Avis de l'Anses
Saisine n° «2017-SA-0235»

Le directeur général

Maisons-Alfort, le 4 avril 2018

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

relatif à la consultation publique sur le document intitulé «*Guidance document for the implementation of the hazard-based criteria to identify endocrine disruptors (EDs) in the context of Regulations (EC) N°1107/2009 and (EU) N°528/2012*»

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.

Le présent avis s'inscrit dans le cadre d'une demande conjointe des Ministres de l'environnement, de l'énergie et de la mer en charge des relations internationales sur le climat d'une part, et des affaires sociales et de la santé d'autre part, adressée à l'Anses le 26 janvier 2017. Les deux ministres demandaient en effet à l'Agence de contribuer activement aux travaux d'élaboration des guides méthodologiques relatifs à la gestion des risques présentés par les perturbateurs endocriniens, notamment au titre des règlements relatifs aux pesticides.

1. CONTEXTE ET OBJET DE LA SAISINE

Le 15 juin 2016 la Commission européenne (CE) a publié une proposition de critères d'identification des perturbateurs endocriniens (P.E.) ainsi que plusieurs textes visant à proposer un projet d'amendement des règlements en vigueur relatifs aux produits biocides et aux produits phytopharmaceutiques, via des projets d'acte délégué au titre du règlement biocides et acte d'exécution pour les produits phytopharmaceutiques. L'Anses a rendu un avis le 19 juillet 2016 visant à proposer des critères définissant les perturbateurs endocriniens (PE) sur la base de ces deux documents, et en réponse à une saisine de la Ministre de l'environnement, de l'énergie et de la mer, en charge des relations internationales sur le climat. Cet avis a servi, entre autre, à définir la contribution française aux discussions communautaires sur cette question.

Les critères d'identification des P.E. dans le cadre de la réglementation (UE) n°528/2012[1] proposés par la Commission européenne ont été publiés au journal officiel le 17 novembre 2017. Ceux-ci sont entrés en vigueur le 7 décembre 2017 et seront applicables à partir du 7 juin 2018.

Les critères d'identification des P.E. dans le cadre de la réglementation (UE) n°1107/2009[2] proposés par la Commission européenne ont été adoptés par les Etats membres les 12-13

[1] Concernant la mise à disposition sur le marché et l'utilisation des produits biocides.

décembre 2017, celui-ci a été transmis pour examen au parlement pour une adoption finale dans un délai de 3 mois.

Dans ce contexte, la Commission européenne a confié à l'Autorité européenne de sécurité des aliments (EFSA), l'Agence européenne des produits chimiques (ECHA) et le Centre commun de recherche (JRC) l'élaboration d'un guide méthodologique pour la mise en application des critères de dangers nécessaires à l'identification des P.E. tels que prévus par ces nouvelles dispositions réglementaires. Le projet de guide méthodologique a été soumis par l'ECHA à une consultation publique du 08 décembre 2017 au 31 janvier 2018, sur son site internet, et l'Anses a décidé de répondre à cette consultation publique.

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) ».

La réponse à cette saisine a été coordonnée par la Direction de l'évaluation des risques (DER) avec la contribution de la Direction de l'évaluation des produits réglementés (DEPR) de l'Anses.

Au vu des contraintes de délai et de la multiplicité des collectifs d'experts de l'Anses concernés par cette consultation, l'Anses a décidé de mettre en place un groupe d'expertise collective en urgence (GECU) chargé de réaliser l'expertise. Ce GECU s'est réuni trois fois entre le 14 décembre 2017 et le 12 janvier 2018 dont une fois en présentiel.

Le GECU a été constitué avec la participation d'experts membres du GT Perturbateurs endocriniens (GT-P.E.), du Comité d'experts spécialisé (CES) «Substances chimiques visées par les règlements REACH et CLP» (CES «REACH-CLP»), du CES «Valeurs sanitaires de référence», du CES «Substances et produits biocides» (CES Biocides)» et du CES «Produits phytosanitaires : substances et préparations chimiques» (CES PPP)» ayant des compétences, notamment, en toxicologie et en réglementation (cf. annexe 1).

L'Anses a répondu à la consultation publique le 31 janvier 2018. Les commentaires généraux transmis par l'Anses à l'ECHA par formulaire électronique dédié sont repris dans le présent avis. Ont également été transmis à l'ECHA des commentaires de l'Anses sur des points plus spécifiques du projet de guide de l'ECHA/EFSA/JRC, qui sont présentés sous forme d'un tableau en annexe du présent avis (cf. annexe 2).

L'expertise s'est focalisée essentiellement sur le chapitre 3 du projet de guide qui porte sur la stratégie d'évaluation à mettre en œuvre pour considérer une substance comme perturbatrice endocrinienne et sur le chapitre 4 qui concerne les sources d'informations requises pour l'identification d'une substance comme un P.E.

[2] concernant la mise sur le marché des produits phytopharmaceutiques ;

3. ANALYSE ET CONCLUSIONS DU *GECU*

Le GECU considère ce projet de guide comme un bon point de départ pour de futurs travaux d'identification des substances P.E. Il est cependant nécessaire de clarifier d'emblée la manière dont ce guide sera actualisé en fonction du progrès des connaissances scientifiques nombreuses dans un domaine où il existe de fortes attentes sociétales. Il s'agit notamment de définir clairement quel est l'organisme pertinent qui sera chargé d'effectuer de telles révisions, selon quelles procédures et avec quelle fréquence. En particulier, le GECU rappelle l'avis du 19 juillet 2016 de l'ANSES relatif à l'identification des P.E. qui proposait que l'ECHA soit identifiée comme agence de référence sur cette question, en particulier pour son rôle dans la caractérisation des dangers.

Le GECU émet les commentaires généraux suivants sur le projet de guide :

Considérant que le projet de guide devrait s'appliquer de manière transversale aux autres réglementations européennes telles que le règlement n°1907/2006 REACH, la proposition de stratégie actuelle d'identification d'un P.E. est jugée inadéquate car elle se concentre en priorité sur les vertébrés. Ainsi, l'identification du caractère P.E. d'une substance doit être menée simultanément pour la santé humaine et pour l'environnement, notamment dans le cadre du règlement REACH, puisque les conséquences réglementaires sur les usages soumis à autorisation seront différentes (cf. article 56.5 du règlement REACH). Les experts estiment donc que ce point devra être rectifié dans la mesure où ce projet de guide devra être applicable à l'ensemble des substances chimiques et non exclusivement aux produits biocides et aux produits phytopharmaceutiques, et de manière subséquente aux autres réglementations en vigueur. Il est aussi rappelé que les données « rongeur » peuvent être utilisées pour identifier une substance P.E. pour les espèces de l'environnement.

