anses

Élaboration d'une liste de substances chimiques d'intérêt en raison de leur activité endocrine potentielle

Méthode d'identification et stratégie de priorisation pour l'évaluation

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

Avis de l'Anses
Collective Expert Appraisal Report

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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 liste de substances chimiques d'intérêt en raison de leur activité endocrine potentielle. Méthode d'identification et stratégie de priorisation pour l'évaluation

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 2019 par les 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 (SNPE2). Le présent avis restitue la contribution de l'Anses à l'action 3 de la SNPE 2.

1. CONTEXTE ET OBJET DE LA SAISINE.

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[1]. 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 SNPE2, l'Anses a été saisie pour rendre *« disponible, dès 2020 une liste de substances d'intérêt en raison de leur activité endocrine potentielle, liste à actualiser annuellement. Cette 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 au niveau européen et international, »* devait ensuite *« être hiérarchisée en fonction d'un score de priorisation ».*

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

La saisine rappelle que *« 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. Toutefois, les critères qui permettent d'établir ces listes varient ».* Elle prévoit la constitution « *d'une liste répondant aux attentes des parties prenantes, exprimées lors des travaux d'élaboration de la SNPE2, de disposer d'une telle liste afin d'informer, agir par prévention ou par précaution pour réduire les expositions. »*

Cette liste pourra servir de base au programme annuel d'évaluation de l'Anses de ces substances au titre du danger de perturbation endocrinienne, sur la base d'une méthode de priorisation transparente. Elle pourra aussi servir de source d'information pour d'autres actions de la SNPE2.

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 des comités d'experts spécialisés (CES) « Substances chimiques visées par les règlements REACH et CLP », pilote, et « Substances et produits biocides » pour les co-formulants présents dans les produits biocides. L'Anses a confié l'expertise des initiatives internationales (volet 3.1 de l'avis) au groupe de travail « Perturbateurs endocriniens **»**. Les travaux ont été présentés à ces collectifs d'experts tant sur les aspects méthodologiques que scientifiques entre le 18 mars 2019 et le 18 mai 2020

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 DPI Santé (https://dpi.sante.gouv.fr/dpi-public-webapp/app/home).

Cette expertise collective a abouti à la réalisation d'un rapport, rédigé en anglais en vue de son partage au niveau européen, et intitulé « Elaboration of a list of substances of interest as regards to a potential endocrine activity and prioritisation strategy for assessment ». Ce travail a été coordonné par l'unité UESC de la Direction d'Evaluation des Risques (DER), avec l'appui de la Direction de l'Evaluation des Produits Réglementés (DEPR). Il comporte plusieurs sections distinctes.

Tout d'abord, afin de construire une liste de substances d'intérêt en raison de leur activité endocrine potentielle, une revue des initiatives nationales, européennes ou internationales a été réalisée. Seule cette partie a fait l'objet d'une expertise du groupe d'experts du GT PE. Au-delà de ces travaux non spécifiques à certains secteurs réglementés, les substances actives phytopharmaceutiques et biocides identifiées dans l'étude d'impact de la commission européenne[2] comme ayant une activité endocrine, ou étant des perturbateurs endocriniens potentiels ont été ajoutées. Enfin, un travail complémentaire conduit en interne à l'Anses visant à identifier les co-formulants présents dans des produits phytopharmaceutiques et biocides comme ayant une activité endocrine potentielle a été effectué.

[2] EU Impact assessment (2016). Screening of available evidence on chemical substances for the identification of endocrine disruptors according to different options in the context of an Impact Assessment. Specific Contract SANTE/2015/E3/SI2.706218. Final report. 2016. https://ec.europa.eu/health/sites/health/files/endocrine_disruptors/docs/2016_impact_assessment_study_en.pdf (accessed September 13, 2019).

Différentes informations sur l'usage, les obligations règlementaires et les éléments scientifiques disponibles au titre de l'activité endocrine des substances d'intérêts ont été compilés.

La dernière partie du travail porte exclusivement sur les substances soumises au règlement REACH qui ont été soumises à un exercice de priorisation en vue de leur évaluation. Cet exercice de priorisation et les modalités associées sont détaillés dans cet avis.

3. ANALYSE

3.1. Identification d'une liste d'intérêt quant à une activité endocrine potentielle

Une revue des initiatives internationales a été réalisée afin d'identifier des perturbateurs endocriniens avérés ou potentiels ainsi que des substances d'intérêt pour leur activité endocrine pour la santé humaine et / ou l'environnement. Le rapport intitulé « Worldwide initiatives to identify endocrine disrupting chemicals (EDCs) and potential EDCs » fourni par le Panel international sur la pollution chimique (IPCP) et publié par le Programme des Nations Unies pour l'environnement (PNUE) en 2018 (IPCP, 2018) donne un panorama relativement exhaustif des initiatives menées sur les PEs et les PEs potentiels jusqu'en mars 2017. Le rapport de l'Anses vise à compléter cette analyse avec d'autres initiatives publiées depuis et ce jusqu'en septembre 2019, ainsi que la prise en compte d'une initiative de l'Union Européenne sur les produits règlementés (étude d'impact de l'Union européenne, 2016) couvrant les réglementations biocides et phytopharmaceutiques.

3.1.1. Revue des listes et travaux existants

Au total, 27 initiatives[3] répertoriant environ 2000 substances chimiques d'intérêt pour leurs activités endocrines ont été identifiées. Elles listent des substances considérées comme des PEs avérés ou potentiels, ainsi que des substances d'intérêt pour leur activité endocrine pour la santé humaine et / ou l'environnement et ce quels que soient les secteurs d'utilisation et les réglementations sectorielles concernées : substances actives phytopharmaceutiques et biocides, co-formulants des produits phytopharmaceutiques et biocides, cosmétiques, dispositifs médicaux, médicaments et substances chimiques à usage professionnel et/ou domestique. Ces initiatives sont présentées dans le rapport *ad-hoc* support du présent avis (cf. annexe 4).

Elles ont été conduites par diverses parties prenantes (universités, syndicats industriels, organismes publics et organisations non gouvernementales) pour identifier les PEs potentiels quel que soit leur secteur d'utilisation et les réglementations sectorielles concernées. Les données d'entrée prises en considération sont avant tout des données relatives aux effets de perturbation endocrinienne issues soit d'études toxicologiques, de données humaines et plus rarement de données écotoxicologiques. Les initiatives nationales ou internationales visant à

[3] Listes publiées par la Commission européenne : (EC Priority List, 2003), (EU Impact Assessment, 2016), (EASIS, 2020), CoRAP (European Union's Community Rolling Action Plan), le PACT (Public Activities Coordination Tool) SVHC[3] identifiées sur la liste candidate pour l'autorisation dans le cadre du règlement REACH.

Initiatives nationales : (Danish Center on Endocrine Disrupters, 2017), (KEMI, 2017), (II-EPA, 1997), (NIEHS CTD, 2020), (US-EPA EDSP, 2017 et US-EPA EDSP21 2017), (FDA EDKB, 2019 et la FDA EADB-2019), (EXTEND-2010 et EXTEND-2016), (Land and Water, 2014.

Initiatives non-gouvernementales (DEDuCT, 2019 publiée par Karthikeyan et al., 2019), (EDCs Databank, 2015), (ETUC, 2010), (PAN, 2016), (RISCTOX, ISTAS, 2012), (Liste Substitute It Now" consists of hazardous chemicals » SIN 2019, Theo Colborn (OurStolenFuture, 2016), Scorecard, 2011 et (TEDX, 2019).

générer des données de criblage des PEs (comme les données *in vitro* ou *in vivo*) sur des substances d'intérêt ont été également répertoriées ainsi que les bases de données correspondantes. Les initiatives identifiées ont été qualitativement comparées selon leur périmètre, les critères de sélection utilisés, les méthodes appliquées, et l'identité chimique des substances listées. Puis les forces et faiblesses de chacune de ces initiatives ont été analysées.

Les caractéristiques de ces initiatives sont synthétisées dans le rapport *ad-hoc* (cf. tableau 1).

3.1.2 Difficultés rencontrées pour combiner ces différentes initiatives:

Des ressources importantes sont investies dans le monde entier pour identifier les perturbateurs endocriniens avérés ou potentiels ainsi que des substances d'intérêt pour leur activité endocrine. Cependant le contexte d'établissement de ces listes et la portée de ces initiatives sont différents, ce qui rend leur agrégation difficile. Les sections suivantes apportent un éclairage sur la comparaison de ces différentes initiatives.

Paramètres d'inclusion des substances chimiques considérés par chacune de ces initiatives :

Ces initiatives dénombrent plusieurs dizaines (par exemple (SVHC[4], 2019)) à plusieurs milliers de substances chimiques (par exemple : (FDA EDKB-2019), (FDA-EADB-2019), (US-EPA-EDSP 21 Dashboard 2017 et 2019). En effet, les critères d'inclusion varient :

- ✓ Certaines de ces initiatives ont sélectionné et évalué des substances chimiques en fonction de leur détection dans l'environnement (par exemple, (Land and Water, 2014) et (EXTEND-2010 et 2016)).
- ✓ Certains de ces programmes incluent les données sur la santé humaine et l'environnement alors que d'autres ont utilisé des critères de sélection ne prenant en compte que les données produites pour évaluer l'effet de ces substances pour l'espèce humaine (DEDuCT 1.0, 2019).
- ✓ Certaines de ces initiatives ont pris en compte des substances chimiques quels que soient leurs usages (par exemple, la liste prioritaire de la commission européenne (EC Priority List, 2003) et la (TEDX, 2019)). D'autres ont limité leur champ d'application à certaines substances chimiques, en fonction de leur utilisation et/ou de la réglementation dont elles relèvent (par exemple, (SVHC, 2019), (CoRAP 2019) et (PACT, 2019) pour les substances chimiques réglementées par le règlement REACH en Europe, (PAN, 2016) pour les pesticides, (ETUC, 2010) pour les substances chimiques de fort tonnage – *high production volume* ou HPV).
- ✓ Certaines initiatives établissent leur liste à partir de la littérature scientifique, tandis que d'autres prennent en compte les substances chimiques déjà incluses dans une ou plusieurs initiatives antérieures. La liste prioritaire de la commission européenne (EC Priority List, 2003), en particulier, a servi de point de départ à un certain nombre d'autres initiatives examinées dans le cadre de ce travail (cf. tableau 1 du rapport *ad-hoc*).
- ✓ La dénomination des substances chimiques n'est pas toujours cohérente : certaines initiatives identifient les substances chimiques par des numéros d'identification PubChem et d'autres par des numéros CAS (Chemicals Abstracts Service). Les initiatives ne précisent pas toujours tous les numéros CAS qui peuvent être applicables

[4] Substance identifiée comme très préoccupante (SVHC)

à une substance chimique ou à un groupe de substances chimiques visés (voir II EPA, 1997) ou qui sont inconnus (voir US-EPA, EDSP 21 2019). Cela peut conduire à une comparaison inexacte ou incertaine des substances chimiques identifiées par ces différentes initiatives.

- ✓ Enfin, certaines de ces listes (ex. SVHC, 2019 et US-EPA-EDSP) sont continuellement mises à jour, tandis que d'autres ne le sont plus (TEDX 2019 représente la dernière version puisque cette initiative n'est dorénavant plus mise à jour).

Objectifs de ces initiatives:

Les objectifs de ces initiatives diffèrent. Ainsi, certaines d'entre elles ont été conçues dans le but :

- d'étudier l'activité endocrine de nombreuses substances chimiques (par exemple, (FDA EDKB-2019), (US EPA EDSP 21 Dashboard 2017), (US EPA 2015)) ou de consolider les connaissances existantes en ce qui concerne les mécanismes spécifiques (principalement axées sur les œstrogènes, les androgènes ((FDA EDKB-2019) et (FDA EADB-2019)) et les voies des hormones thyroïdiennes et de la stéroïdogénèse (voies EATS pour l'(US-EPA- EDSP)), tandis que des paramètres spécifiques sur le métabolisme et l'obésité ou sur les effets sur le développement neurologique dus à l'activité endocrinienne des substances chimiques sont encore en cours de développement dans plusieurs projets européens (par exemple EU Horizon 2020) ;
- de soutenir les évaluations des risques et les décisions de gestion des risques. Par exemple, le programme de recherche EDSP de l'US-EPA implique un test expérimental à deux niveaux pour établir des relations quantitatives dose-réponse et caractériser plus précisément les relations dose-effet ;
- de consolider les connaissances existantes quand une préoccupation concernant une activité endocrine d'une substance chimique survient (par exemple, CoRAP, 2019) ;
- de mettre en évidence les PEs ou les PEs potentiels (par exemple : SIN, 2019, DEDuCT, 2019, TEDX, 2019...) ;
- d'identifier des PEs connus dans le domaine de la réglementation européenne (SVHC, 2019) afin de limiter leurs usages et l'exposition des hommes et de l'environnement à celles-ci (substances candidates à la procédure d'autorisation de REACH).

En conséquence, les approches adoptées par ces initiatives pour sélectionner ou évaluer les substances chimiques diffèrent les unes des autres.

Méthodes de construction de chacune de ces initiatives et conséquences :

- Niveau de preuve nécessaire à l'inclusion d'une substance chimique dans une initiative :

La plupart de ces initiatives disposent d'un ensemble de critères de sélection pour l'inclusion de substances chimiques, tels qu'une évaluation transparente du niveau de preuves scientifiques nécessaire à l'inclusion d'une substance chimique dans une liste, dont les détails peuvent être consultés sur leurs sites internet. Certaines initiatives effectuent un degré d'évaluation préliminaire (par exemple, la liste des perturbateurs endocriniens potentiels de TEDX parfois basées uniquement sur les résultats d'études *in vitro* des récepteurs hormonaux)

quand d'autres font un travail plus systématique du caractère PE (par exemple la liste prioritaire de la Commission européenne), voire très détaillé (SVHC, 2019).

- Consultations multipartites (par le biais du gouvernement, de l'organisme de réglementation, de l'industrie et/ou des ONG) peuvent être conduites en particulier pour celles qui ont un impact réglementaire direct.

Les initiatives règlementaires comme l'inscription de substances PEs à la liste candidate de la réglementation des produits chimiques de l'Union européenne (REACH SVHC) ou le programme américain de screening des perturbateurs endocriniens font systématiquement l'objet d'une consultation publique. Ceci permet une évaluation contradictoire.

Bilan :

Parmi toutes ces initiatives, près de 2 000 substances chimiques ont été identifiées pour une activité endocrine potentielle. Certaines substances chimiques sont présentes dans plusieurs initiatives, tandis que d'autres ne sont incluses que dans une seule liste. Cependant, il est difficile de dresser une liste unique en compilant ces initiatives, car elles diffèrent à bien des égards. Cette conclusion est conforme aux observations générales faites par l'IPCP dans son rapport comparant les initiatives qu'il avait énumérées (IPCP, 2018 ; voir également l'annexe 4 du rapport ad hoc) :

- des ressources importantes ont été et sont encore investies dans l'identification des PEs potentiels, comme en témoignent le nombre et la diversité des initiatives trouvées ;

- l'objectif visé par les initiatives individuelles ainsi que les critères utilisés pour identifier (ou inclure) les substances chimiques en tant que PEs, PEs potentiels ou substances avec activité endocrine varient considérablement ;

- certaines initiatives ont déjà été fortement développées et rendues publiques, tandis que d'autres sont prévues ou en sont à des stades de développement plus précoces ;

- il n'existe pas encore de critères communément acceptés pour l'identification des PEs qui s'appliquent à toutes les substances chimiques quels que soient leurs usages, mais la Commission européenne a établi des critères pour leur identification dans les produits phytopharmaceutiques (règlement (UE) 2018/605 de la Commission) et les produits biocides (règlement délégué (EU) 2017/2100 de la Commission) et la définition WHO/IPCS apparaît consensuelle. Récemment, dans le cadre de sa stratégie pour un environnement non toxique, la Commission a déclaré vouloir établir une identification juridiquement contraignante des dangers des perturbateurs endocriniens, sur la base de la définition de l'OMS, en s'appuyant sur des critères déjà élaborés pour les produits phytopharmaceutiques et biocides, et de l'appliquer dans toutes les règlementations concernées.

Au final, il est donc apparu qu'il n'était pas possible d'agréger tout ou partie des listes de substances identifiées par ces différentes initiatives. Néanmoins, sur la base de l'analyse de l'ensemble de ces initiatives, de leurs forces et faiblesses, les experts ont considéré que l'initiative DEDuCT1.0-2019 permet grâce à des critères d'inclusion clairs, appropriés et définis *a priori* d'identifier des PEs potentiels. Les substances identifiées grâce à cette approche sont donc proposées pour figurer dans la liste d'intérêt quant à une activité endocrine potentielle, comme attendu dans la première partie de l'action 3 de la SNPE 2.

3.1.3. Description de la méthode DEDuCT pour l'établissement de la liste des substances d'intérêt

La méthodologie DEDuCT (pour *Database of Endocrine Disrupting Chemicals and their Toxicity profiles*, version 1.0) a été publiée dans une revue scientifique à comité de lecture en 2019 (Karthikeyan et al., 2019). Cette méthodologie est basée sur une analyse de la littérature scientifique existante contenant des preuves expérimentales de perturbations endocriniennes spécifiques chez l'Homme ou les rongeurs. Un diagramme de décision a été développé par les auteurs (voir Figure 1) afin d'identifier les PEs potentiels à partir des données disponibles dans les articles de recherche publiés.

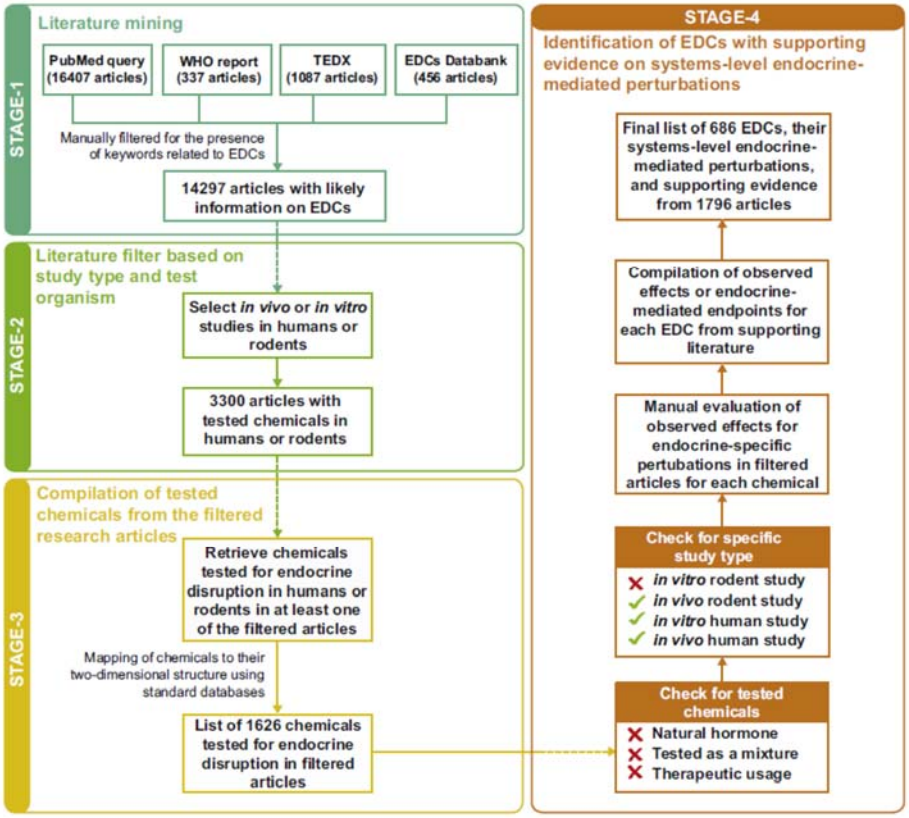

Figure 1 : Diagramme de décision incluant quatre étapes pour identifier les PEs potentiels à partir d'articles scientifiques publiés contenant des preuves expérimentales d'effets issus de perturbations du système endocrinien (en anglais, selon Karthikeyan et al., 2019).

La base de données DEDuCT a été construite à partir d'une recherche bibliographique utilisant une équation de recherche précise sur PubMed effectuée en février 2018 puis enrichie par la littérature scientifique citée dans les trois initiatives suivantes[5] : UNEP/WHO, 2013, TEDX, 2018 et la banque de données EDC, 2015 (EDCs Databank, 2015). Au total, plus de 16 000 articles de recherche publiés ont été rassemblés puis examinés, parmi lesquels, 14 297 articles concernaient effectivement le sujet des PEs. Un grand nombre d'articles (3 300) concernaient des substances chimiques testées chez l'Homme (*in vitro* sur des cellules d'origine humaine, cas d'études ou données épidémiologiques traitant de la problématique PE) ou chez des rongeurs. Ces publications concernaient 1 626 substances chimiques.

Ensuite, certaines substances ont été exclues, à savoir les hormones naturelles, les agents testés en mélange et les substances dont les articles testaient leur pertinence thérapeutique.

[5] Les raisons expliquant l'inclusion de ces travaux et pas d'autres travaux sont expliquées dans l'article scientifique dédié.

De plus, les substances pour lesquelles seules des articles scientifiques rapportant des effets *in vitro* sur cellules de rongeurs ont été exclues, les auteurs jugeant que ces modèles ne permettent pas de refléter la complexité des effets PE observés chez l'Homme. Karthikeyan et al., (2019) ont également exclu les études publiées dans lesquelles seuls des essais de liaison aux récepteurs ou des méthodes *in silico* étaient utilisés pour déduire la perturbation endocrinienne potentielle d'une substance chimique. Enfin, ils ont exclu les études épidémiologiques humaines lorsqu'elles ne contenaient pas suffisamment de preuves mécanistiques reliant les effets néfastes observés aux perturbations endocriniennes potentielles lors d'une exposition à des substances chimiques (Bliatka et al., 2017; Hernandez et Tsatsakis, 2017).

Une fois la base de données d'articles stabilisée, elle contenait 1796 publications regroupées par substance afin d'évaluer le niveau de preuve du caractère PE de chacune d'elle. Finalement, 686 PEs potentiels ont ainsi été identifiés par DEDuCT 1.0, 2019.

Pour ces substances, la base de données contient plusieurs types d'information :

1- Selon les données disponibles, les substances identifiées sont classées en différentes catégories indiquant le niveau de preuve *a priori* (i.e. sans évaluation approfondie):

- ✓ Catégorie I lorsque les effets de perturbation endocrine de la substance sont rapportés *in vivo* chez l'Homme (7 substances identifiées). La quantité d'information disponible sur les substances de cette catégorie devrait permettre de mener une évaluation conclusive sur le statut de la substance au regard de la définition OMS ;
- ✓ Catégorie II lorsque les effets sont rapportés *in vivo* chez des rongeurs et *in vitro* dans des expériences utilisant des cellules humaines (142 substances). La quantité d'information disponible sur les substances de cette catégorie devrait là aussi permettre de mener une évaluation conclusive sur le statut de la substance au regard de la définition OMS ;
- ✓ Catégorie III lorsque les effets sont rapportés uniquement *in vivo* chez les rongeurs (367 substances identifiées), des données sur le mode d'action manquent ;
- ✓ Catégorie IV lorsque les effets sont rapportés *in vitro* sur des cellules humaines uniquement (170 substances identifiées), des données sur l'effet néfaste associé manquent.

2- Les données disponibles pour chaque substance ont été classées en sept catégories d'effets liés au système endocrinien: reproduction, développement, métabolisme, système hépatique, effets immunologiques et neurologiques, et cancers d'origine endocrine (voir figure 2).

3- Leurs secteurs d'utilisation ou lieu de détection des substances : produits de consommation, agriculture, industrie, médecine et soins de santé, polluants, sources naturelles et intrants intermédiaires dans les processus de production.

Avantages principaux:

- La méthodologie suivie par DEDuCT 1.0, 2019 est bien décrite, incluant une première étape de recherche documentaire bien étayée.

- Les publications identifiées à l'aide de la méthodologie DEDuCT 1.0, 2019 ont été vérifiées manuellement par les auteurs eux-mêmes afin de s'assurer que les mots-clés identifiés correspondent bien à des effets sur le système endocrinien.

- Les composés identifiés à partir des publications ont été sélectionnés sur la base de données disponibles telles que définis par l'OMS. Ainsi, les substances conservées sont celles pour lesquelles des données montrant une activité endocrinienne et des effets néfastes induits par la modification des fonctions endocriniennes sont disponibles, que ces effets aient été démontrés lors d'une exposition dans le cadre d'expériences publiées chez l'Homme ou les rongeurs. La méthodologie proposée par DEDuCT, 2019 est donc compatible avec la définition réglementaire des PEs adoptée par l'Union européenne (et conforme à celle du UNEP/WHO, 2013).

- En outre, les données sources d'autres initiatives récentes (UNEP/WHO, 2013, EDCs Databank, 2015 and TEDX, 2018) ont été incluses.

- DEDuCT 1.0, 2019 inclut les publications et les substances chimiques quelles que soient leurs domaines d'utilisations. Par exemple, des substances actives phytopharmaceutiques et biocides mais aussi des polluants de l'environnement sont inclus.

- Les auteurs ont accepté de partager avec l'Anses leurs données brutes afin de garantir un processus plus rapide et une évaluation transparente (voir ci-dessous).

- Enfin, DEDuCT 1.0, 2019 est une publication récente qui garantit une liste actualisée par rapport aux autres initiatives sur les PEs.

Principales faiblesses :

- L'objectif des auteurs de la liste DEDuCT était d'identifier les PE pertinents pour la santé humaine. Cette liste de 686 composés identifiés a été sélectionnée sur la base d'études chez l'Homme (*in vitro* sur les tissus humains, cas d'études ou études épidémiologiques) et d'études *in vivo* sur les rongeurs. Aussi, les études effectuées sur des modèles non mammifères n'ont pas été intégrés, minimisant l'inclusion de PE pour les espèces de l'environnement. Le GT-PE de l'Anses recommande que la recherche documentaire soit mise à jour pour inclure les composés présentant une activité endocrinienne et des effets sur les espèces sauvages (afin d'identifier les PEs pour l'environnement).

- L'utilisation des filtres proposés par le DEDuCT, 2019 exclut certaines substances, ce qui peut expliquer les écarts avec d'autres bases de données (voir Figure 2). Certains filtres utilisés dans DEDuCT, 2019 peuvent ne pas être pertinents dans notre contexte. Par exemple, certaines substances ont été exclues parce qu'elles ont une pertinence thérapeutique, en ignorant que des utilisations autres existaient, qui rentrent dans le champ de REACH avec l'identification des SVHC : voir plus bas l'exemple du résorcinol.

- Certaines substances pour lesquelles peu de données sont disponibles ont été exclues ce qui limite l'utilisation de la liste comme source de substances pour demander des informations complémentaires dans le cadre de REACH (CoRAP). En effet, sur la base de la méthode décrite par DEDuCT, 2019, les données *in vitro* seules ont été exclues ainsi que les études *in silico* et les études épidémiologiques "qui ne sont pas susceptibles de révéler un mécanisme biologique". Seules les substances pour lesquelles des données expérimentales montrant des effets liés à des perturbations endocriniennes spécifiques ont été sélectionnées dans la liste.

Comparaison réalisée entre DEDuCT, 2019 et d'autres initiatives reconnues :

Les filtres utilisés pour la construction de la base de données DEDuCT excluent 58 substances parmi celles listées par l'UNEP/WHO, 2013 (soit 31%), 960 substances parmi la liste TEDX, 2018 (soit 67%) et 350 de la banque de données EDCs Databank, 2015 (soit 57%). Ainsi, 265 substances seulement sont conservées parmi les 615 substances initiales de cette base de donnée (voir Figure 2).

Figure 2 : Comparatif des résultats obtenus avec DEDuCT, 2019, UNEP/WHO, 2013, TEDX, 2018 et EDCs Databank, 2015. Diagramme de Venn (cf. Karthikeyan et al., 2019).

Par conséquent, les filtres appliqués permettent d'identifier les substances disposant d'un jeu de données minimum nécessaire pour évaluer leur statut au regard de la définition de l'OMS, pouvant ainsi conduire à écarter des substances potentiellement d'intérêt pour lesquelles il manquerait des données.

Capacité de DEDuCT, 2019 à détecter de nouveaux PE potentiels

La robustesse de la méthode DEDuCT a été évaluée pour sa capacité à identifier des substances qui n'auraient pas été identifiées comme des PEs potentiels jusqu'à présent. La figure suivante décrit comment DEDuCT 1.0 2019 identifie ou pas les substances proposées par d'autres initiatives. Elle montre qu'aucune initiative ne recouvre totalement une autre. A l'inverse, la liste de la Commission Européenne a été très largement reprise puisque qu'elle ne contient quasiment aucune substance qui n'appartienne pas à au moins une autre initiative.

