Introducing Standard Information Requirements for Endocrine Disruption

REACH Registration requires manufacturers and importers of substances in quantities greater than 1 tonne per year to collect and share information on the properties and uses of such substances. Registrants must assess the intrinsic properties of their substance and whether the substance may cause an adverse effect on human health or the environment. This information is communicated to ECHA in their Registration dossier, and for substances manufactured or imported in quantities greater than 10 tonnes per year, the chemical safety report. Standard information requirements are the minimum required to meet REACH Registration obligations and are dependent on the tonnage that is manufactured or imported into the EU/EEA.

The European Commission has been investigating the regulation of endocrine disruptors for a number of years. In 1999, the EU Commission adopted the Community Strategy for endocrine disruptors, which has led to action in the fields of regulation, research, and international cooperation. Despite significant improvements in our understanding and regulation of endocrine disruptors, there remains a need to update the EU approach in order to ensure that it continues to build on existing knowledge and coherently address these substances throughout the chemical legislative framework.

The Commission Communication 'Towards a comprehensive European Union framework on endocrine disruptors'[1] confirmed the commitment of the Commission to update data requirements in the different legislative frameworks to improve identification of endocrine disruptors. The 2020 Fitness Check on Endocrine Disruptors noted that questions had been raised by stakeholders on the overall coherence of the EU legal framework in relation to EDCs. Building on this, the Chemicals Strategy for Sustainability seeks to "*ensure that sufficient and appropriate information is made available to authorities [on the intrinsic properties of a substance] to allow the identification of endocrine disruptors [which may cause adverse effects on human health and the environment] by reviewing and strengthening the information requirements across legislation*" [2]. To do this, the European Commission shall "*update information requirements to allow the identification of endocrine disruptors in relevant legislation, particularly under REACH*".

In order to meet the ambition of Chemicals Strategy for Sustainability to ensure

sufficient and appropriate information for identification of endocrine disruptors, the Commission proposes to update:

- **Annex I - General provisions for assessing substances and preparing chemical safety reports**
- **Annex VII - Standard information requirements for substances manufactured or imported in quantities of one tonne or more**
- **Annex VIII - Standard information requirements for substances manufactured or imported in quantities of 10 tonnes or more**
- **Annex IX - Standard information requirements for substances manufactured or imported in quantities of 100 tonnes or more.**
- **Annex X - Standard information requirements for substances manufactured or imported in quantities of 1000 tonnes or more.[3]**

Options for introducing standard information requirements for endocrine disruptors at each tonnage level were presented at the 3rd meeting of the CASG-ED in October 2020. Following the advice of the subgroup of the Competent Authorities for REACH and CLP on endocrine disruptors (CASG-ED) experts, the Commission has developed two different options for adaptations of the Annexes, which will include new standard tests providing information on endocrine disrupting properties. Before the potential revision of the REACH Annexes, the Commission following its guidelines on Better Regulation conducts an Impact Assessment of the relevant regulatory options. The purpose of this consultation is to gather the views of key stakeholders on the costs and benefits of including in REACH standard information requirements for endocrine disruption.

[1] COM(2018) 734
[2] COM(2020) 667
[3] Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).

2. Page 2

Your role – what you can do to help us and the EU

We would like to enlist your help in understanding the range of potential impacts (cost and benefits) of the two proposed options for introducing standard information requirements for endocrine disruptors to REACH Annexes VII-X.

Your views and expertise will contribute to our ongoing work on an Impact Assessment of possible revisions to the information requirements of the REACH Regulation.

The Targeted Consultation questionnaire shall run from 3rd August 2021 – 8th October 2021.

Content of this consultation

This Targeted Consultation is divided into seven parts:

Part 1 asks for some information about you, such as which country you come from.
Part 2 aims to gather information on general awareness and views of the impacts of endocrine disruptors and the measures to manage these and existing legislation.
Part 3 contain more detailed questions about the ambitions and relevance of chemical legislation in the EU and views on the revision of REACH Annexes.
Parts 4, 5, 6 and 7 aim to gather evidence of the potential baseline direct and indirect economic, social and environmental impacts of the proposed changes to REACH Annexes to include standard information requirements for endocrine disruption.

Please also note that there will be also be follow-on Targeted Stakeholder online Focus Groups for experts (11th October 2021 – 29th October 2021). At the end of this survey, you are welcomed to let us know if you would like to participate in the follow-on Targeted Stakeholder online Focus Groups.

At the end of the questionnaire, you will also be able to upload one document (e.g. technical information, Position Paper, etc.) supporting and detailing your views.

If your would like to save the questionnaire and come back to it later please use the "Save and Continue" function at the bottom of the page. Once you have submitted your answers, you will receive an email with your completed questionnaire.

If you have any questions, please contact the European Commission at this dedicated email address:

ENV-EDC@ec.europa.eu

Please contact the study team at:

becca.johansen@ricardo.com

Your opinion matters, and we are very grateful to you for taking the time to answer these questions.

3. Page 3

Part One - About You

Language of my contribution

English

I am giving my contribution as

Business association

Please complete:

First name : Lina
Surname : Dunauskiene
EmailThis will not be published : lina.dunauskiene@aise.eu

Organisation/association/institution/authority name

The Downstream Users of Chemicals Co-ordination Group (DUCC)

Scale of your operation

International

Organisation size

Micro (1 to 9 employees or €2 million or less turnover/ balance sheet total)

EU Transparency register number
Check if your organisation is on the transparency register. It's a voluntary database for organisations seeking to influence EU decision making.

