

External evaluation of the Danish Centre for Endocrine Disrupting Substances (CeHoS)

For the period December 2008 – June 2017

Copenhagen September 2017
www.cehos.dk



Preface

The Danish Centre on Endocrine Disruptors (CeHoS) was established in 2008 with the main purpose to build and gather new scientific knowledge on endocrine disruptors with the focus on providing information requested for the preventive work of the regulatory authorities. The Centre is an interdisciplinary scientific network without walls, financed by the Danish Ministry of Environment and Food.

Since 2010 CeHoS has been financed for two 4-year periods via the Danish Chemicals Action Plan of which the current period expires by end of 2017. To evaluate the overall impact and scientific contributions of the Centre since its establishment in 2008, the Danish Environmental Protection Agency (DK EPA) and the CeHoS steering board requested an external expert evaluation of CeHoS in spring 2017.

The evaluation covers the quality of the scientific work and the results of the Centre, including the ability to gather and exchange new and current knowledge on endocrine disruptors within the scientific community and to the general public. Further, the evaluation covers the value of the scientific contributions to the Danish authorities in their preventive work in relation to the chemicals acquis.

The evaluation was performed and written within the 2 days on-site visit in Copenhagen in June 2017 (a further description of the method is provided in the appendices of the report).

The DK EPA would like to thank the reviewers Professor Emeritus Jean-Pierre Bourguignon (Chair), Paediatric Endocrinology, University of Liège, Belgium; Professor Tom Hutchinson, Environment & Health Sciences, University of Plymouth, UK; Senior Investigator Rémy Slama, Environmental Epidemiologist, Inserm, Grenoble, France for accepting to participate as external reviewers in the evaluation.

September 1st 2017

The Danish Environmental Protection Agency, Copenhagen, Denmark

Content

Report on external evaluation of Danish Centre for Endocrine Disrupting Substances

Appendix 1: Description of the evaluation process

Appendix 2: Evaluation report template

Appendix 3: Report of the Danish Centre on Endocrine Disrupting Substances 2008-2017

(Background material provided for the review committee)

**External evaluation of
Danish
Centre for Endocrine Disrupting Substances
(CEHOS)
*for the period December 2008 – June 2017***

By commission of
The Danish Environmental Protection Agency

Conducted by an international expert committee consisting of:

Jean-Pierre Bourguignon (Chair)

Professor Emeritus of Paediatric Endocrinology, University of Liège, Belgium.

Tom Hutchinson

Professor of Environment & Health Sciences, University of Plymouth, UK.

Rémy Slama

Senior Investigator, Environmental Epidemiologist, Inserm (National Institute of Health and Medical Research), Grenoble, France.

Copenhagen, June 20th, 2017

Executive summary

1. *CEHOS is a highly effective multidisciplinary Centre, which generates and disseminates state-of-the-art knowledge on Endocrine Disrupting Chemicals (EDCs) and their effects, for regulatory authorities and the general public. We are not aware of any similar initiative in other countries.*
2. *The Centre integrates expertise on human population studies (endocrinology, clinical research and epidemiology), animal models (toxicology), observations in the environment (ecotoxicology) and translational research;*
3. *In nine years of existence, CEHOS has played a key role in building knowledge on issues crucial for public health and regulation such as on the effects of UV filters, phthalates, Bisphenol A, perfluorinated compounds, all of which have led to regulatory changes at the national, EU or international levels;*
4. *In terms of key contributions, CEHOS has provided essential biomonitoring data on the quality of the environment of Denmark; it has generated knowledge on the exposure to EDCs of the Danish population, in particular sensitive individuals such as pregnant women and newborns, and also young men, together with time trends in health abnormalities possibly related to EDC exposure. To that extent, the Centre has clearly fulfilled its key missions;*
5. *Along its strategic alignment, CEHOS gives efficient and relevant information on EDCs to the Danish Environmental Health authorities and to the public; members of CEHOS also participate to fora allowing interactions with the Danish industry association, individual companies, Danish consumer associations, as well as the general public;*
6. *The foreseeable developments of knowledge on EDCs make it very important for the support to CEHOS to be continued; this would be for example relevant in the question of consideration of mixtures (so-called cocktail effects) in the regulation, a topic on which CEHOS partners have been active in the past;*
7. *One reason why the work of CEHOS has been efficient over the years is that CEHOS partners maintained research activities in parallel to their commitment in CEHOS, so that the funding given to CEHOS could benefit from large infrastructures (such as animal facilities, biobanks and population cohorts) funded by other means; all in all, this guarantees to the Danish taxpayer that the investments done in CEHOS provide an excellent value for the money. Of particular concern to the committee is the fact that the programs funding research on EDCs at the national and EU levels have been reduced in the past decade.*
8. *For the future, it is important to consider, either as part of CEHOS or externally, increasing investment in the development of large cohorts and studies monitoring the contamination of the Danish population (biomonitoring) and the Danish environment. These are essential tools for the development of knowledge relevant for decision-making to protect the population and the environment from the effect of endocrine disruptors and estimate their cost for society. In addition, the public authorities could consider making use of the expertise of CEHOS to evaluate the impact, costs and benefits of regulatory decisions in the area of EDCs;*
9. *For the dissemination of the knowledge generated on EDCs and on efficient prevention strategies in the Danish population, it would be important to consider, either as part of CEHOS or externally, the development of a core set of information on EDCs to be delivered to health care and environment professionals as part of their education.*

1. Overall assessment of the Centre's activities and impact in relation to knowledge building on risk related to human and wildlife exposure to endocrine disrupting chemicals for targeted use by the authorities' preventative work, including regulation

The present evaluation is based on a self-evaluation report provided by CEHOS and interviews conducted separately with scientists from the 3 partner entities and representatives of the Danish Environmental Protection Agency (EPA) and the Danish Veterinary and Food Administration during a two-day on-site visit.

To the best of our knowledge, CEHOS is a unique organization linking the scientific experts and science users in the arena of Endocrine Disrupting Chemicals (EDCs) impact on health and environment. Important science users include policymakers, industry, health professionals, Danish consumers' associations and the general public. A most efficient functional feature of CEHOS is direct communication between scientists and policymakers. This occurs upstream, enabling knowledge building through dialogue between scientific experts and regulators about the gaps to be filled by scientists. CEHOS can build on a broad variety of high-level expertise and on existing biological materials and studies previously conducted by the partners, allowing a cost-efficient and rapid response to new questions on the risks related to exposure to EDCs whenever the authorities have specific needs in this regard. Communication also occurs downstream, enabling knowledge dissemination and translation of science for regulators and for the public.

Our overall assessment is that CEHOS is a pivotal entity for incorporation by policymakers of the science data into regulatory decision and strategies both in Denmark, in the EU and further internationally. Moreover, CEHOS is pivotal in implementation of action towards protection of public health and environment against the adverse effects of EDCs, as well as in building synergy with international scientific experts. The foreseeable rise of questions and issues about EDCs in the next decade make essential the support to CEHOS to be continued and if possible expanded.

We have identified the following strengths:

1. High quality teams of scientists and multidisciplinary approach;
2. In-depth knowledge across a diversity of species and scales (from molecules to population);
3. Ability to generate knowledge relevant for the protection of public health and environmental quality, and to support the regulatory positioning of Denmark at the international level;
4. Integration of CEHOS partners in large institutions, enabling cost-efficient access to biological materials and state-of-the-art technical facilities funded by other means;
5. Plurality of communication about knowledge on EDCs with a diversity of stakeholders (e.g. industry, media, pupils, lay public).

Some key achievements of the centre over its first 9 years are:

1. Generation of evidence about wildlife and human exposures to EDCs and their adverse effects;
2. Identification of the endocrine-disrupting properties of Benzophenone-3 (a UV-filter) and of specific perfluorinated compounds;
3. Contribution to the recognition of specific phthalates and Bisphenol A as EDCs or substances of very high concern in the EU; Pioneering work on the "cocktail" effects of mixtures of EDCs;

4. Contribution to development of international testing guidelines for chemical effects
5. Organization of a unique multidisciplinary conference series gathering in Denmark scientists from all over the world with expertise on environmental and human health;

No significant weaknesses have been identified by the evaluation committee.

2. Conclusions and recommendations on future organisation and actions

CEHOS is an original and highly effective multidisciplinary centre to generate and disseminate state-of-the-art knowledge on Endocrine Disruptors and their effects, with national and international impact and recognition. Undoubtedly, this key component bridging science and use of science deserves further support because it brings benefits to decision-making authorities and many other stakeholders including scientists.

Building on the existing strengths and past achievements of the Centre, the Committee makes the following recommendations:

1. Further support CEHOS; it is a highly effective Centre whose activities will be crucial in the future given the long-term importance of EDCs effects for public health and quality of the environment;
2. Maintain the structure and basic approach of the Centre;
3. Increase resources for long term biomonitoring studies of the Danish population, cohorts, as well as environmental monitoring in order to substantiate protective measures;
4. Consider providing a structured education on EDCs for health and environment professionals, as a way to support information and preventive actions towards the public;
5. Expand the ongoing work on the possible behavioural and neurodevelopmental consequences of EDC exposure.

In addition, it might be useful to identify and follow indicators of the outcome of actions involving CEHOS (e.g. raising awareness, recommendations made to the public authorities...).

3. Organisation and implementation of the Centre in relation to its objectives and the execution of activities

CEHOS is currently based on an interdisciplinary scientific partnership “without walls” including partners from 3 institutions:

- the Rigshospitalet, Dept. of Growth and Reproduction (RH, Copenhagen);
- the National Food Institute at the Technical University of Denmark, Research Group for Molecular and Reproductive Toxicology (DTU-FOOD, Copenhagen);
- and the University of Southern Denmark, Department of Biology (SDU, Odense).

These groups have expertise in endocrinology, clinical research, epidemiology, toxicology and mechanistic studies, both *in vitro* and *in vivo*, environmental monitoring and development of

toxicological test guidelines. Expertise in analysis of exposure to a wide range of EDCs is also available within the centre. Thus, CEHOS covers most of the disciplines and methods relevant to generate knowledge on EDCs.

The Centre is coordinated by a management board, including the Centre director and 1-2 senior members from each partner. The role of this management board is to establish the work programme. This programme is validated by a steering committee, which also serves as an adviser to the centre and brings up specific issues that should be addressed by the Centre. The steering committee includes representatives from the Danish Environmental Protection Agency, by the Danish Veterinary and Food Administration, the Danish Health Authority and the Danish Working Environment Authority. In addition, an independent Scientific Advisory board composed of 4 internationally-recognized experts in the field of EDCs has been set up.

The partners' work is done through projects involving some or all of the CEHOS partners, and also by periodically engaging an external network of collaborators whenever additional expertise is needed. The fact that the projects are consistently led by a CEHOS partner is important in ensuring high quality and efficient working practices and dissemination of results. Some of the projects are initiated by CEHOS while, since 2014, others are commissioned by EPA. This evolving strategy of funding allocation to projects indicates plasticity in the centre functioning based on interaction between the partner scientists and representatives of authorities, with both aiming at meeting the expectations of all the parties.

Overall, the current structure appears to be very effective in supporting the functions of CEHOS, especially regarding addressing key questions and knowledge gaps of EDC assessment. The relatively small number of partners and regular contacts with the steering committee has provided efficiency and flexibility in the action of the Centre.

4. Quantity and quality of the Centre's knowledge-building, including the scientific production in relation to the objectives of the Centre and the resources allocated

CEHOS has coordinated 41 projects since the start of its activities in December 2008, covering a large range of EDCs, health endpoints and different subgroups of the population. Many of these projects were of multidisciplinary nature, bringing together the complementary expertise and approaches of CEHOS partners. Generally, these projects were at the frontier of scientific knowledge. Over the 2009-2016 period, a total of 55 articles in international peer-reviewed journals have been published; the high quality of this scientific output underpins the ability of CEHOS to meet its objectives and it is an excellent scientific achievement in its own right.

