# Élaboration d'une méthodologie d'évaluation du caractère perturbateur endocrinien des substances chimiques

**Contribution à la Stratégie nationale sur les perturbateurs endocriniens 2019-2022**

Avis de l'Anses
Collective Expert Appraisal Report

Avril 2021

Le directeur général

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# AVIS
## de l'Agence nationale de sécurité sanitaire
## de l'alimentation, de l'environnement et du travail

relatif à l'élaboration d'une méthodologie d'évaluation du caractère PE des substances chimiques en vue d'un classement en catégories « avérées, présumées, suspectées »

*L'Anses met en œuvre une expertise scientifique indépendante et pluraliste.*
*L'Anses contribue principalement à assurer la sécurité sanitaire dans les domaines de l'environnement, du travail et de l'alimentation et à évaluer les risques sanitaires qu'ils peuvent comporter.*
*Elle contribue également à assurer d'une part la protection de la santé et du bien-être des animaux et de la santé des végétaux et d'autre part à l'évaluation des propriétés nutritionnelles des aliments.*
*Elle fournit aux autorités compétentes toutes les informations sur ces risques ainsi que l'expertise et l'appui scientifique technique nécessaires à l'élaboration des dispositions législatives et réglementaires et à la mise en œuvre des mesures de gestion du risque (article L.1313-1 du code de la santé publique).*
*Ses avis sont publiés sur son site internet.*

L'Anses a été saisie le 8 octobre par Ministères de la Transition écologique et solidaire, et des Solidarités et de la Santé pour la réalisation de l'expertise suivante : mise en œuvre des actions 1, 2 et 3 de la deuxième stratégie nationale sur les perturbateurs endocriniens (SNPE 2). Le présent avis restitue la contribution de l'Anses à l'action 3 de la SNPE 2 en lien avec l'élaboration d'une méthode de catégorisation des substances dans trois catégories : avérée, suspectée, présumée.

## 1. CONTEXTE ET OBJET DE LA SAISINE

Un perturbateur endocrinien est défini par l'OMS/IPCS (2002) comme :

*An exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations*",

"*A potential endocrine disruptor is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub) populations*".

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ANSES/FGE/0037 [version h] – plan de classement PR1/ANSES/9

Une traduction française de cette définition est introduite dans l'avis de l'Anses de 2012 : « *Une substance ou un mélange exogène, altérant les fonctions de l'appareil endocrinien et induisant en conséquence des effets nocifs sur la santé d'un organisme intact, de ses descendants ou au sein de (sous-)populations. Un perturbateur endocrinien potentiel est une substance ou un mélange exogène, possédant des propriétés susceptibles d'induire une perturbation endocrinienne dans un organisme intact, chez ses descendants ou au sein de (sous-)populations* »[1].

Actuellement, différents règlements européens tirent des conséquences réglementaires pour des substances chimiques dont la caractérisation du danger conduit à considérer qu'elles répondent à la première partie de cette définition de l'OMS, il s'agit en particulier du règlement REACh[2] et des règlements sectoriels biocides[3] et phytopharmaceutiques[4]. Ces conséquences sont variées suivant le règlement considéré (non autorisation, encadrement des usages).

Pour être identifiée PE, une substance doit répondre à la définition de perturbateur endocrinien telle qu'admise au niveau européen, c'est-à-dire que les données disponibles pour cette substance doivent permettre l'identification d'un effet néfaste sur un organisme intègre, d'un mode d'action PE et d'un lien de plausibilité biologique entre les deux. Il faut aussi démontrer la pertinence pour l'Homme ou sur une population des effets observés sur des modèles animaux ou cellulaires. S'agissant du règlement REACh, au-delà de la caractérisation du danger PE, une démonstration d'un niveau de préoccupation équivalent à des effets cancérogènes, mutagènes ou toxiques pour la reproduction (CMR) doit être effectué pour que la substance soit listée – et donc gérée – comme une substance extrêmement préoccupante (SVHC).

Afin de déterminer si une substance est caractérisée comme PE, un guide a été élaboré conjointement par l'EFSA et l'ECHA avec le support du JRC proposant une méthodologie commune aux réglementations biocides et phytopharmaceutiques et harmonisée au niveau européen pour l'identification des PE[5]. Il s'agit aujourd'hui du guide le plus avancé au niveau européen pour l'identification du caractère PE d'une substance. Ainsi, même s'il ne concerne réglementairement que les substances actives biocides et phytopharmaceutiques, les concepts définis peuvent s'appliquer aux autres substances chimiques, telles que celles régies par le règlement REACh. Cependant, ce guide ne conduit pas à distinguer de manière graduée les substances PE en différentes catégories en fonction du niveau de plausibilité biologique alors que l'OMS introduisait déjà en 2002 les notions de PE « suspecté » (2ème alinéa) appuyant ainsi la nécessité d'une identification en plusieurs catégories.

Dans son avis datant de 2016, l'Anses proposait de distinguer les PE en trois catégories : « avérés », « présumés » et « suspectés », en intégrant des niveaux de preuves et

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[1] Avis de l'Anses relatif à une demande d'appui scientifique et technique concernant la révision de la stratégie européenne relative aux perturbateurs endocriniens (avis Anses 2012-SA-0033)
[2] EC, Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), Off. J. Eur. Communities. L 396 (2006) 1–849.
[3] Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products, 2012. doi:2004R0726 - v.7 of 05.06.2013.
[4] EC, Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC, Off. J. Eur. Union. L 309 (2009) 1–50.
[5] Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009

d'incertitudes, et ceci en dehors de tout contexte réglementaire spécifique[6,7]. Ainsi, à l'image de ce qui est actuellement fait pour les substances cancérogènes, mutagènes, reprotoxiques (CMR) dans le cadre du règlement CLP, une approche graduée est de nature à permettre de mieux prendre en compte les incertitudes et faciliter le jugement d'experts. De plus, cette catégorisation permettrait une déclinaison réglementaire adaptée. Des niveaux d'encadrement différenciés pourraient ainsi être introduits en fonction des usages et des populations exposées (par exemple, une règlementation plus sévère pour les jouets avec interdiction des PE « avérés », « présumés » et « suspectés »). Enfin, comme elle s'apparente au système de classification européen existant pour les autres dangers des substances chimiques, son application pourrait être rendue rapidement opérationnelle.

La SNPE 2, lancée par le ministère de la Transition écologique et solidaire et le ministère de la Solidarité et de la Santé dans la perspective du quatrième plan national Santé-Environnement 2020, vise, sur la période 2019-2022, à réduire l'exposition de la population et la contamination de l'environnement aux perturbateurs endocriniens[8]. Elle s'appuie sur le retour d'expérience de la première Stratégie française sur les perturbateurs endocriniens (SNPE 1) publiée en 2014. Afin de mettre en œuvre l'action 3 de la SNPE 2, l'ANSES a été saisie pour rendre disponible dès 2020 une liste de substances PE classées en trois catégories « avérées, présumées, suspectées ». Afin de pouvoir élaborer cette liste, une méthodologie de catégorisation des substances dans ces trois catégories est donc attendue de la part de l'agence. Les critères de catégorisation étant actuellement en cours de développement au niveau européen, l'Anses s'est focalisée sur l'élaboration d'une méthode de catégorisation pour obtenir un consensus sur le niveau de preuve nécessaire pour inscrire des substances à cette liste.

Cette expertise s'inscrit dans une volonté européenne d'améliorer le cadre réglementaire actuel pour la protection de la santé humaine et environnementale au regard des perturbateurs endocriniens en établissant un système juridiquement contraignant d'identification des dangers liés aux perturbateurs endocriniens, sur la base de la définition de l'OMS et en s'appuyant sur les critères déjà définis pour les pesticides et les biocides, et de l'appliquer dans l'ensemble de la législation (Commission Européenne, 2020[9]).

## 2. ORGANISATION DE L'EXPERTISE

L'expertise a été réalisée dans le respect de la norme NF X 50-110 « Qualité en expertise – Prescriptions générales de compétence pour une expertise (Mai 2003) ».

L'expertise relève du domaine de compétences du comité d'experts spécialisé (CES) « Substances chimiques visées par les règlements REACH et CLP ». L'Anses a confié l'expertise au groupe de travail « Perturbateurs endocriniens ». Le GT PE a été mandaté pour

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[6] Note d'appui scientifique et technique de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail relative à la demande d'avis relatif au nouveau projet de la Commission sur les critères PE – 2016-SA-0243

[7] Avis de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail relatif à la définition de critères scientifiques définissant les perturbateurs endocriniens – saisine 2016-SA-0133

[8] https://www.ecologique-solidaire.gouv.fr/perturbateurs-endocriniens-gouvernement-presente-deuxieme-strategie-nationale-afin-reduire

[9] European Commission. Communication from the Commission to the European parliament, the council, the European economic and social committee and the committee of the regions. Chemicals strategy for sustainability towards a toxic-free environment. Brussels, 14.10.2020. COM(2020)667 final

élaborer une méthodologie de catégorisation pouvant être utilisée de façon reproductible et transparente.

Différents outils de formalisation de l'expertise peuvent être envisagés afin de catégoriser les PE. Dans ce contexte, dans une démarche de détermination du poids des preuves, la méthode d'élicitation du jugement d'experts a été retenue par le GT PE en se basant sur les travaux de l'EFSA (EFSA, 2014[10]). Cette expertise collective a conduit à la rédaction d'un rapport en anglais afin de pouvoir être partagé au niveau européen intitulé « *Elaboration of a method to categorize substances of interest as regards to their potential endocrine disrupting activity: assessment and categorization of prioritized substances* », à partir duquel le présent avis a été élaboré.

Les travaux ont été présentés au CES « Substances chimiques visées par les règlements REACH et CLP » tant sur les aspects méthodologiques que scientifiques le 2 février 2021 et le 2 mars 2021*.* Ils ont été adoptés par le CES réuni le 2 mars 2021.

L'Anses analyse les liens d'intérêts déclarés par les experts avant leur nomination et tout au long des travaux, afin d'éviter les risques de conflits d'intérêts au regard des points traités dans le cadre de l'expertise.

Les déclarations d'intérêts des experts sont publiées sur le site internet : https://dpi.sante.gouv.fr/.

## 3. ANALYSE ET CONCLUSIONS DU CES ET DU GT

### 3.1. Description de la méthode

L'objectif de cette expertise est de développer une méthode de catégorisation, transparente, argumentée, et semi-quantitative, prenant en compte l'incertitude, qui renforce la démarche classique d'expertise collective, en relation avec les précédents travaux méthodologiques de l'ANSES[7]. La méthode retenue est une démarche de poids des preuves en relation avec les précédents rapports de l'ANSES et de l'EFSA[11,12,13,14]. Les différentes données disponibles (lignes de preuves) sont évaluées au regard de leur qualité et de leur pertinence, puis l'ensemble des données est évalué. L'étape finale de synthèse de l'information donnée par les lignes de preuves, dans le but de déterminer le niveau de plausibilité d'hypothèses, suit une méthode d'élicitation formalisée du jugement d'experts telle que proposée par l'EFSA (EFSA, 2014). Parmi les différentes méthodes, la méthode Sheffield, est basée sur le partage des informations et des opinions. Cette approche permet des échanges directs d'arguments entre experts au cours d'une phase collective en vue d'obtenir une opinion consensuelle au niveau du groupe. Cette démarche a été retenue par les experts du GT PE.

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[10] EFSA. (2014) Guidance on Expert Knowledge Elicitation in Food and Feed Safety Risk Assessment.

[11] ANSES (2016b). Prise en compte de l'incertitude en évaluation des risques : revue de la littérature et recommandations pour l'Anses

[12] ANSES (2016a). Évaluation du poids des preuves à l'Anses : revue critique de la littérature et recommandations à l'étape d'identification des dangers. Saisine «n°2015-SA-0089 »

[13] ECHA (European Chemicals Agency) and EFSA (European Food Safety Authority) with the technical support of the Joint Research Centre (JRC) (2018), Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009.

[14] EFSA (2017a). Scientific opinion on the Guidance on the use of the weight of evidence approach in scientific assessments.

### 3.1.1. Considérations préalables à la mise en place de la catégorisation

L'approche par élicitation du jugement d'experts se base au préalable sur une revue détaillée de la littérature, puis sur une évaluation de la qualité et de la pertinence des données scientifiques dans une démarche de poids des preuves. La base de données (éco)-toxicologiques (données épidémiologiques, études expérimentales *in vivo, in vitro*) recueillie doit être suffisante afin d'identifier *a minima* un effet néfaste et un mode d'action endocrinien sous-jacent, en accord avec les critères d'identification des PE définis dans le document guide de l'EFSA/ECHA/JRC. Ainsi, c'est sur la base d'au moins un couple effet néfaste / mode d'action jugé pertinent que se fait l'élicitation formelle du jugement d'experts. Cette élicitation permet de recueillir le niveau de confiance des experts sur l'interprétation des données disponibles et de quantifier cette opinion de manière robuste, argumentée et transparente. Cette élicitation se fait de façon individuelle dans un premier temps, chaque expert donnant son avis argumenté de façon indépendante, puis de façon collective par l'ensemble des experts participant à l'élicitation au sein du GT PE, dans un deuxième temps. L'examen structuré des données disponibles, comme prévu dans une démarche de poids des preuves, et l'obtention d'une opinion consensuelle requiert d'y allouer un temps d'expertise scientifique relativement conséquent. Cette méthode ne pourra donc pas être menée systématiquement pour toutes les substances au programme de travail de l'ANSES dans le cadre de la SNPE 2. En effet, en fonction des données disponibles, de l'urgence du délai de réponse attendu, de la charge de travail, incluant les ressources en interne et la disponibilité du GT-PE, du contexte général, du caractère stratégique du dossier et de la présomption d'une identification SVHC, l'ANSES et le GT-PE jugeront de l'opportunité de conduire une élicitation formalisée suite à une démarche d'évaluation du poids des preuves.

### 3.1.2. Stratégie générale de catégorisation

La stratégie proposée suit la définition d'un perturbateur endocrinien selon l'OMS et s'appuie sur le document guide de l'EFSA/ECHA/JRC sur l'identification des dangers relatifs à une perturbation endocrinienne. Ainsi, en accord avec le guide identification d'un PE, une substance est considérée comme ayant des propriétés PE si elle répond aux critères suivants:

*Criteria (1): "It shows an adverse effect in [an intact organism or its progeny]/[non-target organisms], which is a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences;"*

*Criteria (2): "It has an endocrine mode of action, i.e. it alters the function(s) of the endocrine system"*

*Criteria (3): "The adverse effect is a consequence of the endocrine mode of action"*

Sur cette base, en vue de l'élicitation du jugement d'experts, quatre questions sont posées :

- Question 1 : Quelle est la plausibilité que la substance étudiée ait le potentiel de causer un effet néfaste ?

- Question 2 : Quelle est la plausibilité que la substance étudiée agisse à travers un mode d'action endocrinien ?

- Question 3 : Quelle est la plausibilité que le mode d'action endocrinien induise l'effet néfaste identifié ?

Comme indiqué dans le guide de l'EFSA/ECHA/JRC, cette question concerne le lien (plausibilité biologique) entre l'effet néfaste et le mode d'action endocrinien, qui devra être déterminé à la lumière des connaissances scientifiques disponibles. Pour conclure sur la plausibilité biologique du lien, il n'est pas nécessaire d'avoir démontré pour la substance évaluée l'ensemble de la séquence des événements conduisant à l'effet néfaste. Les connaissances générales en endocrinologie et / ou toxicologie peuvent être suffisantes pour aborder le lien et parvenir à une conclusion sur la plausibilité biologique entre les effets néfastes et l'activité endocrinienne.

- Question 4 : Sur la base des plausibilités relatives aux questions 1, 2 et 3, quelle est la plausibilité que la substance étudiée ait le potentiel de causer un effet néfaste par un mode d'action endocrinien ?

Dans cette question, les niveaux de preuves des trois questions précédentes sont intégrés pour pouvoir catégoriser la substance étudiée selon les trois catégories préétablies dans le cadre de la SNPE 2 : PE avéré, présumé, suspecté. De plus, il est apparu lors de cette expertise la nécessité de rajouter deux catégories supplémentaires : une catégorie « non catégorisée » en cas de données insuffisantes pour conclure et une catégorie « non PE » si les données disponibles au moment de l'évaluation permettent de conclure à une absence probable d'effet PE. Il est important de noter qu'une substance peut être élicitée pour son caractère de perturbation endocrinienne sur la santé humaine et sur l'environnement, ou pour l'un des deux en fonction des données.

La stratégie générale de conduite de ce type d'expertise est brièvement décrite en 10 étapes illustrées dans le schéma ci-dessous (figure 1).

**Etape 1**: Une revue détaillée des données disponibles sur la substance étudiée est réalisée.

**Etape 2**: Sur la base de cette revue, un rapport d'expertise détaillé résumant toutes les données toxicologiques de la substance en lien avec la santé humaine et l'environnement est rédigé, ainsi que des données complémentaires, telles que l'identité de la substance, les propriétés physicochimiques, les données de toxicocinétique, les données de biosurveillance et d'exposition. Cette étape permet d'identifier un ou plusieurs effets néfastes pertinents, un ou plusieurs modes d'action endocrinien, et possiblement un lien de causalité entre eux. Une structuration des données (cf. étapes 5 et 6) peut-être nécessaire, pour identifier ce/ces couple(s).

**Etapes 3 et 4**: Le choix de conduire une élicitation est évalué de manière collégiale sur la base des données disponibles et des conclusions présentées dans le rapport d'expertise. Lorsque les données sont insuffisantes pour conduire le processus d'élicitation, la substance étudiée n'est pas soumise au processus d'élicitation et des données complémentaires peuvent être requises. Si les experts considèrent que le manque d'information est partiel (soit sur le mode d'action, soit sur l'effet néfaste ou soit sur lien de causalité) mais que des éléments probants existent concernant des modulations des fonctions endocrines, la substance peut être catégorisée comme suspectée, sans élicitation, avec ou sans demande de compléments d'information. Ainsi, parmi tous les modes d'action et / ou effets néfastes identifiés, au moins un ou plusieurs couples effet néfaste / mode d'action endocrinien sont choisis collégialement pour être élicités.

**Etapes 5 et 6**: La description et l'évaluation de la pertinence et de la fiabilité de chaque ligne de preuves en lien avec chaque question (de la question 1 à la question 4) dans une démarche de poids des preuves sont résumées dans un tableau synthétique. L'évaluation de la cohérence entre chaque ligne de preuve est également évaluée. L'information de

chaque tableau est vérifiée par un groupe d'experts. En accord avec les critères mentionnés plus haut, les quatre questions citées sont posées à l'ensemble des experts ou à un panel d'experts représentatif des problématiques de la substance (question 1 à question 4, cf. annexe 2).

**Etape 7**: Les documents servant de support à l'élicitation sont le tableau synthétique (dans un format type « tableur Excel »), le rapport d'expertise et les données sources. Lors de l'élicitation individuelle, les experts formés à l'élicitation collective, doivent donner leur propre opinion argumentée au regard des quatre questions. Les experts donnent aussi la valeur de cette opinion sous la forme de trois quartiles permettant d'ajuster une distribution. Cette distribution décrit leur probabilité subjective de répondre « oui » à la question posée (ou plausibilité) et l'incertitude associée. Chaque expert répond de manière argumenté et indépendante, et peut vérifier l'ajustement de sa distribution à l'aide d'application(s) en ligne. Après cette étape, les experts transmettent leurs opinions individuelles à la coordination de l'Anses qui analyse les résultats de manière anonyme. Ensuite, l'élicitation collective commence, pendant laquelle chaque expert restitue individuellement de manière argumentée son opinion devant le groupe. Les informations disponibles et pertinentes sont partagées. Une deuxième phase permet aux experts de débattre des arguments dans un contexte formalisé afin d'obtenir une distribution consensuelle et son argumentaire au niveau du groupe. La distribution obtenue décrit l'opinion et l'incertitude du groupe au regard des quatre questions. Tous les argumentaires sont conservés de manière anonyme, au niveau individuel comme au niveau du groupe. Si le consensus ne peut être atteint, une position minoritaire peut être exprimée par les experts, celle-ci sera notifiée dans le rapport final, comme pour toute expertise menée par l'agence.