70941697936-72

Country of origin
Please add your country of origin, or that of your organisation.

Belgium

Publication - Privacy settings

The Commission will publish the responses to this public consultation. Please choose whether you would like your details to be made public or to remain anonymous.

PLEASE TICK THIS BOX if you are happy to make your submission **Public**.
We will publish your identification details (name, organisation name and size, transparency register number, country of origin) and your contribution.

PLEASE TICK THIS BOX to state that you agree with the personal data protection provisions

I agree

4. Page 4

Part 2 – General awareness and views on the impacts of endocrine disruptors and existing legislation

This section asks about your general awareness of the chemicals industry, endocrine disruptors, and existing legislation to gather general views on revising the information requirements, especially under REACH; to improve the identification and management of endocrine disruptors and, in doing so, protecting citizens and the environment better against associated hazards whilst encouraging innovation for the development of safe and sustainable alternatives.

In each question, please select the answer which best represents your views.

Please also note that you do not need to answer all the questions in any of the sections.

1. How familiar are you with the potential role of chemical substances in affecting the endocrine systems of humans and wildlife?

	Expert	Very familiar	Somewhat familiar	Not familiar	Don't know
Familiarity with the role of chemicals affecting the endocrine system of **humans**	X				
Familiarity with the role of chemicals affecting the endocrine system of **animals**	X				

2. For the products that you use (consumer goods) or work with (e.g. manufactured substances, testing chemicals, products for professional or industrial use) on a day-to-day basis, how familiar are you with the chemical components and their potential positive or negative impacts on human and wildlife?

	Expert	Very familiar	Somewhat familiar	Not familiar	Don't know
Familiarity with chemicals used and/or worked with and **potential positive impacts on human health**	X				
Familiarity with chemicals used and/or worked with and **potential negative impacts on human health**	X				
Familiarity with chemicals used and/or worked with and **potential positive impacts on wildlife**	X				
Familiarity with chemicals used and/or worked with and **potential negative impacts on wildlife**	X				

3. Do you have practical experience with registering substances and engaging with the REACH Annexes that outline the existing information requirements?

	Highly experienced	Somewhat experienced	Limited experience	No experience	Don't know
Annex I General provisions for assessing substances and preparing Chemical Safety Reports					
Annex VII Standard information requirements for substances manufactured or imported in quantities of one tonne or more					
Annex VIII Standard information requirements for substances manufactured or imported in quantities of 10 tonne or more					
Annex IX Standard information requirements for substances manufactured or imported in quantities of 100 tonne or more					
Annex X Standard information requirements for substances manufactured or imported in quantities of 1000 tonne or more					

4. How many employees currently work on REACH Registration within your organisation?

	0 FTE	1-25 FTE	26-50 FTE	51-75 FTE	76-100 FTE	101+ FTE	Don't know
Average number of employees per annum working on REACH Registration over the last five years							

5. Page 5

Part 3 – Views on the revision of REACH Annexes I, VII to X to include standard information requirements for endocrine disruption

As outlined in the introduction, in order to meet the ambition of the Chemicals Strategy for Sustainability to ensure sufficient and appropriate information for identification of endocrine disruptors, the Commission proposes to update:

Annex I - General provisions for assessing substances and preparing chemical safety reports
Annex VII – Standard information requirements for substances manufactured or imported in quantities of one tonne or more
Annex VIII - Standard information requirements for substances manufactured or imported in quantities of 10 tonnes or more
Annex IX - Standard information requirements for substances manufactured or imported in quantities of 100 tonnes or more
Annex X - Standard information requirements for substances manufactured or imported in quantities of 1000 tonnes or more.[1]

This part seeks to gather detailed information on the potential costs and benefits of the two options (Option 1, Option 2 ?If you cannot access the document please ensure you are not using an Advertisement Blocker, if the issue persists please contact becca.johansen@ricardo.com) presented by the Commission for revision of the standard information requirements to include endocrine disruption. This data shall be assessed against the baseline.

Baseline Scenario

Current REACH standard information requirements, as published in Annexes VII-X of REACH, including all amendments up to and including Regulation 2018/1881.

Please select the answer that best represents your views. Please note that not all questions need to be answered.

[1] Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).

5. REACH Registration is the first step in the regulation of endocrine disruptors. How important would you say the addition of standard information requirements for the testing of endocrine disruption under REACH could be to inform of their properties?

	Very important	Somewhat important	Hardly important	Not important	Don't know
Addition of standard information requirements for endocrine disruption testing under REACH to inform about endocrine disrupting properties with human health effects				X	
Addition of standard information requirements for endocrine disruption testing under REACH to inform about endocrine disrupting properties with environmental effects				X	

6. Testing for endocrine disruption is currently mainly limited to animal testing due to current knowledge and available test methods for endocrine activity. Use of alternative test methods such as (Q)SAR, read-across and grouping and in vitro studies that could reduce animal testing are available or are under development. Would a greater focus on alternative test methods lead to greater innovation in this field, and a reduction in reliance on in vivo methods?

