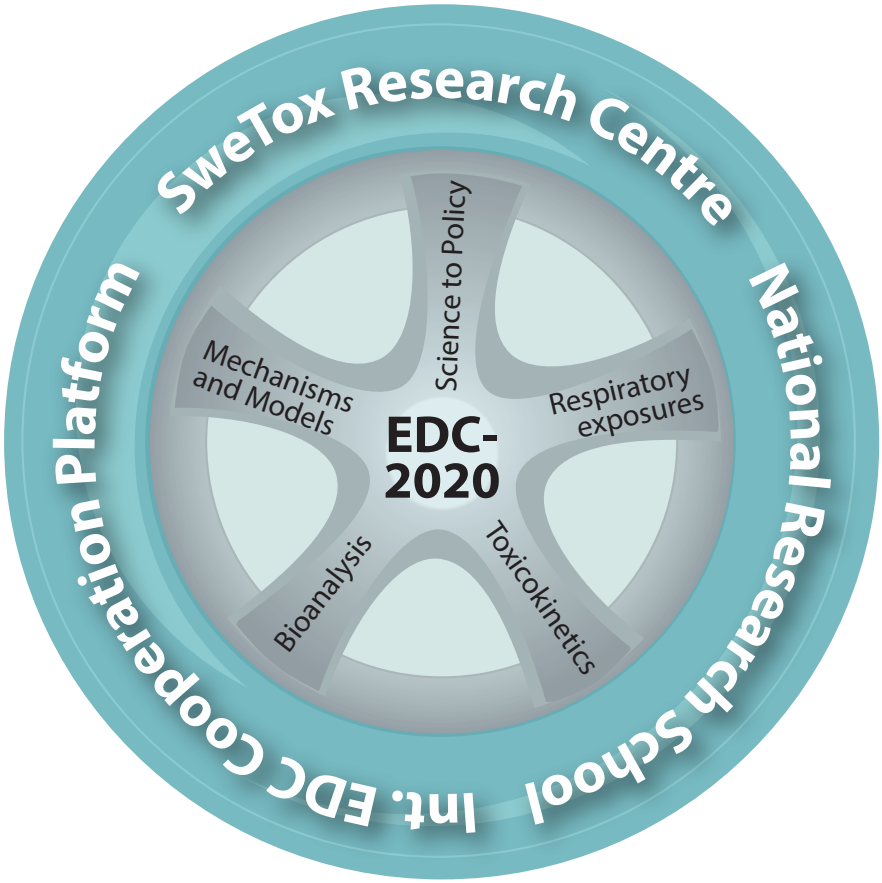
EDC 2020


SweTox Research Centre
National Research School
Int. EDC Cooperation Platform
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Summary

It is time to strengthen the role of Swedish research, international collaboration and education, in relation to chemicals and their actual and potential threats to human health and the environment. Right now there is opportunity to create a national, multidisciplinary, academic infrastructure at the Swedish Toxicology Sciences Institute (SweTox), building on existing expertise at ten Swedish universities, the interface with business activities, and the premises, equipment and scientific expertise available at SweTox.

The research aim is on endocrine disrupter chemical (EDC-2020) based on 3R (Replace, Reduce, Refine; referring to animal use in research) and 3M (Mechanisms, Markers, Models; a mode-of-action approach in toxicology and risk assessment). Research aims to include all relevant scientific areas defined under “toxicology-related sciences”, organized under five spokes.

EDC 2020 is focused to: i) create an enabling environment for strong research on EDCs and for scientific advances and innovations, which will benefit the field of toxicologically related sciences as a whole; ii) establish an overarching national program for research on EDCs, optimizing cooperation between national universities and the SweTox Research Centre, and improve interdisciplinary research; iii) establish an international EDC collaboration platform including world leading experts, and iv) establish a national research school in toxicology-related sciences.

Meeting future regulatory and societal needs regarding endocrine disrupters: Exposure, effects and risks

Acronym: EDC-2020

It is time to strengthen, on a national level, Sweden's role in research, international collaboration and education in relation to chemicals and their actual and potential threats to human health and to the environment. Sweden has a history as a world-leading nation in research and policy action on hazardous substances—it is time to recapture that position.