Some examples of key achievements in terms of knowledge-building :

- Effects of perinatal Bisphenol A exposure on both male and female rat sexual development were identified at doses that could warrant a decrease in the tolerable daily intake of Bisphenol A;
- An evaluation of benzophenone-3 (a UV-filter) using the Fish Sexual Development Test

(OECD test guideline nr. 234) showed a significant impact on the sex ratio of freshwater fish, confirming that BP-3 is an endocrine disruptor. This work was conducted by environmental experts of SDU following results from other CEHOS partners showing the presence of benzophenone-3 in human samples and direct effects on human sperm;

- A human cohort study led to observation of associations between prenatal exposure to flame retardants and development of adiposity in childhood;
- A study of the combined exposure to both anti-androgenic and oestrogenic EDCs deciphered mixture effects for several endpoints such as anogenital distance, nipple retention and weight of male reproductive organs.

5. Relevance and impact of the deliverables of the Centre in relation to usability for national or international regulatory agencies and potential preventive measures, as well as usability for NGOs and the general population

The knowledge generated by the center has been used by regulatory agencies at various levels (from local to European and international levels).

- For example, the report of CEHOS on “Criteria for Endocrine Disruptors” (projects #21 and 22) has been used to support the Danish position in the context of the development of scientific criteria to identify substances with endocrine-disrupting properties in the EU.
- The work of CEHOS partners on mixtures of phthalates and on BPA effects has clearly contributed to the recognition of these substances as having endocrine-disrupting properties by the EU Authorities. Regarding phthalates, the EU decision has followed a proposal of Denmark.
- Another project has documented the possible use of urinary biomonitoring data on non-persistent chemicals for risk assessment (project #15).
- Some of the CEHOS work (e.g. regarding biomonitoring and effects of EDCs) contributed to the Nordic Council of Ministers estimating the costs of EDC exposure related to human fecundity impairment.
- On another level, several CEHOS projects (e.g., projects #8, 16, 17) documenting exposure of pregnant women and young men to a large range of suspected EDCs contributed to the awareness of the Danish population regarding presence of EDCs in the environment.
- All in all, the identification of the presence of EDCs in the general population and of their possible adverse effects also contributed to the production of information leaflets and recommendations published by the EPA for pregnant women (e.g., “advice about chemicals and pregnancy”).

In conclusion, the excellence of the partnership within CEHOS and the efficient interactions with the supporting authorities enabled the knowledge generated by CEHOS on EDCs and their adverse effects to be translated into action by national and international authorities.

6. Quality of dissemination of results and knowledge-sharing in relation to authorities, the scientific community, and the general public

As far as the scientific community is concerned, a very important achievement of CEHOS relates to the organization of the Copenhagen workshop on endocrine disruptors every two years. This is a unique scientific event that actually started as early as 1999 in the context of the EU-USA debates about the consequences of the use of “growth” hormones in beef production in the USA. This event constitutes a multidisciplinary conference series gathering in Denmark scientists with expertise on environmental and human health from all over the world, with generally more than 150 participating high-level scientists. The support to CEHOS allows the organization of such a conference, independent of commercial interests. This has been important for the role and reputation that the Copenhagen Workshops on EDCs have gained among the scientific community internationally. To the best of our knowledge, there is no equivalent multidisciplinary meeting of this size at the international level. The conference is systematically followed by a publication of the proceedings in scientific journals allowing dissemination of the results. Importantly, the Danish EPA, other national authorities as well as scientists from NGOs and from the industry strongly benefit from having the most recent scientific results about EDCs being presented in Copenhagen.

In terms of dissemination towards the general population, CEHOS organizes on a yearly basis (since 2009) a one-day public meeting. The meeting covers the sources and effects of EDCs and allows time for questions and comments from the participants. These meetings (with no participation fees) usually have around 90-120 participants covering a broad spectrum of stakeholders such as NGO representatives, other researchers, agency officials, students, trade association representatives etc. Since 2014, presentations from these meetings have also been posted via the CEHOS website.

Members of CEHOS also participate to fora allowing interactions with the Danish industry association, individual companies, and Danish consumer associations, as well as the general public, including pupils.

7. Resource allocation and “value for money” of Centre activities

One reason why the work of CEHOS has been efficient over the years is that CEHOS partners have maintained research activities in parallel to their commitment in CEHOS, so that the funding given to CEHOS could benefit from large infrastructures (such as cohorts, animal facilities, biobanks) funded by other means; all in all, this guaranteed to the Danish taxpayer that the investments done in CEHOS provided an excellent value for the money.

It is important to stress that CEHOS work relies on a large number of facilities developed by the partners as part of their other missions and of specific research projects. The key facilities and resources upon which CEHOS work relies include:

- A clinical hormonal laboratory;
- Laboratories for state-of-the-art analysis of EDCs in biological fluids and environmental samples;

- Molecular biology, cellular biology and histology laboratories;
- Cohorts of pregnant women and their children conducted in several areas of Denmark and related to European and international cohorts;
- Repeated cross-sectional studies of the reproductive health of young male Danes, providing a unique resource on male reproductive health at the international level.

Several CEHOS projects have been performed as minor addition or spin-off of on-going or already conducted research projects. One example is the biomonitoring studies (e.g. projects #16-18) conducted in order to elucidate the exposure levels in the general Danish population for suspected EDCs, that could build on already collected samples from about 4000 children, adolescent, young men and pregnant women. Reliance on these existing biological samples made it possible to provide information on population level exposure to a range of EDCs within a relatively short time frame and very cost-effectively. Another example is in project #24, where the Centre was able to provide new information on late effects of developmental exposures for a relatively moderate cost by adding a small protocol to an already planned – and funded - developmental exposure study in rats.

CEHOS work relies on very experienced senior investigators with a unique expertise in the field of EDCs; as the committee understands, only a very minor part of the salary of these researchers is actually supported by CEHOS funding. This allowed the investment done by the Danish authorities into CEHOS to be incredibly cost-efficient, a situation that might not last if the institutions of CEHOS partners cannot afford to further share these human resources, or as some key CEHOS senior researchers retire. For this reason, and given the growing importance of this issue, the committee would recommend increasing financial support to CEHOS as a way to invest in the training and retention of tomorrow's experts in the field of EDCs assessment.

8. Additional observations and comments

No further comments

Description of the external evaluation process

The Centre on Endocrine Disrupting Substances was in Spring 2017 commissioned by the Danish Environmental Protection Agency (DK EPA) to organize an external evaluation of the Centre's work and task solution during the period 2008-2017. The external evaluation should be concluded with a written report, to be available by August 2017.

An initial planning meeting

Medio March 2017 at an initial meeting with the Steering Committee of the Centre including members from the DK EPA and the Centre management (Anna-Maria Andersson, and Stine Holmboe) was held, at which the criteria and procedure for the external evaluation were defined.

Criteria for the external evaluation

It was decided that the criteria on which the Centre was to be evaluated by were the following:

- 1) the organisation and implementation of the Centre
- 2) the scientific quality of the work carried out
- 3) the relevance of the work in relation to the regulatory and policy needs of the authorities
- 4) the quality in dissemination to authorities and the public
- 5) the degree of value for money

To make sure that the final evaluation report covered all these aspects it was decided that a template for the evaluation report should be provided to the external Review committee, in which it was clearly indicated that each of these aspects should be covered in individual sections of the report.

Criteria for selection and appointment of members for the external Review committee

At the initial meeting also the criteria for the composition of the external Review committee were decided. As the evaluation should cover both the scientific quality and the relevance for the authorities, it was agreed that the committee should be composed so that the members together covered expertise in research in human and animal hormone disruption, in risk assessment, and in (EU) regulation. The Centre management also emphasized that members of the committee should not be former or current collaborators to any of the partners in the Centre. Furthermore, it was decided that the assessment committee should consist of a chairman and 2-3 members. The Centre management was asked to suggest members of the review committee and the final composition of the committee was to be approved by the DK EPA.

Procedure for external evaluation

By suggestion from the Centre management it was decided that the external evaluation should be carried out as a 2-day on-site visit during which the review committee on the first day would have the chance to interview key persons in the Centre as well as representatives of the Danish authorities, which the Centre have been serving. During the second day the review committee would have time to complete the written report and the Centre management would be available for additional clarifying questions if needed. Prior to the 2-day on-site visit the review committee should be provided with background material about the Centre as well as the aforementioned template for the report at least three weeks before the visit. It was the task of the Centre to generate all the background material as well as the template for the report as well as to plan and carry out the logistics related to the 2-day on-site visit. In order to be sure to have the final external evaluation report ready for August – taking the summer holiday period into consideration – it was decided to aim for having the 2-day site visit in June.

Preparation of the external evaluation

Appointing the members of the Review committee

The Centre management identified three potential members for the Review committee who not only fulfilled the decided criteria but also were available for a 2-day on-site visit in June 2017, as well as for the preparatory work in advance of the visit. Thus, the following persons were suggested by the Centre management:

Jean-Pierre Bourguignon, professor in paediatric endocrinology, who has many years of experience in research on the effects of endocrine disrupters on the development of the brain and puberty. He is also serving as co-chair for the Global and European Endocrine Society EDC Policy Task Forces.

Tom Hutchinson, professor and ecotoxicologist at University of Plymouth with experience in hazard and risk assessment of endocrine disrupting chemicals. He is also experienced in developmental- and reproductive biology and toxicity of chemicals in aquatic organisms.

Remy Slama, epidemiologist from INSERM, with research focus on environment and health including effects of endocrine disrupters.

This composition of the Review committee was subsequently approved by the DK EPA and Jean-Pierre Bourguignon was appointed as chair of the Review committee.

Once the Review committee was appointed the dates for the 2-day on-site visit were agreed on as June 19-20, 2017.

Design of the evaluation report template

Based on the discussions with the Centre's Steering committee and the DK EPA the Centre secretariat designed a template for the evaluation report. The template consisted of fixed headings for obligatory sections and short text describing the expected content to be covered under each heading. The template was tested on 2 different independent persons to secure that the questions to be answered/criteria to be evaluated were clear. The final version of the template was approved by the DK EPA. The template is included in this final report as Appendix 2.

Generation of background material for the Review committee

The Centre secretariat generated and collected all the background material to be sent to the Review committee ahead of the 2-day on-site visit. This background material consisted of a report on the Danish Centre on Endocrine Disrupting Substances 2008-2017 (Appendix 3 in this report), which also included a full list of projects carried out under the Centre. Included in the background material were also a one-page CV and full publication list for each member of the Centre direction and copies of project reports.

Background material, evaluation report template and written practical information about the on-site visit were forwarded to the members of the Review committee on May 1, 2017.

Execution of the 2-day on-site visit

The 2-day on-site visit took place at Dept. of Growth and Reproduction, Rigshospitalet. The programme for the visit is shown in Table 1. In short, the visit was divided into three sessions. Participants in the first session were key persons from the three partners in CeHoS and the Review committee members. Initially, each partner in CeHoS gave a short description of their group. Subsequently, the participants were interviewed by the Review committee, which enabled the committee members to ask for additional information to that given in the background material

and to ask additional clarifying questions. Participants in the second session were representatives from the Food Safety Agency and DK EPA and the Review committee members, allowing the committee members to receive information from the point of view of the agencies. Session 3 was the writing session in which only the Review committee members participated. A room was provided for the Review committee in which they could complete their evaluation report.

The goal of having the evaluation report completed by the end of day 2 was largely met except that the committee wanted a little extra time for the final adjustments. The contact person at DK EPA received the completed evaluation report by mail a few weeks later on July 10.

