will be addressed only by stakeholders in the field, which is why it must be the subject of a separate consultation. For a complete evaluation of criterion 2, the responses from the two consultations need to be pooled and to have obtained responses in each of the consultations. In order to overcome the possibility of non-responses in the societal component, or in the epidemiological component, a lack of response corresponds to a low epidemiological value or low societal interest (point = 1).

5. Classification by combining the two prioritisation criteria

Once a consensus has been arrived at using the Delphi method on the prioritisation criteria assessed for each of the health effects, they will be combined to classify the health effects into 12 categories in order of priority (Category 1 being the highest priority, and12 the lowest priority), as shown in Table 9.

In the long term, this prioritisation is intended to be updated and re-evaluated taking into account new scientific knowledge on the weight of evidence.

I TABLE 9 I

Classification of health effects into 12 categories from the highest to the lowest priority in terms of their link with EDs, based on assessment of weight of evidence and value of monitoring resulting from the Delphi consultation

Classification of the health effect by priority category		**Prioritisation criterion 1:** Weight of evidence			
		Strong	**Moderate**	**Low**	**Undocumented (or no response)**
Criterion 2: Value of implementing surveillance (epidemiological and societal)	**Strong**	Category 1	Category 4	Category 7	Category 10
	Moderate	Category 2	Category 5	Category 8	Category 11
	Low	Category 3	Category 6	Category 9	Category 12

6. Assessment of the feasibility of monitoring

After the classification into 12 categories of different priority levels according to the weight of evidence and the epidemiological and societal value, Santé publique France will study the feasibility of implementing epidemiological surveillance of the health effects in categories 1 to 7. Categories 8 to 12 will not be taken into account in the agency's programming initially, as they have a low or undocumented weight of evidence and surveillance has moderate or low value.

For effects identified as priority, consideration should be given to whether a reliable monitoring indicator already exists or can be obtained and monitored over time. This discussion will be carried out taking into account the programmes already developed at the Agency, as well as the feasibility via the French National Health Data System (SNDS), and may be extended to include other sources (research organisations, registries, etc.)[2].

In addition to indicators of health effects, the biological parameters and biomarkers for effects that have been identified during the collective expert appraisal will also be included as indicators that can be incorporated into epidemiological monitoring.

[2] It is possible that at the end of this monitoring feasibility assessment phase, effects identified as priorities may not prove to be easy for the Agency to monitor currently. In this case, the priority rating assigned will be used as a supporting argument for proposing levers to build or obtain a health indicator for this effect, to be monitored in the context of the ED.

LIMITATIONS

This approach to prioritising using the Delphi consensus method has a number of limitations. Firstly, there are limitations directly linked to the use of the Delphi method. For example, it is difficult to prevent a phenomenon of apathy in the group if the rounds of questionnaires multiply, resulting in a surface-only consensus on a very complex or controversial problem. This method can also be relatively time-intensive for participants (several questionnaire rounds) and cause drop-outs as the various rounds go on.

Another limitation specific to this study is that, given that the participants in the consultation will select the health effects related to EDs they wish to discuss out of the 11 identified (Table 1), it is possible that certain categories of health effects may not be selected at all during the consultation, and therefore that the health effects of this category will all miss the chance to be prioritised. In order to overcome this limitation, as many experts as possible are mobilised so that each of the 11 categories should be selected at some point by at least one participant. In the event of a complete lack of response on questionnaire 1 for an effect category, it is considered this as equivalent to saying that there is currently no scientific and epidemiological expertise in this health effect category (weight of evidence "undocumented", "low" severity and incidence rate "decreasing"), which is open to discussion. For questionnaire 2, a complete lack of response would mean that there is currently no societal concern about this health effect category ("low" societal concern).

Furthermore, in order to prioritise health effects, a consensus needs to be reached for the two prioritisation criteria and for each of the health effects, and it is therefore implicitly necessary for a consensus to be reached for all the questions asked to assess these two criteria (8 questions per health effect).

However, if a category of health effects suspected of being related to EDs is not selected, or if there is no consensus on the prioritisation of a category, this will lead to results being taken into account in full, as this means that at present, as well as there being a lack of scientific data, experts and stakeholders involved in EDs are not able to assess this health effect for its relationship with EDs. As it will be possible to justify responses, differences of opinion can be expressed by the participants, making it possible to make a case for and better understand why consensus about a given health effect could not be reached.

Despite the limitations inherent in the Delphi method, and in the absence of a commonly accepted method or regulation, the proposed method should provide the Agency with the initial basis for decision-making so that the health effects to be monitored as a priority in relation to EDs can be identified.