Considérant que le projet de guide n'aborde que les paramètres des voies oestrogéniques, androgéniques, thyroïdiennes et de la stéroïdogénèse (EATS), une substance ne peut actuellement être identifiée P.E. que selon l'un de ces quatre modes d'action. Ceci devra clairement être souligné dans l'ensemble du projet de guide en commençant par son titre.

Considérant que le guide met l'accent sur les tests vertébrés, les experts soulignent qu'il existe un certain nombre de tests disponibles pour d'autres taxa (voir les documents guide de l'OCDE TG 218, 219 et 233 pour les insectes, le TG 211 pour les crustacés, les TG 242 et 243 pour les mollusques) qu'il convient de prendre en considération. En parallèle, il y a aussi des méthodes non validées permettant de tester d'autres paramètres chez ces espèces. Ainsi une publication récente décrit la manière dont certains marqueurs précoces sont conservés avec un lien de causalité pour des effets néfastes chez les arthropodes (Song *et al.,* 2017). Les experts proposent donc de modifier le titre du document guide comme suit : «*Guidance on identification of EATS-Endocrine Disrupters for vertebrates*» afin que son domaine d'applicabilité soit transparent.

Le GECU a souhaité également rappeler ce qui était déjà exprimé dans la Note d'appui scientifique et technique du 1er décembre 2016 relative à la demande d'avis relatif au nouveau projet de la Commission sur les critères P.E. publiée par l'Anses le 1er décembre 2016 : *« Concernant la notion de périmètre du système endocrinien, l'Anses souhaite rappeler que ce système ne se retrouve pas uniquement chez les vertébrés mais qu'il existe également chez les invertébrés. L'Anses considère cette précision importante afin de ne pas réduire le champ d'application uniquement aux organismes vertébrés de l'environnement mais bien à l'ensemble des organismes non-cibles » (Anses, 2016).* De plus, le système endocrinien n'est pas limité aux hormones circulantes mais il comprend également de nombreuses régulations hormonales intra-organes de type paracrine ou autocrine.

Considérant que l'identification d'un P.E. requiert la description d'un minimum requis d'éléments, celui-ci doit être parfaitement défini et sans ambiguïté. Ce minimum doit réunir la démonstration du «caractère essentiel d'un évènement pour la suite des étapes», de la «cohérence», de l'«analogie» et de la «spécificité» en plus des exigences de la définition d'un P.E. qui sont décrits de manière détaillée dans le projet de guide. Le GECU estime toutefois que la description des minimums requis pour pouvoir affirmer qu'une substance ne perturbe pas le système EATS chez les vertébrés (et non perturbatrice endocrinienne au sens large comme cela est affirmé dans le projet de guide) est abordée de manière incohérente dans plusieurs parties du document. L'effort à fournir pour démontrer qu'une substance n'est pas EATS chez les vertébrés est peu lisible. Le GECU propose ainsi qu'un tableau rassemblant les études disponibles, leur pertinence et leur niveau d'acceptabilité par rapport à la question des P.E. soit fourni par les industriels, afin que puisse être associé un niveau de certitude à la conclusion proposée.

De plus, selon le logigramme proposé dans le guide, le niveau de preuves requis pour conclure à un effet P.E. est bien plus élevé que pour conclure à un effet non P.E. Le GECU propose une harmonisation du niveau de preuves.

Afin d'augmenter la lisibilité du guide, le GECU propose aussi de simplifier les conclusions possibles :

- Conclusion a : La substance est un P.E. car elle remplit les critères pour l'un des effets décrits dans le guide ;
- Conclusion b : La substance ne remplit pas les critères P.E. pour les effets EATS chez les vertébrés et sur la base des données existantes, telles que décrites dans le tableau associé (mentionné ci-dessus).

Cette proposition est synthétisée dans la figure 1 du projet de guide annexée au présent avis (cf. annexe 3) et proposée en alternative à celle se trouvant actuellement dans le projet de guide.

Les questions ayant trait au minimum d'études requises devront être ré-abordées ultérieurement en tenant compte de chacun des contextes réglementaires. De même, la pertinence de demander des études règlementaires, leur design, le nombre et l'étendue des doses par études requises nécessite des travaux plus approfondis.

Actuellement, le projet de guide requiert qu'une revue systématique de la littérature soit faite de manière exhaustive et potentiellement pour tous les effets néfastes. Par souci de faisabilité, le GECU propose que cette revue systématique soit limitée à l'effet néfaste d'intérêt, si on démontre que la substance est P.E. ou de manière exhaustive sur tous les effets touchant à un mode d'action EATS si on veut démontrer qu'une substance ne remplit pas les conditions EATS (conclusion b).

Le chapitre 4 du projet de guide traitant des tests devra être supprimé dans la mesure où il rapporte les grandes lignes d'essais publiés par ailleurs et où il est probable qu'il devienne rapidement obsolète en fonction de l'évolution des connaissances et des méthodologies. Néanmoins, les tableaux de synthèses produits pourront être conservés en précisant que ces données seront régulièrement actualisées (voir le site de l'OCDE).

<u>Au final, le GECU recommande que :</u>

- Les détails apportés dans le projet de guide pour identifier les deux catégories (P.E. ou non EATS chez les vertébrés) soient cohérents et précis dans l'ensemble du document. Il devra de même clairement identifier la dissymétrie de l'effort à fournir pour démontrer qu'une substance ne remplit pas les conditions EATS chez les vertébrés sur la base des études disponibles au moment de l'évaluation.

- Le *corpus* de preuves disponibles et manquantes soit identifié de manière transparente en demandant au déclarant un tableau de synthèse résumant les données disponibles et leur pertinence, afin d'avoir une vision globale des données ayant permis de conclure à l'identification d'une substance comme non EATS chez les vertébrés.

Le GECU propose que l'identification d'une substance aboutisse à deux conclusions :

1/ les critères de perturbation endocrinienne sont démontrés pour l'un des effets EATS.

