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Exchanging Knowledge, Identifying Challenges, Building Synergies

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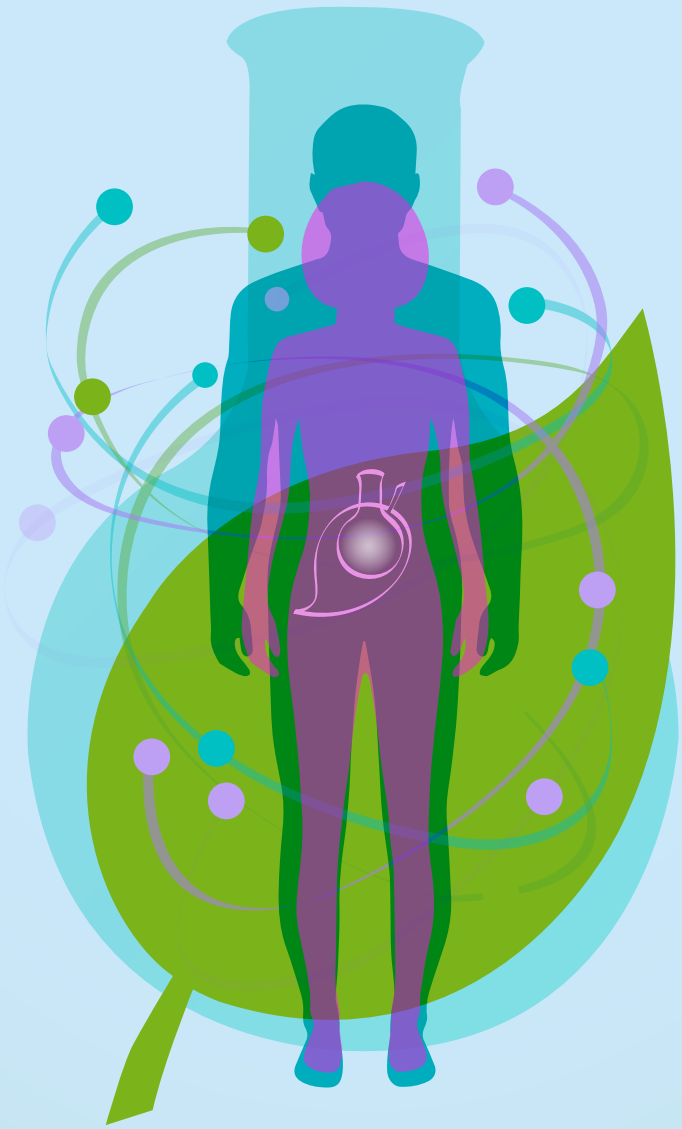
FORUM REPORT



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Opening session

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Virginijus Sinkevičius
European Commissioner for the Environment, Oceans and Fisheries

"Good morning, Ladies and Gentlemen and a very warm welcome to this Second Annual Forum on Endocrine Disruptors. It has been something of a challenge to organise, for obvious reasons, but here we are at last. I am very glad we have still managed to do it in 2020, and so soon after the adoption of the Chemicals Strategy for Sustainability. We promised to deliver the Chemicals Strategy in the European Green Deal, but also said that the regulatory framework should rapidly reflect scientific evidence on the risk posed by endocrine disruptors.

Here in this Forum, we understand the urgent need to act. We know that endocrine disrupting chemicals are of special concern. They affect people and animals at moments when the body is particularly vulnerable, at critical moments such as conception, embryo development, early childhood and puberty. The effects are permanent and sometimes are even carried over to the next generation.

The Commission has always been committed to ensuring a high level of protection of EU citizens and the environment. It is an obligation in our founding treaties and a principle that governs our daily work. Under this Commission, with President von der Leyen, the European Green Deal makes that commitment more explicit than ever before. It starts with the zero pollution ambition for a toxic-free environment by 2030, and it continues through the Chemicals Strategy for Sustainability.

And now it is time to extend that thinking to endocrine disruptors. As you know, we have been looking to improve protection against endocrine disruptors for quite some time. This year we have concentrated our energies into two specific areas. The first of those is updating data requirements for endocrine disruptors in the REACH Regulation. Under the future arrangement, companies will need to submit specific information if the substances they put on the market have been identified as endocrine disruptors. The second area is definitions, more specifically drawing up a definition of endocrine disruptors which can apply to all chemicals legislation. You will be hearing about these actions in much more detail later.

We will also be looking further into the future, with some news about next year. Our plan is to include endocrine disruptors as a hazard classification in the Classification, Labelling and Packaging Regulation. We will be making that proposal in early 2021, but we will not stop there because the scope for action to address endocrine disruptors for sustainability is much broader. We will discuss that tomorrow with ministers from some Member States.

One thing I would like to stress is the need for speed. We are determined to step up the pace. Our goal is to ensure that endocrine disruptors are banned in consumer products as soon as they are identified, unless their use in these articles is essential for society. As you know, over the past two years, the Joint Research Centre has been carrying out a Fitness Check to see how well our current legislation protects us from exposure to endocrine disruptors. The outcome showed a need to step up the protection, and we are determined to apply this as widely as we can. Our colleagues in the JRC will be sharing how they reached those conclusions in a session tomorrow.

It is a full programme and I am sure it will make for some very constructive debates. I wish you the best for these days. At the Commission we will be listening and taking part, and we will be determined to act on the conclusions. Thank you."

The definition of endocrine disruptors in the Classification, Labelling and Packaging of Chemicals Regulation

Photo: © Cristina de Avila

Cristina de Avila
Head of the Sustainable Chemicals Unit in DG ENV, European Commission

The EU Chemicals Strategy for Sustainability was adopted by the European Commission on 14 October 2020, as the first step towards a toxic-free environment under the European Green Deal. The Chemicals Strategy proposes to establish endocrine disruptors as a hazard category in the Classification, Labelling and Packaging (CLP) Regulation.

Cristina de Avila said the new definition of endocrine disruptors in the CLP Regulation was first called for in the Communication 'Towards a comprehensive European framework for endocrine disruptors', adopted in November 2018. In that Communication, the Commission committed to establishing a horizontal identification across EU legislation, broadly based on the accepted WHO definition.

Other Chemicals Strategy actions include an update of the REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) Regulation, through a review of information requirements for endocrine disruptors. This involves having the criteria to identify them, and also the necessary information. It follows a revision of such information requirements in the Plant Protection Products Regulation.

We established an expert Working Group of CARACAL to advise the Commission and ECHA (European Chemicals Agency), which works with competent authorities for REACH and CLP, explained Ms de Avila. This group met three times in 2020, with Member States and stakeholders, to discuss options for implementing endocrine disruptor criteria in the CLP Regulation. This fed into the development of the Chemicals Strategy for Sustainability.

The Chemicals Strategy is based on a lengthy and thorough evaluation of existing legislation, she said. We have in the EU the most advanced knowledge–base on chemicals, and extensive European activity to regulate chemicals.

Over the past five years the efficiency of chemicals legislation has been thoroughly evaluated. This has enabled an overview of how endocrine disruptors are addressed in every piece of relevant EU legislation. The findings were published alongside the Chemicals Strategy, as a Staff Working Document.

The WHO definition:

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

Source: World Health Organisation / International Programme on Chemical Safety (WHO/IPCS) 2002.

The Chemicals Strategy is aiming to give a response to alerts coming from science, stated Ms de Avila. This supports our good regulatory system in reducing citizens' exposure to harmful chemicals. We know endocrine disrupting chemicals can cause chronic diseases, and affect hormonal, immune and vascular systems.

In the Chemicals Strategy we set out a vision to ensure that by 2030 we achieve a toxic-free environment, where chemicals are produced and used in a way that maximises their contribution to society, while minimising harm to the planet and current and future generations.

This well be achieved through overarching and mutually-supporting objectives, she said. We have identified three key enablers to achieve the objectives: simplification and coherence of the chemical legislation framework; an improved knowledge-base that is able to respond faster to science; and the global dimension.

Legislation can be strengthened, for instance, by ensuring all chemicals on the market are used safely and sustainably; by promoting and rewarding the substitution of chemicals that pose long-term risks to humans and the environment; and by avoiding the most harmful chemicals in consumer products or those that affect vulnerable groups.

We want to build on the impressive existing legislation we have in the EU, said Ms de Avila, so we do not want to have a revolution we want to have an evolution. In particular, we want to strengthen the REACH and CLP Regulations, as the cornerstones of the chemicals regulatory system. She highlighted flagship actions on endocrine disruptors in the Chemicals Strategy, in addition to the commitment to establish horizontal hazard identification under the CLP Regulation. Endocrine disruptors will be banned from consumer products, by introducing or extending the existing generic risk approaches for carcinogens, mutagens and reproductive toxins. Such approaches will also be introduced in areas where they do not exist today. The concept of essential uses will be applied, to ensure that the most harmful endocrine disruptors are only used where essential for health, safety or the functioning of society, or if there are no acceptable alternatives.

Other Chemicals Strategy initiatives on endocrine disruptors include the commitment to amend Article 57 of REACH, where we identify Substances of Very High Concern (SVHC), which means that endocrine disruptors will have their own entry. Then, she said, we are committed to accelerating the development of methods used to generate information on endocrine disruptors through the screening and testing of substances.

Ms de Avila clarified that the introduction of hazard classes for endocrine disruptors in the CLP Regulation will be based on the WHO definition; build on criteria already developed for pesticides and biocides; and be applied across all legislation. We also concluded that it was best to separate the classes between human health and the environment, she said, because legislation covering these areas has different scopes, for example, the Cosmetics Regulation only covers health.

Regarding the possibility of sub-categories for hazard classes, Ms de Avila said this will be discussed as part of the proposed criteria under CLP. Sub-classes exist for carcinogens, mutagens and reproductive toxins. A category of 'suspected endocrine disruptors' (in addition to the category for known ones), she said, based on the experience with carcinogens, would better reflect the science and enable a more nuanced response to risk management.

In addition, a targeted impact assessment is planned to estimate the number of substances that will fall under each hazard category, to be used during the review process for each downstream piece of legislation, and when amending legislation. New label elements are also being developed, namely, the H-(hazard) and P-(precautionary) statements.

In terms of the next steps, after the adoption of the criteria under CLP, we will propose the adoption of the new endocrine disruptor classification under the GHS (Globally Harmonized System of Classification and Labelling of Chemicals), as a new building block, said Ms de Avila.

Q&A

Teri Schultz, the moderator on the first day, asked the questions from the live chat at this virtual conference.

***Blanca Serrano** (European Chemical Industry Council - Cefic) expressed surprise that the new hazard classes under the CLP Regulation had been agreed, as they were under the impression that the discussion was still ongoing. She asked if this could be clarified, and if the legal advice is being made available?*

***Natacha Cingotti** (Health and Environmental Alliance - HEAL) asked if there was a need for an impact assessment in order to proceed, given the work done through various chemicals evaluations.*

Cristina de Avila stressed the clear political commitment of the Commission, as established in the Chemicals Strategy.

She noted that the new hazard category in the CLP Regulation has become a sensitive issue for the chemical industry, who believe that adequate provisions are already in place under REACH to review and evaluate endocrine disruptors. However, she said, there is an established system in CLP, used for other hazard classes, such as carcinogens, and the treatment of endocrine disruptors should not be different. The Commission regards the CLP as a cornerstone in EU legislation to identify hazardous substances.

Ms de Avila reiterated that classification is exclusively hazard-based; based on the intrinsic properties of a substance. It is what you do with that substance that determines risk. Therefore, risk-based measures concern specific uses in pesticides, toys, food contact materials, cosmetics and other products. We cannot control their use, she said, so a generic approach is necessary for classification.

Responding to a comment on the importance of data sharing to speed up endocrine disruptor identification, Ms de Avila pointed out that the Chemicals Strategy promoted the 'one substance - one assessment' process, and will ensure data is available to all relevant authorities. The issue of coherence is very important in the Chemicals Strategy, she said.

Another comment concerned the large number of animals still being used for endocrine disruption testing. Ms de Avila agreed that more work is needed to find alternatives to animal testing, for all hazard classes of chemicals. The Commission is committed to reducing animal testing, she said, but the ultimate aim is to protect human health and the environment.

To this end, a Commission Scientific Conference on 2-3 February 2021 'Towards replacement of animals for scientific purposes' will highlight the new technologies enabling a move away from animal testing.

Work in progress on endocrine disruptors

In this session, the European Commission and European agencies summarised their work on endocrine disruptors.
The speakers were: **Arimatti Jutila,** European Chemicals Agency (ECHA); **Maristella Rubbiani,** DG SANTE; **Maria Arena,** European Food Safety Authority (EFSA); **Petra Leroy Čadová,** DG Internal Market, Industry, Entrepreneurship and SMEs, European Commission; and **Vera Rogiers,** Scientific Committee on Consumer Safety (SCCS).


Photo: © JUTILA Arimatti

The European Chemicals Agency (ECHA)

Arimatti Jutila
Hazard Assessment Directorate, ECHA, Helsinki

Arimatti Jutila is the co-chair of ECHA's Endocrine Disruptor Expert Group (ED EG), which provides scientific advice regarding the identification of endocrine disrupting properties of chemicals under REACH and the Biocidal Products Regulation (BPR). He gave a progress report on their activities.

There is a wide range of legislation in ECHA's portfolio, of which REACH and BPR specifically address endocrine disruptors. The Classification, Labelling and Packaging (CLP) Regulation is foreseen as directly addressing them from 2021.

ECHA's regulatory strategy addressing chemical substances of concern under REACH and CLP, involves the use of registration dossiers for regulatory risk management. ECHA screens the data in these dossiers regularly to identify chemicals of concern (candidates) for Member States, competent authorities and ECHA itself, he said.

The focus is on fully registered substances and those structurally similar to them. There is an increasing focus on groups of substances, for example, bisphenols and phthalates in the case of endocrine disruptors. If further information about a chemical is required, this can be requested (dossier and substance evaluation). The wealth of information sent to ECHA is unique in the world. Companies are required to collect or generate information on the properties and uses of their chemicals, assess the risks and recommend safety measures.

Dr Jutila summarised the progress made on regulatory risk management of endocrine disruptors. Currently, there are 17 substances or groups of substances identified as SVHCs (Substances of Very High Concern) that are included in the Candidate List due to their endocrine disruptor properties. Butylparaben was added to the Candidate List in 2020.

We have already received two SVHC intentions for substances with endocrine disruptor properties to look at in 2021, and I think we can expect more, he said.

Further information can be requested from industry to clarify endocrine disruptor concern. There are 105 substances of endocrine disruptor concern on ECHA's CoRAP (Community Rolling Action Plan) list for substance evaluation. In the draft CoRAP list (2021 to 2023) there are 17 potential endocrine disruptors. The Member States doing this substance evaluation work are encouraged to consult ECHA's Endocrine Disruptor Expert Group (ED EG).

The ED EG was established in 2013 to contribute to the efficient assessment of substances with endocrine disruptor properties. Currently the group has 50 external members, from 19 EU Member States and EEA countries, the Commission (DG GROW, DG ENV, DG JRC, DG SANTE), stakeholder organisations (2 industry and 5 public interest), as well as EFSA, OECD and Switzerland.