Table 1: Participants in the 2-day on-site visit		
Session 1: 19. June, 09-14.00		
Partner	Name	Role in CeHoS
Dept. of Growth and Reproduction, Rigshospitalet	Anna-Maria Andersson	Center leader, project leader
	Niels Erik Skakkebæk	Management board member, project leader
	Anders Juul	Management board member, project leader
	Hanne Frederiksen	Project leader
	Katharina Main	Project leader
	Tine Kold Jensen	Project leader
	Stine Holmboe	Center management assistant
Food Institute, DTU	Ulla Hass	Management board member, project leader
	Camilla Taxvig	Project participant
	Marta Axelstad	Project participant
Institute of Biology, SDU	Poul Bjerregaard	Management board member, project leader
	Jane Morthorst	Project participant
Session 2: 19. June, 14-16:00		
Institution	Name	Role in CeHoS
Danish EPA	Pia Juul Nielsen	Special consultant, endocrine disruptors, CeHoS Project contact person at EPA
Food Safety Agency	Mette Holm	Special consultant, Danish FSA Member of CeHoS steering committee
Session 3: June 20, 9:00 – 16:00		
Review committee members only – completing evaluation report		

**External evaluation of
Danish
Centre for Endocrine Disrupting Substances
(CEHOS)
*for the period December 2008 – June 2017***

By commission of
The Danish Environmental Protection Agency

Conducted by an international expert committee consisting of:

[Name]
[Affiliation]

[Name]
[Affiliation]

[Name]
[Affiliation]

[Name]
[Affiliation]

Copenhagen [date]

This is a template for the evaluation report that will be the deliverable of the evaluation committee. It contains eight sections of which section 3-7 covers the five criteria that the Centre should be evaluated on:

- a) Organisation and implementation of the Centre in relation to the objective¹*
- b) Scientific quality of the Centre's knowledge building on endocrine disruptors and their effects*
- c) Relevance and impact of the Centre's work in relation to the objective*
- d) Quality of dissemination of data and knowledge-sharing*
- e) Value for money of the work carried out by the Centre*

Section 1 and 2 are the evaluation committee's statement of the overall assessment and the conclusion with recommendations on the Centre's impact and future organization, respectively. Section 8 is optional in case the committee members feel that there are points or comments they want to express, which were not covered sufficiently by section 3-7.

You are welcome to organise your responses by adding subheadings under each section if you feel this is needed to give a better overview.

Under each section heading is a tooltip text indicating the suggested length of each section and a short description. Please erase these tooltip texts (including this page) from the final version of the report.

¹ The overarching objective of the Centre is to build knowledge for use by the authorities preventive work in relation to endocrine disrupting chemicals, please see also Background material, Appendix A

1. Overall assessment of the Centre's activities and impact in relation to knowledge building on risk related to human and wildlife exposure to endocrine disrupting chemicals for targeted use by the authorities' preventative work, including regulation

(½-1 page: Please give a summary of your overall evaluation of activities and impact; identified strengths/weaknesses/opportunities/short-comings)

2 .Conclusions and recommendations on future organisation and actions

(½-1 page: Please give your overall conclusions and recommendations on organization of the Centre; if the Centre on Endocrine Disruptors should continue, what could be improved, should be changed, should not be changed etc.; suggestions for possible future activities are welcome)

3. Organisation and implementation of the Centre in relation to its objectives and the execution of activities

(~2 pages: Please evaluate if the organisation of the Centre facilitates the objectives of the Centre satisfyingly?; do the activities of the Centre support the objectives and aims of the Centre; is the required knowledge and expertise present/available? (Identify relevant strengths, weaknesses, and possible shortcomings)

4. Quantity and quality of the Centre's knowledge-building, including the scientific production in relation to the objectives of the Centre and the resources allocated

(~1-2 pages: Please evaluate the scientific quality of the knowledge building projects carried out under the Centre taking the available resources into consideration)

5. Relevance and impact of the deliverables of the Centre in relation to usability for national or international regulatory agencies and potential preventive measures, as well as usability for NGOs and the general population

(~1-2 pages: please evaluate if the knowledge building (data and reports) generated by the Center have had an impact on national (or international) regulation (how, why, or why not)? Have activities of the Centre had any impact on awareness or knowledge on endocrine disrupting chemicals among regulators as well as in the general population? This section could cover general aspects of endocrine disrupting chemicals and their effects as well as knowledge on specific chemicals)

6. Quality of dissemination of results and knowledge-sharing in relation to authorities, the scientific community, and the general public

(~1 page: please evaluate the dissemination and knowledge-sharing of the Centre in relation to communication with the authorities, the scientific community and the general public taking the allocated resources and the objectives into consideration)

7. Resource allocation and “value for money” of Centre activities

(~1 page: please evaluate the “value for money” of the Centre activities; is the Centre implemented and activities executed in a way that facilitate good value for money?)

8. Additional observations and comments

(Optional section: this section can be used for comments or pointing to issues not directly covered under the criteria above)

CENTER FOR HORMONFORSTYRRENDE STOFFER

Danish Centre on Endocrine Disrupting Substances

Implementation, activities, and deliverables
Dec. 2008 – April 2017

Copenhagen, April 2017
www.cehos.dk

Content

Foreword.....	2
1. Introduction: purpose and main activities of Centre on endocrine Disrupting Substances - CEHOS.....	3
2. Organisation and implementation of CEHOS.....	3
2.1. The Management board and Centre secretariat	4
2.2. Steering committee	4
2.3. Advisory board	6
2.4. Changes in the organization and implementation of the Centre between the different periods	6
2.4.1. Contract for the 2008-2009 period	6
2.4.2. Contract for the 2010-2013 period	6
2.4.3. Contract for the 2014-2017 period	7
2.5. Expertise, resources, and facilities in CEHOS.....	7
2.5.1. Dept. of Growth and Reproduction, Rigshospitalet (RH).....	7
2.5.2. Research Group for Molecular and Reproductive Toxicology, the National Food Institute at the Technical University of Denmark (DTU-FOOD).....	8
2.5.3. Department of Biology, University of Southern Denmark (SDU)	9
2.6. Strengths and weaknesses of the current Centre organisation and implementation	10
3. Knowledge-building activities of CEHOS	11
3.1. Examples of projects in CEHOS	11
4. Knowledge-sharing and dissemination activities of CEHOS	13
4.1 Contacts to the Danish EPA and other national regulatory agencies.....	13
4.1.1. Reports on new scientific literature on endocrine disruption.....	13
4.2. Public information meetings.....	13
4.3. Scientific publishing	14
4.4. International scientific meetings	14
5. Economy of the Centre	14
Reference List.....	16
Appendix A: Specified requirements of Centre on endocrine disrupting substances 2014-2017	
Appendix B: Selection criteria for selection of tenderers	
Appendix C: CVs and publication lists of key personnel in CEHOS	
Appendix D: Projects initiated and coordinated within CEHOS	
Appendix E: Scientific publications based on studies carried out in CEHOS	

Foreword

The Danish Centre on endocrine disrupting substances was established in December 2008 on a 1-year contract under the Danish Environmental Protection Agency (EPA). The contract was the result of a public call for tenders (EU call for tenders: 2008/S 178-237757) by the Danish Ministry of Environment. The Centre has subsequently been extended twice (from 2010-2013 and again from 2014-2017); each time by contract under the Danish EPA following new rounds of public EU call for tenders (2010/S 27-038779 and 2013/S 220-383310) by the Minister of Environment. Funding for the Centre has been part of the Danish Action Plans on Chemicals 2010-2013 and 2014-2017 on the Danish national bill. Establishment of the Centre was thus a political decision. An Action Plan on Chemicals for 2018-2021 is negotiated among the Danish political parties during spring-autumn 2017 and is expected to be settled by the passing of the national bill in November 2017. Whether a continuation of Centre on endocrine disrupting substances will be included in the final Action Plan on Chemicals 2018-2021 is currently unknown.

In April 2017 the present report and self-evaluation of the Centre was commissioned by the Danish Environmental Protection Agency (j. nr. MST- 621-00148) as part of an external evaluation of the activities of the Centre. The report is intended as background material for an external evaluation committee. It covers the period December 2008 – April 2017.

The report has been prepared by the secretariat of the Centre with input from partners of the Management board. The content and statements are thus those of the Centre Management, although we have strived to give an unbiased and balanced evaluation. All partners in the Centre have contributed to and approved the report.

Anna-Maria Andersson
Centre Director

Copenhagen, April 2017

1. Introduction: purpose and main activities of Centre on endocrine Disrupting Substances - CEHOS

The Danish Centre on endocrine disrupting substances (**C**enter for **H**ormonforstyrrende **S**toffer, CEHOS) is an interdisciplinary scientific partnership without walls. The main objectives of the Centre is to build and gather new knowledge on endocrine disrupters with the focus on providing information relevant for the preventive work of the regulatory authorities as well as to point out important knowledge gaps and provide recommendations for future knowledge building initiatives in relation to endocrine disruption.

More specifically the purpose of the Centre as stated in the tender documents¹ is:

“The purpose of the tender is to enter into a contract for the management of a Centre...for endocrine disrupting substances, to continue the targeted knowledge building to support the Authorities' preventive work, including regulation. The tasks include running the Centre, including scientific advice and knowledge sharing, as well as commissioning and coordination of projects. The offer must ...be carried out within the framework of the fixed remuneration”.

Details on the aims, requirements, and expected deliverables of the Centre as stated in the tender documents are provided in Appendix A, but in short the main activities of the Centre include:

- Management of a centre without walls, consisting of a network of relevant institutions in the health and environmental area.
- Implementation of an annual work program within the economic framework defined by the contract and a professional framework defined by the steering committee. The work program contains the following tasks:
 - Scientific advice and knowledge sharing
 - Coordination with the steering committee (annual work programmes, reports, and meetings)
 - Scientific information and counselling of the authorities on matters related to endocrine disrupters
 - Knowledge sharing/information activities, such as annual public information meetings and biennial international scientific workshops
 - Initiation and coordination of projects related to filling knowledge gaps on endocrine disrupters

The selection criteria stated in the tender documents, and on which the consortium behind the Centre was originally judged on, are included translated to English in Appendix B.

2. Organisation and implementation of CEHOS

The organisational structure of CEHOS in its current form is illustrated in Figure 1. Since 2010 the institutions that are partners in the Centre are: Rigshospitalet, Dept. of Growth and Reproduction (RH); the National Food Institute at the Technical University of Denmark, Research Group for

¹ Translated from the tender document text for the latest tender (2013/S 220-383310), see also Appendix A. The objectives for the Centre have, however, largely been the same in all three contracts. Tender documents are only available in Danish.

Molecular and Reproductive Toxicology (DTU-FOOD); and the University of Southern Denmark, Department of Biology (SDU).

The number and composition of the partners were purposely chosen to aim for a slim organisation while still having a broad cover of relevant expertise. Thus, the three partner institutions together represent expertise in endocrinology and endocrine related diseases as well as in experimental and environmental reproductive toxicology. Also experiences in mechanistic studies (in vitro and in vivo) of endocrine disruption, development of toxicological test guidelines, risk assessment, human biomonitoring, population studies, and in epidemiology are represented. For more details on the resources and experience the partners bring to the Centre, please see section 2.5 and Appendix C.

2.1. The Management board and Centre secretariat

The Centre Management board consists of the Centre director and 1-2 key senior experts from each of the partner institutions. The Management board is the planning and executive body of the Centre. The annual work programmes for the Centre, including initiation of projects to be carried out under the Centre and strategies for dissemination and knowledge-sharing are planned and executed by the Management board. Currently the board consists of: from RH: Anna-Maria Andersson (director of the Centre), Niels Erik Skakkebæk, and Anders Juul; from DTU-FOOD: Ulla Hass and Anne Marie Vinggaard; and from SDU: Poul Bjerregaard (see also Fig. 1, for CVs please see Appendix C). The Management board meets in person twice pr. year and additional management board meetings are planned ad hoc whenever needed. Upcoming issues have often also been sorted by telephone or email correspondence between the Management board members.