2/ les critères de perturbation endocrinienne ne sont pas démontrés pour des effets EATS, sur la base des données existantes.

4. CONCLUSIONS ET RECOMMANDATIONS DE L'AGENCE

L'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail endosse les conclusions et recommandations du GECU.

Dr Roger Genet

MOTS-CLES

Perturbateurs endocriniens, substances biocides et phytopharmaceutiques, identification, critères, classification, Commission européenne, Homme, Environnement.

Endocrine Disrupters, Biocidal and phytopharmaceutical products, identification, criteria, classification, european commission, Human, Environment.

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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.

GROUPE D'EXPERTISE COLLECTIVE EN URGENCE

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ANNEXE 2

	GECU comments: *Guidance on identification of Endocrine Disrupters* (Please use this format as it is in the interests of fast processing and consolidation of all comments)				
Type of comments	**(Sub-)section** Number ONLY	**Page number** (ONLY give 1st relevant page number as integer)	**Line number** (in pdf document; **first** relevant line number as integer **only**)	**Comment** NOTES: (i) if proposing addition or deletion of text please give details of the preceding and following current text so it is clear where the revision is to be made; (ii) if the comment relates to several pages please list ALL pages or the range of pages [in this field, NOT in Column E].	
General				We would like to thank the authors for having integrated many changes in the new version. ANSES foresees the guidance as a good start for building a scientific consensus on how to identify EATS mediated EDs among various regulations. There are however some points that require rectifications, modifications that are described below. In particular, focusing on Human health first seems an inbalanced strategy if this guidance document should be applied to other regulations such as REACH (see below), the number of taxa involved and the volume of available data.	
General				The guidance document should clarify whether metabolites are included in the ED assessment strategy. If metabolites have to be considered, the details on metabolites should be included in the guidance document (i.e. metabolites identified in animal metabolisms, metabolites identified in environment (aquatic system, soil…) or metabolites identified in plant metabolisms…).	

General				Is the guidance document applicable to regulations other than PPP & BP? The guidance considers that if a PPP (or BP) is identified ED for mammals (this kind of strategy could be emphasized more clearly in order to limit animal testing), the evaluation can stop i.e. without having to assess the environmental part (enough to withdraw the authorisation). However, according to the REACH regulation, being an ED for HH or ENV has not the same legal consequences (see article 56.5 of REACH). In the context of REACH, it might be relevant to focus on ENV-ED simultaneously to HH-ED when bearing in mind the regulatory consequences. If it is foreseen to use this guidance for chemicals covered by other regulations such as REACH regulation, substances should be evaluated as ED for environment first or in the meantime as ED for HH. This should be reminded in the « resume » and/ or recommandations.	
General	**2.**	**13**	**187-189**	As mentionned above, an effort should be made in the guidance document to ensure that it will be applicable to all chemical substances.	
General				The guidance deals with estrogen, androgen, thyroid, steroigenic (EATS) only, through the rest of the document. Therefore, we propose to modify the title of the guidance document as such: "Guidance on identification of EATS-Endocrine Disrupters". Furthermore: as this document focuses only on EATS the glossary should precise in their definition that EATS are only a part of the endocrine system. This should be modified in all the figures and text of the document. The document will be stronger if the scope is transparent.	
General				The guidance is written for "data rich" substances and does not cover data poor substances (e.g. "old" PPP-BP substances, old chemical susbtances, low tonnages chemical susbtances), with old data set using old OECD guidelines. For example, how to treat MoA, biological	

				plausible link, essentiality, consistency, Analogy and specificity when very few data are available is not discussed. Conversely the question on when to consider that a susbtance is not an ED is not discussed at all neither(minimum requirement, especially for old substances).	
Specific comments	3.2.2.1.	12	114-120	The use of maximum tolerated dose, is relevant in toxicity studies, but not in case of ED-MOA assessment : ED effects are generally effective at low doses and not at limit doses. The lines 117-120 "Generally speaking, limit doses of 1000 mg/kg/day are considered appropriate in all cases where indications of saturation of exposure or limited/no absorption are provided. If none of these criteria can be achieved, a dose of 2000 mg/kg/day or the maximum feasible dose, whichever is lower, should be considered." do not seem appropriate in an ED context! (these are standard comments inserted systematically in OECD guidelines, and are not relevant here to our opinion). In general, it is proposed to use the toxicity studies (existing or to be carried out) to evaluate the apical/adverse effect (necessary for the general risk assesment and also to fulfill the point related to adversity of EDs) together with ED MOA. An in depth reflexion should be carried out to decide if these objectives are coherent and can be carried out simultaneously. Indeed, and as mentionned later (ln 126-129), one of the difficulties to identify EDs will be to demonstrate ED MOA in presence of general toxicity. In that case, it will be difficult to demonstrate that the ED-MOA observed is not secondary to other non specific toxicities. It has been demonstrated that some ED effects occur at low doses, for which the models and statistical power of the proposed studies are not suited. How many doses should be tested if further tests are requested should also be	

				discussed. The number and range of doses chosen should be adapted to the parameters investigated and the design of the study. The guidance document does not reflect on these key issues. While proposing new tests to be conducted, which lowest dose to be tested should be discussed. The design should be decided case by case depending on the in silico/ in vitro/ in vivo/ exposure data available.	
Specific comments	3.2.2.1.	12	121-125	Same remark as above : the first sentence "For ecotoxicology, the highest test concentration should be set by the maximum tolerated concentration determined from a range finder or from other toxicity data. The maximum tolerated concentration is defined as the highest test concentration of the chemical which results in less than 10% mortality" could be simplified as follows : "For ecotoxicology, the highest test concentration should be set by the maximum tolerated concentration which is defined as the highest test concentration of the chemical which results in less than 10% mortality". We suggest to delete the last sentence of the paragraph "For test on aquatic organisms, the maximum tolerated solubility in water, or 10 mg/L for chronic (sub-lethal) tests, could be considered." We do not consider that it is pertinent to accept results obtained at so high concentrations in aquatic systems.	
Specific comments		2	206-210	The following statement is incorrect : "This is because the EATS modalities are currently the best characterised pathways for which there is a relatively good mechanistic understanding of how substance-induced perturbations may lead to (adverse) effects via an endocrine (disrupting) MoA". In some cases, EATS modalities are less documented than a number of non-EATS ones. e.g. : The estrogen-like mechanism of action of bisphenol A is largely unknown. The implication of ERRgama, the role of ERalpha36, the role of membrane steroid	