Strongly agree

7. Which of the following in vivo tests can possibly be replaced by non-animal testing methods?

	QSARs	Read-across/ Grouping	In vitro tests
Short-term toxicity testing on fish (OECD TG 203)			
Uterotrophic Bioassay in Rodents (OECD TG 440)			
Hershberger Bioassay in Rats (OECD TG 441)			
Fish Short Term Reproduction assay (OECD TG 229)			
Amphibian Metamorphosis Assay (OECD TG 231)			
Fish early-life stage (FELS) toxicity test (OECD TG 210)			
Fish, juvenile growth test (OECD TG 215)			
Fish Sexual Development Test (OECD TG 234)			
Fish Life Cycle Toxicity Test (OPPTS 850.1500)			
Medaka Extended One-Generation Reproduction Test (OECD TG 240)			
Zebrafish Extended One-Generation Reproduction Test			
Larval Amphibian Growth and Development Assay (OECD TG 241)			

8. Please state any additional non-animal testing methods that can be used or other in vivo tests that could be replaced.

DUCC believes that now, through application of the latest science, is the best time to develop and apply a new research toolbox based on non-animal approaches and to break free of the belief that animal models are the best experimental tools available

Alternative tests can be appropriately used to exclude specific endocrine activity that is detected in all these tests and thus, support the decision that ED properties in vivo are unlikely. However, available in vitro screening assays are designed to investigate endocrine activity and mode of action, but not adverse effects. As a result, they cannot fulfil the requirements for EDs identification as stated by the WHO, which are i) endocrine modes of action ii) adverse effects in an intact organism and iii) a causal link/relationship between the two. Care must therefore be applied in using them as part of the registration requirements to replace in vivo animal data like-for-like.

DUCC promotes New Approach Methodologies (NAMs) underlying Next Generation Risk Assessment (NGRA) as a useful tool for the collection of Weight of Evidence (WoE).

An increasing number of non-animal approaches are available to help provide bioactivity data to characterise the specific activity of a chemical in different parts of the endocrine system. A thorough understanding of human and environmental exposure can be used alongside these non-animal bioactivity data to judge whether an exposure is likely to result in endocrine bioactivity (Wetmore et al. 2015 (https://doi.org/10.1093/toxsci/kfv171); Becker et al. 2014 (https://doi.org/10.1002/bdrb.21085); Dent et al. 2019 (https://doi.org/10.1093/toxsci/kfy245)). This is important because where there is no bioactivity there can be no adversity, meaning that a safety decision can be made more efficiently and without needing to generate any animal data. This is only possible using an exposure-led and risk-based approach.

DUCC is of the opinion that, full dossiers following the NGRA framework for safety assessment should be evaluated in the context of downstream regulations. As in general these in vitro screening assays are known to lead to a high rate of irrelevant positive results because of their low specificity and high sensitivity, thus the dossiers would imply an extensive level of protection for the consumers.

As some preceding questions are ambiguously formulated, DUCC cannot reply to these but is instead providing input below:

- Clarifications for Q5: We do not see an added value in the addition of standard information requirements for the testing of endocrine disruption activity under REACH since this is a mode of action and its consequences are not only covered by safety assessments by REACH. The same experimental results could be used for classification for Carcinogenic, Mutagenic and Reprotoxic (CMR) substances, substances classified as very toxic or toxic for aquatic organisms with long lasting effects (when classification is based on true chronic data) and ED. For example, an endocrine Mode of Action (MoA) could lead to reproductive toxicity.
- Clarifications for Q6: We agree with the statement "greater focus on alternative test methods lead to greater innovation in this field". We also believe that in vitro tests have the potential to reduce the need for additional ED animal testing i.e., if a compound clearly does not show endocrine activity in vitro, then it is not necessary to test for adverse effects in vivo. This has already proven to be the case in cosmetics, where a ban is implemented.
- Clarifications for Q7: In general, no in vitro test can identify adverse effects in intact organisms thus all the in vitro tests need to be used alongside information on exposure. No definitive conclusion can be drawn on positive in vitro studies regarding whether a substance meets the WHO ED criteria. Regarding, Q7, the listed in vivo tests are mainly environmental. Replacing all these tests by QSARs or in vitro tests would need further research. In particular, an effort should be made to identify batteries of test/models to replace the in vivo existing ones (as has been done for the uterotrophic assay), as one to one test replacement is almost impossible. The industry would welcome the launch of a dedicated European Commission research program.

9. For substances to be 'fully registered' under REACH, the information in REACH Annexes VII-X must be submitted with the registration. If in vitro testing for EDs was added to the REACH information requirements as indicated in the options, for what percentage of these 'fully registered substances' (including identified EDs or substances for which available classification provides information e.g. tests for reprotoxicity that provide information on ED effects) would you estimate the in vitro tests would provide an indication for an ED mode of action, sufficient information on the ED mode of action or on ED related effects?

	0	1-5%	>5-10%	>10-25%	>25-50%	>50-75%	>75-100%	Don't know
Indication for ED mode of action								
Sufficient information on the ED mode of action								
Sufficient information on ED related effects								

10. For substances to be 'fully registered' under REACH, the information in REACH Annexes VII-X must be submitted with the registration. If in vitro testing for EDs was added to the REACH information requirements as indicated in the options, and if the in vitro testing results in indication of an ED mode of action or ED related effects, what percentage of these 'fully registered substances' would be confirmed as actual EDs by further (in vivo) testing (100% = all 'fully registered' substances)?

11. Please provide an explanation for your response that is supported by evidence and sources (including whether or not your assessment is based on the portfolio of substances you are producing/ using). We would especially welcome any evidence on substances you have identified and/or have evidence to suspect that they might have ED properties.