The day-to-day management of the Centre is handled by the Centre secretariat located at Dept. of Growth and Reproduction, Rigshospitalet and headed by the centre director. She is assisted by a part time financial official, a part time secretary and a part time scientific assistant. The secretariat is responsible for the contact with the EPA and the Steering Committee regarding financial, executive, and scientific reporting. It is also responsible for preparing the reports (with input from the partners); for the logistics, planning, and follow-up of meetings of the Management board and the Steering committee; for subcontracts with project leaders; for the contact with partners and project leaders about progress of tasks and projects; communication with the Advisory board; and for maintenance of the website (www.cehos.dk) and other dissemination and communication activities regarding the Centre. For financial reporting and contract preparations, the Centre secretariat communicates directly with the Danish EPA. With respect to preparing subcontracts the Centre secretariat can also draw on the services provided by Rigshospitalet's financial and legal departments.

2.2. Steering committee

A Steering committee is appointed and chaired by the Danish EPA. The director of the Centre is also member of the steering committee. The composition of the Steering committee has changed slightly over the years (see section 2.4), but a consistent feature is that in addition to the Danish EPA also the Danish Veterinary and Food Administration, the Danish Health Authority, and the Danish Working Environment Authority are represented in the Steering committee.

The role of the steering committee is to ensure that the work of the Centre is in line with the stated purpose and objectives and follows the principles for good scientific work. It also serves as an adviser to the Centre. The Centre's annual work programmes, including the selection of

projects to initiate, as planned and presented by the Management board, are approved by the Steering committee. Any major changes or adjustments in activities in relation to the project contracts and approved annual work programmes must be reported to and sanctioned by the Steering committee.

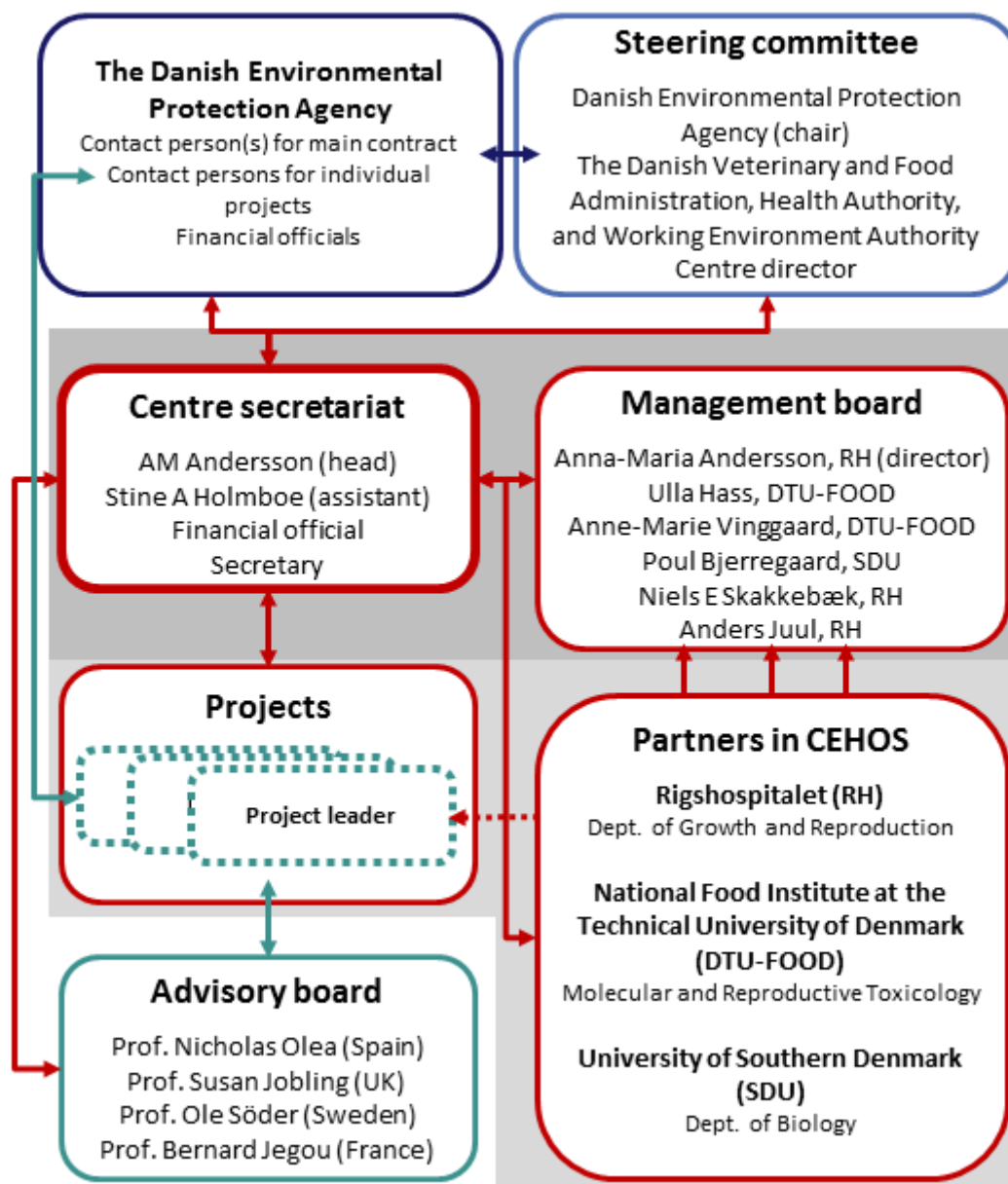


Fig. 1 Organisational structure of Centre on endocrine disrupting substances (CEHOS)

The Centre is a partnership without walls between the three partner institutions in CEHOS. The core of the Centre is the Management board and the secretariat. A Steering committee appointed by the Danish EPA oversees the activities in the Centre. An independent Scientific Advisory board is also affiliated to the Centre. Arrows indicate the main routes of communication and information flow within the Centre. The roles of the different bodies of the Centre are described in more details in section 2.1 -2.3.

2.3. Advisory board

An independent scientific Advisory board is affiliated to the Centre and its members are involved in the planning of the experimental projects within the Centre. Thus, they are engaged to review drafts of protocols of planned projects and comment on the feasibility, scientific soundness, and scientific relevance of the planned project, as well as to give advice and suggestions. They are also updated on the progression of the projects. Comments from the scientific Advisory Board members on planned projects are presented together with the projects to the Steering Committee. Members of the Advisory board have also over the years been invited as members of the scientific programme committee for the Copenhagen Workshops on Endocrine Disrupters.

The composition of the Advisory board was suggested by the Management board and approved by the Steering committee. Members were selected based on their own scientific qualifications and experiences, which were deemed relevant for projects within the Centre. Thus, they were selected to cover different aspects of the field of endocrine disruption including human and animal effects as well as experimental and environmental toxicology of endocrine disrupting chemicals. In addition, they were selected on the basis that they did not have any close collaborations or ties with any of the partners of the Consortium. The members of the Advisory board as listed in Figure 1, have until now been the same since the start of the Centre.

2.4. Changes in the organization and implementation of the Centre between the different periods

While the overall scope of the Centre and the setup of the Centre have been largely the same over all three periods, some changes were introduced with every new call for tenders and subsequent contract. In the following the differences between the three contract periods are briefly listed.

2.4.1. Contract for the 2008-2009 period

The first call for tenders was a call for: “Establishment and management of the Centre for Endocrine Disrupters and a number of projects to be coordinated by the Centre. The centre management and one or more projects can be offered independently of each other”. This meant that the consortium that won the tender for the management of the Centre had no influence on the projects to be coordinated as the approved tenders for projects under the Centre were selected by the order giver i.e. the Danish EPA.

The consortium that won the establishment and management of the Centre in this first call was slightly larger than in the following calls. In addition to the three current partners, two other partners were included: Dept. of Environmental Medicine at University of Southern Denmark and Institute of Pharmacology and Analytical Chemistry at University of Copenhagen.

The first Steering Committee included five members from the academia (of which two were also part of the Management board), in addition to representatives from the agencies.

2.4.2. Contract for the 2010-2013 period

For the second call the call text had rephrased to: “Management of a Centre for Endocrine Disrupting chemicals....The tasks include both the running of the Centre, including scientific advice, dissemination and knowledge sharing, as well as commissioning and coordination of projects”, meaning that projects were planned and initiated under the contract and mainly on the initiative of the Management board. In the contract the allocation of resources between “running of the Centre” and “projects” were specified (see also section 5)

Under this contract the current consortium of three partners were established. From this contract and onwards the Steering committee consisted only of representatives from the agencies and the Centre director. However, the agencies' representatives have the option to bring scientific experts within their field to the Steering committee meetings.

2.4.3. Contract for the 2014-2017 period

The only minor change, which was introduced in the contract for 2014-2017, was that for the resources allocated to projects within the Centre a sum of 450.000 DKK (60.000 €) per year was earmarked for projects suggested/initiated by the EPA.

2.5. Expertise, resources, and facilities in CEHOS

The Centre draws on the academic and scientific expertise available within the research groups of the three partner institutions. The three groups have been carrying out pioneering research on endocrine effects for many years. As mentioned our respective expertise complement each other well so in combination we cover most aspects of endocrine disruption. All partners are also active in international networks of endocrine disruption and have a good overview of the research field at both the national and international level. Most of the assignments and tasks of the Centre have thus been possible to carry out within the consortium. However when deemed appropriate or needed, additional expertise or resources have been involved or commissioned. In the management of the Centre, the opportunity to make use of the skilled personnel at Dept. of Growth and Reproduction has played a key role.

Information on the members of the Management board and other academic key persons in the consortium is presented in Appendix C as short CVs and publication lists. Below is given a short introduction to the three partners in the consortium and a description of the resources and facilities they bring to the Centre.

2.5.1. Dept. of Growth and Reproduction, Rigshospitalet (RH)

The research group at Dept. of Growth and Reproduction has an interdisciplinary profile that combines clinical and basic research in andrology and paediatric endocrinology. The department has extensive expertise in the regulation of endogenous sex hormones and their function in controlling normal development and reproduction as well as the clinical effects that may occur when the hormone balance is disturbed.

The research group has accumulated extensive experience in planning and conducting major cross-sectional and longitudinal population studies over the last 25 years. These comprise studies of male reproduction including sperm quality, the incidence of congenital malformations in the male genital organs, and trends in pubertal development of Danish children. The association between environmental factors and sexual development, reproduction and body composition has been an important research focus area of the department over these years. Researchers from the department are internationally recognized as having contributed significantly to raise the awareness of endocrine disrupting effects in the human population. In addition, the department has contributed significantly to the biomonitoring of substances with endocrine disrupting effects in the Danish population over the last 10-15 years. It is also noteworthy that members of the department's team have played a role as consultants for the EU system in its twist with the US government in WTO about use of anabolic steroids in beef production.

The department has well-equipped laboratory facilities with skilled technical personnel for histology (including sperm laboratory), molecular biology, biochemistry (hormone measurements)

and analytical chemistry (biomonitoring). All laboratories of the department are accredited according to the "ISO 15189:2013 Medical laboratories: Requirements for quality and competence" standard. The research group consists of Clinical Director Anders Juul, five research leaders: Anna-Maria Andersson, Ewa Rajpert-De Meyts, Katharina M Main, Niels Jørgensen and Niels E. Skakkebak, and senior researchers: Kristian Almstrup, Hanne Frederiksen, Martin Blomberg Jensen, and Anne Jørgensen as well as affiliated PhD students and fellows. Part time affiliated is also epidemiologist Tina Kold Jensen.

The research group has participated in and coordinated international and national research projects on hormone disrupting substances for several years. In 2014 the International research and research training Centre on Endocrine Disruption of Male Reproduction and Child health (EDMaRC.net) was established at the department. The department has organized several international workshops on endocrine related diseases and endocrine disruption; including the series of "Copenhagen Workshops on Endocrine Disruption", of which the 9th workshop will be held in May 2017 as an activity under CEHOS.