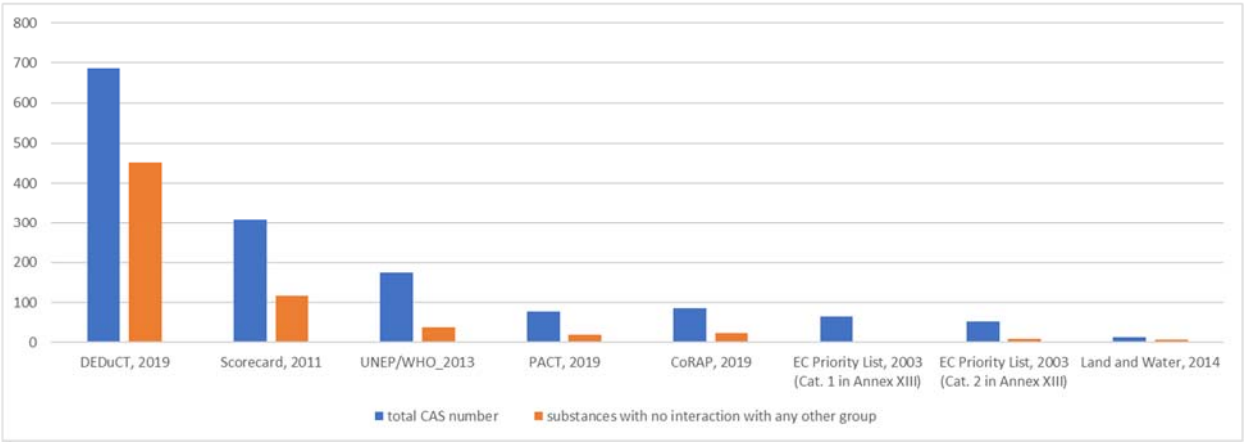

Figure 3: Histogramme représentant le nombre total de numéros CAS identifiés par chaque initiative (histogramme en bleu) et le nombre de numéros CAS retrouvés uniquement par l'une des initiatives incluses (histogramme en orange) dans cette analyse : DEDuCT, 2019, Scorecard, 2011, UNEP/WHO, 2013, PACT, 2019, CoRAP, 2019, EC Priority List, 2003 (Cat. 1 in Annex XIII), EC Priority List, 2003 (Cat. 2 in Annex XIII) and Land and Water, 2014

Les substances identifiées par DEDuCT 1.0, 2019 ont été recoupées avec les listes ECHA (CoRAP, 2019 et PACT, 2019) et la liste prioritaire de la Commission européenne de 2003, car elles représentent des initiatives de l'Union européenne sur les PEs. En outre, la base de données Scorecard-2011 a également été comparée avec DEDuCT, étant donné qu'un large ensemble de sources de littérature scientifique (par exemple, les principales publications scientifiques, les rapports scientifiques ou les programmes fédéraux ou internationaux) ont été consultés. De manière générale, on observe un faible taux de recouvrement entre l'ensemble des différentes initiatives.

Capacité de DEDuCT 1.0, 2019 à détecter des perturbateurs endocriniens reconnus

La robustesse de la méthode DEDuCT a aussi été évaluée quant à sa capacité à détecter des PEs connus.

Un critère important pour juger de la robustesse de DEDuCT 1.0, 2019 était d'évaluer comment cette initiative a pu identifier des PEs d'ores et déjà reconnus au niveau européen (i.e identifiés SVHC, 2019). Les substances PEs SVHC répondent à la définition de l'OMS et suscitent un niveau de préoccupation équivalent aux propriétés CMR (cancérogènes, mutagènes, reprotoxiques) ou PBT (persistantes, bioaccumulables, toxiques), en accord avec l'article 57f du règlement REACH.

Au mois de décembre 2019, les substances chimiques identifiées comme PE dans cette liste sont au nombre de 16 (4 substances chimiques pour la santé humaine, 10 pour l'environnement et 2 à la fois pour la santé humaine et l'environnement). Sur ces 16 substances, 4 n'ont pas été identifiées dans DEDuCT 1.0, 2019 rapportées dans le tableau 2 du rapport. Il s'agit de substances sans composition bien définie (comme des mélanges), exclues par la méthodologie de DEDuCT, ce qui démontre la capacité de DEDuCT 1.0, 2019 à identifier les PE avérés.

Afin d'évaluer l'influence des filtres proposés par DEDuCT 1.0, 2019, les substances répertoriées dans cette initiative ont été comparées à celles classées dans la liste prioritaire de la Commission européenne de 2003 (EC Priority List, 2003 incluse dans la banque de données EDCs Databank et donc normalement présentes dans DEDuCT 1.0, 2019. Deux substances proposées comme catégorie 1 dans la liste prioritaire de la Commission européenne de 2003 n'étaient pas présentes dans la liste finale proposée par DEDuCT, 2019. Le résorcinol (numéro CAS 108-46-3) et le mélange Arochlor 1260 – Clophen A60 (numéro CAS 11096-82-5). L'absence de ce dernier est facilement compréhensible, car l'un des premiers filtres appliqués dans la liste DEDuCT était d'omettre les mélanges. En revanche, l'absence du résorcinol est plus discutable, bien que de nombreux métabolites soient présents dans la liste DEDuCT. Son absence est probablement due à l'exclusion des molécules testées pour des usages thérapeutiques (autre filtre utilisé), le résorcinol ayant pendant longtemps été étudié dans la littérature pour ses effets néfastes après utilisation comme crème anti-variqueuse.

3.1.4. Conclusion

Les comparaisons effectuées ci-dessus montrent que, quelles que soient les initiatives évaluées, elles identifient des substances différentes, en raison des divers critères de sélection appliqués, du contexte et des objectifs. Il n'y a pas d'initiative montrant un recouvrement préférentiel avec les autres, à l'exception de la liste prioritaire de la Commission européenne de 2003 qui a servi de base à de nombreuses initiatives mais qui n'a pas été maintenue à jour. Ainsi, une approche visant à agréger différentes initiatives apparait peu pertinente car ces initiatives relèvent de critères très différents. Il a donc été décidé de sélectionner une initiative parmi toutes celles analysées.

Ainsi, l'Anses propose d'inclure dans la liste des substances d'intérêt les 686 substances identifiées par la base DEDuCT, 2019 pour les raisons exposées ci-dessus.

3.2. Cas des substances présentes dans les produits biocides et phytopharmaceutiques

3.2.1. Substances actives biocide et phytopharmaceutiques

Substances actives d'intérêt identifiées dans l'étude d'impact de la Commission européenne de 2016

Dans le cadre d'une étude d'impact des différentes options de définition d'un PE proposées par la commission européenne, un exercice d'identification de substances actives phytopharmaceutiques et biocides qui pourraient être identifiées comme PEs a eu lieu en 2016 (EU Impact Assessment, 2016).

Parmi les options analysées, l'option 3, basée sur la définition de l'OMS / IPCS, conduisait à identifier 197 substances actives, selon différentes catégories en fonction du poids des preuves différent :

- ✓ Substances de catégorie I : PE confirmés lorsque des effets indésirables ont un lien plausible avec un ou des mode(s) d'action endocrinien disponibles ou, dans certains cas spécifiques, le schéma des effets indésirables peut être le diagnostic d'un mode d'action PE.
- ✓ Substances de catégorie II : PE présumés lorsque des effets indésirables spécifiques indiquant une perturbation endocrinienne ont été identifiés sans preuves mécanistiques à l'appui, ou inversement des preuves mécanistiques *in vivo* sans preuves d'effets indésirables.
- ✓ Substances de catégorie III identifiant les substances ayant une activité endocrine sans preuves *in vivo*.

Il était clairement mentionné que cet examen préalable ne pouvait en aucun cas être considéré comme une évaluation approfondie au titre du règlement concerné. Néanmoins, il permet l'identification de substances actives avec un effet PE potentiel. Aussi, en complément de la liste DEDuCT, cette liste de substances actives phytopharmaceutiques et biocides est incluse dans la liste des substances d'intérêt produite dans le présent exercice.

Comparaison avec les données issues de DEDuCT 1.0, 2019

Comme évoqué précédemment, DEDuCT est une méthodologie travaillant sans *a priori* sur les domaines d'usage d'une substance. Elle se fonde sur les données disponibles dans la littérature scientifique. Sur la base de ces informations, Karethikeyan et al. (2019) ont classé les substances proposées dans 7 grandes catégories et 48 sous-catégories d'usages, sans expliciter la méthodologie suivie pour effectuer cette catégorisation. Ainsi, parmi les 276 substances identifiées comme pesticides dans DEDuCT 1.0, 109 (40%) sont des substances actives biocides ou phytopharmaceutiques sur le marché européen. Les autres substances ne sont pas ou plus approuvées sur le marché européen.

Les travaux de screening sur les perturbateurs endocriniens les plus récents au niveau de l'Union européenne ont été réalisés lors de l'étude d'impact telle que décrite ci-dessus (EU Impact assessment, 2016).

DEDuCT identifie 45 substances sur les 197 qui ont été catégorisées I, II ou III (EU Impact assessment, 2016). DEDuCT comprend en outre 2 substances actives (Imidacloprid et Esfenvalerate) sur les 6 considérés non PE dans l'étude d'impact de la Commission européenne (voir tableau 3 du rapport). Aussi, la comparaison entre les deux listes montre que DEDuCT identifie 23% des substances actives identifiées dans l'étude d'impact avec toutefois une catégorisation pouvant diverger.

Ce faible taux de recouvrement entre les deux études s'explique probablement par le fait que DEDuCT est basé sur les données de la littérature scientifique publiée et ne peut donc pas tenir compte de l'intégralité des données produites par les industriels en application des réglementations européenne et qui, sont disponibles essentiellement dans les rapports d'évaluation des dossiers réglementaires. L'entrée en application des dispositions de la Food Law sur les données relatives aux substances actives des produits phytopharmaceutiques va permettre à un accès plus large à ces données..

Sur la base de cette comparaison et afin d'être aussi exhaustif que possible, les 152 substances des catégories I, II et III de l'étude d'impact de l'UE, 2016 (option 3) qui ne sont pas identifiées par DEDuCT sont ajoutées dans la liste des substances d'intérêt.

3.2.2 Cas particulier des co-formulants présents dans des produits réglementés

Concernant les produits biocides, leur mise sur le marché est encadrée par le règlement européen (UE) 528/2012. Ce règlement prévoit des dispositions spécifiques pour ce qui concerne les PEs. Les critères scientifiques permettant d'identifier un PE ont été définis dans le règlement délégué (UE) 2017/2100 entré en application le 7 juin 2018.

Ainsi, depuis le 7 juin 2018, l'Anses doit se prononcer sur le caractère PE des produits biocides qu'elle évalue. Un produit biocide est considéré comme PE si un des composants l'est, ces composants pouvant être la substance active ou l'un des co-formulants du produit. Ainsi, les critères définis doivent s'appliquer tant aux substances actives qu'aux co-formulants présents dans des produits biocides

En accord avec le document guide endossé par l'ensemble des autorités compétentes biocides[6] en mars 2018, l'évaluation du caractère PE de la substance active est menée au moment de son approbation/ ré-approbation, ce qui n'est pas le cas des co-formulants, associés à la définition du produit. Pour ce qui concerne les autres substances qui composent le produit biocide (co-formulants), l'Anses vérifie si les co-formulants ont fait l'objet d'une évaluation dans les réglementations pour lesquelles une identification du caractère PE d'une substance chimique est possible, en particulier :

- le règlement REACH (identification en tant que substance extrêmement préoccupante au titre de l'article 57(f)) ;
- le règlement (CE) no 1107/2009 (règlement phytopharmaceutique) ;
- le règlement (UE) no 528/2012 (règlement biocide).

Si aucune évaluation de ce type n'a été menée, l'Anses réalise un criblage (« screening ») en s'appuyant sur les informations à sa disposition, afin d'identifier s'il existe des indications que ces co-formulants pourraient présenter une activité sur un système endocrinien. En effet, dans les temps impartis pour l'évaluation d'un dossier de demande d'AMM, et avec les données à disposition, il n'est pas possible de réaliser une évaluation approfondie du danger relatif à la perturbation endocrinienne pour chacun des co-formulants.

Les base de données consultées sont les suivantes :

- liste des activités sur les substances dans le cadre de REACH (CoRAP, PACT…) ;
- liste de l'UE sur les PE potentiels[7] ;
- programmes d'évaluations des organismes publics européens ou internationaux ;

[6] CA-March18-Doc.7.3.bFinal - The implementation of scientific criteria for the determination of endocrine-disrupting properties in the context of biocidal product authorisation

[7] Par exemple http://ec.europa.eu/environment/chemicals/endocrine/documents/studies_en.htm

- base de données ToxCast et EDSP, compilant un ensemble de résultats d'essais *in vitro*.

La classification de la substance (classification harmonisée ou notification de classifications proposées par les déclarants), pour des effets reprotoxiques ou pour une toxicité répétée avec effets sur la thyroïde (classification STOT-RE - Thyroïde) est également considérée.

L'ensemble des informations fournies par les pétitionnaires déposant les demandes d'AMM est également analysé.

Au 1er novembre 2019, l'Anses a réalisé le criblage de 282 substances chimiques présentes dans au moins un produit biocide. Parmi ces 282 substances,

- 205 ne présentent aucune indication d'une activité endocrine sur la base des informations consultées telles que détaillées ci-dessus,
- 77 présentent des indications d'une activité endocrine potentielle.

De manière similaire, 4 co-formulants présents dans un PPP qui pourraient présenter une activité endocrine ont aussi été identifiés.

Ainsi, 81 substances présentes dans au moins un produit pour lequel l'Anses est en charge de délivrer des autorisations de mise sur le marché, sont susceptibles de présenter une activité endocrine. Une évaluation approfondie, sur la base de données expérimentales robustes serait nécessaire pour identifier si celles-ci peuvent être qualifiées de PE.

Considérant que ces substances sont soumises au règlement REACH, qu'elles sont possiblement présentes dans de nombreux mélanges et produits de consommation qui ne sont pas forcément des produits réglementés, et que les données expérimentales nécessaires sont disponibles ou exigibles auprès des fabricants des substances et non des utilisateurs aval, l'évaluation des propriétés de perturbation endocrinienne de ces substances devrait être menée dans le cadre de REACH. Une fois cette évaluation menée, les conséquences réglementaires s'appliqueront pour l'ensemble des produits dans lesquels elles sont incorporées.

En comparant la liste proposée par DEDuCT 1.0,2019 (686 substances) avec les 81 substances utilisées comme co-formulants dans les PPP et BP identifiées par l'Anses lors de leur évaluation, il apparaît que 13 substances sont communes. Ces substances sont listées dans le tableau 4 du rapport

Les différentes méthodologies, sources d'information et critères utilisés dans DEDuCT et dans les travaux effectués pour identifier les substances d'intérêt pour leurs propriétés PE parmi les coformulants peuvent expliquer le faible niveau de recouvrement (16%) entre ces deux bases de données. Afin d'être aussi exhaustif que possible dans la constitution de la liste des substances d'intérêt, les 68 co-formulants non identifiés dans DEDuCT, 2019 ont été ajoutés.

3.4. Méthode de sélection des substances à inclure au programme de travail de l'ANSES à partir de la liste des substances d'intérêt

3.4.1. Définition de la liste des substances d'intérêt

La liste de substances d'intérêt, susceptibles de présenter un caractère PE, a été établie suite à la revue d'initiatives internationales existantes tel que détaillé précédemment.

En s'appuyant sur les recommandations de son groupe de travail sur les PE, l'Anses propose de retenir l'initiative (DEDuCT 1.0, 2019) comme outil d'identification pour les substances chimiques. Cette liste comporte 686 substances. En complément et en s'appuyant sur ses travaux d'expertise sur les produits réglementés, l'Anses propose d'ajouter, d'une part, une liste de 81 co-formulants de

produits biocides et phytopharmaceutiques pour lesquels des indications d'activité endocrine potentielle ont été identifiées (Anses, 2019), dont 13 en commun avec DEDuCT 1.0, 2019 soit un total de 754 substances et, d'autre part, les 197 substances actives identifiées dans l'étude d'impact de la Commission européenne (EU Impact assessment, 2016), parmi lesquelles 45 substances actives ont déjà été identifiées par DEDuCT 1.0 (2019). En ajoutant les 152 substances actives restantes aux 754 substances identifiées**,** la liste d'intérêt est ainsi constituée de 906 substances chimiques. Cette liste a pour objectif l'identification de substance à suivre dans divers milieux ou produits de consommation. Elle peut aussi servir de base pour la sélection de substances au programme de travail de l'Anses. Pour évaluer l'intérêt d'une évaluation plus approfondie, un certain nombre d'informations a été obtenu et concaténé pour ces substances d'intérêts. L'origine de ces informations et leur date d'obtention est précisé dans la légende de l'annexe mise à disposition sur le site sous format pdf.

3.4.2. Méthode de priorisation visant à définir le programme de travail de l'Anses

Processus d'évaluation du caractère PE des substances actives et conséquence pour la priorisation des substances actives phytopharmaceutiques et biocides

Les substances actives biocides et phytopharmaceutiques sont encadrées respectivement par le Règlement européen (UE) 528/2012 du Parlement Européen et du Conseil du 22 mai 2012 concernant la mise à disposition sur le marché et l'utilisation des produits biocides (BPR) et le règlement européen (CE) n° 1107/2009 du Parlement Européen et du Conseil du 21 octobre 2009 concernant la mise sur le marché des produits phytopharmaceutiques (PPPR). Ces deux règlements prévoient des dispositions spécifiques pour les substances actives identifiées comme des PEs. En particulier, les substances actives qui sont identifiées comme des PEs ne respectent pas les critères d'approbation.

Les critères pour identifier une substance comme PE sont inscrits dans le Règlement délégué (UE) 2017/2100 et le Règlement (UE) 2018/605 pour les substances actives biocides et phytopharmaceutiques respectivement. Un guide commun a été préparé conjointement par l'EFSA et l'ECHA proposant une méthodologie commune aux deux réglementations et harmonisée au niveau européen pour l'identification des PE (Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009).

Depuis que les critères ont été adoptés, les propriétés de perturbation endocrinienne de chaque substance active sont examinées au moment de son évaluation en vue de son approbation / ré-approbation. En effet, l'état membre rapporteur doit conclure lors de son évaluation si les critères définis dans les règlements *ad hoc* en vue de l'identification d'un PE sont remplis ou non. Cette évaluation est ensuite revue par les Etats membres dans le cadre de la revue communautaire qui est coordonnée par l'ECHA (pour les substances actives biocides) ou l'EFSA (pour les substances actives phytopharmaceutiques).

Le calendrier d'évaluation/ réévaluation des substances actives ainsi que la répartition de toutes les substances actives entre les Etats membres de l'Union européenne sont inscrits dans des règlements européens qui ont été adoptés après discussion entre les autorités compétentes[8].

[8] Le programme d'examen des substances actives phytopharmaceutiques est présenté dans les textes :

- programme AIR2 : Regulation EU 1141/2010;
- programme AIR3 : Draft Working Document - Renewal Programme (SANCO/2012/11284);
- programme AIR4 : Commission Implementing Decision 2016/C 357/05;
- programme AIR5 : Commission Implementing Decision C/2018/3434.

Cette information est disponible sur le site de la Commission Européenne :
https://ec.europa.eu/food/plant/pesticides/approval_active_substances/approval_renewal_en.

Le programme d'examen des substances actives biocide est présenté dans les textes : Commission Delegated Regulation (EU) No 1062/2014 ; Commission Delegated Regulation (EU) 2019/157 et Commission Delegated Regulation (EU) 2019/227 of 28 November

Les substances actives biocides sont réévaluées tous les 7 à 10 ans, et les substances actives phytopharmaceutiques tous les 5 à 15 ans, la durée d'approbation étant dépendante du niveau de danger identifié lors de l'évaluation européenne initiale. Ainsi, d'ici 2025, les Etats membre, dont la France, évalueront les effets perturbateurs endocriniens d'environ 300 substances actives phytopharmaceutiques et d'une centaine de substance active biocides. L'Anses sera en charge de l'évaluation du caractère PE des substances actives pour lesquelles la France est rapporteur et apportera ses commentaires sur les évaluations menées par les autres Etats membres dans le cadre de la revue par les pairs pour les autres substances.

Pour ces raisons, les 175 substances actives identifiées dans la liste d'intérêt ne sont pas retenues pour l'exercice de priorisation présenté ci-après, dans la mesure où leur évaluation est déjà programmée dans le cadre communautaire. En France, une liste de substances préoccupantes a notamment été proposée par l'Anses afin de prioriser les actions au cours des prochaines années[9].

Plusieurs autres substances chimiques sont également exclues de l'exercice de priorisation :

- Les substances déjà identifiées comme très préoccupantes (SVHC) en raison de leurs propriétés PE, soit 12 substances.

- Les 12 substances actives d'ores et déjà interdites en Europe (notamment pour leurs usages phytopharmaceutiques et cosmétiques).

- 2 substances ne présentant pas de numéro d'identification CAS ou EC.

Au final, **705 substances sont retenues** comme pouvant faire l'objet d'une programmation de leur évaluation approfondie de leurs caractéristiques au titre du danger PE. Le travail ici consiste à identifier des éléments objectifs pour prioriser des substances sur lesquelles travailler en priorité

Parmi les 705 substances de la liste d'intérêt, 266 sont enregistrées dans le cadre du règlement REACH :

- ✓ 159 à plus de 100 tonnes par an ;
- ✓ 65 entre 1 et 100 tonnes par an ;
- ✓ 40 pour un usage exclusivement comme intermédiaire de synthèse ;
- ✓ 2 substances dont le statut d'enregistrement est confidentiel.

Ces informations sont importantes car elles indiquent les substances utilisées, fabriquées ou importées sur le territoire européen, donnant un premier niveau d'indication sur l'exposition relative à cette substance. Par ailleurs, le niveau d'informations disponibles est fonction du tonnage d'enregistrement (conformément aux requis des annexes du règlement REACH) et impacte la capacité de l'État membre à demander des données supplémentaires par la procédure d'évaluation (par exemple, les intermédiaires isolés utilisés dans des conditions strictement contrôlées sont exemptés de cette procédure). A contrario, on doit noter que les substances non enregistrées peuvent néanmoins être trouvées sur le marché européen (importées dans des articles ou sous forme de résidus s'ils sont persistants dans l'environnement). Les substances qui ne sont pas enregistrées peuvent être évaluées sur la base de la littérature scientifique disponible ou en utilisant

2018 amending Delegated Regulation (EU) No 1062/2014 (Brexit). Cette information est disponible sur le site de l'ECHA : https://echa.europa.eu/fr/information-on-chemicals/biocidal-active-substances

des informations provenant de substances structurellement similaires, ce qui constitue un challenge sur le plan scientifique.

En outre, les catégories du niveau d'information disponible utilisées par DEDuCT 1.0 (2019) (voir section 1.2) et dans l'étude d'impact de la Commission européenne (2016) constituent des critères de sélection pour l'Agence, car elles reflètent l'état des données disponibles pour chaque substance et donc la capacité de l'Agence à évaluer le caractère PE de ladite substance. Les catégories proposées par ces deux initiatives sont cohérentes mais pas similaires. Afin de conserver cette information, elles ont été alignées par l'Anses comme suit :

- Catégorie I, reprenant les catégories I et II de DEDuCT (2019) et la catégorie I de l'étude d'impact de la Commission (2016) ;
- Catégorie II, reprenant les catégories III de DEDuCT (2019) et la catégorie II de l'étude d'impact de la Commission (2016) ;
- Catégorie III, reprenant les catégories IV de DEDuCT (2019) et la catégorie III de l'étude d'impact de la Commission (2016).

Enfin, certaines substances de la liste font d'ores et déjà l'objet d'actions au sein de l'Union européenne (évaluation par d'autres agences, génération de données, etc.) ou bien font l'objet d'un encadrement réglementaire. Ces informations constituent également des critères de sélection. Ainsi, on peut noter que le méthyl tert-butyl éther – MTBE (CAS 1634-04-4), disulfure de carbone (CAS 75-15-5), tert-butyl-4-methoxyphenol - BHA (CAS 25013-16-5), 2,6-di-tert-butyl-p-cresol - BHT (CAS 128-37-0), dioxyde de titane (CAS 13463-67-7) sont déjà au programme de travail de l'Anses 2021 et vont, de fait, être exclues de l'exercice de priorisation présenté ci-dessous.

Sur la base de ces indications, les ministères chargés de la mise en œuvre de la SNPE 2 ont ainsi proposé de retenir la méthode de priorisation suivante pour mettre les susbtances au programme de travail, aboutissant à l'élaboration d'une liste restreinte de 59 substances, en appliquant le diagramme de tri détaillé dans la figure n°4 ci-après.

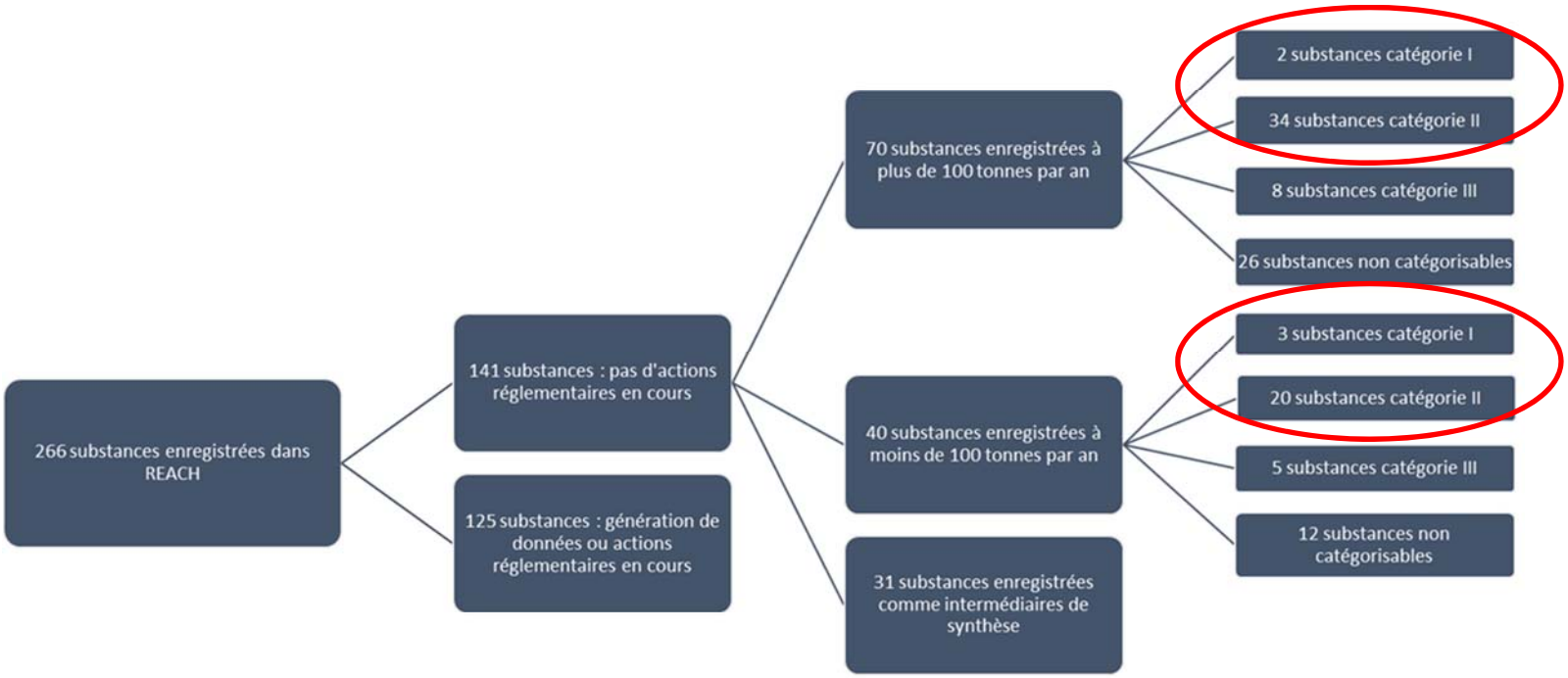

Figure 4 : Critères de sélection proposés par les Ministères chargés de la mise en œuvre de la SNPE 2

Sur ces 59 substances, et en vue d'établir un score de priorité, l'Anses a proposé d'intégrer une étape supplémentaire pour retenir 16 substances qui apparaissent être les meilleurs candidats pour une évaluation approfondie et en vue d'une catégorisation du caractère PE, dans le périmètre des activités de l'Agence. A cette étape, le recueil de certaines données s'est fait manuellement : la disponibilité de données toxicologiques, le statut réglementaire et les usages des substances ont été ré-analysés.