**Etapes 8 et 9**: Sur la base des opinions exprimées pour établir la plausibilité d'au moins un effet néfaste (question 1), la plausibilité d'au moins un mode d'action endocrinien identifié (question 2) et la relation causale entre les deux (question 3), il est demandé aux experts d'exprimer leur opinion au regard de la question 4 concernant la plausibilité que la substance soit un PE pour la santé humaine et/ou l'environnement. Le processus d'élicitation établit trois valeurs de quartiles (Q25, Q50 et Q75) à partir desquels une distribution est ajustée. Cette distribution ajustée est résumée par les valeurs de sa médiane et de ses percentiles 5% et 95% pour une interprétation à l'étape 10.

**Etape 10**: Cette étape correspond à la catégorisation telle que conclue de manière collégiale par le groupe d'experts. Il s'agit de faire traduire les caractéristiques quantitatives de l'opinion relative à la question 4 (médiane, 5ème et 95ème percentile de la distribution) en une opinion qualitative selon les catégories établies: PE avéré, PE présumé, PE suspecté, non catégorisé, non PE. Un arbre de décision est utilisé pour interpréter les résultats de l'élicitation, en établissant une relation entre les résultats quantitatifs (quartiles de la distribution) et un résultat qualitatif sous forme de catégories (Figure 2). Un rapport poids des preuves / élicitation présentant les données utilisées, les argumentaires, et les résultats (de manière anonyme) synthétise et clôture le travail de catégorisation.
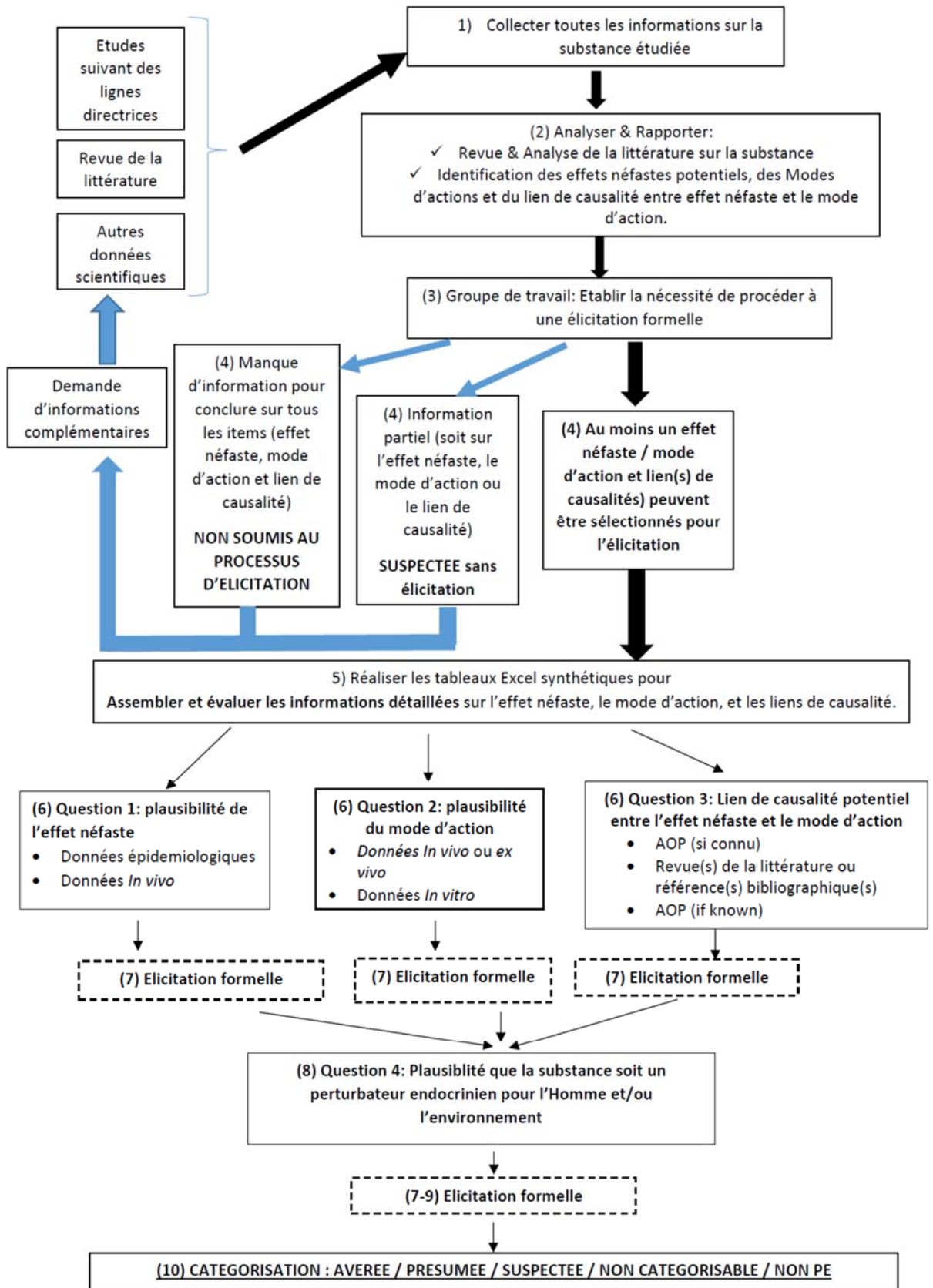
Figure 2: Schéma illustrant la méthodologie de catégorisation d'une substance potentiellement PE

### 3.1.3.Interprétation des catégories issues des résultats de l'élicitation

Une catégorisation des substances potentiellement PE en cinq catégories telles que PE avéré, présumé, suspecté, non catégorisé ou non PE est proposée par le GT PE afin de prendre en compte une approche graduée, décrivant une plus grande variabilité de résultats possibles. Cette catégorisation en 5 catégories permet notamment de mieux prendre en compte les incertitudes et facilite le jugement des experts.

La plausibilité d'être un PE, sous la forme d'une distribution décrivant l'opinion du groupe, et son incertitude, sont prises en compte dans la catégorisation. Cette catégorisation se veut simple, non ambiguë, basée sur un valeur centrale (la médiane) et deux valeurs complémentaires (quantiles 5 et 95%) pour décrire l'étendue de l'incertitude de la distribution.

Des valeurs pivots basées sur les quantiles 5% (Q5), 50%(médiane, Q50) et 95% (Q95) de la distribution sont utilisées dans un arbre de décision, pour traduire des notions quantitatives en valeurs qualitatives.
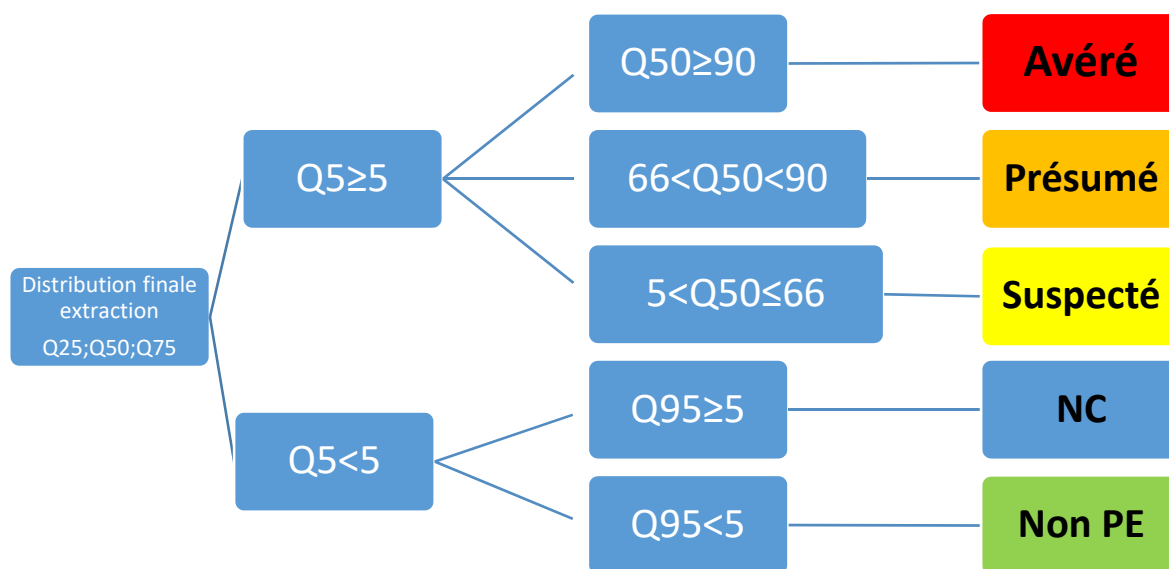


**Figure 1**: Arbre de décision permettant de traduire la probabilité subjective en une catégorie.

Définition des catégories "PE avéré, PE présumé, PE suspecté":

Pour pouvoir classer une substance dans une de ces catégories, il faut tout d'abord que le 5ème percentile de la distribution soit au-dessus de 5% de probabilité subjective d'être un PE (Q5>5).

Trois catégories sont alors possibles :

- **Catégorie "PE avéré"**, si la médiane de la probabilité subjective d'être un PE est au-dessus de 90% (Q50≥90)
- **Catégorie "PE présumé"**, si la médiane de la probabilité subjective d'être un PE est entre 66% et 90% (66<Q50<90)
- **Catégorie "PE suspecté"**, si la médiane de la probabilité subjective d'être un PE est entre 5% et 66 % (5<Q50≤66)

Une substance peut également être catégorisée en « PE suspecté » sans élicitation du jugement d'experts dans les cas où les données sont insuffisantes pour conduire le processus d'élicitation du fait d'information partielle (soit sur le mode d'action, soit sur l'effet néfaste ou soit sur lien de causalité) mais que les experts du GT PE jugent que le potentiel endocrinien de la substance ne doit pas être négligé.

Définition des catégories: « non catégorisée et non PE »:

En plus des catégories PE « avérés, présumés, suspectés », les experts du GT PE ont souhaité définir des critères pour classer des substances en tant que « non PE ». Une catégorie « non catégorisée » a également été établie dans les cas où les données ne sont pas suffisantes pour conclure, en terme de quantité et/ou de qualité.

Une substance peut être classée dans une de ces catégories lorsque le 5ème percentile de la distribution est en-dessous de 5% de probabilité subjective d'être un PE (Q5<5).

Deux catégories sont proposées :

- **Catégorie « non catégorisée »**, si la probabilité subjective d'être un PE, en considérant 95% d'incertitude (Q95>=5) est au-dessus de 5%, alors la substance est non catégorisée car l'incertitude est considérée comme trop importante pour que la substance soit classée.
- **Catégorie « non PE »**, la probabilité subjective d'être un PE, en considérant 95% de l'incertitude de sa distribution (Q95<5) est en-dessous de 5%.

## 4. CONCLUSIONS ET RECOMMANDATIONS DE L'AGENCE

*Un danger de perturbation endocrinienne dont l'évaluation doit se traduire par une catégorisation fonction du poids des preuves scientifiques disponibles*

Le danger de perturbation endocrinienne constitue un mode d'action conduisant à un/des effet(s) délétère(s) des substances chimiques pour l'Homme ou pour les espèces de l'environnement dont la définition et les critères d'identification sont - en relatif - plus récents et moins stabilisés que d'autres grandes classes de danger (tel que le caractère cancérogène, mutagène, toxique pour la reproduction...) inscrites de longue date dans le règlement visant à identifier ces dangers (règlement CLP). En effet, ce règlement permet de prendre en compte de manière graduée l'état des connaissances via un mécanisme de catégorisation qui traduit en pratique le niveau des preuves scientifiques existantes quant aux propriétés de la substance. La catégorisation qui en résulte a des conséquences variées en matière de gestion des risques en fonction des règlementations sectorielles pour des réponses là aussi graduées au regard des préoccupations, des conditions d'exposition associées, voire des populations concernées.

À ce jour, et alors qu'une définition de l'OMS est clairement énoncée depuis 2002 pour définir les substances présentant un danger PE, les critères d'identification définis par les règlements (Reach, biocide, phytosanitaire) qui le prennent en compte ne permettent pas une telle catégorisation en fonction du niveau de preuve.

Dans le cadre de la Stratégie Nationale sur les Perturbateurs Endocriniens (SNPE 1), un avis de l'Anses (Anses, 2016) avait recommandé de distinguer les PE en trois catégories : PE «avérés », PE « présumés » et PE « suspectés ». Cette préconisation s'appuyait déjà sur cette définition de l'OMS tout en reflétant le niveau d'incertitudes et ce, en dehors de tout contexte règlementaire spécifique. L'Agence considère d'ailleurs qu'une telle gradation est d'autant plus nécessaire que la complexité des mécanismes sous-jacents au danger PE – par exemple les différentes régulations endocrines à considérer – et le corpus de données encore largement en construction, conduisent à intégrer des connaissances parcellaires.

L'Anses a été mandatée, dans le cadre de l'action 3 de la SNPE 2, pour définir une méthodologie d'évaluation du caractère PE de substances chimiques permettant, à l'issue de cette évaluation de les classer dans ces catégories. L'une des finalités de cette méthode est de pouvoir élaborer une liste de substances PE classées, à l'issue de leur évaluation par l'Anses, selon a minima trois catégories « avérées, présumées, suspectées ».

***Une méthode d'évaluation pour la catégorisation PE fondée sur la définition de l'OMS, cohérente avec le guide d'identification européen et permettant de peser les données disponibles et les incertitudes associées***

La méthode d'évaluation élaborée par l'Anses a conduit à identifier, in fine, 5 catégories possibles : PE avéré, présumé, suspecté, non catégorisé et non PE. Elle est fondée sur une démarche de pesée du poids des preuves, avec une étape d'élicitation du jugement d'experts par la méthode Sheffield. Le formalisme de cette démarche permet la traçabilité du raisonnement menant à la conclusion et s'appuie sur une expertise collective. L'agence précise que l'enclenchement d'une action d'évaluation ne conduira pas nécessairement à mettre en œuvre l'étape formelle d'élicitation du jugement d'experts, et que certaines substances pourront être catégorisées sans cette étape, en fonction des enjeux stratégiques réglementaires et des données scientifiques disponibles. Dans ces cas-là, la catégorisation se fera avec les experts de façon qualitative selon la démarche classiquement utilisée à l'Anses sur la base d'un rapport d'expertise.

Un des enjeux majeurs est que la méthodologie proposée soit compatible avec les standards européens en vigueur ou en développement. À ce jour, il n'existe pas de critère harmonisé au niveau européen pour catégoriser les PE. Le guide d'identification des PE élaboré par l'ECHA/EFSA/JRC permet d'évaluer si une substance répond aux critères définissant un PE mais n'inclut pas de catégorisation en fonction du niveau de preuve. Afin de contribuer à la cohérence des méthodes, les concepts développés par ce guide ont été pris comme référence pour ce qui concerne, notamment, la manière de recueillir les données, leur structuration et l'analyse selon les lignes de preuves dans une démarche de poids des preuves. La méthodologie proposée par l'Anses sur la base d'élicitation du jugement d'experts issue de cette expertise constitue une plus-value par rapport à ce guide par l'ajout de critères d'analyse supplémentaires dans l'analyse du poids de la preuve en vue d'identifier le(s) couple(s) effet(s) néfaste(s) / mode d'action.

La méthode développée se rapproche ainsi de ce qui existe actuellement pour la classification des CMR tels que définis par le règlement CLP. Cependant, dans le règlement CLP, la notion d'effet néfaste est un élément clé de la décision de catégorisation même si le mécanisme sous-jacent, lorsqu'il est connu, peut permettre de renforcer ou de diminuer le niveau de preuve. Au contraire, dans la définition d'un perturbateur endocrinien, il est nécessaire de considérer ces deux aspects au même niveau. Il est de ce fait nécessaire d'avoir des données suffisantes sur l'effet néfaste et le mode d'action. La force probante des données est le point critique pour catégoriser, et non l'origine des données, qu'elles soient expérimentales ou épidémiologiques.

***Une catégorisation résultant d'une évaluation à date, dont il est nécessaire d'identifier les conséquences pour les meilleures options de gestion du risque***

L'Anses rappelle que la catégorisation d'une substance est conclue au vu des données et connaissances disponibles au moment de son évaluation : elle peut donc nécessiter une mise à jour en fonction de nouvelles données scientifiques. Cela concerne également les substances classées comme « non PE ».

Lorsque les données ne sont pas suffisantes pour conclure, une substance pourra être classée en tant que « non catégorisée ». La génération de nouvelles données dépend du cadre réglementaire applicable à la substance considérée en fonction des usages prévus. L'Anses estime à cet égard qu'une impossibilité de classement voire une classification comme PE suspecté à l'issue de l'application de la présente méthode, lorsque les données sur les effets néfastes ou sur le mode d'action endocrinien sont trop parcellaires, devrait constituer une préoccupation de nature à requérir des données complémentaires auprès des industriels ayant déclaré son usage.

Pour une substance donnée, les suites d'un travail d'évaluation de substances au titre du danger PE, peuvent entraîner différents types de conséquences sur la manière de gérer les risques associés à leur utilisation ou leur intégration dans des produits. Mener une analyse de type RMOA (« risk management option analysis » pour analyse des options de gestion des risques) est une méthode pour identifier une ou plusieurs mesure(s) de gestion réglementaire(s) appropriée(s) pour chaque substance compte tenu de ses usages.

D'autres actions en lien avec cette expertise sont inscrites dans la SNPE 2, telle que l'action 4 relative à la mise en place d'un dispositif d'information obligatoire sur la présence de substances présentant certaines caractéristiques de danger PE dans des produits de la vie courante et articles manufacturés, produits alimentaires (aliments, emballages, contenants), des produits de santé et des cosmétiques. Cette volonté d'information des consommateurs est portée par la loi n°2020-105 du 10 février 2020 relative à la lutte contre le gaspillage et à l'économie circulaire dite « loi AGEC ».

***Un outil de plus dans la panoplie des leviers réglementaires pour identifier et gérer les substances PE***

Cette expertise s'inscrit dans une volonté européenne d'améliorer le cadre réglementaire actuel pour la protection de la santé humaine et environnementale au regard des perturbateurs endocriniens en établissant un système juridiquement contraignant d'identification des dangers liés aux perturbateurs endocriniens, sur la base de la définition de l'OMS et en s'appuyant sur les critères déjà définis pour les pesticides et les biocides, et de l'appliquer dans l'ensemble de la législation (Commission Européenne, 2020[15]). Cela implique entre autres, l'introduction d'une catégorie de danger PE dans le règlement CLP pour l'Homme et les espèces de l'environnement. L'Anses note à cet égard que sa méthodologie de catégorisation, principalement développée pour les effets sur la santé humaine, est applicable à la toxicité pour les espèces de l'environnement.

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[15] European Commission. Communication from the Commission to the European parliament, the council, the European economic and social committee and the committee of the regions. Chemicals strategy for sustainability towards a toxic-free environment. Brussels, 14.10.2020. COM(2020)667 final

Enfin, l'Anses insiste sur la nécessité qu'une évaluation de substance au titre du danger PE en vue de sa catégorisation soit faite, de manière unique, indépendamment de tout contexte règlementaire. De plus, cette catégorisation des PE permettra de mettre en place des mesures de gestions adaptées selon les réglementations sectorielles, ce qui n'est actuellement pas le cas. Elle rappelle à cet égard sa recommandation (Anses, 2016) qu'au niveau européen une instance unique ait la mission de les établir. L'agence a noté que la stratégie européenne pour les produits chimiques a posé un principe général dans ce sens, le présent avis vise à doter la France d'une méthodologie cohérente avec ces ambitions.

Dr Roger Genet

## MOTS-CLÉS

Catégorisation, PE avéré, PE présumé, PE suspecté, élicitation, poids de la preuve, perturbateur endocrinien, incertitude.

Categorization, Known-EDC, Presumed-EDC, Suspected-EDC, elicitation, weight of evidence, endocrine disrupters, uncertainty.

## ANNEXE 1

**Présentation des intervenants**

**PRÉAMBULE** : Les experts membres de comités d'experts spécialisés, de groupes de travail ou désignés rapporteurs sont tous nommés à titre personnel, intuitu personae, et ne représentent pas leur organisme d'appartenance.