				receptors remain a matter of debate. On the contrary, the mechanism of action of insulin, adrenaline, gonadotrophins . are well documented. It would be more relevant to emphasize that these are the only pathways for which there are OECD validated test methods currently requested in the regulations.	
Specific comments	2. Scope of the guidance document	2	210-213	This sentence is correct	
General	2. Scope of the guidance document	2	219-222	Contrarily to what is written in the current guidance, **there are several reasons for including other endocrine pathways to be tested**: • some compounds are known to disrupt these endocrine axes. Examples are provided for pesticides that disrupt arthropods development with clear effects and mode of action; • As mentioned, there are tests available including for arthropods and other invertebrate species. Beside validated tests there are other measurements that are currently used in the field of ecotoxicology; • There is a testing strategy available and an AOP has been published (Song et al 2017)	
General	2. Scope of the guidance document	**2**	**229-234**	The guidance deals with vertebrate only. A reason of this choice is given ln 229-234. Contrarily to what is written, methods exist (cf GD150) on insects (TG 218,219, and 233), for crustaceans (TG 211), and mollusks (TG 242 et 243)... and some invertebrate tests are even mentioned in table 9 pg 46. The new TG 211 has been recently completed with parameters allowing to conclude on EDs. Therefore, ANSES wonders why such a choice is made. The other taxa should be emphasized all along the document or the scope clearly stated from the onset by modifying the document: "Guidance on identification of EATS-Endocrine Disrupters with a focus on vertebrates" and modified all along the document. If the willingness is to integrate more thoroughly the other taxa than mammals, further indications	

				on how to introduce toxicity data for non-mammalian organisms, especially non-vertebrates, in the reporting of lines of evidence would be welcome for example.	
Specific comments	3.2.2.1	12	12	What to do with old SA. Will the registrant have to carry new tests ?	
Specific comments		VII	Endocrine activity	Modify the entry by "Endocrine activity of xenobiotic". The definition provided so far does not apply to all the natural hormones (insulin does not interact with the endocrine system but directly with certain cells). Another option would be to take the definition of endocrine disruptor as such: "An exogenous substance or mixture that interact with the endocrine system".	
Specific comments		VII	Endocrine system	"That orchestrates a states of metabolic equilibrium or homeostasis, among the various organs of the body" is a restrictive view of the function of the endocrine system. We therefore proposed to add "and an constant adaptation to external or internal changes" E.g.: the stress induces hormonal changes that disregulates homeostasis). The definition provided here is based on an "old" concept, document ANSES (GECU Anses 2016 0133 opinin): Indeed, while a strict definition is given in the OECD guidance document, for example, the state of the art shows that it is today difficult to distinguish paracrine/autocrine/intracrine effects from endocrine effects. Thus, the hormone (or the chemical messenger) is not necessarily conveyed by the blood. The cells of a given organ interact through chemical signals that diffuse in the interstitial lymph fluid within the organ. These chemical signals can be what are known as "hormones" or "factors.	

Specific comments		VII	Endocrine system	"In endocrine signaling, the molecule, i.e. hormones act on target cells that are generally distant from their sites of synthesis" is inaccurate. One outstanding example is the effect of testosterone produced by the Leydig cells that is absolutely necessary for spermatogenesis by acting on the neighbouring Sertoli cells. When endogenous testosterone is suppressed it is not possible to maintain spermatogenesis by restoring normal plasma level of testosterone.	
Specific comments		VII	Endocrine system	"An hormone is frequently carried by the blood from its site of release to its target" is inaccurate and should be replaced by " An endocrine hormone is carried by the blood or by the interstitial lymph from its site of release to its target" as paracrinology and autocrinoly are important part of the endocrine system. We propose to delete the last sentence: An endocrine hormone is frequently carried by the blood from its site of release to its target.	
Specific comments		VII	Essentiality	line 3 : "the adverse effect is prevented if an upstream event..." should be replaced by "the adverse effect is prevented/decreased if an upstream even.	
Specific comments			Hormone	To continue with the previous remark: there is no definition of the term hormone in the guidance document. Hormone cannot be simplify as "endocrine hormone". Proposed definition for hormone: A chemical substance produced in the body by endocrine cells that controls and regulates the activity and/or the fate of certain target cells that are specifically receptive to the hormone because they express specific receptors	
Specific comments		VII	line(s) of evidence	The meaning of " of similar type" is not understandable as such and needs to be clarified.	
Specific comments		VIII	Reliability	line 6 : The sentence " Reliability of data is closely linked to the reliability of the test method used to generate the data (Klimisch, Andreae, and Tillmann 1997)". Other methods than Klimish are available to evaluate the reliability of tests methods.	

				Add : "or any other approaches to evaluate their reliability (ToxRTool, Sci-Rap, OHAT for example)".	
Specific comments	abbreviations			embrionic should be embryonic	
Specific comments		2	192	add "and mixture "	
Specific comments	3. Strategy to assess whether a substance meets the endocrine disruptor criteria	3	258	There seems to be confusion about "endocrine activity" and "endocrine MoA". An "endocrine activity" is the specific effect of one hormone on its target. An endocrine MoA covers the various ways for a compound to affect the endocrine system (alteration of synthesis, and/or release of the hormone, interaction with transport and metabolism of the hormone, interaction with the action of the hormone in the target cell). Whereas "Activity" might be misleading as there are many other ways for a compound to affect the endocrine system (alteration of synthesis, interaction with transport, metabolism…). All the sentences here should be deleted (l.257-266). The definition is clear enough and more comprehensive. The following sentences should be corrected as follows: • Are there plausible MoA and sub consequent adverse effect(s) relevant for humans ? • Are there plausible MoA and sub consequent adverse effect(s) relevant for non-target organism? Consequently, all "endocrine activity" mentioned in the text should be replaced by MoA throughout the document.	
Specific comments	3. Strategy to assess whether a substance meets the endocrine disruptor criteria	3	273-276	Paragraph to be deleted. This paragraph is useless and only a repetition of the definition. Furthermore conditions a, b and c is also applying to human relevance	
Specific comments	3.1	6	323	What is described are parameters within their models	
Specific comments	3.1	6	330-334	Other types of models such as *ex vivo* or organotypic models are not mentionned. They should be integrated as models allowing to identify both MOA and supporting identification of adverse effects in level 2 of OECD.	
Specific comments	3	5		put endocrine mode of action	