Le schéma ci-dessous synthétise les différentes étapes de sélection des substances pour lesquelles établir un score (« substances à scorer ») en vue de les hiérarchiser :

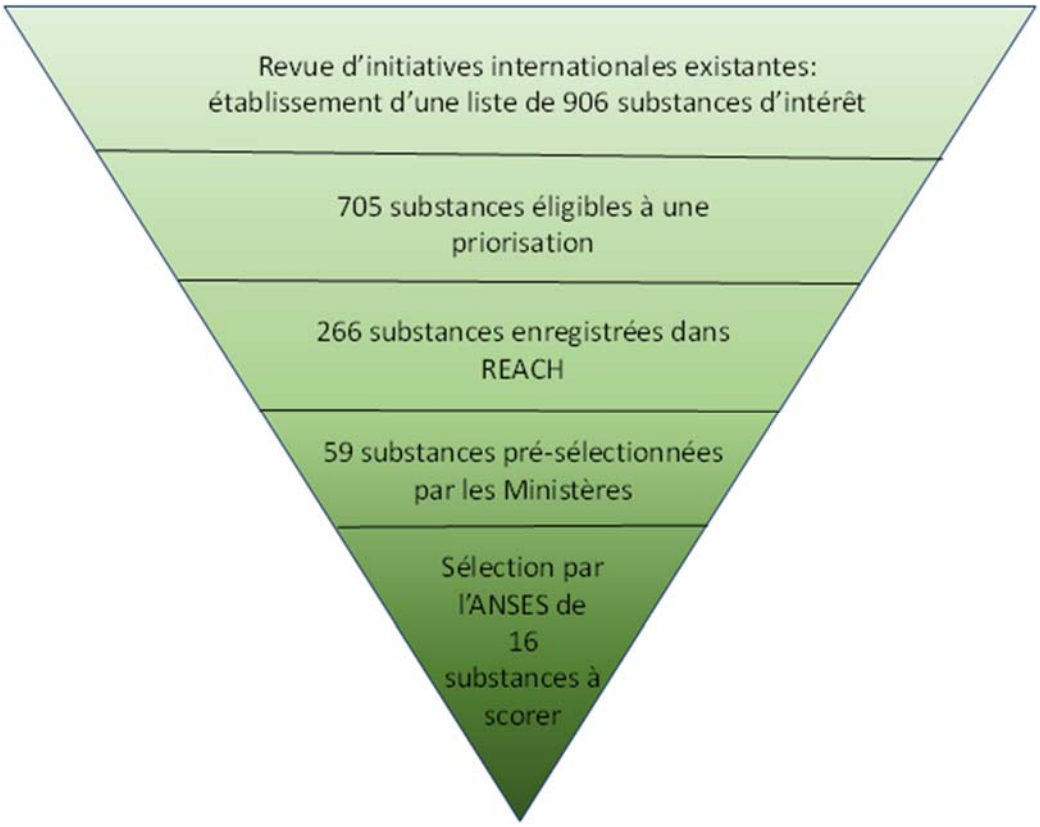

Figure 5 : Etapes de sélection des substances à scorer

L'Anses souligne que ces étapes successives ne constituent pas une expertise qui dédouane les substances non sélectionnées de leur appartenance à la liste d'intérêt. En cohérence avec l'attendu de l'action 3 de la SNPE 2, il s'agit d'une étape dans une démarche structurée pour préparer l'inscription au programme d'évaluation de l'agence. L'étape avant cette décision inclue une consultation des parties prenantes en vue d'élaborer une liste documentée de substances auxquels est associé un score composite détaillé ci-après.

Les 16 substances retenues feront l'objet d'une hiérarchisation, tenant compte de leurs dangers (représentés par le score HSc), des expositions (représentés par le score ESc) et du niveau de préoccupation sociétale qu'elles suscitent (représenté par le score SSc).

Le poids accordé à chacune de ces 3 catégories a fait l'objet d'une discussion avec le GT PE de l'Anses, aboutissant à retenir le poids suivant dans le calcul du score total :

- Danger (WiH) : 43% ;
- Expositions (WiE) : 43%
- Préoccupation sociétale (WiS) : 14%.

Ainsi, le score total qui déterminera le rang de chaque substance peut être calculé par l'équation suivante : HSc * WiH + ESc * WiE + SSc * WiS.

Le calcul des scores sera réalisé sur la base d'informations collectées par l'Anses, pour ce qui concerne les dangers et les expositions de ces 16 substances retenues. Le score de préoccupation sociétale pourra être défini par les parties prenantes de l'Anses assurant le suivi de la SNPE 2 (membres du comité thématique sur les PEs, l'« Inter-COT PE » se réunissant périodiquement), en votant pour les substances dont l'évaluation leur apparait comme prioritaire.

Les scores serviront à hiérarchiser les substances entre elles, pour permettre ensuite aux ministères de choisir les substances à évaluer prioritairement par l'ANSES.

La stratégie de priorisation vise ainsi à être transparente et durable, afin d'alimenter les travaux des agences pour les prochaines années. L'utilité et la faisabilité de fournir toutes les informations nécessaires pour établir les priorités d'action sont à considérer sur le long terme. La collecte des données pour chaque substance d'intérêt constitue à la fois une charge de travail et un défi, compte tenu de la disparité des informations selon les substances et des possibles contraintes d'accès ou de confidentialité. Par ailleurs, la littérature scientifique évolue constamment, nécessitant des mises à jour régulières des données sources.

L'utilisation d'outils informatiques capables d'analyser un grand nombre de données (« data mining ») sont désormais en mesure de collecter les résultats des tests expérimentaux qui ont été publiés dans des revues scientifiques. Ces nouveaux outils pourraient permettre de faciliter l'identification de substances candidates à l'évaluation de leur caractère PE dans les travaux futurs, sous réserve de disposer des moyens nécessaires.

4. CONCLUSIONS ET RECOMMANDATIONS DE L'AGENCE

Conformément à l'action n° 3 de cette stratégie, l'Anses a été mandatée pour identifier les substances chimiques susceptibles de présenter des propriétés PEs. Cette saisine avait pour objectif de partager une information transparente et exhaustive et de définir le programme de travail d'évaluation à réaliser en France : avec la saisine relative à l'élaboration d'une méthode d'évaluation du caractère PE conduisant à une catégorisation des substances, il s'agit de l'un des deux nouveaux outils méthodologiques attendus dans le cadre de la 2ème stratégie nationale sur les perturbateurs endocriniens (SNPE 2).

Selon la définition donnée par l'OMS, un perturbateur endocrinien est une substance qui altère la (les) fonction (s) du système endocrinien et provoque de ce fait des effets néfastes sur la santé. Le challenge de l'identification d'une liste de substances chimiques d'intérêt en raison de leur activité endocrine potentielle résidait dans l'identification de substances dont les données disponibles permettent d'envisager une évaluation au regard des trois points de la définition de l'OMS.

Sur la base de la revue des initiatives existantes listant des PE avérés, des PE potentiels ou des substances chimiques susceptibles de présenter des propriétés de perturbation endocrinienne et de l'analyse des forces et des faiblesses de chaque initiative, le groupe de travail de l'Anses sur les PE propose, dans le cadre de l'action 3 de la SNPE 2, de retenir l'initiative (DEDuCT 1.0 2019) qui s'est basée sur l'information scientifique au regard des critères de la définition OMS pour la sélection des substances d'intérêt. Néanmoins, seuls les composés susceptibles d'être pertinents pour l'Homme ou les rongeurs ont été répertoriés dans DEDuCT à travers l'identification d'études *in vitro* sur

cellules humaines et *in vivo* sur les rongeurs et chez l'Homme. Ainsi, la liste des composés identifiés est susceptible d'omettre l'identification de substances d'intérêt qui n'affecteraient que les espèces autres que les rongeurs ou l'Homme. Par conséquent, l'Anses souligne un besoin de mise à jour de la recherche documentaire pour inclure les composés montrant une activité endocrinienne et des effets sur toutes les espèces non prises en compte dans l'initiative sélectionnée.

En plus des 686 substances identifiées par DEDuCT, l'Anses a également retenu d'inclure dans la liste des substances d'intérêt celles présentes dans les produits réglementés formulés (biocides et produits phytopharmaceutiques) ayant une activité endocrine potentielle. 81 co-formulants d'intérêt au regard d'indications scientifiques sur leur activité endocrine ont été identifiés lors de l'évaluation des demandes d'AMM pour des produits biocides ou phytopharmaceutiques (dont 13 substances déjà identifiées par DEDuCT). En outre, il est proposé d'ajouter les 197 substances actives du PPPR ou du BPR classées dans les catégories I, II, III telle que définies dans l'option 3 de l'étude d'impact de 2016 de la Commission européenne. Ceci porte ainsi le nombre total de substances d'intérêt à 906 substances. L'intégralité de cette liste figure en annexe 5 du rapport ad *hoc*, support au présent avis qui comprend les substances d'intérêt pour leur activité endocrine identifiées à l'issue de cette expertise.

L'Anses souhaite insister sur le sens que revêt, pour une substance, le fait d'apparaître dans la liste des substances d'intérêt au titre d'une activité endocrine potentielle. Comme le met en évidence la définition de l'OMS/IPCS de 2012, la caractérisation du danger PE résulte de la concomitance de trois caractéristiques : l'action endocrine, la survenue d'effets sanitaires et un mécanisme biologique sous-jacent. La caractérisation, qu'elle soit partielle ou totale, d'une seule d'entre elle ne suffit pas à conclure qu'une substance est un PE. Aussi, l'Agence considère que seule une expertise approfondie des données disponibles sur ces trois points permet de conclure. Elle a d'ailleurs élaboré au titre de l'action 3 une méthode d'évaluation à cette fin.

Aussi, et dans un second temps, une stratégie de priorisation est nécessaire afin de sélectionner les candidats pour une évaluation approfondie de certaines de ces substances. En effet, pour mener un processus d'évaluation approfondi, il faut prendre en compte la disponibilité des données et des connaissances. La perturbation endocrinienne étant étudiée depuis peu par rapport à d'autres effets néfastes sur la santé, le manque de références dans les normes d'essais et, jusqu'à récemment, dans les exigences réglementaires, augmente la difficulté de rassembler des données pertinentes et donc de réaliser une évaluation concluante pour une substance donnée. Cette étape de priorisation vise à réduire la liste initiale de substances d'intérêt identifiées lors de la première phase de l'expertise. Les travaux de priorisation sont limités aux substances dont l'Anses pourrait être chargée, dans le cadre de son activité dans le champ des substances soumises au règlement REACH.

L'agence privilégie ainsi l'évaluation des substances chimiques ayant une quantité de données susceptible de lui permettre de l'examiner au regard de la définition OMS. Par ailleurs, les substances actives phytopharmaceutiques et biocides qui font l'objet de leur propre calendrier d'évaluation au niveau européen ne sont pas soumises à priorisation. En effet, le calendrier prédéfini d'évaluation des substances oblige les producteurs à fournir des données évaluant le caractère PE de leurs substances. A cet égard, l'Anses évaluera les substances actives pour lesquelles la France est l'État-membre rapporteur, et participera à la revue communautaire des autres substances actives. Par conséquent, malgré leur présence dans la liste d'intérêt, les substances correspondantes n'entrent pas dans le processus de hiérarchisation proposé. Un certain nombre de substances chimiques déjà règlementées a aussi été écarté.

Des critères pour une sélection plus poussée ont été proposés par les ministères chargés de la mise en œuvre de la SNPE 2, aboutissant à une liste restreinte de 59 substances.

Les substances ont fait l'objet d'une analyse pour tenir compte de leur statut réglementaire, leurs dangers, leurs usages et des possibilités d'exposition. Sur cette base, une liste de 16 substances candidates pour une évaluation de leur danger en tant que PE fera l'objet d'une consultation du

comité d'orientation thématique de l'Anses sur les perturbateurs endocriniens. A l'issue de cette consultation, l'application d' une méthode explicite de scores conduira l'Anses à recommander aux ministères chargés de la SNPE 2 les substances à inclure au programme de travail de l'agence pour les prochaines années.

Un retour d'expérience sera effectué à la fin du premier exercice, afin d'identifier les propositions d'amélioration. En particulier, devant l'importance du nombre de substances d'intérêt de la liste, l'Anses appelle à la mobilisation de ressources supplémentaires par des collaborations nationales et internationales (au moins au niveau européen) :

- Avec l'ECHA (propriétaire de la base de données d'enregistrement REACH et ayant l'expérience de l'application de méta-scénarios traitant un grand nombre de données). Les travaux de DEDuCT ayant classé les substances identifiées en fonction de leur structure chimique, celles-ci pourraient être comparés ou inclues dans l'approche holistique développée par l'ECHA pour cartographier l'univers des substances chimiques. Cela devrait permettre d'accélérer la gestion des perturbateurs endocriniens et de leurs substituts, enregistrés ou non, sur la base d'une évaluation comparative de leurs effets tenant compte de leur similarité de structure, tel que proposé dans le cadre des initiatives européennes en cours sur les groupes bisphénols et phtalates. En outre, la modification des annexes de REACH pour inclure des données permettant d'évaluer les propriétés PE des substances chimiques devrait améliorer la possibilité de travaux d'évaluation des substances au titre du danger PE ;

- Avec les États Membres travaillant sur des initiatives similaires ;

- Avec la Commission européenne qui a récemment réaffirmé des objectifs clairs concernant les perturbateurs endocriniens dans sa stratégie pour les produits chimiques, et avec le JRC (propriétaire de la base de données EASIS[10]).

Enfin, l'Anses recommande la poursuite de travaux afin d'étendre les résultats de l'initiative DEDuCT, 2019 afin d'identifier les substances susceptibles de présenter des effets néfastes en lien avec une activité endocrinienne sur tous les êtres vivants, sans limitation à l'espèce humaine en cohérence avec l'approche « One Health ».

Dr Roger GENET

[10] https://ec.europa.eu/jrc/en/scientific-tool/endocrine-active-substances-information-system-easis.

MOTS-CLES

Perturbateurs endocriniens, SNPE 2, identification, priorisation.

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CITATION SUGGEREE

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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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COMITÉ D'EXPERTS SPÉCIALISÉ

Les travaux, objets du présent rapport ont été suivis et adoptés par le CES suivant :

CES « Substances chimiques visées par les règlements REACH et CLP » ***(troisième mandature, du 1e septembre 2017 au 31 août 2020)***

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Elaboration of a list of substances of interest as regards to a potential endocrine activity and prioritisation strategy for assessment

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

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Key Words

Endocrine disruptors, perturbateurs endocriniens, exercice de priorisation, prioritisation strategy, exercice de priorisation de potentiels perturbateurs endocriniens, prioritisation strategy of endocrine disruptors

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.

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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).

EXPERTS PANEL "ENDOCRINE DISRUPTORS" (GT PERTURBATEURS ENDOCRINIENS) INVOLVED IN THE WORK PRESENTED IN CHAPTER 2 AND LATER MENTIONNED AS ANSES-WG-ED

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COMITÉ D'EXPERTS SPÉCIALISÉ REVIEWING CHAPTER 1, 2 AND 5

Les travaux, objets du présent rapport ont été soumis à la relecture du CES suivant : **«Substances chimiques visées par les règlements REACh et CLP » (2017-2020).**

COMITÉ D'EXPERTS SPÉCIALISÉ REVIEWING CHAPTER 3

La démarche décrite au chapitre 3 a été présentée au CES **« Substances et produits biocides » (2016-2019).**

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TABLE OF CONTENTS

Sigles et abréviations

BP : Biocidal Products
BPR : Biocidal Products Regulation
BPD : Biocidal Products Directive
CAS : Chemicals Abstracts Service
CCRIS : Chemical carcinogenesis research information system;
CLH : Classification and labelling
CMR : Carcinogenic, Mutagenic, and Reprotoxic
CoRAP : Community Rolling Action Plan
EADB : Estrogenic activity database
EASIS : Endocrine Active Substances Information System
EAT : Estrogen, Androgen and Thyroid
EC : European Commission
ECHA : European Chemicals Agency
ED: Endocrine Disruptor
EDC : Endocrine Disrupting Chemical
EDKB, established knowledge base for endocrine disrupting chemicals;
EDSP : Endocrine Disruptor Screening Program
eCA: evaluating Competent Authority
EFSA : European Food Safety Authority
EPA : Environmental Protection Agency
EU : European Union
ESc : exposure score
EXTEND : Extended Tasks on Endocrine Disruption
GENE-TOX : genetic toxicology data bank;
HSc: hazard score
HSDB : hazardous substances data bank;
HTML : hypertext markup language;
ICCM : International Conference on Chemicals Management
IOMC : Inter-Organization Program for the Sound Management of Chemicals
IPCP : International Panel on Chemical Pollution
IPCS : International Program on Chemical Safety
IRIS : integrated risk information system;
ITER : international toxicity estimates for risk;
JRC : Joint Research Center
MoA : Mode of action
MS : Member States
NGO : Non-Governmental Organization
OECD : Organization for Economic Co-operation and Development
PBT : Persistent, Bioaccumulative, and Toxic
PHP : PHP hypertext preprocessor;
POPs : persistent organic pollutant;
PPP: Plant Protection Products
PPPR: Plant Protection Regulation
REACH : Registration, Evaluation, Authorisation and Restriction of Chemicals
rMS : Rapporteur Member States
SAICM : Strategic Approach to International Chemicals Management
SIN : Substitute It Now
SMILES : Simplified molecular input line entry specification;
SNPE1: first national strategy on EDCs
SNPE2: second national strategy on EDCs
SPEED : Strategic Programs on Environmental Endocrine Disruptors
SVHC : Substance of Very High Concern
SSc: societal score

TEDX : The Endocrine Disruption Exchange
TOXNET : Toxicology data network.
UN – United Nations
UNEP : United Nations Environment (UN Environment) Program
US : United States
UV : Ultraviolet
vPvB : very Persistent and very Bioacummulative
WiH, WiE and WiS: weighting coefficients for Hazard, Exposure and Societal concern
WHO : World Health Organization
4-t-OP : 4-tert-Octylphenol

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1 Background and purpose of the request

1.1 Context

Endocrine Disruptor Chemicals (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 second national strategy on EDCs (SNPE 2), 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 including, as a first priority, "the creation of a list of potential EDCs of interest to be shared among EU member states (MSs) and the European Commission in 2020".

In the frame of the action number 3 of SNPE 2[1], 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 identify and prioritize "*chemicals that may present Endocrine Disruptor (ED) properties"* for building a list that is scientifically robust, resulting from an inventory of published lists at European and international levels. This list aims, firstly, at **informing on substances that may have potential endocrine properties regardless of their sectors of use and the sectorial regulations applicable,** thus warranting an in depth evaluation of the ED data available.

Indeed, in order to be identified as an EDC according to the European regulatory framework, the substance needs to fulfil the WHO-IPCS definition that includes the conjunction of the following elements:

- Adverse health effects;
- Endocrine mode of action (MoA);
- Biologically plausible causal link between adverse effects and endocrine MoA;
- Human or populational relevance of the finding of interest as the above mentioned are generally identified using toxicological or ecotoxicological models.

[1]https://www.ecologique-solidaire.gouv.fr/sites/default/files/SNPE%202%20english%20-%20Action%20plan.pdf

If the dataset on a substance allows to fulfil this definition, EDCs can be recognised and regulated in order to limit their uses and to reduce the exposure in different regulatory framework. Until now, three regulations have established provisions for evaluating EDCs within the EU (Michel, 2019):

1) Biocidal active substances are regulated by the European Regulation (EU) 528/2012.

2) Phytopharmaceutical active substances as regulated by the European regulation (EC) N° 1107/2009.

Both regulations include provisions with regard to endocrine disruption properties of the active substances. Criteria for identification of ED criteria have been established and formally adopted in dedicated European Regulations:

- The Commission Delegated Regulation (EU) 2017/2100 specifying the scientific criteria for the determination of endocrine-disrupting properties (ED criteria) under Regulation (EU) No 528/2012 (BPR)
- The Commission Regulation (EU) 2018/605 of 19 April 2018 amending Annex II to Regulation (EC) No 1107/2009 by setting out scientific criteria for the determination of endocrine disrupting properties
- A common guidance has been prepared and released by ECHA and EFSA (Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009) on the methodology for ED identification applicable for biocidal and phytopharmaceutical active substances.

3) The REACH Substances of Very High Concern (SVHC) are gathered in the Candidate List for Authorisation under the European Chemicals Regulation (REACH[2]). EDCs identification is based on article 57(f) of REACH. The first element needed to fulfil the criteria of article 57(f) of REACH is to demonstrate that the substance is an EDC based on the recommendations of the European Commission's Endocrine Disruptors Expert Advisory group that were agreed in 2013 (JRC, 2013). In addition, it has to be demonstrated that the ED property of the substance leads to a level of concern that is equivalent to CMR or PBT/ vPvB substances (ELOC).

Therefore, an in-depth evaluation of the existing data has to be performed on the substances before being able to conclude on the EDC status. However, all the substances of the list of interest are not deemed to be evaluated in details by Anses for at least two reasons: firstly, there is substances for which a calendar of evaluation is already scheduled. Secondly, evaluations of the same kind might have been performed by different agencies across Europe or under other regulations.

Contrarily to substances under biocide and pesticide regulation that have a defined calendar for evaluation, chemicals covered by REACH need to be proposed for evaluation. Therefore, a second aim of this list, is to prioritise some substances and assign them to ANSES work program, for assessment and categorization (this part will be described in an upcoming report). It might finally lead to regulatory actions, according to the results of the assessment process. As ANSES will carry on the evaluation of 6 to 9 substances per year, the list will be provided

[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.

to the other Member States to share the burden of evaluation and with ECHA to place this work in the ongoing approach consisting in mapping the chemical universe[3]. For practicality, all the European activities aiming at identifying EDCs, and whatever the sector of use are now available here: https://edlists.org/the-ed-lists (see 4.3 for further details).

After evaluation, if the data available of these substances added to the work program do not allow to fulfil this demanding definition, additional data can be requested if the substance is registered under REACH.

1.2 Handling the objectives of the request

Through the action 3 of SNPE 2, ANSES is mandated to **establish a list of substances to be assessed for their ED properties and a priorisation strategy** based in particular on a literature review and existing lists at the European and international levels. ANSES was requested to describe the methods used to build up these lists, identifying their strengths and weaknesses. The chapter 2 of this report therefore reviews publicly accessible initiatives produced by various stakeholders (academia, public bodies, industry, and non-governmental organizations) to identify known, potential EDCs or substances with endocrine activities, although the level of certainty or data used for such qualification is not always specified, regardless of their sector of uses and the sectoral regulations concerned: phytopharmaceutical, biocidal products, co-formulants in phytopharmaceutical and biocidal products, cosmetic products, medical devices and medicines and industrial chemical substances. In total, **27 initiatives have been identified and compared** to later select a methodology enabling to propose substances of interest as regards to a potential endocrine activity. At this stage, the proposed methodology aimed at **identifying accurate candidates for in-depth evaluation or additional monitoring**.

In parallel to the work described in chapter 2, the evaluation of regulated phytopharmaceutical and biocidal products (respectively called PPP and BP later in the report) performed by ANSES requires to identify substances having potential endocrine activity which are present in the products as co-formulants or active substances. How the co-formulants are identified as being of interest regarding their endocrine properties is described in chapter 3. As these substances are regulated within REACH regulation, they will be added to the substances of interest with regards to a potential endocrine activity identified in the chapter 2 in order to be prioritised for in depth assessment. In addition, as the methodology selected in chapter 2 is built on scientific literature, it fails at detecting as many active substances having endocrine activities as the screening performed at the European level during the impact assessment for ED definition, based on unpublished regulatory dossiers. Based on this observation, it is proposed to complement the list of substances of interest with regards to their endocrine activities issued from the methodologies proposed in chapters 2 and 3 with the active substances identified at the European level. The aim is to propose a list of substances as complete as possible, regardless of their sectors of use.

This list of 906 substance of interest with regards to a potential endocrine activity presented in annex 5 identifies accurate candidates for in depth evaluation or additional monitoring **and**

[3] https://echa.europa.eu/fr/-/mapping-the-chemical-universe-list-of-substances-by-regulatory-action-published

does not provide any kind of level of certainty of the ED properties of each substance. It contains substances, for which ED activity is more or less certain, including:

- In particular, known EDCs are substances that have been identified within a regulatory framework after an in depth evaluation.
- Potential suspected EDCs are substances that have been evaluated but not leading to a proper identification (either because no scientific assessment has been carried out or because the available data are not sufficient to conclude).
- Substances with endocrine activities are substances that have been identified by some initiatives but not further evaluated.

The “list of substances of interest with regards to a potential endocrine activity” may be used by other agencies as described in action 2 of the SNPE2 “in order to enhance the assessment of hazards and risks of potential EDs in cosmetics and health products (medicines for human use, medical devices etc.)” or in the context of action 15 to “clarify the relationship between exposure and impregnation”.

Moreover, it will also be used as a source among others to define the work programme of ANSES with an objective of 6-9 substances to evaluate per year regarding their endocrine activities. As part of the global prioritisation process, this list will be used for discussions with stakeholders (cf. actions 1 and 2 of SNPE2). ANSES was asked to propose a prioritisation method taking into account scientific criteria (e.g. true appearance or relevance of the intrinsic danger, use, exposure of the vulnerable population, etc.) in order to assign a priority score to the substances of interest. The task of prioritisation is described in chapter 4 for the substances identified under chapter 2 and 3.

Considering that ED assessment is already scheduled for phytopharmaceutical and biocidal active substances at European level therefore providing a schedule for data to be produced by the submitters in accordance with the corresponding regulation, and for these data to be assessed, they will not be included in the prioritisation strategy unless a detailed justification is provided (Point developed in point 4.2 hereafter). Coformulants that are dealt within REACH regulation, have no schedule for evaluation as described above and will be kept for prioritisation. Similarly, the known EDCs that are already regulated will be excluded for prioritisation, leaving only 705 out of the 906 substances of interest for prioritisation. Additional parameters such as the fact that the substance is registered under REACH in EU can also be considered. The first part of the chapter 4 describes the information reported in annex 5 that might be helpful for prioritisation. The second part of chapter 4 describes the proposed method for the prioritisation.

1.3 Means implemented and organization

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

The review presented in chapter 2 falls within the sphere of competence of the ANSES Working Group on "Endocrine disruptors" (ANSES-WG-ED) who 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 18 March 2019 to 27 March 2020. The chapter 2 of the report was adopted on 2 March 2020. 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)". The prioritisation work presented in chapter 4 also falls within the sphere of competence of the ANSES-WG-ED but the specific criteria have not been validated yet. The entire report has been presented to the CES REACH for information. In addition, the methodology enabling to screen the ED properties of biocidal products co-formulants and how they are dealt with has been presented to the CES “Substances et produits biocides” on the 23rd of May 2019.

ANSES analysed 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” portal.

2 From the strategies identifying substances of interest with regard to a potential endocrine activity to the methodology identifying potential endocrine disruptors

This chapter aims at compiling worldwide initiatives that identified substances of interest as regards to a potential endocrine activity for the human health and/or the environment. These initiatives were identified from public sources apart from scientific journals and individual studies submitted in a regulatory context. The Overview Report I called “Worldwide initiatives to identify endocrine disrupting chemicals (EDCs) and potential EDCs” provided by the International Panel on Chemical Pollution (IPCP) published by United Nations Environment Program (UNEP) in 2018 (**IPCP, 2018**) gave a rather exhaustive review of initiatives on EDCs and potential EDCs until March, 2017. This chapter therefore complete this review with other initiatives published since then and until September, 2019.

In total, 27 initiatives have been identified as presented in Table 1. These initiatives were qualitatively compared and grouped according to their scope, selection criteria, processes, and information included. It appeared that it was not possible to merge different initiatives together as they rely on too different basis. However, they were considered for building a list of substances of interest with regards to their potential endocrine activity for the human health and/or the environment in 2020. Based on this detailed analysis of the different initiatives and due to its specific strengths, the DEDuCT-2019 methodology was selected as a starting list by the experts, in particular because it has a robust selection process to identify potential EDCs (see chapter 2.3.1) rather than substances having endocrine activities only. The substances identified through this methodology are therefore fully qualified to fill the list of substances of interest, as requested in the first part of action 3 of SNPE 2.

2.1 Identification and comparison of existing international initiatives identifying EDCs, potential EDCs and substances of interest having endocrine properties

UNEP and WHO published an update of the IPCS (2002) document, entitled State of the Science of Endocrine Disrupting Chemicals, 2012 (**UNEP/WHO, 2013**). This report provides the global status of scientific knowledge on exposure to and effects of EDCs and potential EDCs with 175 listed substances. This report was then updated by IPCP in 2018 and compiled the “Worldwide initiatives to identify endocrine disrupting chemicals (EDCs) and potential EDCs”. It was used as a basis for the work presented below.

Governmental and non-governmental initiatives identifying EDCs or potential EDCs are summarized in the Table 1 and are briefly presented below in alphabetical order. Further details can be found in **Annex 4.** Databanks are presented afterwards.