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**Vice-président**

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## COMITÉ D'EXPERTS SPÉCIALISÉ

- CES « Substances chimiques visées par les règlements REACH et CLP » *(quatrième mandature, du 1ᵉʳ janvier 2021 au 31 décembre 2023)*

### Président

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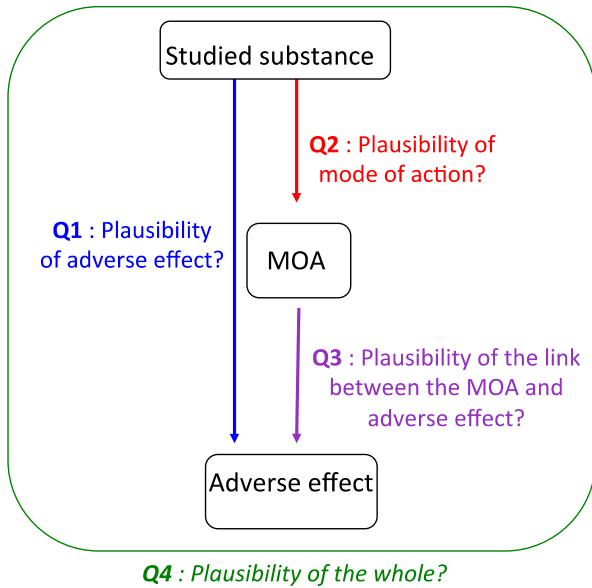Mme Cécile MICHEL - Chef d'unité (UESC) – ANSES- phase de la finalisation de l'avis


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## ANNEXE 1

Schéma illustrant l'intégration des différentes questions de la question 1 à la question 4.



**Q1**: What is the plausibility that the studied substance has the potentiality to cause the adverse effect? This step can be conducted on more than one adverse effect.

**Q2**: What is the plausibility that the studied substance acts through an endocrine mode of action (MOA)? This step can be conducted on more than one MOA.

**Q3**: What is the plausibility that the endocrine MOA induces the adverse effect identified? This step is based on the literature, independently of the substance, and can use existing AOPs when available.

**Q4**: Knowing the plausibility of Q1, Q2 and Q3, what is the plausibility that the studied substance has the potentiality to cause the adverse effect through the endocrine MOA ?

**ANNEXE 3**

Comparaison de la catégorisation par élicitation et des critères de classification selon le règlement CLP

| ANSES metholodogy for categorisation by elicitation | CLP regulation<br><br>Example for reprotoxicity |
|---|---|
| **Category Known**, the median (Q50) of the subjective probability of being an EDC, is above 90 %.<br><br>*Based on the level of confidence.*<br><br>*Whatever the data come from epidemiological data and/or experimental data* | **Known human reproductive toxicant**<br><br>The classification of a substance in Category 1A is largely based on evidence from humans. |
| **Category Presumed**, the median of the subjective probability of being an EDC, is between 66% and 90 %.<br><br>*Based on the level of confidence.*<br><br>*Whatever the data come from epidemiological data and/or experimental data* | **Presumed human reproductive toxicant**<br><br>The classification of a substance in Category 1B is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate. |
| **Category Suspected**, the median of subjective probability of being an EDC, is between 5% and 66 %.This category is covering a large range of possible median and is requesting more information/data.*Based on the level of confidence.*<br><br>*Whatever the data come from epidemiological data and/or experimental data* | **Suspected human reproductive toxicant**<br><br>Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification.<br><br>Such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects. |

| | |
|---|---|
| **Category non categorized**, the subjective probability of being an EDC, taking into account 95% (Q95>=5) of uncertainty is above 5% but the 5 percentile is below 5%. This category is essentially non informative. This category requests also more information and data. | **Not classified (due to inconclusive data)** |
| **Category non ED**, the subjective probability of being an EDC, taking into account 95% (Q95<5) of uncertainty is below 5%. | **Not classified (based on conclusive data)** |

# Elaboration of a method to categorize substances of interest as regards to their potential endocrine disrupting activity: assessment and categorization of prioritized substances

**Contribution of ANSES to the Action 3 of the second French National Strategy on Endocrine Disruptor (SNPE 2)**

Request n°2019-SA-0179 « mise en œuvre de la SNPE 2 »

# Report

**CES REACH-CLP**

**GT PE**

**March 2021**

**Key words**

Categorization, Known-EDC, Presumed-EDC, Suspected-EDC, elicitation, weight of evidence, endocrine disrupters, uncertainty.

# Presentation of the contributors

ANSES undertakes independent and pluralistic scientific expert assessments.

ANSES's public health mission involves ensuring environmental, occupational and food safety as well as assessing the potential health risks they may entail.

It also contributes to the protection of the health and welfare of animals, the protection of plant health and the assessment of the nutritional characteristics of food.

It provides the competent authorities with the necessary information concerning these risks as well as the requisite expertise and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).

**GROUPE DE TRAVAIL (PERTURBATEURS ENDOCRINIENS) IS INVOLVED IN THE WORK PRESENTED AND LATER MENTIONED AS ANSES-WG-ED**

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# SOMMAIRE

# Definitions

**Adverse effect (AE):**   An adverse effect is a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences (WHO/IPCS 2009).

**Adverse Outcome Pathway (AOP) :** An AOP is an analytical construct that describes a sequential chain of causally linked events at different levels of biological organisation that lead to an adverse health or ecotoxicological effect (ECHA/EFSA/JRC, 2018).

**Biological plausibility:** relies on an understanding of the fundamental biological processes involved and whether they are consistent with the causal relationship being proposed. In the context of this guidance, the biological plausibility is considered to be the level of support for the link between the adverse effect and the endocrine activity. In addition, in the context of the MoA (mode of action)/AOP frameworks, biological plausibility is one of the elements to be considered in the weight of evidence analysis based on the evolved Bradford Hill considerations, where reference is made to the biological plausibility of the key event relationships (ECHA/EFSA/JRC, 2018).

**Elicitation or expert knowledge elicitation:** drawing out of knowledge from one or more experts (EFSA, 2014).

**Endocrine activity:** Interaction with the endocrine system that can potentially result in a response of the endocrine system, target organs and tissues. A substance that has an endocrine activity has the potential to alter the function(s) of the endocrine system (ECHA/EFSA/JRC, 2018).

**Endocrine mode of action**, *i.e.* it alters the function(s) of the endocrine system (ECHA/EFSA/JRC, 2018).

**Endocrine disruptor compound (EDC)** is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations (WHO/ICPS, 2002).

**Endocrine system:** The endocrine system is a highly integrated and widely distributed group of organs that orchestrates a state of metabolic equilibrium, or homeostasis, among the various organs of the body. In endocrine signaling, molecules, *i.e.* hormones, act on target cells that are separate from their site of synthesis (ECHA/EFSA/JRC, 2018**).**

**Formal elicitation:** elicitation of a quantitative value with its uncertainty with an adapted procedure such as Sheffield, Coke or Delphi protocol.

**Key event (KE):** A change in biological or physiological state that is both measurable and essential to the progression of a defined biological perturbation leading to a specific adverse outcome (ECHA/EFSA/JRC, 2018).

**Line(s) of evidence:** A set of relevant information of similar type grouped to assess a hypothesis. There is no fixed rule on how much similarity of the information is required within the same line of evidence. This is for the assessor(s) to decide, and depends on what they find useful for the purpose of the scientific assessment (ECHA/EFSA/JRC, 2018**).**

**Mode of action (MoA):** A biologically plausible sequence of key events at different levels of biological organisation, starting with the exposure to a chemical and leading to an observed (adverse) effect (ECHA/EFSA/JRC, 2018**).**

**Molecular Initiating Event (MIE):** A specialised type of key event that represents the initial point of chemical interaction on molecular level within the organism that results in a perturbation that starts the adverse outcome pathway (ECHA/EFSA/JRC, 2018**).**

**Plausibility** (used for elicitation process): subjective probability (with its uncertainty) that the answer is yes to the question.

**Potential endocrine disruptor:** An exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub)populations.

**Sensitive to, but not diagnostic of, EATS'(parameters) :** Parameters measured *in vivo* that may contribute to the assessment of adversity, however, due to the nature of the effect and the existing knowledge as described in OECD GD 150, these effects cannot be considered diagnostic on their own of any one of the EATS modalities. Nevertheless, in the absence of more diagnostic parameters, these effects might provide indications of an endocrine MoA that might warrant further investigation. This includes parameters from OECD CF levels 3, 4 and 5 *in vivo* assays and labelled in OECD GD 150 as endpoints potentially sensitive to, but not diagnostic of, EATS modalities' (ECHA/EFSA/JRC, 2018**).**

**Subjective probability**: a subjective probability is a measure of a person's degree of belief in something (EFSA, 2014).

**Systematic review**: A systematic review is an overview of existing evidence pertinent to a clearly formulated question, which uses pre-specified and standardized methods to identify and critically appraise relevant research, and to collect report and analyze data from the studies that are included in the review (ECHA/EFSA/JRC, 2018**)**.

**Weight of evidence** (WoE): Weight of Evidence can be generally described as a stepwise process/approach of collecting and weighting evidence to reach a conclusion on a particular problem formulation with (pre)defined degree of confidence (ECHA/EFSA/JRC, 2018**)**.

# Figures

# Tables

# 1  Background and purpose of the request

## 1.1  Context

### 1.1.1 Definition

EDCs are substances that alter function(s) of the endocrine system and consequently cause adverse health effects. The endocrine system consists of many cells and tissues that interact with each other and the rest of the body by means of hormones. This system is responsible for controlling a large number of processes in the body from gamete formation, to conception and early developmental processes such as organogenesis, and to most tissue and organ functions throughout life. EDCs interfere with endocrine function by many ways and, in doing so, lead to adverse effects on the health of humans and/or wildlife. Some of the observed health effects associated with EDCs include, but are not limited to cancer, reproductive, developmental, immunological, neurological, metabolic disorders and obesity. More background information on endocrine disruption and the endocrine system is available in the report "State of the Science of Endocrine Disrupting Chemicals – 2012" from UNEP/WHO, 2012.

The definition of an endocrine disrupter proposed by WHO/IPCS (2002), which is internationally accepted by scientific consensus stated that:

An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations.

A potential endocrine disruptor is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub)populations.


### 1.1.2. French context

The second national strategy on endocrine disrupting chemicals (EDCs) also called SNPE2, launched by the French Ministry of Ecological and Solidarity Transition and the French Ministry of Solidarity and Health in the perspective of the fourth national Health-Environment 2020 plan, aims, over the 2019-2022 period, at reducing the impact of EDCs on the population and on the environment. This second strategy is based on the first French Strategy on EDCs (SNPE 1) published in 2014. The SNPE 2 strategy will develop for a further 4-year period with three priority areas for action.

In the frame of the action number 3 of SNPE 2 and for the purpose of managing and informing about the risks linked to EDCs, the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) was mandated on 8 October 2019 to categorize chemicals that may present EDC properties. Specifically, based on the level of scientific evidence available to prove their EDC properties, endocrine disruptors should be assigned to one of 3 categories in accordance with the CLP regulation (regulation 1272/2008/EC) relative to Classification, Labelling and Packaging of substances and mixtures.


### 1.1.3. EU regulatory context

While evaluating the possibility of different options for the definition used to identify EDCs under the plant protection regulation (PPR) and biocidal products regulation (BPR), an impact assessment of these different options on the number of potential EDCs was conducted (EU Impact Assesment, 2016).

The screening study resulted in a in-depth quantifiable estimation about chemical substances used in PP and BP that may be identified as EDCs under Options 1 No policy change (baseline), to 4 (WHO/IPCS definition to identify EDCs with potency criteria). Option 3 of Roadmap proposed to follow the WHO/IPCS definition leading the substances to be allocated in one of the three different categories based on the different weight of evidence for fulfilling the WHO/IPCS definition.

These categories are the following:

• Category 1 substances: confirmed EDCs with adverse effects with plausible link (i.e. same pathway) to mechanistic (endocrine mode of action) information or, in some specific cases, the pattern of adverse effects may be diagnostic of an EDC mode of action.

• Category 2 substances: suspected EDCs when specific adverse effects indicating endocrine disruption were identified without supporting mechanistic evidence, or *in vivo* mechanistic evidence without evidence for adverse effects.

• Category 3 substances: identified endocrine active substances with no *in vivo* evidence.

The choice of the EC, corresponding in part only to Option 2, results in only "known" EDCs and not "presumed" EDCs being identified.

However, breaking down this definition into three categories (as proposed in Option 3 of the roadmap) would enable a more flexible application of the regulations.

In this context, the European Commission has entrusted the European Food Safety Authority (EFSA), the European Chemicals Agency (ECHA) and the Joint Research Center (JRC) with the development of a methodological guide for the application of the hazard criteria leading to the identification of EDCs as provided for these new regulatory.

The guidance document published for the identification of endocrine disruptors (EFSA/ECHA/JRC, 2018) and the criteria developed to identify endocrine disruptors are based on the definition of WHO/IPCS. According to the ED criteria, a substance shall be considered as having ED properties if it meets all of the following criteria:

*a) it shows an adverse effect in [an intact organism or its progeny]/[non-target organisms], which is a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences:*

*b) it has an endocrine mode of action, i.e. it alters the function(s) of the endocrine system;*

*c) the adverse effect is a consequence of the endocrine mode of action;*

The advantage is that the empirical support (experiments, publications) is different between each item (a, b, c).


### 1.1.4 Anses mandate

Based on this preliminary work, the French Ministry of Ecological and Solidarity Transition and the French Ministry of Solidarity and Health has mandated Anses to define and categorize EDCs as Known, Presumed, or Suspected, which is aligned with existing classification of CMR in the CLP regulation.

In 2016, while participating to the consultation concerning the definition of criteria for identifying EDCs as well as several texts proposing a draft amendment to the regulations in force concerning biocidal products and plant protection products, via draft delegated acts, as presented above, ANSES recommended retaining the EDC definition and identification criteria of Option 3 previously proposed in the Commission roadmap. It also proposed, as stated in the SNPE, to distinguish EDCs into three categories: "known" EDCs, "presumed" EDCs and "suspected" EDCs (Anses, 2016a).

As with the current CLP (classification and labelling of products) guidance for classification of carcinogenic, mutagenic and reprotoxic (CMR) substances applicable in Europe, a graduated approach would make it possible to more effectively take the uncertainties into account and facilitate the experts' judgment. In addition, this categorization would allow tailored regulatory implementation. Different levels of management could thus be introduced according to the uses and exposed populations (for example, stricter regulations for toys, with a ban on "known", "presumed" and "suspected" EDCs). Finally, as it is comparable to the existing European classification system (CLP regulation n°1272/2008/EC) (see below), its application could be rapidly made operational (Anses, 2016a).

Therefore, and based on the ECHA/EFSA/JRC guidance, it was decided in this report to distinguish 2 independent categories: not EDC and not categorised, therefore allowing also to identify compounds that have not been studied yet. Depending on the current discussions on creating ED hazard category within CLP, this distinction might be revised.

A categorization of EDCs in fifth categories such as known, presumed, suspected, not categorized, or not EDC is therefore proposed, in order to take into account all possible outcomes.

Currently, there is no consensus about an adequate methodology to categorize an EDC based on existing data (in vitro, in vivo and human) and the associated weight of evidence.

To follow this categorization and to describe the degree of uncertainty around categories, it seemed a relevant choice to define these ordinal scales in terms of the range or plausibility of the outcomes (Morgan *et al*., 2014).

The aim of this work was then to develop a robust and reproducible methodology, based on the weight evidence approach and formal elicitation process for the categorization of EDC in 5 categories such as known, presumed, suspected, not categorized, or not EDC. The list of categorized EDCs was designed for publication on the Anses website and for sharing with our European partners. The ultimate goal of the categorization is to provide a transparent means for communicating decision-making such that decisions can be clearly understood and discussed by all stakeholders.

## 1.2  Objectives of the request

Through the action 3 of SNPE 2, ANSES is mandated to determine a methodology to categorize substances as known, or suspected, presumed endocrine disruptor, therefore not categorized, or not EDC is also proposed in order to take into account all possible outcomes.  Based on this methodology, ANSES is asked to assess and categorize the substances included in the prioritized list for their ED properties (list 1). The chapter II describes the methodology, which required the stratification of the process to identify an EDC in regard to the WHO/IPCS definition.

In parallel to the work described in chapter 2, methodology performed by ANSES requires to gather and assess the evidence about substances having a potential adverse effect and an endocrine activity (chapter 3 and 4). How are assessed and integrated the selected lines of evidence to categorize substances is described in chapter 5 and 6.

The chapter 7 of the report presents the formal elicitation process to integrate the evidence and the chapter 8 explain how to interpret the results and how to use them in a regulatory management process.

## 1.3  Means implemented and organization

To address this mandate, ANSES relies on its dedicated experts committees and working groups.

This work falls within the sphere of competence of the ANSES Working Group on "Endocrine disruptors" (ANSES-WG-ED) which was entrusted with the scientific analysis in this request. The methodological and scientific aspects were discussed at the WG-ED meetings that took place from April 2019 to December 2020. The categorization work presented in chapter 2 also falls within the sphere of competence of the Working Group on "Endocrine disruptors" (ANSES-WG-ED). The entire report has been presented to the 11th of December 2020 for information. In addition, the methodology enabling to categorize the ED substances has been presented to the CES "Reach" on the 2nd of February 2021. The report was adopted on the 2nd of March 2021 by the CES "Reach". The expert appraisal was carried out in accordance with the French Standard NF X 50-110 "Quality in Expert Appraisals – General Requirements of Competence for Expert Appraisals (May 2003)".

This document is intended to provide a structured, robust, transparent and understandable approach to establish a categorizing method for substances having a potential ED adverse effect linked to an endocrine mode of action. The members of the ANSES working group on "endocrine disruptors" (ANSES-WG-ED) have tested this methodology on two practical cases with internal ANSES support. Experts were trained and these experiences show that training people to use the methodology is

necessary. Furthermore, each expert must have gathered a very good and precise knowledge of the data before the elicitation process. This methodology could be implemented and be updated in function of the scientific knowledge and the substances investigated.

## 1.4 Prevention of the risk of interest conflicts.

ANSES analyzes the links of interest declared by the experts prior to their appointment and throughout the work, in order to avoid potential conflicts of interest with regard to the matters dealt with as part of the expert appraisal.

The experts' declarations of interests are made public via dpi santé. ([www.anses.fr](www.anses.fr)).

# 2   Overall strategy

The strategy follows the definition of an EDC given in WHO/IPCS 2002 and is in agreement with the guideline EFSA/ECHA/JRC describing hazard identification for endocrine-disrupting properties for pesticides or biocides (EFSA/ECHA/JRC, 2018). So far, ECHA/EFSA/JRC guidance request that a substance is either recognised EDC or non EDC. However, when positioning this question in the perspective of CLP criteria, when a substance is not harmonized in terms of classification, it could either be because:

-   It has not been studied/ discussed,
-   It has been studied/discussed but it was judged that there is not enough information to decide if it is C, M and/or R,
-   It has been studied/discussed but it was judged that it was not C, M and/or R,

It should be emphasized that this guideline has been written for data rich substances (pesticides and biocide). It is important to note, that a substance could be identified for its potential endocrine disrupting activity for environment or human health or both depending on the data available. According to the EDC identification guideline (EFSA/ECHA/JRC, 2018), a substance is considered as having ED properties if it meets all of the following three criteria:

***Criteria (1):*** *"It shows an adverse effect in [an intact organism or its progeny]/[non-target organisms], which is a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences;"*

***Criteria (2):*** *"It has an endocrine mode of action, i.e. it alters the function(s) of the endocrine system"*

***Criteria (3):*** *"The adverse effect is a consequence of the endocrine mode of action"*

The overall strategy is briefly described below in 10 steps; the chapters detailing the description of each step are indicated. It is also represented in a flowchart illustrated in Figure 1.

**Step 1**: A detailed review of the substance is done by Anses containing all available sources of data collected, and analyzed. This step is described in (chapter 3).