				in brackets	
Specific comments	3	5	314	The last line of table 1 mentions "the concept of the limit dose, and international guidelines on maximum recommended doses… What is the rationale of such considerations in a WoE assessment regarding the ED context ? While it is understood that excessive toxicity, which is likely to produce confounding effects, has to be accounted for in WoE, considering a limit dose generally high or a maximum dose does not seem pertinent in the context of ED assessment. We propose to delete this comment and to keep in the boxes (factors for humans/for non-target organisms) only :"assessing confounding effects of excessive toxicity".	
Specific comments	3. Strategy to assess whether a substance meets the endocrine disruptor criteria	5	318	"ED" should be deleted and leave "all relevant information"	
Specific comments	3	6	330	The use of ER binding Assay (US EPA OPPTS 890.1250) seems outdated as the new version of guidance 150 proposes 2 new tests instead: The Freyberger-Wilson (FW) In Vitro Estrogen Receptor (ER) Binding Assay Using a Full Length Human Recombinant ERα or The Chemical Evaluation and Research Institute (CERI) In Vitro Estrogen Receptor Binding Assay Using a Human Recombinant Ligand Binding Domain Protein. Those tests are not cellular test but molecular ones and so some figure of the guidance together with the text have to be changed in that sense.	
Specific comments	3. Strategy to assess whether a substance meets the endocrine disruptor criteria	6	371-374	If the test shows that an endpoint is "sensitive to", the conclusion should be that the adversity is questionable (and not unlikely) and further testing are needed. The conclusion would be "unlikely" if the result of the test shows that it is "not sensitive to".	

Specific comments	3. Strategy to assess whether a substance meets the endocrine disruptor criteria	6	366	the conclusion should not be that it is not an ED but not an EATS-ED.	
Specific comments	3.1	7	381-384	The following sentence should be corrected: "If based on this assessment the criteria are not met for mammals as non-target organisms, ONLY THEN the assessment should proceed to consider the other taxonomic groups, which may require the generation of additional data". It means that "considerations of mammals are predominant" in the ED assessment and that other taxonomic groups - non-mammalian vertebrates and invertebrates - are secondary and negligible which is scarcely acceptable as a principle! This cannot be accepted. We propose to delete "ONLY THEN" and to add "ALSO" before "should", as follows : "If based.... as non-target organisms, the assessment should ALSO proceed to consider the other taxonomic groups, which may require the generation of additional data on vertebrates and invertebrates, if data have not already been provided". In addition, in the precedent sentence (line 382), we suggest to replace "should" by "could" as follows: "With regard to non-target organisms, the assessment for mammals could be performed first. If based...."	
Specific comments	3.1	7	393	We propose to add a sentence after "vice versa" line 393 :"In such cases, the "non-relevance of an adverse effect should be justified taking all mechanisms of disturbances into consideration, and not a unique well-known (historical) explanation" (the subsection refers to thyroïd adverse effects in rats non relevant in humans)	
Specific comments	3.1	9	Fig. 1	The flow chart title should be modified as follows "Flowchart illustrating the EATS-Assesment strategy". Modify the rest of the flowchart accordinglly: The conclusion "STOP ED criteria ARE NOT MET" should specify "ED criteria	

				not met for an EATS-effects on the existing data". Indeed it has been reminded that other endocrine systems than EATS may be disturbed!	
Specific comments	3.1	9	Fig. 1	See attached figure proposed to replace the figure 1. The modifications proposed comes from the observation the order proposed for the questions seems not logical. They reflect different paradigms linked to the definition: * to fulfil the definition there should be an adverse effect (later called ED-adverse effect to distinguish it from any other adverse effects: one effect that one assume to be able to carry on the ED-identification) AND and ED-MOA. Both points should be demonstrated together with the plausibility of their biological link. *As adverse effects are the "consensual part", and more currently documented , it seems efficient to start with this part of the definition. *If an ED-adverse effect is identified, it is more efficient to focus on THIS adverse effect for reviewing the literature instead of the entire dataset and carry on the ED-evaluation. There is no need to look at numerous ED-adverse effect in principle and no need to look to any other effects. One is sufficient if strong enough to demonstrate EDness. *If no ED adverse effect can be detected, it has to be substantiated with systematic review. In that case, and in order to justify that no other study needs to be carried on that topic, it has to be proven that no endocrine activity has been described. So far, this activity mainly focusses on EATS instead of broad ED.	
Specific comments	3.1	9	Fig. 1	Our comments show that the conclusion "ED criteria not met" are indeed based on partial data (EATS on vertebrates). Therefore, we believe, it will be more straightforward to merge this conclusion with "Conclusion currenlty not possible" by creating the conclusion "ED criteria not met for an EATS-effects based on the existing data". Indeed, it somehow	

				reflect the same idea: we are not capable to conclude on part of the broad question. To be efficient, the conditions to fulfil this conditions needs to be much more detailed (see below for additional proposal).	
Specific comments	3.1	9	Fig. 1	To follow up on the previous comment, the guidance does not deal with the level of certainty of the conclusion " ED criteria not met" although it defines in much more details the criteria of certainty to fulfil the conclusion "ED criteria are met". This is **an unbalanced situation that needs to be MODIFIED**. One manner to increase the transparency and criteria to fulfil "ED-criteria not met" (we propose to modify the cording of this conclusion see above), would be to request a table (called table9-new in the proposed figure 1 based on the entry of the OECD conceptual framework) showing the data available and their limits to clearly show the data gaps and uncertainty linked to the conclusion "not met". So far, this part is not sufficiently covered in the guidance and should be expanded, maybe in a second version. Especially, this will be the part that will be mainly used by applicants/ registrants (For most of the substances that will be clearly EDs, the applicants will probably withdraw them from market without building long and complicated dossiers). Having a consensus on how to identify EDs is a good starting point but emphasis on what to fulfil while demonstrating a substance is NOT an EATS (on existing data) is mandatory.	
Specific comments	3.1	9	Fig. 1	To follow up on the previous comment, a reflexion should be open to identify the testing strategy depending on the regulatory context and data gaps/uncertainties identified in the table 9-new to be able to diminish the level of uncertainty of the conclusion "not met" depending on the regulatory context. The level of uncertainty acceptable compared to the precautionary principle should be discussed within each regulation context.	