There is currently an opportunity to create a national, multidisciplinary, academic infrastructure at Swedish Toxicology Sciences Institute (SweTox) in Södertälje (Gärtuna), building on existing expertise at Swedish universities, on the interface with business activities at SweTox (cf. Encl. J and L), and on the premises, equipment and competences available at SweTox. The project to create the SweTox Research Centre (SweTox RC) is a unique joint project, supported by ten Swedish universities. The center's research is to be based on 3R ("Replace, Reduce, Refine," referring to animal use in research) and 3M ("Mechanisms, Markers, Models," a mode-of-action approach in toxicology and risk assessment) and focus on research tasks relating to endocrine disruptors. It is intended to include all relevant scientific areas defined under "toxicology-related sciences" (TRS) (defined below).

The reason for focusing on endocrine disrupting chemicals (EDCs) is found in UNEP/WHO (2013), "State of the science of endocrine disrupting chemicals – 2012" which presents the following six "future needs": *i)* strengthening knowledge of EDCs; *ii)* improving testing for EDCs; *iii)* reducing exposures and thus vulnerability to disease; *iv)* identifying EDCs; *v)* creating enabling environments for scientific advances, innovation and disease prevention, and *vi)* developing methods for evaluating evidence, all of which are relevant to the creation of a strong body of Swedish research in the field of EDCs. Moreover, in September 2012 the Strategic Approach to International Chemicals Management (SAICM) voted to make EDCs and their effects an "emerging policy issue" (EPI) which implies extensive work on these types of chemicals on a global basis, an undertaking currently in progress.

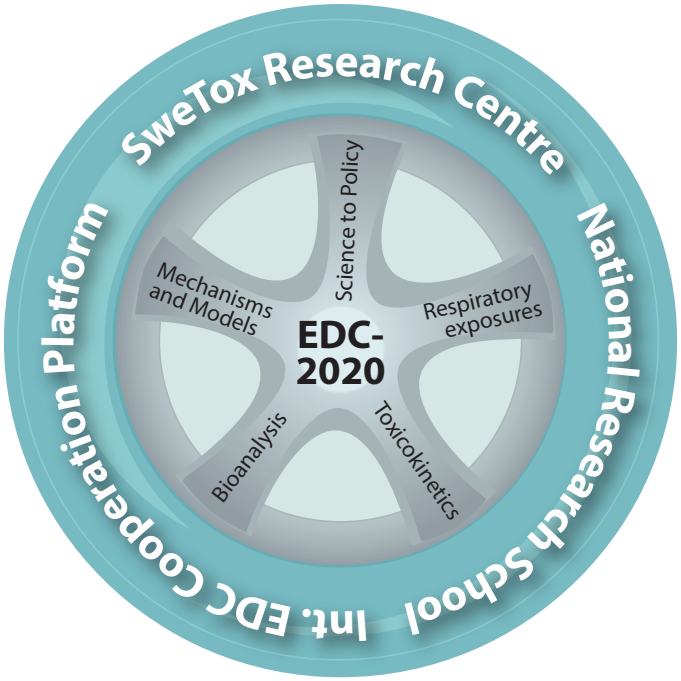
The 3R concept captures not only the ethical aspects of modern research and regulatory testing, but also the most urgent matters related to defining aspects of mode of action and adversity. There is a documented need for new methods, and for markers and models in the field of EDC bridging the gap between science and practice (UNEP/WHO, 2013; ENV/JM/MONO(2012)22; ENV/JM/MONO(2012)23). The SweTox initiative offers a platform for improving all of the elements needed to close this gap.

The 3M refers to a paradigm shift, moving from pathology-based risk assessment to assessment based on knowledge of toxicological mechanisms. Such knowledge is critical to mode of action-based predictions of risk, and can be obtained through research on adverse outcome pathways (ENV/JM/MONO(2013)6).