To date ECHA has hosted 18 ED EG meetings, with 3 scheduled for 2021. The Expert Group provides informal and non-binding scientific advice for assessing endocrine disrupting properties of chemicals. Our experience is that in the vast majority of cases, the subsequent regulatory follow-up has been in line with the ED EG's advice, noted Dr Jutila.

Since 2013, the ED EG has provided scientific advice on 99 substance cases, roughly 80% under REACH and 20% under BPR. Of those, 15 substances were considered as endocrine disruptors and 4 not, but for many the assessment is ongoing.

The assessment of biocides for endocrine disruptor properties under the BPR is also supported by the ED EG. Scientific criteria for endocrine disruptors, based on the WHO definition, has been applied under BPR since June 2018. ECHA, together with EFSA (European Food Safety Authority) and the Commission's JRC (Joint Research Centre), developed guidance for the implementation of the criteria.

So far, the ED EG has discussed 22 biocidal active substances, 2 of which were considered endocrine disruptors, while for 20 more information is needed. The Biocidal Products Committee has discussed 21 biocidal active substances and produced 17 opinions, of these 3 were endocrine disruptors, 3 not, and for 11 no conclusion was possible. The Biocidal Products Working Groups discussed 12 active substances, with 4 not considered endocrine disruptors, but more data is required for most substances.

Dr Jutila concluded by mentioning some further endocrine disruptor-related activities where ECHA is involved. They are supporting the development of information requirements for endocrine disruptors under both REACH and BPR, for example, and the development of criteria under the CLP Regulation. In addition, ECHA are currently updating the guidance for safety data sheets to cover requirements for endocrine disruptor properties, and are contributing to EURION Cluster projects on endocrine disruptor identification.

Q&A

The moderator ***Teri Schultz*** *asked the questions from the live chat, starting with a query about ECHA's interaction with EFSA.*

Arimatti Jutila replied that EFSA is a member in the ED EG. A good example of their work with EFSA and the JRC is the development of guidance for endocrine disruptor criteria, for which there is close collaboration.

Q&A

Teresa Bernheim *(Lanxess Deutschland) asked how will ECHA's Risk Assessment Committee (RAC) and the ED EG work together for harmonised classification.*

Arimatti Jutila said that this is for classification that is yet to come, so it may be too early to say. However, for the part the ED EG plays, she said that we are discussing the hazards of the substances and then risks will be covered elsewhere.

Cécile Michel (ANSES, France) commented that experts are often left in a position were data does not allow conclusions, showing why a suspected class is important.

Q&A

Natacha Cingotti *(HEAL) asked if, considering the work ahead and the lack of data for many substances, the ED EG has enough resources to do its job?*

Arimatti Jutila said that the ED EG is a really useful resource for what we are doing and having 50 experts in the same room/remote meeting is very valuable, but there is only so much they can do. Initiatives come from Member States, and so far we have managed to discuss all the substances they have brought into the meetings.

Q&A

Pia Juul Nielsen *(EDC-Free Europe / CHEM Trust) added that when concluding a substance is not an endocrine disruptor, does it mean not fulfilling the criteria or it is scientifically justifiable that it is not an endocrine disruptor?*

Arimatti Jutila said that for categories and CLP the discussion is ongoing. At the moment, there is no category for suspected endocrine disruptors, and that is how we are working at the moment. When a substance is shown to not be an endocrine disruptor there is no follow-up regulatory action, at least concerning endocrine disruptor properties, though it may have other hazardous properties.

Q&A

Emma Grange *(Cruelty Free Europe) asked, from the observations of ECHA's handling of SVHC it seems that even for relatively data-rich substances, deciding on endocrine disruptor status on the basis of animal test data is very difficult, with a high degree of uncertainty. Would you agree?*

Arimatti Jutila thought that here the ED EG guidance is very valuable, as it describes how criteria should be implemented to decide if a substance is an endocrine disruptor or not. Of course, it requires expert judgement, and in some cases that can be tricky as the science of endocrine disruption is not the easiest one.

Q&A

Anne-Laure Demierre *(Federal Office of Public Health, Switzerland) asked, can you certify that substances are not assessed many times by different agencies or authorities that reach different conclusions?*

Arimatti Jutila replied, concerning the harmonisation of approaches, the aim is that there should be only one hazard assessment for each substance. He is aware that there are cases where more than one agency is working on the same substance, so it is very important to harmonise the approaches.

Q&A

Angel Nadal *(Universidad Miguel Hernández de Elche, Spain) asked what the consequences are once a substance, such as bisphenol A (BPA), has been classified as a SVHC because of its endocrine disruptor properties.*

Arimatti Jutila replied that only when a substance has been moved from the Candidate List as a SVHC to the Authorisation List do users have to apply for an authorisation to use it. However, there are certain obligations that apply in relation to the Candidate List also, such as notification of substances in articles and communication in the supply chain. BPA is in the Candidate List. BPS and BPF are different bisphenols, and this is where screening and grouping becomes important.

He agreed that substances already discussed by EFSA could also potentially be discussed by ECHA. Different pieces of legislation can have different information requirements and regulatory environments, so substances may be discussed under pesticides regulations and also under REACH and PBR.

Pesticides, biocides and food safety

Two speakers contributed to this section on the work in progress on endocrine disruptors: **Maristella Rubbiani,** *Policy Officer from Unit E4 Pesticides and Biocides, DG for Health and Food Safety (DG SANTE), European Commission; and* **Maria Arena,** *Senior Scientific Officer at the European Food Safety Authority (EFSA).*

Photo: © Maristella Rubbiani

Maristella Rubbiani (DG SANTE) gave an overview of the application of endocrine disruptor criteria for plant protection products and biocides.

A joint ECHA/EFSA Guidance Document was published in June 2018 to help implement the new endocrine disruptor criteria, followed by a review to align plant protection products (PPP) and biocidal products (BP) with the Guidance. Amendments of regulations and procedures for PPP and BP have been made to specifically foresee implementation of criteria for ongoing and future applications.

For PPP and BP, endocrine disruptor criteria are already applicable, and in force for ongoing and future evaluations, said Dr Rubbiani. This meant 'stopping the clock' at EFSA and Commission level, to give assessors enough time to evaluate and conclude on endocrine disruptor criteria. A review of test methods for fulfilling requirements for PPP is ongoing, in light of the ECHA/EFSA Guidance Document.

When there is a substance that is going to be renewed, or a new substance to be evaluated, we need to consider the new endocrine disruptor criteria, explained Dr Rubbiani. Under DG SANTE, decisions made since November 2018 by the Standing Committee on Plants, Animals, Food and Feed (PAFF Committee) have taken into account the criteria. The reporting Member States have also applied the new criteria, when dossiers are at their level.

Under the new criteria, cases have been initiated for three biocidal substances due to significant indications of endocrine disruptor activity (iodine, PV/iodine, and the fungicide zineb); and for three biocidal active ingredients (cholecalciferol or vitamin D3, cyanamide, and DBNPA (2,2-Dibromo-2-cyanoacetamide)). In addition, 16 biocidal active substances have been discussed in the ED EG at ECHA.

There have also been discussions on non-active substances contained in biocidal products having indications of endocrine disruptor properties, said Dr Rubbiani, including at what strength of indication to make public the names of substances that are under confidentiality. Other discussions related to the presence of impurities identified as endocrine disruptors, and biocidal products generating disinfection by-products identified as having endocrine disruptor properties are ongoing.

For both PPP and BP, training has been conducted on applying the new guidance and criteria, under the Better Training for Safer Food (BTSF) umbrella, for assessors in Member States. This training was prepared jointly by the Commission, EFSA and ECHA.

Photo: © Maria Arena

Maria Arena (EFSA) then gave a summary of the endocrine disruptor assessments for pesticides.

For 23% of substances assessed for humans and ED assessment in line with the ECHA/EFSA ED Guidance was waived as not considered scientifically justified, 12% were classified as endocrine disruptor, and 29% were considered as not having endocrine disruptor properties. For the remaining substances, additional data were requested.

For EAS-modalities (estrogen, androgen and steroidogenic), for humans additional data was requested in 41% of cases compared to 3% for the T-modality . This was because the dataset for assessing the endocrine disruptors through the T-modality is often complete, as a number of studies are available and have generated the data to comply with other data requirements.

For NTOs (non-target organisms), additional information was requested for 73% of cases (46 substances). When the substance was considered to meet the endocrine disruptor criteria in NTOs, this was mainly based on adversity for mammals which was considered relevant at population level.

From the substances assessed from November 2018, until 2 days before this Forum, 8 of the 66 were identified as endocrine disruptors. Of these, 5 were identified as endocrine disruptors through the T-modality, with 1 each for E, A, and S modalities, said Dr Arena. Out of the 8, 4 were considered to meet endocrine disruptor criteria for both human health and NTOs.

Dr Arena explained that according to the ECHA/EFSA guidance, an endocrine disruptor assessment can be waived when not scientifically justified due to a substance's physio-chemical properties or (eco)toxicological profile, or because testing is not technically feasible. For 15 substances, a full ED assessment was waived for human health, and in 9 cases for NTOs.

For 15 substances, an EFSA conclusion is publicly available on endocrine disruptor properties, though for most active substances additional data have been requested. There are differences in the assessment of human health and NTOs (e.g. availability of data, conditions for waiving), though the ECHA/EFSA Guidance Document was always followed.

EFSA has built a database containing all the assessments done so far, along with rationale for the decisions, which is shared with Member States and ECHA. The next steps, concluded Dr Arena, will be an Annex on how to consider XETA (OECD TG 248), in the assessment strategy of the ECHA/EFSA ED Guidance which will be published early next year after a webinar with stakeholders; and the establishment of an EFSA Working Group on endocrine disruptors in 2021.

Q&A

***Claire Beausoleil** (ANSES - French Agency for Food, Environmental and Occupational Health & Safety): What is planned in order to include non-EATS modalities in the guidance (e.g. for metabolic disruptors)?*

Maria Arena answered that for non-EATS modalities, this depends on the available knowledge and test methods. Once new test methodology becomes available that capture other modalities, it will be discussed with the European Commission how and when a revision of the Guidance Document may be needed.

Cosmetics and consumer safety

Two speakers contributed to this section concerning work in progress on endocrine disruptors: **Petra Leroy Čadová,** *Policy Officer in Unit D4 'Consumer Industry' of DG Internal Market, Industry, Entrepreneurship and SMEs (DG GROW); and* **Vera Rogiers,** *Co-chair of the Scientific Committee on Consumer Safety (SCCS).*

Petra Leroy Čadová (DG GROW) reported on the European Commission's review of the Cosmetics Regulation with regard to substances with endocrine-disrupting properties.

Published in November 2018, the review concluded that (i) the cornerstone of the Cosmetics Regulation is the scientific risk assessment of ingredients carried out by the SCCS; (ii) scientific concerns with regard to endocrine-properties can be addressed in this safety assessment; and (iii) the Regulation provides adequate tools to regulate the use of cosmetic substances that present a potential risk for human health and enables the Commission to take appropriate regulatory measures.

The report also made reference to the cross-sectoral fitness check on endocrine disruptors, launched just after its publication, and the Commission's commitment to establish a priority list of substances with potential endocrine disrupting-properties used in cosmetics by 2019.

Ms Leroy Čadová informed that a consultation of the Working Group on Cosmetics Products (comprising Member States, industry, SMEs, and NGOs) had taken place leading to the consolidation of a list of 28 potential endocrine disrupting substances, 14 in Group A[1] with higher priority, and 14 in Group B[2]. A call for data on the Group A substances was organised in 2019.

Following the call for data, the Commission submitted five mandates to the SCCS for risk assessment regarding three UV-filters (octocrylene, benzophenone-3 and homosalate), one preservative (propylparaben) and one hair dye (resorcinol). Three preliminary SCCS opinions (homosalate, propylparaben and resorcinol) have already been published for a commenting period.

An ongoing call for data on the remaining nine Group A substances is running until 15 January 2021. The Commission is planning to launch another call for data in early 2021 on the Group B substances.

1. Benzophenone-3 (BP-3); kojic acid; 4-methylbenzylidene camphor (4-BC); propylparaben; triclosan; resorcinol; octocrylene; triclocarban; butylated hydroxytoluene (BHT); benzophenone; homosalate; benzyl salicylate; genistein; daidzein.
2. Butylparaben; methylparaben; tert-butylhydroxyanisole / butylated hydroxyanisole (BHA); cyclopentasiloxane / decamethylcyclopentasiloxane / D5; ethylhexyl ethoxycinnamate (EHMC) / octylmethoxycinnamate (OMC) / octinoxate; cyclomethicone; benzophenone-1 (BP-1); salicylic acid; benzophenone-2 (BP-2); butylphenyl methylpropianol / BMHCA; benzophenone-4 (BP-4); triphenyl phosphate; benzophenone-5 (BP-5); deltamethrin.


Photo: © Vera Rogiers

Vera Rogiers talked in more detail about the activities of the Scientific Committee on Consumer Safety (SCCS) concerning potential endocrine disruptors.

The SCCS is an independent group of scientists who provide advice to the European Commission. Usually, the SCCS responds to given mandates from DG GROW, and conducts a risk assessment based on scientific criteria. Endocrine disruptors are approached like any other chemicals of potential risk to human health, on a case-by-case basis. To be clear, she said, we are not classifying substances, we do risk assessment. This is done according to the publicly available SCCS Notes of Guidance for the testing of cosmetic ingredients.

We follow the WHO definition of endocrine disruptors (see page 3), explained Prof Rogiers, in which three important points must be fulfilled: i) an adverse effect must be seen in an intact organisms, ii) which is shown to be due to endocrine activity, and iii) there must be correlation or causality between mode of action and adversity.

We take the conceptual framework of the OECD (see p. 12) into consideration, she said. Levels 1 and 2 can be done by us as assessors. Level 1 consists of historical animal data and existing physico-chemical information, in silico data, databases with endocrine disruptor properties of chemicals, and new technologies, while Level 2 covers *in vitro* assays for EAS modalities. Levels 3 to 5 are based on in vivo testing (mammalian species and non-mammalian species, e.g. amphibians, fish, daphnia). These are not done by the cosmetics industry because of the animal testing and marketing bans.

From our work on Levels 1 and 2, we derive a PoD (Point of Departure) - a dose that does not give adversity. We use for existing compounds historical information, their physico-chemical properties, in silico (computer) data and models (e.g. QSAR, and 'read across' to see if information from similar substances can be used), toxicity databases, and new technologies ('omics, e.g. proteomics, genomics). For Level 2, *in vitro* assays focus on estrogen, androgen and steroidal modalities (EAS). Together, this all provides a Weight-of-Evidence (WoE) that can be used to assess the likelihood of causing adverse effects.

Prof Rogiers stressed three points that characterise the risk of any substance of concern. Firstly, a hazard identification giving the intrinsic properties of a chemical, then a dose-response assessment in which different doses are used to observe which dose cause adversity, and thirdly an exposure assessment giving the time, frequency and amount to which one is exposed.

Since we want safe cosmetics, SCCS calculates a very conservative margin of safety based on the highest dose that humans can be exposed to without any adversity. This approach was used in the three publicly-available SCCS opinions to date.