Specific comments	3.1	9	Fig. 1	Is it a intentional to affirm that it is possible to demonstrate that ED criteria are met even if no EATS adversity has been observed in cases of validated AOPs? When KE demonstrating endocrine activity is shown by acceptable data, is it sufficient to conclude that the substance is an ED (further animal testing not necessary because scientific consensus that the KER will lead to adverse effect)? We would support such idea but it should be clearly stated in the guidance as the current version can lead to different interpretations (see case studies).	
Specific comments	3.1	9	Fig. 1	The asterix should be deleted: For adversity, the ''EATS-mediated'' parameters foreseen to be measured in an Extended one-generation reproductive toxicity study (OECD TG 443; with cohort 1a/1b including the mating of cohort 1b to produce the F2 generation) are not sufficient to have been sufficiently investigated. For non-target organisms the corresponding 'EATS-mediated'' parameters to be measured in the Medaka extended one generation test (MEOGRT; OECD TG 240) and the Larval amphibian growth and development assay (LAGDA; OECD TG 241) are not sufficient to be able to claim that adversity has been sufficiently investigated. Moreover, those requirements are minimum requirement to demonstrate that a substance IS an ED although none is necessary (one could in principle identify that a substance is an ED whatever the type of good-quality study available. What would be necessary is a minimum requirement to define that a substance IS NOT an ED (see below for comments on that topic).	
Specific comments	3.1	9	Fig. 1	ANSES recognizes that OECD 443 or 416 are the best available tests to evaluate repro-EDs in mammals & TG 240 and 241 very good for other species. Those 3 tests would therefore constitute a strong basis for working on EATS effects. There is however other adverse effects/ MoA that are not covered by these tests.	

				For the time being, it is not clear why the 3 tests OECD 440, 441 and AMA are mentioned at all as they are not proposed as the minimum requirement for claiming that a substance is not an ED. Moreover, they are not sufficient to identify all EDs (invertebrates and birds not tested in this flowchart for ex.).	
Specific comments	3.2.1.	10	37-39	The following part of the sentence "such investigations were carried out under GLP" should be deleted, because most research studies provided by a review of scientific literature, are generally NOT CARRIED OUT UNDER GLP ! The new sentence proposed is : ""Although not conducted following "Internationally agreed protocols", such investigations shall be considered as part of the information extracted from the dossier, after an assessment of their quality according to section 3.2.2.""	
Specific comments	3.2.1	10	29	Systematic reviews will be carried out only for old active substances or chemical substances. For most of the substances, there is no scientific littérature existing and therefore, systematic review is useless.	
Specific comments	3.2.2	11	75	This paragraph is tendencious. Also it does not say Klimish should be applied, it cited its criteria. Other sources/ tools should be cited such as ToxRTool, Scirap, OHAT.	
Specific comments	3.2.2.2	13	164 et suivantes	This paragraph is tendencious. Also it does not say Klimish should be applied, it cited its criteria. Other sources/ tools should be cited such as ToxRTool, Scirap, OHAT.	
Specific comments	3.2.2.	11	80-81	To cover the fact that research studies do not use standardised methodology generally, is the formulation of Reliability, sufficient ? : " evaluating the inherent report or publication relating to preferably standardized methodology…." Or is it useful to add "(and not exclusively)" to reinforce preferably ? as follows : " evaluating the inherent report or publication relating to preferably standardized methodology (and not exclusively)…."	

Specific comments	3.2.2.1.	11	130	It seems that studies using guideline protocols are the only important studies to consider. The existing text states that results from academic with non guideline studies should be assessed but less important or easy to reject. .We would like the weight of the different type of studies been rediscussed in a much balanced manner.	
Specific comments	3,2,2,2	12	141	why limited to open literature ? Delete open	
Specific comments	3.2.2.2.	13	156	"consistency among substances with similar attributes and effects, etc". This criteria of reliability should be ponderated, with in mind the fact that outliers exist among a series of chemicals with the same structural characteristics (this is often the basis for the search of alternative chemicals to the hazardous ones in a same series !) Therefore, we propose to add this parenthesis at the end of the sentence, as follows : .... consistency among substances with similar attributes and effects, (yet, having in mind that outliers cannot be excluded), etc."	
Specific comments	3.2.2.2	13	189	Anses suggests to refer to the recent Efsa report describing the methodology on bisphenol A (Bisphenol A (BPA) hazard assessment European Food Safety Authority (EFSA), Ursula Gundert-Remy, Johanna Bodin, Cristina Bosetti, Rex FitzGerald, Annika Hanberg, Ulla Hass, Carlijn Hooijmans, Andrew A. Rooney, Christophe Rousselle, Henk van Loveren, Detlef Wölfle, Fulvio Barizzone, Cristina Croera, Claudio Putzu and Anna F. Castoldi December 2017. In this guidance tools and datasheets were elaborated to assess in a weight of evidence approach Epi studies as well as experimental studies. In the current version, the guidance does not propose any assessment these kind studies. In addition, the bias and limits of epi studies should be reminded in one sentence.	
Specific comments	3.2.3	14	241	reference error compilation	
Specific comments	3.3.3.	18	336	is it acceptable to accept ED results when a chemical has been tested at the limit dose ? It is suggested to delete	

				the parenthesis :"(unless tested at the limit dose)".	
Specific comments	3.3.4.	19-22	366	The title of the column "Dose" mg/kg/day has to be completed: What does represent the "Dose" indicated ? Maximum (or minimum ?) dose tested with effective effects? Upper limit of the range of doses ? A footnote should be included at a minimum. - add a column reporting the NOAEL for the effect - include information on general systemic toxicity for each line describing an EATS-related parameters in order to directly include these data in the WoE analysis - add a column including the reference of the study in which each effect was observed for better clarity	
Specific comments	3.3.4.	23-25	370	same remark as above : the title of the column "Doses (mg/L)" should be more explicit	
Specific comments	3.4	26	380	Bird data are available in PPP DAR. It is a pity that these data are not incorporated in the assessment more thoroughly. So far, the guidance looks like a mammals one. Even when animals other that mammals are cited In 380), only fish and amphibians are!	
Specific comments	3.4.1	28	418-420	This statement is erroneous: If the" 'EATS-mediated' parameters considered by OECD TG 240 and 241 [...] have been investigated and found negative", it CANNOT be claimed that "the substance does not meet the ED criteria for non-target organisms". It might be able to claim that the substance is not an EATS-mediated ED for fish and amphibians BUT NOT MORE. Please modify accordingly.	
	3.4.2	28	432	ANSES recognizes that OECD 443 or 416 are the best available tests to evaluate repro-EDs in mammals & TG 240 and 241 very good for other species. Those 3 tests would therefore constitute a strong basis for working on EATS effects. There is however other adverse effects/ MoA that are not covered by these tests. For the time being, it is not clear why these 3 tests are mentioned at all as they are not proposed as the	