**Step 2**: A detailed analysis of the different effects and properties of the substance is given in an expert report (chapter 4). The expert report contains toxicological and epidemiological data relative to the studied substance in the field of human health and environment, with additional information related to the identity, physicochemical properties, toxicokinetics, human biomonitoring and exposure information on the studied substance. This step identifies potential relevant adverse effect(s), endocrine mode of action (MoA), and causal link between them.

**Step 3 and 4**: The opportunity to conduct an elicitation process is discussed collegially on the basis of this report and the level of information obtained (chapter 5). When data to conduct elicitation process are scarce, the studied substance is not subjected to elicitation, and data completion is requested. If experts consider that the lack of information is partial (either MoA, adverse effect or causal link) but the endocrine potential of the substance should be not neglected, the substance can be categorized as suspected and data completion is also suggested. In any case, the elicitation process should be considered, taking into account challenges, deadlines and human resources (ANSES 2016b, 2016c, 2016d, 2017). For this purpose, among all MoA and / or adverse effects identified, at least one or more couples adverse effect/endocrine MoA are chosen collegially for elicitation.

**Step 5 and 6**: In relationship with the weight of evidence process, description and assessment of relevance, reliability of each line of evidence belonging to each question (QUESTION 1 to QUESTION 4) is described in synthetic Excel tables (detailed in chapter 6). Assessment of consistency (agreement, complementary aspects) between lines of evidence is also evaluated. Information in tables is checked by expert group or subgroup, and can be re-evaluated during elicitation process. The last step of weight of evidence is given by elicitation process.

According to the criteria mentioned above, the four questions (QUESTION 1 to QUESTION 4) submitted to the elicitation process are the followings:

QUESTION 1: What is the plausibility that the studied substance has the potentiality to cause the adverse effect? The adverse effect induced by the substance has to be indicated.

QUESTION 2: What is the plausibility that the studied substance acts through an endocrine mode of action (MoA)? The pathway has to be indicated, and can concern an endocrine MoA related to oestrogenic (E), androgenic (A), thyroid (T) or steroidogenesis (S) pathways of the substance; but it is not limited to EATS pathways (other hormonal signaling pathways can be taken into account).

QUESTION 3: What is the plausibility that the endocrine mode(s) of action induces the adverse effect(s) identified? This question concerns the link (biological plausibility) between the adverse effect and the endocrine mode of action, *which shall be determined in the light of current scientific knowledge. However, to conclude on the biological plausibility of the link, it may not be necessary to have demonstrated for the substance under evaluation the whole sequence of events leading to the adverse effect. Existing knowledge from endocrinology and/or toxicology may be sufficient to address the link and come to a conclusion on the biological plausibility between adverse effects and the endocrine activity* (EFSA/ECHA/JRC, 2018).

QUESTION 4: Knowing the plausibility of QUESTION 1, QUESTION 2 and QUESTION 3, what is the plausibility that the studied substance has the potentiality to cause the adverse effect through the endocrine MOA? The last question integrates the evidences from QUESTION 1 to QUESTION 3 and relates to both the environment (ENV) and the human health (HH).

The methodology proposed in this report focuses on the categorization of the studied substance based on the answer to QUESTION 4.

**Step 7**: The synthetic Excel tables, the complete report, the publications themselves are the documentation made available to the experts who will be involved in the elicitation process. After experts were trained and agreed with definitions, documentation and the four questions presented above, each expert has to give its own and documented opinion, with a distribution of uncertainties defined by its quartiles (see chapter 7). Each expert, independently, can check its distribution using a shinyapp[1]. Experts send their opinion to the coordination team which will analyze the results anonymously for synthesis report. At the following meeting, each expert gives its own opinion and argumentation. Then collective elicitation begins, with behavioral aggregation, in order to obtain a consensual subjective probability distribution for the group. The distribution is describing uncertainty of the group. The approach uses most aspect of Sheffield protocol (see chapter 7.1.3). Each question is related to specific documentation and argumentation, which are reported. If a consensus cannot be reached, minority position is assessed separately.

**Steps 8 and 9**: From the opinions given for establishing plausibility of at least one adverse effect (QUESTION 1), plausibility of one identified endocrine Mode of action (QUESTION 2) and the relationship between them (QUESTION 3), an opinion is asked considering the plausibility of the substance of being an EDC for Human Health (HH) or Environmental Health (EH) (QUESTION 4) (chapter 6, subchapter 6.3). The elicitation process is the same as described in chapter 7. The

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[1] Rshiny application : https://shiny-public.anses.fr/elicittools/

probability distribution of uncertainty is fitted and summarized with median, 5 and 90% percentile for further interpretation in step 10.

**Step 10**: Categorization: Correspondence between summary characteristics of the opinion from the group of elicitated experts (medians, 5 and 95% percentile of the distribution) for QUESTION 4 and qualitative category of opinion: known, presumed, suspected, not categorized, not EDC, was assessed collegially by expert group.  We propose to use this grid of correspondence for interpreting results of elicitation for all substances to be elicitated ([chapter 8](#)) (illustrations in shinyapp[2]).
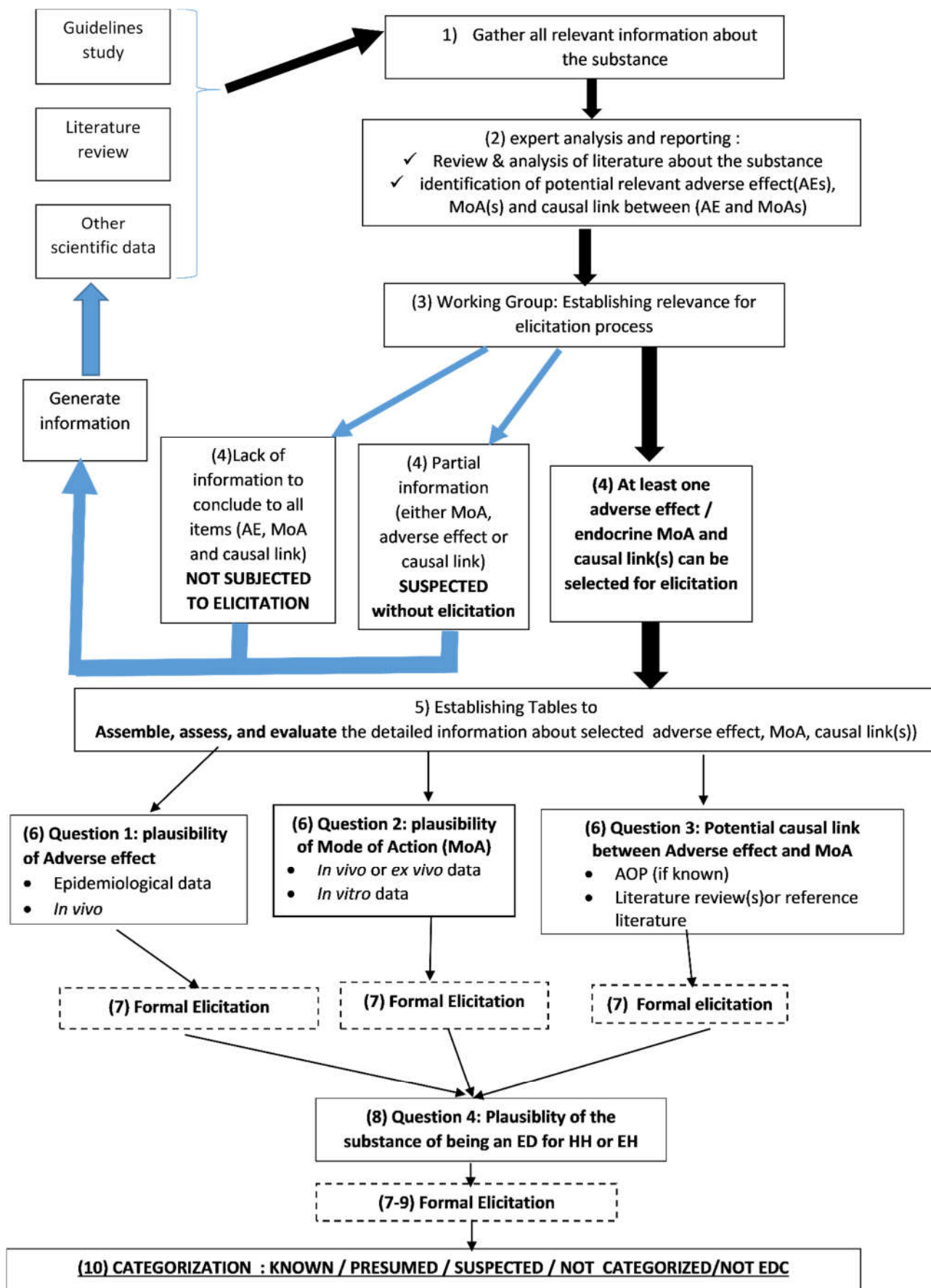
**Figure 1: flow chart illustrating the EDC categorization strategy**

# 3 Gather relevant information: detailed review methodology

The detailed literature review follows the methodology described by Anses (2017, 2016) and all steps are recorded for traceability of the process. These steps could be adapted on a case-by-case basis. This work could be used as part of PECO statement, which is a concept of defining the Population (including animal species), Exposure, Comparator, and Outcomes (PECO) as pillars of the detailed literature review. It is noted that a prisma chart could also be included with the literature finally selected and the couples AE/MoA elicited.

As described in the flowchart, the different steps of the bibliographic review are reported below (report from ECHA/EFSA/JRC, 2018):

1. <u>Identification of available data/selection of most relevant publications</u>:

Peer-reviewed articles and research articles are identified through a minimum of two databases: e.g. PubMed and Scopus®. Secondary literature is also taken into account, for examples, from industry reports, IARC, OECD, NIOSH, ECHA, EFSA and SCCS. The methodology of the literature review (eligibility criteria and key words) is defined with specific requests.

2. <u>Selection of studies and screening</u>,

Studies to be include in the data set are selected without limitation of the publication year (on case-by-case basis, some limitations could be possible):

The selection and screening is performed by applying exclusion/inclusion criteria leading to the exclusion of records based on title and abstract. The first filtering is based on title and abstract screening by independent reviewers, and second on full text screening by reviewers in their field of expertise. When checking title and abstract are insufficient to decide if the paper is relevant, full screening is applied.

<u>The exclusion criteria are</u>:

Studies performed with a mixture including the substance,

Not toxicological studies (ex. Food and cosmetic preservatives, biotechnology, analytical method, biomonitoring, exposure, etc.),

No original data or abstract only,

Full text not available in English,

<u>The inclusion criteria are</u>:

- Epidemiological Human study (descriptive, analytic, transversal, case-control, nested case-control (inside a cohort), cohorts (retrospective, historical, prospective), interventional, meta-analysis), or in vivo animal toxicological study, in vivo mechanistic study, in vitro mechanistic study (organs, cells).

- Full text available in English,

   3. <u>Eligibility and Analysis of relevant publications</u>

The intrinsic quality of the publications is assessed based on the integral text.

Further exclusions concern the absence of an experimental protocol or of statistical analysis, no toxicity assessment or no health events assessed. The included literature is then grouped by biological system studied (endpoints) such as male reproductive system, female reproductive system, obesity and metabolism, neuro-development, thyroid system. Two reviewers, with specific expertise on endpoint of interest share the second screening phase and discuss any conflicts or discrepancies by complementary full-text screening (with double reading). Finally, a report containing all relevant information (as described in step 2) related to the studied substance is produced.

# 4   Hazard analysis report

## 4.1   Review of literature about the substance

The hazard analysis report presents the Human and environmental hazards properties of the studied substances based on available data retrieved from the detailed literature reviews.

The aim of this report is to provide a description of hazard information (environment and human health) relevant for the assessment of the studied substance. The sections included in this report are (but not limited to):

- Identity of the studied substance, chemical and physical identity,

- Uses, EU regulation, classification,

- Environmental fate properties (degradation, distribution, bioaccumulation),

- Human Health Hazard assessment (Human and non-human information on toxicokinetic, repeated dose toxicity, carcinogenicity, toxicity for reproduction, endocrine disruptor properties , in vitro mechanistic data, in vivo mechanistic data, in vivo endocrine disruptors properties link between MoA and adverse effect…),

- Environmental hazard assessment (environmental fate and behaviors, ecotoxicity, endocrine disruptor properties link between MoA and adverse effect),

## 4.2   Identification of potential relevant adverse effect(s), MoA(s) and causal link between both

Based on the conclusion on endocrine disruption of the studied substance as described above, this step allows the identification of a couple(s) adverse effect/MoA (for human health and/or environment).

For identification of the relevant adverse effect, all the criteria needed for description (human and *in vivo* data) are discussed and assessed collegially within the expert group.

For identification of a relevant MoA(s), two types of studies are considered: *in vivo* or *in vitro* mechanistic studies. These studies are discussed collegially within the expert group.

The identification of a couple(s) adverse effect/MoA is a first pre-requisite, which is followed by the identification of a causal link that is the final step to enter in the elicitation process and EDC categorization of the studied substance.

The plausible link for the identified couple(s) adverse effect/MoA is investigated and discussed collegially within the expert group. The link could be based on expert knowledge and / or on existing link such as an existing AOP.

The conclusion of this hazard analysis report (combined or separated for human health and environment) should provide all information on the rationale and choices to identify the couple(s) adverse effect/MoA of the studied substance.

# 5   Establishing relevance and selection for elicitation process

The reporting is allowing the expert group to evaluate the level of information available for the substance. Three situations can be raised (cf. figure 1):

- If information is completely lacking or of too bad quality to assess any of the questions, the elicitation process cannot be performed and data completion could be requested.

- In the case where the knowledge available is too partial (i.e. lack of an identified couple Adverse Effect/MoA), elicitation process cannot be performed. The group can evaluate collegially if with those partial information the substance should be classified as suspected EDC. Again, data completion could be requested.

-From the report, available information can be used to select at least one adverse effects associated with an endocrine mode of action (MoA) and a causal link between them. The elicitation process can then be performed.

The selection should be based on the quality and number of publications or general knowledge. The report grouping all data by endpoints is discussed at an ED expert's working group meeting. The most relevant couple(s) of adverse effect / endocrine MoA(s) that could be used for elicitation is/are selected and validated by the expert group.

The elicitation process has to be considered as "gold standard approach" since it takes time and needs human resources. It should be considered if challenges, deadlines and human resources were taken into account (ANSES, report ACCMER, on going). If elicitation is not possible in the time frame, the substance could be preliminary classified based on the conclusion of the report, and evaluated by elicitation later.

# 6 Assessing the evidence for elicitation

At this step, the information from the selected publications and reports is summarized and integrated in synthetic Excel tables for the analysis of overall quality of the lines of evidence. This step is repeated for QUESTION 1, QUESTION 2, and QUESTION 3. Information relative to the description of the line of evidence, and information relative to the assessment of their intrinsic quality are assessed separately.

To assess the evidence, the type of information needed is given by the EFSA guidance (EFSA Scientific Committee, 2017). All the criteria needed for description and assessment are ranked and chosen collegially. The figure 2 is summarizing the overall view of the methodology.
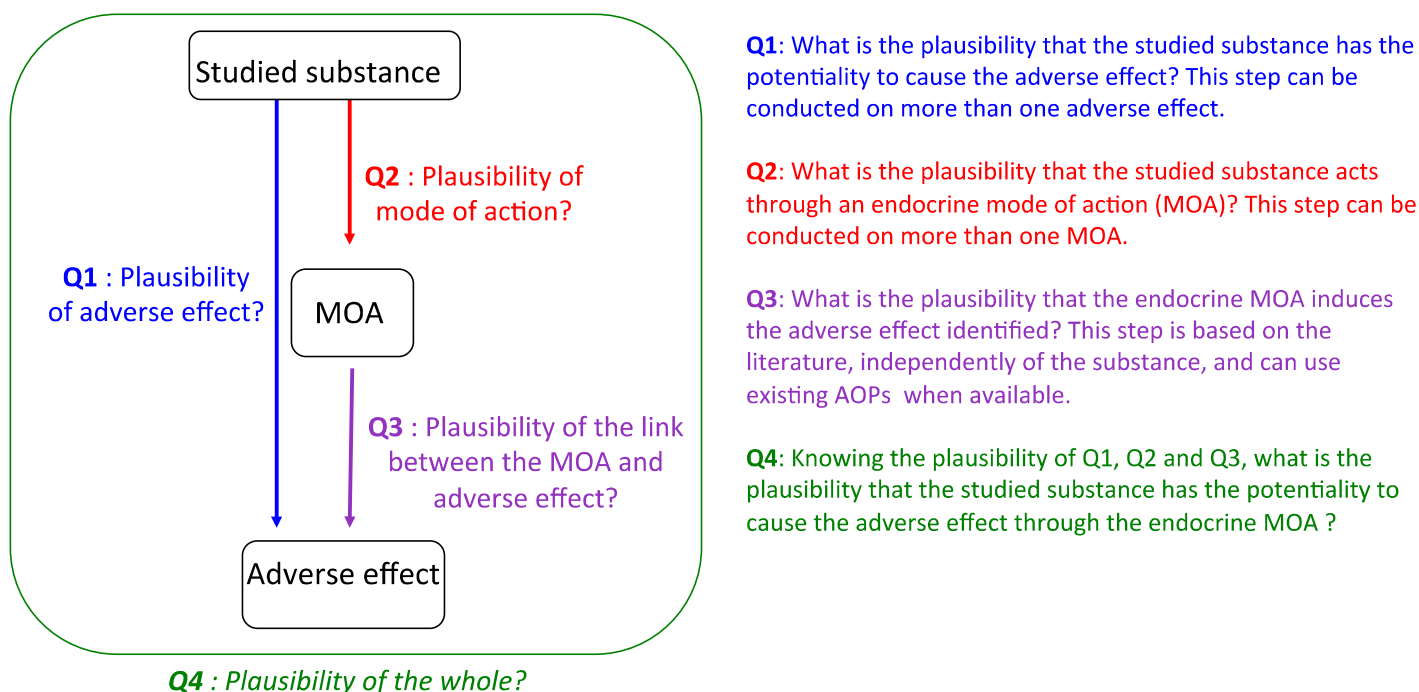


**Q1**: What is the plausibility that the studied substance has the potentiality to cause the adverse effect? This step can be conducted on more than one adverse effect.

**Q2**: What is the plausibility that the studied substance acts through an endocrine mode of action (MOA)? This step can be conducted on more than one MOA.

**Q3**: What is the plausibility that the endocrine MOA induces the adverse effect identified? This step is based on the literature, independently of the substance, and can use existing AOPs when available.

**Q4**: Knowing the plausibility of Q1, Q2 and Q3, what is the plausibility that the studied substance has the potentiality to cause the adverse effect through the endocrine MOA ?

**Figure 2: scheme illustrating the integration of the different questions QUESTION 1 to QUESTION 4.**

## 6.1 Question 1: What is the plausibility that the studied substance has the potentiality to cause the adverse effect

The type of scientific information to answer the question can be classified in two types of studies:

•        Studies performed in intact animals (*in vivo*),

•        Epidemiological human studies,

General considerations can be added such as:

•        Dealing with human health, studies performed in environmental organism (ex. fish) can be considered only if they reinforce the level of evidence on the adverse effect.

•        The knowledge of other members of the structural analogy substance could be used if these data can reinforce the level of evidence of an adverse effect.

•       The exposure parameters are not considered. Only the intrinsic hazard of the substance causing the harmful effect is assessed (in accordance with CLP methodology), regardless of dose or concentration (provided these are compatible with the test). However high doses inducing a general toxicity are excluded.

Assessment criteria as relevance and reliability have to be evaluated for experimental and epidemiological studies.

### 6.1.1   Criteria for description of the information given by a relevant study related to question 1

This section is relative to the description to the type of information needed. All the criteria needed for description and assessment are discussed collegially within the expert group.

Following as much as possible the guidelines and items defined in the report of ECHA/EFSA/JRC, 2018, the information reported in synthetic excel tables concern specific items (Serra *et al*., 2019) but are also debated and completed collegially. The objective is to summarize the information with defined harmonized items, to ensure transparency and traceability, because the opinion is made on those studies, but also to ensure the same interpretation that can be shared easily in the group during collective elicitation.