Initiatives screening or assessing the endocrine disrupting properties of chemicals were mostly led by governmental organisms. These initiatives include screening programs for chemicals to be evaluated for their endocrine disrupting potential (e.g. EU agencies or regulatory bodies, US or Japanese governmental agencies) together with lists of substances fully assessed. Their main characteristics are captured in the Table 1 hereafter (alphabetical ranking). The literal presentation groups the list of similar type.

Table 1: Worldwide initiatives identifying endocrine active substances, potential or known EDCs with accessible lists (alphabetical order)

Initiative Name	Use of existing sources (brief summary)	Monitoring	Regulate	Evaluate	Generate data	Create list	Gather Publicatio	Gather Studies (also unpublished)	Create Database	latest update (as observed in dec 2019)	Nb of substances contained	Specific EDCs	Availl able online	Author or context
CORAP, 2019	Based on alerts from registration dossier or literature			x	x					Updated yearly	86		x	EU member states
Danish Center on ED, 2017	SIN list			x		x	x			2017	30			Danemark
DEDUCT, 2019	TEDX-2018 + EDCs Databank, 2015 + WHO-UNEP-2013 + Pubmed query			x		x	x			2019	686		x	Institute of Mathematical Sciences in Chennai
EASIS, 2020	"underdevelopment"					x				not available	513		(x)	EU-JRC
EC Priority List, 2003 Cat. 1 ED	Literature			x		x	x			May 2007	65		x	European first initiatives on EDCs
Cat. 2 ED	Literature					x	x				52		x	
Cat. 3 ED	Literature					x	x						x	
EDCs DataBank	EC-PrioList-2003 Cat. 1 &2 + TEDX 07-2014					x	x			2015	615		x	Carthagena University
ETUC, 2010 Cat. 1	EC-PriorityList Cat. 1					x					42	HPV	x	European Trade Union Confederation
Cat. 2	EC-PriorityList Cat. 2					x				Year 2010	29	HPV	x	
EU Impact Assesment, 2016	Active substances registration dossiers			x		x				2016	630			European
EXTEND 2010 and 2016	Based on environmental monitoring	x		x	x					June 2016	132			Japan
FDA-EADB-2019					x	x	x	x		16 May 2014	8212	Estrogenic	x	US-FDA
FDA-EDKB-2019					x	x	x	x		14 August 2019	>3200	Estro/Andro	x	US-FDA
Il EPA-1997						x				Year 1997				Illinois-FDA
IPCP, 2018	Summary of all exisiting initiatives			x		x				2018	45			WHO
KEMI-2017			x	(x)						Year 2017	37	Bisphenols		Sweden
Land and Water, 2014		x (water extracts)			x					April 2014	14	Estro/Andro and steroid H +		Australia
NIEHS-CTD, 2020							x		x	4 February, 2020	20		x	US-NIEHS
OurStolenFuture, 2016	Our Stolen Future book, 1996 from Theo Colborn					x	x		x	Regularly updated	86		x	Theo Colborn
PACT, 2019	Review regulatory activities on potential EDCs					x				Regularly updated	77		x	EU member states
PAN-2016	EC-PriorityList-2003 Cat. 1 or CMR Cat2					x				December 2016	52	Pesticide ingredients		NGO
RISCTOX, ISTAS, 2012	EC-PriorityList-2003 Cat. 1 & 2					x				July 2012	2281			EU Trade Union Initiative
Scorecard, 2011	Very rich (see annexes for further details)					x	x		x	unclear	310		x	NGO
SIN, 2019	EC priority list of chemicals & TEDX			x		x	x		x	12-sept-19	127 EDCs		x	NGO: Chemsec
SVHC, 2019	Full review of existing information		x	x		x				16-sept-19	16		x	EU REACH regulation
TEDX, 2019	Literature			x		x	x		x	sept-18	1482	(until Sept, 2022)	x	Theo Colborn then NGO
US-EPA-EDSP21-2017	ToxCastTM "ER Model" for bioactivity			x	x				x	3 February 2017	> 1800		x	US-EPA
US-EPA-EDSP21-2019	ToxCastTM "ER Model" for bioactivity				x				x	24 June 2019	9414		x	US-EPA
WHO/UNEP, 2013	Holistic summary						x			Year 2013	175			International organisation

2.1.1 Governmental initiatives:

2.1.1.1 European initiatives:

- Some of these initiatives are EU-based, including the European Commission (EC) Priority List of Chemicals (**EC Priority List, 2003**). This list encloses 564 chemicals being suspected EDCs by various organizations, or in published papers or reports. This work from the Commission included two phases, first an independent review of evidence of endocrine disrupting effects and human/wildlife exposure, and second a priority-setting exercise in consultations with stakeholders and the Commission Scientific Committees. Using expert opinion, information on the subset of chemicals identified by Step 2 as either persistent or HPV chemicals were reviewed to determine the strength of evidence for endocrine disruption. Chemicals were assigned to one of three categories depending on the data available to prove their ED properties:

  - Category 1 - evidence of endocrine disrupting activity in at least one species using intact animals;
  - Category 2 - at least some *in vitro* evidence of biological activity related to endocrine disruption;
  - Category 3 - no evidence of endocrine disrupting activity or no data available.

Category 1 and 2 lists have been used by numerous initiatives described hereafter. The latest update of this initiative is reported in 2007.

- Another exercise to identify EDCs took place in 2016. While evaluating the possibility of different options for the definition used to identify EDCs under the PPPR and BPR, an impact assessment of these different options on the number of potential EDCs was conducted (**EU Impact Assessment, 2016**).

The screening study resulted in a quantifiable estimation regarding how many and which chemical substances used in PPP and BP may be identified, after an in-depth evaluation, 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 ED mode of action.
- Category 2 substances as 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 identifying endocrine active substances with no *in vivo* evidence.

It was clearly mentioned that the results of the screening cannot be considered as the result of an evaluation process of individual substances to be carried out under the respective regulation.

- Finally, an Endocrine Active Substances Information System (EASIS) has been created by the Joint Research Center (JRC). Currently the system contains information for over 600 different chemicals on their potential to interact with the endocrine system. This information is derived from approximately 10,000 studies that cover both *in vitro* and *in vivo* assays in different species, including some human data. EASIS data is structured according to the OECD Harmonised Templates making it compatible with other international data collecting efforts. Unfortunately, the first version of the Endocrine Substances Information System (EASIS 1.0) has been discontinued and EASIS 2.0 is currently under development (**EASIS, 2020**).

- Since 2012 (first year of evaluation under the REACH regulation), ED properties can be evaluated for chemicals covered by the REACH regulation. When added to the European Union's Community Rolling Action Plan (EU-CoRAP[4]), additional data may be requested. **CoRAP, 2019** as defined in this report is the list of the 86 substances planned to be evaluated (extraction performed the 16th of September 2019) for an ED concern out of more than 350 substances put on CoRAP for other concerns. The evaluation leads to different conclusions: additional information are necessary to clarify the concern, the concern is clarified or lead to the proposal of EU-wide risk management measures such as restrictions, identification of substances of very high concern (the list of SVHC[5] identified based on ED properties are available under **SVHC, 2019**) or other actions outside the scope of REACH e.g. harmonised classification. All these activities are notified on the PACT. The PACT published here (**PACT, 2019,** extracted the 16th of September 2019) contains 77 substances out of the 137 substances on PACT on ECHA website at this date **see annex 7**). It provides information up-to-2019 on the activities planned, ongoing or completed by ECHA and/or MSs on ED assessment or ED identification of various substances.

- During 5 years (2012-2017), ECHA and Member State Competent Authorities have screened approximately 200-300 substances/ year to identify substances that may raise concerns among which ED properties for human health or the environment. These exercises have helped member states to identify potential EDCs. This initiative is neither mentioned nor developed further in the report as no list is available but was, in France, fully integrated in the first national strategy on EDCs (SNPE1) selection process.

2.1.1.2 National initiatives across Europe :

- The **Danish Center on Endocrine Disrupters, 2017** is an update of a previous work on endocrine disrupters. This work was based on the analysis of background lists and a master list which include several thousands of substances suspected to be EDCs. The amount of data for the substances being listed as suspected EDCs on various lists appears to vary considerably from no data found in published literature, over e.g. some MoA data (*in vitro*, QSAR) to comprehensive *in vivo* and MoA data. A prioritization step with regards to hazard scenarios, mode of action and risk for exposure was applied resulting in around 180 substances being placed on the prioritized basis list. A "literature ED hazard screening" step was conducted in order to select those suspected substances of highest relevance for ED assessment. A literature review of 52 of the prioritized substances showed that there was a lack of relevant mechanistic and/or adverse effect data for around 40-50% of the substances. Finally, the thorough evaluations of 13 of the prioritized suspected EDs selected based on the "literature ED hazard screening" step, concluded that 9 fulfil the WHO definition of an EDC,

4 https://echa.europa.eu/fr/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table.

5 https://echa.europa.eu/candidate-list-table.

whereas 4 are suspected EDCs. A re-evaluation of 17 substances previously evaluated as EDCs (Hass et al. 2012a, Hass et al. 2012b) confirmed that 10[6] substances fulfilled the WHO-definition of an EDC, while limitations in data precludes obtaining international agreement for the remaining 7[7] substances.

- Additionally, **the Swedish Chemicals Agency, KEMI** (Kemikalieinspektionen), published also a report in October 2017 indicating that 37 of 39 bisphenols surveyed on the European market may have potential endocrine disrupting properties. KEMI adopted a screening method which groups substances based on their chemical structure, possible use in different applications, and potential endocrine disrupting properties according to data simulations. The Swedish Chemicals Agency has identified over 200 substances with a chemical structure similar to BPA and which can occur on the European market (**KEMI (2017)** available at https://www.kemi.se/en/global/rapporter/2017/rapport-5-17-bisfenoler-en-kartlaggning-och-analys.pdf and KEMI personal communication).

2.1.1.3 The USA initiatives:

- The Illinois EPA elaborated a first endocrine disruptor strategy which includes numerous chemicals from families of substances such as phthalates and bisphenols (**Il-EPA, 1997**).

- The **NIEHS CTD, 2020** (NIEHS- Comparative Toxicogenomics Database) is a database which provides manually curated information about chemical - gene/protein interactions, chemical-disease and gene-disease relationships. Functional and pathway data are integrated to aid in development of hypotheses about the mechanisms underlying environmentally influenced diseases including endocrine disruption.

- The US Environmental Protection Agency (EPA) initiated the two-tiered Endocrine Disruptor Screening Program (EDSP) in focusing on pesticide active ingredients used in the US (**US-EPA EDSP, 2017**). It was developed through public consultation involving a number of task forces, committees, and advisory panels with representation from multiple sectors (federal agencies, chemical companies, and environmental and public health organizations) (**US-EPA, 2015**). Priorities were set based on examined exposure potential **(US-EPA, 2015**). EDSP results are available on the EPA's Endocrine Disruption website through a dynamic table of preliminary ER model scores from the EDSP Dashboard (**US-EPA EDSP21 2017**) which .includes estrogen bioactivity results from ER binding *in vitro* assay ranging from 0 to 1 and AUC (Agonist Area Under the Curve) for over 1800 chemicals. **US-EPA EDSP21, 2017** gives an index based on AUC for agonist or antagonist estrogenic properties (effects) ranging from 0 (no effect) to 1.06 (e.g. 17 alpha-estradiol) for agonistic and, from 0 to 0.686 (4-hydroxy-tamoxifen) for antagonistic ER bioactivity. In addition, US-EPA displays bioassay information, bioactivity concentrations, estrogen and androgen receptor (ER and AR) model results, predicted physicochemical properties, and more on an ad-hoc dashboard. Current chemical and bioassay data on 9414 chemical substances can be accessed (see: https://comptox.epa.gov/dashboard and https://www.epa.gov/chemical-research/toxicity-forecaster-toxcasttm-data), published ER (PMID 26272952) and AR (PMID 27933809) where model results are available for citation). Although this information is useful, it is difficult to set up criteria defining substances that should be considered endocrine active substances from

[6] 4-methylbenzylidene camphor, Butylparaben, Dicyclohexyl phthalate (DCHP), Dihexyl phthalate (DHP), Ethylhexyl methoxycinnamate (OMC), Metam natrium, Quadrosilan, Tert-butylhydroxyanisole, Tebuconazole, Triclosan

[7] 3- benzylidene camphor, Benzophenone-2, Methyl tertiary butyl ether (MTBE), Pentachlorophenol (PCP), Resorcinol, Zineb, Thiram

those that should not. In addition, an absence of response in estrogen receptor bioactivity testing does not preclude androgenic or steroidogenic activities in upcoming testing.

- The US Food and Drug Administration (FDA) federal agency created the Endocrine Disruptor Knowledge Base (**FDA EDKB, 2019**). Data for more than 3200 chemicals (including drugs, pesticides, industrial chemicals, consumer product chemicals, and new chemical entities) and 2000 relevant citations are available. The following resources are included in FDA-EDKB-2019: a biological activity database, QSAR (Quantitative Structure-Activity Relationship) training sets, in vitro and in vivo experimental data for more than 3000 chemicals, literature citations and chemical-structure search capabilities. Among the experimental data included in FDA-EDKB-2019, Estrogen Receptor (ER) and Androgen Receptor (AR) training *in vitro* datasets together with *in vivo* assays (e.g. uterotrophic assay) are included. The estrogenic activity database (**FDA-EADB, 2019**) includes results from binding assays (ER subtypes and ER protein domains (full-length or ligand-binding domain)), reporter gene assays and cell proliferation assays and *in vivo* assays for 8212 chemicals tested in 1284 binding assays, reporter-gene assays, cell-proliferation assays, and *in-vivo* assays in different species. The relational database provides chemical structure search, boolean searches on EDs, graphical and table displays, as well other capabilities and data export functions (**FDA EDKB, 2019**).

2.1.1.4 Other national initiatives:

- **In Japan, the Ministry of the Environment** (formerly the Environment Agency) published "The Environment Agency's Basic Policy on Environmental Endocrine Disruptors – Strategic Programs on Environmental Endocrine Disruptors: SPEED'98" in May 1998. Therein, 67 chemicals (revised to 65 chemicals in November 2000) were identified as those having the highest priority in the survey and research in order to clarify the occurrence, the strength, and the mechanisms of ED effects. In the following program named "Extended Tasks on Endocrine Disruption" (**EXTEND, 2010**), the aims were to further develop test method, to select and to assess test chemicals based on their detection in the Japanese environment and the evaluation of related information and knowledge on ED effects. Through reliability evaluation of existing knowledge, 132 substances candidate for environmental risk assessment were identified **(EXTEND, 2010**). Reliability evaluation was completed for 122 of them, judging 85 as "Chemicals that can be subjected to tests for endocrine effects". The scheduled testing program is reported in the **EXTEND, 2016** for the *in-vitro* and *in-vivo* tests. However, results generated by this program are not available yet.

- An initiative was led by Australia (**Land and Water, 2014**). In this study, 73 river sites across mainland Australia were sampled quarterly for one year. Concentrations of 14 known endocrine active substances including natural and synthetic hormones (estrone, 17α-Ethinylestradiol, androstenedione) and industrial compounds (Bisphenol A and 4-tert-Octylphenol (4-t-OP)) were quantified by chemical analysis. Anti-estrogenic, progestagenic and androgenic activities were not detected in any samples whereas 19% of samples displayed an estrogenic activity and 16% an antiprogestagenic activity.

2.1.2 Non-governmental initiatives (presented by alphabetical order):

- A databank on Endocrine Disrupting Chemicals and their Toxicity Profiles named **DEDuCT**, **2019** has been built by The Institute of Mathematical Sciences in Chennai (India) (Karthikeyan et al., 2019). DEDuCT is based on an analysis of existing scientific literature containing supporting experimental evidence for endocrine-specific perturbations in humans or rodents (see below for further details). It also uses different existing initiatives (UNEP/WHO 2013 and 2 initiatives described below: EDC Databank and TEDX).

- The Colombian University of Cartagena developed a databank named **EDCs Databank, 2015** that is accessible online (http://edcs.unicartagena.edu.co). This databank is built on MySQL using the EU Priority list, 2003 of potential endocrine disruptors and TEDX (see below for further details) dataset. It contains also the three-dimensional chemical structures available on PubChem, as well as a wide variety of information from different databases such as TOXNET, ACToR, Fable, PubMed and several text-mining tools described in Montes-Grajales and Olivero-Verbel, 2015. This EDCs DataBank hosts 615 molecules, including pesticides, natural and industrial products, cosmetics, drugs and food additives, along with other xenobiotics.

- The **European Trade Union Confederation** prioritized chemical substances based on an overall score including previous categorization (Cat.1 or Cat.2) on the EC Priority List, high production volume (HPV), a known use and not already banned by other means, not a residue or intermediate, not only used as a pesticide or biocide, and not a complex hydrocarbon distillate (**ETUC, 2010**). In total, ETUC considered 70 substances as priority substances for their ED properties.

- The **Pesticide Action Network (PAN)** International List of highly hazardous pesticides provides a basis for action to implement the progressive ban of highly hazardous pesticides and replace them with safer, agro-ecological and other appropriate non-chemical alternatives. Pesticide ingredients fulfilling one of the following criteria: i). those that have been categorized in the EU Commission's priority list as Cat.1 (at least one study providing evidence of endocrine disruption in an intact organism) or ii) those that have been classified Cat. 2, including CMR compounds. Fifty-two pesticides are included in the **PAN, 2016.**

- ISTAS developed a database commissioned by the European Trade Union Institute (ETUI). This database named **RISCTOX, ISTAS, 2012** contains 2,281 substances categorized based on their previous inclusion within other initiatives such as the EC Priority List, 2003 and Scorecard, 2011. This database is not anymore updated.

- The **SIN List by ChemSec**, abbreviation for Substitute It Now" consists of hazardous chemicals that are used in a wide variety products and manufacturing processes. This initiative aims at facilitating chemicals management and at identifying and substituting hazardous chemicals with safer alternatives. A database is available on line. It includes 127 chemicals indexed as EDCs among the overall 991 chemicals referenced in SIN, 2019. In order to be included in this list, the chemical substance has to fulfil the following selection criteria:

  - Chemical listed as category 1 or 2 on the EC priority list, 2003 or included in scientific papers, reports, priority lists from authorities and from organisations,
  - Have known uses relevant to EU REACH and not used only as intermediates,
  - Have peer-reviewed, high quality, relevant, primary research literature showing an endocrine mode of action, a probable serious effect and a plausible link between the two (ChemSec 2020) as recommended in the WHO/IPCS definition.

Lastly, the data are reviewed by external EDC experts following the REACH guidance document (**SIN, 2019**).

- Following the eponym book in 1996 written by Theo Colborn (also founder of TEDX), a website named **Our Stolen Future** was developed where information on Widespread Pollutants with endocrine-disrupting effects is made available (**OurStolenFuture, 2016**). At least one scientific publication is linked to each of the 86 chemicals included in this website.

- Scorecard, 2011 published also a list of Suspected Endocrine Toxicants (310 substances). Each chemical is linked to a reference source that is either a journal article or a report from a governmental agency or a non-governmental organization (NGO). For further details on this initiative, please refer to **Annex 4**.

- The Endocrine Disruption Exchange usually called TEDX list (**TEDX, 2019**) aimed at producing and sharing scientific evidence on endocrine disruption. TEDX published scientific reviews in collaboration with other scientists, commentaries, and original researches. Their website was regularly updated until July, 2019 and will remain available until September, 2022. A list of Potential EDCs (i.e. acknowledged endocrine active substances from TEDX) is available online which includes 1482 substances for which effects on the endocrine system are reported in at least one peer-reviewed study published.

2.2 Difficulties encountered in combining and comparing the different sources

Significant resources are being invested worldwide into identifying EDCs, potential EDCs, or substances of interest regarding their potential to have endocrine activity and have been listed above. The context and scope are different between these initiatives rendering their aggregation difficult:

2.2.1 Source of chemicals considered

The pool of chemicals considered in these initiatives varies from thousands of chemical substances (e.g. US initiatives **FDA EDKB, 2019**, **FDA-EADB, 2019, US-EPA- EDSP 21 Dashboard 2017 and 2019**) to several tens of substances (e.g. **SVHC, 2019**).

- Some of these initiatives selected and assessed chemicals based on their detection in the environment (e.g. **Land and Water, 2014** and **EXTEND, 2010 and 2016**).

- Some of these programs did not distinguish human health and environmental data sources when other had specific selection criterion (**DEDuCT, 2019**).

- Some of these initiatives considered chemicals from an almost unrestricted pool of all existing chemicals (e.g. the **EC Priority List, 2003** and **TEDX, 2019**). Whereas others limited their scopes to some chemicals, depending on their uses and subsequent regulations in EU (e.g. **SVHC, 2019, CORAP, 2019** and **PACT, 2019** for chemicals regulated by REACH regulation, **PAN, 2016** for pesticides, **ETUC, 2010** for HPV chemicals, **EU Impact Assessment, 2016**).

- Some initiatives build their list from scientific literature while others consider chemicals already included within one or more former initiatives. The EC Priority List in particular has served as the starting point for a number of other initiatives reviewed within this report.

- Lastly, naming of and reference to chemicals included across the initiatives is not always consistent. Some chemicals are referred to PubChem identification numbers and others to Chemicals Abstracts Service (CAS) numbers. Initiatives do not always specify all the CAS numbers that may be applicable to an intended chemical or group of chemicals (see. **IEPA, 1997**) or are unknown (see **US-EPA, EDSP 21 2019)**. This can lead to inaccurate comparison of chemicals across these different initiatives.

2.2.2 Objectives of the initiatives and their consequences

The objectives of these initiatives may differ from each other; some of them intended to:

- Screen chemical substances for their potential endocrine activity (e.g. **FDA EDKB-2019, FDA EADB-2019, US-EPA- EDSP 21 Dashboard 2017** or **EPA- EDSP 21 Dashboard 2019**, **EXTEND** program).
- Consolidate existing knowledge in relation to EDCs (e.g. **CoRAP, 2019**).

- Consolidate existing knowledge in relation to specific mechanisms. Most of the screening initiatives or the programs in relation to EDC were primarily focused on the estrogen, androgen (**FDA EDKB-2019, FDA EADB-2019)** and thyroid hormone pathways and steroidogenesis (EATS pathways for the **US-EPA- EDSP**).
- Highlight EDCs or potential EDCs (e.g. **SIN, 2019, DEDuCT, 2019, TEDX, 2019**…).
- Build a common understanding on known EDCs in the European regulatory field (**SVHC, 2019**).

As a consequence, the approaches taken by these initiatives to screen or evaluate chemicals differ from one another. For example, the European Commission's impact assessment is strictly on the screening level, whereas the US EPA's screening program involves a two-tier experimental testing to establish quantitative dose-response relationships, thus producing data. The intended outcomes of these initiatives may differ from another. The evaluations completed within the CoRAP, 2019 often lead to further testing or regulation of a chemical, including listing the REACH regulated substance as SVHC on the candidate List for authorisation. The US EDSP aims at screening chemicals in a large number of chemical substances in order to identify any interaction with the endocrine system, to further characterize dose-effect relationships, and to use the resulting information to support risk assessments and risk management decisions. In contrast, the **EXTEND, 2010 and 2016** programs of the Ministry of the Environment, Government of Japan promote testing and assessment to identify target compounds for regulatory environmental risk assessment whereas the EU's Impact Assessment was specifically developed to understand what types of socio-economic impacts implementation of different EDC identification criteria might have. The target compounds for review are also set (or prioritized) differently depending on an agency's focus or legal mandate as discussed above. The timelines for the review processes also vary.

2.2.3 Building process

• Some initiatives explain and communicate the sets of selection criteria for including chemicals on the initiative's website. The process used to assess the existing scientific evidence is also explained in some initiatives more than in others. In DEDuCT, the entire process and all the criteria are transparent and accessible.

• The extent of scientific evidence included in the assessment varies between initiatives. Some lists are very inclusive, relying mostly on *in vitro* hormone receptor assay results (e.g. **TEDX, 2019).** This leads to large lists of endocrine active substances when considering the WHO/ EU definition. Others are built with higher level of evaluation and stronger selection criteria for the identification of EDCs such as availability of appropriate *in vivo* assays (e.g. the EC Priority List of Chemicals).

• Similarly, the experimental testing used to screen or assess the ED properties of a large number of chemical substances is different from an initiative to another. This ranges from *in vitro* binding, reporter-gene, cell-proliferation assays on numerous substances as well as some *in vivo* assays in different species (e.g. **EXTEND 2010** and 2016, **FDA EDKB-2019**, **FDA EADB-2019**, **US-EPA- EDSP 21 2017** and 2019, **TEDX, 2019**) to focus on *in vivo* experimental testing (e.g**. CoRAP, 2019** or **EXTEND 2016**).

• In addition, some initiatives allow(ed) contradictory assessment. Multi-stakeholder consultation (through government, regulatory body, industry and/or NGO) occur(ed) during the development of some of the initiatives (such as the US-EDSP or the European Union's chemicals regulation (REACH) SVHC program) in particular for those that have direct regulatory impacts.

• Finally, some of these lists such as the **SVHC, 2019**, **US-EPA- EDSP 21** and **SIN, 2019** are continuously updated while other are now frozen (e.g. **TEDX, 2018**).

Therefore, among all these initiatives, almost 2,000 chemicals have been identified as substances of interest as regards to a potential endocrine activity. Some chemicals are present in several initiatives, whereas some others may be included in one list only (cf. Figure 6). However, it is difficult to build a list by comparing these initiatives as they differ in many different ways. Our conclusions are aligned with the general observations made by IPCP in their report comparing the initiatives they had listed (IPCP, 2018 see also Annex 4):

- Substantial resources have been and are being invested into identifying EDCs, as reflected by the number and diversity of the initiatives found.

- The intended purpose of individual initiatives as well as the criteria used to identify (or include) chemicals as EDCs or potential EDCs vary considerably.

- Some initiatives have already been heavily developed and publicized, whereas others are planned or currently in earlier development stages.

2.3 *Choice of the methodology for listing the substances of interest*

As written above, based on the detailed analysis performed by the experts of the different initiatives, the DEDuCT-2019 methodology was selected as a starting list of substances of interest regarding their potential endocrine activity. The DEDuCT-2019 list is therefore described in more details in this chapter

2.3.1 . More information on DEDuCT

DEDuCT methodology was published in a peer-reviewed scientific journal in 2019 (Karthikeyan et al., 2019) and all the dataset is fully accessible on the web: . Its methodology is based on an analysis of existing scientific literature data containing experimental evidence on endocrine-specific perturbations in humans or rodents. A detailed workflow was developed (see Figure 1) to identify potential EDCs from published research articles.