For homosalate, the maximum allowed concentrate was 10%. SCCS found no robust data for possible endocrine disruptor activity or a PoD study on endocrine activity, so they calculated the lowest Margin of Safety by dividing the PoD through the highest exposure value for which no adversity could be observed (30mg/kgbw/day taken from a repeated dose toxicity study). The outcome was that the SCCS recommended the allowable concentration for this UV filter be lowered to 1.4%.

Propylparaben is allowed in a maximum concentration of 0.14% as a preservative. It is also used in cosmetics, food and medications. Using the same approach as for homosalate, the SSC concluded that the concentration of 0.14% may be kept for cosmetic products. Similarly, the maximum concentration of resorcinol allowed in hair dyes of 1.25% was also considered safe and may be kept.

Prof Rogiers concluded:

- **Risk assessment carried out by SCCS is driven not only by toxicity, but also by exposure on the basis of solid scientific evidence;**
- **When adverse effects are shown in reliable historical animal data, a systemic PoD can be derived for toxicological endpoints, covering endocrine disruptor effects;**
- **For new ingredients, animal studies (after 2013) are not allowed for the purpose of cosmetics (only Level 1 and 2 test methods);**
- **For environmental reasons and workplace safety, animal data may be requested by agencies, and SCCS has to consider this;**
- **Animal-free test methods are not yet available to derive a systemic PoD for human safety assessment.**

Q&A

***Ann Gils** (KU Leuven, Belgium) asked when the SCCS looks for a safe dose for an individual substance, do they also study the cocktail effect of the substances? Other participants asked about vulnerable people, such as pregnant women.*

Vera Rogiers said that vulnerable groups are considered in particular in the finished product dossier, which is the responsibility of the cosmetic industry. When the SCCS looks to different endpoints, maternal toxicity and teratogenicity are included. Aggregate exposures take into account multiple ingredients. We do risk assessment of single ingredients, and that is determining 'what is a safe dose' of that ingredient when present in a cosmetic product; the finished product is the responsibility of the cosmetic industry.

In Europe we have a dual system. The Commission looks for substances of concern for human health and Member States give information on ingredients, and then industry has the responsibility to create a dossier for each cosmetic product on the market. As co-chair of the SCCS, I can say that, because of that dual system, Europe has the safest cosmetics in the world, and I really mean it!

Advances

in test methods

Advances in test methods


Photo: © Anne Gourmelon

Anne Gourmelon
OECD, Paris

The OECD Conceptual Framework for testing endocrine disruptors:

Level 1:
Existing (historical) data and non-test Information;

Level 2:
In vitro assays providing data about endocrine mechanisms/ pathways;

Level 3:
In vivo assays providing data about endocrine mechanisms/ pathways;

Level 4:
In vivo assays providing data on adverse effects on endocrine-relevant endpoints;

Level 5:
In vivo assays providing more comprehensive data on adverse effects on endocrine relevant endpoints over more extensive parts of the life cycle of the organism.

Anne Gourmelon, of the Organisation for Economic Cooperation and Development (OECD), started her presentation by providing an overview of existing OECD Test Guidelines (TGs), collected in the Revised Guidance Document 150 on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption.

These include a diverse range of bioassays, toxicity studies and other tests, within Levels 2 to 5 of OECD's Conceptual Framework, covering EATS (estrogen, androgen, thyroid, and steroidogenic) modalities.

Ms Gourmelon then gave examples of the large number of ongoing projects to develop new TGs and update existing ones, such as 'TG 458: *in vitro* androgen receptor transactivation'. Most ongoing projects are led by OECD member countries, but benefit from international cooperation. The majority of current projects are in the field of ecotoxicology, or are looking at new endocrine pathways (beyond EATS), such as the retinoid signalling pathway.

The retinoid signalling pathway is critical for neural tube development, axial patterning and other developmental processes in organisms. OECD member countries have prioritised the development of new in vivo and *in vitro* methods for this pathway, along with additional endpoints in existing in vivo assays. A detailed review paper will be published on this in 2021.

Development of new or modified TGs follows a well-established process, with experts from member countries playing a central role alongside Expert Groups. The R&D stages are key for robust new methodologies for testing endocrine disruptors. We started to observe that new methodologies require our Test Guideline Programme to evolve to accommodate the diversity of technologies, said Ms Gourmelon. We are proposing solutions to regroup similar methodologies addressing the same question, while maintaining clarity for users.

Therefore, she continued, we are evolving from single method Test Guidelines to Test Guidelines containing several methods evaluating the same biological target and using the same technique (PBTG) or different technologies (KETG). We are now developing a proof-of-concept for combining TG methods that are technologically and functionally diverse to predict the same adverse effect, through a Defined Approach (DA-TG).

This evolution of testing methods reflects an increased understanding of the underlying biology. Defined Approaches, agreed across countries, will also extend the benefits of mutual acceptance of data beyond single TG methods. They can, for instance, reduce duplication of testing across countries, and through consensus-building and a rule-based approach reduce the need for subjective expert judgements when interpreting data.

The IATA (Integrated Approaches to Testing and Assessment) case study project, which exists outside of the Test Guideline Programme, reviewed a Defined Approach for estrogen receptor pathway in 2019, paving the way for future testing strategies that combine multiple non-animal methods.

A problem flagged up by researchers and regulatory authorities has been the use of different terms to describe the same biology. This hampers systematic reviews and data mining. It is being addressed in the new OECD Harmonised Templates for Reporting study summaries for endocrine disruptor *in vitro* assays.

One takeaway message from my talk today, concluded Ms Gourmelon, is that there are various ways to engage in projects in relation to endocrine disruptor assessment, beyond just TG development. In particular, Adverse Outcome Pathways (AOPs) development, as a one-stop-shop in knowledge management for endocrine disruptor pathways, and the IATA case study project that is enabling countries to share and explore the use of novel methodologies.

Q&A

***Anthony Tweedale** (R.I.S.K. Consultancy) noted that under the proposed amendments to the REACH data requirement Annexes, animal test doses are to be 'sufficient to generate adequate data to assess hazard'. Given these high doses, how can endocrine disruptors active at low doses be detected? Are the OECD test methods sensitive enough?*

Anne Gourmelon replied that endocrine disruptors have to be evaluated in terms of adverse outcomes observed in animal studies, but also with Mode of Action that can be tested *in vitro* or by screening in vivo assays. All of the available evidence is integrated for evaluation, not just long-term studies conducted at high doses.

A lot of effort is put into the development and validation of OECD TGs, she said. Some people may think they are insensitive, others may think they are too sensitive or burdensome. Among the diversity of testing methodologies that have been standardised and harmonised, there are certainly sensitive assays that have been developed and they need to be integrated overall.

Q&A

***Emma Grange** (Cruelty Free Europe) queried whether the question of how well animal testing methods reliably identify endocrine disruptors has been sufficiently addressed?*

Anne Gourmelon responded with two points. Firstly, we are exploring new pathways, new *in vitro* methods, and new endpoints to integrate into in vivo methods to make them more sensitive to endocrine disruptors. Secondly, she said, for the test methods that exist there is concern, and work ongoing to make animal tests more sensitive and more relevant to endocrine disruptor testing. All the work at the OECD builds on research efforts from member countries and industry, who generate a lot of data, which is integrated in a way that ensures robustness and reliability.

Q&A

***Suzanne Butt** (Glaxo Group Research, UK) noted that it is critical to know and understand the limitations of the (in vitro) methods; what they do not cover can be more important than what they do. How do they cover the unexpected effect that an in vivo study would catch?*

Anne Gourmelon replied that when a method does not cover a particular endocrine pathway, it does not mean there will never be an issue with endocrine activity of this substance for other endocrine modalities. As we gain more tools for newer pathways, we may better understand the behaviour and potency of chemicals and their action on the endocrine system and effects at the organism level. A negatively tested chemical may be considered a temporary negative until it is tested positive for another endocrine modality.

Q&A

***Paul Fowler** (Professor in the Institute of Medical Sciences at the University of Aberdeen), asked if the OECD is considering the IGF (Insulin-like Growth Factor) system as a target for endocrine disruption.*

Anne Gourmelon said that, for the moment, there is nothing specifically on IGF, but the OECD has a new project on the work plan that is a review paper, led by a consortium of European member countries, to gain a better knowledge and understanding of endocrine disruption of metabolic pathways.

EURION Cluster:

testing and screening methods to identify endocrine disruptors

Presentations in this session were made by:
Andreas Kortenkamp, Brunel University, UK;
Juliette Legler, Utrecht University, the Netherlands; and
Majorie van Duursen, Vrije Universiteit Amsterdam, the Netherlands.

The EURION Cluster (European Cluster to Improve Identification of Endocrine Disruptors) comprises eight projects funded through the European Commission's Horizon 2020 Research and Innovation Programme, with a total investment of close to €50 million.

The projects focus on different aspects of testing and screening methods for endocrine disruptors. Together, they can optimise synergies to maximise their impact. In particular, they focus on three areas with significant gaps and challenges: the thyroid hormone system, metabolic hormones, and female reproduction.


Photo: © Andreas Kortenkamp

Thyroid hormone system

Andreas Kortenkamp summarising work published in 2016 by Tim Korevaar and colleagues in the Netherlands, which showed that low levels of thyroid hormone during pregnancy lead to low IQ in infants. This revealed the sensitivity of the system and the importance of babies getting the right amount of thyroid hormone.

The thyroid hormone system is very complex, he said, with several entry points where it is possible to disturb the system. Research is focusing on entry points for which there are no assays: the transport processes for thyroid hormones from the placenta to the developing foetus, and to the brain of the foetus.

Thyroid hormones are essential for three major steps in brain development: i) radial cell migration (neurons moving to their correct position in the outer cortex); ii) the GABA switch, which plays a vital regulatory role for the maturation of neurons; and iii) the differentiation of different types of neurons.

Prof Kortenkamp then gave an overview of thyroid-relevant tests necessary in the data submitted for placing products on the EU market. These tests concern thyroid hormone serum levels and thyroid histopathology, in line with the Plant Protection Products Regulation, Biocidal Products Regulation, and REACH.

None of these data testing requirements specify the need for *in vitro* tests or downstream effects on brain function. This is a problematic situation that we think endangers the correct identification of thyroid hormone system disrupting chemicals, he said. It also means that regulators have to make decisions on the basis of rather incomplete data sets.

When measuring thyroid hormone serum concentrations the assumption has been that decreasing levels equate to disruption of thyroid hormone action in peripheral tissues such as the brain. However, explained Prof Kortenkamp, this is not always the case, due to the complexity of thyroid hormone transport from the blood brain barrier to neurons.

To highlight this, he described two cases of severe defects in hormone action that occur without substantial changes in serum thyroid hormones. The first is due to a mutated thyroid receptor unable to respond to hormones, resulting in neurodevelopment deficits and skeletal abnormalities. The second is due to a mutated thyroid hormone transporter preventing the brain taking up hormone, leading to severe intellectual disability (Allan-Herndon-Dudley Syndrome). In both cases, serum thyroid hormone levels can be in the normal range.

The dilemma is therefore this, said Prof Kortenkamp: changes in thyroid hormone levels alone cannot detect the risks to neurodevelopment, but at the moment we have nothing else. In the absence of biomarkers for altered neurodevelopment, thyroid hormone change is seen as an appropriate starting point for risk assessment.

Three EURION Cluster projects are addressing this challenge: Athena, ERGO and SCREENED. All three are developing *in vitro* assays, including 3D models in the SCREENED project. These testing strategies are based on Adverse Outcome Pathway (AOP) networks and 'read across' between vertebrate classes.

The idea is to highlight which entry points of the thyroid hormone system have the most drastic effects on hormone disruption, and develop a testing strategy that starts with these entry points; for example, inhibition of iodide uptake or inhibition of hormone synthesising enzyme. We are also developing downstream markers of disrupted brain development in the Athena project, he said.

Prof Kortenkamp concluded by focusing on one downstream test being developed by the Athena project, which he coordinates. Work in the USA established a disorder involving misplaced brain neurons, when animals were treated with a chemical that disrupts thyroid hormone synthesis. We are developing this further to see if it is a useful biomarker for disrupted brain function, he said.

Metabolism disrupting chemicals

Juliette Legler introduction the three EURION Cluster projects focusing on metabolism disrupting chemicals (MDCs): EDCMET, Goliath and OBERON.

The incidence of obesity and metabolic disorders has increased exponentially over the past few decades, and we know this is not only due to genetic disposition, she said. Exposure to the class of endocrine disruptors called MDCs has been linked to disorders like obesity, diabetes, and non-alcoholic fatty liver disease.

MDCs affect energy homeostasis; affect multiple endocrine mechanisms and cell types implicated in metabolic control; and affect gene expression and biosynthesis of key enzymes, hormones and adipokines essential for controlling energy homeostasis. Many types of tissues are involved: liver, pancreas, muscle, heart, brain, and adipose.

However, there are no tests currently available for MDCs. All three projects therefore aim to identify the action of these chemicals, define key events, and provide stronger evidence for their role in adverse outcomes. Together, the projects will create a large battery of *in vitro* and in silico assays, and improved animal studies for metabolic disorders, said Prof Legler.

The EDCMET (Metabolic effects of Endocrine Disrupting Chemicals: novel testing METhods and adverse outcome pathways) project is developing *in vitro* and in silico assays within an AOP framework, for key molecular initiating events that lead to adverse outcomes. Key events are being studied in rodents, and adverse outcomes also from human epidemiological studies.

One example of an assay being developed within EDCMET is a new reporter gene assay for determining the binding of chemicals to human nuclear receptors involved in energy metabolism and metabolic disorders. This will involve the high-throughput screening of chemicals for their interaction with key receptors, including androgen and estrogen receptors that are important in energy homeostasis, as well as another suite of receptors involved, for example, in fat cell differentiation, insulin regulation in liver cells, and uptake in muscle cells.

GOLIATH (testing metabolism disrupting chemicals), which I coordinate, is looking to generate novel and harmonised approaches for testing MDCs, said Prof Legler. The project team are developing *in vitro* and high-throughput screening assays, using human adipose, skeletal muscle and pancreas tissue. They are focusing on regulation and uptake of insulin, working with epidemiologists to identify the most important outcomes in humans, and also conducting fish assays to look at effects in vertebrate models.

An example of an assay being developed in GOLIATH is the CYP Induction Assay, based on one originally developed for pharmaceuticals. It can quickly detect if chemicals can be metabolised by CYP (cytochromes P450) enzymes. We think it is an excellent and sensitive method for detecting metabolites in human liver cells, and we are extending its application to include MDCs, explained Prof Legler.

The OBERON project is developing an integrated strategy to test endocrine disruptors for the role they play in metabolic disorders. The project takes a multi-disciplinary approach, combining human epidemiological studies, in silico and *in vitro* assays, animal studies and computation studies, within an integrated framework, to augment in vivo studies.

One example of an OBERON project assay is the zebrafish obesogenic test (ZOT), a tool to identify MDCs involved in obesity. The test identifies the effects of chemicals on the size and function of fat cells in larval zebrafish. It is being taken to pre-validation by the PEPPER consortium (see p. 24).