Objectives

The program focuses on EDCs (see also the "Wheel," below, and Encl. J):

- to create an enabling environment for strong research on EDCs and for scientific advances and innovations, which would benefit the field of toxicology-related sciences as a whole
- to establish an overarching national program for research on EDCs, optimizing cooperation between national universities as well as with the SweTox RC, and improve interdisciplinary research
- to establish an international EDC collaboration platform including world-leading experts
- to establish a national research school on toxicology-related sciences (TRS).



The Wheel: This figure summarizes the objectives of EDC-2020 and defines the research program, discussed below, cf. Encl. J, Figure J2.

Background

"*Human and wildlife health depends on the ability to reproduce and develop normally. This is not possible without a healthy endocrine system*" which is the first of 14 key concerns expressed by UNEP/WHO (2013). Another involves EDCs, with regard to *i)* their high incidence and to the increasing temporal trends of EDC-related disorders; *ii)* observed and documented EDC effects in wildlife and *iii)* experimental data on chemicals linking their properties to hormonal effects. The report points out that "*Disease risk due to EDCs may be significantly underestimated,*" which may be extended to yet-unconfirmed effects in wildlife. The hormonal systems of vertebrates and invertebrates, including humans of course, are, due to their conservative nature, rather similar. This makes it possible to work experimentally across species.

Some of the major achievements in EDC research over the past decade may be worth mentioning. After discussing only a few persistent organic pollutants (POPs) ten years ago (IPCS, 2002), we are now faced with more than 800 chemicals shown to have some ED response (TEDX, 2011). The chemicals are coming from all of the major areas of application of anthropogenic chemicals, such as cosmetics, current-use pesticides, pharmaceuticals, antioxidants, plasticizers and flame retardants, and chemicals known as natural products (UNEP/WHO, 2013, Ch. 3). Their effects are currently being discussed in relation to mixture effects, non-monotonic dose response, and low-dose effects—factors that are also of relevance to areas other than EDCs. Science appreciates the effects on many more hormonal systems than in the past—that is, we now talk about approximately 50 systems with more than 100 signaling endogenous compounds. The fetus and child are the primary focus of EDC-related concerns, as are, consequently, women of child-bearing potential. Exposure during windows of susceptibility, development programming and transgenerational effects are other areas of concern. It is evident that much more has to be done on EDCs and their effects in the decades to come.

It is obvious that both the research and the commercial activities at SweTox must be permeated with the concept of 3R. The increased regulatory and societal focus on 3R is exemplified by the new EU directive (2010/63/EU) on the protection of animals used for scientific purposes, the requirement of 3R in implementing the REACH regulation, the ban on animal testing for cosmetics (EC/1223/2009) and the formation of the European Union Reference Laboratory for Alternatives to Animal Testing (EURL-ECVAM).

Program description

Toxicology-related sciences (TRS) are here defined to include all academic disciplines that address and intend to improve our understanding and knowledge of the toxic effects of exposure to EDCs and potential EDCs, on wildlife and humans; disciplines feeding into hazard and risk assessments and forming the basis of policy and regulatory actions, nationally and on intergovernmental levels. The present call is an excellent chance to promote the formation of a national resource platform—a center—for TRS. We therefore propose that a *national research program on EDCs* be established, a program that would collaborate closely with SweTox. The research, based on 3R and 3M, would focus on EDC-related research tasks. To further promote national TRS, the EDC-2020 aims to create an *international EDC cooperation platform* and a *national research school.*

National research program on EDCs

In order to meet the multilevel goals of this program we propose that the scientific effort be focused on a selected number of "spokes", as specified below (cf. the Wheel). The spokes connect the extensive competence among Swedish scientists at the ten universities behind this application to a high potential to promote the SweTox RC activities, while taking advantage of the SweTox premises, equipment, and expertise (Encl. C, D and L). Spokes 1–5 are presented below, and the competences at the ten universities to which the spokes refer are tabulated in Table J1 in Encl. J.