CONCLUSION

Santé Publique France has undertaken a project to prioritise the health effects associated with EDs that require epidemiological surveillance, with a view to setting the framework for the agency's surveillance programme on this topic. The proposed prioritisation methodology combines both available data from the literature and expert opinion on the subject using the Delphi consultation method. This project is part of an approach focused on the population and health effects, rather than on ED products or exposures.

In the field of endocrine disruptors and environmental health in general, there are few specific effects of exposure to an environmental risk factor identified. New knowledge regularly questions the robustness of the causal relationship between exposure to EDs and the onset of certain diseases. However, this must not prevent us asking whether there is a value in broadening the epidemiological surveillance of health effects suspected of being related to EDs.

In this specific context and in accordance with the objectives and needs set out, the proposed methodology aims to seek the best compromise between a scientifically robust, workable and clear process for all.

In order to prioritise health effects they will be classified, following a consultation with experts using the Delphi method, on the basis of two fundamental criteria to be taken into account when dealing with the issue of EDs:

- the weight of evidence
- the value of monitoring this indicator (composite criterion that takes into account epidemiological relevance and societal concern).

The effects identified as priorities according to these two criteria will then be analysed in terms of how feasible it is for the agency to monitor them, with the objective of determining whether a reliable monitoring indicator already exists or can be obtained and monitored over time. This discussion will be carried out taking into account the programmes already developed at the Agency, as well as the feasibility via the French National Health Data System (SNDS), and may be extended to include other sources (research organisations, registries, etc.).

Although as many questions as possible are directed for consultation on the subject of EDs, here Santé publique France is using a methodology that calls on the knowledge and judgement of a collective expert appraisal. The process of setting up the expert groups to be consulted is instrumental to the success of the Delphi consultation and has been addressed with great care.

This approach to constructing a method for prioritising health effects suspected of being related to EDs is reproducible and it means that the selection of health indicators studied can be adjusted with changes in knowledge and available data as well as in response to societal developments.

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APPENDICES

Appendix 1 / List of all health effects suspected to be related to EDs exposure based on the results of the literature review

I TABLE A1 I

Impaired reproductive health in women	
Endometriosis Uterine fibroids Polycystic ovary syndrome Gestational Diabetes[3]	Premature ovarian failure Irregular menstrual cycles Late-onset menopause
Impaired reproductive health in men	
Cryptorchidism Hypospadias	Impaired sperm quality Testicular cancer (non-hormone dependent)
Impaired reproductive health without sex distinction	
Adverse pregnancy outcomes: - miscarriage, - pre-eclampsia, - preterm delivery, - low birth weight, - death of the foetus.	Infertility Early puberty Altered sex ratio at birth: most often male sex decreases Reduced fertility/subfertility
Thyroid disorders	
Hyperthyroidism (Thyrotoxicosis) Congenital hypothyroidism	Hypothyroidism or subclinical hyperthyroidism
Paediatric neurodevelopmental disorders: cognitive and behavioural effects	
Behavioural disorders: - Relationship disorders[1] - Emotional disorders[1] - Cognitive impairment [1]	Learning disability - lower IQ Attention deficit hyperactivity disorder (ADHD) Cerebral palsy[1] Autism Spectrum Disorder (ASD)
Hormone-dependent cancers	
Breast cancer Prostate cancer Endometrial cancer	Ovarian cancer Thyroid cancer
Adrenal disorders	
Cushing's disease (chronic hypercortisolism) Addison's disease (hyposecretion of adrenal hormones)	
Bone disorders	
Bone fractures Osteoporosis Enamel development abnormalities 1, hypomineralisation[1], dental fluorosis[1], hyperdontia[1], hypodontia[1]	Irregular calcification of the skull [1] Impaired skeletal development
Metabolic disorders	
Being overweight and obesity Type 2 diabetes Cardiovascular diseases Type 1 diabetes	Metabolic syndrome: *a combination of at least three of the five following dysfunctions: hypertension, abdominal (central) fat, elevated serum triglycerides, low serum HDL and hyperglycaemia*
Immune function disorders	
Allergies Autoimmune thyroid disease (e. g. Basedow's disease)	Asthma Lymphoma and leukaemia in children Disorders of haematopoiesis and malignancies
Skin and eye disorders	
Chloracne[1] Skin pigmentation disorders[1] Atopic dermatitis[1]	Skin cancer[1] Ageing of the skin[1] Ocular surface impairment: dry eye[1] Retinal disorders: visual impairment and retinopathy[1]

[1] New health effects, not identified in the 2012 WHO and EC reports.