Persons at Dept. of Growth and Reproduction, who have contributed actively to the solution of the scientific tasks of the Centre include centre director Anna-Maria Andersson; members of the Management board: Niels E. Skakkebak and Anders Juul; Pls of project under CEHOS: Katharina M. Main, Hanne Frederiksen, and Tina Kold Jensen. In addition, a number of Ph.D-students have also over the years been assigned to projects carried out under CEHOS. For technical laboratory as well as administrative assistance the skilled staff of the department has been enrolled in projects and tasks as needed. Finally, from 2008-2016 postdoc Katrine Bay served as part time assistant to the Centre director. Since 2016 postdoc Stine Holmboe has filled this role.

2.5.2. Research Group for Molecular and Reproductive Toxicology, the National Food Institute at the Technical University of Denmark (DTU-FOOD)

The research group for Molecular and Reproductive Toxicology at DTU-FOOD has an interdisciplinary profile that combines experimental research projects on the mechanisms and effects of hormone-disrupting substances on foetal development and reproduction with research-based advisory services to regulatory authorities such as the Danish Environmental Protection Agency and the Danish Veterinary and Food Administration.

The group has extensive expertise on effects of endocrine disrupting chemicals on the normal development and reproduction of experimental animals, as well as the many different types of effects that may occur when the natural hormone balance is disturbed. The research team has more than 25 years of experience with experimental studies of hormone disrupting effects in vitro and in experimental animals and has accumulated extensive experience in planning and carrying out large studies of mixture effects of endocrine disrupting substances in experimental animals within the last 15 years. The group has previously demonstrated mixture effects of anti-androgens at dose levels where the individual substances do not have effects. In recent years, mixture effects of environmentally relevant endocrine disrupters have been demonstrated in experimental animals. The department has experienced personnel and well-equipped animal and laboratory facilities for the dosing of experimental animals, registration of developmental parameters and behaviour in experimental animals, histopathology, molecular biology, hormone measurements and in vitro assays. The research group consists of two professors: Ulla Hass and Anne-Marie Vinggaard, four senior researchers: Julie Boberg, Marta Axelstad, Camilla Taxvig and Sofie Christiansen as well as a number of post docs, researchers and PhD students.

The research group has participated in a large number of national and international research projects on endocrine disrupting substances for many years and is currently involved in research projects focusing on, among other things, effects of substances that affect thyroid hormones, developmental effects on females, effects on development of mammary glands and mixture effects of estrogens and anti-androgens. The research group has organized international conferences and workshops on mixture effects of endocrine disrupting substances and regulatory aspects. In addition, the research team participates in the development of regulatory guidelines for endocrine disrupting activity and effects in the OECD, as well as discussions of hazard identification, risk assessment and testing strategy in the EU chemicals policy REACH. Overall, the research group has the necessary skills to contribute significantly to the solution of the tasks in the project applied.

Persons, who have contributed actively to the solution of the scientific tasks of the Centre include Ulla Hass (member of the centre management), Anne-Marie Vinggaard (member of the centre management), Sofie Christiansen, Marta Axelstad, Julie Boberg and Camilla Taxvig as well as young researchers within research group for Molecular and Reproductive Toxicology. The department's laboratory and animal assistants have also contributed significantly.

2.5.3. Department of Biology, University of Southern Denmark (SDU)

Since the early 1990's the Ecotoxicology group at the Department of Biology, (SDU) has contributed to the understanding and interpretation of the effects of endocrine disrupting substances in the aquatic environment with main focus on fish, molluscs, and amphibians.

The laboratories include both freshwater and marine exposure facilities and the group members are highly experienced in planning and conducting both field investigations and short and long-term aquatic chemical exposures in the laboratory. The laboratory has well equipped facilities for chemical analyses (GC-MS and LC-MS/MS), histology, immunohistochemistry, and immunoassays, and the research group has extensive experience in chemical analyses and the development and validation of endocrine endpoints and biomarkers; the developed immunoassays for yolk proteins (endocrine biomarker) and histopathological techniques have been incorporated in OECD test guidelines. The research group has been lead or main participant in the coordination of international cross-disciplinary exposure studies such as validation and development of OECD test guidelines for endocrine disrupters in fish and molluscs (OECD TG 234, 242 and 243). Currently, the group is involved in research projects concerning biomarkers for thyroid disruption in fish, effects of liver toxicants on yolk protein levels in fish, and the development and validation of endocrine biomarkers in molluscs.

For several years the group has been an active part in the discussions on hazard and risk assessment of endocrine disrupters, criteria settings, and testing strategies for identification of endocrine disrupters in the environment (at national as well as EU and OECD level). The group members participate actively in several international activities related to endocrine disrupters (e.g. UNEP, OECD, ECHA and SETAC) and are engaged in public outreach and the national public debate about endocrine disrupters (e.g. Folkeuniversitetet, Forskningens Døgn (National Science Days) and Folkemødet).

The research group is led by Professor Poul Bjerregaard (member of the CEHOS management board) and the group members conducting the scientific tasks in the Centre are: associate professor Knud L. Pedersen, associate professor Henrik Holbech, PhD Karin L. Kinnberg, and assistant professor Jane E. Morthorst. The laboratory technicians Bente Holbech and Annette Duus

also contribute significantly to the experimental and laboratory work such as chemical analyses.

2.6. Strengths and weaknesses of the current Centre organisation and implementation

Strengths: It is a major strength of the Centre that all partners are university researchers, independent of EPA, who can deliver objective and unbiased and solid information to the stakeholders, including EPA, the parliamentary system and the general population through media. The partners all have a long-standing experience in research on endocrine disruption and endocrine disrupting chemicals (EDCs) and due to their international recognition and contacts within Europe and abroad, they can be - and have been - instrumental in canalizing new international research developments to the attention of EPA and other Danish regulatory bodies. The Centre thus represents a direct link between research and risk assessment and policy. In that respect we also think it is important that the Centre director as well as the Management board is only part time occupied in the Centre and - most importantly - also are active researchers. Furthermore, we believe that the fact that the Centre consists of strong, active, and independent research groups has been key to the successful completion of a large number of projects for a relatively moderate budget. Almost all of the knowledge-generating projects carried out in the Centre have built on data, samples, or methods that were made available for the Centre from on-going larger research projects, not funded by EPA (see also section 3).

Weaknesses: While the relatively small size of the Centre, and its limited budget, has been sufficient to fulfil the objectives of the Centre hitherto, we see some obstacles for the future. The current Centre has been able to exploit already gathered research data within the three partners of the Centre. A sign of weakness, which is already evident for the partners, is that both national and international extramural funding for EDC research has decreased significantly over recent years in spite of the fact that large areas of endocrine disruption is largely unexplored. We are therefore concerned that a new Centre may suffer from this lack of basic research funding.

Paradoxically the existence of the Centre itself may have contributed to some misconception about national resources allocated for research in EDCs. Both in the political landscape and in the research community CEHOS is often mistakenly assumed to be a research centre and the funding of the Centre accordingly mistaken as national funding for EDC research. A possible explanation for this misconception may be the aforementioned fact that all three partners previously have been able to attract short term research funding from national and international bodies, including EU. However, these funding sources have subsequently to a large degree dried out. The success of a continuation of the Centre may depend on the concurrent availability of future research grants within the field of EDCs.

3. Knowledge-building activities of CEHOS

Knowledge-building activities are the essence of the work carried out in CEHOS. Since 2010 80% of the total budget for the Centre has been assigned to knowledge-building activities, corresponding to ~500,000€/year. In addition, the Danish EPA has on several occasions made use of the contractual option² to commission additional projects to be implemented and administered under CEHOS. Thus, more than 40 individual projects have been conducted in CEHOS since December 2008. Of these seven projects are still ongoing. A full list of project under CEHOS from 2008-2017 is given in Appendix D.

In general, projects within the Centre's remuneration are suggested by the Management board as part of the preparation of the annual work programme. For each of these projects the Management board appoints a principal investigator, who then prepares the detailed project protocol. If the resulting project protocol is deemed appropriate by the Management and Advisory board the project is presented for Steering committee for approval. Once approved a project contract is signed and each project have a contact person from the Danish EPA associated, who will follow the project. Progress of the project is reported biannually to the contact person, the Centre secretariat (for the report to the Steering committee), and the advisory group. In the 2014-2017 contract 60,000€/year of the budget for knowledge-building activities were reserved for projects suggested by the EPA rather than the Management board. This annual sum was set aside to make it possible to address emerging or upcoming issues that may not have been foreseen at the start of the contract period. These projects suggested by the EPA may therefore not follow the normal approval process of projects as part of the annual work programme of the Centre. Rather these projects can be initiated on short notice at any time during the year. Thus the procedure of projects suggested by the EPA within the Centre's remuneration is similar to the procedure for additional commissioned projects (see below).

For additional projects commissioned by EPA it is the EPA that suggests each project. Some of these projects aim at providing information in relation to EU matters concerning EDCs. The Management board, in dialog with the EPA, appoints a principal investigator to the project, which then prepares the project protocol; usually in close dialog with the EPA contact person(s). Once the project protocol and budget is approved by the EPA a contract is signed. These additional projects are thus not necessarily approved by the Steering committee. Due to an often short time frame this kind of projects are most often not discussed with the Advisory board.

3.1. Examples of projects in CEHOS

Projects conducted in CEHOS include both experimental studies aiming at closing knowledge-gaps as well as more 'conceptual' or 'translational' projects on how to interpret or use research data for policymaking. Examples of the latter are projects # 15, 21-23, 25-26, 35, 37, and 39-41 in the list in Appendix D. The reports of these projects have often been used directly in the policymaking work of the EPA at national as well as EU level. An example is shown in the Danish proposal for

² Translated from the contract: "...The contracting entity (*e.g. EPA*) has the option to purchase additional deliverables in the form of administration and implementation of additional projects, in addition to those initiated annually by the Centre under the fixed remuneration. The option can be used for the purchase of extra deliverables for up to 5,000,000 DKK per year on average. Such additional deliverables can, as the projects initiated during the Centre's annual work program, investigate issues related to endocrine disrupting substances, whose effects on humans and the environment are not completely elucidated. The deliverables can also be scientific contributions to the regulatory processes in the EU, including, for example, criteria development".

criteria for endocrine disrupters, which can be seen on the homepage of the Danish EPA (<http://eng.mst.dk/topics/chemicals/endocrine-disruptors/danish-proposal-for-criteria-for-endocrine-disruptors/>).

The knowledge-generating experimental projects have often been performed as minor additions or spin-offs of on-going or already conducted research projects. One example is the biomonitoring studies (e.g. project #16-18) conducted in order to elucidate the exposure levels in the general Danish population for different known or suspected EDCs: Having free access to already recent collected samples from ~4000 healthy children, adolescence, young men and pregnant women to use for biomonitoring, made it possible to provide information on population level exposure to a range of EDCs within a relatively short time frame and very cost effectively [1]. Another example is in project #24, where the Centre was able to provide new information on late effects of developmental exposures for a relatively moderate cost by adding a small protocol to an already planned – and funded - developmental exposure study in rats [2]. When needed or good opportunities were available projects have been commissioned to expertise outside the research groups of the partners in CEHOS (see e.g. project #12-13). In project 12 and 17 we thus collaborated with the PIs of ongoing mother-child cohorts as an opportunity to gather new knowledge on links between prenatal exposures and health outcomes [3–6].