Spoke 1: *Mechanisms and models*

Early life-stage exposure to EDCs may result in permanent structural alterations, as well as functional alterations demonstrated at different levels of biological organization. As demonstrated by experimental toxicology and indicated in epidemiological research, early life-stage exposure to chemicals affecting the endocrine and other signaling systems may result in altered differentiation of the organs, which may manifest as, e.g., decreased fertility, cognitive disturbances, and neurogenerative disease in children, adults and elderly. In order to define and understand the role of chemicals in the etiology of such disorders, experimental research based on 3M is required, making use of in silico, in vitro, and in vivo experimental models and tools. An improved understanding of toxicological mechanisms and how these translate across species is required, as well as improved (bio)markers for monitoring organ toxicities resulting from endocrine disruption in humans and wildlife.

Internationally agreed and validated test methods for the identification and characterization of endocrine disruptors capture only a limited range of the known spectrum of endocrine disrupting effects. There is consequently a need for improved test assays and disease models that can be used to identify and characterize chemical toxicity,

particularly the mechanisms behind various manifestations of endocrine disruption (ENV/JM/MONO(2012)22; ENV/JM/MONO(2012)23). In addition to focusing on 3M, Spoke 1 will contribute further development and validation of new test guidelines based on a broad range of assays in relevant vertebrate and invertebrate species, covering also endocrine-mediated adverse effects on embryogenesis, development and reproduction, and long term effects. Several tiers of testing will be covered, using computational/QSAR models, screening of in vitro and in vivo test systems, and regulatory assays. While screening methods are used for early prioritization of testing, mechanistic studies using intact organisms with functional signaling systems are necessary to understand how and why chemicals can promote disease development in humans and wildlife.

The research in Spoke 1 will require collaborative input from Spokes 2–4 and will play an important role for the research in Spoke 5.

Spoke 2: *Bioanalysis*

There is a need to develop new strategies and chemical analytical methodologies to assess exposures at low levels in various toxicity studies, including human samples. The advances in chromatographic and mass spectrometric instrumentation during the last decade have been significant, allowing the analysis of ultralow levels in small amounts of sample. Target analysis of organic micro-pollutants using state-of-the-art technology nowadays enables detection levels in biota samples down to femtograms per injection. Parallel to this, techniques for non-target analysis including advanced data interpretation coupled with large libraries of mass spectra are evolving, with the potential to discover new EDCs. Taken together these techniques permit the analysis of samples from biobanks and epidemiological research. In Sweden, a number of internationally recognized biobanks are either available or under development. The extensive access that exists in Sweden to different national registers is another advantage for epidemiological studies. There is also a need for advanced analytical techniques for assessing exposure in toxicological experiments and toxicokinetic studies. Here, it is of the outmost importance to know the internal dose. Often extremely small volumes of samples are available from in vitro systems, tissues, or other biomedia.

This highlights the need to develop the next generation of analytical tools to provide improved sample throughput and reduced sample size in addition to the acquisition of more relevant data. Methods have to be developed to enable the analysis of large numbers of samples in cohort studies to achieve sufficient statistical power or facilitate toxicological studies. This will demand advanced methodology based on mass spectrometry assuring high sample through-put and integration of EDC analysis with untargeted screening. Collectively, EDC-2020 participants possess the relevant competence in the chemical analysis of EDCs and sufficient experience with advanced analytical instrumentation. The laboratories are specialized in the analyses of different compounds and together have the capacity to analyze a large number of EDCs. We foresee a further development and specialization of the chemical analysis of low-volume samples, integrating screening of a range of EDCs with untargeted analysis in a variety of samples provided within EDC-2020 and from other sources, such as Swedish or international biobanks.

Techniques and methodologies developed in Spoke 2 will be applied to analyze compounds discovered and samples generated in Spokes 1, 3, and 4.

Spoke 3: *Toxicokinetics*

Several well-known environmental pollutants and EDCs are not primarily active as such but as metabolites. There is a large number of potential EDCs for which no metabolic studies have yet been performed, implying a lack of knowledge of the potential inherent endocrine or toxicological activities of these metabolites. Unfortunately metabolic studies of environmental contaminants are not currently prioritized. This spoke is designed to focus on metabolism studies, performed both in vitro and in vivo to promote a better understanding of mixture toxicities of compounds. The chemical synthesis of metabolites can feed directly into Spokes 1, 2 and 4—that is, toxicity testing and analytical methodology development.