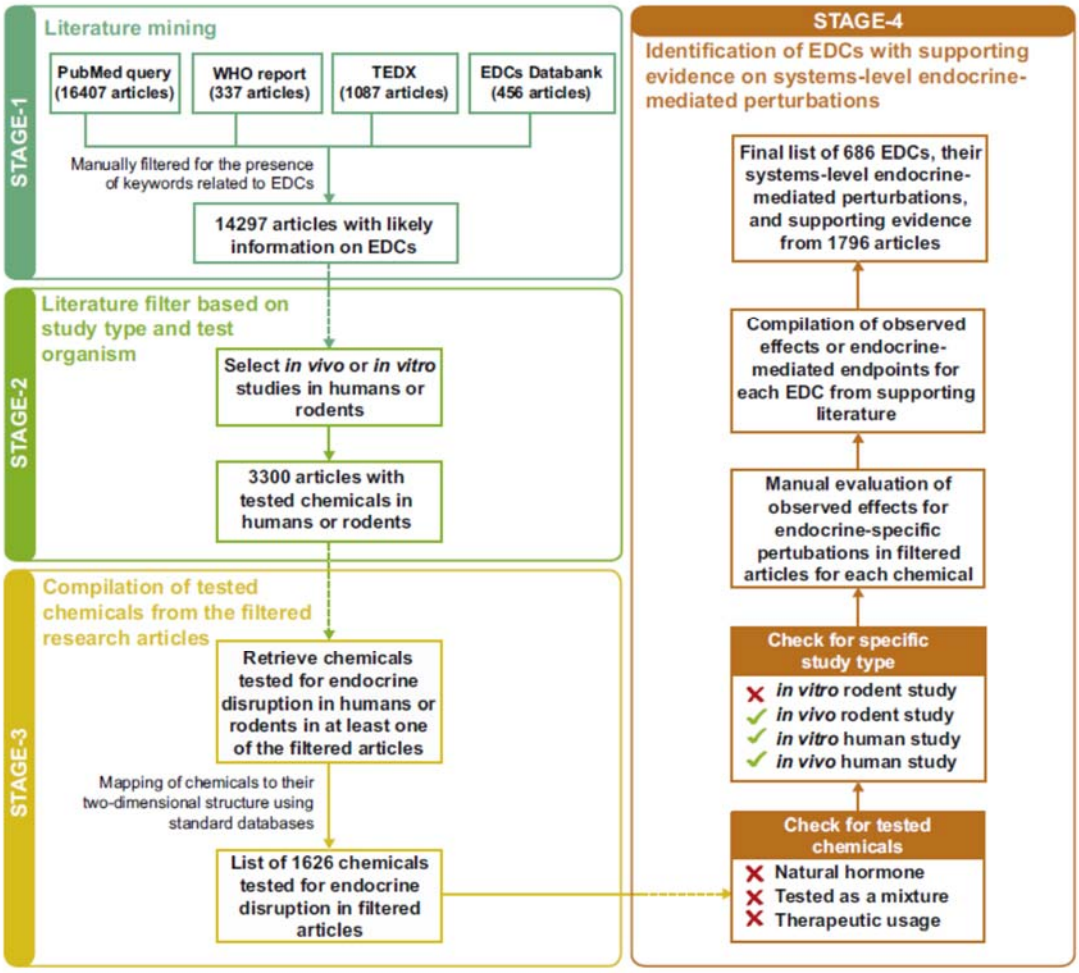

Figure 1: Detailed workflow with four stages to identify potential EDCs from published research articles containing supporting experimental evidence of systems-level endocrine-mediated quoted from Karthikeyan et al., 2019

The DEDuCT database was constructed based on an extensive PubMed literature review using a specific set of EDC related keywords. This search was run in February 2018 to compile articles which were likely to contain information on EDCs. They have also strengthened their tool by adding scientific publications related to their topic of interest by taking them from three

existing initiatives the **UNEP/WHO, 2013**, **TEDX, 2018** and **EDCs Databank, 2015** (see above for further details). More than 16,000 published research articles were scrutinized. Among this pool of articles, 14297 articles were related to EDCs topic. A large number of articles (3300) was related to chemicals tested in humans (*in vitro* or *in vivo* i.e. epidemiological data when linked with ED indications) or in rodents. These publications dealt with 1,626 chemical agents. Then, some exclusion criteria were applied, namely for natural hormones (while analysing the publication, it seems to us that it is more the native hormones that have been excluded), agents tested as a mixture and agents tested for therapeutic relevance (i.e. experiment conducted to test therapeutic use) as well as agents for which only data from *in vitro* testing on rodent systems were available since the authors considered that the observed effects in an *in vitro* rodent system do not adequately reflect the complexities observed in humans. Karthikeyan et al., 2019 also excluded published studies where receptor - binding assays, or *in silico* methods were solely employed to infer the potential endocrine disruption of a chemical. Lastly, they excluded human epidemiological studies when they did not contain sufficient mechanistic evidence to link the observed adverse effects to potential endocrine disruption upon chemical exposure (Bliatka et al., 2017; Hernandez and Tsatsakis, 2017). Overall, they ended up with 1796 publications identifying 686 potential EDCs. For each chemical which passed the above-mentioned criteria, the authors next evaluated the level of supporting evidence for endocrine disruption in humans or rodents upon exposure based on published experiments contained in the filtered research articles. For this evaluation, they manually compiled the observed effects upon exposure of each chemical in associated published experiments in humans or rodents. A published experiment in humans or rodents was considered as strong supporting evidence for endocrine disruption by a chemical if the chemical upon exposure leads to observed effects or endpoints related to endocrine-specific perturbations such as changes in morphology, physiology, growth, reproduction, development and lifespan (WHO/UNEP, 2013). Thereafter, if a chemical had at least one published experiment with strong supporting evidence for endocrine disruption upon exposure, then it was identified as a potential EDC.

For a given substance, the database can be searched through three different sets of criteria:

1- In DEDuCT, the identified substances were classified in different categories that differ from those described above in paragraph 2.1.1.1:

- Category I substances are those for which effects were observed in humans (7 substances identified: Perchlorate compounds, Ibuprofen, Paraquat (1,1'-dimethyl-4,4'-bipyridinium), Diethylstilbestrol, Crizotinib (CAS 877399-52-5), Detirelix (dichlormezanone), and 1,2-dibromo-3-chloropropane). This category could correspond, after evaluation of the quality and relevance of the available information to known EDCs in humans.

- Category II substances are those for which e ffects were observed *in vivo* in rodents and *in vitro* in experiments with using human cells but not from *in vivo* human experiments (142 substances). Based on this description, it can be assumed that these substances should fulfill the WHO/IPCS definition. This would be confirmed after evaluation of the quality and relevance of the available information.

- Category III substances when their effects were observed solely *in vivo* in rodents (367 substances identified), here, data on mode of action might be missing.

- Category IV substances when their effects were observed *in vitro* using human cells only (170 substances identified).Here, *in vivo* data showing adverse effects might be missing to fulfil the definition.

2- The database can be searched through criteria of effect categories. Seven general effect categories linked to the endocrine system were determined: reproduction, development, metabolism, the hepatic system, immunology and neurology, and, endocrine-dependent cancers (see Figure 2). For each of these categories, the database can be used to verify if

specific effects have already been identified in the scientific literature regarding particular substances.

3- A third possible research approach concerns the sectors of use and detection of the substances: consumer products, agriculture, industry, medicine and healthcare, pollutants, natural sources, and intermediate inputs in production processes.

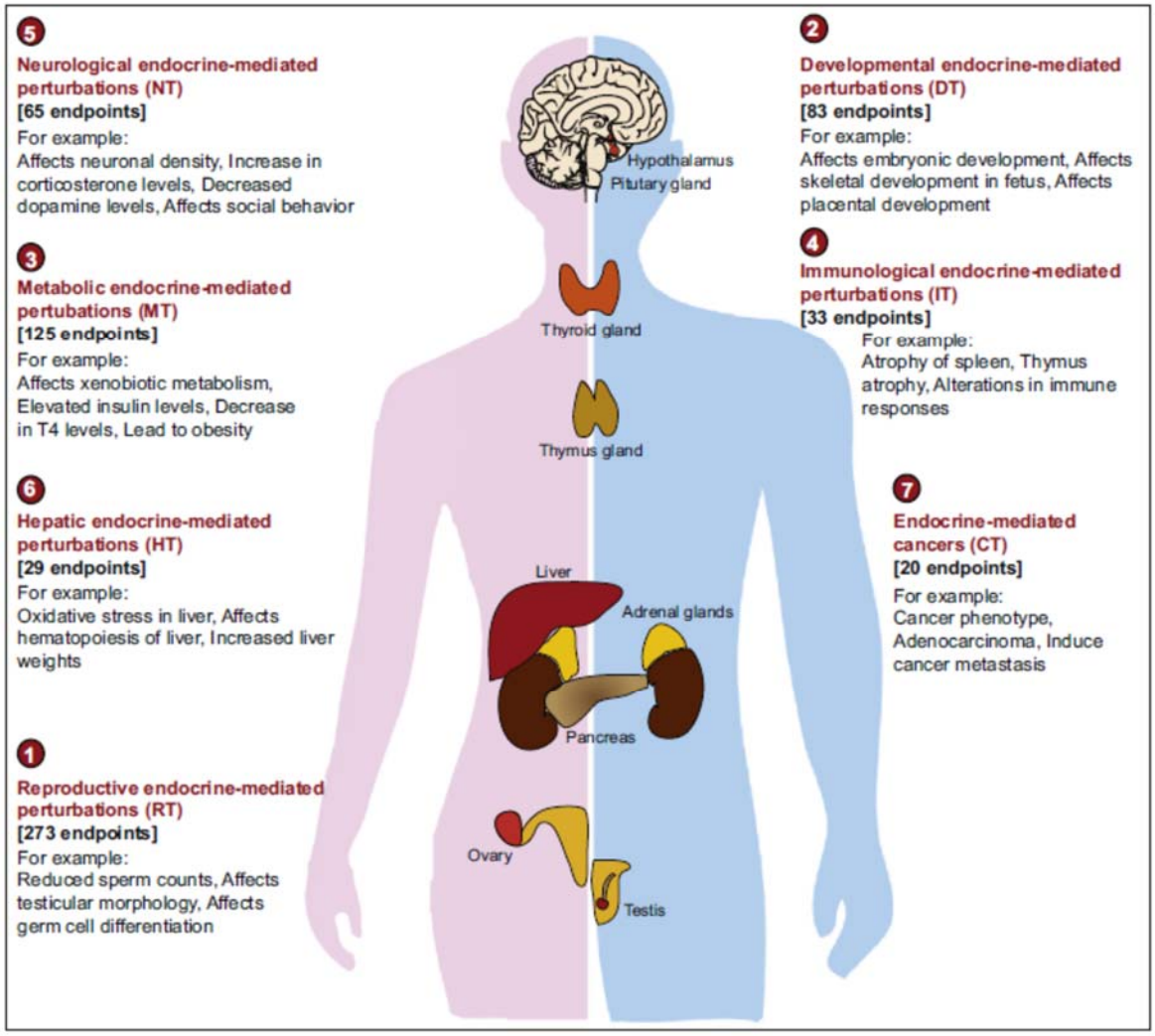

Figure 2: Schematic figure depicting the classification of the 514 endocrine-mediated endpoints into 7 systems-level perturbations quoted from Karthikeyan et al, 2019

2.3.2 Strengths

Among the different approaches reviewed in this report, the methodology followed in **DEDuCT, 2019** (Analysis of more than 16,000 published research articles to identify 686 potential EDCs with supporting evidence of endocrine disruption in published experiments in humans or rodents) presents main advantages:

- Their methodology is transparent and well-described, including a first step of literature mining conducted as recommended by various international bodies. All available relevant information was collected using a systematic review methodology performed on PubMed. It was conducted using terms associating "endocrine" and "disruption" (or related variants) indicating that the

scientists who carried out the studies were associating downstream biological effects to their endocrine system.

- The publications retrieved using the DEDuCT methodology have been manually checked by the authors themselves in order to ensure that the identified keywords are indeed corresponding to effects related to endocrine systems.

- The authors agreed to share with ANSES their raw data to ensure a faster evaluation process and a transparent assessment (see below).

- Moreover other recent initiatives (**UNEP/WHO, 2013, EDCs Databank, 2015** and **TEDX, 2018)** were included.

- Compounds identified from the publications were selected on the basis of observed effects on endocrine-specific perturbations as defined by the WHO definition. Therefore, the substances being kept are those that showed both endocrine activity and effects by assessing the functional significance of observed alterations of endocrine functions upon exposure in published experiments in humans or rodents. The list proposed by DEDuCT is therefore close to the regulatory definition of EDCs adopted by the European Union (and in line with that of **UNEP/WHO, 2013**).

- Publications and subsequent substances are included whatever their uses. For example, active biocides and pesticides are included.

- Lastly, DEDuCT, 2019 is a recent publication that ensures an updated list compared to the other initiatives on EDCs.

2.3.3 Limits

- DEDuCT was based on literature review and did not access regulatory dossiers.

-The use of the filters as proposed by DEDuCT, 2019 exclude 940 substances according to Figure 1 (1626 substances down to 686). It clearly limits the overlaps with other databases (see Figure 3). Some filters used in DEDuCT may not be relevant while considering certain follow-ups for which we conduct this review (ex SVHC identification). For example, some substances have been excluded because they have therapeutic relevance, ignoring that other uses could also exist that enter into the scope of SVHC identification. How many substances and which substances have been excluded by each filter is not available neither in the paper nor on the website.

- It should be noted that this list of 686 identified compounds have been selected based on *in vitro* studies on human tissues and *in vivo* studies in humans and rodents. Therefore, they are likely to be relevant for humans or rodents only. The list might miss compounds being EDCs for non-mammalian species. ANSES-WG-ED recommends that the literature search must be updated to include compounds showing endocrine activity and effects on wildlife species (to possibly identify EDCs for environment) without restriction.

- Substances with few data have been excluded with the filters applied by DEDuCT potentially limiting the use of the list for further evaluation (CoRAP). Indeed, based on the method described by DEDuCT, *in vitro* alone dataset have been excluded: *in silico* and binding results that "do not provide sufficient information on whether chemical exposure can actually lead to adverse effects due to endocrine disruption" and epidemiological studies "which are not likely to reveal biological mechanism". Only those substances having experimental data showing effects related to endocrine-specific perturbations have been kept in the list.

2.4 Challenging DEDuCT: comparison performed and outcomes

This paragraph aims at understanding the impact of the filters used in DEDuCT, 2019. It is also important to evaluate if DEDuCT, 2019 manage to identify substances that have not been identified as potential EDCs up to now. Finally, checking how DEDuCT was efficient in detecting known EDCs was also helpful to determine the robustness of the methodology.

2.4.1 Impact of the filters used in DEDuCT, 2019

Figure 3: Quoted from (Karthikeyan *et al.*, 2019) itself: Comparison of the 686 EDCs in DEDuCT, 2019 with those in UNEP/WHO, 2013, TEDX, 2018 and EDCs Databank, 2015.

From the Venn diagram (quoted in DEDuCT, 2019), it is seen that 198 EDCs in DEDuCT are new compared to the other sources.

- The criteria set up for building the DEDuCT database (**DEDuCT, 2019**) have excluded substances belonging to **UNEP/WHO, 2013** (58 substances excluded i.e. 31%), **TEDX, 2018** (960 substances excluded i.e. 67%) and **EDCs DataBank, 2015** (350 substances excluded i.e. 57%) and 265 substances are kept from the 615 initial substances from the EDC databank) (see **Figure 3**). This is depicted by the **Figure 3** produced by the authors of DEDuCT, 2019 themselves.

To dig into more details on the influence of the filters, the substances listed in **DEDuCT, 2019** were compared with those categorized in the **EC Priority List, 2003**, which have been included in the data considered by DEDuCT through the EDCs Databank. Two substances proposed as Cat.1 in EC Priority List, 2003 were not present in the final list proposed by DEDuCT. Resorcinol (CAS number 108-46-3) and the mixture Arochlor 1260 (ClophenA60 - CAS number 11096-82-5). The absence of the latter is easily understandable, as one of the first filters applied in the DEDuCT list was to omit the mixtures. On the other hand, the absence of resorcinol, although many metabolites are present in the DEDuCT list, is more questionable. Its absence is probably due to the exclusion of molecules for therapeutic use, (another filter used), which is one of the historical uses of resorcinol. However, those days, resorcinol is used for other purposes and it might be necessary to adapt the filters applied in order to still list the molecules used in multiple categories.

Therefore, the filters proposed allow the capture of chemical substances with human or rodent *in-vivo study* and *in-vitro* study mediated endocrine effects at the exclusion of *in-vitro* rodent study. While reducing the database to a lower number of potential EDCs, these filters allow the capture of substances with a minimum acceptable dataset (see below). However, they might also exclude some substances of interest.

2.4.2 Capacity of DEDuCT, 2019 in detecting new potential EDCs

Figures 4, 5 and 6 describe how **DEDuCT, 2019** overlap with other initiatives. They show that no initiative fully overlap any other. It also shows that DEDuCT, 2019 is the one proposing the most important number of new potential EDCs compared to the other initiatives.

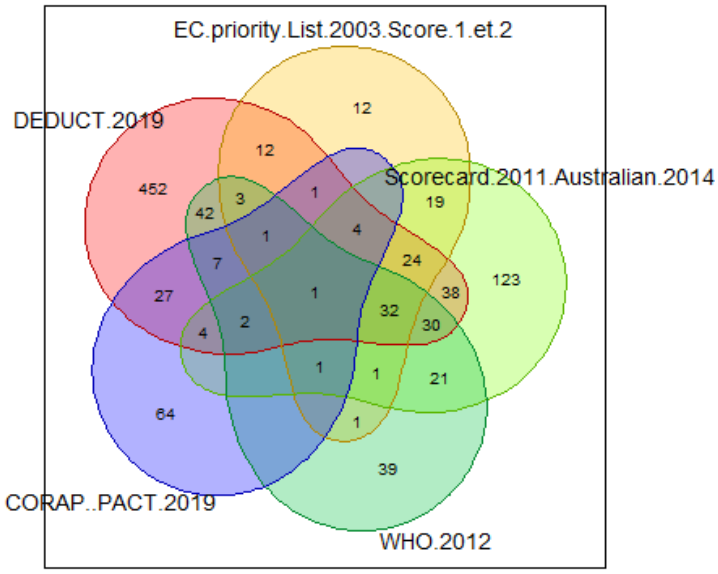

Figure 4: Venn diagram comparing EDCs identified in several initiatives

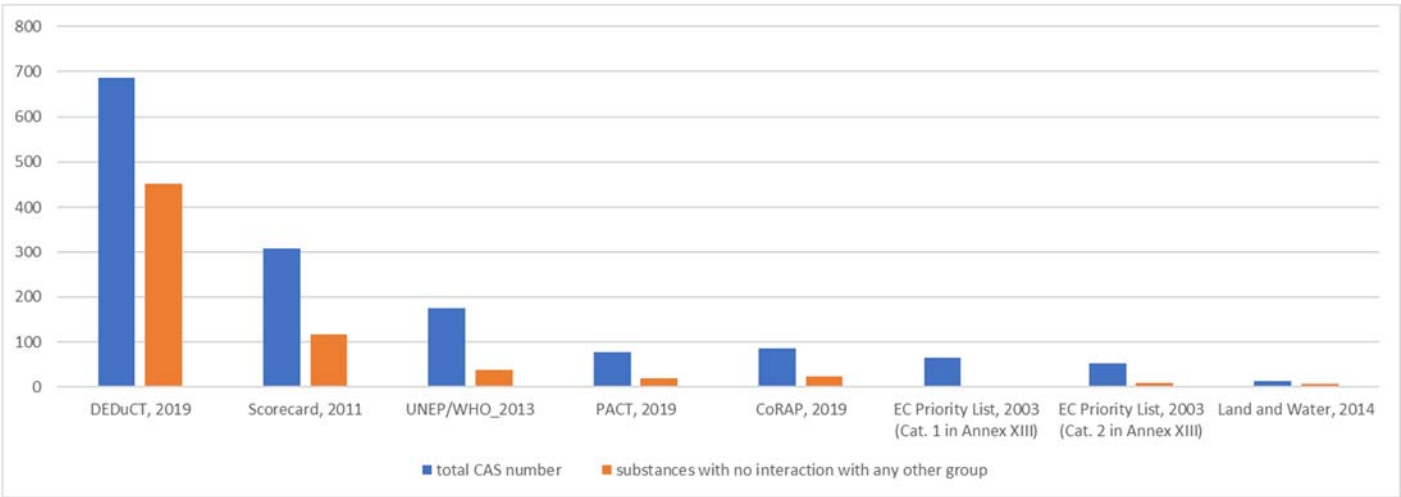

Figure 5: Histogram of the total CAS number (in blue), total number of substances with no interaction with other groups (in orange) for DEDuCT, 2019, Scorecard, 2011, UNEP/WHO, 2013, PACT, 2019, CoRAP, 2019, EC Priority List, 2003 (Cat. 1 in Annex XIII), EC Priority List, 2003 (Cat. 2 in Annex XIII) and Land and Water, 2014

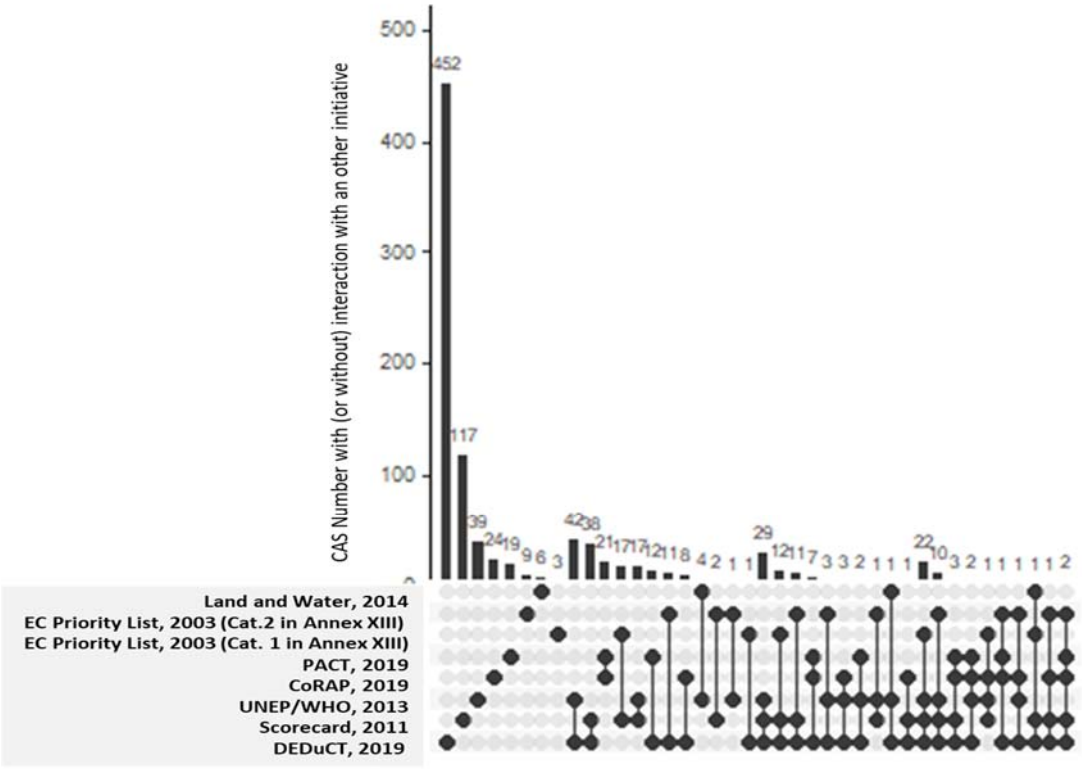

Figure 6: **UpSet plot of the intersection of CAS numbers as a matrix**

Legend:
When cells are empty (shown with light grey dot), this means that the CAS number (CAS N°) retrieved by the corresponding initiative is not a part of that intersection.
When cells are filled (shown with black dot), this means that the data set is participating in the intersection.
Each line corresponds to a set of data (e.g.) and each column corresponds to one segment in the Venn Diagram.

For example, in this figure, the first line corresponds to Land and Water, 2014 dataset:

- The 1st part of the graph (left hand side) shows the absence of intersection between all the initiatives. Only 1 cell is filled for each initiative. In the example of Land and Water, 2014, the number of CAS numbers retrieved only in this initiative, is shown (namely 6 CAS N°),
- In the 2nd part of the graph, 1 intersection with another list is indicated by 2 filled cells (namely 4 CAS N° in Land and Water, 2014 are common with UNEP/WHO 2013).
- In the 3rd part, CAS N° common with 2 other initiatives are indicated by 3 filled cells (namely 1 CAS N° from Land and Water, 2014 are common with UNEP/WHO, 2013 and DEDuCT, 2019).
- In the 4th part, CAS N° common with 3 other initiatives are indicated (in this case, no commonalities are found).
- In the 5th part, CAS N° common with other 4 initiatives are indicated (in this case, 1 CAS N° from Land and Water, 2014 is common with EC Priority List, 2003 Cat. 1, EC Priority List, 2003 Cat. 2, Scorecard, 2011 and DEDuCT, 2019).
- Overall, for Land and Water, 2014, the sum of all the intersection corresponds to 12 CAS N°as shown also in Figure 5

Substances proposed by **DEDuCT, 2019** were cross-checked with **CoRAP, 2019**, **PACT**, **2019** and **EC, Priority List, 2003** since they represent current and past EU initiatives/programs on EDCs. **UNEP/WHO, 2013** was plotted to be able to see how well-known initiatives overlap with each other. In addition, **Scorecard-2011** database was also compared with DEDuCT since a large set of scientific literature sources (e.g. main scientific publication, scientific reports or federal or international programs on potential environmental or human health potential EDCs) were covered. Lastly, **Land and Water, 2014** initiative was presented since the Australian program covered environmental EDC pollutants. The Venn-diagram proposed in Figure 4 allows only 5 sources to be represented. Therefore, in this figure the two last initiatives were merged. It shows that 43% of the substances proposed by **Scorecard, 2011** and **Land and Water, 2014** (corresponding to 165 substances among a total of 322) are captured by **DEDuCT, 2019**. Similarly, this Figure 4 shows that DEDuCT, 2019 picks up 33 substances that are currently under scrutiny at the European level under REACH (to this number the BP and PPP active substances should be added) but also proposes enough “new” candidates to fulfills its role for prioritization.

In addition, if we limit the comparison of DEDuCT, 2019 to CoRAP, 2019 and PACT, 2019, 633 substances identified by a unique CAS number were identified by DEDuCT, 2019 and not by CoRAP, 2019 and PACT, 2019, whereas 65 substances listed by CoRAP, 2019 and PACT, 2019 program are not retrieved by DEDuCT, 2019.

2.4.3 Capacity of DEDuCT, 2019 in detecting confirmed EDCs

One important criteria to judge about the robustness of DEDuCT, 2019 was to evaluate how this initiative was able to capture confirmed EDCs (**SVHC, 2019**).

- SVHC substances fulfill the WHO definition and give rise to an equivalent level of concern [than the one led by other properties leading to an SVHC identification, i.e. carcinogenicity, mutagenic, reprotoxic or PBT (persistent, bioaccumulative, and toxic) properties] due to their ED properties. In December 2019, 16 chemicals were identified as EDC with 4 chemicals for the human health, 10 for the environment and 2 both for human health and environment.

Table 2 : How DEDuCT-2019 identifies regulated EDCs identified for their effects on human health or the environment: Comparing DEDuCT and the Candidate list of REACH regulation (SVHC, 2019)

Substance Name	N° CE	N° CAS	SVHC inclusion	Date	Identified by DEDuCT, 2019
4-(1,1,3,3-tetramethylbutyl)phenol	205-426-2	140-66-9	EDC: 57(f)- environment	19/12/2011	YES
4-Nonylphenol, branched and linear	-	-	EDC: 57(f)- environment	19/12/2012	YES
Nonylphenol	203-199-4	104-40-5	EDC: 57(f)- environment	19/12/2012	YES
4-Nonylphenol, branched and linear, ethoxylated	-	-	EDC: 57(f)- environment	20/06/2013	NO
p-(1,1-dimethylpropyl)phenol	201-280-9	80-46-6	EDC: 57(f)- environment	12/01/2017	YES
4-heptylphenol, branched and linear	-	-	EDC: 57(f)- environment	12/01/2017	NO
Reaction products of 1,3,4-thiadiazolidine-2,5-dithione, formaldehyde and 4-heptylphenol, branched and linear (RP-HP)	-	-	EDC: 57(f)- environment	15/01/2018	NO
3-benzylidene camphor; 3-BC	239-139-9	15087-24-8	EDC: 57(f)- environment	15/01/2019	YES
TNPP with ≥ 0.1% w/w of 4-nonylphenol, branched and linear (4-NP)	-	-	EDC: 57(f)- environment	16/07/2019	NO
4-tert-butylphenol	202-679-0	98-54-4	EDC: 57(f)- environment	16/07/2019	YES
Bis (2-ethylhexyl)phthalate (DEHP)	204-211-0	117-81-7	EDC: 57(f)- env. & h. health	28/10/2008	YES
Bisphenol A; BPA	201-245-8	80-05-7	EDC: 57(f)- env. & h. health	12/01/2017	YES
Benzyl butyl phthalate (BBP)	201-622-7	85-68-7	EDC: 57(f)- human health	28/10/2008	YES
Dibutyl phthalate (DBP)	201-557-4	84-74-2	EDC: 57(f)- human health	28/10/2008	YES
Dicyclohexyl phthalate	201-545-9	84-61-7	EDC: 57(f)- human health	27/06/2018	YES
Diisobutyl phthalate	201-553-2	84-69-5	EDC: 57(f)- human health	13/01/2010	YES

As shown in Table 2, DEDuCT, 2019 includes all the substances identified EDC for human health and half of the substances identified EDC for the environment. In particular, the substances with no defined composition (such as mixtures) are not identified by DEDuCT as this is one of the exclusion criteria from DEDuCT. These results are coherent with the methodology used for DEDuCT's construction. While comparing DEDuCT (DEDuCT, 2019) with the 77 substances currently studied for their endocrine properties at the EU level under REACH (**PACT, 2019**), 33 substances are common as reported in Annex 6.

2.5 Conclusion

The comparisons performed above show that whatever the initiatives, they identify different substances, due to the different criteria applied, in accordance with their respective context and purposes. There is no initiative showing preferential overlapping with the others except EC-Priority List-2003 that served a basis for many initiatives (see Table 1) but is now outdated. Thus, an approach of the identification of substances of interest for endocrine activity aggregating different initiatives seems counterproductive and not scientifically sound because based on criteria that differ a lot. The rational for such an aggregation of different initiative appears difficult to defend. It was therefore decided to select one initiative among all.

In addition, it appears that some initiatives have been built on strict criteria, allowing selecting substances that are potential EDCs rather than endocrine active substances only. Based on the observations made above, it may be concluded that new initiatives based on well-conducted scientific literature search are now able to capture recent experimental testing results published in scientific journals that have not been taken into account so far. Indeed, these new tools can identify additional information to support the identification of potential EDCs as shown in figures 3 and 4 where 452 chemical substances were only captured by this database (DEDuCT, 2019). In addition, the filters apply aims at fulfilling the WHO definition, trying to focus on EDCs rather than endocrine active substances.