Ultimately, we want to develop an internationally harmonised, integrated approach to testing and assessment, with a suite of assays for MDCs that are much needed for their regulation, concluded Prof Legler.

Female reproductive and endocrine disrupting chemicals

Majorie van Duursen introduced the FREIA (Female Reproductive toxicity of EDCs: a human evidence-based screening and Identification Approach) project, the only EURION Cluster project dealing with female reproduction.

One in six couples worldwide face fertility problems, and ovulation disorders - such as irregular menstrual cycles, polycystic ovary syndrome, and early menopause - account for infertility in one out of four infertile couples. That is why the FREIA project focuses on the ovary.

There are several studies in humans showing that effects on the ovary during early life development can lead to problems later in life, she said, this is called Ovarian Dysgenesis Syndrome (ODS). Chemical exposure early in life can affect ovarian development, but mechanisms are mostly unclear.

Therefore, we need a better understanding of biology and the processes underlying ovarian development, in order to develop better testing methods. One aim of the FREIA project is to address this knowledge gap.

Because biology is different for different life stages, it is logical to assume that the effects of endocrine disruptors are different for different life stages. Females are born with a pool of follicles and do not gain more during their life. Depending on life stage, exposure to EDCs may result in fewer oocytes, changes in onset of puberty, or fertility problems later in life.

The FREIA project focuses on different life stages, explained Prof van Duursen. For the development of the fetal ovary, ovaries from terminated pregnancies cultured *in vitro* are exposed to selected chemicals, to observe effects on number of germ cells present and germ cell death.

In adult life, every month one oocyte matures and is released for fertilisation. However, results from the FREIA project show that the fluid surrounding the oocyte contains many known and suspected endocrine disruptors; plasticisers and PFAS were measured in Swedish and Estonian follicular fluids. Within the FREIA project the effects of these chemicals on oocyte maturation processes and subsequent fertility outcomes will be assessed.

Prof van Duursen questioned whether the current Test Guideline endpoints for female reproduction are sensitive enough. For example, vaginal opening as a marker of puberty onset in animal studies. The pulsatory release of gonadotropin-releasing hormone (GnRH) by the hypothalamus appears to be a more sensitive marker. Another sensitive endpoint is the mammary gland, she said.

With a move away from animal-based risk assessment towards more mechanism-based risk assessment, there is a need for clearer descriptions of pathways leading to adverse health outcomes. Several putative AOPs for female reproductive toxicity have been postulated by the FREIA consortium, including one for activation of the androgen receptor leading to reduced ovulation.

In a nutshell, FREIA conducts experimental studies with EDCsin human tissue (ovary, adrenal, follicles), *in vitro* and in silico studies, and rat studies, to provide human-relevant biomarkers, and mechanistic descriptions of AOPs with a focus on sensitive life stages for female reproductive toxicity. In the end, we hope to see female reproductive toxicity dealt with across regulations, concluded Prof van Duursen.

The moderator Teri Schultz put questions from the live chat to the three speakers.

Q&A

***Nigel Sarginson** (ExxonMobil Chemical Europe) noted that standard OECD sub-chronic animal tests required under REACH look at thyroid histopathology, so are in vitro tests necessarily?*

Andreas Kortenkamp replied that thyroid gland histopathology is valuable, but the thyroid gland is not the only target organ of the thyroid hormone system. We are totally missing downstream effects on the brain. Histopathology does not help when evaluating the wider effects of chemical disruption on the thyroid hormone system.

Q&A

***Marco Cordaro** (Corteva Agricsciences) asked, given that assays seem to address endocrine biological activity (not adversity), how the MDC projects take decisions on each test method's prediction models, and how many chemicals will be tested?*

Juliette Legler replied that they are currently developing assays using well-known chemicals that are known to cause metabolic disorders in animals. Using well-established OECD guidelines they are selecting test chemicals. We hope to develop some very useful candidate assays within this AOP framework.

Q&A

***Thomas Holmes** (Chemical Regulation & Food Safety, UK) asked, for metabolic disorders, how did you disentangle MDC exposure as being causative, from just over-eating a sugar and fat-rich diet and a sedentary life style?*

Juliette Legler said that the way to disentangle these effects is by developing the AOPs that show links between molecular mechanisms and adverse outcomes. We are not addressing life style factors, only preventable exposure to chemicals that play a role in metabolic diseases.

Q&A

***Dimitra Nikolopoulou** (Benaki Phytopathological Institute, Greece) asked about other endpoints to detect thyroid toxicity.*

Andreas Kortenkamp said that the best use of investment would be to incorporate some *in vitro* assays for, say, inhibition of thyroid hormone synthesis or transport, which are available but not validated. The bottleneck is the validation process.

Q&A

***Suzanne Butt** (Glaxo Group Research, UK) asked: if the FREIA project is considering gap junctional disruptions within the context of the growth and maturation of follicles?*

Majorie van Duursen said that this is not specifically addressed at this point, but it is a good suggestion.

The “integrated Fish Endocrine Disruptor Test” (iFEDT)

The "integrated Fish Endocrine Disruptor Test" (iFEDT)


Photo: © Lisa Baumann

Lisa Baumann
Heidelberg University, Germany

Lisa Baumann introduced the EU-tender project iFEDT (the integrated Fish Endocrine Disruptor Test), which is aiming to develop a new standard for endocrine disruptor testing in fish. The project is a collaboration between the Universities of Heidelberg, Antwerp and Southern Denmark. The focus of the project is on the environment and aquatic species.

A JRC report in 2017 showed the gaps and challenges in this area. OECD Test Guidelines (TGs) are complex, lengthy and expensive. Only a few TGs cover all life stages and include population-relevant endpoints, a distinction from general toxicity is not always possible, and they do not cover all modalities (EAS in fish, but T only in amphibians). Therefore, multiple tests may need to be run. This is not in accordance with the 3Rs principle (replace, reduce or refine the use of animals).

Existing TGs for fish include 'TG 229: fish short-term reproduction assay' and 'TG 234: fish sexual development test'. The first takes 21 days from adult to eggs, assessing fecundity, secondary sexual characteristics, vitellogenin, and gonad histopathology. The second takes 63 days, embryo-larvae-juvenile, looking at sexual differentiation, sex ratio, hatch survival, growth, vitellogenin, and gonad histopathology.

Dr Baumann said the project's aim was to merge these two TGs to create a new/merged TG, by hatching eggs from the first test and raising them through the juvenile stage. This will require only minimal protocol modification (e.g. egg collection). The new test will take 84 days. Though a relatively long time, she said, it is shorter than the 133 days for TG 240 'MEOGRT' (3-generation fish test) and covers all life stages (adult, embryo, larvae and juvenile) in one test.

Many people are not aware that fish undergo metamorphosis, she said. Though not as obvious as in amphibians, there are dramatic changes in pigmentation and body shape in the development from embryo to adult. In fish, thyroid hormones regulate many developmental processes (e.g. neurodevelopment, swimbladder) and physiological processes like energy metabolism and the immune system. However, little is known about the adverse outcomes of environmental exposure of fish to thyroid hormone axis disruptors.

Therefore, we want to implement thyroid-related endpoints in the new fish TG, explained Dr Baumann. A list was drawn up of thyroid hormone endpoints in fish to study: swimbladder inflation, pigmentation, eye development, thyroid histopathology, fin development. According to the AOP (Adverse Outcome Pathway) concept we also need mechanistic endpoints for biomarkers, she said, so we are also developing measures to assess thyroid hormone and gene expression levels.

Altogether, this new integrated Fish Endocrine Disruptor Test (iFEDT) will cover all life stages and modalities in fish in a comparatively short time. It will be demonstrated using a 2-step experimental approach, which will include running it with a model thyroid hormone axis disruptor (propylthiouracil) and a model estrogen disruptor (17α-ethinylestradiol) known to disrupt sexual development.

The first experiments have been successfully completed. These showed that the model endocrine disruptors impaired their intended endpoints, but did not show non-specific toxicity or affect non-target tissues or organs.

One histopathological and population-relevant endpoint looked at was the retinal pigment epithelium layer of the eyes. This is a promising endpoint to investigate further, said Dr Baumann. Early eye development is easily disrupted, and is very meaningful as a fish that cannot see properly will have problems finding food or will easily be caught by predators.

The preliminary results show the feasibility and benefits of merging the two existing TGs, and adding the thyroid modality for fish in a way that is comparable to amphibians, concluded Dr Baumann. She also stressed the importance of continued EU funding for this area of applied research.

Human Biomonitoring for Europe

(HBM4EU)


Photo: © Carsten Jost

Human Biomonitoring for Europe (HBM4EU)

Marike Kolossa
German Environmental Agency, Germany

The European Joint Programme HBM4EU (Human Biomonitoring for Europe) is a project designed to answer open policy-relevant questions as defined by EU services and the 30 HBM4EU partner countries.

It operates at the science-policy interface, said **Marike Kolossa.** It directly supports the European Green Deal, and provides data, indicators and monitoring for its initiatives: Farm to Fork, Biodiversity Strategy, Circular Economy, Zero Pollution Action Plan, and Chemicals Strategy for Sustainability.

HBM4EU is a European Joint Programme under Horizon 2020. It involves 30 National Hubs, the European Environment Agency (EEA), and 120 partner institutions. Its most important goal is to answer policy-relevant questions. Additionally, we want to give policymakers fast and easy access to our results and data, said Dr Kolossa.

Human biomonitoring (HBM) plays a key role in science-based recommendations in chemical, health and environmental policy. It reveals internal human exposure and the exposure sources, delivers data and advice to policy, and is an important instrument for communication with a broad variety of different audiences. We have built a network at the science-policy interface to find out what is really needed, she explains, to provide the foundations for sustainable HMB in Europe, contribute to regulation, and improve EU chemicals policy.

This includes the development and maintenance of a large network of qualified laboratories in Europe, for which colleagues at the Spanish Institute of Health Carlos III (ISCIII) have designed an ambitious quality assurance programme, she said. These qualified laboratories deal with priority biomarker chemicals in a harmonised way.

Dr Kolossa gave the example of bisphenol A (BPA), a chemical of public concern which has been extensively investigated. It is analysed in 22 qualified laboratories. A smaller number of laboratories have established methods for detection of a second group of related chemicals which are now used as substitutes and that are less well investigated: 16 for bisphenol S (BPS) and 10 for bisphenol F (BPF).

The priority substances also include a range of other chemicals with endocrine disrupting properties, including chromium VI and cadmium. A scoping report will be done for each of the priority substances to provide background information on human exposure.

A harmonised sampling framework for Europe is being established to align ongoing and planned studies fulfilling defined quality criteria for the collection of HBM data, for priority samples with EU coverage. This will include a focus on specific chemicals per age group, for example, for BPA, this will be for adults between 20-39 years of age.
The project's case studies will deliver exposure distributions, geographical comparisons, analyse time trends, and exposure determinants (e.g. lifestyle, environmental factors). This can be combined with two longstanding biobanks in Europe, in Denmark and Germany, which enable analysis of data over many years to reveal trends.
In both collections, for example, for DEHP (diethylhexyl phthalate), which is today strictly regulated, a clear decline in internal exposure levels is observed in the study populations. DPHP (2-propylheptyl phthalate) is not regulated and no significant change is observed. This trend over time therefore enables the effectiveness of actions taken or the need for new actions to be assessed, said Dr Kolossa.

Internal exposure is important as the public want to know if their health is impacted by exposure and policymakers want to know if they need to take action. We have derived HBM Guidance Values (HBM GV), she explained, to assess the exposure levels found in general and working populations concerning health impact. They correspond to internal exposure levels below which risks are not expected, and above which health effects are either not excludable or likely to occur. Within HBM4EU, HBM GV have been developed and adopted so far for plasticisers (5 different phthalates, Hexamoll® DINCH), plastic ingredients (BPA), and cadmium.

Human biomonitoring is a tool to investigate chemical mixtures. We analysed about 100 chemicals in a population-representative German study, correlating them with age group, living conditions, and other factors, she said. This showed which combinations of chemical are typical under which conditions. HBM4EU can play a role in supporting occupational safety by answering policy-relevant questions. For example, our first such study was an occupational chromium VI exposure study, recalled Dr Kolossa. This concluded that, regardless of REACH authorisation, chrome plating workers still showed elevated exposure.

The European network built by HBM4EU can respond rapidly to policy questions, for example, one from DG SANTE about copper compounds in plant protection products. For this, we mobilised expertise in the consortium, consulted with partners via National Hubs, and delivered answers based on 35 HBM data collections from 13 countries. When the Chemicals Strategy for Sustainability was being developed, we also summarised some of our conclusions to support the 'one substance - one assessment' approach, said Dr Kolossa.

She concluded by stressing the need for a sustainable and continuously-run human biomonitoring system, combining traditional and innovative approaches, that is focused on the needs of policymakers. Communication is a key component, and HBM4EU's numerous results, deliverables and target specific communication materials can be accessed free of charge on the website **www.hbm4eu.eu.**

The PEPPER platform:

a French initiative for the pre-validation of test methods for endocrine disruptors

The PEPPER platform: a French initiative for the pre-validation of test methods for endocrine disruptors


Photo: © Philippe Hubert

Philippe Hubert
PEPPER platform, France

Philippe Hubert introduced **PEPPER,** a unique non-profit public-private platform for the pre-validation of endocrine disruptor characterisation methods. It is a French initiative, being part of the National Strategy on Endocrine Disruptors, but very much European in scope, he said.

The platform was launched in December 2019. It helps fund laboratories, with about €2 million a year of public-private money; helps them to organise the pre-validation process; and works to speed up international validation. It targets this very specific link in the chain from research to regulatory use, he said. And it addresses gaps in the characterisation of endocrine disruptor properties that need to be filled thanks to validated methods.

PEPPER's workflow starts with the identification of test methods that are mature and scientifically-sound enough to start pre-validation. The second step is selection of the most promising methods by the Relevance Committee, comprising 40 stakeholders. The identification involved interviewing stakeholders, looking at databases, an AI-assisted literature survey, and assigning each method a Technical Readiness level, he said.

Then come the pre-validation operations, which form the bulk of the work. The validation for each method is then declared a success or failure, by a Scientific Council of 12 members. Finally, submissions are made, for example, to OECD.

We arrived at 17 methods that we felt were eligible for the first series of pre-validation, continued Mr Hubert. From these, the Relevance Committee (which includes people from industry, research institutes, agencies, and NGOs) selected the first three methods to carry forward.

The first method selected was called nPLACENTOX-PE, an *in vitro* assay using placental cells. It measures secretion of relevant hormones (progesterone, Beta hCG, hPL, estradiol) and activation of P2X7 receptors, implicated in placental pathologies (e.g. miscarriage, pre-eclampsia, premature birth). It uses available placental cell lines, and has a record of historical data on at least 12 substances.

The second method was an improvement on OECD TG 456 for the dynamic modelling of the steroidogenesis pathway in adrenocarcinoma H295R cells. It measures the levels of steroids produced by human adrenal cells (19 measurements across pathway). The method has high throughput, high accuracy, and uses commercially-available cell line.

The third method was the zebrafish obesogenic test (ZOT), a tool for assessing molecules that target adiposity, and hence obesity and metabolic dysfunction. This method is being developed by OBERON, a EURION Cluster project (see p. 16). It measures adipose droplet size using fluorescent microscopy.