DUCC would like to note that in vitro tools are useful in an exposure led safety assessment to ensure that relevant exposures will not cause endocrine activity (and therefore adversity). However, as in vitro tools themselves do not yet distinguish between endocrine activity and adversity, they will identify endocrine activity in many substances that are not endocrine disruptors (Tinwell et al, 2013).
In our view both concentration and potency of the test substance should also be taken into account when performing a test, since adverse effects depend on both concentration and potency of the test substance. Exogenous compounds are often too weak to compete with endogenous substances, thus in vivo adverse effects are unlikely to occur. For example, putative environmental estrogens exhibit potencies three or more orders of magnitude below that of the endogenous 17β-estradiol (Borgert et al., 2013). In addition, in the context of concentrations active in vitro, these are often close to cytotoxicity and thus, not meaningful (Natsch et al, 2021).
In general, DUCC could support the addition of in vitro tests in combination with information on exposure, as otherwise they will not lead to the relevant conclusion on the endocrine safety of chemicals. We believe that a proportionate and science-based regulatory framework for chemicals must be based on sound science reflecting both hazard and exposure (i.e., safe use). This is the vision that we believe should be pursued with the REACH revision in mind, to allow the full application of NAMs, if we want to meet the ambition of the Green Deal, Chemicals Strategy for Sustainability and Zero Pollution Action Plan.

Please upload any evidence or sources to support your response.

Borgert_et_al._2013.pdf
Natsch_et_al_2021.pdf
Tinwell_at_al,_2013.pdf
Fentem_et_al_2021.pdf

12. When considering the possible new information requirements to identify substances that may have endocrine-disrupting properties, how would you assess their importance?

	Very important	Important	Hardly important	Not important	Don't know	Clear answer not possible/answer is case-dependent
Literature review	X					
Systematic literature review	X					
In silico methods						X
Estrogen receptor transactivation assay (OECD TG 455)						X
Androgen receptor transactivation assay (OECD TG 458)						X
H295R steroidogenesis assay (OECD TG 456)						X
Aromatase assay (OPPTS 890.1200)						X
Short-term toxicity testing on fish (OECD TG 203)						X
Uterotrophic Bioassay in Rodents (OECD TG 440)						X
The output data from the ToxCast ER Bioactivity Model						X
Hershberger Bioassay in Rats (OECD TG 441)						X
Fish Short Term Reproduction assay (OECD TG 229)						X
Fish early-life stage (FELS) toxicity test (OECD TG 210)						X
Fish, juvenile growth test (OECD TG 215)						X
Fish Sexual Development Test (OECD TG 234)						X
Fish Life Cycle Toxicity Test (OPPTS 850.1500)						X
Amphibian Metamorphosis Assay (OECD TG 231)						X
Medaka Extended One-Generation Reproduction Test (OECD TG 240)						X
Zebrafish Extended One-Generation Reproduction Test						X
Larval Amphibian Growth and Development Assay (OECD TG 241)						X

13. With regards to animal welfare considerations or costs to companies, do you believe it is proportionate to require in vivo animal, testing for low tonnage (<10 tonnes) substances?

Cost to companies

No

Animal welfare

No

Please explain your answer with reference to any evidence that may support it

Automatic triggering of animal testing is contrary to the EU commitment to in vivo testing as last resort (Fentem 2021). Specific endocrine testing should be initiated at Annexes VIII-X as for other hazard based assessments. Tests proposed in Annex VII are limited to in vitro screening for endocrine activity without indication of adverse effects and contradicts the proposals made for Annexes VIII-X. Reliance on only in vitro screening for activity could lead to unnecessary animal testing

14. A weight of evidence approach uses a combination of information from several independent sources to give sufficient evidence to fulfil an information requirement. This approach is beneficial when the information from a single piece of evidence alone is not sufficient to fulfil an information requirement. Option 1 suggests in Annex VIII to trigger in vivo studies informing on endocrine mechanisms or adverse effects using a weight-of-evidence approach. What would be – in your view – sufficient information in a weight-of-evidence approach for requesting further tests?

	Agree	Disagree	Don't know/neither agree or disagree
A single positive in vitro assay		X	
At least two positive in vitro assays pointing to the same mechanisms			X
A single positive in vitro assay plus some other information (e.g. either QSAR, in vivo effect data, read-across …)			X
Read-across to another substance with known mode of action			X
QSAR		X	
In vivo effect data that give reasonable cause for assuming an ED mode of action.			X
The information needed is case dependent. It is not possible to set clear rules.	X		

15. For substances registered in the tonnage band of above 1 tonnes and below 10 tonnes (low tonnage substances), Option 2 requests in vivo mechanistic studies on the basis of a single positive result in any of the in vitro assay. Do you agree or disagree to the following statements?

	Agree	Disagree	Don't know/neither agree or disagree
A single positive in vitro assay sufficiently justifies requesting an in vivo mechanistic test		X	
The trigger for in vivo testing should be strengthened	X		
The positive in vitro assay should be confirmed by a second in vitro assay before triggering in vivo testing		X	
A positive in vitro assay sufficiently evidences an ED mode of action – no confirmation with an in vivo test required		X	

16. For substances registered in the tonnage band of 10 tonnes or more, Option 2 requests in vivo mechanistic studies as well as in vitro tests. Option 1 requests in vivo mechanistic studies on the basis of a weight of evidence (WoE) approach that takes account of available information. Thus Option 1 may be less expensive than Option 2 but Option 2 may identify a greater proportion of the substances that are EDs

Which would be your preferred option for substances registered in the tonnage band of 10 tonnes or more?