The inclusion of the 686 identified potential EDCs retrieved by DEDuCT, 2019 into the list of substance of interest is therefore proposed in the annex 5 (reported from lines to 1 to 686).

While implementing this methodology, the other initiatives ongoing will be scrutinized, in particular at the EU level (EASIS for example). Anses will continue to monitor the efficiency of DEDuCT-2019 while evaluating the substances prioritized (see chapter 4) and see if they are good candidate for SVHC identification or for human biomonitoring surveys. If DEDuCT, 2019 methodology is implemented in a long-term basis, the filters applied should be fine-tuned. In particular, it is important for the future to ensure that the method also identifies substances of interest for their endocrine properties on the wild-life species (environment).

3 Substances having an interest regarding their ED properties in biocidal and phytopharmaceutical products

The mandate given was to create a list of substances that may have potential endocrine properties regardless of their sectors of use and the sectorial regulations applicable. The work performed in chapter 2 together with the ANSES-WG-ED was dedicated to propose a methodology for identifying those chemicals. While working on that topic, it was decided to add the work performed elsewhere on the same topic in ANSES. In particular, while evaluating PPP and BP, substances having potential endocrine activity which are present in the products as co-formulants or active substances can be identified. This chapter aims at creating bridges between works that have been performed in different context and hence, separatly.

3.1 What about the active substances in the phytopharmaceutical and biocidal products?

3.1.1 Strategy for evaluating the ED properties of biocide and phytopharmaceutical active substances

As recalled in § 1.1 above, criteria have been established at European level, in phytopharmaceutical and biocidal products regulations, to assess whether an active substance meets ED criteria. To that extent, regulatory provisions are put on the applicants to provide the necessary scientific data.

Consequently, the ED properties of all active substances will be assessed, according to a known timetable at the European level[8], associated with data provision by the applicants and a repartition of the evaluation among Member States, according to usual processes operated by the competent European agencies (EFSA, ECHA).

Hence, by 2025, Member States (including France) will have assessed ED effects of about 300 phytopharmaceutical active substances and 100 biocidal active substances. Among them, Anses will have assessed active substances for which France will be rapporteur and will comment the assessment made by other Member States in the frame of European peer-review program.

Of course, as every Member State, France has the possibility to introduce, with appropriate elements, demands to the competent European authorities, to accelerate the regulatory calendar of active substances evaluation. Anses performed an analysis of several phytopharmaceutial active substance of interest for which a concern was identified (including on ED properties). From this

[8] References for PP active substance on-going renewal program: AIR2 program: Regulation EU 1141/201A0; AIR3 program: Draft Working Document - Renewal Programme (SANCO/2012/11284); AIR4 program: Commission Implementing Decision 2016/C 357/05; AIR5 program: Commission Implementing Decision C/2018/3434. Information available on COM website .

References for biocidal active substance evaluation program: Commission Delegated Regulation (EU) No 1062/2014; Commission Delegated Regulation (EU) 2019/157 and Commission Delegated Regulation (EU) 2019/227 of 28 November 2018 amending Delegated Regulation (EU) No 1062/2014 (Brexit). Information available in ECHA website : https://echa.europa.eu/fr/information-on-chemicals/biocidal-active-substances

analysis, Anses proposed an early revision of the ED status of one active substance, namely for prochloraz[9].

Considering that ED assessment is scheduled for all active substances at European level, they will not be included in the prioritisation strategy presented below, even if identified as substance of interest.

Therefore, the substances identified as substances of interest within the process defined by ANSES (from DEDuCT,2019), and identified as active substances of PPP or BP with a calendar of reapproval, will stay in the list of interest but shall not be included to the nomination and ranking processes.

3.1.2 DEDuCT, 2019 as a source of information for substance having endocrine properties in PPPs and BPs

As mentioned earlier, DEDuCT is a methodology working without *a priori* on the use of a substance but is based on literature review of accessible information. “Based on the environmental source of EDCs”, Karethikeyan et al. (2019) have classified the substances proposed within 7 broad categories and 48 sub-categories of uses thought the sources used and methodology followed to perform this categorisation is not detailed further.

While looking at the 276 substances identified “pesticides” in DEDuCT, only 109 are identified by the PPP or BP regulations. The others are either not approved, have an application cancelled or no longer supported. The differences observed can be due to different reasons:

- The definition of what is considered as pesticide within DEDuCT is not clear as well as the sources used to define such uses.
- Due to EU-law on pesticide (PPPR), some substances used outside EU may be different from those authorised within EU.
- The information of which substance is incorporated in which product and for which use is not easily extractable.

The specificity of the EU-law on PPP and the rather limited access to PPP data limit the capacity of DEDuCT to identify substances used in PPP and BP.

3.1.3 Comparison of DEDuCT, 2019 with the EU last effort to list potential EDCs and endocrine active substances: Capacity of DEDuCT, 2019 in detecting active substances categorised in the (EU Impact Assessment, 2016).

As described in 2.1.1, the last EU global effort for screening EDCs was performed while evaluating the impact on active substances of the different options proposed for the EDC definition. Comparing the active substances from PPPR and BPR categorized within the option 3 of the EU Impact

[9] Additional information for France are available in a dedicated appraisal:

Assessment, 2016 , DEDuCT identifies 45 active substances out of the 197 ranked category I, II, III (respectively EDC, suspected EDC and endocrine active substances). DEDuCT also includes 2 active substances (Imidacloprid and Esfenvalerate) out of the 6 claimed to be not EDC by the EU Impact Assessment, 2016 (see Table 3). This highlights that DEDuCT identifies 23% of the active substances proposed by the Impact assesment and that the outcome of the categorization can diverge. This low detection rate can be explained by the fact that DEDuCT is based on the accessible published data which did not cover regulatory dossiers.

Table 3: 47 substances found by DEDuCT-2019 and EU Impact Assessment, 2016

Common Name	CAS number
Boric acid	10043-35-3
Glyphosate	1071-83-6
Tebuconazole	107534-96-3
Glutaraldehyde	111-30-8
Thiacloprid	111988-49-9
Fenbuconazole	114369-43-6
Fipronil	120068-37-3
Malathion	121-75-5
Zineb	12122-67-7
Maneb	12427-38-2
Fenhexamid	126833-17-8
Fludioxonil	131341-86-1
Thiram	137-26-8
Ziram	137-30-4
Imidacloprid*	138261-41-3
Flufenacet	142459-58-3
Thiamethoxam	153719-23-4
Bromoxynil	1689-84-5
Thiophanate-methyl	23564-05-8
Chlorpyrifos	2921-88-2
Diuron	330-54-1
Linuron	330-55-2
Imazalil	35554-44-0
Iprodione	36734-19-7
Pendimethalin*	40487-42-1
Cypermethrin	52315-07-8
Permethrin	52645-53-1
Deltamethrin	52918-63-5
Triadimenol*	55219-65-3
Chlorpyrifos-methyl	5598-13-0
Terbuthylazine*	5915-41-3
Propiconazole	60207-90-1
Amitrole*	61-82-5
Esfenvalerate*	66230-04-4
Penconazole	66246-88-6

Flutolanil*	66332-96-5
Prochloraz	67747-09-5
Triflumizole*	68694-11-1
Abamectin (aka avermectin)	71751-41-2
Iodine*	7553-56-2
Mancozeb*	8018-01-7
Myclobutanil*	88671-89-0
2-Phenylphenol (incl. sodium salt orthophenyl phenol)*	90-43-7
Lambda-Cyhalothrin*	91465-08-6
2,4-D	94-75-7
2,4-DB	94-82-6
Cyproconazole*	94361-06-5

*: represents substances for which the category proposed by DEDuCT is different that the one proposed by the Impact assessment (see 4.1.3)

Based on this comparison and in order to be as exhaustive as possible**, it is decided to add all the 152 category I, II and III substances in the (EU Impact Assessment, 2016 – option 3) to the list of substances of interest that were not identified by DEDuCT**. It should be reemphasized that based on reasoning exposed in the previous paragraph, the substances of this list that have a reapproval date will not be subject to the prioritisation process, unless another use exposing the population can be demonstrated. Therefore, only 31 substances of these 199 (152 substances not identified so far + 47 already present in DEDuCT) enter the prioritisation process.

3.2 Endocrine activity of co-formulants present in the biocidal and PP products

3.2.1 Screening of the endocrine activity of co-formulants present in biocidal products

Biocidal products are regulated by the Biocidal Products Regulation (BPR, Regulation (EU) No 528/2012). This regulation specifically includes restrictions for ED substances present in the biocidal products on the market in Europe. Briefly:

- ED active substances shall normally not be approved;
- Biocidal product containing ED substances shall normally not be used by the general public.

The Commission Delegated Regulation (EU) 2017/2100 specifying the scientific criteria for the determination of endocrine-disrupting properties (ED criteria) under BPR establishes ED criteria that apply to Active substance and any other co-formulant in the biocidal product. This Delegated Regulation has become applicable by 7 June 2018.

From this date, all reference Member State and evaluating Competent Authority (rMS/eCA) must consider the ED properties of a biocidal product in any procedure. This involves considering the ED criteria for both the active substance(s) and the non-active substances (so-called ‘co-formulants’) in the product.

- The ED properties of the active substance are assessed in the context of the approval of the active substances, at the European level.

- The ED properties of the co-formulant must be analysed by the rMS/eCA in charge of biocidal product assessment.

Considering that the appropriate procedure for EDC identification of a chemical substance, which is not an active substance, is the REACH Regulation, a general approach is being proposed among Member States. A screening of available database is made to identify if there are indications of an endocrine activity. This analysis is performed for each co-formulant, leading to the following conclusions:

- The co-formulant is an ED and has already been assessed as having ED properties by other regulatory bodies at EU level.

  or

- There is no indication of concern regarding ED properties of the co-formulant.

  or

- There are indications that the co-formulant may have ED properties, but it has not yet been assessed as EDC in any regulatory process. Hence, rMS/eCA sends to the REACH Competent Authorities and to ECHA their preliminary assessment and requests to launch an appropriate REACH procedure for further analysis - unless the compound is already registered as an active substance under Biocidal Products Regulation (BPR) or Biocidal Products Directive (BPD).

Screened database to identify indicators of an endocrine activity for the co-formulant are the following:

- REACH substance on-going activities (CORAP, PACT …)
- EU priority List of potential EDCs Category 1 &2 (EC Priority List, 2003)
- Other recognised public institutes review programs (WHO, national agencies programs…)
- US databases ToxCast and EDSP (see above for further details on these initiatives), which mainly gather results from screening assays, most of them being *in vitro*.
- Classification - Repr Tox or STOT-RE (thyroid) classification under CLP

All information provided in the technical dossier for a marketing authorization is also checked.

In France, ANSES, which is the French Evaluating competent authority for the evaluation of biocidal products, has applied this methodology for all biocidal products for which marketing authorization decision has been issued from June 2018 onward. By the November 1st, 2019, this analysis was conducted for 23 applications for marketing authorization for biocidal products or product families. 282 chemical substances, present in at least one of these biocidal products, were screened. Among these 282 substances,

- 205 have no evidence of endocrine activity based on the information consulted and,

- 77 have indications of endocrine activity.

Similarly, 4 co-formulants present in plant protection products with potential ED activity have been identified.

Screening of co-formulants present in formulated regulated products for which ANSES is the competent authority has led to identify 81 substances of interest. The list of these substances is accessible in Annex 5.

3.2.2 Comparison of the substances identified for having an endocrine activity as co-formulants present in biocidal products and those proposed by DEDuCT, 2019

While comparing the list proposed by the ANSES ED-WG (DEDuCT-2019: 686 substances) together with the 81 substances used as co-formulants in PPP and BP identified by ANSES during their evaluation, it appears that 13 substances are common as shown in Table 4:

Table 4: Substances found by DEDuCT-2019 and as co-formulants in PPP and BP

Common Name	CAS number
Styrene	100-42-5
Triethanolamine	102-71-6
Toluene	108-88-3
Benzyl salicylate	118-58-1
BHT	128-37-0
Titanium dioxide	13463-67-7
Disodium 6-hydroxy-5-[(4-sulphonatophenyl)azo]naphthalene-2-sulphonate	2783-94-0
LILIAL (p-tert-Butyl-alpha-methylhydrocinnamic aldehyde)	80-54-6
Tween 80 /Radiasurf	9005-65-6
Methyl 4-hydroxybenzoate	99-76-3
Ethyl 4-hydroxybenzoate	120-47-8
Propyl 4-hydrybenzoate	94-13-3
Butyl 4-hydrybenzoate	94-26-8

The different methodologies and criteria used in DEDuCT and in the work performed for identifying the substances of interests for their ED properties among the coformulants may explain the low level of overlap (16%) between these two databases. **In order to be as exhaustive as possible for the list of substances of interest, it has been decided to add the 68 coformulants not identified so far by the methodology proposed in chapter 2. In addition, it should be reminded that co-formulants are regulated within REACH regulation, and are therefore candidates for assessment during prioritisation.**

4 Aim of the list of substances of interest and example of its use for ANSES purpose

Based on the mandate received in October 2019, the substances of the list should "*be ranked according to a prioritization score. […] A prioritization method taking into account objective criteria (likelihood and relevance of the intrinsic propertie(s), use, exposure of the vulnerable population, etc.) which will then be applied to the above list with the objective of 'assign a priority score*" should be proposed.

The mandate further elaborates that:

- *"This list will be used in particular for discussions with stakeholders with a view to establishing the annual program for assessing the hazard of these substances to be carried out by ANSES (actions 1 and 2 of the SNPE2).*
- *This list could also be used within the framework of the evaluation work planned by SNPE 2 and involving the other agencies concerned, in particular the ANSM within the framework of action 1 on cosmetic products and health products and AFB and INERIS in the context of action 15 on the impregnation of environments with these substances."*

4.1 Description of the content of the list of substances of interest as regards to their potential endocrine activity (Annex 5)

4.1.1 Description of the list of substances available in Annex 5

The starting point for this prioritisation exercise is the list of substances of interest. This list covers all substances regardless of their sector of use or the sectoral regulations concerned, based on the methodology established by the ANSES ED-WG (DEDuCT-2019: 686 substances) together with the 81 substances used as co-formulants in PPP and BP identified by ANSES during their evaluation. It also contains the 197 substances ranked category I, II, III in the (EU Impact Assessment, 2016 – option3). As 13 co-formulants and 45 active substances were initially proposed by DEDuCT, the list of substances of interest as regards to their potential endocrine activity contains:

Number of substances of interest = 686 + (81-13) + (197-45) = 906 substances.

4.1.2 Description of the information reported for each substance in Annex 5 when available

The list of substances of interest therefore contains 906 substances presented as an excel table in the annex 5, with the following additional data:

- The columns C-E indicate if the substance has been identified by the DEDuCT initiative, the work performed for coformulant and/ or the EU Impact Assessment (2016). This origin informs on the uses (a co-formulant substance as used in BP may lead to significant exposure) and impacts the level of data available (DEDuCT substances could have more

information on their ED properties than coformulant when considering the methodologies applied for building each list).

- Together with their EC and CAS numbers, their public names are provided respectively in columns F to H.
- Their classification is displayed in column I. The classification and labelling inventory contains classification information on notified and REACH-registered substances received from manufacturers and importers (self-classification). It has been merged with the list of harmonised classifications (Tables 3.1 and 3.2 of Annex VI of the CLP Regulation) that is identified in bold in the same column.
- The tonnage when the substance is registered under REACH, its regulatory status and if it is under an evaluation for its ED properties is reported in column J to L. This is complemented with information on the fact that the substance is a candidate for authorisation (annex XIV in column M) or restricted under REACH (annex XVII in column N). All these information have been gathered from December 2019 to March 2020 and have not been updated thereafter.
- When the substances are registered as biocides[10] , the status or expiration date of the current approval (as extracted in 06/2020) is provided in column O.
- When the substances are registered as PPP[11], their renewal date of approbation or other current regulatory status is given in column P (information gathered in June 2019).
- If the substance is regulated by the Cosmetic Regulation (as available here:), the information is provided in columns Q and R (respectively if it is prohibited as mentioned in annex II of this regulation or if it has some restriction in uses as mentioned in annex III, IV, V of the regulation or mentioned elsewhere as ingredient).
- Their toxicological category (see below for more details).

This information was collected between June 2019 and June 2020. Despite the best efforts to avoid errors, this information is not necessarily complete or up to date. Also these elements are communicated for information only and should not be used to conclude whether a substance is dangerous or whether it can be used safely. French authorities retain the right to initiate any regulatory action on a substance regardless of what is stated in this annex.

It should be noted that internally, ANSES had access to additionnal information that has been used for prioritisation. This cannot be made public due to legal issues:

- For REACH registered substances, the uses and uses advised against as available on the ECHA dissemination website in February 2020 are listed.
- For DEDuCT substances, the uses proposed by this database have been considered by Anses although not specifically checked. It should be noted that this data comes from publications in the scope of that initiative and discrepancies may appear with the uses as reported on the ECHA dissemination website. In particular, we are not sure what pesticide really means in DEDuCT. If coformulants and packaging ingredients are taken into account while reporting this use category, it could explain the discrepancies observed for some

[10] https://echa.europa.eu/fr/information-on-chemicals/biocidal-active-substances extractede

[11]https://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=activesubstance.selection&language=EN

substances. It should also be kept in mind that the information provided by DEDuCT does not represent the uses allowed in the regulated EU market.

Each piece of information is available on the source database.

4.1.3 How the categories as proposed in Table 5 inform about the availability of data to evaluate the ED potential of a given substance

The aim of our prioritisation exercise is to propose accurate candidates for an in-depth evaluation and further regulatory identification (if needed) or additional monitoring. We propose then to flag substances for which the ED properties have not been assessed so far but that the present work indicates that they should be considered having enough data to fulfil the WHO/IPCS definition.

One of the strength of DEDuCT is that Karethikeyan et al. have categorised the substances of their list depending on the data available.

This effort of evaluating how the data available for a substance allow to fulfil the WHO/IPCS definition based on an evaluation of the available data (i.e. not performing an in depth evaluation) has also been performed in the Impact assessment perform by EU-Commission (**EU Impact Assessment, 2016**) where the substances have been put into different categories as well.

Unfortunately, the categories used within these 2 initiatives, thought informing both on the data availability are defined differently. In order to concatenate these two lists in the annex 5, we propose to align categories between the EU impact assessment and the DEDuCT initiative as shown in the Table 5 below:

Table 5: Comparison of the categories between (DEDuCT-2019) and (EU Impact Assessment, 2016)

Category proposed in annex 5	**Category in (DEDuCT, 2019)**	**Category in (EU Impact Assessment, 2016)**
I	I: substances having data showing effects observed *in vivo* in human beings (from Karthikeyan et al., 2019)	Not specified in this study
	II: substances having data showing effects observed *in vivo* in rodents and *in vitro* in experiments using human cells (from Karthikeyan et al., 2019) *but not from in vivo human experiments.*	I: substances being considered as confirmed EDCs. Data available show 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 ED mode of action (from EU Impact Assessment, 2016). *This definition means that in vivo data are available.*
II	III: substances having data showing effects observed solely *in vivo* in rodents (from Karthikeyan et al., 2019).	II: suspected EDCs having data showing either adverse effects identified without supporting mechanistic evidence, or *in vivo* mechanistic evidence without evidence for adverse effects (from EU Impact Assessment, 2016).

III	IV: substances having data showing effects observed *in vitro* using human cells only (from Karthikeyan et al., 2019).	III: substances identified as endocrine active substances with no *in vivo* evidence (from EU Impact Assessment, 2016).

It should be noted that thought different, the categories of the two initiatives can be aligned as they are based on coherent principles: they inform on the sets of data available for a given substance, either in the scientific literature for DEDuCT or in regulatory reports for the EU Impact assessment 2016. These categories are not based on an in depth evaluation but appreciation of the available data.

For the 47 substances common to DEDuCT and the EU Impact assessment 2016, categories were proposed by DEDuCT and the EU impact assessment. The categories proposed by DEDuCT differed from the one proposed in the Impact assessment for 25 substances (see the substances marqued with* in Table 3). In that case, the category reported in Annex 5 is the highest (i.e. informing on a smaller degree of certainty regarding the ED property).

While Category I substances of the annex 5 might be of interest to build dossiers for their formal identification within the appropriate regulatory framework, category II and III substances could be evaluated under substance evaluation of REACH regulation for requesting further data if proven necessary after in depth evaluation.

4.1.4 Conclusions regarding the list of substances available in Annex 5

It should be emphasized that, the only substances of this list to be considered as known EDCs are those that have been identified ED after an in-depth evaluation at the EU level (see Table 2 paragraph 2.4.3). They are all category I substances instead of p-(1,1-dimethylpropyl)phenol identified category III (category as defined in annex 5): in DEDuCT, this substance is indicated as category IV, probably because this is an EDC for environment under REACH.

The other substances are of interest as regards to their potential endocrine activity but cannot be considered EDCs before an in depth evaluation. Some substances, but not all can be evaluated in details in the near future. It shows the necessity of prioritising substances for this work (see below 4.2). **It is important to bare in mind that this table has been built by gathering information available within databases accessible to ANSES which contain information that can easily be linked to the current work (i.e. substances identified by CAS number for example).** If these information are used later for identifying substances for further work, it might be necessary to update them. However, this update cannot be done automatically and is therefore not planned so far.

As mentioned above, the information automatically gathered by ANSES concern uses and tonnages related to REACH regulation. Based on this limitation, it is important to note that the following work on prioritisation focuses on the establishment the ANSES annual program for assessing the hazard of these substances. ANSES is not tooled to rank appropriately the list of substances of interests regarding the second bullet point of the request, i.e. the priorities for other end-users. Other agencies are welcome to use the list of substances of interest with their own data on uses, exposure of the vulnerable population, etc.to identify their own priorities from the list of substances of interest.

4.2 Prioritisation method to define ANSES work program on ED identification.

As mentioned earlier, only some of the substances of Annex 5 can be proposed within ANSES annual work program. The following paragraph aims at explaining which substances can be prioritised for this work and why.

4.2.1 From the list of substances of interest to the list for prioritisation for ANSES annual work program of evaluation.

The list of substances of interest needs to be fine-tuned before being proposed for prioritisation (column B of Annex 5):

- DEDuCT-2019 proposes 2 substances with no CAS nor EC number that have to be excluded for prioritisation:
  - 2-MeO-BDE-123 (number 683 of DEDUCT) is a remanent substance found in wildlife from Northern Europe. This is a PBDE metabolite produced by widlife species. This substance is of interest as it is found in the environment and exhibits aromatase activity. However, it is not included in the list for prioritisation because its parent substance, PBDE is already SVHC and regulated to decrease its presence in the environment.
  - Lipopolysaccharide (number 684 of DEDUCT), also known as endotoxin is the major component of the outer membrane of Gram-negative bacteria, contributing greatly to the structural integrity of the bacteria, and protecting the membrane from certain kinds of chemical attack. This family of natural molecules cannot be treated as a single substance and cannot be treated under any EU regulation.
- From the list of the 906 substances of interest, 12 are already identified as substances of very high concern (SVHC) due to their ED properties (see Table 2). There is no need to assess them further for this property.

In addition 12 active substances are already banned in PPP under 79/117/EC[12] and/or 850/2004/EC[13] and prohibited in cosmetics. Among them, 7 are Persistent Organic Pollutants that are very strictly regulated (see column P from annex 5). These 12 substances are already known hazardous substances. Independently of any ED property, they are regulated and do not need to be prioritized for further assessment and potential regulation.

As mentioned above, the evaluations of all the biocides and plant protection active substances have their own timetable and the priority of their re-evaluation has been already analysed by Anses[14]. The 163 active substances regulated by PPPR and the 39 BPR (among which 27 are also planned under PPPR) will be evaluated with the calendar defined by these regulations (see date of current approval respectively in column O or P) and are therefore not entering the pool of prioritisation setting unless other uses exposing population can be demonstrated. ANSES will be in charge of several of these assessments.

[12] Council Directive 79/117/EEC of 21 December 1978 prohibiting the placing on the market and use of plant protection products containing certain active substances

[13] Regulation (EC) 850/2004 of the European Parlement and Council of 29 April 2004 on persistent organic pollutants and amending Directive 79/117/EEC

[14] Avis Anses 2018-SA-0163 relatif à « la revue des substances phytopharmaceutiques préoccupantes pour la santé publique ou l'environnement » : https://www.anses.fr/fr/system/files/PHYTO2018SA0163.pdf

Therefore, on the 906 substances identified initially, the **remaining 705 substances are considered** for further evaluation and are therefore proposed for prioritisation. A prioritisation strategy is needed for the selection of a manageable list of substances that will be in-depth assessed with respect to their ED properties.

Indeed, the last step of Action 3 is an evaluation of substances included in ANSES' work program (9 substances per year from 2021 onward, 6 being covered by REACH regulation) in view of issuing a categorisation. The challenge relies on choosing annually these 6 substances among the 705 for prioritisation, in a consistent and transparent way. If this exercise had to be reproduced later, it should be kept in mind that the information was gathered from mid 2019, mid 2020. Information on regulatory status, uses and toxicological and ecotoxicological data available evolve all the time and should be updated regularly. Similarly, the work performed by Karthikeyan et al., 2019 would evolve with the scientific literature available. In the mandate received to perform the current work, it is requested that this list is updated yearly. However, the means to perform such update have not been scheduled so far.

4.2.2 How the actual ANSES workprogram covers the annex 5 substances.

From the work carried on during SNPE1, ANSES requested extra data on different substances. As the registrant have provided/ are providing these information, ANSES need to re-evaluate these new studies together with the new scientific literature on these substances. From our workprogram, at least 4 substances belongs to annex 5 and will be evaluated in 2021:

Table 6: Substances from ANSES workprogram 2021 belonging to Annex 5

CAS number	**Public substance name**	**Classification (harmonized or self from registrations)**	**Information from the disseminated website**		**Subst. used in Cosmetics**		**Category as proposed in Table 5**
			Tonnage	Regulatory status	Prohibited	Used	
1634-04-4	Tert-butyl methyl ether	Flam. Liquid 2; Skin Irrit. 2; NA	> 100 tpa	Data generation		x	II
75-15-0	Carbon disulphide	Repr. 2 ; Eye Irrit. 2, STOT RE 1, Flam. Liq. 2, Skin Irrit. 2	> 100 tpa	Data generation	x		II
25013-16-5	tert-butyl-4-methoxyphenol	Acute Tox. 4; Aquatic Chronic 2; NA; Skin Irrit. 2; Eye Irrit. 2; Carc. 2; Repr. 2	> 100 tpa	Regulatory risk management under consideration		x	I
128-37-0	2,6-di-tert-butyl-p-cresol	Aquatic Acute 1; Aquatic Chronic 1; NA	> 100 tpa	Regulatory risk management under consideration		x	III
13463-67-7	Titanium dioxide	Carc. 2	> 100 tpa	Data generation		x	II

4.2.3 Strategy of prioritisation based on the data gathered automatically

4.2.3.1 Information important to consider while identifying candidates for further evaluation

Among the 705 substances proposed for prioritisation, 266 only are registered under REACH (column J filled in annex 5): 159 above 100t/year, 65 below 100t/ years, 40 being intermediates only, and 2 claiming this information as confidential. This information is important because it impacts the level of information available and the capability for the member state to request additional data. The substances that are not registered can nevertheless be found on the European market imported within articles or as residues if persistent in the Environment. The substances that are not registered could be assessed based on available scientific literature or using information from structurally similar substances, rendering the entire process scientifically challenging.

The categories proposed in the annex 5 are indications provided by those who listed the substances of the level of information already available and supposably capable of fulfilling the WHO definition. They could be used as incentive to evaluate those substances quicker than others. On the other hand, there are many substances for which data are currently produced (additional studies have been requested). It is therefore counterproductive to evaluate them while important pieces of information will be (soon) made available. The importance of this piece of information should be evaluated in regard to the delay required for them to be provided.

Other substances have risk management measures that are currently developed. For those, it might be interesting to evaluate if these measures can impact the population exposure in the future.

Finally, it should be bared in mind that DEDuCT has gathered information regarding the ED properties of substances whatever their use. It should then be considered the added value of digging into the ED properties of certain substances depending on their use(s).