#### 6.1.1.1   For Human studies (epidemiological studies) description criteria are:

**Study reference/type (Anses, 2017)**

- Study reference: identification number of a report or reference for a published paper,
- Source: scientific published literature/other,
- Year of the study,
- Study type : such as chronic toxicity,
- Objective of the study,
- Study typology: descriptive, analytic, transversal, case-control, nested case-control (inside a cohort), cohorts (retrospective, historical, prospective), interventional, meta-analysis,
- Number of exposed,
- Number of control,
- Measurement of exposure,
- Dose unit,
- Route of exposure,
- Median duration of exposure ,
- Life stage,
- Sex,

**Exposure/design**

- Chemical exposure definition,
- Exposure type,
- Exposure measurement,
- Exposure probability/frequency exposure,
- Level of exposure,
- Duration of exposure,
- Cumulative exposure,
- Definition of sanitary effect,
- Description of measurement of sanitary effect,

- Individual selection/inclusion,
- Individual recruitment,
- Population or groups description,
- Country,
- Size of sampling (theoretical/done) by group or population,
- Population description,
- Temporal sequence,

**Statistical analysis**

- Statistical analysis method,
- Covariate fitting,
- Statistical power,
- Other statistical comments,

**Results and limitations**

- Type of effect,
- Type of association indicator (OR, IR, RR),
- Value and confidence interval of effect,
- P significativity,
- Stratification,
- Matching criteria,
- Complementary information (missing),
- Selection, misclassification bias,
- Confounder bias,
- Dose-response relationship,
- Discussion and conclusion by authors,
- Other bibliographic reference to consider,
- Conflict of interest,
- Study reference: identification number of a report or reference for a published paper,
- Source: scientific published literature/other,
- Year of the study,

### 6.1.1.2 For animal studies (*in vivo*) description items are:

**Study reference/type**

- Study reference: identification number of a report or reference for a published paper
- Source: scientific published literature/other
- Year of the study
- Study type : such as chronic toxicity

**Exposure/design**

- Species (or biological model as defined in Serra *et al.* 2019): *i.e* dog/rat,
- Age (animals or subjects) at exposure,
- Age (animals or subjects) at analysis,
- Intact animals, (as defined in ECHA/EFSA/JRC, 2018)
- Numbers of doses tested and experimental range dose value (min-max),
- Number of animal tested in each group/number of group,
- Route of administration/exposure/feeding conditions,
- Duration of exposure
- Duration of exposure / frequence & unit,
- Studied parameters,

- Group control (not exposed),
- Positive control (effect with another substance),
- Inhibitor substance,
- Experimental Contamination (phytohormones in food and / or plastic cage),
- Vehicle use and degree of purity of tested substance,
- Reference protocol published (elsewhere) or OECD reference,

**Results and limitations**
- Type of significant critical effect /endpoint (describe each effect in individual columns),
- Type of non significant effect /endpoint (described each effects in individual columns),
- Sex of animals for the observed effects,
- Essentiality of the effect (reversibility),
- Sense of critical effect: negative/positive,
- Pathway or mode of action identified,
- Internal dose measurement,
- Life stage of measured effect,
- Parameter estimate and confidence interval & value,
- Statistical analysis method,
- Dose-response relationship,
- Discussion/author limitation,

### 6.1.2 Criteria for assessing the quality of a relevant study related to question 1

Only the relevant literature related to the selected couples adverse effect/MoA are described in details in synthetic excel tables and criteria are applied to assess the quality of the studies.

In ECHA/EFSA/JRC report, 2018 ; "each piece of evidence" (…) "has to be assessed for its relevance and reliability". The definition of this concept is also provided in this report.

- Data Relevance: "*refers to the appropriateness of the data for the intended purpose of the assessment*" (ECHA/EFSA/JRC, 2018).
- Reliability of the data: "*reliability of the data is linked of the reliability of the test method used to generate the data*" (ECHA/EFSA/JRC, 2018). Deviations to the recommendations in the standard guidelines should be reported and assessed on a case-by-case basis.

In the EFSA/ECHA report two criteria for evaluating QUESTION 1 are mostly described as relevance and reliability qualities and additional remark.

For *in vivo* studies, the reliability is evaluated through items that are based on the cotation using Toxicological data Reliability Assessment Tool (ToxRtool) or klimisch. The relevance to the targeted population is analyzed taking into account the species/sex/lifestage. The relevance of the doses tested (e.g. cytotoxic doses), the nature of the effect in terms of reversibility are also assessed.

For helping the process of elicitation, for each line of evidence the overall risk of false positive, false negative or non conclusive are investigated to describe the magnitude of uncertainty (in terms of possible change of significativity of results).

For epidemiological human studies, the relevance of the studies are assessed using global methodology to identify sources of major/minor bias that can potentially affect results and conclusion.

### 6.1.3 Criteria of agreement between studies related to question 1

The assessment of lines of evidence by experts should be based on the available empirical support and expert judgement.

The empirical support consists of some criteria:

- « Dose-response » assessment ECHA/EFSA/JRC, 2018.

- « Consistency among studies » ECHA/EFSA/JRC, 2018.

- « Consistency among species » ECHA/EFSA/JRC, 2018.

- « Repeatability of lines of evidence » ECHA/EFSA/JRC, 2018.

More precisely those different items are investigated:

- Total number of independent studies for this substance,

- Different biological models (mammals) for which the same effect was observed,

- Different type of studies with same effect (epidemiology, *in vivo*),

- Different taxa (ex. fish, mammals) for which the same effect was observed,

- Consensus agreement between studies for same adverse effect (same or different species),

- Minority concordance (or disagreement with low score studies),

- Divergence between high score studies with equivalent cotation,

- Meta-analysis done,

- Complementarity of studies inside each question,

- Generalisability species involved in the experimental: species involved in the experiments,

- Generalisability to human population (sex, physiology),

- Generalisability to other species than those involved in the experiment (taxa, sex, physiology),

- Generalisability to ecosystem: excretion in environment, inter-generational transmission,


The opinion regarding all these elements can be expert-specific and can be argued by experts for elicitation.


## 6.2 Question 2: What is the plausibility that the studied substance acts through an endocrine mode of action (MoA)

This section is relative to the description to the type of information needed. All the criteria needed for description and assessment are ranked and chosen collegially within the expert group.

Two types of studies are considered: *in vivo* or *in vitro* mechanistic studies.

### 6.2.1 Criteria for description of the information given by a relevant study related to question 2

For question 2, the description of lines of evidence ( see tables 2 and 3 from ECHA/EFSA/JRC, 2018 ; OECD 2016, 2017 ; LaMerril *et al*., 2019 ; Meek *et al*., 2014a, 2014b) are based on specific items, but are close to those given for question 1.

#### 6.2.1.1 For *in vivo* mechanistic criteria are:

**Study reference/type**
   o   Study reference,

- o Study type,
- o Included in a meta-analysis,
- o Included in a review,
- o Tested system (non-intact animals, organs, tissues, ATCC references for cell lines),
- o Tested methods,
- o Tested substance and degree of purity,
- o Used vehicle,

**Exposure/design**

- o Species, sex…
- o Duration of exposure/frequence & unit,
- o Age of animals at exposure
- o Age of animals at analysis
- o Number of doses/concentrations tested & experimental range dose/concentration values (min-max)/route of exposure,
- o Numbers of replicates /doses or concentrations,
- o Group control (not exposed),
- o Positive control (effect with another substance),
- o Inhibitor substance and/or KO models for specificity of the effects = demonstration of the couple adverse effect/endocrine MoA,
- o Reference protocol published (elsewhere) or OECD reference,
- o Statistical analysis method,

**Results and limitations**

- o Type of critical effect (with figure or table reference),
- o Essentiality of the effect (reversibility),
- o Sense of the effect: negative/positive,
- o Pathway or mode of action identified,
- o Parameter estimate and confidence interval & value,
- o Dose-response relationship,

### 6.2.1.2  For in vitro mechanistic, criteria are:

**Study reference/type**

- o Study reference,
- o Study type,
- o Included in a meta-analysis,
- o Included in a review,
- o Tested system (organs, tissues, ref ATCC for cell lines),
- o Tested methods,
- o Tested substance and degree of purity,
- o Used vehicle,

**Exposure/design**

- o Number of doses tested & experimental range dose values (min-max),
- o Number of replicates /doses or concentrations,
- o Group control (not exposed),
- o Positive control (effect with another substance),
- o Inhibitor substance for specificity = demonstration of the couple adverse effect/endocrine MoA,
- o Reference protocol published (elsewhere) or OECD reference,
- o Statistical analysis method,

**Results and limitations**

- o Type of endpoint (with figure or table reference),
- o Essentiality of the effect (reversibility),

 o   Sense of the effect: negative/positive,
 o   Pathway or mode of action identified,
 o   Parameter estimate and confidence interval & value,
 o   Dose-response relationship,

### 6.2.2 Criteria for assessing the quality of a relevant study related to question 2

The criteria for assessing the quality of a relevant study are the same as for question 1 (see 6.1.2).

### 6.2.3 Criteria of agreement between studies related to question 2

The criteria for agreement between studies are the same as for question 1 (see 6.1.3).

## 6.3 Question 3: What is the plausibility that the endocrine MOA induces the adverse effect identified?

"*A Mode of Action analysis (MoA) can be described as a series of biological events, key events that result in the specific adverse effect*" (ECHA/EFSA/JRC, 2018).

The link between the potential endocrine related adverse effects and endocrine activity are mainly based on the criteria of biological plausibility (ECHA/EFSA/JRC, 2018).

As stipulated in the European guidance for the identification of endocrine disruptor used in PP and BP, to conclude on the biological plausibility of the link, it may not be necessary to have demonstrated for the substance under assessment the whole sequence of events leading to the adverse effect. This reflexion is based on the literature and independently of the studied substance, the existing knowledge from endocrinology and/or toxicology may be sufficient to assess the link and to come to a conclusion on the biological plausibility between adverse effects and the endocrine activity (ECHA/EFSA/JRC, 2018. This step is based on the literature, in particular, from the same chemical family and can use existing AOPs when available. In this last situation, for the same substance, it is then possible to obtain different AOPs, supported by different empirical lines of evidence, and ranking can be difficult between different EATS pathways. Independent elicitations could be then necessary for the QUESTION 3.

### 6.3.1 Description of data for establishing the causal link

The pathways linking effects studied in QUESTION 1 and QUESTION 2, or relationship between adverse effect and the MoA already selected in previous steps have to be examined (Figure 2).

Detailed reviews or synthetic bibliographic references can be used to inform the plausibility of the biological link. This reference literature will be mentioned before QUESTION 3 elicitation from endocrinology or toxicology domain. As mentioned previously, this literature is independent of the studied substance. The reference literature should be accessible to all members of the group, and, will be evaluated collectively.

If an AOP is available, set by OECD AOP wiki, or published or elaborate from analysis of existing literature and expert knowledge, the different key events (KE), and the relationship between them (KER) should be detailed. At a first step schemes from AOP should be provided.

Each KE of the pathway has to be explained in synthetic Excel table (see table 1). For supporting the provided information, an example of table is provided in (ECHA/EFSA/JRC, 2018) for describing empirical support of KERs. For each step of the scheme, MIE (molecular initiating event), KE (key event), KER, and AE (adverse effect), a brief description of event (as «inhibition of androgen synthesis») is provided, and supporting evidence. *KEs are those events that are considered essential to*

*the induction of the (eco)toxicological response as outlined in the postulated MoA. They are empirically observable and measurable steps and can be placed at different levels of biological organisation (at cell, tissue, organ, and individual or population level)* (ECHA/EFSA/JRC, 2018).

| |
|---|
| Source identified |
| causal pathway diagram available (based on expert proposals or existing AOP) |
| Molecular initiating event (MIE) |
| Adverse Effect (AE) |
| description of key events (KEs) |
| Key events shown with studied substance (Question 2) (for question 4) |
| Adverse outcome shown with studied substance (Question 1) (for question 4) |
| Define the domain of application (Human, animals) |
| Duration of AOP from MIE to AE (if precised) |

**Table 1: Table summarizing items related to AOP description**

### 6.3.2  Criteria for assessing the quality/plausibility of a relevant causal link

This question is a general one, contrarily to the previous ones (question 1 or 2) which are related to the studied substance.

The objective of QUESTION 3 is to evaluate the plausibility of a causal link between the disturbances of the endocrine system observed in QUESTION 2 and the adverse effect observed in QUESTION 1.

The plausibility should be evaluated in relation with criteria defined in the report (ECHA/EFSA 2018). This question concerns available knowledge not shown with the studied substance.

- Analogy: « *Is the same sequence of KEs observed with other substances for which the same MoA has been established*? *Would the MoA be anticipated based on broader chemical specific knowledge?*». It is particularly important if the data set for the substance of interest is limited. The different criteria are detailed in (ECHA/EFSA/JRC, 2018) and are concerning:

- Empirical support.

- Dose-response/incidence and temporal concordance.

- Essentiality: « *Is the sequence of events reversible if dosing is stopped or a KE prevented?* »(ECHA/EFSA/JRC, 2018). "*Stop/recovery studies (if available), or experiments conducted in knock-out animal models for a postulated KE, showing absence or reduction of subsequent KEs or the adverse effect when a KE is blocked or diminished are an important test for demonstration of essentiality*" (ECHA/EFSA/JRC, 2018).

- Consistency: « *Is there consistency across studies for the relevant parameters*? And *Is the pattern of effects across studies/species/strains/systems consistent with the hypothesised MoA*?».

- Specificity: «*Could the adverse effect be the result of another MoA (i.e. non-endocrine-mediated)?*» Somehow, this criterion could be documented from expert knowledge, or by quoted citation. If the adverse effect could by totally attributed to another non endocrine pathway, there's a lack of specificity.

- The relevance for the target population.

## 6.4  Question 4: Knowing the plausibility of QUESTION 1, QUESTION 2 and QUESTION 3, what is the plausibility that the studied substance has the potentiality to cause the adverse effect through the endocrine MOA (i.e. be considered as an endocrine disruptor for environment (ENV) or human health (HH))?

The evidence should be based on answers to the QUESTION 1 and QUESTION 2 and QUESTION 3 regarding the adverse effect, the mode of action investigated for the studied substance and the biological link (Figure 2).

### 6.4.1  Data and information to consider

The causal pathway is now analyzed with all available data from question 1, 2 and 3. The objective of each sub-question was to separate the analysis of information needed to answer the final question. Each of the three previous questions should be evaluated as independent as most possible from each other. The data set considered is different for each question 1, 2 and 3.

If an AOP is available, events or KER shown with studied substance, as defined in question 1 and 2 can be highlighted.

If no data is available for Question 1 or Question 2 for the substance under study, information related to those question can take into consideration the data established from another substance, considered as relevant or general endocrine knowledge.

## 6.4.2  Criteria for assessing the question 4

The different questions are shown in figure 2, from the overall classical pathway of an endocrine disruptor. We can see that each question is relative to complementary aspect. The assessment should consider the synthesis of the response in question 1, 2 and 3, their strength and weakness, and their uncertainty.

For each substance, human health and the environment must be considered independently (i.e. ask the four questions on the human health component and four questions on the environmental component or not) (see before).

As for other questions, strength and weakness for the overall synthesis have to be assessed in this last elicitation process. As support the criteria of question 6.3.2 could be applied specifically to the substance and taking the information as assessed in question, 1, 2, and 3:

On the basis of the answer to this question, the final categorization will be made. The previous ones will be used to clarify the expert judgment.

# 7 Integrating evidence by formal elicitation process

## 7.1 Context and methodological choices

### 7.1.1 Context of method and definitions

Different methods were used for building weight of evidence (WOE) (Linkov, 2009). Bayesian approach are complex to build, but are also the best quantitative standard for WOE. However integrating by Bayesian approach or scoring criterias (e.g quality criteria, agreement criteria) inside a category and between heterogeneous categories of evidence is also rapidly complex, time and resource consuming and remains subjective. At this step, we assume that elicitation is a simpler process for establishing WOE in relationship with definition of an ED (EFSA/ECHA/JRC 2018). WOE should also report uncertainty analysis and its potential impact on results (EFSA, 2017a). Formal elicitation, with quantitative expert judgement, as detailed below allow a minimum consideration of the uncertainty (Anses, 2016b, 2016c).

***Elicitation,*** *as "drawing out of knowledge from one or more experts"* (EFSA, 2014), corresponds to the estimation of information or judgment based on the experience or specific knowledge of experts. Elicitation can be implemented when the data allowing a direct estimate are not available, not directly transposable to the desired context or when the bibliographic elements are contradictory (Morgan, 2014 ; EFSA, 2014). Uncertainty reflects here the lack of knowledge, while variability reflects variable characteristics in a given population (Vose *et al*., 2000 ; Anses, 2016b, 2016c). The relationship with elicitation is straightforward, with another definition in bayesian context (Gosling, 2019): "*Expert elicitation is the process of deriving quantitative measures of experts' uncertainty*".

The statements provided by EFSA (2017a) is expliciting recommendations:

« *Where expert judgement is required, use an appropriate procedure for this. Expert judgement should always be careful, reasoned, evidence-based and transparently documented. This may be achieved through formal expert knowledge elicitation" (EFSA, 2014), or semiformal expert knowledge elicitation or expert discussion (EFSA, 2016a, 2016c)"*(EFSA, 2017a) .

"*The cited documents focus on eliciting distributions for quantitative parameters, but the underlying principles can be applied also to eliciting probabilities for alternative answers » (…) « Assessors should choose a procedure that is appropriate for the needs, timeframe and context of their assessment. For example, if the judgement is likely to be critical for decision-making, that would be a reason for more formal methodology, if time and resources allow* » (EFSA, 2017a)

**The objective of formal elicitation** is to capture expert knowledge on uncertain quantities in the form of a probability distribution. It is a quantitative method, as a part of bayesian approach (Martin *et al*., 2018; ANSES, 2016b), but is recognized as a quantitative approach to **describe a parameter of interest and its uncertainty** (ANSES, 2017b, ANSES, 2016b).

The different methods of elicitation have in common the definition of **a subjective probability**, defining the level of confidence or uncertainty of an expert on the estimated value, or in order to estimate present or future values of uncertain quantities (Morgan, 2014). Indeed, it can be assumed that the expert does not know the true value, but that he can estimate, thanks to his knowledge, an interval in which the sought value is found, the width of the interval representing the uncertainty on the value sought.

The question expressed as "what is the plausibility that" (…) is assumed to be equivalent "what is the subjective probability that" and is the way the question is expressed in the rest of this report.

### 7.1.2 Quality of formalized methods and conditions for achievement

Only formalized methods allow to correctly and quantitatively describe the uncertainty around a desired value (EFSA, 2014), and have been developed, aiming to guarantee:

• The relevance of the elicitation,

Special care is taken to define the question and its context. In particular, it is necessary to also define concepts, which will be used to answer the question.

• The unbiased nature of the elicitation,

The choice of experts is essential.  The training for different types of bias is also provided to experts. During the organization of the elicitation, we also make sure that the relative importance of each participant remains equal. Finally, depending on the formal methods, individual responses can be weighted or reviewed collegially. In the Sheffield method, individual's responses are reviewed collegially.

• Transparency of the elicitation,

Elicitation process transparency is often criticized and is a critical point (EFSA, 2017a). "*An important issue in WoE is the influence of expert judgements that needs to be recognised and made explicit as far as possible. It should be documented what type of information is assessed, why it is assessed, and which quality criteria are used. The interpretative methods as well as the weighting procedure should be transparent*" (Vermeire *et al*., 2013).

To guarantee this item, all the elements used for elicitation, and the rationale used for elicitation by experts, at individual and collective phases are documented and recorded. The results of individual elicitations are however always anonymous.

- The reliable and reproducible nature of the elicitation,

« *Reproducibility is defined such that consistent results should be expected if the same method were to be repeated using the same input data (but note that results are unlikely to be identical, dependent on the degree to which expert opinion is involved)* » (EFSA, 2017a).

The challenge here is to avoid a non-reproducible and non consistent (or not reliable) method. This why this document is explaining the different aspects of the method. At the end, we test the method with two examples and give comparison with theoretical situation of level of knowledge (see above).