Details of Option 1 and Option 2 ?If you cannot access the document please ensure you are not using an Advertisement Blocker, if the issue persists please contact becca.johansen@ricardo.com

Option 1

Please provide an explanation for your response that is supported by evidence and sources.

DUCC disagrees with option 2 since it misses two key elements for assessing endocrine disruption, which are expert judgment and WoE. Without the adoption of a case-by-case approach, there is no opportunity to avoid performing animal tests when not needed. WoE is a well-established scientific principle already adopted by REACH and particularly relevant for complex endpoints like ED which allows to make use of best mechanistic scientific knowledge and not simply ticking boxes. We also disagree with some elements of option 1 (see position papers attached).

Please upload any supporting evidence

DUCC_comments_to_3rd_and_-_4th_CASG-ED.pdf

17. The Options list several established in vitro assays. As any test method, in vitro assays can lead to false positive and false negative results. If you have suitable expertise, could you provide an estimation for the prevalence of false positive and false negative results for the following assays?

False positive

	<2%	<5%	<10%	<20%	<30%	<50%	Don't know
Estrogen receptor transactivation assay (OECD TG 455)							
Androgen receptor transactivation assay (OECD TG 458)							
H295R steroidogenesis assay (OECD TG 456)							
Aromatase assay (OPPTS 890.1200)							

False negative

	<2%	<5%	<10%	<20%	<30%	<50%	Don't know
Estrogen receptor transactivation assay (OECD TG 455)							
Androgen receptor transactivation assay (OECD TG 458)							
H295R steroidogenesis assay (OECD TG 456)							
Aromatase assay (OPPTS 890.1200)							

18. Please provide an explanation for your response that is supported by evidence and sources.
Do you know examples of false-negatives/positives?

DUCC disagrees with the notion of false negatives/positives as used in the questions, since this is used for the comparison of the outcome of the in-vitro test to the outcome of the in-vivo end point, but in-vitro screening assays, as also previously mentioned, can only provide information on endocrine activity and mode of action but not on adverse effects. In-vitro assays can only be used effectively in a weight of evidence approach when used in combination with information on exposure. This also illustrates the need for a mindset change in chemical safety assessment when moving away from outdated animal models to new, best scientific methods.
In addition, DUCC would like to note that in line with the genotoxicity approach, in vitro assays can produce irrelevant positives when considered in the context of a safety assessment rather than "false positives". Moreover, DUCC would like to stress that OECD guidelines should not be used for regulatory decision making since that goes beyond their scope. DUCC urges to further validate these assays for predictivity prior to adding them to the REACH legislation.

Please upload any supporting evidence or sources.

19. The current options differ as regards in vitro thyroid assays to be introduced in Annex VII. Option 1 suggests the use of (multiple) thyroid assays in Annex VII that address different key events in the thyroid modes of action. Option 2 does not specify the assays yet but contains a placeholder. Which of the following key events do you think are important to address in in vitro assays?

	Very important	Important	Hardly important	Not important	Don't know
Binding to and (in)activation of thyroid hormone receptors;					
Thyroid stimulating hormone receptor binding and (in)activation;					
Thyroid releasing hormone receptor binding and (in)activation;					
Binding to thyroid hormone serum transporters					
Inhibition of thyroid hormone cellular transporters					
Thyroid peroxidase inhibition					
Sodium/iodide symporter inhibition					
Deiodinase inhibition					
Inhibition and/or induction of thyroid hormone biotransformation enzymes					
Altering thyroid hormone levels affecting in vitro organ systems.					

20. How many of the thyroid assays listed in Q17 do you believe is appropriate to include in the standard information requirements?

21. Please provide an explanation for your response that is supported by evidence and sources, where possible.

Please upload evidence and sources, where possible.

22. Please mark in the table below those in vitro assays (or any combination) that in your view provides sufficient information to provide evidence on a thyroid mechanism for triggering further in vivo testing for thyroid disruption mediated effects.

23. Are there any combinations of assays that should trigger further in vivo testing (please indicate combinations by using a '+'-sign and separate combinations by ';'. Examples: 1+7+8; 2+5)

As was noted previously, in vitro tools are useful in an exposure led safety assessment to ensure that relevant exposures will not cause endocrine activity (and therefore adversity). Since these tools do not yet distinguish between endocrine activity and adversity and could provide irrelevant positive results, full NGRA bioactivity assays should be performed. Thus, DUCC believes that the number and combination of assays should be evaluated in a case-by- case manner

24. Please rank the different Commission options for introducing standard information requirements for endocrine disruption testing as regards the potential costs and benefits of each option.
If you would expect an action e.g. use of alternative test methods to have a high cost or benefit please select 5.
If you would expect a low cost or benefit, please select 1.

Details of Option 1 and Option 2 ?If you cannot access the document please ensure you are not using an Advertisement Blocker, if the issue persists please contact becca.johansen@ricardo.com

	Use of alternative test methods	Number of animal tests	Costs to Industry
Option 1 - Cost	4	4	4
Option 1 - Benefit	2	2	2
Option 2 - Cost	5	5	5
Option 2 - Benefit	1	1	1

25. Please provide an explanation for your response that is supported by evidence and sources, where possible.

DUCC in its answer to Q16 already noted that disagrees with option 2 since it misses two key elements for assessing endocrine disruption, which are expert judgment and WoE. Without the adoption of a case-by-case approach, there is no opportunity to avoid performing animal tests when not needed. WoE is a well-established scientific principle already adopted by REACH and particularly relevant for complex endpoints like ED which allows to make use of best mechanistic scientific knowledge and not simply ticking boxes. However, DUCC suggests clarifying the level of WoE that will be applied for the assessment of EDs.