Appendix 2 / Participant selection criteria for Delphi consultation

The stage of selecting the experts is instrumental to the success of the Delphi consultation. First, a full list of French and international experts involved in the field of EDs, either from a scientific or societal perspective, was compiled. This initial list was created by identifying the following persons:

- SNPE1 and SNPE2 stakeholders (via the Groupe Santé Environnement);
- Stakeholders of the Agency's Board of Directors;
- Members of the French High Council of Public Health environmental risk committee;
- Authors of reports from the WHO [6], the European Commission [5] and the Society of Endocrinology [11], which have been used in constructing the prioritisation methodology;
- Members of the Endocrine Disruptors working group of the French National Food Safety Agency (ANSES),
- Members of and participants in major congresses on ED and health (Gordon Research Conference (GRC), Copenhagen Workshop (COW), French environmental health symposiums, conference of the French National Environment-Health-Work Research Programme, European workshop on the impact of endocrine disruptors on human health and wildlife, etc.);
- Authors of recent publications on the subject.

Two groups of experts can therefore be created, suited to the two Delphi questionnaires. The table below shows the inclusion and exclusion criteria for each group.

I TABLEAU A2 I

Selection criteria for the two groups of participants

Group 1: Scientific component ***Evaluation of the weight of evidence, severity, change in the incidence***	**Group 2: Societal component** ***Evaluation of societal concern***
Inclusion Criteria	
French and international experts	All stakeholders in SNPE1 and SNPE2
Teaching and research	Members of the Agency's Board of Directors
Health professionals	
Experts who have published on the subject	
Exclusion Criteria	
Already in group 2	Already in group 1
Area of expertise outside the scope of the study (ecotoxicology, ecology, environment, etc.)	Representatives of central government and state operators
No email address	No email address

Appendix 3 / Ranking health effects according to the weight of the evidence available in the literature

Work to assess the weight of evidence concerning the association between exposure to EDs and each of the health effects identified was conducted at the same time through a literature review by Santé publique France. In order to do so, since the standard weight of evidence assessment approach defined by Anses could not be carried [7] due to the characteristics and specific features of endocrine disruptors (low dose effects, dose-response curves that can be non-monotonic, exposure windows, etc.), existing publications and work of the HURGENT International Working Group, which developed a methodology for assessing the weight of evidence for reproductive health and exposure to EDs, were used [4]. This methodology is based on two institutional reports that have summed up the state of our understanding of EDs and their health effects: the 2012 WHO report [6] and the 2012 [5] European Commission report, which are the most recent "reviews of reviews" carried out by a panel of international scientists. In order to update this data, the most recent results from the work of Trasande *et al.* (2015, 2016) [13] were also incorporated, which meant that the likelihood of causality between exposure to EDs and three categories of health effects (metabolic disorders, neurodevelopmental disorders, male and female reproductive health) could be described based on Delphi consensus method.

A score could be attributed to each health effect using this method, except for a few indicators where the information was unavailable or only partially available in the WHO and EC reports. The results are shown in the table below.

I TABLE A3-1 I

Results of the classification of health effects according to the weight of evidence from the literature review

Sufficient level of evidence	Plausible level of evidence[4]	Insufficient level of evidence	Undocumented
- Endometriosis - Uterine fibroids - Cryptorchidism - Hypospadias - Impaired sperm quality - Sex ratio - Adverse pregnancy outcomes - Breast cancer - Prostate cancer - Behavioural disorders in children - Cognitive impairment in children - Lower IQ scores - Autoimmune thyroid diseases - Asthma - Lymphoma and leukaemia in children	- Testicular cancer - Early puberty - Decreased fertility - Infertility - Endometrial cancer - Ovarian cancer - Autism spectrum disorders - Relationship disorders - Emotional disorders - Attention deficit disorder with or without hyperactivity - Cerebral palsy - Obesity - Type 2 diabetes - Allergies - Disorders of haematopoiesis	- Polycystic ovary syndrome - Irregular menstrual cycles - Premature menopause - Thyroid cancer - Bone fractures - Osteoporosis - Irregular calcification at birth - Impaired skeletal development - Developmental abnormalities of the teeth (enamel, hypomineralisation, etc.) - Congenital hyperthyroidism - Congenital hypothyroidism - Subclinical hyper and hypothyroidism - Type 1 diabetes - Cardiovascular diseases - Metabolic syndrome	- Premature ovarian failure - Cushing's disease - Addison's disease - All skin disorders - Gestational diabetes - Ocular surface impairment - Retinal impairment

[4] This category is for weight of evidence levels identified as "possible" and "probable" in the literature reviews used.

Details of the methodology used

The following paragraphs present the methodology used that resulted in this prioritisation.