Pre-validation for these first three methods was engaged in November 2020. In conjunction with this, the PEPPER consortium is establishing a Validation Management Group to help define pre-validation processes and criteria, so that solid procedures can be applied across partner laboratories.

The next steps are to feed OECD with mature submissions for the first three methods, and start new actions for the next three methods. This action encourages research teams in very practical pre-validation operations (both funding and advice); acts as an accelerator for regulatory toxicology; and reduces the 'opposition' between regulatory and "academic" science. Among the lessons learned to date are that it is very difficult to find methods that are relevant, scientifically-sound and mature (e.g. 12 000 papers scanned to find out about 250 methods). On the positive side, efficient and strong cooperation has been established within PEPPER and the laboratory network at EU level.

Addressing a query about whether a public-private partnership enables the PEPPER model to proceed faster and more efficiently, Mr Hubert said that having both in the governance gives more strength to the process and helps to establish confidence.

We expect the availability of resources such as PEPPER to motivate research teams to develop assays and practical tools, concluded Mr Hubert. He hopes that other partners will join the platform, to improve efficiency and extend the approach to other fields. Improvement in regulatory science will help address the challenges in the European Green Deal and the Chemicals Strategy for Sustainability.

The Fitness Check

on Endocrine Disruptors

The second day of the Forum started with presentations by **Andrew Worth, Antonio Franco** and **Sharon Munn,** of the Chemical Safety and Alternative Methods Unit of the DG Joint Research Centre (JRC) of the European Commission.


Photo: © Andrew Worth

Introducing the Fitness Check

Andrew Worth explained how the Fitness Check originated after a series of political developments and Commission initiatives since the late 1990s. In particular, the 1999 Strategy for Endocrine Disruptors set out actions for information gathering, test development and legislative reform.

In November 2018, one action in the Commission's Communication 'Towards a comprehensive European Union framework on endocrine disruptors', was a commitment to undertake a Fitness Check of relevant EU legislation. This was to assess whether legislation is achieving its objectives to protect human health and the environment, by minimising exposure to endocrine disruptors.

The Fitness Check was unique in that it took a cross-cutting look at legislation on endocrine disruptors, to identify possible gaps, inconsistences or synergies, and assess their collective impact. It paid particular attention to areas where legislation does not contain specific provisions for endocrine disruptors, such as toys, cosmetics and food contact materials, said Dr Worth.

It was led by the JRC, but involved input from 15 other DGs. The Fitness Check had to be completed in a short time to inform the new Commission's policy agenda, he said, in particular the Chemicals Strategy for Sustainability.

The JRC developed a step-wise methodology with emphasis on assessing the effectiveness and coherence of EU legislation. This started in March 2019 with the identification of in-scope legislation, followed by an analysis of policy and scientific sources of evidence. Case studies were developed for representative chemicals or chemical groups. A series of consultation activities were also conducted, explained Dr Worth.

All this evidence was synthesised, he said, to address the five Fitness Check criteria of effectiveness, coherence, efficiency, relevance, and EU added value. The final draft report received a positive opinion from the Regulatory Scrutiny Board. Their insightful recommendations were taken onboard when finalising the report, he said.

The JRC conducted two types of case study. In the "cross-sector" case studies, three chemicals with known endocrine disruptor properties were used to look at the interplay between different pieces of legislation in assessing and managing these chemicals. In the economic case studies, carried out by the JRC's Competence Centre on Microeconomic Evaluation, the impacts of risk management measures on trade flows were assessed, both within the EU and between the EU and non-European countries.

The consultation activities provided information not obtainable in policy documents or scientific reviews, said Dr Worth. Different questions were addressed to the three target groups: the public, stakeholders, and small and medium-sized enterprises (SMEs). The findings from the consultations, and the preceding Roadmap, are referenced throughout the Fitness Check report and included as an Annex.


Photo: © Antonio Franco

The state of play

Antonio Franco continued by looking at the 34 in-scope regulations and directives identified in the first step of the Fitness Check methodology. The diverse scope explains why we need to work with 15 DGs, he said.

Legislation within the scope of the Fitness Check covers the following policy areas:

Biocidal products; plant protection products; REACH; classification, labelling and packaging; persistent organic pollutants; toys; food including food contact materials; cosmetic products; medical devices and in vitro diagnostics; human and veterinary medicines; occupational safety and health (OSH); water; waste; detergents; fertilising products; ecolabels; general product safety; industrial emissions; air quality.

Together, all the relevant legislation forms a comprehensive framework for protecting human health and the environment by minimising overall exposure to chemicals. The JRC mapped the legislation with respect to pathways of exposure to humans and the environment throughout the life cycles of materials, products and substances. This showed that interconnecting policies (e.g. REACH, CLP and waste legislation) are complementary, but the JRC needed to establish in more detail how the whole framework functions to understand to what extent and in what way endocrine disruptors are (or could be) addressed, he said.

Each policy area was described by grouping provisions under three main components: i) scientific assessment (including identification) of endocrine disruptors; ii) provisions for risk management; and iii) links between the various pieces of legislation, said Dr Franco.

Regarding identification, four main types of legislation were distinguished: i) requiring identification using endocrine disruptor criteria (e.g. BPR, PPPR); ii) requiring identification of substances of concern (e.g. SVHC under REACH, Priority Substances under Water Framework Directive) with explicit reference to endocrine disruptors; iii) referring to one of the two cases above for identification, including medical devices, ecolabels and drinking water; and iv) not explicitly requiring identification of endocrine disruptors (e.g. CLP, OSH).

Risk management was considered in terms of three main principles: generic risk, specific risk, and risk-benefit. Often legislation is mainly based on one of these principles, but includes elements of the others.

Provisions across multiple pieces of legislation are often triggered for the same group of substances, especially when these are used across many sectors. Interconnections can be explicit, or less explicit (e.g. data generated for one piece of legislation is used under another).

Dr Franco used REACH to illustrate the interplay of policy components. REACH intersects with sector-specific legislation (e.g. cosmetics, toys and food contact materials) in all its core components: registration, chemical safety reporting, authorisation and restriction. However, the type of regulatory interplay varies between human health and the environment, and between different sector-specific legislation.


Photo: © European Union

The findings

Sharon Munn provided further details of the findings of the Fitness Check, for: Identification (criteria, data requirements, sufficiency of test methods); risk management (coherence across legislation); and effectiveness (minimising exposure, including vulnerable groups).

In terms of information relating to chemical safety, manufacturers and importers have legal obligations to provide it; but there are differences in data requirements across sectors. Data generation is not necessary in all regulations, as long as there is ready access to the necessary data.

There is also a need to strengthen information and data requirements to aid the identification of endocrine disruptors, she said. For example, for PPPs, BPs and REACH substances there is a comprehensive dataset for adverse effects, but a lack of 'mechanistic' or 'endocrine activity' data since it is not currently required.

Regarding the sufficiency of test methods, available OECD Test Guidelines detect endocrine disruptors that interfere with EAS (estrogen, androgen and steroidal) pathways, and some aspects of T (thyroid) pathways, but are not sufficient for assessing all the different endocrine modes of action. There is a need to further develop methods for identifying endocrine disruptors, particularly *in vitro* and *in silico*, said Ms Munn.

Differences in risk management do not imply incoherence if the underpinning scientific assumptions are consistent, or if there are clear rationales for different risk management approaches and decisions.

However, it may be difficult to determine a safe threshold with reasonable certainty for endocrine disruptors, explained Ms Munn. The generic risk (hazard-based) approach avoids the need to derive thresholds. REACH may use thresholds when a case can be made. Sectoral regulations (e.g. cosmetics) have not clarified how to deal with endocrine disruptors where no safe (or acceptable) threshold can be established.

Case studies looking at scientific coherence across legislation, for DEHP, BPA, and nonylphenol, led to the conclusion that there is no evidence of scientific incoherence due to the lack of a horizontal approach.

However, when the rationale for differences in risk management approaches between policies was analysed, it was concluded that the rationale was not always clear and transparent.

When the JRC focused on vulnerable groups in society, those with the highest exposure or greatest sensitivity to endocrine disruptors, they concluded that it is important that the data requirements for endocrine disruptor assessment include tests that cover vulnerable people and sensitive life stages.

Conclusions

Andrew Worth summarised the main conclusions of the Fitness Check:

- *A lack of a unified approach renders decision-making less transparent and more complex;*
- *A cross-sector approach could build on the criteria for endocrine disruptors in the Plant Protection Products and Biocidal Products Regulations;*
- *Effective regulatory interplay will depend on ready access to data;*
- *Information requirements need to be strengthened to aid endocrine disruptor identification across sectors, ensuring effects on vulnerable groups are covered;*
- *There is a need to further develop and apply test methods, including a wider range of endocrine modes of action, focusing on non-animal approaches;*
- *Certain sectors need to clarify how to deal with endocrine disruptors for which safe thresholds cannot be established;*
- *No evidence of incoherent risk management was found due to endocrine disruptor-related scientific inconsistencies;*
- *There is a need for consolidation, simplification (in line with 'one substance - one assessment') and better communication of risk management principles;*
- *The identification and management of endocrine disruptors has contributed to decreasing exposure trends;*
- *However, overall, the Fitness Check could not draw conclusions on the effectiveness of legislation in reducing adverse health and environmental impacts;*
- *Future actions should focus on identifying and assessing endocrine disruptors and monitoring the effectiveness of regulatory interventions (e.g. with better indicators based on environmental and human biomonitoring programmes).*

***Andrew Worth, Antonio Franco** and **Sharon Munn** were joined by **Maurice Whelan,** Head of the Chemical Safety and Alternative Methods Unit of the JRC, and **Cristina de Avila,** DG ENV, on this panel. The co-moderator **Chris Burns** introduced two invited contributors and selected questions from the live chat.*

Q&A

Pia Juul Nielsen, representing the EDC-Free Europe coalition, acknowledged the good work carried out by the JRC. A clear message is that vulnerable groups are still not sufficiently protected, she said. There is also still a huge lack of information for many substances, and therefore data requirements need to be strengthened. It is crucial that all the commitments in the new Chemicals Strategy for Sustainability lead to actions that really protect human health and the environment against endocrine disrupting chemicals.

We have three main takeaways: i) existing legal tools such as group restrictions under REACH must be used to immediately protect EU citizens, ii) very few substances will be identified under current criteria for biocides and pesticides, therefore data requirements should be expanded and categories of suspected endocrine disruptors are needed for horizontal classification and regulation, and iii) the Fitness Check discusses the treatment of endocrine disruptors as non-threshold chemicals and this is the right way forward to minimise exposure, given that endocrinologists have pointed out that it is not possible to establish safe thresholds.

There are high expectations from EU citizens to see the effect of improvements in regulations on endocrine disruptors without further delays, she concluded.

Q&A

***Heli Miriam Hollnagel** (Dow Europe) asked, should the JRC framework analysis differentiate between hazard identification and hazard characterisation?*

In response, **Sharon Munn** said that this needs to be discussed, but more clarity is first needed on how endocrine disruptors are going to be considered under the legislation.

Q&A

Csilla Magyar speaking on behalf of Cefic (European Chemical Industry Council) also thanked the JRC and said that the chemical industry welcomes the comprehensive and transparent Fitness Check exercise. We agree that a horizontal approach is needed, she said, that is applying the endocrine disruptor criteria for biocides and pesticides to other legislation including REACH.

The Fitness Check report in its conclusion does not, however, point to any policy options. Therefore, there may be a need to strengthen the links between legislation that includes provisions for generating data on substances, such as REACH, and sectoral product-specific legislation that relies on such data for risk management purposes. One of the questions we have is, how does the Commission intend to strengthen these links in practice and what would be the role of the Classification, Labelling and Packaging (CLP) Regulation specifically.

Cristina de Avila (DG ENV) replied that the CLP is a cornerstone in European law to identify the hazardous properties of substances. There is a commitment to make it the central tool to identify all hazardous chemicals, including endocrine disruptors, in the Chemicals Strategy for Sustainability, and to introduce new hazard classes.

Maurice Whelan (JRC) added that the Fitness Check is an evidence-based analysis of what we have, and what policy options there are going forward is up to the policy-making part of the Commission.

Q&A

***Cécile Michel** (ANSES, France) asked if the JRC looked at the added value of three categories compared to black/white (either/or) identification.*

Ms Munn replied, yes, we did look at that, and had quite a lot of comments on it from stakeholders and we tried to capture all the described pros and cons in the staff working document. However, it should be remembered that it is a Fitness Check and not an impact assessment, so evaluating the potential impact of different categories was not the point of the exercise.

Q&A

***Emma Grange** (Cruelty Free Europe) asked the JRC if they see the use of health indicators via biomonitoring programmes as a promising way to lessen the reliance on animal studies for endocrine disruptor identification, and to move to a more reliable way of identifying them.*

Antonio Franco said that in principle yes but this is a long-term ambition. Our conclusions are mostly related to the current context of policy regulation, whereas this question is about potential future options that science is providing. Maybe rather than informing the identification of endocrine disruptors this type of knowledge can, for instance, address the lack of proper exposure and risk indicators.

Andrew Worth added that when we talk about human biomonitoring data we talk about biomarkers of exposure and biomarkers of effect, so in principle they can be used to reduce reliance on animal testing, because we will have evidence of the effects of chemicals in the species of interest, i.e. humans. But, as Antonio says, the time course for getting that information could be much longer.

Q&A

***Nigel Sarginson** (ExxonMobil Chemical Europe) asked: What is the point of the Fitness Check if the European Commission ignores the results? For instance, the inclusion of hazard categories in the CLP when stakeholders are clearly split on such an approach, and when REACH already satisfactorily identifies endocrine disruptors and could be strengthened with horizontal criteria.*

Dr Worth identified this as rather a provocative question. Our job was to bring the evidence together, and draw conclusions from findings, he said. The next steps are for policymakers.

The Commission is not ignoring the Fitness Check conclusions replied **Ms de Avila,** but it is not a beauty contest where we look at the number of votes from stakeholders' reports. The results are there, and the commitments made.

Q&A

***Claire Beausoleil** (ANSES, France): If no mechanistic data are required in the different regulations, how can the endocrine disruptor criteria be fulfilled?*

This is why we are strengthening the requirements to request mechanistic data to fill this gap, answered **Ms Munn.**

Prof Whelan added that this is why there is so much funding being dedicated to the development of mechanistic data. We are validating mechanistic methods, as a step to translating them into regulatory practice.

Q&A

***Martina Jäger** (Kemira Espoo Research Centre, Finland) noted that endocrine disruption is not a hazard directly comparable with other hazards. It is dependent on the dose if the effect might be hazardous or even beneficial. How is that taken into account?*

Dr Franco replied that the dose thresholds for endocrine disruptors are complex, which makes it difficult, in most cases, to derive a safe threshold. The Commission position is that it may or may not be possible to derive a safe threshold, and therefore it would not be wise to have an approach that assumes it is possible to derive safe thresholds for all endocrine disruptors. However, on a case-by-case basis you may be able to use this approach.

Dr Worth noted that EFSA had published an opinion recently on non-monotonic dose response relationships. For example, nutrients that are obviously beneficial at low doses may become toxic at high doses. However, these are essentially two different dose response curves, and they can be treated as such.