				minimum requirement for claiming that a substance is not an ED (OECD 440, 441 and AMA) but are not sufficient to identify any ED (invertebrates and birds not tested in this flowchart for ex.).	
Specific comments	3.4.1.	28	416-417	It should be specified that the conclusion only deals with EATS criteria and should be :"the substance does not meet the ED criteria with regard to humans and to EATS endpoints" or "the substance does not meet the EATS criteria with regard to humans".	
	3.4.2.ii	29	461-473	This paragraph focuses on defining the minimum requirement necessary to claim that a substance is not an ED. **This question is very important in a regulatory point of view and instances such as OECD has tried for numerous years to answer this question. The proposal made in the guidance is clearly UNACCEPTABLE**: "To sufficiently cover the EATS modalities with regard to endocrine activity the level 3 tests: Amphibian Metamorphosis Assay (OECD TG 231, (OECD 2009c); Uterotrophic Bioassay in Rodents (OECD TG 440; (OECD 2007d); and Hershberger Bioassay in Rats (OECD TG 441; (OECD 2009d) must have been conducted; for additional guidance see Chapter 4. If this is the case and no endocrine activity is observed, then it is not possible to postulate an endocrine MoA, and it can be concluded that the substance does not meet the ED criteria for humans and non-target organisms." **The proposal is not acceptable as such**. Indeed, it is now well described that Uterotrophic and Hershberger Bioassay lead to **numerous false negative**. Most of the time, their sensitivity is too low and leads to to numerous false negative results. High doses of known EATS-interfering molecules are required to be detected by the mammals assays (eg BPA on Uterotrophic assay). Based on publications concerning estrogenic effects on uterine	

				by several endocrine disruptors to low dose, while requesting these studies, they should be provided with additional data by investigating uterine epithelium thickness, histological and immune histological studies on proliferative cells that are ER-alpha related endpoints undergoing as prior steps in uterotrophy events (see Kwebel et al 2005; and Diel et al 2006; Heneweer et al 2007; Varayoud et al 2017 for applications) In the same manner, histopathological data of vagina smears could be completed by histological measurement of thickness of vagina epithelia (see varaydoud et al 2017 , for reviews). Additionnally , estrogenic effects on vagina are ER beta mediated (Kang et a 2003). Similarly, histopathology should also be requested for the amphibian test as it is a much more sensitive parameter. Instead of an AMA, a LAGDA would be more welcome as more sensitive. Even as such the strategy proposed only covers EAS for rodents and T for amphibians. It should be recognized and clearly stated if the minimum requirement remains as such. Finally, this minimum requirement should also request level 1 and 2 data (In silico models + guidelines 493, 455, 457, 456).	
Specific comments	3.4.2ii	29	461 - 473	Alternative to the previous comment if the proposal made above is not accepted: If the authors decide that it is not possible to define a minimum requirement (as requested above), we propose to modify the text as follows: It is not possible to define a set of tests identified as the minimum requirement to claim that a substance is not an ED. The registrants will have to build a case by case demonstration that they have investigated the relevant parameters depending on the substance (*in vitro* battery and a few sensitive level 3 tests), its uses (window of sensitivity), its presumed MoA. They will also need to explain why the available data evidence is enough and that there is no remaining uncertainty regarding the EDness of	

				their substance.	
Specific comments	3.4.2	30	Table 5	Thyroïd is missing, mention that there is no exhaustive *in* vitro testing battery available or add those proposed later in the document such as in table 9 (TPO inhibition, TTR binding).	
Specific comments	3.4.2iii	29	480	The difference in treatment of the amphibian tests on thyroïd compared to the previous paragraph are not understandable. Uterotrophic and Hershberger Bioassay do not give any indication oin the Thyroïd pathway. It is therefore not understandable why it is written: "Level 3 assays OECD TG 440 and 441 should be conducted. Special consideration should be given to the thyroid pathway. If the information available from the data set on mammals allows to conclude that the thyroidal endocrine system was not affected, this may be considered as an indication that thyroidal adverse effects in other vertebrate non-target organisms (i.e. 484 amphibians) are unlikely and thus further testing may not be necessary. If such a conclusion cannot be drawn, amphibian testing (i.e. OECD TG 231) should be considered. "Assays on thyroid such AMA or LAGDA should be added as a first requirement to 440 and 441, same for steroidogenesis for which a test should also be added. Otherwise, the title of the pathways tested should be clarified in the title.	
Specific comments	3.5	31	523	Modify the flowchart presented according to the attached proposal submitted. The "sufficient information" proposed is not acceptable and should rather be the one proposed above : "It is not possible to define a set of tests identified as the minimum requirement to claim that a susbtance is not an ED. The registrants will have to build a case by case demonstration that they have been investigating enough the relevant parameters depending on the substance (in vitro battery and a few sensitive level 3 tests), its uses (window of sensitivity), its presumed MoA. They will also have to explain why the available data evidence is enough and that there is no remaining uncertainty	