The Joint Report of the World Health Organization (WHO) and the United Nations Environment Programme (UNEP) published in 2012 reviewed our current understanding ten years after an initial release published in 2002 [6]. At the end of each chapter, the weight of evidence for each effect or group of effects was expressed and qualitatively summarised (e.g., sufficient evidence, limited evidence), considering the data as a whole. For our purposes, the weight of evidence was divided into four qualitative categories. Each category corresponds to a score as shown in the table below.

I TABLE A3-2 I

Scores attributed according to the weight of evidence defined by the WHO report

	Weight of evidence expressed in line with the WHO report (2012)			
Qualitative categories	Sufficient	Plausible, Probable, Possible, Limited Evidence	Insufficient	Undocumented, no information
Score assigned	**3**	**2**	**1**	**0**

Independently of this, the European Commission's report, coordinated by Andreas Kortemkamp [11], also published in 2012, set out the state of science on the same subject, for the purposes of the draft regulation on EDs, with a focus on the biological plausibility of the link between exposure to EDs and possible effects. The link was quantitatively documented on a scale from zero to eight. Eight criteria defined on the basis of an International Programme of Chemical Safety (IPCS) 2002 report [12], intended to qualify the potential for endocrine disruption of each indicator, were reviewed in this report. A score of one was attributed when the criterion was completely met, 0.5 when it was partially met and zero when it was not met. Finally, the scores of the eight criteria were added up. The different scores are divided into four different ranges, each corresponding to a score, as shown in the table below.

I TABLE I

Scores attributed according to the weight of evidence defined by the EC report

	Weight of evidence in line with the EC report (2012)			
Quantitative categories	[6.25 - 8]	[5 - 6.25]	[0 - 5]	/
Score assigned	**3**	**2**	**1**	**0**

The quantitative weight from the EC report is scored from 0 to 8, divided into four categories of scores in order to be able to combine it with the WHO score. In order to select the limits for the quantitative weight of the EC report, the distribution of WoE levels for each of the two reports was analysed to determine consistent and relevant ranges. For example, when the weight of evidence is classified as "insufficient" by the WHO, for the comparable weight of the evidence level in the EC report was studied. It turned out that assigning a value for the weight of evidence was relatively consistent between the two reports, with no real contradictory findings identified for any pathology, and the distribution of WoE levels meant that these ranges could be determined.

When the weight of evidence was available in both reports, only the highest weight was taken intou account. This is because these reports date from the same year, so they are based on the same studies available at that time. In addition, when a pathology was not documented by one of the two reports, the weight assigned by the second report was taken into account.

Trasande *et al.* (2015) [13], and its update in 2016 [14], which assessed the likelihood of causality also by using the DELPHI method to look at four categories of health effects:

- metabolic disorders
- neurodevelopmental disorders
- reproductive health in men
- reproductive health in women.

The results of this study were included in our weight of evidence assessment in order to update the data on the diseases in question. For the work carried out by *Trasande et al.,* the weight of the evidence is evaluated for several EDs products (phthalates, PBDE, etc.). For this project, the EDs substance is unimportant because the study is based on a population-based approach. We are interested in the likelihood of causality between exposure to EDs (any kind, mixture of EDs) with the onset of a pathology. We only use the strongest weight for each health effect studied. In Trasande's work, experts commented on the level of epidemiological and toxicological evidence via the DELPHI method. By combining the two levels of evidence, a range of probability of causality was obtained as a percentage and assigned to one of five qualitative categories: *very low*, *low*, *medium*, *high*, *very high*.

I TABLE A3-4 I

Percentage probability of causality and associated qualitative categories in Trasande *et al*., (2015)

90-100%	70-89%	40-69%	20-39%	0-19%
Very high	**High**	**Medium**	**Low**	**Very Low**

These weight of evidence categories as the basis for assigning a score according to the likelihood of causality. "Very high" and "high" categories were combined because the highest percentages of probability calculated by their work fall within a single range of "70-100%". This score will be taken into account using the same methodology as for the other reports: the highest score of the three reports is retained.

I TABLE A3-5 I

Score assigned according to the probability of causality based on Trasande *et al*., (2015)

Probability of causality according to Trasande report	**Very high**	**High**	**Medium**	**Low**	**Very Low**
	90-100%	70-89%	40-69%	20-39%	0-19%
Score assigned	**3**		**2**	**1**	**0**

Appendix 4 / Questionnaire Grid #1

Below is the template of the grid of questionnaire 1 for participants from the scientific field (epidemiologists, toxicologists, academics, etc.), which is identical for the 11 categories of health effects, with the various questions used to assess criterion 1 (weight of evidence), and part of criterion 2 (epidemiological value: severity and change in the incidence rate).