Q&A

***Yvonne Andersson** (Swedish Chemicals Agency) asked if it is possible to say something further about the conclusion that consolidation and simplification options should be explored. Have you identified parts of regulations that could be consolidated?*

Ms Munn said that this is related to 'one substance - one assessment'. We see that there are different approaches, and we are asking for a clear rationale to be given to those approaches and to simplify where we can. It is a complex system that has grown over many years, so there are possibilities for simplification.

Ms de Avila added that 'one substance - one assessment' and simplification were studied thoroughly when preparing the Chemicals Strategy. ECHA and EFSA can come to different conclusions about substances, but there are good reasons for this that are difficult to explain to the public. When there are differences, we should be able to explain them better, as endocrine disruption is a big area in the Strategy.

Q&A

***Françoise Audebert** (Scientific and Regulatory Advisor for the French cosmetics company FEBEA) asked if substances identified as endocrine disruptors under REACH are banned in cosmetics.*

Dr Franco replied that for substances of very high concern (SVHC) under REACH (including some identified endocrine disruptors) there is no hard-coded trigger that activates a ban for use in cosmetics.

Q&A

***Olena Kucheryavenko** (Federal Institute for Risk Assessment (BfR), Germany) asked Ms de Avila what role the RAC would play if the proposal of horizontal regulation via CLP is going to be realised.*

Ms de Avila said that the Risk Assessment Committee (RAC) in ECHA gives advice in terms of harmonised classification. Currently, Member States present a harmonised classification dossier for a substance, on the basis of obligations of companies. Now there is also the possibility of introducing harmonised classification for endocrine disruptors, a set of hazard classes that are done through a European-level mechanism, but the Commission so far has no plans to change the procedure.

*The co-moderator **Chris Burns** asked if more chemicals will be regulated as a result of the Fitness Check.*

Prof Whelan replied that we think it has been very valuable for moving forward the Chemicals Strategy for Sustainability. What we have learned in this exercise puts us in a strong position to exploit that knowledge and learning.

Q&A

Dr Worth, addressing a query about the most important gaps from a toxicological point of view, identified gaps at three levels: i) in knowledge of chemicals in relation to adverse effects on human health and the environment; ii) in information requirements for some pieces of legislation; and iii) in the availability of suitable test methods. We need to address all those scenarios, he said.

Prof Whelan noted that the information requirements we have today were from 8 years ago, when only 12 tests relevant to endocrine disruptors satisfied such requirements. There is a need to bring new approaches into play, especially non-animal tests. New approaches play an important role in the safe-and-sustainable-by-design concept. Companies need to efficiently and cost-effectively generate toxicological hazard data when developing molecules and designing out unwanted hazard.

Nigel Sarginson (ExxonMobil Chemical Europe) wrote on the live chat that endocrine disruptors have been assessed for decades, with adverse effects identified and then modes of action investigated. Regulators now want to 'put the cart before the horse', starting first with mode of action, he said. This seems illogical and not a robust scientific approach, like starting a journey without a destination.

Dr Worth said that the journey can be considered to start with a pathway, the initiating event, and to cascading events to adverse reaction. It is useful to look at the early stages.

Prof Whelan said that regulations follow the WHO definition of endocrine disruptors, which need mode of action evidence, as well as to show in vivo adverse effects.

Ms Munn added that you can't do animal studies on every substance, so looking at mode of action is useful for prediction of hazard.

Q&A

***Johanna Hausmann** (Women Engage for a Common Future - WECF): What are we doing until we will have the outcomes of the risk assessments? There is a lot of scientific proof of negative impacts on health and environment. How is the precautionary principle reflected?*

Dr Franco replied that the precautionary principle is applied across legislation, but policy choices determine how and when it is applied and this depends on policy-specific risks and benefits. We have not seen any clear incoherence in the way it is applied for substances we looked at, or for substances flagged in the stakeholders' consultation, he said. I think the way it is applied at the moment is broadly consistent.

Dr Worth added that precautionary measures are not only built into risk management. In the risk assessment process, toxicologists use a point of departure which is based on the most sensitive endpoints in the most sensitive species, and this is a concept we can also apply *in vitro*, so precautionary thinking is also brought into the scientific part of the process.

Q&A

***Anne-Laure Demierre** (Swiss Federal Office of Public Health, Division Chemical Products): Introducing data requirements will be useful for new substances, but how to deal with substances already in use?*

Ms de Avila said that we no longer have the distinction between existing substances and new substances, so once we have the information requirements in REACH this would apply to all substances on the market.

In conclusion, she said that she thought the Fitness Check a necessary thing to do. We have long discussed endocrine disruptors, in often polarised debates, so the Fitness Check was needed to move on. The future is now set by the Chemicals Strategy for Sustainability, to which the Fitness Check contributes.

Chemicals Strategy for Sustainability:

High Level Segment

In this session, contributions were made by **Virginijus Sinkevičius,** European Commissioner for the Environment, Oceans and Fisheries, and top officials from EU Member States: **Lea Wermelin,** Minister for the Environment, Denmark; **Dirk Messner,** President of the German Environment Agency; **Ismael Aznar Cano,** Spanish Ministry of Ecological Transition and Demographic Challenge; **Barbara Pompili,** Minister of Ecological Transition, France; **Roald Lapperre,** Vice Minister for the Environment, Netherlands Ministry of Infrastructure and Water Management; and **Isabella Lövin,** Deputy Prime Minister and Minister for Environment and Climate, Sweden.

Commissioner Virginijus Sinkevičius stressed that, knowing the outcome of the Fitness Check, there is a sense of urgency for consolidated actions. With the Green Deal, the focus is on sustainability, and green and circular economic growth. Work on endocrine disruptors is an important part of the Chemicals Strategy.

All the scientific evidence leads to the same conclusion, he said, endocrine disruptors affect babies and children during their development, and when they become adults, so these substances are behind many serious diseases. We need to take clear and coherent measures to stop the trend.

The Commission has been acting on endocrine disruptors since 1999, and it has addressed them in many legal acts to better protect people and the environment, but we need to do more. This is about the future of our children, their IQ levels and overall health, and it is important for the future health of the economy and society.

For this Second Forum, riding the wave of the new Chemicals Strategy, we invited six ministers from Member States, said Commissioner Virginijus Sinkevičius, and were delighted when the invitations were accepted.

The first step is to identify chemical substances that are endocrine disruptors, and to do this we need legally-binding hazard identification criteria based on the WHO definition. They will apply across all relevant legislation, from REACH to the Biocidal Products Regulation and Cosmetics Regulation, for example.

As we heard from the JRC, we still lack this coherence and that is a barrier to reaching the object of minimising exposure. With legally-binding criteria, we want to make endocrine disruptors a hazard classification in the CLP Regulation from 2022.

The JRC has shown that data requirements in different pieces of legislation are not fully harmonised, so we will review and strengthen the information requirements across legislation, to ensure we have the right information to hand.

In addition, our flagship action will ensure that as soon as endocrine disruptors are identified, they are banned in consumer products. The only exception would be if there is proof that the use of a certain endocrine disruptors in a particular case is essential for society, and it cannot currently be replaced. We will encourage innovation to replace them as soon as possible.

We will need the support of Member States to achieve all this, and I know I can count on your support, said Commissioner Virginijus Sinkevičius; in particular, France who will hold the Presidency of the Council in the first semester of 2022.

Member States' work on endocrine disruptors

The moderators asked Member State representatives about national initiatives and future plans for addressing endocrine disruptors.

Photo: © Steen Brogaard

Lea Wermelin
Minister for the Environment

Denmark

Chris Burns:

Why do we need a category 2 for suspected endocrine disruptors in the classification system?

"When we first got the Chemicals Strategy from the Commission it felt like an early Christmas present, because it is what we have been working on for so long from the Danish side. Now we need to turn ambition into action, and strategy into solutions. We all need to deliver, and you can be certain that Denmark will help and support the process in any way we can. In particular, the reason why we need the category on endocrine disruptors is that it would lead to better protection of our citizens and the environment, based on available data.

If a substance could be harmful to our health or the environment, we should take the appropriate caution. The inclusion of category 2 on suspected endocrine disruptors is not a new concept - this is how we already classify carcinogenic, mutagenic or repro-toxic substances based on the level of evidence available. If suspected endocrine disruptors are identified, it would also be possible to regulate these substances, for example, banning them in cosmetics, as is the case for suspected carcinogens. The identification of a substance as a suspected endocrine disruptor would also encourage manufacturers to clarify whether the suspicion could be confirmed or not and encourage downstream users to substitute the substances with less hazardous ones. Finally, ecolabels could also communicate restrictions on the use of endocrine disruptors, giving consumers an informed choice.

Now we need an important step to improve the identification of endocrine disruptors, and for this the common criteria for identification is the key, as part of the classification and labelling system we use for all chemicals. It is important that criteria are followed up by strong and sufficient data requirements that will allow us to conclude on the endocrine disrupting potential of a substance. In particular, we need data sufficient to protect the most sensitive groups, such as children, teenagers and pregnant women.

The goal is to ban or regulate endocrine disruptors much more than we have done to date. We welcome the ambitious Chemicals Strategy and look forward to its timely implementation."

Germany


Photo: © German Environment Agency

Prof Dirk Messner
President of the German Environment Agency
(standing in for Jochen Flasbarth, State Secretary for Federal Ministry for the Environment, Nature Protection and Nuclear Safety)

"This has been an intense 2-day conference on endocrine disruptors, which can be a controversial subject. What we have achieved to date is very important. In 1962, in 'Silent Spring', Rachel Carson wrote about DDT and its effect on estrogen, and was criticised for being unscientific. What the Commission have set out, and our discussions today, can be traced back to that time.

The second point I want to underline is not to be naïve when looking toward the future. There will be difficult negotiations because of disagreements about the effects of these substances on humans and the environment. Scientific discussion have been going on for decades, and will continue in the future.

If you look at Member States, we have a common perspective as far as sustainable chemistry is concerned and a common stance on endocrine disruptor regulation. However, when we look at the actual regulation we have to discuss questions of new criteria, and how we can adopt the criteria on the basis of a consensus.

I would like to underline that for the Germany side, the precautionary principle has to be set at the beginning of any discussion. If there is any suspicion of a health hazard that is not dispelled within a certain time, then we have to have regulation. The way the Commission addresses this, through risk management, is an important step in the right direction.

Finally, I mention three points from during the German Presidency of the Council. Firstly, we worked intensively on the chemistry as part of the Green Deal, in close collaboration with Portugal who are next in the Presidency. Now Member States have to pool their views and become more practical, so that the Commission can reach a common agreement; Secondly, we should be working on updating legislation in this area, not twiddling our thumbs, for example, so REACH can be used to review the endocrine disruptor situation for the next generation of chemicals; and thirdly, from my own institution, we have expressed our intention to restrict bisphenol A, an important endocrine disrupting chemical, and that is a good example of a Member State contribution as we are doing our own research in that area."

Spain


Photo: © Ministerio para la Transición Ecológica y el Reto Demográfico

Ismael Aznar Cano
Director-General of Quality and Environmental Assessment at the Spanish Ministry of Ecological Transition and Demographic Challenge
(replacing Teresa Ribera, Deputy Prime Minister and Minister for the Ecological Transition and the Demographic Challenge)

"We are particularly concerned with the issue of endocrine disruptors and have been fully involved in the run-up to the Chemicals Strategy for Sustainability, which Spain welcomes very much. In Europe we have one of the most advanced and protective systems in the world, but we have to move forward and the Strategy provides a good basis for that.

We have to move forward on implementation and on adopting revised chemicals legislation in a targeted manner, and Spain will be fully involved in that process. At national level, we are working closely with our Ministry of Health on a comprehensive National Plan on Health and Environment. It covers many aspects of human health and the environment, such as air and water quality, and we foresee as a specific objective a Strategy on endocrine disruptors.

It is important to measure the presence of endocrine disruptors at an early stage, so we can act. Regulation and protection must be addressed through a comprehensive national strategy on endocrine disruptors.

It is also important to have transparency and to know which substances are considered as endocrine disruptors. To this end, Spain has recently joined the initiative "edlists.org" to provide lists of endocrine disruptors with other EU countries.

In our Ministry we have a small group working on chemicals, which has experience at evaluating endocrine disruptors under the Biocidal Products Regulation. When a chemical is identified as an endocrine disruptor, it cannot be approved except in some very specific cases, subject to conditions. I think we are properly addressing the issue and removing substances from the market.

However, I believe there are aspects we should improve and strengthen, across legislation. We need coordinated action across all legislation on chemicals, so when one

evaluation is carried out under one standard, it can also be taken into account in other pieces of legislation. This will avoid duplication and make sure we create an equally safe environment across sectors, and for different products.

Finally, the Chemicals Strategy is important to boost the development of ecotoxicological tests to determine risks of endocrine disrupting compounds. We need more tests, better quality tests, which properly address the issues, so that our policies are trusted and effective. It is a field that also needs progressive evolution, based on knowledge acquired, and the fostering of innovation."

Barbara Pompili
Minister of Ecological Transition

France

"The negative impact of endocrine disruptors on society is very costly. We have launched a new national strategy, and we have training for parents and education for society in general to increase awareness of endocrine disruptors. Furthermore, we are aiming to identify substances that are endocrine disruptors in food.

Looking to the Chemicals Strategy, we want to have a harmonised definition that is cross-cutting for all endocrine disruptors, and ban them from consumer items and foods. We have looked at endocrine disruptors in pesticides and in cross-cutting legislation, with the same approach as for carcinogens and reprotoxic substances.

We want to better manage risks linked to these substances and look forward to working with the Commission on these issues. This is going to be one of the priorities for the French Presidency in 2022.

For the Presidency, we have planned a number of activities in France that we will evolve in 2022 and beyond. Our Food, Health and Environment agency, for example, is looking at bisphenol A and other bisphenols. We have identified a number of endocrine disrupting substances that need to be looked at in more detail. Along with other Member States, including Denmark, Sweden and the Netherlands, France launched a joint initiative on online lists of endocrine disruptors.

It is essential to develop tests and methods which have been validated at International level, to better identify the deleterious effects of endocrine disruptors on the environment, humans and animals. PEPPER is a private-public partnership initiated in France, which has a number of European members (see p. 24). I would invite both industry and authorities of other Member States to join this platform to advance work on testing for endocrine disruptors.

What we need now is very good coordination. It is essential to reinforce the links between the Cosmetics Directive and REACH, for example, and in order to do that we really need the European Chemicals Agency (ECHA) to focus on these chemical substances, and we need to continue to fund this agency because they establish a link between all the initiatives we are starting."

The Netherlands

Chris Burns:

The Netherlands has launched a website with three other EU countries. Can you explain further?

"We have launched a ***website,*** *with France, Denmark and Sweden, with a list of endocrine disruptors, to give an overview of all substances identified as endocrine disruptors under EU legislation. There is also a list of suspected endocrine disruptors. These lists will help create consistency, and inform stakeholders. Here, we would like to invite authorities in other Member States.*

We support the Chemicals Strategy in its full width, but I think this part is particularly important and we are happy to work with the Commission and other Member States to bring this further as fast as we can.