Many of the projects in the Centre have been conducted with active participation of all three partners, while in some projects only one or two of the partners have been involved. A good example of how the partners (and the projects) in the Centre interact and complement each other is illustrated by the Centre's knowledge-generating activities regarding the chemical UV-filter benzophenone-3 (BP-3). The research group at Dept. of Growth and Reproduction were already around 2009-10 interested in chemical UV-filters as potential EDCs and thus had started measuring benzophenone-1 and -3 in human samples. The methodology developed for this was exploited in e.g. projects #8, 14, 18, and gave information on the levels of human exposures to BP-3. UV-filters were also included in the panel of compounds that were tested for direct effects on human sperm (project #19) and several of the compounds that had an effect were chemical UV-filters including BP-3 [7]. In 2012 the Centre was asked by the EPA to assess 22 substances, which were on the NGO ChemSec's SIN 2.0³ list, against the Danish proposal for criteria for endocrine disrupters (project #22). BP-3 was among the 22 substances that had been added to the SIN list solely due to their endocrine disrupting properties. Our report concluded that according to the Danish criteria BP-3 was a suspected endocrine disrupter (cat. 2a), but it was also recognised that *in vivo* data with endocrine disrupting endpoints was scarce for BP-3. Subsequently, a test of BP-3 in the Fish Sexual Development Test (OECD test guideline nr. 234) was conducted in the Centre to fill this knowledge gap (project #29b). The test concluded that BP-3 caused a monotone dose-dependent skewing of the phenotypic sex ratio toward fewer males and more female zebrafish, confirming that BP-3 is an endocrine disrupter [8].

³ SIN= "Substitute it now"

4. Knowledge-sharing and dissemination activities of CEHOS

4.1 Contacts to the Danish EPA and other national regulatory agencies

Communication and information-sharing between the Centre and the Danish EPA occur regularly at several levels. At the biannual Steering committee meetings the Centre Director informs about the progress of the on-going activities in the Centre and also brings forward suggestions from the Management board on new activities. Qua the composition of the Steering committee this forum also facilitates bilateral communication between the Centre (and affiliated researchers) and the policymaking agencies about new developments, issues and identified needs for policymaking within the field of endocrine disruption. The Centre Director and Management group are also in direct contact with key persons at EPA in the process of planning and implement new projects commissioned by the EPA.

Every project initiated under the Centre has assigned a contact person at the Danish EPA. Depending on the nature of the project, the involvement of and communication with the EPA contact person may differ from project to project but communication with this contact person occurs at least biannually in connection with the biannual progress report. All projects conducted under the Centre are reported to the EPA upon completion. The form of the report may depend on the project and may be confidential between the Centre and the EPA until results are published scientifically. These reports provide the EPA with the new data significantly faster than the data can be made available to the scientific community through peer-reviewed publishing.

Direct communication between EPA officials and CEHOS researchers also occur ad hoc e.g. as request for a scientific evaluation, comment or opinion on a new study or new data. Finally, researchers of all three partners in the Centre are also members of the EPA's "Hormone network", which is an informal network of independent researchers and EPA risk assessors and officials that work within the area of endocrine disrupters.

4.1.1. Reports on new scientific literature on endocrine disruption

The Centre quarterly provides reports on new scientific literature within the field of endocrine disruption to the EPA. These reports are also posted on the Centre website (www.cend.dk/kort-om-ny-forskning.html) and are based on literature searches performed in the Centre. Together with the list the EPA also receives highlights and comments on selected new papers on the list; typically for 5-7 of the papers per report.

The Centre also have an agreement with the EPA on informing EPA officials on relevant publications in the pipeline; this includes papers that are to be published based on projects conducted in the Centre, in the research groups of the Centre, or in collaboration with other research groups.

4.2. Public information meetings

Another obligatory recurring deliverable of the Centre is an annual public meeting on endocrine disruption and endocrine disrupting substances. This is a one-day meeting targeted layman and aimed to inform the public about new knowledge on endocrine disrupting substances; what is endocrine disrupting; concepts within the field of endocrine disrupting substances etc. There are also time for questions and comments from the participants.

These meetings have been held annually since 2009 and usually have around 90-120 participants covering a broad spectrum of stakeholders such as NGO representatives, other

researchers, agency officials, students, trade association representatives etc. It is free to participate and we announce the meetings broadly. Since 2014 we have also posted presentations from these meetings at our website. In 2016 we had all presentations filmed and the videos are also posted on our website (www.cend.dk/presentationer.html). It is our impression that this material is often used by students as well as journalists.

4.3. Scientific publishing

The time frames and budgets of projects under the Centre in general have not covered or allowed for the time and resources needed to bring new data or knowledge to scientific publishing. Nevertheless, we have always strived to not only report new knowledge to the EPA but whenever possible or relevant to also publish data scientifically. Scientific publishing is not only important for the researchers in the Centre, but also benefits the agencies using the generated data in policymaking, as policymaking is more transparent when it is possible to refer to peer-reviewed scientific data. In addition, publishing data in indexed journals makes it accessible to a broader group of stakeholders thereby facilitating knowledge-sharing. Thus, the resources needed for preparing the data/results for scientific publishing – including person hours for in-depth digestion and evaluation of data, publishing costs, editing etc. is usually provided by the partners themselves. A list of the scientific peer-reviewed papers based on projects carried out in the Centre is included in Appendix E.

4.4. International scientific meetings

Copenhagen Workshops on Endocrine Disruption are a series of international scientific workshops that have been held at Rigshospitalet biennially since 2000. They are organised by Dept. of Growth and Reproduction and since 2009 the workshops have been deliverables from the Centre with the Management board and Advisory board being part of the Scientific programme committees and the Centre secretary being involved in the local organising committee of the workshops. The funding for the workshops is largely covered within the Centre remuneration and thus the Centre has been instrumental in securing the continuation of these workshops that attracts researchers from all over the world. This is significant as we believe that independence of commercial interests has been particularly important for the role and reputation that the Copenhagen Workshops on Endocrine Disruptors have gained worldwide. The next Copenhagen Workshop on Endocrine Disruptors (COW) is held May 2-5, 2017. The programme for the meeting can be seen at www.reproduction.dk/cow2017 and more than 150 participants are currently registered. Thus the 2017 meeting will have a similar size as previous meetings.

5. Economy of the Centre

Remuneration of the Centre for the three periods stratified by cost for running the Centre and for projects under the Centre is shown in Table 1. Indicated is also the total amount remunerated for commissioned additional projects pr. period. The amounts allocated to individual projects are indicated in Appendix D under each project.

Average person months per year allocated to the Centre secretariat are shown in Table 2. There have been slightly changes over the years in relation to changes in the needs, e.g. more person months were allocated to the Centre director and assistant in the first period due to the work related to implement the Centre structure.

Table 1: Remuneration of the Centre for Endocrine Disrupting Substances over the three periods. Amounts are given in € rounded to nearest 1,000

Period	Running cost of Centre and fixed deliverables*	Projects within the Centre	Total Remuneration		Ad hoc commissioned projects
Dec 1, 2008 - Dec 31, 2009	93.000	624.000	717.000		-
Jan 2010 - Dec 2013	533.000	1.867.000	2.400.000		2.674.000
Jan 2014 - Dec 2017	533.000	1.867.000	2.400.000		203.000
Total	1.159.000	4.358.000	5.517.000		2.877.000

* Covers all activities of the Centre secretariat and Management group including person months and expenses related to the recurrent obligatory deliverables (reports on new literature, website, annual public meetings, biennial international workshops)

Table 2: Approximate average person months per year* allocated to the Centre secretariat stratified by period and profession groups

Period	Centre Director	Assistant	Financial officer	Secretary
Dec 1, 2008 - Dec 31, 2009	7	8.5	-	-
Jan 2010 - Dec 2013	0.5	4.5	2.5	1.5
Jan 2014 - Dec 2017	3.5	3.5	1	0.5

*Excluded person months related to planning and executing annual public information meetings and biennial international workshops

Reference List

1. Frederiksen H, Jensen TK, Jørgensen N, Boye KH, Husby S, Skakkebæk NE, Main KM, Juul A, Andersson AM (2014) Human urinary excretion of non-persistent environmental chemicals: an overview of Danish data collected 2006-2012. *Reproduction* 147: 555-565.
2. Isling LK, Boberg J, Jacobsen PR, Mandrup KR, Axelstad M, Christiansen S, Vinggaard AM, Taxvig C, Kortenkamp A, Hass U (2014) Late-life effects on rat reproductive system after developmental exposure to mixtures of endocrine disrupters. *Reproduction* 147: 465-476. REP-13-0448 [pii];10.1530/REP-13-0448 [doi].
3. Wohlfahrt-Veje C, Andersen HR, Jensen TK, Grandjean P, Skakkebæk NE, Main KM (2012) Smaller genitals at school age in boys whose mothers were exposed to non-persistent pesticides in early pregnancy. *Int J Androl* 35: 265-272.
4. Wohlfahrt-Veje C, Main KM, Schmidt IM, Boas M, Jensen TK, Grandjean P, Skakkebæk NE, Andersen HR (2011) Lower birth weight and increased body fat at school age in children prenatally exposed to modern pesticides: a prospective study. *Environ Health* 10: 79.
5. Wohlfahrt-Veje C, Andersen HR, Schmidt IM, Aksglæde L, Sørensen K, Juul A, Jensen TK, Grandjean P, Skakkebæk NE, Main KM (2012) Early breast development in girls after prenatal exposure to non-persistent pesticides. *Int J Androl* 35: 273-282.
6. Tefre dR-M, Frederiksen H, Christensen J, Boye KH, Andersson AM, Husby S, Barington T, Main KM, Jensen TK (2014) Current exposure of 200 pregnant Danish women to phthalates, parabens and phenols. *Reproduction* 443-453.
7. Schiffer C, Muller A, Egeberg DL, Alvarez L, Brenker C, Rehfeld A, Frederiksen H, Waschle B, Kaupp UB, Balbach M, Wachten D, Skakkebæk NE, Almstrup K, Strunker T (2014) Direct action of endocrine disrupting chemicals on human sperm. *EMBO Rep* 15(7): 758-765. embr.201438869 [pii];10.15252/embr.201438869 [doi].
8. Kinnberg KL, Petersen GI, Albrechtsen M, Minghlani M, Awad SM, Holbech BF, Green JW, Bjerregaard P, Holbech H (2015) Endocrine-disrupting effect of the ultraviolet filter benzophenone-3 in zebrafish, *Danio rerio*. *Environ Toxicol Chem* 34: 2833-2840. 10.1002/etc.3129 [doi].

Appendix A: Specified requirements of Centre on endocrine disrupting substances 2014-2017

(google-translated to English from the Requirements Specifications stated in the tender for Centre on endocrine disrupting substances 2014-2017, the full document in Danish can be provided on request)

Purpose

The overall purpose of continuing a Centre for Endocrine disrupting substances is to continue the targeted knowledge building on endocrine disrupting substances to support the preventive work of the authorities, including regulation. The centre will continue the work that was initiated during the Centre for Endocrine Disrupting Substances in 2008-2013 in relation to creating and nurturing a cross-disciplinary professional network. During its annual work program, the Centre will initiate and coordinate new studies on endocrine disrupting substances. In addition, the Centre will initiate and coordinate projects that are initiated on an ongoing basis with agreement with the contracting entity.

The Centre presents proposals for the annual work program and carries out projects for the following purposes:

- Investigate relationships between the occurrence of hormone disruptors and effects / combination effects in the environment, including source detection.
- Investigate relationships between exposure to endocrine disrupting agents and the occurrence of effects / combination effects in the population, including important sources of exposure.
- Identify new hormone disruptors, investigate drug grouping options, uncover adverse outcome pathways (AOPs) and illuminate effects of endocrine disrupting substances isolated and in interaction with other factors, including, for example
 - relationships with diabetes, obesity, cardiovascular disease and influence on brain development
 - effects on the female reproductive system, effects late in life as well as on postpartum exposure lead to increased sensitivity later in life
 - combination effects
- Examine the relevance of current principles for risk assessment in assessing the risk of exposure to endocrine disrupting substances, including the following factors: The occurrence of low dose effects, which are currently considered safe, of non-monotonous dose response curves for endocrine disrupting agents and of combination effects - and pointing to appropriate adjustments to the principles.