Questions		**CATEGORY OF HEALTH EFFECT 1 to 11 (depending on categories selected by the participant)**		
		HEALTH EFFECT NO. 1	**HEALTH EFFECT NO. 2**	**HEALTH EFFECT NO. …**
NO. 1	**In your opinion, the level of knowledge today makes it possible to conclude that the link between exposure to endocrine disruptors and the onset of the health effect is**	Strong Moderate Low Not sufficiently documented	Strong Moderate Low Not sufficiently documented	Strong Moderate Low Not sufficiently documented
	Rationale for your response	Open response	Open response	Open response
NO. 2	**In your opinion, the level of severity of the health effect is**	Very severe Severe Mild	Very severe Severe Mild	Very severe Severe Mild
	Rationale for your response	Open response	Open response	Open response
NO. 3	**How do you think the number of people affected by this health effect has changed over the last 20 years?**	Increasing Stable Decreasing	Increasing Stable Decreasing	Increasing Stable Decreasing
	Rationale for your response	Open response	Open response	Open response
NO. 4	**Do you have any suggestions for methods for monitoring the health effect (other than biological parameters)? E.g.: existing monitoring systems or in process of being set up, relevant indicator to be monitored, etc.**	Open response	Open response	Open response

Additional questions at the end of each health effect category

Additional questions were also added to this questionnaire. These questions will not be used for the classification of effects, but will complement and enrich the results of the DELPHI consultation.

NO. 5	**Are you aware of a health effect suspected of being linked to exposure to endocrine disruptors that we have missed?**	Open response	Open response	Open response
NO. 6	**Which biomarker(s) of an effect related to exposure to endocrine disruptors do you think is the most relevant to look at in this category? E.g.: epigenetic markers, inflammation markers, etc.**	Open response	Open response	Open response
NO. 7	**Do you have any comments about this category?**	Open response	Open response	Open response

Appendix 5 / Questionnaire Grid #2

Below is the template of the grid for questionnaire 2 for stakeholders in the field, which is identical for the 11 categories of health effects, with the statements to be evaluated for each of the health effects in order to assess societal concern (which is part of the prioritisation criterion 2 "epidemiological and societal value").

Statements to be evaluated		**CATEGORY OF HEALTH EFFECT 1 to 11 (depending on categories selected by the participant)**		
		HEALTH EFFECT NO. 1	**HEALTH EFFECT NO. 2**	**HEALTH EFFECT NO. …**
NO. 1	**The French population is concerned about the occurrence of this health effect in the general population**	Totally disagree Somewhat disagree Somewhat agree Totally agree	Totally disagree Somewhat disagree Somewhat agree Totally agree	Totally disagree Somewhat disagree Somewhat agree Totally agree
NO. 2	**The public should have more information about this health effect**	Totally disagree Somewhat disagree Somewhat agree Totally agree	Totally disagree Somewhat disagree Somewhat agree Totally agree	Totally disagree Somewhat disagree Somewhat agree Totally agree
NO. 3	**There should be greater prevention of this health effect**	Totally disagree Somewhat disagree Somewhat agree Totally agree	Totally disagree Somewhat disagree Somewhat agree Totally agree	Totally disagree Somewhat disagree Somewhat agree Totally agree
NO. 4	**There is insufficient scientific literature and knowledge on this health effect nationally and internationally**	Totally disagree Somewhat disagree Somewhat agree Totally agree	Totally disagree Somewhat disagree Somewhat agree Totally agree	Totally disagree Somewhat disagree Somewhat agree Totally agree
NO. 5	**The consequences of this effect on human health are severe (i.e. this effect impairs daily quality of life and/or leads to a risk of death in the short or long term)**	Totally disagree Somewhat disagree Somewhat agree Totally agree	Totally disagree Somewhat disagree Somewhat agree Totally agree	Totally disagree Somewhat disagree Somewhat agree Totally agree
NO. 6	**You and your organisation are interested in the implementation of surveillance of this health effect in France**	Totally disagree Somewhat disagree Somewhat agree Totally agree	Question disappears from the following rounds	Question disappears from the following rounds

Additional question at the end of each health effect category

Additional questions were also added to this questionnaire. These questions will not be used for the classification of effects, but will allow us to complete and enrich the results of the Delphi consultation.

NO. 7	**Are you aware of a health effect suspected of being linked to exposure to EDs that we have missed?**	Open response	Question disappears from the following rounds	Question disappears from the following rounds
NO. 8	**Do you have any comments about this category?**	Open response	Question disappears from the following rounds	Question disappears from the following rounds