4.2.3.2 Example of possible reduction of the list to identify valuable substances for further evaluation

In order to identify the substances to be assessed by ANSES in the frame of it's annual work program**, the ministries have proposed selection criteria based on REACH registration status and on-going regulatory actions (see**

Figure 7**).**

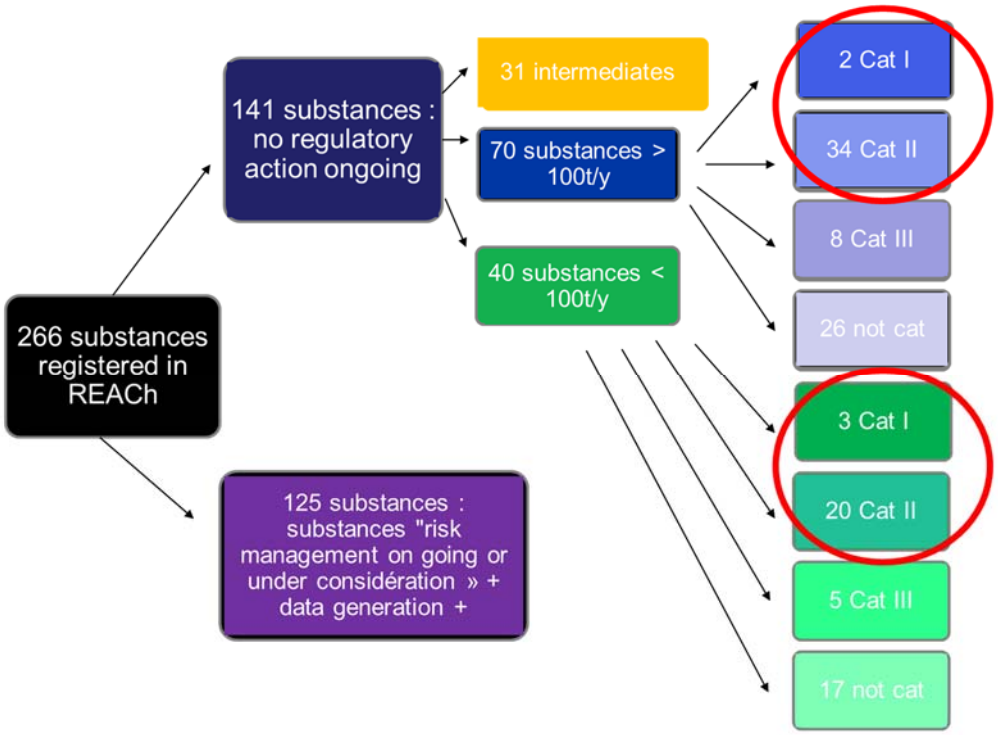

Figure 7: Overview of the proposed prioritisation strategy

After applying the criteria proposed by the ministries, 59 substances have been selected. This choice need to be further tighten due to internal limitations for gathering the necessary data for a proper ranking as proposed below. Therefore, ANSES introduced additional criteria aiming to select a target of around 20 substances for the scoring exercise, focusing on substances in the scope of its activities and for which a higher impact is expected:

- Substances registered as intermediates or registered below 10 tonnes per year under REACH have been deprioritised.
- ED properties of p-cresol have already been evaluated under REACH[15] for the human health part (conclusion: not ED). The substance has therefore been deprioritised. Similarly, ethanol and chlorine dioxide have been deprioritized due to their biocidal substance evaluation by another Member State.
- As nickel sulphate has an harmonised classification carcinogen 1A, mutagen 2 and reprotoxic 1B, regulatory management options are already in place (e.g. for consumer products – generic restriction in entries 28 to 30 of Annex XVII of REACH, for toys, for cosmetics, for workers…). Similarly, chromium VI compounds are already regulated due to their CMR classifications. The added value to assess these substances in REACH has been considered limited and theses substances have been deprioritised.
- Caffeine is present in a variety of food and food products including dietary supplements and synthetic drugs. The main sources of caffeine are coffee, tea, sodas, energy drinks. Caffeine

[15] Substance evaluation conclusion,United Kingdom, March 2016.
https://echa.europa.eu/documents/10162/47e4156c-53e6-c5ea-360a-f5ea6b0f7bad

is also part of the composition of many analgesic drugs. The added value to assess this substance in REACH has been considered limited and the substance has been deprioritised.

The remaining 16 substances candidates for the ranking stage are presented in Table 7.

Table 7: Substances prioritised to enter the ranking methodology

CAS number	Public substance name	Classification (harmonized or self from registrations)	Information from the disseminated website		Substances used in Cosmetics		Category as proposed in Table 5
			Tonnage	Regulatory status	Prohibited	Used	
100-41-4	Ethylbenzene	Flam. Liquid 2; Asp. Tox. 1; Acute Tox. 4; STOT Rep. Exp. 2; Aquatic Chronic 3; NA; Muta. 1B; Carc. 1A;	> 100 tpa	Already evaluated: no further action proposed		x	II
10024-97-2	Dinitrogen oxide	Oxid. Gas 1; Liquefied gas; NA; STOT Single Exp. 3	> 100 tpa	Already evaluated: no further action proposed		x	II
102-71-6	2,2',2''-nitrilotriethanol	Eye Damage 1; Repr. 2; NA;	> 100 tpa	Already evaluated: no further action proposed		x	II
108-78-1	Melamine	-	> 100 tpa	Already evaluated: no further action proposed			II
127-18-4	Tetrachloroethylene	Skin Irrit. 2; Skin Sens. 1B; Eye Irrit. 2; STOT Single Exp. 3; Carc. 2; Aquatic Chronic 2; NA	> 100 tpa	Already evaluated: no further action proposed	x		II
1344-09-8	Silicic acid, sodium salt	Met. Corr. 1; Skin Corr. 1B; Eye Damage 1; STOT Single Exp. 3; Eye Irrit. 2A; NA; Skin Irrit. 2; INCORRECT;	> 100 tpa	Already evaluated: no further action proposed		x	II
557-34-6	Zinc di(acetate)	-	> 100 tpa	Not yet assigned		x	II
7440-42-8	Boron	-	> 100 tpa	Already evaluated: no further action proposed			II
7632-00-0	Sodium nitrite	Ox. Sol. 3, Acute Tox. 3, Aquatic Acute 1	> 100 tpa	Not yet assigned		x	II
7646-85-7	Zinc chloride	Acute Tox. 4, Aquatic Chronic 1 Aquatic Acute 1 Hazard Category: Skin Corr. 1B	> 100 tpa	Currently no further actions proposed		x	II

7647-15-6	Sodium bromide	-	> 100 tpa	Already evaluated: no further action proposed			II
7681-49-4	Sodium fluoride	Eye Irrit. 2Acute Tox. 3 Hazard Skin Irrit. 2	> 100 tpa	Not yet assigned		x	II
7773-01-5	Manganese dichloride	-	> 100 tpa	Not yet assigned		x	II
79-43-6	Dichloroacetic acid	Aquatic Acute 1, Skin Corr. 1A	> 100 tpa	Not yet assigned			II
92-88-6	Biphenyl-4,4'-diol	-	> 100 tpa	Already evaluated: currently no further actions proposed			II
994-05-8	2-methoxy-2-methylbutane	STOT SE 3, Acute Tox. 4 Flam. Liq. 2	> 100 tpa	Already evaluated: currently no further actions proposed			II

4.2.4 Ranking method for prioritising candidates for further evaluation.

4.2.4.1 Method

The objective is to develop and implement a science-based approach to rank the remaining 20 substances against a set of prioritisation criteria. The proposed set of criteria will be structured into 3 groups: hazardous properties will help defining the hazard score (HSc); exposure and uses (with a focus on susceptible populations) will be used to define the exposure score (ESc); societal concern will be quantified through the societal score (SSc). These groups of criteria have not the same weight in the calculation of scores. The weighting coefficients (WiH, WiE and WiS respectively for Hazard and Exposure and Societal concern) proposed by ANSES, after consultation of its ED-WG, are the following:

- WiH = 43%;
- WiE = 43%;
- WiS = 14%.

A global score for each short-listed candidates will then be calculated as such:

Global sore of substance A = HScA * WiH + EScA * WiE + SScA * WiS

4.2.4.2 HSc and ESc and SSc scores calculation for each substance

A systematic approach for scoring the substances against the criteria ‘hazardous properties’ and ‘exposure and uses’ will be elaborated based on their estimated severity (seeTable 8): ‘high’ (score of 6), ‘moderate’ (score of 3) or ‘low’ (score of 1). It could also be scored as ‘data gap’ (score of 2), where more data is deemed necessary.

Table 8: Proposed scoring approach

Severity and level of certainty	High	Moderate	Low	Data gap – unknown
Score	6	3	1	2

In order to allocate the score, relevant information with regard to the following groups of criteria is of interest:

1- Hazard criteria: the level of available data (*in vitro*, *in vivo*, human data) vary among substances of interest. In particular, the amount of information concerning the hazard of a substance, notably its ED properties, strongly depends on the regulation applicable to this substance. For example, in REACH, the volume to which the substance is produced or imported into Europe influences the amount of information to be provided (Article 12 of REACH). This situation favours substances produced at high tonnage because generally more documented and studied. The level of evidence (and therefore the possible actions) can indeed vary and must be taken into account. This could be counter-balanced by informing if the substance belongs to a well-known family or looks like a known EDC (structural similarity). The CLP classification of the substance is also informative.

For the 2021 scoring exercice, we propose to fill this criteria by summing the scores from the following information:

a. CLP classification of the substance (harmonised and self-classification)

Substances having a harmonized classification STOT RE 1 and Aquatic chronic toxicity 1 have the highest score (score 6). Regarding CMR categories 1A and 1B, it is acknowledged that sufficient regulatory management measures are already in place. Substances self-classified according to CLP criteria (CMR 1, STOT RE 1 and Aquatic chronic toxicity 1) have an intermediate score (score 3). All the other classifications and those with no classification have the lowest score (score 1).

b. PBT/vPvB properties

Substances with known PBT properties have the highest score (score 6). If some data in ECHA dissemination website indicate potential PBT properties, they got an intermediate score (score 3). Substances with no data on PBT properties have the lowest score (score 1).

c. DEDuCT Category

Substances identified in category I got the score 6 and substances in category II got the score 3.

d. Studies identified by DEDuCT initiative*, in vitro* and/or *in vivo (*endocrine data*)*

The scores are different depending on the level of information needed to assess endocrine disrupting properties: *in vivo* and *in vitro* studies (DEDuCT and reproductive toxicity peer-review) with identification of EATS pathways (score 6), *in vivo* studies with identification of EATS pathways (score 3), Studies without identification of EATS pathways (score 1).

e. Environmental data (endocrine or reproductive or developmental studies)

Such studies are outside the scope of DEDuCT initiative, however it has been considered by a quick literature search[16]. If reproductive or developmental effects or endocrine studies are available in environmental area, a score 3 is allocated. If no data are identified, a score 1 is given.

[16] PubMed with the following keywords: (substance names) + (environment) and ((endocrine) or (reproductive toxicity) or (developmental toxicity)).

To sum up, the 2021 score for the 'hazard' criteria is the following:

Hazard Criteria= sum of the following scores		**High level**	**Moderate level**	**Low level**
Hazardous properties	*Source or information*	(score of 6)	(score of 3)	(score of 1)
Reprotoxicity / STOT RE / aquatic chronic toxicity	ECHA	Harmonized classification	Notified	Not classified
Persistence and bioaccumulation potential	ECHA	PBT / vPvB	little evidence	Not PBT / vPvB
ED properties / DEDuCT category	DEDuCT category	Category I	Category II	/
Endocrine Disruptor data (Health)	DEDuCT / Peer-reviewed literature (reproductive data)	*In vivo* and *in vitro* studies with identification of EATS pathways	*In vivo* studies with identification of EATS pathways	*In vivo* without identification of EATS pathways
Environmental data	Peer-reviewed literature	/	Data	No studies

2- Exposure potential and uses: for the chemical substances covered by REACH, tonnages and types of uses reported to ECHA by the industry are interesting sources of information. Per se, the fact that the substance is registered under REACH (with a various number of registrants) is already an information. Other sources of information could also inform if the substance is used for a specific purpose (e.g. Cosing List for cosmetics).

The 2021 proposed scoring method to define exposure criteria is the following:

Exposure Criteria= sum of the following scores		**High level**	**Moderate level**	**Low level**
Exposure characteristics	*Source or information*	(score of 6)	(score of 3)	(score of 1)
Tonnages	ECHA	> 10 000 tpa	1000 - 10 000 tpa	100- 1000 tpa
Active registrations	ECHA	> 50	> 10	< 10
Availability of HBM data	Peer-reviewed literature	-	Some evidence in peer-reviewed literature	No data identified
Exposure sources	ECHA	Manufacture / Formulation / Use at industrial sites/ Use by professional workers/ consumer uses / Article service life	Manufacture / Formulation / Use at industrial sites/ Use by professional workers/ Article service life	Manufacture / Formulation / Use at industrial sites/ Use by professional workers
Environmental releases	ECHA	Different releases	Limited releases	No release

4- Societal concern: the "societal concern" criteria will be reflected by the stakeholders from InterCOT Group (see below for further details).

According to its organization's provision and as prescribed in the French Public Health Code, ANSES includes in it's external governance, periodic meeting with stakeholders to exchange about the scientific work performed and to be performed by the agency. Concerning the ED characterization of chemical substances, ANSES had introduced a special session, on a yearly basis, of these stakeholders meeting named "InterCOT PE". In the framework of the SNPE 1, ANSES submitted each year to the members of this "interCOT PE", a limited list of substances of interest. They were invited on a yearly basis by the agency to a stakeholders meeting to discuss this draft list of substances to be assessed. The Ministry of Ecology made the final choice of substances included in the work programme, after taking into account the comments received from stakeholders during this consultation.

Within the SNPE2 framework, the prioritisation process proposed by ANSES will include a more formal stakeholder's consultation. Indeed, the substances short-listed will be communicated to "interCOT PE" group to take into account their priorities, reflected by the societal concern criteria. Then Anses intends to present the results of the ranking of the substances prioritised before the adoption of the assessment list included in ANSES work programme by the ministries.

4.3 Workability and potential improvement in the future

Sustainability is an essential pre-requisite of the strategy. Updating this information in the future for many EDC candidates will be time-consuming and sometimes impossible (in the case of lack of data or confidentiality constraints). The usefulness and feasibility of providing the information needed for prioritisation in a sustainable manner is an important parameter to be considered in the long term basis.

New initiatives including literature-mining tools are now able to capture experimental testing results which have been published in scientific journals. These new tools can identify additional information to support the identification of EDC candidates in future work.

A feedback will be performed at the end of the 2021 exercise, in order to evaluate if the strategies developed for identifying substances of interest and prioritising them can be improved.

Additional resources or international collaborations (at least at the European level) should be encouraged:

- With the European Commission that recently reaffirmed clear objectives regarding EDCs in its Chemical Strategy for sustainability towards a toxic-free environment[17] and with JRC (owner of EASIS database[18]).
- With ECHA as owner of the REACH registration database and having experiences of in data-mining. In addition, DEDUCT has also classified the substances identified based on their chemical structure. From the 686 substances proposed by DEDUCT, 646 are organic classified into 19 super-classes and 40 are inorganic compounds separated into 3 super-classes. As for the use categories proposed by DEDUCT, this information has not been evaluated by ANSES. However, this work could be compared with or included in the holistic approach developed by ECHA for mapping the chemical universe. It might allow to speed up managing EDCs and their substitutes based on similar structure leading to know similar

[17] https://ec.europa.eu/environment/strategy/chemicals-strategy_fr

[18] European Commission Joint Research Center, Endocrine Active Substances Information System, (2016). https://easis.jrc.ec.europa.eu/veil.

effects such as the ongoing initiatives for working on bisphenols or phthalates as groups at the EU level.

In addition, the modification of REACH annexes to include data allowing to evaluate ED properties will impact such work on identifying substances with endocrine activities.

- With Member States working on similar initiatives or others in order to gather our strengths on evaluations. In particular, France already collaborates with some Member States to a website administered by the Danish Environmental Protection Agency and recently released at the following link: https://edlists.org/the-ed-lists. The aim of this website is to primarily inform stakeholders about the current status of substances identified as known EDCs at the EU level (List I), substances that have undergone an evaluation and a proper identification in their regulation. Substance under evaluation or planned for evaluation for endocrine disrupting properties within the EU are communicated in the List II. Finally, those evaluated and considered to have endocrine disrupting properties by a participating National Authority are communicated in the List III (due to e.g. ED properties or structural similarities with known EDCs). These lists contain substances that have undergone (List I) or will undergo (List II) an evaluation in an EU legislative process due to concerns for possible endocrine disrupting properties (REACH), or as part of the mandatory process for approval or renewal (BPR and PPPR). The work carried on this report is therefore independent of this initiative. The substances prioritised for the work program will enter the list II. After evaluated, and if ED properties are confirmed, the substances will enter list III and list I if a regulatory dossier has been validated at the EU level.

5 Conclusion

Endocrine Disruptor Chemicals (EDCs) are substances that alter function(s) of the endocrine system and consequently cause adverse health effects. The second national strategy on EDCs (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. **According to the action number 3 of this strategy ANSES was mandated to identify chemicals that may present ED properties. This aimed at communicating a transparent and exhaustive information to all interested parties and to define the assessment work programme to be performed in France**.

The identification of an EDC for its health impact consequently to its endocrine activity with respect to the definition given by WHO, is the result of a thorough evaluation process, which needs to take into account the availability of data and knowledge. ED being a more recently studied hazard than others, the lack of references in both testing standards and, up to recently, in precise regulatory requirements enhances the difficulty to gather pertinent data and hence, to perform a conclusive evaluation for a given substance. Therefore, within this list, the availability of data plays a key role on the possibility to launch an assessment work that might be conclusive.

Concerning the identification, after reviewing the existing lists and methodologies, **ANSES ED-WG recommends to select the DEDuCT approach,** for the clarity of the method used for identifying the substances and based on the criteria applied selecting potential EDCs coherent with the WHO definition. This method identifies 686 substances of interest with regards to their endocrine properties. In addition, 81 co-formulants are added to the list of substances of interest after being identified while evaluating PPPs and BPs (13 substances already identified by DEDuCT). In addition, it is proposed to add the 197 active substances from PPPR or BPR ranked category I, II, III as defined applying the option 3 of the EU Impact Assessment, in 2016, and not yet identified by Deduct (45 among the 197) leading to a total number of 906 substances.

From these 906 substances of interest, the work performed on prioritisation is limited to the substances ANSES might be in charge of, with regard to its field of missions. Indeed, clear scientific data have not been made available to ANSES to prioritise the list of substances of interest for other purposes. In addition and due to major discrepancies in the data availability, different strategies have been ran in parallel in order to enhance the chance of evaluating the substances of concern for their endocrine activity in the appropriate timeframe.

- First of all, the phytopharmaceutical and biocidal active substances have their own timetable for substance evaluation for which data concerning ED characterization of the active substances is mandatory and planned to be provided by the applicants. To that respect, ANSES will evaluate the active substances for these products as part of France's assignment of the scheduled programme. Therefore, despite their potential presence in the list of interest, the corresponding substances will not enter the prioritisation process developed in that report. Three substances will be evaluated yearly within PPPR or BPR based on the timeframe designed within these regulations.

- For all other 705 substances, ANSES has designed different steps aiming at selecting the next substances for an in-depth evaluation of their ED properties. Chemicals substances already tightly regulated have been put aside. In addition, criteria were proposed using the information gathered automatically from available databases, to create a short and workable list for a ranking exercise. From the actual list of 59 substances, a manual analysis of their status (uses registered as manually rechecked for dedicated sources, tonnages, regulations applicable) allow to reduce the list down to 16 substances. This short-list of candidates will indeed be scored and ranked according to their hazards, exposure potential and societal concern (the latter defined by « Inter-COT PE » stakeholders). The ultime choice of the candidate substances will be performed by ministries in charge of SNPE 2.

The whole list of substances of interest as regards to a potential endocrine activity is available in Annex 5 of this report.

A feedback will be performed at the end of the first round of the process, in order to evaluate if the strategies developed for identifying substances of interest and prioritising them can be improved. Additional resources or international collaborations (at least at the European level) should certainly be encouraged: for instance with ECHA (owner of the REACH registration database and having experiences of in data-mining), with Member States working on similar initiatives, and with JRC (owner of EASIS database[19]). If the result of this process is encouraging, work will have to be done in order to extend the results of the DEDuCT initiative to pick up substances showing endocrine activity and effects on all living beings without limitations. Indeed, the number of substances that might have an impact on endocrine disruption (up to several thousands in some lists examined by ANSES) compared to the evaluation capacities, even when considering forces at European level, needs to establish and consider a list of substances to organize the work to be done, and to pay consideration to the evaluation performed by similar agencies.

[19] European Commission Joint Research Center, Endocrine Active Substances Information System, (2016). https://easis.jrc.ec.europa.eu/veil.

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ANNEXES

Annex 1 : Lettre de saisine

COURRIER ARRIVE
18 OCT. 2019
DIRECTION GENERALE

2019-SA-0179

Liberté • Égalité • Fraternité
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 08 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.

1

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^{os} 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

- **LISTE 2 : 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^{os} 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.

3

➡ **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

4

Annex 2 : Présentation des positions divergentes

Aucune

Annex 3 : Suivi des actualisations du rapport

Date	Version	Description de la modification
May 2020	V1	
July 2020	V2	The list of substances of interest and its table are modified as follows: Columns indicating the regulatory status, the tonnage and uses are added for each substance. Substances of the impact assesment (EU Impact Assessment, 2016) added.
November 2020 January 2021	V3	Chapter 4 added. Consultation of the CES REACh.
March 2021	V4	Scoring process detailed. Uses provided by ECHA dissemination website and by DEDuCT database are deleted from annex V for confidentiality and intellectual properties issues.

Annex 4 : Overview of governmental, agency or regulatory bodies: initiatives identifying chemicals as EDCs or potential EDCs

Initiative Name	Number of Chemicals or Chemical Groups Identified as EDCs or Potential EDCs	Selection Criteria and Process	Organisation Name and Related Information	Reference
BY GOVERNMENTAL ORGANISATIONS				
European initiatives				
Endocrine Active Substances Information System (EASIS)	**513**	- Contains data collected from over nine thousand studies with in vitro and in vivo assays from different species (including some human data). - Includes existing results from the 2000-2007 studies completed during creation of the EU Priority List of Chemicals within the EU-Strategy for Endocrine Disruptors. - Collects results from peer-reviewed studies, and more data will be added in the future either by the EU Joint Research Center (JRC) or through a crowdsourcing approach with input from stakeholders.	European Commission DG Joint Research Centre Initiative information: - Mandate to start development received in 2010. - Web-based application (EASIS 1.0) launched in September 2016 but now discontinued -New version (EASIS 2.0) is awaited.	**EASIS, 2020**
EC, Priority List of Chemicals for further evaluation of their role in endocrine disruption, 2003	**320**	Selection criteria: - Highly persistent and/or high production volume substance (HPV chemicals, i.e. more than 1000 tons each year) - Scientific evidence of endocrine disruption (ED) related effects: • For Category 1: At least one study showing evidence of ED activity in intact animals • - For Category 2: - at least some *in vitro* evidence of biological activity related to endocrine disruption; • - For Category 3 - no evidence of endocrine disrupting activity or no data available. -Process: • - Working list of chemicals was compiled from suspected EDCs published by organizations and in scientific literature. They were then discussed in a stakeholder meeting with government, industry, and civil society. - Expert reviews placed the chemicals into Category 1, 2, or 3.	European Commission (EC) Initiative information: - First established in the year 2000 a candidate list of 553 chemicals with 194 chemicals identified as Category 1 and 126 identified as Category 2. This categorization was further refined during an expert meeting which leads to 65 chemicals in Category 1 and 52 in Category 2. - Current database file available for download is: "EDS_2003_DHI2006.mdb". - This list is no longer updated, but it serves as basis for the EU Endocrine Active Substances Information System (EASIS).	**EC Priority List of Chemicals for further evaluation of their role in endocrine disruption 2003**

		- For the chemicals assigned to Category 1, the available information was reviewed to decide, if it was possible, that humans or wildlife might actually be exposed. Highest concern was allotted to those where human or wildlife were expected to be exposed, medium concern related to those where humans were not expected to be exposed but wildlife could be, and lowest concern was scored for those where neither humans or wildlife were exposed. Which means that chemicals were further categorised as having high, medium, or low exposure concern for humans and wildlife.		
EU Impact Assessment on Criteria to Identify Endocrine Disruptors 2016	**630**	Selection criteria: - Regulated under the Plant Protection Products and Biocidal Products except: substances of no concern or capacity to cause endocrine disrupting effects, low risk substances, natural extracts/mixtures/repellents, and attractants/plant hormones. - Regulated under REACH regulation and were on the Candidate List as SVHCs for endocrine disruption (ED), had opinion available from Member State Committee regarding it as an SVHC due to ED, were on the Candidate List as an SVHC due to reprotoxicity 1A/1B, were listed in AnnexXVII due to ED concern as reprotoxic 1A/1B, or were placed on CoRAP list due to ED concern. - Regulated under the Cosmetic Products Regulation and: had opinion available from the Scientific Committee on Consumer Safety (SCCS) discussing ED potential, had SCCS opinion due to	European Commission Initiative information: - Impact assessment launched in July 2013 on the criteria options to identify endocrine disruptors. - Goal is to assess which chemicals would fall under the different criteria options presented in the roadmap of the impact assessment [European Commission, Roadmap, 2014]. - Results of the impact assessment were published in June 2016 [European Commission Report, 2016; Arapaki et al., 2016].	**EU Impact Assessment, 2016**
CoRAP-2019 List of Substances	**86 substances** having an initial ground for concern as being a potential EDC)	Selection criteria: - In need of evaluation based on risk-based criteria considering hazard information, exposure information, and tonnage (following REACH Regulation Article 44(1)). - Examples include: suspected/known endocrine disrupting properties, PBTs, vPvBs, CMRs, and sensitizers; having wide dispersive use, high aggregated tonnage, high risk characterization ratio, etc (ECHA, 2011). Process: - Agency defines risk-based criteria and then selects substances to be evaluated (or receives nominated substances from member states for evaluation). - A member state is designated to evaluate each substance.	European Chemicals Agency (ECHA) Initiative information: - The first Community Rolling Action Plan (CoRAP) list was adopted in 2012 for a period of three years. - Updated each year to define new substances to be reviewed.	**CoRAP, 2019**
PACT (Public activities coordination tool)	**135 substances** having an initial ground for concern as being a potential EDC (search with key	PACT provides up-to-date information on the activities planned, ongoing or completed by ECHA and/or MSCAs for a given substance in the following areas: Data generation and assessment – dossier evaluation, substance evaluation, informal hazard assessment (PBT/vPvB/ED). Regulatory management option analysis (RMOA). Regulatory risk management – harmonised classification and labelling (CLH), SVHC identification, restriction. A summary of the all the substance-specific activities can be found under 'Details' for each entry.	European Chemicals Agency (ECHA) Initiative. Updated every 48 hours.	**PACT, 2019**

	word: endocrine)			
	79 substances retrieved when "Endocrine Disruptor Assessment" is selected in the field further information	This ECHA's endocrine disruptor (ED) assessment list includes the substances undergoing an ED assessment under REACH or the Biocidal Products Regulation that have been brought for discussion to ECHA's ED Expert Group		
REACH Substances of Very High Concern Candidate List for Authorisation	**16** chemicals with 6 for HH and 12 for ENV	Selection criteria: - May have serious effects on human health or the environment - Based on WHO/IPCS 2002 definition of EDCs, together with the recommendations from the Endocrine Disruptor Expert Group. Process: - A chemical is proposed by an EU member state or the European Chemicals Agency as an SVHC and opened for comments or further information. - The Member State Committee reviews the proposal and comments and must unanimously agree to identify it as an SVHC. Otherwise, the matter is referred to the European Commission.	European Chemicals Agency (ECHA) Initiative information: - The assessment of individual chemicals is provided on the ECHA's website. - Inclusion of a substance on this list initiates legal obligations for companies that manufacture or import the substance. - The Candidate List is regularly updated.	**SVHC, 2019**
EU national initiatives				
Danish Center on Endocrine Disrupters (2017)	**30** substances (with 19 ED and 11 « suspected ED »)	Selection criteria: - 22 substances placed on the ChemSec SIN List 2.0 due to their endocrine disrupting properties [Hass et al., 2012a] and an additional 4 substances requested by the Danish EPA for review [Hass et al., 2012b]. - Scientific evidence of endocrine disruption (ED) related effects [Hass et al., 2012a]: For Category 1: Adverse in vivo effects where an ED mode of action is highly plausible; ED mode of action in vivo that is clearly linked to adverse in vivo effects (by e.g. read-across) For Category 2a: Adverse effects in vivo where an ED mode of action is suspected; ED mode of action in vivo that is suspected to be linked to adverse effects in vivo; ED mode of action in vitro combined with toxicokinetic in vivo data (and relevant non-test information such as read across, chemical categorisation and QSAR predictions) For Category 2b: In vitro/in silico evidence indicating potential for endocrine disruption in intact organisms; observed effects in vivo that could be ED-mediated Process:	Danish Environmental Protection Agency (EPA) Initiative information: - Resulted in 25 of 26 assessed substances considered as known or suspected EDCs according to the Danish criteria (Hass et al., 2012a). - Denmark submitted its proposal for EDC criteria to the European Commission in May 2011. - The Danish EPA contracted the Danish Centre on Endocrine Disrupters to do the assessments, and the reports were published in May 2012. - In August of 2016, the Danish EPA announced that they are planning to update the list. 1 - Danish center on endocrine disrupters published a final report "List of Endocrine Disrupting Chemicals Final report" in December 21th, 2017	**Danish Center on Endocrine Disrupters (2017)**