At the same time, the Centre aims to ensure that new knowledge is disseminated both to scientific circles and to the public.

In addition, the Centre aims to provide advice to the authorities about endocrine disrupting substances based on the latest knowledge in the field.

Centre structure

The centre must consist of a centre leader, possibly a secretary and a centre management whose size is defined by the bidder. The professional composition of the centre management should reflect the Centre's professional areas of action.

The centre must be continued as a centre without walls, ie. a network of relevant institutions in the health and environmental field. The centre must possess highly qualified knowledge of endocrine disrupting substances for the guidance of the authorities, both in health and environmental matters. The centre must have a centre leader, supported by a centre management. The Centre shall also act as a scientific advisor to the authorities

represented by the contracting entity, and the Centre Manager acts as the contractor's contact person at the Centre.

The Centre Leader shall act as coordinator of the Centre's work and have a natural or health science background as well as relevant experience from work on the topic of endocrine disrupting substances and from the coordination of projects. The Centre Leader must be affiliated with a unit that can support the Centre Leader's work both with relevant knowledge and experience and with relevant scientific contacts at national and international level.

The Centre will be responsible for the possible procurement, commissioning, contract writing, coordination and financial coordination of projects approved by the Steering Committee, as well as the projects that are initiated on an ongoing basis by agreement with the contracting entity.

The Centre prepares the agenda, convening and organizing at least 2 steering group meetings a year. The Centre is responsible for preparing minutes for meetings, which must be approved by the steering committee.

The Centre delivers a progress report of the Centre's activities and results to the Steering Committee, which approves each six months. In addition, the results of the Centre's activities shall, as far as possible, be published in scientific journals. At the end of the contract, the Centre will deliver a final report describing the total activities in the centre of the steering committee.

Steering Group

A steering group for the centre is set up, as the centre leader refers to. The steering committee is appointed by the contracting entity, who is also the chairman of the group.

The steering committee will ensure that the Centre's work follows the Centre's purpose and the agreed work program, and serves as an adviser to the Centre. In addition, the steering committee must ensure that the work follows current principles for scientific work.

The steering committee approves the academic framework for the Centre's work annually, the Centre's work program and final selection of projects under the Centre's annual work program, following presentation by the Centre Management. The work program must include interim targets for the activities of the coming year, including projects for initiation, and any proposals for changes in activities in relation to the contracts entered into must be reported.

Deliverables

The tasks include management of the Centre for Endocrine Disrupting Substances, including scientific advice and knowledge sharing, as well as commissioning and coordination of projects.

The Centre investigates issues related to endocrine disrupting substances whose effects on humans and the environment are not fully clarified cf. the Purpose section. This requires interdisciplinary cooperation between several environmental and health care units. The centre manager / management ensures through close interdisciplinary cooperation with relevant collaborators at home and abroad that the authorities can be consulted broadly in relation to the problem of endocrine disrupting substances both in relation to humans and the environment.

The efforts in the centre are thus coordinated with existing initiatives in the field, and the projects take place in conjunction with national and international knowledge building in this area.

Attention is drawn to the fact that the supply includes the running of the centre while the annual work programs for the centre are prepared after the contract has been concluded.

Deliverables under the fixed annual remuneration are detailed below:

A) Management of a centre without walls, consisting of a network of relevant institutions in the health and environmental area.

B) Implementation of an annual work program within an economic framework defined by the contracting entity and a professional framework defined by the steering committee. The work program contains the following tasks:

- 1) Scientific advice and knowledge sharing (approximately 15% of the Centre's total workload)
 - 1.1) Coordination with the steering committee.
 - 1.2) Scientific advice to the authorities.
 - 1.3) Knowledge sharing / information activities.
- 2) Initiation and coordination of projects (approximately 75% of the Centre's total workload)

Ad 1.1) Coordination with the steering committee contains the following elements:

- Annual preparation of presentation to the academic framework for the Centre's work and proposals for work program.
- Preparation of semi-annual status reports and a final report at the end of the contract.
- Holding and reporting of at least 2 steering group meetings per year.

Ad 1.2) Scientific advice to the authorities contains the following elements:

- Scientific advice (ad hoc) to the Danish authorities represented by the contracting entity on the effects of hormone-disrupting substances on humans and the environment. It is expected that the Centre will provide ad hoc advice to the authorities - in the order of approx. 100 hours a year.
- Information to the authorities regarding relevant new national and international knowledge in the field.

Once a quarter of the quarter, but also ad hoc, when important new studies are published, the authorities will receive an update from the Centre on new knowledge in the field.

Ad 1.3) Knowledge sharing / information activities include:

- At least one international scientific research workshop every two years.
- Annual organization of public dissemination meeting, where project results and latest knowledge are presented, and where stakeholders have the opportunity to make proposals for the Centre's work program.
- Management and maintenance of the website.

Ad 2)

Initiation and coordination of projects contain the following elements:

- Presenting suggestions of new project for the steering committee.
- Provision and commissioning of projects approved by the Steering Committee, including contract writing.
- Coordination of projects' activities, including financial management and ensuring agreed reporting.

C) A system must be established to ensure relevance, academic ambition and quality of projects under the work program.

D) Administration and coordination of projects initiated on an ongoing basis by agreement with the contracting entity (approximately 10% of the Centre's total workload)

E) As part of the service, a quality assurance system will be established in relation to the Centre, which ensures the professional quality of the individual projects' implementation and reporting.

In addition to deliverables under the fixed annual fee, the contracting entity has the option to purchase additional deliverables in the form of administration and implementation of additional projects than those undertaken annually by the Centre under the fixed remuneration. The option can be used to purchase additional deliverables for up to 5 million. DKK per. year on average. Such additional supplies, like projects initiated in the Centre's work program, can investigate issues related to endocrine disrupting substances whose effects on humans and the environment are not completely clear, cf. the Purpose section. Deliverables can also be scientific contributions to regulatory processes in the EU, including, for example, criteria development.

Appendix B: Selection criteria for selection of tenderers

(translated to English from the tender document)

“The applications will be judged on the following criteria:

Quality of service offered (50%)

- The tenderer's account of how the bidder will solve the task and organize it. This will be assessed on the basis of the extent to which the bidder's solution proposal will adequately fulfill all conditions in the entire tender document, including the deliverables set out in Appendix 1 (requirement specification). This will be assessed from the tenderer's completed Appendix 5 (Solution Description) and Annex 6 (Time and Resource Plan).
- If the offer is considered to contain an organization that will ensure the necessary coordination between employees associated with the task, any subcontractors or any participants in a consortium, avoiding duplication and ensuring that the delivery complies with the description in the entire tender document. This will be assessed on the basis of the tenderer's completed Annex 5 (solution description).
- Whether the method (s) offered (s) are suitable to ensure that the required expertise is involved in the different areas covered by the task. This will be assessed on the basis of the tenderer's completed Annex 5 (solution description), the tenderer's completed Annex 6 (time and resource plan) and the tenderer's completed Annex 7 (fixed remuneration and hourly rates as well as team and subcontractor (s) stated with name and qualifications).
- Bidder's project-specific quality assurance with a view to ensuring timely and correct performance of the contract. This will be assessed on the basis of the tenderer's completed Annex 5 (solution description)

Qualifications of the team offered (40%)

The criterion will be assessed on the basis of the qualifications of the centre management offered, including relevant experience in solving the task of the overall team at the tenderer and any subcontractors. Special attention will be paid to the qualifications of the centre manager offered by the tenderer.

The assessment will be based on information in the tenderer's completed Appendix 7 (fixed remuneration and hourly rates as well as team and subcontractor (s) stated with name and qualifications).

Price (10%)

The criterion will be judged on the basis of the prices offered by the bidder for the management of additional deliverables as well as hourly prices by category of employees, see Annex 7 (fixed salary and hourly rates as well as team and subcontractor (s) indicated by name and qualifications). If the tenderer specifies more than one hourly rate per Employee category (eg for the supplier as well as for a subcontractor or for different consortium participants), the contractor will make an average calculation for the assessment.

Appendix C: CVs and publication lists of key personnel in CEHOS

Please note that Appendix C was provided as a separate document for the Review committee but is not included in this report due to its length (158 pages). This document can be provided on request.

CV and publication lists are included for:

Dept. of Growth and Reproduction, Rigshospitalet (page 2-110)

Anna-Maria Andersson
Anders Juul
Niels Erik Skakkebæk
Katharina Main
Hanne Frederiksen
Tina K. Jensen

Research Group for Molecular and Reproductive Toxicology, the National Food Institute at the Technical University of Denmark (page 111-137)

Ulla Hass
Anne Marie Vinggaard
Sofie Christiansen
Marta Axelstad
Julie Boberg
Camilla Taxvig

Dept. of Biology, University of Southern Denmark (page 138-158)

Poul Bjerregaard
Knud L. Pedersen
Henrik Holbech
Karin Kinnberg
Jane E Morthorst

Appendix D: Projects initiated and coordinated within CEHOS

Projects coordinated in the Centre in 2008-2009 (2008-2009 project were selected through tender – reports and descriptions only available in Danish)	
1	Eksponering af fostre, børn og voksne til hormonforstyrrende stoffer: mulig betydning for udvikling af kryptorkisme, hypospadi, fedme, dårlig sædkvalitet, nedsat fertilitet og andre hormonsygdomme <i>Exposure of fetuses, children and adults to endocrine disrupters: possible role in development of cryptorchidism hypospadias, obesity, poor sperm quality, impaired fertility and other endocrine disease)</i> PI: Anders Juul, Dept. of Growth and Reproduction, Rigshospitalet Funding: 160,000€
2	Undersøgelser af hormonforstyrrende kemikalier i vandløb (HORM-DMAU) <i>Studies of endocrine disrupting chemicals in the aquatic environment (HORM-DMAU)</i> PI: Pia Lassen, DMU, University of Aarhus Funding: 160,000€
3	Kryptorkisme og hypospadi: Ætiologisk betydning af prænatal miljøeksponering for phthalater og tobaksrøg: Et biomarkørstudie med måling af phthalater og kotinin i fostervand <i>Cryptorchidism and hypospadias: Aetiological significance of prenatal environmental exposure to phthalates and tobacco smoke: A biomarker study with measurement of phthalates and cotinin in amniotic fluid</i> PI: Morten Søndergaard Jensen, Dept. of Occupational Medicine, Aarhus University Hospital Funding: 127,000€
4	Hormonlignende xenobiotika og kvinders reproduktion: Effekt af phthalater <i>Hormone like xenobiotics and female reproduction: effects of phthalates</i> Projektansvarlig: Gunnar Toft, Dept. of Occupational Medicine, Aarhus University Hospital Funding: 45,000€
5	Kombinationseffekter af hormonforstyrrende stoffer, herunder pesticider I <i>Mixture effects of endocrine disrupting chemicals, including pesticides I</i> Projektansvarlig: Ulla Hass, Research Group for Molecular and Reproductive Toxicology, DTU-FOOD Funding: 133,000€
Projects coordinated in the Centre in 2010-2013 Projects initiated within the Centre's remuneration	
6	Danish children and adolescents' urinary excretion and inter- and intra-individual variation of bisphenol A (BPA) and other suspected environmental endocrine disrupters PI: Hanne Frederiksen, Dept. of Growth and Reproduction, Rigshospitalet Funding: 56,000€
7	Phthalate exposure and effects on breast development in healthy children: A novel biomarker PI: Anders Juul, Dept. of Growth and Reproduction, Rigshospitalet Funding: 94,000€