				regarding the EDness of their substance." Alternatively and as a minimum for changes, the order of the questions should be modified in such a way that the question "have all EATS mediated parameters been investigated" arrives after "has eats mediated adversity been observed".	
Specific comments	3.5.1	32	fig.5	we propose to delete the green boxes: cell, tissue, organ, individual and population as Some in vivo mechanistics (level 3) assays are done on individuals and population . in vitro mechanistic, not at the cell level for binding to ER for example. Individual and population at the same level.	
Specific comments	3.5.1	33	Table 6	To be discussed : it seems to me that the table 6 should be better represented as a flow chart	
Specific comments	3.5.2.1.	35	682	Modify: "The biological plausibility is weighed as follows" by "The biological plausibility is expressed as follows"	
Specific comments	3.5.2.1.	35	687	Weak and not conclusive (as likely as not) should be distinguished and separately proposed. Biological plausibility weighted "Weak : the structural or functional relationship between KEs shows possible and other non ED-MOA are possible". If the biological plausibility is not understood, it should be expressed (weighted in the current guidance): "non conclusive or as likely as not."	
Specific comments	3.5.2.2	35	719-720	It is therefore expected that early KE should be seen at lower doses than the adverse effects they are leading to: this statement is strong and could be impaired by numerous parameters (sensitivity of the specie or strain, design in terms of windows of exposure, culling time. are not discussed) could be sufficient. In that sense, the lines 719-720 should be developed as such: "The description made above is idealistic and most of the time the available database will not allow to draw such a clear picture. Parts of the sequence will be missing and depending on	

				the specificity of the different studies used (design, windows of exposure, susceptibility of the species or strain used, route of exposure), events might be messy. The work will consist in evaluating (expert judgement) the plausibility of the sequence proposed compared to the available data."	
Specific comments	3.5.2.3.	37	745-746	Essentiality is not easy to understand with the explanation given. Clarification would be appreciated; especially when weighted "Weak : if there is …. or there is evidence for no reversibility" ! hard to understand ! Indeed, absence of reversibility is a negative factor in terms of adverse effects and, on the opposite, may be seen to reinforce the association of the KEs with the adverse effect ! Then, why considering that essentiality is weak in these conditions ?	
Specific comments	3.5.2.3.	37	745-746	It is not clear how the absence of data for fulfilling these elements will impact the identification of Eds. Indeed, data such as Essentiality will be provided through non guideline studies (performed on knock-out or with antagonists). Also available for substances such as BPA, they will be missing for most (>95%) of the chemical substances. The sentence 766-767 is very obscure and should be revised. Hence, if it is shown that a KE event is not essential but endocrine-related adverse effects due to chemical exposure are observed, then this is probably because the right KE has not been found rather than due to a lack of a plausible KE. Similarly, the consistency of a KE depends on the species, dose range, life-stage of exposure, endpoints examined, only the same type of studies can be compared. In relation to specificity, this is already addressed in the way TGs are performed and results are interpreted. Endocrine-related adverse effects should occur in the absence of systemic toxic effects. And the dose-range selected should not result in systemic toxicity when examining endocrine disruption (only the high dose may result in	

				systemic toxicity) otherwise the experiment will have to be repeated. **We propose to delete this section, as all are basic elements for Risk Assessment.** When available, these elements will always be considered in the weight of evidence approach. Is it necessary to give a strong focus on them? What will be the impact if they are not available???	
Specific comments	3.5.2.4.	38	773	well written and very understandable	
Specific comments	3.5.2.5.	38	791	well written and very understandable. Shall the new PPP definition impact the reference to non-target organisms?	
Specific comments	3.5.2.6.	39	825-826	the sentence is quite obscure and requires clarification. "The essentiality, where or if experimentally provided (??), of the KEs is influential in considering confidence in an overall postulated MoA being secondary only to biological plausibility of KERs (references)!!!!! As mentioned earlier, ANSES doubt on the existence of such data for many of the substances covered by this guidance and wonder how this will be fulfilled. Indeed, the sentence should be clarified and also completed as such :"When not experimentally provided, the essentiality should be reflected based on general knowledge".	
Specific comments	3.5.2.6.	39	837-838	What does a "re-evaluation of technical correctness" imply practically ? In the sentence "In absence of dose, temporal and/or incidence concordance, study design(s) should be first re-evaluated for technical correctness" What does that means ?	
Specific comments	3.5.3	42	872-874	Where no EATS mediated adversity is observed for a sufficient dataset (…) it is possible to by-pass the MoA analysis and conclude that the criteria are not met. This conclusion will lead to false negative. there are too many variables here that could potentially lead to a false negative, which make these elements unfit for risk assessment. We need to	

				keep in mind that this document focuses only on EATS modalities, and these are not completely addressed by the current available tests.	
General	**Chapter 4**	**44-**		**To be deleted as will be outdated as soon as written.** **In addition, it is already incomplete. A non exhaustive list of links or references, sources (OECD for example), various publications should be provided in the chapter "Gather information". Table 9 should appear in the core of the text while the rest of the tables should be kept in annexes and updated regularly.**	
General				**To conclude, this guidance is a good starting point for further work. The review period of the guidance, the instance relevant for such review (ECHA as this is an hazard assessment) and the missing parts should be identified and processes defined.**	
	If chapter 4 and 5 should be deleted. The tables should be kept and placed elsewhere: table 11-17 could be incorporated within the 3.1 "Grouping the parameters relevant for identification of ED properties"				
Specific comments	Table 14	63	1600	• It seems that the Table 14 on page 63 ("Mammalian in vivo parameters – parameters 'EATS-mediated' (highlighted in blue) and parameters 'sensitive to, but not diagnostic of, EATS' 1595 (highlighted in purple)") has been truncated. Several parameters "sensitive to, but not diagnostic of, EATS" (all the lines below "Number of implantations, corpora lutea") were included in a former draft guideline, but not in the Draft for public consultation.	
Specific comments	Appendix B	99		Should be more detailed. It should be expanded to other pathways than EATS.	
	Appendix A . Thyroïd disruption		2672	This paragraph is a good example of how registrants/ applicants will try to demonstrate human non relevance of some findings. It is important that the guidance elaborate on the data necessary to accepts such claims. This should be expanded to all the effects usually claimed as rodent specific. Additional consideration on how to consider these susbtances for the species of environment should be	

				substantiated.	
	Appendic D			Some links do not work.	
	Appendic E			• Although the Excel template (Appendix E) to be used for reporting the available information was not produced in the context of this case study, it is considered that filling this table would be useful during the EU assessment of active substances. It could be recommended to the applicant to use this template in the context of an active substance dossier submission. Again, it shows that the reality of PPP/BP substances will be very different that chemical substances for which this recommendation will de facto not apply, leaving the burden of proof to authorities.	

ANNEXE 3 : DIAGRAMME ILLUSTRANT LA STRATEGIE D'EVALUATION D'UN PERTURBATEUR ENDOCRINIEN