		- Selected chemicals were assessed according to Denmark's proposed criteria for identifying EDCs. - The Danish Center on Endocrine Disrupters, 2017 updated their previous work on endocrine disrupters following the request of the Danish EPA. This work was based on the analysis of background lists and a master list which include several thousands of substances suspected to be EDCs. The amount of data for the substances being listed as suspected EDCs on various lists appears to vary considerably from no data found in published literature, over e.g. some MoA data (in vitro, QSAR) to comprehensive in vivo and MoA data. A prioritization step with regards to hazard scenarios, mode of action and risk for exposure was needed which led to around 180 substances on the prioritized basis list. A "literature ED hazard screening" step was conducted in order to select those suspected substances of highest relevance for ED assessment. A literature screening of 52 of the prioritized substances showed that there was a lack of relevant MoA data and/or adverse effect data for around 40-50% of the substances. The time needed for ED assessment of individual suspected EDs varies substantially depending mainly on the amount of data available (e.g. from a few to many studies). Finally, the thorough evaluations of 13 of the prioritized suspected EDs selected based on the "literature ED hazard screening" step, concluded that 9 fulfil the WHO definition of an EDC, whereas 4 are suspected EDCs. A re-evaluation of 17 substances previously evaluated as EDCs (Hass et al. 2012a, Hass et al. 2012b) confirmed that for 10 substances it is evaluated that the data show that these substances fulfil the WHO-definition of an EDC. The remaining 7 substances are evaluated as likely to fulfil the WHO-definition of an EDC, however various limitations in the data indicate that it may be more difficult to obtain international agreement that these 7 substances are EDs, compared to the 10 substances.		
KEMI, (Kemikalieinspektionen) the Swedish Chemicals Agency, report 2017	**37 bisphenols**	Investigation on 39 bisphenols: - surveyed on the European market -screening method that groups substances based on their chemical structure, possible use in different applications, and potential ED properties according to data simulations. -KEMI concludes that 37 Bisphenols are identified as Potential EDCs	KEMI published in October 2017	**KEMI, 2017**
International initiatives				
Japan-EXTEND-2010 and EXTEND-2016 (Japan Extended Tasks on Endocrine Disruption (EXTEND))	**132**	Selection criteria: - Chemicals detected in the ambient aquatic environment are selected for testing and assessment if a certain amount of knowledge with any indication of potential or suspected endocrine disrupting effects are obtained through literature review. [**Japan-EXTEND-2010**]	Ministry of the Environment, Government of Japan Initiative information: - Originally established as "SPEED'98" (May 1998), with a list of 65 suspected endocrine disruptors (now abolished).	**EXTEND-2010 and EXTEND-2016**

		Process: - A conservative reliability evaluation is conducted for the selected chemicals, and candidate chemicals for testing are identified. - A two tiered framework for testing and assessment of endocrine disrupting effects of chemicals to aquatic organisms was developed: Tier 1 with in-vitro and short-term in-vivo assays for detection of endocrine activity and Tier 2 for identification of adverse effects. - Relevant test protocols have been developed for the two-tiered framework, in most cases using the OECD Test Guideline Program. - The selected candidate chemicals are subjected to Tier 1 testing. In-vitro assays are conducted first for prioritization of in-vivo assays. Via the Tier 1 assessment, candidate chemicals for Tier 2 testing are identified. - Referring to all available knowledge, including data obtained by Tier 2 in-vivo assays, environmental risk assessments will be conducted. [**Japan-EXTEND, 2010**].	- Fully reorganized into "EXTEND 2005" (March 2005) focusing only on environmental effects with emphasis on basic research and observation of wildlife. - Evolved into new programs "**Japan-EXTEND 2010**" (July 2010) and "**Japan-EXTEND 2016**" (June 2016), where testing and assessment have been accelerated under a newly-developed framework, aiming at future risk assessment and management. - Knowledge obtained in the program will be referred to in the existing risk assessment practices (both in the screening-level risk assessment program and in comprehensive ones for relevant regulation, such as environmental risk assessment under the Chemicals Substances Control Law and for setting Environmental Quality Standards). The results generated by this program are not available yet.	
NIEHS Comparative toxicogenomics database (CTD)	**20**	CTD is a publicly available database that aims to advance understanding about how environmental exposures affect human health. It provides manually curated information about chemical–gene/protein interactions, chemical–disease and gene–disease relationships. These data are integrated with functional and pathway data to aid in development of hypotheses about the mechanisms underlying environmentally influenced diseases.	This program is supported by funds from the National Institute of Environmental Health Sciences (). CTD Base was released on November 2004.Last update: 4 février 2020	**NIEHS CTD, 2020**
US – Illinois –EPA – 1997. Endocrine Disruptors Strategy		Preliminary List of Chemicals Associated with Endocrine System Effects in Animals and Humans or In Vitro.	Endocrine Disruptors Strategy. 1997. (Table 1: Preliminary List of Chemicals Associated with Endocrine System Effects in Animals and Humans or In Vitro). http://www.nihs.go.jp/hse/environ/illiepatable.htm	**Il EPA, 1997**
US – EPA –EDSP - 2017 (US – EPA - Endocrine Disruptor Screening Program (EDSP) 2017)	**174 (**for Tier 1 screening)	Selection criteria: - Pesticide active ingredient, high production volume pesticide inert ingredient, or chemical identified under the Safe Drinking Water Act. - Selected at the agency's discretion and based on identified exposure potential. - Priority given to chemicals present in all of four investigated exposure pathways. - Produced or used in the United States [US-EPA, 2015]. Process: - Two-tiered approach created to screen pesticides, chemicals, and contaminants for potential effect on estrogen, androgen, and thyroid hormone systems. - Substances found to exhibit potential to interact with any of these three hormone systems through experimental assays or other scientifically relevant information (including submissions) during Tier 1 will continue to Tier 2. - Chemicals selected for Tier 2 are tested to identify adverse endocrine-related effects and to create a quantitative relationship between the dose and adverse effect.	United States Environmental Protection Agency Initiative information: - Public and stakeholder consultations have taken place during the establishment of the program. - Initial list of 67 chemicals for Tier 1 screening published in April 2009 (pesticide active ingredients and high production volume pesticide inert ingredients). - Second list of 107 chemicals for Tier 1 screening published in June 2014 (pesticide active ingredients and chemicals identified under the Safe Drinking Water Act). - Results for 52 chemicals that have completed Tier 1 screening have been published (last update September 2015).	**US-EPA-EDSP21--2017** **US-EPA-EDSP21--2019** **US EPA, 2009**

			- The EPA is developing computational toxicology methods and high throughput assays to rapidly screen chemicals. The EDSP will transition to rely on these tools as they become ready for use.	
US-EPA- EDSP 21 Dashboard 2017 (US-Endocrine Disruption Screening Program for the 21st Century (EDSP21) Dashboard)	**>1800**	- Contains chemical screening data from the EPA's ToxCast and Tox21 projects, chemical exposure data and prediction models, chemical structures and annotations, and a physical chemical properties database.	United States Environmental Protection Agency Initiative information: - Part of the US EPA's Endocrine Disruptor Screening Program and created to help the program to evaluate chemicals. - Still under development to add functionality.	**US-EPA-EDSP 21, 2017**
US-EPA-EDSP21-Dashboard-2019	**9414**	US-EPA displays bioassay information, bioactivity concentrations, estrogen and androgen receptor (ER and AR) model results, predicted physicochemical properties, and more on an ad-hoc dashboard. and https://www.epa.gov/chemical-research/toxicity-forecaster-toxcasttm-data), published ER (PMID 26272952) and AR (PMID 27933809) where (see: https://comptox.epa.gov/dashboard and https://www.epa.gov/chemical-research/toxicity-forecaster-toxcasttm-data), published ER (PMID 26272952) and AR (PMID 27933809) where model results are available for citation).	United States Environmental Protection Agency Initiative information: - Part of the US EPA's Endocrine Disruptor Screening Program and created to help the program toevaluate chemicals.	**US-EPA-EDSP21--2019**
US - FDA - EADB, 2019 (US-FDA-Estrogenic Activity Database (EADB))	**8,212 chemicals**	- Set of estrogenic activity data from a variety of data sources. - 18'114 estrogenic-activity data points collected for 8'212 chemicals tested in 1'284 binding assays, reporter-gene assays, cell-proliferation assays, and in-vivo assays in 11 different species.	United States Food and Drug Administration Initiative information: - Part of the Endocrine Disrupter Knowledge Base (EDKB).	**US - FDA - EADB, 2019**
US-FDA-EDKB-2019 (US FDA Endocrine Disruptor Knowledge Base (EDKB database))	**>3'200** chemicals	The EDKB database is a curated database containing the Estrogen Receptor (ER) and Androgen Receptor (AR) training datasets together with considerable additional data from the literature for various types of *in vitro* and *in vivo* assays. Data for more than 3200 chemicals and 2000 relevant citations are available. The relational database provides Boolean and chemical structure search, graphical and table displays, as well other capabilities and data export functions.	United States Food and Drug Administration Initiative information:	**US - FDA - EDKB - 2019**
Australian Government, Land and Water Australia (Williams et al., 2007 (report not available) and Scott et al., 2014)	**14**	Selection criteria: - Identified to be the most significant chemicals due to their relative potency to the steroidal hormone estradiol (E2) (taken as a benchmark for estrogenic potential), concentrations detected in wastewater treatment plant effluent, and observed biological effects. Process: - Reviewed published literature for data detailing the relative potency of chemicals to E2, wastewater effluent concentrations, and reported in vivo effects. - CAS number is not reported only chemical name is mentioned.	Land and Water Australia Initiative information: - Published in 2007 as part of a three-year pilot study by the Australian Government. - Identified chemicals are listed in Table 3.1 of the report and are used to select target chemicals for sampling in the Australian riverine environment. - Information on follow-up studies is unclear.	**Land and Water, 2014**
BY NON-GOVERNMENTAL ORGANISATIONS				

EDCs Databank from University of Cartagena, 2015	**615 substances** including pesticides, natural and industrial products, cosmetics, drugs and food additives, among other low molecular weight xenobiotics.	Selection criteria: -substances listed as EU potential EDCs -substances from the TEDX list. Includes: -Three-dimensional structures retrieved from PubChem, -Information from different databases and search engines (e.g. PubChem, TOXNET, ACToR, Fable, PubMed cf. Appendix 1). Built with: HTML, CSS and PHP languages. This database can be used to study the toxicological effects of these molecules, or to develop pharmaceuticals targeting hormone receptors, through docking studies, high-throughput virtual screening and ligand-protein interaction analysis. Accessible online at: http://edcs.unicartagena.edu.co	University of Cartagena in Colombia.	**EDCs Databank, 2015**
DEDuCT, 2019	**686 substances**	DEDuCT is based on an analysis of existing scientific literature containing supporting experimental evidence for endocrine-specific perturbations in humans or rodents. A detailed workflow was developed (see Figure 1) to identify potential EDCs from published research articles cf. Karthikeyan et al., 2019 also available at: https://www.sciencedirect.com/science/article/pii/S004896971933339X). The following sources were considered: PubMed query (until February, 2018), WHO report, TEDX (February, 2018), EDCs Databank, 2015.	Institute of Mathematical Sciences in Chennai (India)	**DEDuCT, 2019**
European Trade Union Confederation, Trade Union Priority List for REACH Authorisation, 2010	**29 substances (Cat. 2 ED) 42 substances (Cat. 1 ED) with a total number of 70 chemical substances**. numerous substances are associated with several CAS numbers	Selection criteria: - Listed as category 1 or 2 on the European Commission's priority list of potential endocrine disruptors and seen to meet the requirement of being an SVHC. - High production volume chemical for which a substance information exchange forum (SIEF) was formed by March 19, 2010 and was expected to be registered by December 2010. - Having a known use and not already banned by other means, not a residue or intermediate, not only used as a pesticide or biocide, and not a complex hydrocarbon distillate. Process: - Prioritization criteria were set and scores were given for each chemical. - Chemicals were ranked by score to set priority (Romano et al., 2011).	European Trade Union Confederation (ETUC) Initiative information: - Chemicals selected have been identified as causative agents for recognised occupational diseases in the European Union. - Objective is to reduce chemical-related occupational diseases and incentivise innovation and safer alternatives. - First established in 2009 and updated with 29 new entries in 2010.	**ETUC, 2010**

IPCP (International Panel on Chemical Pollution) 2018	**45**	- State of the Science of Endocrine Disrupting Chemicals (WHO/UNEP, 2013). - Literature review of more than 100 pesticides for endocrine activity [1] An assessment of endocrine disrupting properties in the European Food Safety - Authority (EFSA) conclusions on a pesticides peer review [2] Studies included in the Endocrine Active Substances Information System (EASIS) database [3]. - Results of ongoing screening and evaluation programs such as the US EPA's Endocrine Disruptor Screening Program (EDSP 2016) EU's Community Rolling Action Plan (CoRAP, 2016). [1] R. McKinlay, J.A. Plant, J.N.B. Bell, N. Voulvoulis, Endocrine disrupting pesticides: Implications for risk assessment, Environ. Int. 34 (2008) 168–183. doi:10.1016/j.envint.2007.07.013. [2] European Food Safety Authority, Assessment of endocrine disrupting properties in EFSA Conclusions on the Pesticides Peer Review, 2015. http://www.efsa.europa.eu/en/supporting/pub/867e. [3] European Commission Joint Research Center, Endocrine Active Substances Information System, (2016). https://easis.jrc.ec.europa.eu/veil/ (accessed October 20, 2016). According to the IPCP report, the SIN List is a comprehensive list of substances that have been identified by ChemSec as fulfilling the criteria for Substances of Very High Concern (SVHC), as described in the EU chemicals regulation REACH article 57. Three categories are included in REACH article 57, and the SIN List encompasses substances from these three categories: 1. Chemicals that can cause cancer, alter DNA or damage reproductive systems. These are called CMR substances (Carcinogenic, Mutagenic or Toxic to reproduction.) 2. Harmful substances that do not easily break down and thus accumulate in the food chain. These are known as PBT substances. There is also the abbreviation vPvB, short for very Persistent and very Bio-accumulative. 3. Substances called "substances of equivalent concern". This category covers substances that are not automatically covered by the other two categories, but which		**IPCP, 2018**

		nonetheless give rise to equivalent level of concern in terms of potential damage to health and environment. This category includes endocrine disrupting chemicals. All substances on the SIN List have been screened to identify substances covered by the authorisation provisions in REACH. Substances exempt or otherwise not regulated by REACH, such as pesticides, intermediates and unintentionally produced substances, have accordingly been removed. Information about chemical companies producing SIN substances in the USA was added in July 2016. This information is based on the US EPA registry data.		
Our Stolen Future, Widespread Pollutants with Endocrine-Disrupting Effects (2016)	**86**	Selection criteria: - Each chemical included is linked to at least one scientific publication, and a call for submissions of new chemicals and feedback exists.	Our Stolen Future Initiative information: - Website of the 1996 book of the same name written by Theo Colborn (founder of TEDX). - Only chemical name is reported. No indication on the CAS number is given - Information on updates is unclear.	**OurStolenFuture, 2016**
Pesticide Action Network (PAN) International List of Highly Hazardous Pesticides	**52**	Selection criteria: - Pesticide ingredient identified by PAN as being highly hazardous following PAN's published methodology. - Two criteria have been used as the selection basis for endocrine disrupting potential: i). those that have been categorized in the EU Commission's priority list as Category 1 (at least one study providing evidence of endocrine disruption in an intact organism), or ii). those that have been classified as Category 2 for Globally Harmonized System (GHS) carcinogenicity and as Category 2 for EU reproductive toxicity (following European Commission regulation 1272/2008).	Pesticide Action Network (PAN) Initiative Information: - First list published in 2009 and updated in 2015 and 2016.	**PAN, 2016**
RISCTOX, ISTAS, 2012	**2281 substances**	- Contains toxic and hazardous substances and data regarding their health risks, environmental risks, and related regulations. - 2281 substances are categorized within the database as endocrine disrupters based on their inclusion within other initiatives such as the EU Priority List and Scorecard list.	ISTAS & the European Trade Union Institute Initiative information: - Database commissioned by the European Trade Union Institute and developed by ISTAS. Last update July 2012	**RISCTOX, ISTAS, 2012**
Suspected Endocrine Toxicants, Scorecard, Endocrine Toxicants, 2011	**310**	Selection criteria: - Each chemical included is linked to a reference source that is either a journal article or a report from a government agency or NGO. - Environmental Defense's list of suspect endocrine toxicants is compiled from the following sources: - ATSDR: Agency for Toxic Substances and Disease Registry. Minimal risk Levels for Hazardous Substances. January 2004. http://www.atsdr.cdc.gov/mrls.html	Scorecard (sponsored by GoodGuide) Initiative information: - Information on updates is unclear.	**Scorecard, 2011**

		BKH: BKH/European Commission. Towards the establishment of a priority list of substances for further evaluation of their role in endocrine disruption: - preparation of a candidate list of substances as a basis for priority setting. Final report-November 2000. http://europa.eu.int/comm/environment/docum/01262_en.htm#bkh. Category 1 chemicals from Annex 1: Candidate list of 553 substances. http://europa.eu.int/comm/environment/docum/bkh_annex_01.pdf -BRUC: Brucker-Davis, F. Effects of Environmental Synthetic Chemicals on Thyroid Function. Thyroid. 8(9): 827-856. 1998. -EDF: See Environmental Defense's Custom Hazard Identification documentation. -EPA-HEN: US EPA, Air Risk Information Support Center. Health Effects Notebook for Hazardous Air Pollutants. http://www.epa.gov/ttnatw01/hlthef/hapindex.html -EPA-SDWA: UUS EPA. Announcement of the Draft Drinking Water Contaminant Candidate List; Notice. 62 Federal Register 52193-52219 (October 6, 1997). (Table 6). http://www.epa.gov/safewater/ccl/dwccl.pdf -EPA-TRI: US EPA. Addition of Certain Chemicals; Toxic Chemical Release Reporting; Community Right to Know. Proposed and Final Rules. 59 Federal Register 1788 (Jan 12, 1994); 59 Federal Register 61432 (November 30, 1994). Summarized in Hazard Information on Toxic Chemicals Added to EPCRA Section 313 Under Chemical Expansion. http://www.epa.gov/tri/chemical/hazard_cx.htm -GUIL: Guillette, L. J., and E. Guillette. Environmental Contaminants and Reproductive Abnormalities in Wildlife: Implications for Public Health? Toxicology and Industrial Health. 12(3): 537-550. 1996. -IL-EPA: Illinois EPA. Endocrine Disruptors Strategy. 1997. (Table 1: Preliminary List of Chemicals Associated with Endocrine System Effects in Animals and Humans or In Vitro). http://www.nihs.go.jp/hse/environ/illiepatable.htm JNIHS: Japanese National Institute of Health Sciences. Lists of Paradigmatic Chemicals. http://www.nihs.go.jp/hse/endocrine-e/paradigm/paradigm.html KEIT: Keith, L.H. (ed.). Environmental Endocrine Disruptors. John Wiley & Sons, NY. 1997. http://www.wileyeurope.com/cda/product/0,,0471191450%7Cdesc%7C3037,00.html NJ-FS: New Jersey Department of Health Services. Right to Know Program, NJDOH, Trenton, NJ. http://www.state.nj.us/health/eoh/rtkweb/rtkhsfs.htm OEHHA-CREL: California EPA, Office of Environmental Health Hazard Assessment. Air Toxics Hot Spots Program Risk Assessment Guidelines, Part III: Technical Support Document "Determination of Noncancer Chronic Reference Exposure Levels". Includes all Chronic Reference Exposure Levels (CRELs) adopted by OEHHA as of August 2003 (http://www.oehha.ca.gov/air/chronic_rels/AllChrels.html, plus draft CRELS proposed through March 2004 (http://www.oehha.ca.gov/air/chronic_rels/index.html. RTECS: National Institute for Occupational Safety and Health's Registry of Toxic Effects of Chemical Substances. See Environmental Defense's Suspect Hazard Identification documentation. WWF: World Wildlife Fund. Our Stolen Future. Widespread Pollutants with Endocrine-disrupting Effects. http://www.ourstolenfuture.org/Basics/chemlist.htm. The WWF list is derived from references detailed at http://www.ourstolenfuture.org/Sources/chemsources.htm and was originally		

		published in: Colborn, T., F.S. vom Saal, and A.M. Soto. Developmental Effects of Endocrine-Disrupting Chemicals In Wildlife and Humans. Environmental Health Perspectives 101(5): 378-384. 1993.		
SIN List – 2019 by ChemSec	**127** (12 sept. 2019)	Selection criteria: - For the update in 2011, the set of chemicals listed as category 1 or 2 on the European Commission's priority list of chemicals were considered; for the second round in 2014, other initiatives including the TEDX List were considered. - Have known uses relevant to EU REACH and not used only as intermediates. - Have peer-reviewed, high quality, relevant, primary research literature showing endocrine related effect(s). In 2011, at least three studies required (two of which must be in-vivo) that pass an internal peer review by an internal research team. In 2014, the WHO/IPCS definition was used requiring studies that clearly showed endocrine mode-of-action linked to a probable serious effect. (ChemSec, 2018) Process: - Reviewed by external EDC experts following the REACH guidance document (ChemSec, 2018).	International Chemical Secretariat (ChemSec) Initiative information: - Substances having EDC properties were added to the list as "equivalent level of concern". Endocrine disruption being one of several endpoints investigated for those substances. -A new SINimilarity tool is now available? - The SIN List is regularly updated.	**SIN, 2019**
TEDX List of Potential Endocrine Disruptors, (2019).	1482	Selection criteria: - At least one peer-reviewed study has been published demonstrating effects on the endocrine system.	The Endocrine Disruption Exchange (TEDX) Initiative information: - From 2003 to July 2019 TEDX produced and shared scientific data on EDC. - Regularly updated until July, 2019. - The website will remain available until September 2022.	**TEDX 2019**
WHO-UNEP, 2013. State of the Science of Endocrine Disrupting Chemicals.	**175**	In 2013, UNEP and WHO published an update of the IPCS (2002) document, entitled State of the Science of Endocrine Disrupting Chemicals (WHO/UNEP, 2013). This report provides the global status of scientific knowledge on exposure to and effects of EDCs and potential EDCs.		**WHO-UNEP, 2013**

Annex 5 : list of substances of interest as regards to a potential endocrine activity provided in .xls.

Annex 6 : Does DEDuCT picks up REACH substances of interest for their ED potential identified in PACT, 2019

Substance name	CAS no	Identified by DEDUCT, 2019
3-benzylidene camphor; 3-BC	15087-24-8	YES
(±)-1,7,7-trimethyl-3-[(4-methylphenyl)methylene]bicyclo[2.2.1]heptan-2-one	36861-47-9	YES
1,1'-(isopropylidene)bis[3,5-dibromo-4-(2,3-dibromo-2-methylpropoxy)benzene]	97416-84-7	NO
1,1'-(isopropylidene)bis[3,5-dibromo-4-(2,3-dibromopropoxy)benzene]	21850-44-2	NO
1,2,4-triazole	288-88-0	NO
1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylindeno[5,6-c]pyran	1222-05-5	YES
1,3-dihydro-4(or 5)-methyl-2H-benzimidazole-2-thione	53988-10-6	NO
1,3-dihydro-4(or 5)-methyl-2H-benzimidazole-2-thione, zinc salt	61617-00-3	NO
1-[2-(allyloxy)-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole	35554-44-0	YES
2,2',6,6'-tetra-tert-butyl-4,4'-methylenediphenol, 2,2′,6,6′-Tetra-tert-butyl-4,4′- methylenedi	118-82-1	NO
2,2,6,6-tetrabromo-4,4-isopropylidenediphenol, 2,2',6,6'-tetrabromo-4,4'-isopropylidenedip	79-94-7	YES
2,2'-dimethyl-4,4'-methylenebis(cyclohexylamine)	6864-37-5	NO
2,2-dibromo-2-cyanoacetamide	10222-01-2	NO
2,4-di-tert-butylphenol	96-76-4	NO
2,6-di-tert-butyl-p-cresol	128-37-0	YES
2-(4-tert-butylbenzyl)propionaldehyde	80-54-6	YES
2-Ethylhexyl trans-4-methoxycinnamate	83834-59-7	NO
2-methyl-1-(4-methylthiophenyl)-2-morpholinopropan-1-one	71868-10-5	YES
3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl acrylate	17527-29-6	NO
3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl methacrylate	2144-53-8	NO
3,5,5-trimethylcyclohex-2-enone	78-59-1	NO
3-methylpyrazole	1453-58-3	NO
3-phenoxybenzyl-2-(4-ethoxyphenyl)-2-methylpropyl ether	80844-07-1	NO
4,4'-(1,3-phenylene-bis(1-methylethylidene))bisphenol, 4,4'-(1,3-phenylene-bis(1-methylet	13595-25-0	YES
4,4'-(1-methylpropylidene)bisphenol	77-40-7	YES
Bisphenol A; BPA	80-05-7	YES
4,4'-Isopropylidenediphenol, oligomeric reaction products with 1-chloro-2,3-epoxypropane	25068-38-6	NO
4,4'-methylenedi-2,6-xylenol	5384-21-4	NO
4,4'-sulfonyldiphenol, 4,4'-sulphonyldiphenol	80-09-1	YES
4-heptylphenol, branched and linear	-	NO
4-tert-butylphenol	98-54-4	YES
6,6'-di-tert-butyl-4,4'-thiodi-m-cresol	96-69-5	NO
ammonium perchlorate, Ammonium perchlorate	7790-98-9	YES
Benzotriazole	95-14-7	NO
Chrysanthemum cinerariaefolium extract from open and mature flowers of Tanacetum cinera	89997-63-7	NO
Chrysanthemum cinerariaefolium, extract from open and mature flowers of Tanacetum cinera	89997-63-7	NO
Climbazole	38083-17-9	NO
Cyanamide	420-04-2	NO
Dapsone	80-08-0	NO
dichloromethane; methylene chloride, Dichloromethane	75-09-2	YES
Dicyclohexyl phthalate	84-61-7	YES
Diethylmethylbenzenediamine	68479-98-1	NO
diuron (ISO); 3-(3,4-dichlorophenyl)-1,1-dimethylurea, Diuron	330-54-1	YES
Ethylene dinitrate	628-96-6	NO
Ethylene oxide	75-21-8	YES
Formic acid	64-18-6	NO
Homosalate	118-56-9	YES
Isopentyl p-methoxycinnamate	71617-10-2	NO
K-HDO	66603-10-9	NO
Methyl 4-hydroxybenzoate	99-76-3	YES
Methyl salicylate	119-36-8	NO
Nitrobenzene	98-95-3	YES
Oligomerisation and alkylation reaction products of 2-phenylpropene and phenol [Previously	-	NO
Oxybenzone	131-57-7	YES
Oxydiethylene dinitrate	693-21-0	NO
Ozone	10028-15-6	NO
p-(1,1-dimethylpropyl)phenol	80-46-6	YES
p-cresol	106-44-5	YES
Phenol, dodecyl-, branched	121158-58-5	NO
Phenol, styrenated, phenol, styrenated,reaction mass of 2,4,6-tris(1-phenyl-ethyl)phenol an	61788-44-1	NO
propyl 4-hydroxybenzoate, Propyl 4-hydroxybenzoate	94-13-3	YES
Resorcinol	108-46-3	NO
Silver copper zeolite	130328-19-7	NO
Silver sodium zirconium hydrogenphosphate	265647-11-8	NO
silver zinc zeolite (Zeolite, LTA framework type, surface-modified with silver and zinc ions)[T	130328-20-0	NO
sodium perchlorate, Sodium perchlorate	7601-89-0	NO
Sulphur dioxide	7446-09-5	NO
Terephthalic acid	100-21-0	YES
tert-butyl methyl ether, Tert-butyl methyl ether	1634-04-4	YES
tert-butyl-4-methoxyphenol	25013-16-5	YES
Tetraphenyl m-phenylene bis(phosphate)	57583-54-7	NO
Thiram	137-26-8	YES
Tributyl citrate	77-94-1	YES
Tributyl O-acetylcitrate	77-90-7	YES
Triphenyl phosphate	115-86-6	YES
Tris(2-ethylhexyl) benzene-1,2,4-tricarboxylate, tris(2-ethylhexyl)-benzene-1,2,4-tricarboxy	3319-31-1	NO
Ziram	137-30-4	YES

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