When setting up new test methods, knowledge of metabolism (in the tested species and in "target" species) and levels of the tested compounds is critical to achieving a well-supported interpretation and species translation. If kinetic species differences so allow, this information can make it possible to choose, e.g., a non-mammal species over a mammal one for a particular study

We will extend these efforts by generating tissue models and dynamic whole-body models of different species. This unique capacity to simulate processes across species, including man, will be of great translational value to biomedical research in general and to research on EDCs in particular. The numerical challenges to be addressed include tools for the computational analysis of the resulting models. Important areas to be covered will be efficient numerical simulation, sensitivity analysis (for biomarker and target identification), characterization of uncertainty, and visualization of simulation results. This approach will position Sweden among the world's leaders in the provision of toxicokinetic solutions for advancing healthcare and environmental risk assessment, and will become a central element of an international push toward the use of metabolic models for risk assessment to understand metabolic diseases.

Spoke 4: *Respiratory exposures*

Many EDCs are of low-volatility, while others are higher-mass lipophilic substances that tend to adsorb onto solid surfaces (dust/particulates). With many sources of EDCs in the home environment, prolonged contact with household dust may potentiate the inhalation route as one important portal of entry for human exposures, particularly in small children (UNEP/WHO, 2013). In fact, small children are showing higher levels of many EDCs than are their parents (e.g., Lunder et al., 2010). However, little is known about the overall bioavailability of EDCs adsorbed on inhaled household dust or other potential carrier particles. Largely unknown is also the rate at which the adsorbed EDCs are desorbed from lung-deposited dust, potentially metabolized and absorbed into the circulation. All of these are important parameters for the selection of suitable biological endpoints for further study and ultimately for supporting more accurate risk assessment models.

SweTox has unique equipment and competence for studying inhalation as a route of exposure, which can be used in combination with other capabilities (bioanalytical, kinetic, histopathological, etc.) at the same location. In addition to state-of-the-art in vivo exposure technologies for multiple animal exposures, the PreciseInhale platform (developed by Inhalation Sciences Sweden AB) will also be available. This will enable inhalation exposures using milligram amounts of powder materials that are aerosolized into small volumes of concentrated aerosol, which enables smaller scale inhalation testing with more accurate endpoints, such as the proposed study on inhaled EDCs. Generated aerosols are ready for immediate exposure of different study subjects from cell cultures, isolated perfused lungs, nose-only or intubated rodents, and dogs, and eventually of humans. All of this links Spoke 4 to the research in Spoke 3, in particular.

Spoke 5: *Science to policy*

In a recent decision, the European Parliament called on the European Commission to take further action in the area of chemicals policy—and intensify research efforts—in EDCs (EP, 2013). The decision points to the need to strengthen processes for identifying EDCs, assessing the cumulative impact of combinations of EDCs, and enabling the assessment of groups of substances having the same mode of action and properties.

The decision also states that the identification of EDCs should be based on criteria for defining adverse effect and endocrine mode of action, using the WHO/IPCS definition, and that a weight-of-evidence approach should be used. In addition, it is noted that all peer-reviewed scientific data and information, including non-GLP studies, should be taken into account after being evaluated with regard to their reliability and relevance to risk assessment. Criteria for the identification of EDCs were to be agreed upon by the end of 2013, but this is obviously a difficult task and the deadline has recently been postponed.

The need to develop new test methods in close collaboration with "testing expertise" (cf. EDC-2020 as a whole) and to introduce them as testing requirements in all relevant EU legislation is also acknowledged, taking the 3R principles into account. The lack of tests for many areas of the endocrine system is noted, as is the fact that appropriate test methods need to consider possible low-dose and mixtures effects, and non-monotonic dose–response relationships, in particular with regard to critical windows of exposure during development.