### 7.1.3   Choice of a particular formalized method: Sheffield method

Due to the critical assessment of categorizing endocrine-disruptor substances, we choose to follow formal elicitation guidelines. Three formalized methods are described (EFSA, 2014):

•       the Delphi method.

•       the Sheffield method.

•       The Cooke method.

The three methods have in common a phase of preparation, selection of experts, individual and then collective elicitation.

The number of experts involved and the modalities of interaction during collective elicitation differ between the three methods. Compared to the other two methods, Delphi and Cooke, the Sheffield method recommends that the experts can freely exchange their arguments during the collective elicitation, to lead to a consensual distribution, which reflects the opinion of the group and not that of opinions individual, during a single collective meeting (EFSA, 2014). It is a behavioral aggregation of opinions, unlike the other two approaches, close to expert group activities. The Sheffield method was chosen because it is ensuring that all experts have the same deep understanding of questions and rationales of answers by direct exchanges, transparencies of rationale, and potential consensus of a group for a specific rationale. The direct exchanges involves a limited number of participants, but we try to adapt the methodology to our context with a number of experts between 12 and 20.

The Sheffield method of elicitation is described in different documents such EFSA report (2014), the O'Hagan' book (2006), as well as several published studies (Pietrocalli, 2008 ; Butler *et al*., 2015) and online material http://www.tonyohagan.co.uk/shelf/ecourse.html, sponsored by the U.S. Office of Naval Research).

The elicitation process method is already used for chemical weight-of-evidence risk assessment (Buist *et al*, 2013 ; Gosling., 2013 ; Gosling, 2019) as an important tool for integrating evidence, associated with bayesian framework.

The principle of the Sheffield method is based on five structured stages:

1. Definition of the question (already seen in the first parts of the report)

2. Selection of experts: based on complementary skills, representative of the different aspects of the question.

3. Expert training: detailed in appendix 3

4. Individual elicitation stage (see below)

5. Collective elicitation stage (see below)

## 7.2　Selection of expert choices and human resources for elicitation

ED Anses group is composed of about 20 experts, with an expertise profile on endocrinology or neuroendocrinology (human and animals), male/female reproductive function (human and animals), toxicology (*in vitro*, *in vivo*, human), epidemiology, ecotoxicology, metabolic function (human and animals), thyroid function (human and animals), toxicokinetics. By default, we consider that all experts should contribute to the elicitation process, as the final decision relies on the expression of the working group. However, in some situations, all experts cannot contribute to the process. In this case, an expertise panel can be considered for elicitation but only if the different aspects of questions and the available data are covered.

The process of elicitation, whenever tables are fulfilled requests at least two coordinators dedicated to report and understand arguments, and one elicitator educated in Expert Knowledge Elicitation (EKE). Close elicitation process method was already used in ANSES (ANSES, 2017, 2019b).

## 7.3　Quantitative aspects

### 7.3.1　Subjective probability and representation of probability distributions

Experience in EKE shows that training and communication is very important to guarantee that the expression of results is well understood by all experts.

To represent a probability distribution, there are two possibilities: the probability density function and the cumulative distribution function. The interpretation of the axes of a probability density function is as follows: the abscissa axis corresponds to the elicited value, the ordinate axis to the frequencies corrected by a normalization constant. A cumulative distribution function describes the probability or quantiles (y-axis) that the value sought is less than or equal to a certain value (x-axis).

Uncertainty about a probability is classically described by a distribution of values according to a beta distribution (Vose, 2000).

Different examples of opinion to the uncertainty of an expert or a group of experts can be given in figure 3.

- For example, for the Figure 3 at the top left, the probability density function is showing an equal probability of values between 0 and 1. Describing the same situation, the Figure 4 at the top left the cumulative distribution function, show the probability increases regularly with the value on the x-axis, indicating that all the values between 0 and 1 are equiprobable. This situation corresponds to the absence of information on the value sought: this is generally the level of information before elicitation.

- The level of information (or its corollary of uncertainty) expected after elicitation could be, for example, what is shown at the lower left quadrant. This distribution of values illustrates the level of uncertainty around an unknown value, which would be placed between 0.2 and 0.8.

- The graphic at the top left from the two figures 4 and 5, show the same probability for two extreme values of subjective probability: it is the way to figure out discrepancy opinion in the group.

- The graphic at the bottom right is showing an extreme position, where the level of uncertainty is very low. It can be problematic if it can be interpreted as an overconfidence situation in comparison with level of information provided.

A specific application was created on RShiny https://shiny-public.anses.fr/elicittools/. in order to view directly the results, during collective elicitation meetings, by the graphical representation of the distribution of values obtained, the uncertainty on the value determined by the group for each question. It enabled immediate interaction between the experts on the elicited values and the results of the adjustment.
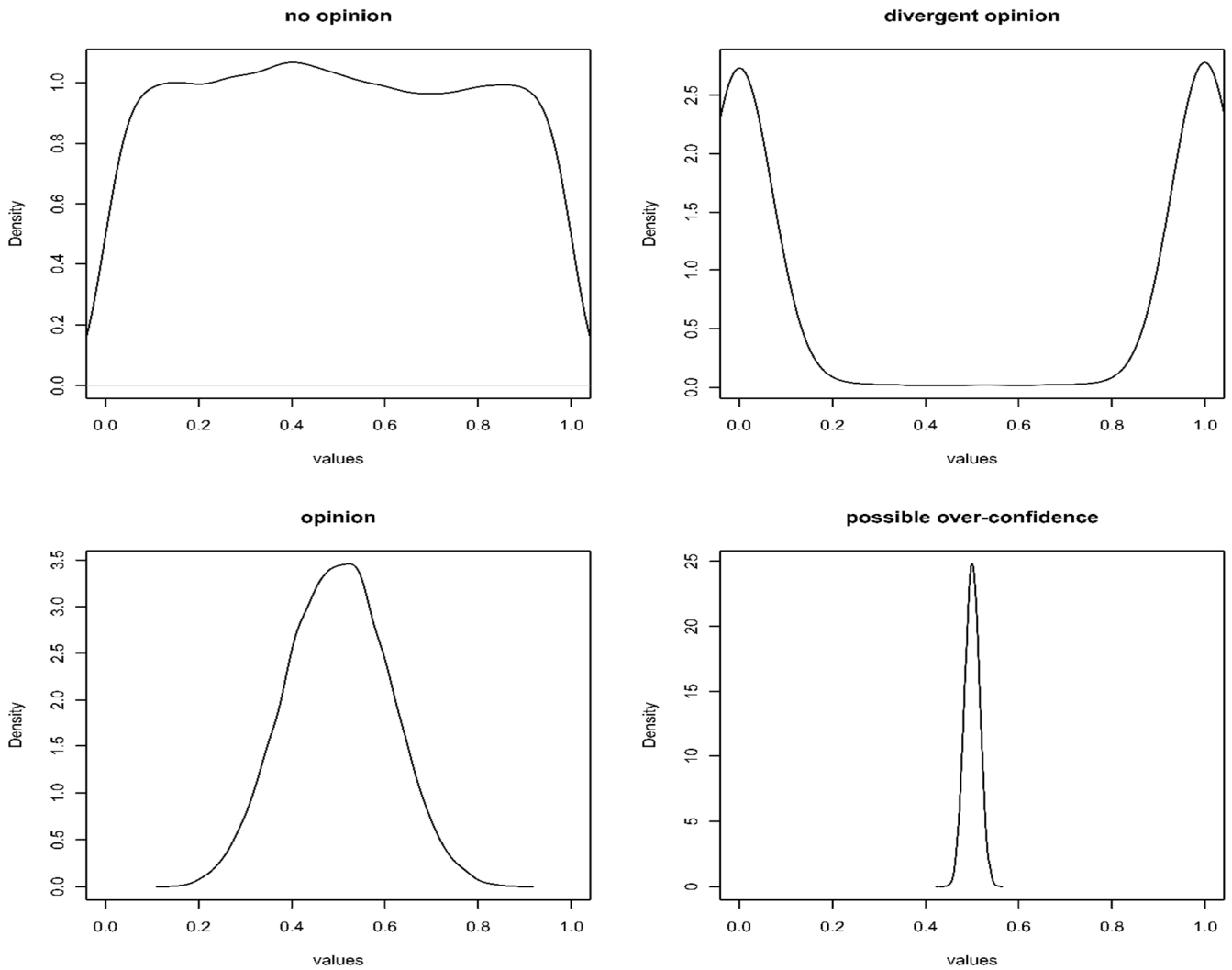


**Figure 3: level of information and density plot**
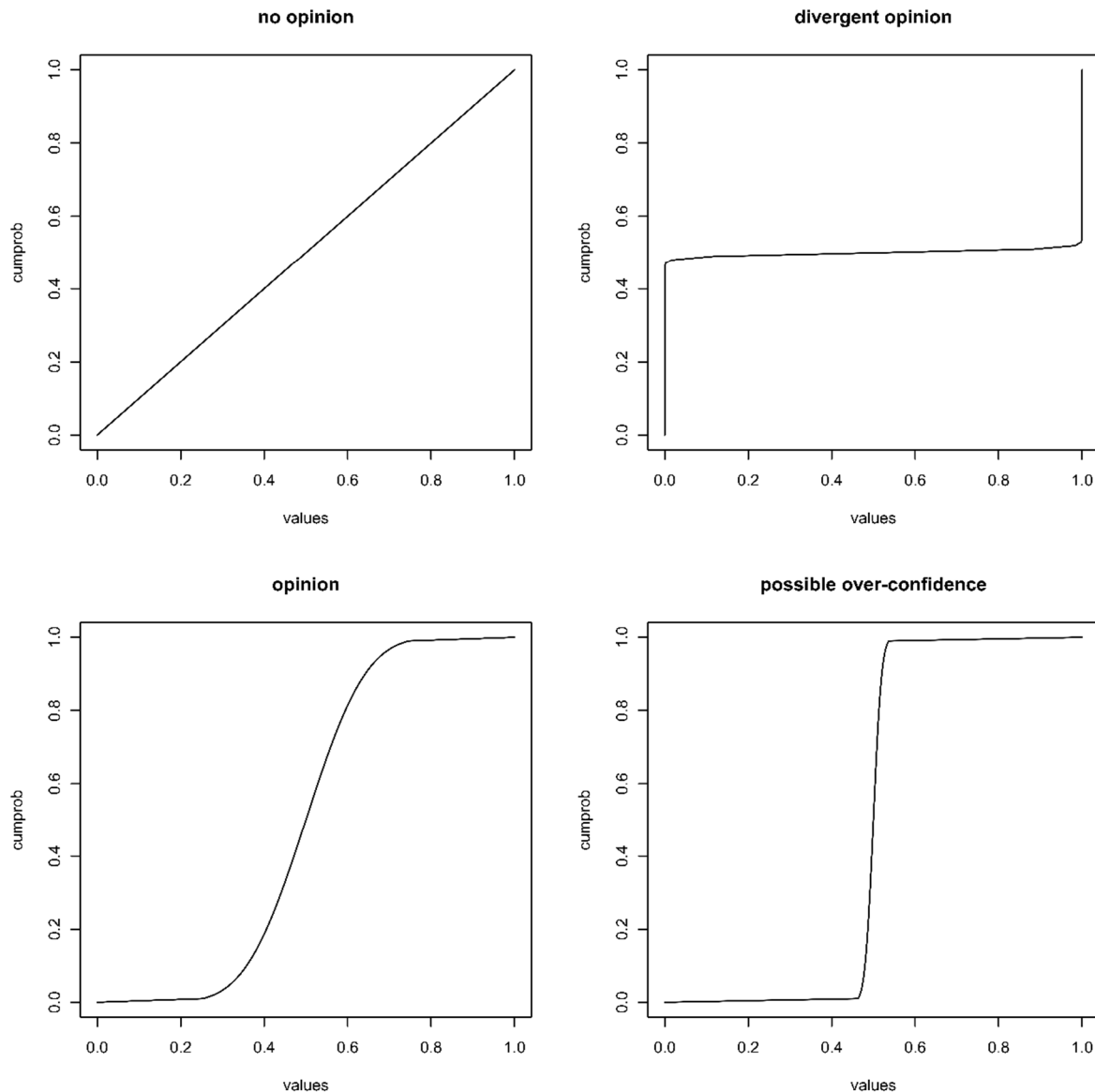
**Figure 4: examples of level of information and possible cumulative density plot**

### 7.3.2  Choice of summaries of a probability distribution

In order to simplify and to promote the reproducibility, it was chosen that:

•       The elicited values being a probability, the minimum and maximum limits are bounded between 0 and 1. The high and low intervals were not requested given the limits already set between 0 and 1 to allow easier comparisons between the substances. The concept of extreme values ("very unlikely" - "not very plausible") is also difficult to define and therefore to estimate by elicitation.

•       The appropriate distribution to the judgements is set by default as the beta distribution (Figure 5: cumulative density plot of a beta distribution.). Uncertainty on a probability is classically described by a distribution according to a beta distribution (Vose, 2000), which has appropriate characteristics such as limits between 0 and 1. Knowing that we have to fit the beta distribution from only 3 elicited summaries values (Q25, Q50, Q75), we expect a high quality of fitting. Other distributions can be fitted if the experts are not satisfied with the quality of fitting of their quantitative opinion.

•       The choice of quantiles of the probability distribution.

The quantiles of a sample of numbers are remarkable values used to divide the set of these ordered data (i.e. sorted) into consecutive intervals containing the same number of data. Quartile, tercile and decile are quantiles of a distribution. A quantile is also the probability of being equal or above a specific value.

In the Sheffield method, there are three possibilities for elicitating an uncertainty distribution from different quantiles:

• The quartile method: the expert gives a high and low limit value, then the 25, 50 and 75% quantiles

• The tercile method: the expert gives a high and low limit value, then the quantiles 33, 50 and 66%

• The roulette method: the expert gives a high and low limit value, then for each decile (1 / 10th) of the interval obtained, the expert assigns tokens (generally 10) which will describe the probability distribution.

In the Sheffield method, a collective elicitation follows the individual elicitation. The quartile method is being more commonly used than the tercile method. Also for reasons of simplicity, the quartile summaries were provided for individual and collective elicitation.

From the values of these quartiles, a distribution is fitted (by the maximum likelihood method). The adjusted distribution obtained makes it possible to describe other characteristics of the uncertainty distribution, such as its credibility interval at 95%, 99% or the average. This information allows the experts to express their feedback and to validate or not their elicitation with regard to the distribution obtained.

The quartile can be interpret easily from a cumulative distribution function. In the example below the y axis is showing the quantile 25% (Q25) at the value 0.25, the quantile 50% or median at the value 0.4 (Q50), and the quantile 75% (Q75) at the value 0.55.
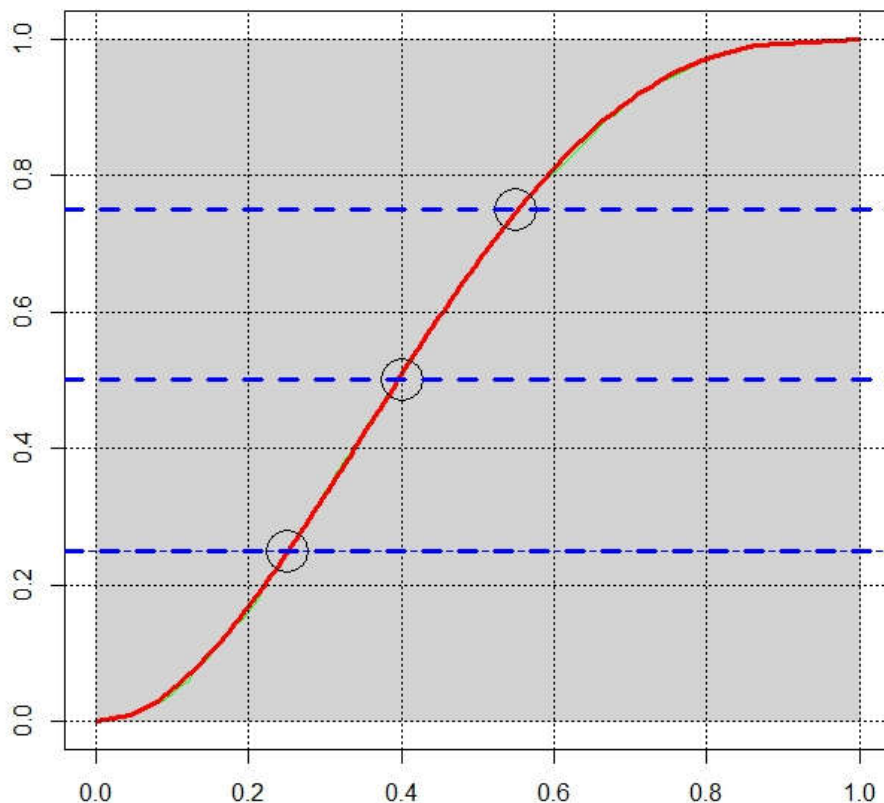


**Figure 5: cumulative density plot of a beta distribution.**

The interpretation of Q25 is that the subjective probability has a 25% chance of being lower than this 0.25 and a 75% chance of being higher. The interpretation of Q50 is that the subjective probability 50% chance of being above the 0.4 and 50% of being below the 0.4. The 75% quartile (Q75): the

subjective probability is 25% likely to be above this quartile and 75% to be below. However, different explanations can be given to explain quartiles (EFSA, 2014) such as:

The median value is describing no preference of being smaller or larger, or using the example of a bag with red and white balls in different proportions for explaining Q25 or Q75 (EFSA, 2014). The quartiles can also be interpreted with regard to the uncertainty described by the distribution:

• If the 25% quantile and 75 % quantile are closed to the median, the uncertainty is limited, the data are informative.

From the three elicited quartiles a corresponding beta distribution (red line) is fitted in figure 7: the 3 elicited points (empty circles) are very well predicted, aligned with the red line.

## 7.4  The individual elicitation

All the experts were trained in a special day meeting (see appendix 3 for the training program).

Before evaluating the substance, coordination collects expert analyzes and builds synthetic Excel tables, which are a compilation of the evidence and their assessment. Those Excel tables are checked once by experts involved in the analysis report. Before the individual elicitation, a reminder of objectives, definitions, context, data sharing is provided.

The individual elicitation for each question is done between two meetings for all questions QUESTION 1/QUESTION 2/QUESTION 3/QUESTION 4. Each expert has to do his expertise independently from others, with the time he needs, and can ask for help the coordination by phone call. For the first elicitation test, all experts were asked to participate to an individual phone call with the elicitator and coordinator, to be sure of understanding questions and the way to answer.

For supporting their elicitation, the experts have a permanent access to the report, to the synthetic Excel tables filled with the information described in previous chapters, to the documentation (publications by example), and to an online webtool to fit their opinion. Summary statistics with median, quartile 25 and quartile 50% of their fitted distribution, for each question as explained above, and their arguments have to be sent by email to the coordination before the collective meeting.

Results expressed in the final report are anonymous, documented (argumented by each expert) and made independently between experts. At this stage, high heterogeneity between responses is a prognosis of potential divergences of interpretation.

## 7.5  Collective elicitation

The principle of collective elicitation is an originality of the Sheffield method. The group must reach a consensus via a "psychological aggregation" (behavioral aggregation) by debate of ideas and controlled interaction. Collective elicitation takes place in different phases:

1.      Restitution of individual elicitations to the group:

The group takes note of the balance sheet of individual elicitations, and in particular the median of the group for each elicited value. Each expert gives his arguments justifying his values given during the individual elicitation, starting with the extremes from the median values of the individual elicitations. This can lead the group to share reasoning or documents. The rationale for/against is collected and synthetized during the meeting. Each expert can visualize if his arguments are new or in agreement/disagreement with other experts.

2.      Collective phase:

Each member is asked to adopt the position of an independent expert who looks at the group. The group is led to propose new values more or less distant from the median of the individual elicitations. The results of the adjustment are viewed interactively. Finally, people are once again asked about their agreement with this new distribution. 90% and 95% interval are given with the result of the fitting from the quartile. The qualitative equivalence into categories (known etc) is also given. A final agreement to the rationale behind the distribution has to be also obtained. If consensus is not

reached, an expert can ask a minority /separate opinion. In this case, this opinion will be noted in the final report.