I would like to mention three short-term measures that can be taken. Firstly: we believe that we should exploit current possibilities to improve information on endocrine disruptors, in particular by demanding the relevant cohorts in extended 1-generation reproductive toxicity studies, such as measuring developmental neurotoxicity and immunotoxicity endpoints.

Secondly, we should protect the most vulnerable people from exposure, in advance of the application of the generic preventative approach, and thirdly, the Netherlands believes that we should step up efforts to better identify endocrine disruptors, while reducing the number of animal tests needed."

Roald Lapperre
Vice Minister for the Environment, Netherlands Ministry of Infrastructure and Water Management
(replacing Stientje van Veldhoven, State Secretary for Infrastructure and Water Management)

Sweden

Chris Burns:

What would be the next steps in addressing endocrine disruptors for you?

"Regulation of chemicals and hazardous substances has been a priority for the Swedish government for a very long time, and we very much welcome the Chemicals Strategy for Sustainability. We know there are a number of chemicals out there that might be hazardous for our hormonal system, and these are really dangerous substances that we need to ban. Unborn children are exposed, and babies are born 'pre-polluted'. This is something we have to stop.

First of all we need to speed up the identification of endocrine disruptors. We also need to look at how we can regulate them in all relevant legislation, including for toys, cosmetics and food contact materials, so that we ensure a level of protection that is equal in all legislation.

The second thing is to develop a ban on endocrine disruptors in consumer products. There is no other option if our citizens are to feel safe, and we can take this responsibility for our children. We are finding these substances now, not only in our own bodies, but in fish and the marine environment, everywhere. This is something that we need to take responsibility for. We also need effective implementing measures in place. From the Swedish side we expect the Commission to present legislative proposals and measures in the near future, and we will for sure support those.

A third thing to mention is the question of essential uses. We must ensure that we do not create loopholes and accept substances that are not really essential. The definition of essential uses must be very strict."

Isabella Lövin
Deputy Prime Minister and Minister for Environment and Climate

Chris Burns:

Endocrine disruptors are not only a European problem. How should the problem be tackled from a global perspective?

Isabella Lövin: *"It is not a national problem or a European problem, this is a global problem and we live in a globalised world. Markets are not really controlled in the way we are used to. We need to work together internationally and agree on a global framework for chemicals and waste management.*

Private imports are a big problem here, but also the fact that the majority of the chemicals produced in the world are produced in developing countries with less strict or even no-existing legislation in this field. We need to take responsibility here.

Sweden together with Uruguay have launched a High Ambition Alliance on chemicals and waste, where we are working to have a follow up of the SAICM agreement that expired in 2020, but the pandemic has caused delays to this process. We invite other countries to join the High Ambition Alliance and companies are also very welcome. We need to push and get support at UN level to get a new global agreement on chemicals and waste in order to support developing countries and protect our own health.

I think developed countries need to take responsibility, because we have a demand for those chemicals. We need to ensure chemicals are sustainable and safe, both for consumers and at the production starting points, for workers producing them and for the environment around where they are produced. We know that many of those sites are not safe and we need to support countries to set up regulations, to be able to control those regulations and to share research and development, so we can get away from hazardous substances and have safe and greener chemicals to replace them."

Q&A

The moderator Chris Burns started this discussion by asking the Commissioner what can be done to further advance research on endocrine disruptors to protect consumers.

Commissioner Virginijus Sinkevičius said that the Chemicals Strategy has several aims. On the one hand, we have prevention and this is why we need to strengthen our rules, and on the other hand, we have innovation and the development of chemicals and products that are safe-and-sustainable-by-design.

We cannot achieve these aims without research, which the Commission has support over many years. On endocrine disruptors, we have funded projects receiving over €150 million from the EU since 2000. This includes the EURION Cluster of projects and Horizon 2020 projects.

Research will help us radically change the way we produce and use chemicals. This is a win-win agenda for all, as it will increase the protection of people and the environment, and boost the competitiveness of the industry in the EU. It also supports the circular economy by facilitating non-toxic material cycles.

Here in the EU, we have industry frontrunners that can be a model for others. With the Chemicals Strategy, we will promote and give incentives for developing, promoting, producing and using safer alternatives. We will set up a specific EU-wide support network and funding will be provided through the EU research and innovation programmes. We want to encourage more companies, whether producer or downstream users, to follow the path of safe-and-sustainable-by-design. We will also ensure that the rules are enforced on the ground. It is important to use all these approaches at the same time.

Questions on live chat asked for further information about the progress of the lists of endocrine disruptors, which France and Denmark announced at last year's Forum.

Barbara Pompili (France) said that working on this requires a lot of coordination and discussion so it is supported by as many people as possible. It is important that we publish a list that covers everyday items and looks at vulnerable groups of people.

Lea Wermelin (Denmark) added that in collaboration with Belgium, France, the Netherlands and Sweden, lists of identified and suspected endocrine disruptors are now publicly available. With the lists, we aim to improve transparency, raise awareness of citizens, strengthen the collaboration between authorities, and support industry to address substances of concern, he said.

A question addressed to the Netherlands asked what specific means they have in mind to protect vulnerable people from exposure, in advance of a generic approach.

Roald Lapperre (Netherlands) replied that in the short-term, effective information is crucial, especially for the most vulnerable, such as young children and pregnant women, which can be accessed on the website. Effective information also supports the preparation of more far-reaching proposals.

Chris Burns asked **Ismael Aznar Cano** (Spain) how much EU support do Member States need. He replied that Member States work in a coordinated manner between themselves and with the relevant agencies, it is important that we devote the right funding to the European Agencies. For countries like Spain the work done by ECHA is key. It would be difficult to develop effective national chemicals policies without that interaction with ECHA and with other agencies, he said.

Dirk Messner (Germany) added the chemicals industry wants certainty. Frameworks and regulations are necessary to create the stability for innovation to work, in particular for substitute chemicals. We should ensure the substitution is not as hazardous as the original. There is a political will in industry to do substitutions but there needs to be clear benefits in terms of hazard.

Roald Lapperre (Netherlands) agreed and added that clarity for industry and other stakeholders is important. Clarity is also crucial for transparent and consistent identification of endocrine disruptors, based on one definition, one set of criteria, one set of information requirements, and one evaluation procedure. By ensuring the procedure is consistent and clear, we can ensure that expectations of what should be done are clear from the outset. The introduction of endocrine disruptors as a category of substances of very high concern is a necessary element to enable such a uniform method of identification.

In the Netherlands, for example, PFAS has been quite an issue we needed to tackle and we now see that, in consumer products, the substitution of PFAS occurs relatively quickly. With a clear regulatory framework, we can stimulate industry to work on substitution by non-toxic alternatives and of course prevent regrettable substitution.

Ismael Aznar Cano (Spain) said that we need to bring chemicals higher up the agenda. This forum is a specialised one but we also need to raise public awareness on endocrine disruptors, and the challenges of replacing them. It is not something we see often in the media in Spain, despite it being important for health and environment. When citizens are informed, they realise the importance of the topic.

Isabella Lövin (Sweden) concluded the session by addressing the need to build back better following the pandemic. We see links between biodiversity, climate, health and chemicals, and also unsustainable animal treatment and the pandemic, she said.

It is frequently heard that jobs in Europe could be lost due to strict endocrine disruptor regulations. However, from the EU we have proved that we can change the working conditions for people even outside Europe by setting very strict regulations on trade, and we should not allow the import of products containing endocrine disruptors.

The aim is not to push jobs out of Europe, but to create a sustainable future for our children and for generations to come.

We have now with the Green Deal many actions and strategies, one of which is the circular economy. One of the proposals that Sweden supports is to introduce a product passport that should contain information on the substances that any product contains, where it is produced, how it is produced (with environmental impacts), and how it can be repaired and recycled, said Ms Lövin. With the circular economy, we need to get away from hazardous substances and remove them from loops.

Panel Discussion

with stakeholders on endocrine disruptors

The panellists in this session were:
Sylvie Lemoine, Cefic;
Apolline Roger, ClientEarth/EDC-free Europe;
Erik Prochazka, PETA International Science Consortium Ltd;
Josef Köhrle, European Society of Endocrinology; and
Michel Cassart, PlasticsEurope.


Photo: © Cefic

The voice of the chemical industry in Europe

Sylvie Lemoine, representing Cefic (European Chemical Industry Council), said the European chemical industry understands the need to respond to public concerns about endocrine disruptors. We share these concerns and want to play our part.

The chemical industry supports the Green Deal. 96% of goods manufactured in Europe rely on chemicals, so we are part of the solution to deliver the Green Deal, whether it is solar panels, batteries, wind turbines, chemicals to insulate buildings, or more powerful electronics, we are going to deliver the hi-tech and sustainable chemicals that are needed.

We also need to transition to climate neutrality, she said. It is a transformative time for the industry. The choices we are going to make to implement the Chemicals Strategy for Sustainability provide an opportunity and can accelerate how we deliver on the Green Deal, together with the EU recovery package.

In line with the Fitness Check we fully support a harmonised and horizontal implementation of the criteria for identification of endocrine disruptors, said Ms Lemoine. However, we think the REACH Regulation, and not the CLP Regulation is the best option for doing that.

REACH is the umbrella legislation for chemicals, she stated. It's the 'one-stop shop', the single place for data generation, for hazard identification, and for risk assessment. With endocrine disruptors added to the SVHC list under REACH you get one single list at EU level, we do not need a multiplicity of lists. And you can introduce restrictions for consumer products for which there is no sector legislation.

For CLP, we question the added value of establishing new hazard criteria for endocrine disruptors, there is a logic we don't get, said Ms Lemoine. First because many products that consumers are worried about, such as cosmetics, baby and childcare articles, are not subject to CLP labelling.
Second, it also means departing from the UN globally harmonised system, and we completely agree that this is a globalised industry. The EU has politically committed to implement GHS (Globally Harmonised System of Classification and Labelling of Chemicals), so why are we introducing new criteria in Europe before we know if the UN and other jurisdictions will agree to harmonise with them, she asked.

I am not saying we should wait, I am saying that the identification and classification of endocrine disruptors can be done under REACH, concluded Ms Lemoine. We have all the tools in place, and REACH has been shown to work.


Photo: © ClientEarth

Health and environment NGOs

Apolline Roger, representing the environmental law organisation ClientEarth and the NGO coalition EDC-Free Europe, said that the Fitness Check is an important source of information that the Commission can work with, alongside the REACH Review, non-REACH Review, toy and cosmetics evaluations, and other sources.

The starting point however is now the Chemicals Strategy, and we want to see its promises delivered.

Cefic is saying that REACH is the only horizontal chemical regulation and therefore should be the place to handle endocrine disrupting chemicals. But REACH and the CLP are the two arms of the chemical regulation system. They work together, she said. The reason why it makes sense doing endocrine disruptor identification under CLP is because this is how sectoral laws identify which substances are harmful and must therefore be regulated. That is why it makes sense to have the endocrine disruptors identified under CLP, even though the REACH SVHC (substances of very high concern) Candidate List can be used as a complement.

REACH will still play an important role. The Commission is planning to implement easier identification of endocrine disruptors as SVHC under REACH, with a new Article 57 provision done just for them. It will be possible to place endocrine disruptors identified under CLP nearly automatically on the SVHC list, which can be used when relevant.

Sylvie Lemoine (Cefic) responded that under CLP it will take longer, because you are going to overload the system. The Risk Assessment Committee (RAC) will have to approve all the necessary reviews, but there is already a shortcut with REACH. It is a policy choice, she said, and I hope there will be an impact assessment looking into that. There is really a logic, if you want to deliver quick action, to speed up the science and develop test methods, to do this under REACH.

Apolline Roger replied that she is very happy that Cefic want quick action, but reminded that the REACH system the chemicals lobby seems to support has had trouble providing results on endocrine disrupting chemicals – and was attacked by industry when it did lead to endocrine disruptor identifications. I think that while we are waiting for CLP, we can absolutely continue to have endocrine disruptor identification as SVHC under REACH; but one of the main advantages of CLP identification is the inclusion of the known and suspected categories, which was recognised as desirable according to the Fitness Check.

Animal welfare NGO

Erik Prochazka, representing the PETA International Science Consortium Ltd., said that the way to speed up the transition to animal-free toxicology is by directed and focussed investment in non-animal test methods


Photo: © Erik Prochazka

We know that these are superior to animal-based tests, which are time-consuming, ethically unjustifiable, and suffer from issues of reliability, reproducibility and relevance to human health, he said. They are also poorly-suited to predict low-dose effects, which is an important consideration for endocrine disruptors, and are not suitable for chemical cocktails.

The PETA International Science Consortium calls for more investment to support non-animal testing, which can achieve a higher level of protection for human health and the environment.

We have heard about the EURION Cluster projects and other initiatives, showing the range and sophistication of non-animal tests, including those currently available as well as those under development, said Mr Prochazka. We have in our toolbox high-throughput *in vitro* systems, organ-on-chip technologies, and even organism-on-chip technologies, various 'omics approaches, computational methods, innovative ways to use biokinetics, clinical and human biomonitoring data, and more. We have the tools, now we need to get them validated as quickly as possible, so they are acceptable to the regulators.


Photo: © Josef Köhrle

The voice for endocrinology

Josef Köhrle, speaking on behalf of the European Society of Endocrinology, said that the Fitness Check has shown that science has delivered: there is enough data and now is the time for action. We have several identified endocrine disruptors that we need to phase out.

We heard from EFSA that of 66 suspected compounds tested, 8 were endocrine disruptors and 5 of these affected the thyroid hormone system (see p. 9). As a thyroidologist, a biochemist and an endocrinologist, I really would demand, supported by the Society, that agents that affect the thyroid hormone system, which impact on unborn babies, need to be stopped in production and replaced by non-regrettable compounds, he said. We have I think enough alternatives.

There was a discussion of Vitamin D on the chat, with incredulous comments that such a commonplace group of compounds be restricted. As an endocrinologist, explained Prof Köhrle, I see Vitamin D as a hormone. It should only be used by endocrinologists, by experts, who know what they are doing. It should not be a cosmetic, it should not be used as a supplement when there is no deficiency, and I think there are enough substitutes to replace Vitamin D as a rodenticide.

As a rose is a rose is a rose, a hormone is a hormone is a hormone, and an endocrine disruptor is an endocrine disruptor. We should be precise in our terminology, and precise in our science, he stressed. Then, when it comes to rational science-based decision-making concerning the identification and regulation of endocrine disruptors, we are ready to immediately act.

The voice of the plastics industry

Michel Cassart, of PlasticsEurope and Director Strategic Council - Sustainable Use of Plastics, said he thought there were several important elements in the Chemicals Strategy for Sustainability with regard to endocrine disruptors.

One of those is related as well to 'one substance - one hazard assessment' and the link between all legislation via REACH while maintaining risk assessment into the various sectors.

PlasticsEurope requested a harmonised approach and to facilitate communication between the ECHA hazard assessment and EFSA.

I think it is important to have harmonisation based on sound science, he said. In that sense, we support assessments, particularly those that are complex such as the ones for endocrine disruptors, based on clear scientific protocols, agreed during public consultations and publicly accepted by all stakeholders.