Please upload evidence and sources, where possible.

26. Finally, do you have any suggestions for changes to the options for new REACH Annex VII-X standard information requirements for endocrine disruption testing? E.g. different triggering system, use of different tests?

DUCC would like to reiterate what has already been stated above. We are concerned that the proposed new information requirements in regulatory (eco)toxicology will highly increase the need for new animal testing, with no benefit for protection of human health or the environment.
We see the targeted revision of REACH as a unique opportunity to break free of the belief that animal models are the best experimental tool available to protect citizens or the environment, which is increasingly demonstrated not to be the case, and additional investment is needed to ensure that ECHA has the resources and scientific knowledge to support an increased use of New Approach Methodologies (NAM) under REACH. Chemical safety assessments should reflect both hazard and exposure (i.e., safe use). This is the vision that we believe should be pursued with the REACH revision in mind, if we want to meet the ambitions of the Green Deal.

6. Page 6

Part 4 – Baseline

This part seeks to develop a quick baseline of the administrative activities and testing that may be required by the proposed changes to REACH Annexes and may have already been carried out by industry. Further, this part seeks to gather updated evidence on the general costs of Substance Registration.

Please note that not all questions need to be answered.

27. How many unique substances have you registered under REACH?

28. Please indicate which of these tests and administrative activities you have already performed for your Registration, and on what percentage of your Registrations you have performed this.

	Already performed			Select Ranges 0-100% Registrations
	Yes	No	Don't know	
Literature review on ED				
Systematic literature review on ED				
In silico methods regarding ED				
Estrogen receptor transactivation assay (OECD TG 455)				
Androgen receptor transactivation assay (OECD TG 458)				
H295R steroidogenesis assay (OECD TG 456)				
Aromatase assay (OPPTS 890.1200)				
Uterotrophic Bioassay in Rodents (OECD TG 440)				
ToxCast ER Bioactivity Model				
Hershberger Bioassay in Rats (OECD TG 441)				
Fish Short Term Reproduction assay (OECD TG 229)				
Fish early-life stage (FELS) toxicity test (OECD TG 210)				
Fish, juvenile growth test (OECD TG 215)				
Fish Sexual Development Test (OECD TG 234)				
Amphibian Metamorphosis Assay (OECD TG 231)				
Fish Life Cycle Toxicity Test (OPPTS 850.1500)				
Medaka Extended One-Generation Reproduction Test (OECD TG 240)				
Zebrafish Extended One-Generation Reproduction Test				
Larval Amphibian Growth and Development Assay (OECD TG 241)				
OECD 426 Developmental Neurotoxicity				

29. Please indicate the geographical area of the laboratories you use to perform (eco)toxicological testing for Registration purposes.

30. Please provide your best estimates of the average costs of Registration-related administrative activities per Registration, across all Registrants.
Where no cost applies, please indicate "0".

	Annex VII >1 tonne	Annex VIII >10 tonnes	Annex IX >100 tonnes	Annex X >1000 tonnes
Cost for preparing the Registration Dossier				
Physicochemical requirement study costs				
Toxicological requirement study costs				
Ecotoxicological requirement study costs				
Costs of read across and QSARs				
Costs for a chemical safety assessment / report				
Costs of letter of access				
Cost of legal support				
Costs of training or changes to company systems				
Updating dossier as a result of new information (historical)				
Other				

If you have entered costs under "Other" please add detail on the "Other administrative activities".

31. Please provide any evidence and sources as well as the general time frame in which these costs may have been incurred.

Please upload any evidence and sources to support this.

32. Do you offer in vitro thyroid assays that address one of the following key events in the thyroid modes of action? If yes, please indicate costs and assay capacity. Do you intend to offer in vitro thyroid assays that address one of the following key events in the thyroid modes of action if those tests would become a standard information requirement under REACH? Please indicate approximate costs and assay capacity.

	Currently offer such assay	Current Costs per assay	Current Assay capacity per year	Intend to offer such assay	Intended Costs per assay	Intended Assay capacity per year
Binding to and (in)activation of thyroid hormone receptors;						
Thyroid stimulating hormone receptor binding and (in)activation;						
Thyroid releasing hormone receptor binding and (in)activation;						
Binding to thyroid hormone serum transporters						
Inhibition of thyroid hormone cellular transporters						
Thyroid peroxidase inhibition						
Sodium/iodide symporter inhibition						
Deiodinase inhibition						
Inhibition and/or induction of thyroid hormone biotransformation enzymes						
Altering thyroid hormone levels affecting in vitro organ systems.						

7. Page 7

Part 5 – Costs Related to Inclusion of ED Testing in REACH Annexes VII-X

This part seeks input on regulatory costs that may be associated with administrative and testing activities that will be required upon the introduction of the legislative options considered herein.

Please note that not all questions need to be answered

33. On average, what is the cost of preparing and submitting new testing proposals to ECHA for in vivo tests in Annexes IX and X?

	Values	Don't know
		.
Costs of preparing (€/proposal)		
Costs of submitting (€/proposal)		

34. If the following tests were introduced as a result of standard information requirements under REACH, would you expect the costs of testing to increase or decrease? Please refer to your previous answers for the current costs of these tests against which we should consider this question.