In order to achieve science-based policy development, as called for by the Parliament, a close connection to science and collaboration with relevant scientists is needed. Research at SweTox will in fact address several of the aspects raised by the Parliament, and Spoke 5 will be designed to put the research into a regulatory perspective and endeavor to communicate the results in a manner that will be useful to decision-makers and policy development in Sweden and the European Union.

Areas in which the SweTox RC will be particularly strong include: development and validation of new and refined test methods and tiered test strategies for testing a wide range of different mechanisms and modes of action of endocrine disruption, criteria for evaluating the reliability and relevance of non-GLP studies, the exposure and metabolism of potential and actual EDCs, and the development of weight-of-evidence (including mode-of-action pathway analysis) approaches for EDC. Spoke 5 links to each of the other spokes, and also links strongly to the international EDC collaboration platform activities proposed here.

Implementation of the research program

To catalyze the establishment of the SweTox RC and the EDC-2020, a workshop is planned for December, 2013—that is, prior to the formal start of the project. This is intended to bring together all interested parties, experts from the ten universities, and other funding agencies and stakeholders, to discuss and make plans for the start-up of the SweTox RC and for announcements of available positions.

EDC-2020 research focuses on five areas where expertise is available at the ten universities behind EDC-2020 and for which the SweTox RC can contribute specifically through its facilities, instrumentation and expertise. To promote research development at SweTox, this applica-

tion concentrates on the assignment of new six researcher positions, announced under competition (cf. Encl. B2). The researchers should be linked to one or more universities where one or more senior researcher(s) is the primary contact point. The researchers will be key to contributions to the development of interdisciplinary cooperation at the SweTox RC, as well as on a national basis, interlinking the ten academic institutions. Similarly, the senior researchers at the applying universities are expected to make contributions. Researchers at these universities will be invited to link their ongoing projects to the potential benefits created by the SweTox facility. The researchers will also bring in PhD students and form teams, enabling them to approach the tasks under the appropriate EDC-2020 spoke areas. The links between researchers at the applying university and Spokes 1–5 are presented in Table J1 (Encl. J).

Establishment of an international EDC cooperation platform

Team science and interdisciplinary cooperation has been put forward as a "future need" by the UNEP/WHO (2013). To make the SweTox RC as competitive as possible we propose that a platform of internationally highly recognized institutions, from the Nordic countries and the EU, be formed. These institutions, listed below, should be approached within the EU context to solicit their support in promoting the development of the national research school (cf. below).Professional researchers at these institutions have confirmed their availability to promote and cooperate on the platform as suggested below.

The researchers approached represent the following eight academic institutions in Europe: Rigshospitalet/the University of Copenhagen and the University of Southern Denmark (Denmark); the University of Turku (Finland); the Free University, Amsterdam and Utrecht University (the Netherlands); the Norwegian School of Veterinary Sciences (Norway); Brunel University and the University of Exeter (UK).

The International EDC Cooperation Platform will host an annual meeting to discuss advances in ED research and regulatory issues. Our financial situation should allow us to invite researchers from the cooperating academic institutions to work on EDC-2020 and make use of the SweTox RC facilities. The plan is to invite 2–3 experts on EDCs per year to work on EDC-2020, both at the center and with the appropriate universities from among "the ten". The visits are proposed to be in the range of 1–2 months per person and year. The experts will be invited as teachers for activities at the national research school.

Establishment of the SweTox National Research School

Today, PhD students in TRS can take part in a wide variety of courses given at Swedish universities. While some of them are elements of degree programs, there is no coordinated program covering the breadth and depth of this complex area.

A national research school in TRS, in the unique environment at SweTox, would tie together courses for students in a range of PhD programs at Swedish universities. The overarching aim is to provide a network and a training environment, created jointly under EDC-2020 by the SweTox RC and the Swedish universities, in which participants might achieve a wider perspective and further knowledge in TRS.

The research school would:

- organize new courses in areas relevant for TRS, taking care to complement and link these new courses with existing courses at Swedish universities
- organize regular workshops on specific techniques and methods
- organize an annual networking meeting for both junior and senior participants from academia, industry, and agencies.