With good guidance developed jointly by ECHA and EFSA, this is the type of approach we support. To address this properly, we are in favour of doing it in the REACH process, said Dr Cassart.

In the long-term, we believe that Bioassays can be interesting for evaluating substances that potentially migrate from plastics into food or other products directly in contact with plastics, he said. This is still very complicated, and cannot be used to regulate today, because there are still developments to be done there.

We are supporting those types of projects, for example, together with the German Environment Agency (UBA), he said. We are doing the same in Austria with, for example, the MigraTox project, which is developing an approach based on *in vitro* bioassays to support safety assessment of non-intentionally added substances in food contact materials.

Panel discussion

Sylvie Lemoine (Cefic) asked if the EU has given itself the means and the budget to match the height of its political ambition. She added that if we are really serious about protecting the public, there are two things we should do. First is enforcement, particularly imported articles containing endocrine disruptors that are banned in Europe and that are on the market. Second is explaining the situation regarding endocrine disruptors better to the public. For example, holding up a container of table salt, she said, iodine is listed on the label and is needed by the body, but iodine is also about to be identified as an endocrine disruptor under the Biocidal Products Regulation. How do we explain that to consumers?

Regarding 'one substance - one assessment', Cefic agrees that there should not be two agencies or national bodies coming up with different conclusions on the hazard side, said Ms Lemoine, as it is confusing to everyone. It also helps optimise resources and gets clarity on who does what.

Apolline Roger (ClientEarth/EDC-Free Europe) said that whether 'one substance - one assessment' will improve the situation in practice depends on how it is defined and implemented. It makes sense to share data between agencies and authorities, but if it creates a very heavy process and more requirements then I am not in favour of it.

Michel Cassart (PlasticsEurope) highlighted contradictions in the case of bisphenol A (BPA), a chemical used to make plastics. At the same time as it was being identified as an endocrine disruptor under REACH, it was also written on the EFSA website that according to WHO criteria BPA was not an endocrine disruptor. There were also very large ongoing studies on BPA in the US. So the ECHA evaluation seemed to have been going too fast, he said, and not taking into consideration all the available scientific evaluations.

The moderator **Chris Burns** referenced a court case that concluded on 16 December 2020, the day before this Forum; the third such case PlasticsEurope has lost in the European courts over the regulatory status of BPA. The European General Court ruled in favour of ECHA's 2018 categorisation of BPA as a SVHC under REACH due to endocrine disrupting effects on wildlife. BPA mimics the function of natural hormones, with adverse effects on fish and amphibian reproduction.

Michel Cassart said it was not for him to decide the next steps following yesterday's decision. The first thing would be to review its contents. I think we have to separate two things, he noted, the court case and the REACH process. For the use of BPAs, the plastics industry had already taken action even before its identification as an endocrine disruptor. For example, it is no longer used in baby bottles or in the

European production of PVC due to voluntary commitments already in the previous century. However, it may still be found in imported PVC items, so enforcement is extremely important.

I was not providing any judgements on whether BPA is an endocrine disruptor or not, that was not the debate, I was stating the fact that we have a difference in the evaluations, clarified Dr Cassart. It is an extremely complex dossier, and we are waiting the latest US study results before, as an industry, we adopt a final position.

On the chat **Suzanne Butt** (Glaxo Group Research) asked Prof Köhrle if the European Society of Endocrinology have a response to the published "consensus" on the key characteristics of endocrine disruptors for hazard identification.

Josef Köhrle (European Society of Endocrinology) said that they are in close agreement with the US-based Endocrine Society, a worldwide organisation they work closely with, in that when it comes to bringing endocrine disruptors into the regulatory context, specialist endocrinologists are not represented, and neither are patients.

A lot of the discussion, he said, uses the classical toxicology concept. For example, industry regulations look at thyroid gland morphology, but the impact is also happening elsewhere, such as the action of thyroid hormones on brain development.

Rather, we need urgently to use the accepted endocrinology concepts, he said. In most cases this is not a linear dose-response, but actions have bimodal curves so there is toxicity in deficiency and in excess. We need to really understand endocrinology, but many toxicologists have not yet got enough basic endocrinology understanding. Hormones act differently from many chemicals. They act at very low concentrations, unlike many other environmental agents, and we need to take this into consideration.

Quoting Albert Einstein, "Everything should be made as simple as possible, but not simpler", then it might be wrong, he said. We need endocrine expertise in politics, in regulation, and in decision-making.

I think endocrinology has delivered sufficient scientific evidence to enable us to significantly reduce, refine or replace a lot of animal experiments, added Prof Köhrle. However, we cannot totally substitute an in vivo system, using hormones as a biological communication compound, with *in vitro* models that do not represent the whole system. We still need some animal tests.

Erik Prochazka disagreed and said there should be a focus on eliminating all animal testing. Obviously, that is not going to happen overnight, but the indications are that it is possible, he said. We have seen in one of the presentations yesterday that accurately predicting in vivo response for a particular endocrine endpoint using a combination of *in vitro* and in silico methods is achievable. Building on this, we may be able to fully model potential adverse endocrine effects in an intact organism without having to use live animals at all.

It is also important to remember that the mechanistic data from many of the new approach methodologies is often fundamentally different from the apical effect data obtained from animal-based tests, and cannot be easily applied to the current risk assessment methodology. Hence, we also need to re-think the ways we conduct risk assessment as a whole, not just the element of hazard assessment. We need to focus on the development of strategies and methodology for efficient use of the new types of data, and a good example would be the Next Generation Risk Assessment framework, which offers the needed flexibility and robustness. This has been demonstrated in a number of recently published case studies.

The PETA International Science Consortium supports the Chemicals Strategy for Sustainability's aim to reduce animal testing, but the Strategy in its current form doesn't reach as far as it should. It needs to be more ambitious when it comes to reducing our reliance on animal testing, and present an actual commitment with clear timelines and deliverables.

Simone Mühlegger (Chemicals & Biocides Environment Agency, Austria): Does industry accept regulation based on data not using animals for regulation?

Sylvie Lemoine would like to see robust hazard assessment that does not rely at all on animals. However, what I am hearing from experts is that for adverse effects, we still unfortunately rely on animal data. If we are to only rely on *in vitro* tests, we know they are tweaked towards false positives because we do not want to miss any hazard. It is an alert, she said, not what we could call a robust assessment.

Michel Cassart agreed. With the work we are supporting on bioassays, one of the big issues is false positives/negatives. In the case of endocrine disruptors we need to have this type of alert, for example, for recycling materials say for food contact materials, but then we need to go into details and have full studies. It is the toxicologists who really have to provide the good science and support for that.

Suzanne Butt (Glaxo Group Research): How do you address data protection issues with 'one substance - one assessment'?

Apolline Roger replied that it is useful to look at what is happening under general food law. There was a big transformation, which will enter into force in January 2021, giving full transparency for all the data about the safety or toxicity of chemicals put on the market in relation to foods, food contact materials, GMOs, pesticides, and so on. Dr Roger thought that this approach is the way forward when thinking about 'one substance - one assessment' across the board.

Michel Cassart said the plastics industry fully supports transparency, and they have provided input to consultations and have cooperated with EFSA about this via stakeholder groups. Transparency for risk assessment is particularly important and certainly when the substance is on the market.

However, we have to take care when EFSA is starting the process of evaluation, as we still need to protect the details of the confidential information coming from new developments. If we start too quickly to provide all the information visibly, explained Dr Cassart, there is a risk that due to the length of the process products could be copied and introduced into markets other than Europe, even before they are on the European market. We have to be careful about protecting the industry in Europe.

Josef Köhrle said that scientists in this area are reducing or replacing animal experiments as much as possible. However, there is no way yet to model or simulate the effect of, for example, low-level maternal thyroid hormone for foetal embryonal and post-natal development. We might get there, but we need a lot of innovation.

He stressed that low dose actions demand that you really look at test systems (in vivo, *in vitro*, etc.) at specific time points, because low dose actions happens at a specific window of susceptibility. In humans, this is the first three months for the thyroid and the brain, for example. This cannot currently be modelled.

Sylvie Lemoine added that in terms of innovation, the Chemicals Strategy mentions the potential of artificial intelligence (AI) and computers to predict hazardous properties from a mass of data. This could predict very early in the development of a chemical whether it has potential endocrine disruptor properties.

Apolline Roger made a general comment on the Forum's debate. We are acting as it we are outside the theatre discussing the choice of movie. But we have the Chemicals Strategy, so the choice has been made, and we are in the movie theatre. The discussions we should be having is what to include in the endocrine disruptor chemicals regime we will build, not if we need to build one. Regarding CLP, how do we expand it and which sectors should refer to CLP to identify the substances submitted to their strictest position, for example, food contact materials?

Sylvie Lemoine agreed that this debate has taken place, in 2017 when it was finalised and policy decisions made. It was not the decision industry was calling for, but we respect it, like we respect the pesticides and biocidal products regulations. However, why don't we simply reapply what has been agreed after years of discussion, why would we change it now. With CLP are we going to reassess all pesticides and biocides now? In other words, why don't we watch the movie we chose until the end, rather than changing rooms and starting another movie before this one is finished?

Nigel Sarginson (ExxonMobil Chemical Europe and ECHA committee) asked Dr Roger if banning chemicals based on hazard for endocrine disruptor properties could have unintended consequences, such as bans on beneficial substances which risk assessment shows can be safely used. Also, please advise on what are the "non-hazardous" green chemicals?

Apolline Roger replied that regulatory consequences can be adapted to sectors, and for specific activities that are absolutely essential for society. For example, uses that are critical for health or safety can be derogated under very strict conditions, and with very clear monitoring and traceability. Even in the Pesticides Regulation, for example, there is a derogation for emergency situations. Derogations can be applied, she said, so it is not as black-and-white as was implied.

Sylvie Lemoine remarked on the 12 principles that underpin Green Chemistry. If you can produce a less hazardous chemical with, say, less energy, then go for it, as long as societal function is fulfilled. However, to make non-hazardous chemicals, you may still need hazardous chemicals as a building block, she said. You need polyurethane to insulate buildings, for example, what matters is how they are used to minimise exposure. What is required is better criteria for safe-and-sustainable-by-design, so industry knows how to play the game. We can develop these chemicals, as there is a lot of innovation in this industry.

Michel Cassart added that when industry is using chemicals to make plastic products, we need to consider the full life cycle, including production, use phase and end of life handling. However, in many cases plastics add value and are important in reducing CO_2 emissions, for example, when used in wind turbines to generate green energy or in reducing the weight of a car or reducing food waste and food contamination.

Nigel Sarginson mentioned there is a SIN (Substitute It Now) List, so how about a VIRTUE (Use It Now) list?

Apolline Roger acknowledged the SIN List, a database developed by the NGO ChemSec. This has been very useful as a gauge of what should not be in consumer products, though it has not been fully taken up.

Josef Köhrle said the list was helpful, but not a full solution. Industry has a lot of information, and if it can be communicated to its full extent then authorities would have better knowledge. We need education, in schools, on biology and chemistry. We need to communicate fact to avoid fictional belief.

The SIN list is a good start, he said. In Germany, for example, Friends of the Earth Germany have produced the ToxFox app. By scanning a product, the app tells you what chemicals are in it.

Sylvie Lemoine said that industry knows about the SIN List. What we struggle with is a proliferation of lists, because we lose the clarity. I think that behind all these things, there should be one standard reference list in Europe. She added a further thought on substitution. This happens every day in industry, in new or better products, for instance, but we don't shout about it because it is daily business, not just for hazard reasons.

Apolline Roger, in summary, said that political decisions have been made and we are now working on implementation. We need criteria for known and suspected endocrine disruptors, and we need to adopt a REACH restriction while we are working on updates. It is a big undertaking in front of us, so it is good to hear the Commission has the political will.

Erik Prochazka, in conclusion, stressed, firstly, there is a need to focus on the prioritisation of substances for which we have existing information, and secondly, on implementing and integrating non-animal testing methods from various EU-funded projects. For the latter, we need information requirements under REACH which offer the flexibility to make use of the data generated by non-animal methods. We also need more funding to fill the gaps in knowledge and technology, so we can move forward to better outcomes for human health, the environment, and animal welfare, he said.

Sylvie Lemoine said that Cefic is happy to hear that science is evolving, but more has to be done. On the policy side, details will matter as we move into implementation. In the end, the right balance is needed between the objectives of the Chemicals Strategy and having a thriving industry.

Michel Cassart summed up by stressing the need to improve sector evaluations, where plastics are most involved, such as food contact materials. He mentioned that plastics are heavily regulated, particularly for food contact use, toys and cosmetics packaging, thanks to high safety standards. He added that only additives and starting substances that have been evaluated by EFSA can be used.

What I learned during the two days of the forum is that we still have gaps in the science, he said. We fully support a collaborative approach with the value chain, academia and authorities, to push forward the science. We support investment in platforms where we can work together with academia and in supporting the right selection of substance, while respecting confidential business information.

Josef Köhrle said he hoped that the transparent communication between Member States, stakeholders, science and authorities, seen over the past 2 days, will continue. There is a need to take this issue seriously, with new funding and research. He concluded by noting the link between COVID-19 and endocrine disruptor exposure, via their effect on hormone-related diseases, such as diabetes, obesity, metabolic diseases and cardio-vascular system diseases. Endocrine disruptors are not monocausal, they are contributing together with other factors to disease development, and we have to act as soon as possible, and based on science.

Conclusions and next steps

Cristina de Avila
DG Environment, European Commission

"These past two days we have seen more common ground than we are used to seeing, but we have also seen, particularly in the last panel, that the issue of endocrine disruptors still raises passions. It is good to see that I am not the only one in the world that is so passionate about chemicals legislation!

We have also seen throughout these days that we have a solid scientific base, but we need to evolve, and to continue developing the necessary scientific tools to better identify endocrine disruptors.

As for what we know today, we cannot continue waiting. We need to take action, as the Commissioner said. We need to have science-based hazard criteria in the CLP legislation, as we have promised in the Chemicals Strategy, and we need action to regulate chemicals in consumer products, in order to obtain a high level of protection, in particular for consumers. So I think the jury is not only out, but the verdict has been given, and it is in the form of the Chemicals Strategy for Sustainability.

We have the financial means to continue supporting the development of scientific tools, but also to help industry make a transition to safe and sustainable chemicals. We also have the regulatory tools in place to better protect human health and the environment.

We have seen that we have the political will. We saw it today in our High-Level Segment at this Forum, but also yesterday in the Environment Council where 26 Member States talked in support of the Chemicals Strategy almost unanimously; there was no voice against the Strategy. There was support for not only the measures proposed for endocrine disruptors, but for hazardous chemicals in general.

The political will is there to translate the commitments that we have made in the Strategy into a reality. Basically, the Strategy is not a one-sided communication, it is not only focusing on chemicals exclusively. It is a proper child of the Green Deal, it is looking to sustainability, into climate neutrality, to circularity, and bringing all the elements together, for the future of chemicals in Europe.

There is an opportunity to create green jobs and a competitive economy. The boat is sailing and we want all of you to come onboard to profit from these opportunities that are opening up in front of us.

I will be working hard to make our hopes a reality, and I hope to see you all again at the Third Annual Forum on Endocrine Disruptors next year."

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