	Decrease by >50%	Decrease by >40%-50%	Decrease by >30%-40%	Decrease by >20%-30%	Decrease by >10%-20%	Decrease by >0%-10%	No change	Increase by >0%-10%	Incre b >10 20
In silico methods									
Estrogen receptor transactivation assay (OECD TG 455)									
Androgen receptor transactivation assay (OECD TG 458)									
H295R steroidogenesis assay (OECD TG 456)									
Aromatase assay (OPPTS 890.1200)									
Short-term toxicity testing on fish (OECD TG 203)									
Uterotrophic Bioassay in Rodents (OECD TG 440)									
Hershberger Bioassay in Rats (OECD TG 441)									
Fish Short Term Reproduction assay (OECD TG 229)									
Amphibian Metamorphosis									

Assay (OECD TG 231)									
Fish early-life stage (FELS) toxicity test (OECD TG 210)									
Fish, juvenile growth test (OECD TG 215)									
Fish Sexual Development Test (OECD TG 234)									
Fish Life Cycle Toxicity Test (OPPTS 850.1500)									
Medaka Extended One-Generation Reproduction Test (OECD TG 240)									
Zebrafish Extended One-Generation Reproduction Test									
Larval Amphibian Growth and Development Assay (OECD TG 241)									
OECD 426 Developmental Neurotoxicity									

35. Based on your costs of updating a registration dossier recently, what would be the likely cost of updating the dossier as a result of EDC testing?

Note that the costing of updating the dossier should include the cost of testing that has not been carried out previously for the substance. Previous studies have indicated the costs of updating registration dossiers to lie within the €1000-10,000 range.

	More than the historical Dossier Updating costs	Similar to the historical Dossier Updating costs	Less than to the historical Dossier Updating costs	Don't know
Annex VII				
Annex VIII				
Annex IX				
Annex X				

36. Please provide any evidence and sources.

Please upload any evidence and sources.

37. Would you need to employ additional staff as a result of introducing EDC testing requirements and the need for updating Registration dossiers?

8. Page 8

Part 6 – Costs Related to Further Regulation of ED

This part seeks evidence on the likely implications of substance registration, especially for industry.

Please note that not all questions need to be answered.

38. What might be the implications for industry of the positive indication of endocrine disrupting properties of substances as a result of the testing carried out for REACH Standard Information Requirements, where the substance is then classified under the CLP Regulation?

	Very likely	Likely	Possible	Limited likelihood	Unlikely	Don't know
Applications for derogations or for authorisation in REACH or downstream legislation e.g. sector specific legislation under the premise that EDC are regulated as CMRs as announced in the CSS. Legislation may includeREACH Regulation (EC) No 1907/2006 Regulation (EC) No 1223/2009 on cosmetic products Directive 2009/48/EC on the safety of toys Regulation (EC) No 450/2009 on active and intelligent materials intended to come into contact with food Commission Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food Regulation (EC) No 1107/2009 on plant protection products Regulation (EU) No 528/2012 biocidal products			X			
Introduction of additional risk management measures where no previous hazard classification has warranted similar risk management measures					X	
Identification of substance alternatives/ substitution					X	
Discontinuation of manufacturing/ use of these substances			X			
Other						

39. Let us assume that your business identifies 10 unique substances that may have endocrine disrupting properties, what would be your most likely response, on average? For example, 5 or 50% could be substituted/ alternatives would be found, a further 4 or 40% would be discontinued/ no longer manufactured as a result of a positive indication of endocrine disrupting properties under REACH Registration, and for the final 1 or 10% of substances, the company may seek derogation from restriction or prohibition of use in REACH or downstream legislation after harmonised classification and labelling introduced by the CLP Regulation.
Note, responses should add to 100%

	0	1-10%	11-20%	21-30%	31-40%	41-50%	51-60%	61-70%	71-80%	81-90%	91-100%
Introduction of risk management measures after positive identification of endocrine disrupting properties via REACH Annexes VII-X											
Identification of substance alternatives/ substitution after positive identification of endocrine disrupting properties via REACH Annexes VII-X											
Discontinuation of manufacturing/ use of these substances after positive identification of endocrine disrupting properties via REACH Annexes VII-X											
Applications for derogations or for authorisation after harmonised classification and labelling according to CLP and subsequent regulatory management under one or more of the legislations. Legislation may includeREACH Regulation (EC) No 1907/2006 Regulation (EC) No 1223/2009 on cosmetic products Directive 2009/48/EC on the safety of toys Regulation (EC) No 450/2009 on active and intelligent materials intended to come into contact with food Commission Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food Regulation (EC) No 1107/2009 on plant protection products Regulation (EU) No 528/2012 biocidal products											
Other											

40. Please provide the context/ reasoning behind your answer.

DUCC cannot answer Q39. DUCC believes that it is not necessarily the number of substances acquiring an ED flag that matters; what is important is their usage, the possibility to replace them. Further on, DUCC would like to note that answering such a question with an approximation would be inaccurate, invalid. An impact assessment should be performed in order to provide a correct percentage.

41. Would this manifest in indirect regulatory/ compliance costs for your business?

Yes, significantly

42. Please provide any evidence and sources for these indirect regulatory / compliance costs.

Taking into account possible changes, mixture formulators will need to review their portfolios and possibly reformulate. Since every single reformulation has a huge cost, this will cause a huge business impact. If suitable alternatives are not available, then companies will have to research and find alternatives before they can reformulate the product. This adds to the time, cost, and complexity. However, without proper impact assessment it is hard to estimate the full effects.

Please upload any evidence or sources for these indirect regulatory / compliance costs.