To assess that dispersion is not so high, we can check that all medians proposed by each individual are falling into an interval given by Q25 and Q75 of the median of the group.

3.       The result of the collective elicitation is the only one that will be used for the decision analysis. The distribution obtained represents the group's uncertainty around the value sought.

A summary of the day in terms of values obtained in comparison with other substance or calibration probabilistic approach is presented in order to ensure the ultimate adhesion of the group to the elicited values. The rationale and final distribution is registered.

# 8 Interpretation of elicitation results for management strategy

## 8.1 Context

ANSES recommended retaining the EDC definition and identification criteria of Option 3 previously proposed in the Commission roadmap. It also proposed, as stated in the SNPE, to distinguish EDCs into three categories: "known" EDCs, "presumed" EDCs and "suspected" EDCs (Anses, 2016a).

As with the current CLP (classification and labelling of products) guidance for classification of carcinogenic, mutagenic and reprotoxic (CMR) substances applicable in Europe, a graduated approach would make it possible to more effectively take the uncertainties into account and facilitate the experts' judgment. In addition, this categorization would allow tailored regulatory implementation.

A categorization of EDCs in fifth categories such as known, presumed, suspected, not categorized, or not EDC is therefore proposed, in order to take into account all possible outcomes.

Currently, there is no consensus about an adequate methodology to categorize an EDC based on existing data (in vitro, in vivo and human) and the associated weight of evidence.

To follow this categorization and to describe the degree of uncertainty around categories, it seemed a relevant choice to define these ordinal scales in terms of the range or plausibility of the outcomes (Morgan et al., 2014). Other Decision trees, Integrated Testing Strategies (ITS), have been developed and used for regulatory purposes (Jaworska *et al*., 2010 ; Buist *et al*., 2013, EFSA, 2018).

We try here to take into account the subjective probability and its uncertainty in the categorization.

## 8.2 Constraints and rules for establishing decision tree

•       We try to establish a relationship between quantitative results (quantiles of distribution Q5 (5%), Q50 (50% or median) and Q95 (95%) and 5 ordinal qualitative categories (Known, presumed, suspected, non-categorized and non-EDC).

•       Qualitative estimates category are given by three pivotal values (Q5, Q50 and Q95).

•       Integration of uncertainty in decision category is needed (at least three quantiles of distribution are needed).

•       Simplicity and parsimony principle is requested (Occam's razor rule).

•       No doubtful area.

•       A central criteria (median), lower or upper bound of elicitation (Q5 or Q95), describing the range of uncertainty is driving the decision analysis.

  •    Q5 and Q95 are obtained after fitting of elicited distribution and this results is shown and agreed by experts.

•       The median are directly defined by experts' elicitation in the idea to achieve objectivity and transparency.

•       Easy and transparent to communicate.

Grid establishing correspondence between quantitative and qualitative grids were also proposed in the past: Terms and abbreviations was already used to express probability in the uncertainty evaluation for hazard characterization (adapted from Mastrandrea *et al.,* 2010, likelihood scale) (Table 2)

**Tableau 2: Likelihood scale used to express probability in the uncertainty evaluation for hazard characterization (adapted from Mastrandrea et al., 2010).**

| Virtually certain (VC) | 99-100 % of probability |
|---|---|
| Very likely (VL) | 90-99 % of probability |
| Likely (L) | 66-90 % of probability |

| As likely as not (ALAN) | 33-66 % of probability |
|---|---|
| Unlikely (U) | 10-33 % of probability |
| Very unlikely (VU) | 1-10 % of probability |
| Exceptionally unlikely (EU) | 0-1 % of probability |

However this table does not take the uncertainty inherent to the weight of evidence establishment into account.

- Establishing qualitative ordinal interpretation from quantitative data is always reaching a part of subjectivity (Morgan *et al*., 2014). However there's common sense as saying that the lowest uncertainty is, the highest is the level of plausibility (as subjective probability) as well as the level at ordinal scale (more explanation below). The suitability for the Anses expert group will be given with different examples done for that purpose via a dedicated shiny application (Rshinyapplication : https://shiny-public.anses.fr/elicittools/)

## 8.3 Description of decision tree for categorizing EDC from uncertain probability distribution

The quartile method demonstrated to be the most appropriate method for dealing the elicitation of questions. The quartile method allowed taking into account the uncertainty in the decision process (confidence level gives for the expert's judgment about question 1, question 2, question 3 and question 4). From these quartiles, the distribution is fitted (by default, Beta distribution) in order to estimate the quantiles 5 (Q5), 50 (Q50) and 95% (Q95). This method seems adequate in the context of collective expertise due to its simplicity, rapidity and unequivocal results.

Pivotals values based on the Q5, Q50 and Q95 of the distribution are used to quantify the results (figure 6).
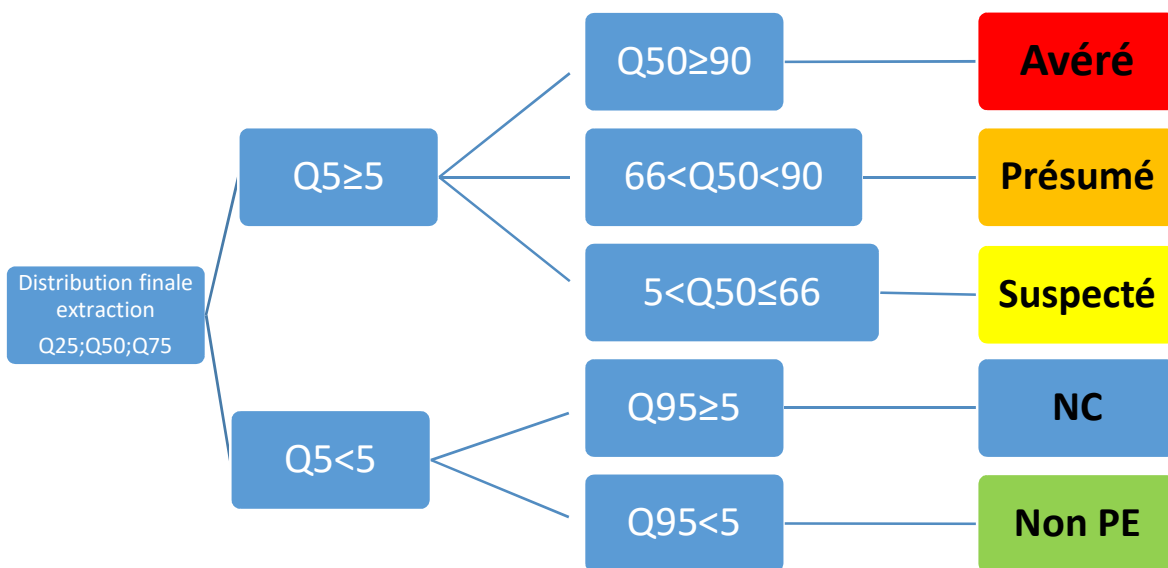


**Figure 6**: **decision analysis tree**

The elicitation process is establishing Q25, Q50 and Q75 quartiles. Those quartiles are fitted with a beta distribution, giving 5 and 95 percentile (see the dedicated shiny application for examples).

**Interpretation of categories known, presumed and suspected EDC:**

For the 5 percentile of uncertainty distribution, the subjective probability of being an EDC is above 5% (the lowest 5 percentile (Q5) is above 5%).

- **Category "Known"**, the median (Q50) of the subjective probability of being an EDC, is above 90 % (Q≥90).
- **Category "Presumed"**, the median of the subjective probability of being an EDC, is between 66% and 90 % (66<Q50<90).
- **Category "Suspected"**, the median of subjective probability of being an EDC, is between 5% and 66 %.This category is covering a large range of possible median and is requesting more information/data.(5<Q50≤66)

**Interpretation of categories not categorized and not EDC:**

The 5 percentile of the distribution is below 5 % of subjective probability of being an EDC (including zero).

- **Category not categorized**, the subjective probability of being an EDC, taking into account 95% (Q95>=5) of uncertainty is above 5% but the 5 percentile is below 5%. This category is essentially non informative. This category requests also more information and data.
- **Category not EDC**, the subjective probability of being an EDC, taking into account 95% (Q95<5) of uncertainty is below 5%.

# 9   Conclusions and recommandations

The methodology described in this report is dedicated to the categorization of substances, which are prioritized as compounds of interest due to their ED properties.

**Training for elicitation:**

Before the implementation of the elicitation process, the experts have to be trained at the beginning of the process, and practice on a complete elicitation to familiarize with the process and the judgments required, and to identify and resolve any initial misunderstandings.

The expert training phase aims to familiarize experts with the principle of elicitation, the probability distributions reflecting the uncertainty sought, the notion of subjective probability (chapter 7 and appendix 3 for details). Practical exercises put the experts in situation, in order to prepare the individual elicitation.

The elicitation training staff could be composed of an experienced /trained elicitator, at least two scientific coordinator (facilitator/reporting). The duration of expert training lasts around 3-5 hours.

**Precision about steps 1 and 2: gather information on the studied substance:**

The implementation of the strategy steps prior to elicitation corresponds to all steps required from an assessor to perform a substance assessment (detailed bibliographic review, selection of relevant studies, description and analysis of adverse effect (AE) and MoA, analysis of the link between the AE and MoA). The report and conclusions have to be discussed between the experts of the working group and validated in expert's committee meeting. Then, depending of the data available at least one couple(s) of adverse effect (AE)/MoA has to be identified by the working group before the elicitation process following a collective debate.

- Members of the experts working groups implicated in the elicitation process: ED Anses expert group is composed of 20 experts on endocrinology or neuroendocrinology (human and animals), male/female reproductive function (human and animals), toxicology (*in vitro*, *in vivo*, human), epidemiology, ecotoxicology, metabolic function (human and animals), thyroid function (human and animals), toxicokinetics. A minimal expertise panel involved in elicitation should be composed of members with expertise covering the data/questions/substance.

- Scientific coordinator(s): two assessors.

- Duration of steps 1 and 2: The preparation of the report is the most consuming time process. It is dependent on the studied substance and available data.

**Precision about step 3 and 4: table to assemble, integrate and assess the lines of evidence.**

Before the elicitation meeting, an evidence dossier has to be prepared. Coordinators of the dossier and scientific experts are implicated in this step. The most relevant evidence about the couple(s) AE/MoA has to be reported into a single document (synthethic Excel tables) in a format that is readily accessible during the expertise. The opportunity to conduct an elicitation process is discussed collegially on the basis of this report and the level of information obtained

- Members of the experts working groups: two reviewers depending on the couple(s) AE/MoA.

- Scientific coordinator(s): The assessor of the studied substance is in charge of the completion of the synthetic excel table, which is used during elicitation process.

- Duration of the step 4: Depends of the numbers of couple AE/Moa identified and the numbers of publications (around 1 to 2 hour(s) by study to fulfill relevant items for an experienced reader). Each relevant information has to be described in the synthetic Excel tables. The tables are presented and checked by experts involved in the synthesis report and debated collectively before the individual elicitation. Files for individual elicitation and questions are then sent to experts just after the meeting.

**Precision about steps 5 to 10: Integration and elicitation process:**

It is characterized by two quantitative rounds of judgments from the experts to cover the range of opinion within the relevant community.

**Individual elicitation**

It occurs between two meetings, all individual experts have to prepare a writing opinion with the reasons for their judgments, provide quartile of their opinion for the 4 questions, including references (during this period and until the meeting, experts have not to share their opinion with the other experts). The duration of work for an expert is varying from some hours to one days. They can ask for help, especially for their first elicitation, to the elicitator or coordinator by a dedicated phone call.

The synthesis of all opinions has to be prepared before the meeting by elicitator.

**Collective elicitation**

- Phase 1: at the meeting, in a first round table, experts are asked to give and explain the reasons for their judgments about the substance.

- Phase 2: Collective discussion step: One half day (around 2-3 hr, ideally the same day). At the meeting, in a second round, all experts discuss in view to share and understand the reasons for the different opinions (behavioral aggregation). Each expert is asked to adopt the position of an independent expert who looks and give opinion for the group. It is during this collegially discussion that the group agrees on ''consensus'' judgments.

- Members of the expert working groups: all experts (or a minimal panel covering…) who have participated to the individual elicitation.

- Members of the elicitation staff and coordinators of the substance dossier: the elicitation process requires two coordinators and one elicitator, which are familiarized with the methodology. Specific reporting is asked with argumentations for each collecting phase, which needs sometimes clarification.

- Duration of elicitation process: the collective elicitation could be performed in half day and previous discussion preparing directly individual elicitation lasts less than a half day. Considering that only one couple AE/MoA is elicited per day per studied substance. If more than one couple AE/MoA per studied substance needs to be elicited, this will require some additional time.

The synthesis of the elicitation, the feedback about the fitting and the categorization are asked to be adopted collegially at the end of the elicitation process. A specific report has to be written to provide all documentation associated with the elicitation (synthethic excel table, synthesis of individual and collective elicitation, arguments and values).

This proposed method is providing guidelines for future categorization of potential ED substances, with questions in agreement with EFSA definition, where a substance is considered as having ED properties if it meets all of the following three criteria:

*Criteria (1): "It shows an adverse effect in [an intact organism or its progeny]/[non-target organisms], which is a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences;"*

*Criteria (2): "It has an endocrine mode of action, i.e. it alters the function(s) of the endocrine system"*

*Criteria (3): "The adverse effect is a consequence of the endocrine mode of action"*

And the questions in agreement with this definition are:

Question1: What is the plausibility that the studied substance has the potentiality to cause the adverse effect?

Question 2: What is the plausibility that the studied substance acts through an endocrine mode of action (MoA)?

Question 3: What is the plausibility that the endocrine mode(s) of action induces the adverse effect(s) identified?

Question 4: Knowing the plausibility of QUESTION 1, QUESTION 2 and QUESTION 3, what is the plausibility that the studied substance has the potentiality to cause the adverse effect through the endocrine MOA?

In the context of this proposed method, the data and argumentation provided and stored could be useful to better understand what is critical in the expert opinion to the weight and integration of the lines of evidence. The synthetic Excel tables could be useful to establish standardized and checked data basis about a substance, and could also allow comparing and ranking between substances, and estimating if the ranking is appropriate.

As mentioned in chapter 5, not all substances can be necessarily submitted to the elicitation process, depending on the available data, time and human resources. In addition, the different steps of the proposed strategy are not frozen and could be adapted if necessary. Different advantages emerge from elicitation approach: the method is formal, transparent and traceable, in particular for documentation and argumentation for each question. It is also estimating quantitatively subjective probability and uncertainty associated with each questions which are more precise than qualitative estimates. Experts are better and deeper sharing, with a formal elicitation knowledge and argumentation, and criteria for decision are transparent. The disadvantage is the time needed for the overall process including training.

Future research program comparing the results between different methods of weighing evidence (MCDA, Bayesian methods, …) could be useful to estimate the robustness of the elicitation method.

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# APPENDIX

# Appendix 1: Request

COURRIER ARRIVE

1 8 OCT. 2019

DIRECTION GENERALE

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RÉPUBLIQUE FRANÇAISE

**Ministère de la Transition
écologique et solidaire**

Direction générale
de la prévention des risques

**Ministère des Solidarités
et de la Santé**

Direction générale
de la santé

Paris, le    0 8 OCT. 2019

Le Directeur général de la prévention des risques
Le Directeur général de la santé

A

Monsieur le Directeur général
Agence Nationale de Sécurité Sanitaire de
l'Alimentation, de l'Environnement et du Travail

**OBJET :** Mise en œuvre des actions 1, 2 et 3 de la deuxième stratégie nationale sur les perturbateurs endocriniens (SNPE2).

Dans la continuité de la première stratégie nationale sur les perturbateurs endocriniens, la SNPE2 comporte un volet dédié à l'expertise des substances chimiques au titre de l'évaluation du danger qu'elles pourraient présenter via une altération des fonctions du système endocrinien.

La SNPE1 a permis à la France, grâce notamment au travail de l'Anses dans le cadre du règlement REACH et au titre des règlements sur les pesticides, d'être identifiée comme faisant référence sur le sujet au niveau communautaire.

De nombreuses substances chimiques sont susceptibles de modifier le fonctionnement du système endocrinien, sans qu'il soit facile de conclure avec robustesse sur les effets délétères que cela entraîne. Plusieurs listes de perturbateurs endocriniens ont déjà été établies par des autorités européennes, des agences d'expertises d'autres pays ou des organisations non gouvernementales. Les critères qui permettent d'établir ces listes varient, si bien qu'il est difficile d'avoir une vision fiable, compréhensible par le grand public, sur les substances aux propriétés de perturbation endocrinienne et sur leur caractérisation en termes de danger, en vue de mettre en œuvre les actions adaptées pour réduire les expositions.

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Une attente forte des parties prenantes, exprimée lors des travaux d'élaboration de la SNPE2, est de disposer d'une telle liste pour informer, agir par prévention ou par précaution. Les ministres ont annoncé lors des rencontres nationales santé environnement de janvier dernier l'élaboration de cette liste en tant qu'action phare de la SNPE2.

À partir d'un recensement des substances aux propriétés de perturbation endocrinienne potentielles en fonction des éléments de connaissance disponibles, la construction d'une démarche de priorisation des travaux à mener pour leur caractérisation est un préalable indispensable. Elle permettra, d'une part, une instruction efficace et organisée des dossiers d'évaluation et de gestion réglementaire grâce à la mise à disposition d'outils de gestion aux autorités publiques et parties prenantes et, d'autre part, une amélioration de l'information et de la communication autour des perturbateurs endocriniens au niveau national.

### *En ce qui concerne l'action n° 3 de la SNPE2 relative aux listes*

À des fins de gestion et d'information des risques liés aux perturbateurs endocriniens, il est demandé à l'Anses d'établir deux listes de substances :

-   **LISTE 1 : une liste de substances d'intérêt issues d'un recensement de substances retenues en raison de leur activité endocrine, et des effets identifiés, et figurant dans des listes publiées aux niveaux européen et international. Ces substances seront hiérarchisées en fonction d'un score de priorisation**

Cette liste de substances d'intérêt en raison de leur activité endocrine établie par l'Anses concernera toutes les substances quels que soient leurs secteurs d'utilisation et les règlementations sectorielles concernées. Pour cela, l'Anses pourra utiliser les travaux existants (TEDXlist, liste ECHA, SIN list, travaux EPA...). Un descriptif des modes d'élaboration de ces listes sera réalisé de manière à identifier les forces et faiblesses de chaque source. Par ailleurs, pour chaque substance, son domaine d'utilisation (produits chimiques, phytosanitaires, biocides, cosmétiques…) sera renseigné sur la base des informations disponibles.

L'Anses proposera une méthode de priorisation prenant en compte des critères objectifs (vraisemblance ou pertinence du danger intrinsèque, utilisation, exposition de la population vulnérable…) qui seront ensuite appliqués à la liste ci-dessus dans l'objectif d'attribuer un score de priorité.

Cette liste sera rendue disponible pour janvier 2020 et fera ensuite l'objet d'une réactualisation annuelle. Elle servira notamment aux discussions avec les parties prenantes en vue d'établir le programme annuel d'évaluation des dangers de ces substances à mener par l'Anses (cf. actions n°s 1 et 2 de la SNPE2).

Cette liste pourra également être utilisée dans le cadre des travaux d'évaluation prévus par la SNPE 2 et impliquant les autres agences concernées, notamment l'ANSM dans le cadre de l'action 1 sur les produits cosmétiques et les produits de santé et l'AFB et l'INERIS dans le cadre de l'action 15 sur l'imprégnation des milieux par ces substances.

2

-    <u>**LISTE 2**</u> **: liste de substances PE classées en trois catégories « avérées, présumées, suspectées »**

À partir de cette première liste, une évaluation substance par substance de ces substances sera réalisée par l'Anses (avec l'ANSM selon le secteur d'usage des substances) à l'issue de laquelle un classement en trois catégories "avérée, présumée, suspectée", sera établi par l'Anses sur la base des propriétés de dangers.