8	The Chemical Cocktail of 'Tomorrow's Danes: Non-persistent chemicals in amniotic fluid and maternal urine and serum PI: Anders Juul, Dept. of Growth and Reproduction, Rigshospitalet Funding: 225,000€
9	Evaluation of anti-müllerian hormone as a biomarker for effects on ovarian function and puberty PI: Anders Juul, Dept. of Growth and Reproduction, Rigshospitalet Funding: 163,000€
10	Mixture effects of endocrine disrupting chemicals, including pesticides II PI: Ulla Hass, Research Group for Molecular and Reproductive Toxicology, DTU-FOOD Funding: 533,000€
11	Endocrine disruption in the Danish aquatic environment PI: Poul Bjerregaard, Dept. of Biology, SDU Funding: 333,000€
12	Impact of prenatal pesticide exposure for child growth and pubertal development PI: Helle Raun Andersen, Environmental Medicine, Institute of Public Health, SDU Funding: 262,000€
13	Food packaging and food as a source of suspected endocrine disrupting per- and polyfluorinated alkyl surfactants (PFAS) in humans PI: Henrik Frandsen, National Food Institute, DTU Funding: 200,000€
Projects initiated and coordinated by the Centrs as purchased additional deliverables (2010-2013)	
14	Undersøgelse af danske børns eksponering for UV-filtre (part I) og associationer mellem UV-filtereksponering og børns vækst- og kønshormoner (part II) <i>Investigation of the exposures of Danish children to chemical UV filters (part I) and the association to growth- and sex hormone levels (partII)</i> PI: Hanne Frederiksen, Dept. of Growth and Reproduction, Rigshospitalet Funding: 272,000€
15	Use of human urinary biomonitoring data on non-persistent chemicals for risk assessment PI: Anna-Maria Andersson, Dept. of Growth and Reproduction, Rigshospitalet Funding: 27,000€
16	Exposure to endocrine disrupters in the Danish population PI: Tina K Jensen, Environmental Medicine, Institute of Public Health, SDU & Dept. of Growth and Reproduction, RH Funding: 479,000€
17	Exposure to endocrine disrupting chemicals among Danish pregnant women PI: Tina K Jensen, Environmental Medicine, Institute of Public Health, SDU & Dept. of Growth and Reproduction, RH Funding: 186,000€
18	Danskernes eksponering til UV filtre <i>The Danes' exposure to chemical UV filters</i> PI: Anna-Maria Andersson, Dept. of Growth and Reproduction, Rigshospitalet Funding: 129,000€
19	Mulige effekter af hormonforstyrrende stoffer på humane sædceller <i>Possible direct effects of endocrine disrupting chemicals on human sperm cells</i> PI: Niels Skakkebak, Dept. of Growth and Reproduction, Rigshospitalet Funding: 67,000€

20	The effect of early exposure on childhood body composition and overweight/obesity PI: Katharina Main, Dept. of Growth and Reproduction, Rigshospitalet Funding: 187,000€
21	Report on Criteria for Endocrine Disrupters PI: Ulla Hass, Research Group for Molecular and Reproductive Toxicology, DTU-FOOD Funding: 67,000€
22	Evaluation of 22 SIN List 2.0 substances + 4 additional compounds according to the Danish proposal on criteria for endocrine disrupters PI: Ulla Hass, Research Group for Molecular and Reproductive Toxicology, DTU-FOOD Funding: 93,000€
23	Assessment of the endocrine disrupting potential of 23 UV-filters PI: Ulla Hass, Research Group for Molecular and Reproductive Toxicology, DTU-FOOD & Poul Bjerregaard, Dept. of Biology, SDU Funding: 38,000€
24	Effects late in life after developmental exposure to mixtures of endocrine disrupters PI: Ulla Hass, Research Group for Molecular and Reproductive Toxicology, DTU-FOOD Funding: 120,000€
25	Input til REACH - Review 2013 om hormonforstyrrende stoffer <i>Input to REACH - Review 2013 on endocrine disrupting chemicals</i> PI: Ulla Hass, Research Group for Molecular and Reproductive Toxicology, DTU-FOOD Funding: 40,000€
26	Testkrav i forbindelse med identifikation af hormonforstyrrende stoffer <i>Information/testing strategy for identification of substances with endocrine disrupting properties</i> PI: Ulla Hass, Research Group for Molecular and Reproductive Toxicology, DTU-FOOD Funding: 33,000€
27	Kombinationseffekter/gruppering af hormonforstyrrende stoffer <i>Combination effects and grouping of endocrine disrupting compounds</i> PI: Ulla Hass, Research Group for Molecular and Reproductive Toxicology, DTU-FOOD Funding: 633,000€
28	Ekstra undersøgelser af effekter af Bisphenol A på udvikling af brystvæv, østrucykus og adfærd <i>Additional investigations of the effects of Bisphenol A on the development of breast tissue, oestrus cycle and behavior</i> PI: Ulla Hass, Research Group for Molecular and Reproductive Toxicology, DTU-FOOD Funding: 80,000€
29	a)Vitellogenin hos ferskvandsmuslinger <i>Vitellogenin in freshwater clams</i> b)Test af SIN-listestof <i>Test of compounds on the SIN list</i> PI: Poul Bjerregaard, Dept. of Biology, SDU Funding: 163,000€
30	Hormus – hormonforstyrrende stoffers påvirkninger af muslinger i ferskvandsmiljøet <i>Hormus – endocrine disrupting chemicals effects on clams in the fresh water environment</i> PI: Pia Lassen, DMU, University of Aarhus Funding: 60,000€

Projects coordinated in the Centre in 2014-2017 <i>Projects initiated within the Centre's remuneration</i>	
31	Prenatal exposure to environmental chemicals and reproductive health in teenage girls PI: Katharina Main, Dept. of Growth and Reproduction, Rigshospitalet Funding: 607,000€ Ongoing – no report yet available
32	Association between urinary excretion of phenols, parabens and UV filters and testicular function in young Danish men carrying filaggrin gene loss-of-function mutations PI: Hanne Frederiksen, Dept. of Growth and Reproduction, Rigshospitalet Funding: 33,000€
33	Undersøgelse af UV-filtre i unge danske mænds sædvæske, serum og urin <i>Investigation of UV-filters in seminal fluid, serum and urine of young Danish men</i> PI: Hanne Frederiksen, Afd. for Vækst og Reproduktion, Rigshospitalet Funding: 16,000€
34	Hormonforstyrrende effekter af perfluorerede stoffer (PFCer): in vitro profilering og effekter i rotter efter eksponering under udviklingen for en PFC plus/minus baggrundseksponering for en blanding af kendte hormonforstyrrende stoffer <i>Endocrine disrupting effect of perfluorinated compounds: in vitro and in vivo</i> PI: Ulla Hass, Research Group for Molecular and Reproductive Toxicology, DTU-FOOD Funding: 641,000€ Ongoing – no report yet available
35	Interpretation of knowledge on endocrine disrupting substances (EDs) – what is the risk? – Scope 1+2 PI: Ulla Hass, Research Group for Molecular and Reproductive Toxicology, DTU-FOOD Funding: 120,000€
36	a) Effekter af hormonforstyrrende stoffer hos muslinger <i>Effects of endocrine disrupting compounds in clams</i> b) Monitorering af vandkvaliteten i Danmark (vitellogenin måling i ørred) <i>Monitoring of the water quality in Denmark (Vitellogenin measurements in trout)</i> PI: Poul Bjerregaard Funding: 326,000€ Ongoing – no report yet available
37	Eksperthjælp vedr. brug af testmetoder og fortolkning af data ved vurdering af hormonforstyrrende effekter i miljøet <i>Expert assistant regarding use of test methods and interpretation of data in evaluation of endocrine disrupting effects in the environment</i> PI: Henrik Holbeck, Dept. of Biology, SDU Funding: 17,000€ Ongoing – no report yet available

Projects initiated and coordinated by the Centre as purchased additional deliverables (2014-2017)	
38	External evaluation of Centre on Endocrine Disrupting chemicals PI: Anna-Maria Andersson, Dept. of Growth and Reproduction, Rigshospitalet Funding: 33,000€ Ongoing – no report yet available
39	Cumulative risk assessment of anti-androgens with focus on exposure of the Danish population to phthalates PI: Ulla Hass, Research Group for Molecular and Reproductive Toxicology, DTU-FOOD Funding: 7,000€
40	International workshop om risikovurdering af hormonforstyrrende stoffer - Scope 3 <i>International workshop on risk assessment of endocrine disrupting chemicals – Scope 3</i> PI: Ulla Hass, Research Group for Molecular and Reproductive Toxicology, DTU-FOOD Funding: 53,000€ Ongoing – no report yet available
41	Udvikling af liste over hormonforstyrrende stoffer (fase 1) <i>Development of list of endocrine disrupting chemicals (phase 1)</i> PI: Ulla Hass, Research Group for Molecular and Reproductive Toxicology, DTU-FOOD Funding: 93,000€ Ongoing – no report yet available

Amounts are rounded to nearest 1,000€

Appendix E: Scientific publications based on studies carried out in CEHOS

Publication	Project number
2009	
Aksglaede L, Sørensen K, Petersen JH, Skakkebaek NE, Juul A. Recent decline in age at breast development: the Copenhagen Puberty Study. <i>Pediatrics</i> . 2009 May;123(5):e932-9. doi: 10.1542/peds.2008-2491.	1
Christiansen S, Scholze M, Dalgaard M, Vinggaard AM, Axelstad M, Kortenkamp A, Hass U. Synergistic disruption of external male sex organ development by a mixture of four antiandrogens. <i>Environ Health Perspect</i> . 2009 Dec;117(12):1839-46. doi: 10.1289/ehp.0900689.	5
Joensen UN, Bossi R, Leffers H, Jensen AA, Skakkebaek NE, Jørgensen N. Do perfluoralkyl compounds impair human semen quality? <i>Environ Health Perspect</i> . 2009 Jun;117(6):923-7. doi: 10.1289/ehp.0800517. Epub 2009 Mar 2.	1
2010	
Aksglaede L, Sørensen K, Boas M, Mouritsen A, Hagen CP, Jensen RB, Petersen JH, Linneberg A, Andersson AM, Main KM, Skakkebaek NE, Juul A. Changes in anti-Müllerian hormone (AMH) throughout the life span: a population-based study of 1027 healthy males from birth (cord blood) to the age of 69 years. <i>J Clin Endocrinol Metab</i> . 2010 Dec;95(12):5357-64. doi: 10.1210/jc.2010-1207	9
Boas M, Frederiksen H, Feldt-Rasmussen U, Skakkebaek NE, Hegedüs L, Hilsted L, Juul A, Main KM. Childhood exposure to phthalates: associations with thyroid function, insulin-like growth factor I, and growth. <i>Environ Health Perspect</i> . 2010 Oct;118(10):1458-64. doi: 10.1289/ehp.0901331	1
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- Joensen UN, Frederiksen H, Andersson AM et al. Tentative title: *Endocrine disruptors in urine and testicular function: Associations are modified by variations in the Filaggrin gene* 32
- Rehfeld A, Skakkebaek NE, Dissing S et al. Tentative title: *Chemical UV filters can affect human* 19

sperm function in a progesterone-like manner

Frederiksen H, Rehfeld A, Krause M, Skakkebæk NE, Andersson AM Tentative title: 33
Distribution of UV filters in human seminal fluid, urine, and serum

Ramhøj L, Hass U, Axelstad M, et al. Tentative title: *Early-life Endocrine Disrupting Effects in* 34
the Rat after Developmental Exposure to Perfluorohexane Sulfonate (PFHxS) and/or a Mixture
of Endocrine Disrupting Chemicals

Ramhøj L, Hass U, Axelstad M et al. Tentative title: *Developmental neurotoxicity and thyroid* 34
effects of Perfluorohexane Sulfonate (PFHxS) in rats

Morthorst, JE, KK Mathiesen, H Holbech, KL Pedersen, P Bjerregaard. Tentative title: 36
Improved sewage treatment in rural areas eliminates feminization of fish in Danish streams

* While these publication are not directly linked to a specific project under the Centre, knowledge generated in the Centre was used in these publication, which one or more of the partners in the Centre co-authored