Part 7 – Other economic, social and environmental impacts

Part 7 seeks input and evidence on other economic, social and environmental impacts, direct or indirect, that may be expected or result from the legislative options.

Please note that not all questions need to be answered.

Economic impacts

43. How would you expect establishing additional standard information requirements for endocrine disruption testing under REACH to affect the following in the EU, directly and indirectly?

	Strongly positive	Weakly positive	No or limited impact	Weakly negative	Strongly negative	I don't know
Research and Development / innovation for the chemicals industry. For example, increased R&D could have a positive social and economic impact. It could also have a negative impact through the diverting of funds for R&D in other areas.					X	
Competitiveness of the EU chemicals sector and wider industry in the global market. For example, improving the industry's competitiveness could be a positive economic impact. Where costs are high, this could lead to a negative impact through decreased competitiveness					X	

Social impacts

44. How would you expect establishing additional standard information requirements for endocrine disruption testing under REACH to affect the following in the EU?

	Strongly positive	Weakly positive	No or limited impact	Weakly negative	Strongly negative	I don't know
Employment levels. For example, increased testing leading to a net increase in employment for laboratories and public authorities could have a positive social impact. An increase in costs of production may result in product withdrawal, leading to a negative impact on employment in the industry. An increase in dossier updates may lead to an increase in employment in the chemicals industry.						
Public health and health system impacts associated with endocrine disruptors. For example, reducing incidence of endocrine-related human health impacts could have a positive social impact.						

45. In the EU, what would you say is the contribution of human exposure to substances with endocrine-disrupting properties registered under REACH on the onset of the following diseases or health hazards?

	Significant	Moderate	Low	None	Don’t know
Metabolic disorders -obesity					
Metabolic disorders -Type II diabetes					
Other cardiovascular disease not related to obesogenic and diabetogenic effects of ED					
Metabolic disorders -Thyroid disorders					
Neurodevelopmental disorders e.g. attention-deficit/hyperactivity disorders					
Diminished immunity response in children					
Hormone-dependent cancers – breast, ovary, testes, prostate					
Reproductive disorders – declining sperm count					
Congenital malformation in children e.g. hypospadias, cryptorchidism					
Other					

46. If known, please provide examples of exposure to substances causing the following effects.

47. Please provide any evidence and sources on the links between substances with ED properties and human health challenges (diseases and health hazards) and lifestyle factors, e.g. phytoestrogens from soy.

DUCC refrained from answering Q44 o Q46. We therefore prefer to provide short comment in this section. With the increasing amount of information requirements for REACH annexes, many substances might be banned even if safe (e.g., just based on false positive results). As a consequence, we may lose many important products, with an associated negative impact for the health of the consumers.

Please upload any evidence or sources on the links between substances with ED properties and human health challenges (diseases and health hazards) and lifestyle factors, e.g. phytoestrogens from soy.

Environmental impacts

48. How would you expect that establishing additional standard information requirements for endocrine disruption testing under REACH to affect the environment in the EU?

49. The table below lists some effects on wildlife organisms that are sometimes considered to be linked to exposure to endocrine disruptors. Some of the effects can also be caused by other mechanisms (e.g. exposure to chemicals exhibiting a mode of action that is not endocrine related; environmental conditions like temperature affecting developing of organisms). What would you say is the contribution in the EU of environmental and wildlife exposure to substances with endocrine disrupting properties registered under REACH on the following environmental effects?

	Significant	Moderate	Low	None	Don't know
Egg thinning					
Disturbed nesting behaviour					
Skeletal abnormalities - birds					
Skeletal abnormalities - frogs					
Skeletal abnormalities - other					
Imposex					
Feminisation - fish					
Impaired reproductive function – e.g. whales, seals polar bears					
Impaired immune system - seals					
Other					

50. Please provide examples of substances registered under REACH causing the effects in case you answered 'significant', 'moderate' or 'low' previously.

51. Please provide any evidence and sources on the links between substances with ED properties and animal welfare/ wildlife.

DUCC refrained from answering Q48 o Q50. We therefore prefer to provide short comment in this section. With the increasing amount of information requirements for REACH annexes, many substances might be banned even if safe (e.g., just based on false positive results). Therefore, we may lose many important products, with an associated negative impact for the health of the consumers.

Please upload any evidence or sources on the links between substances with ED properties and animal welfare/ wildlife.

10. Final Page

Any other comments

Please include any further information that would be useful for the ongoing impact assessments of revisions to the information requirements associated with the identification and management of endocrine disruptors in chemicals legislation, particularly under REACH. Where possible, provide public references to relevant studies, position papers, and case studies or alternatively, please upload relevant documents.

52. Please add any additional comments here.

DUCC would like to note that not all the questions in this questionnaire were answered as:
1) The questions are addressed to REACH registrants
2) The questions are too ambiguous, and we preferred to answer with a free text

53. Please upload any supporting documents here

54. If you are familiar with the European Chemicals' legislation and the associated information requirements, please indicate if you are happy to be contacted to participate in targeted consultation activities.

YES, please include me / **my organisation** in further consultation activities on the revision of information requirements to allow the identification of endocrine disruptors in relevant legislation, particularly under REACH.

Thank you

On behalf of the DG Environment Chemicals Team and of the REACH unit of DG GROW, thank you very much for your contribution to this Consultation!

If you have any questions, please contact the European Commission at this dedicated email address:

ENV-EDC@ec.europa.eu

Please contact the study team at:

becca.johansen@ricardo.com

11. Thank You!

Thank you for taking our survey. Your response is very important to us.