Cette liste pourra prendre en compte les résultats d'évaluation d'autres agences européennes effectuées dans le cadre des règlements communautaires. Des collaborations pourront aussi être envisagées avec d'autres États membres et leurs agences d'évaluation. Il appartiendra à l'Anses de proposer les modalités de travail les plus efficientes en collaboration avec les agences européennes et nationales des autres États membres. Les ministères pourront être associés pour mobiliser les autorités nationales et européennes (agences et ministères).

Une réflexion sera également à mener quant à la possibilité de faire figurer dans cette liste issue des résultats de l'évaluation scientifique les conséquences de ce classement au niveau des règlements européens.

**Cette liste de substances classées en trois catégories "avérée, présumée, suspectée" sera publiée (première publication en 2020) puis complétée au fur et à mesure des nouvelles évaluations.**

**Les critères de catégorisation des substances dans ces trois catégories, définis par l'Anses seront partagés avec les partenaires européens et rendus publics.**

**Une réflexion sera également à mener quant aux modalités de communication autour de ces deux listes (type d'évènement, participant…).**

*En ce qui concerne les actions n°s 1 et 2 de la SNPE2 relatives à l'expertise réglementaire et à la collaboration inter-agence*

L'Anses poursuivra l'expertise des substances selon les modalités de la première SNPE qui sont reprises dans l'action 2 de la SNPE2 sur la base de la liste 1 des substances priorisées, selon le calendrier suivant :

-    En 2019 et 2020, l'Anses évaluera au moins 3 substances par an au titre du règlement REACH en vue de proposer l'identification de substances comme PE ; l'Anses expertisera également au moins 3 substances actives biocides et phytopharmaceutiques par an, en présentant une évaluation de danger via la perturbation endocrinienne, notamment en valorisant l'évaluation menée en tant qu'État membre rapporteur.

    ⇨    **6 substances par an au total en 2019 et 2020 seront évaluées**

-    À partir de 2021, l'Anses évaluera au moins 9 substances par an et en transmettra ses conclusions à l'ECHA et à l'EFSA selon les domaines d'utilisation de ces substances. S'agissant des 6 substances couvertes par le règlement REACH, les dossiers réglementaires (analyses de la meilleure option de gestion des risques, dossiers d'identification de substances fortement préoccupantes) seront à intégrer dans le programme de travail correspondant ; s'agissant des 3 substances pesticides, les travaux seront pris en compte dans les instructions définies en vue de l'approbation des substances actives biocides et phytopharmaceutiques concernées.

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➡ **9 substances par an au total à partir de 2021 seront évaluées**

Les travaux effectués dans le cadre de cette saisine feront l'objet d'une présentation dans le cadre du comité d'orientation thématique de l'Anses sur les perturbateurs endocriniens afin d'échanger avec les parties prenantes sur la méthodologie utilisée et l'avancée des travaux.
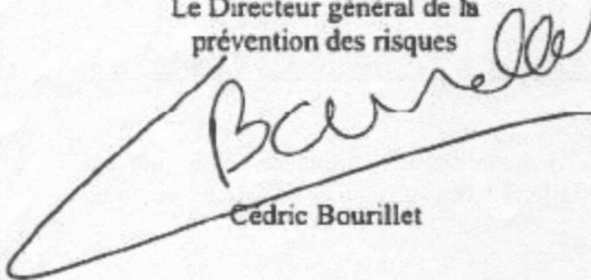
_**En ce qui concerne les actions relatives aux exigences des règlements européens**_

L'Anses sera mobilisée pour assister le Gouvernement afin de faire évoluer les réglementations européennes en vue de garantir un niveau de protection satisfaisant face aux perturbateurs endocriniens.

En particulier l'Anses formulera des propositions, dans le cadre du _fitness-check_ qui pourrait être conduit à l'automne 2019 par la Commission européenne en vue de l'amélioration des règlements en ce qui concerne les dispositions d'évaluation des dangers et des risques associés à la perturbation endocrinienne, et notamment les exigences de tests.
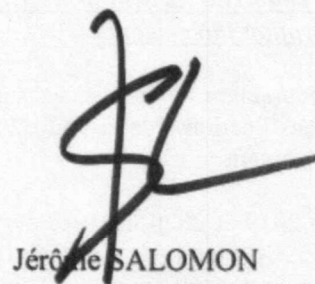
En vous remerciant pour votre mobilisation sur ce sujet prioritaire pour le Gouvernement, nous vous prions de bien vouloir nous transmettre une proposition de contrat d'expertise comprenant notamment les modalités de traitement et de restitution des travaux.

Le Directeur général de la prévention des risques

Cédric Bourillet

Le Directeur général de la santé

Jérôme SALOMON

Copie
M. Christophe Aubel, directeur général de l'AFB
M. Dominique Martin, directeur général de l'ANSM
M. Raymond Cointe, directeur général de l'INERIS

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# Appendix 2 : Minority opinion

If necessary.

# **Appendix 3**: elicitation training

The duration of expert training is lasting around 3-5 hours.

## 1. Training to probabilistic aspects of elicitation

The expert training phase aims to familiarize experts with the principle of elicitation, the probability distributions reflecting the uncertainty sought, the notion of subjective probability (as mentioned above). Practical exercises put the experts in situation, in order to prepare the individual elicitation. Two examples are provided:

- the first is based on an example of which the elicitor knows the answer (for example known or published value on the height of a monument). Each expert is led to give an interval of values and to develop some arguments (his approach). At the group level the actual value effectively falls between the minimum and the maximum of the group. This example shows that on a collective scale, elicitation is a success.
- The second example concerns a value similar (but different) to the desired elicitation in order to test the elicitation and its modes of representation which will be used next.

The training covers familiarization and / or reminders on the concepts of statistics, probability, uncertainty and visualization interpretation of these. Two estimation and visualization methods were used: the roulette method, aimed at familiarizing with the densities of probabilities, was used for the and the quartile method finally adopted, since it was directly linked to the decision criteria. At the meeting, each individual are asked to make their own elicitation with the help of elicitator using online tools such as MATCH tools http://optics.eee.nottingham.ac.uk/match/uncertainty.php for roulette method, or dedicated online application for quartile method using beta distribution fitting (https://shiny-public.anses.fr/elicittools/).

## 2. Training to avoid bias-rationale for organization

- 1/ Individual bias

Particular emphasis is placed during training on sources of bias in individual and collective elicitation. Indeed, mental shortcuts can cause bias (heuristics). Four types of bias relate to individual and collective elitation (O'Hagan, 2006; Tvserky and Kahneman, 1974; Pietrocatelli, 2008). These fairly general biases are detailed below:

- **The bias of affect**: people can be influenced in their judgment according to their emotional state:
  - Can go as far as non-response.
  - Anchoring and adjustment bias:
  - Influence of a first experience or a first opinion;
  - Influence of first quantified values;
  - Not enough adjustment to new information, to information from other groups;

- **Availability bias**:

The most recent and available facts can have an overestimated impact. It is a heuristic that eliminates older facts and information, often by not looking deep and systematically enough into the past.

- examples :
- particular events with dramatic results can mark opinion;
- significant studies are more published than studies with non-significant results, and may therefore have more impact;
- more recently published studies are more accessible .

- **Representation bias**:

This bias consists in estimating the probability of an event based on the probability of another event associated with it or similar. It is often the bias of over-generalizing (extrapolating) observations obtained on a particular population or particular circumstances.

The collective part of the elicitation will, by the multidisciplinarity of approaches, smooth these representation biases, and with the Sheffield method confront points of view before arriving at a consensus.

2/ collective bias.

Experts are warned during the training of these potential biases:

• Possible relative influence from one expert to other (charisma, celebrity);

• Anchoring around a central estimate, or a value (to be checked);

• Representation bias effect (sample);

• Difficulty judging extreme events;

• The group can "get carried away" and become too confident in its estimate;

• Group can be divided irreducibly. In this situation a minority statement can be taken into account.

All of these biases justify the directive nature of group management during collective elicitation because the elicitor and the coordination who must ensure the sharing of information and balanced debates

## 3. Training about specific question, context, and definitions

Those points are already described in the report. Shortly questions, data, grid of criteria and definitions were debated collectively.

# Appendix 4: Examples of interpretation

Some illustration of virtual probability by Beta distribution below will help the user to interpret the category in regard to the result.
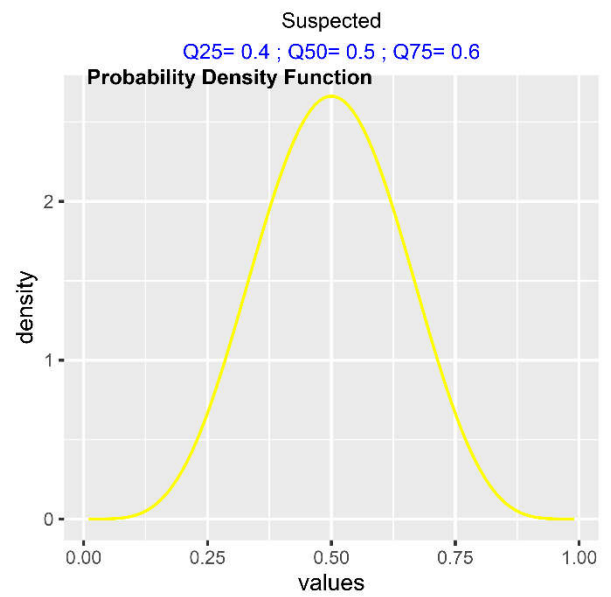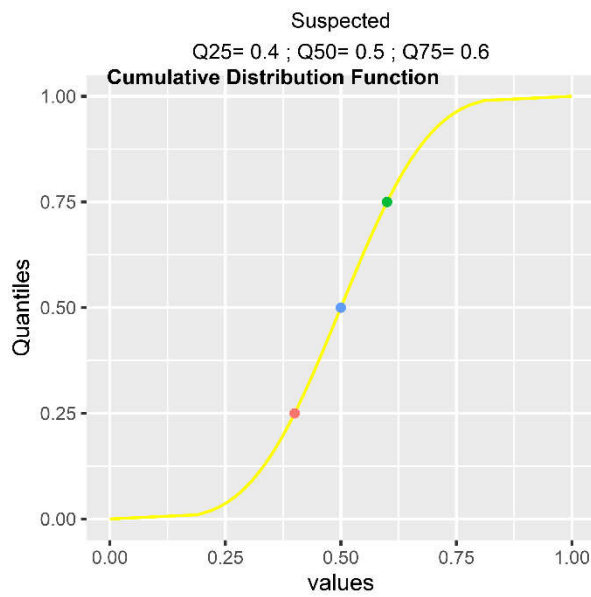
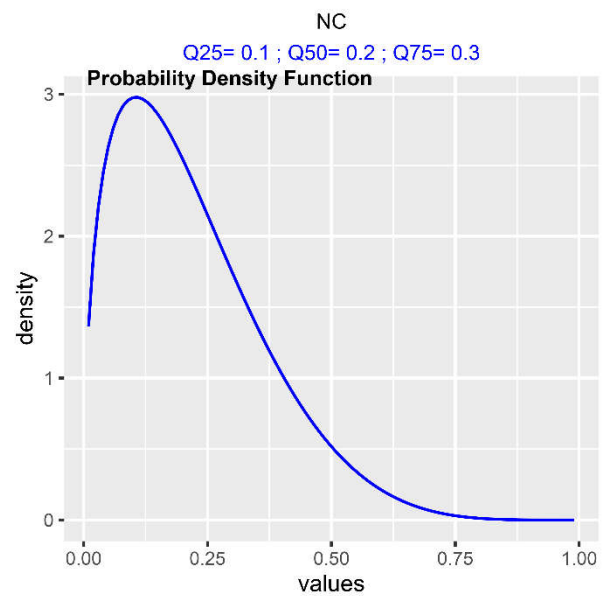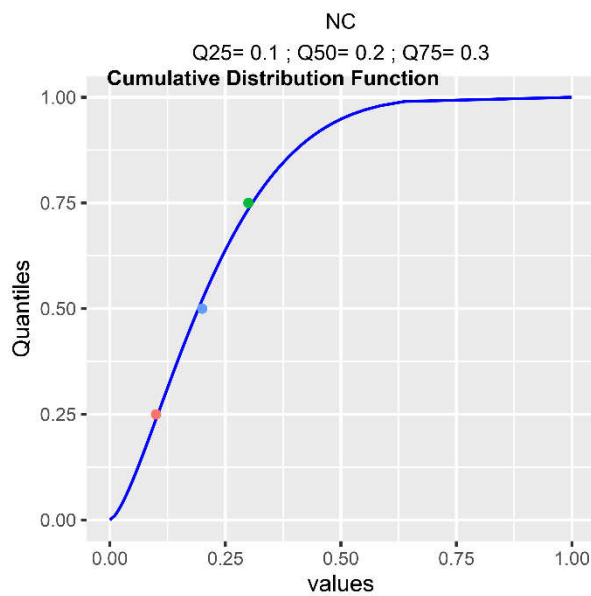- Example of distribution for a result categorized as « Known"
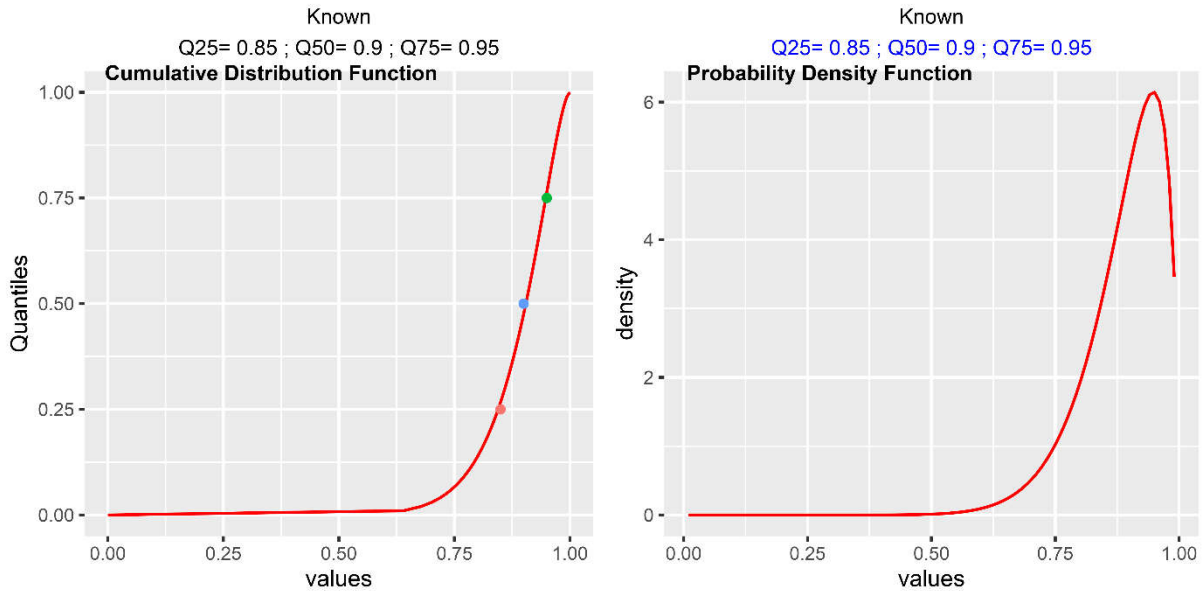


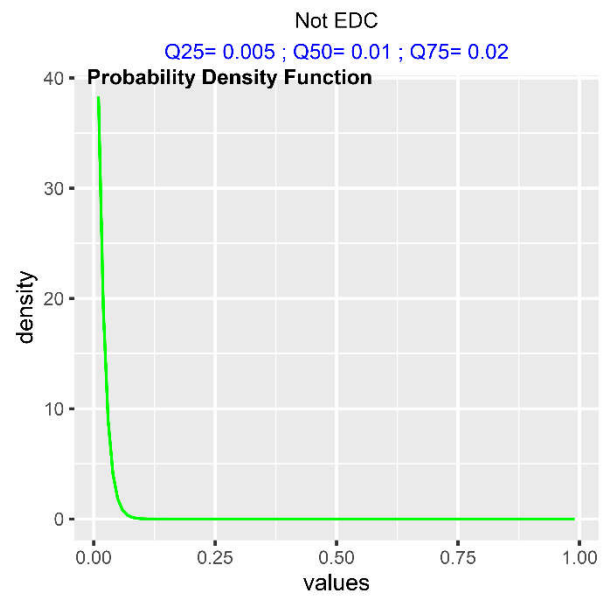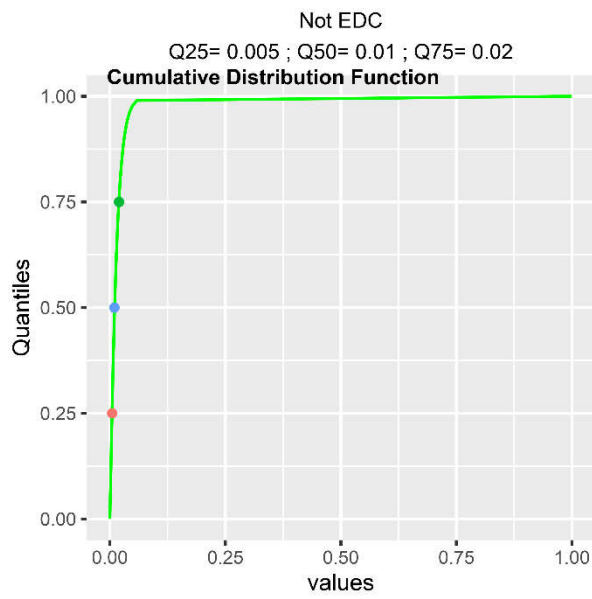- Example of distribution for a result categorize as "Presumed".
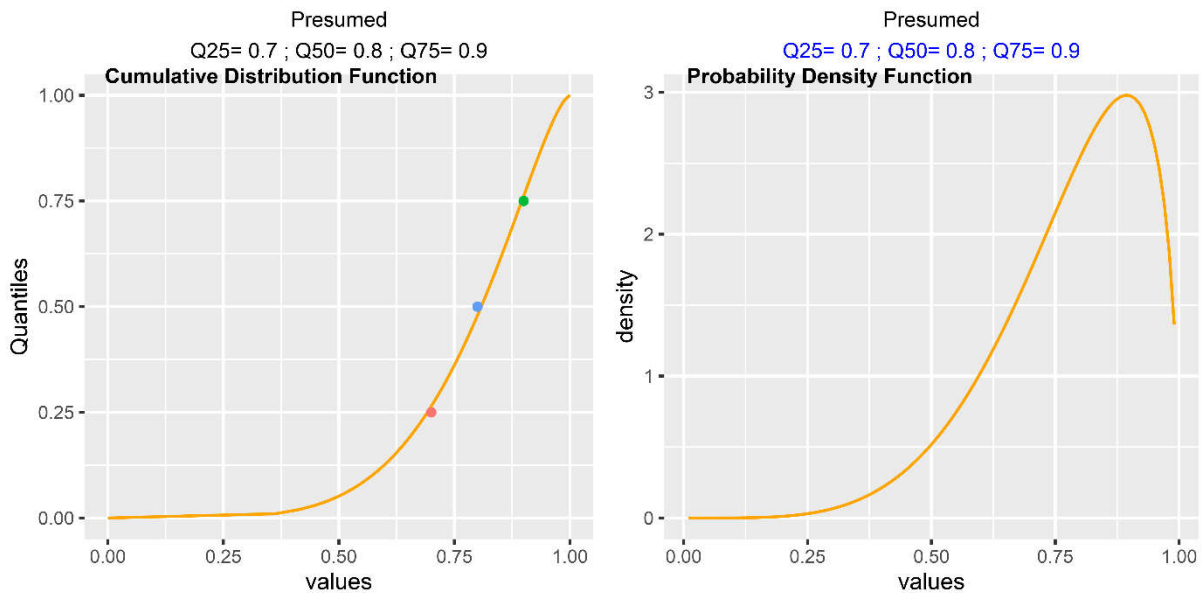
- Example of distribution for a result categorize as "Suspected".



- Example of distribution for a result categorized as "Not categorized".

- Example of distribution for a result categorize as "Not ED".



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**Notes**