PhD students and postdocs with a research focus in TRS could register with the SweTox national research school on top of their affiliation with a Swedish university, and could thus gain access to the SweTox network.

The SweTox national research school would give PhD students and postdocs from different research areas a wider perspective and deeper knowledge in TRS, in addition to a network also encompassing industry. It would also give students the greater knowledge required to meet future needs in industry authorities and in research.

Expected outcome of EDC-2020

As stressed under "Background," above, the accumulated evidence suggests that EDCs are the source of many hormonal-related diseases and disorders. The overall outcome of this project is expected to improve understanding of the mechanisms involved in EDC-related diseases. It should be emphasized that the risk of certain serious diseases and functional disorders may be significantly reduced when the mechanisms of action of EDCs are understood and when preventive actions are taken. Additionally, the SweTox RC:

- would be a hub for collaboration between Swedish national universities and a new platform that would enable the rejuvenation of toxicological competence in Sweden. The latter would also be supported by the cre-

ation of a research school and structured international collaboration.

- would become a national resource for TRS that could be linked to other platforms with related activities, such as SciLifeLab and biobanks.

- would be an opportunity for young scientists in the TRS field to find collaborative partners, to benefit their own research

- would create new opportunities for interactions to secure research funding through collaborations with international scientists and scientific organizations.

Coordinating function

The PI of EDC-2020, Prof. Harriet Wallberg-Henriksson, the former vice-chancellor of Karolinska Institutet (KI), is the coordinator of this joint effort involving Karolinska institutet and nine other Swedish universities (GU, KTH, LiU, LU, SLU, SU, UmU, UU and OrU (abbreviations explained in Encl. J). The PI was appointed national coordinator for the academic part of SweTox in October 2012 by the Governor of Stockholm. Duties of the appointment include coordinating all universities and university colleges interested in participating in the initiative, coordinating other applications for funding for SweTox, and coordinating negotiations with Acturum, the company that acquired the facilities in Gärtuna. These negotiations, which are ongoing, are aimed at forming an agreement between the company and the Academic Center for the renting of appropriate space during a period of five years.

In addition to the co-applicants presented in the main part of the application, the EDC-2020 incudes Professors Amelie Eriksson Karlström, Susana Cristobal, and Bert van Bavel as co-applicants, representing KTH, LiU, and OrU, respectively.

Representation from each of the ten universities, under the lead of the PI, is intended to form a board for EDC-2020. The project will be formally placed under KI. The broader organizational structure is presented in figure J3 (Encl. J).

Ethical considerations

Any sampling or other activity involving humans will follow Government Law Decision U 2003:460, which accords with the revised version of the Declaration of Helsinki, the "Note for guidance on Good Clinical Practice" (GCMP/ICH/135/95), and Council Directive 95/46/EC on the protection of individuals with regard to the processing of personal data.

Animal experiments would be performed according to Directive 2010/63/EU on the protection of animals used for scientific purposes, incorporated on 21 November 2012 into Swedish legislation SJVFS 2012:26, and would follow the rules for Good Laboratory Standard, established by the EU and the OECD.

All planned experiments on animals and humans would be applied for and approved by an Ethical Committee before being started. Applications to the regional Ethical Committee for the use of animals in research will be prepared in close collaboration between the researcher, the veterinarian, and the local laboratory animal organization at SweTox.

All animal experiments would be performed according to the principles of the 3Rs and appropriate veterinary care would be available at all times. The staff would be adequately educated and trained before taking care of animals, carrying out procedures on animals or designing procedures and projects. The local laboratory animal organization at SweTox would work in close collaboration with the department for comparative medicine at Karolinska Institutet.

Gender aspects

The *EDC-2020* applicants are four women and six men. The gender perspective is central and would be considered in all appointments to be carried out, and throughout the entire duration of the project.

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Costs applied for

		Year 1		Year 2		Year 3		Year 4 (see call)		Year 5 (see call)		Year 6 (see call)	
Specification Costs- Direct (in 1000SEK)	indirect cost (OH%)	Direct costs kSEK	Total costs kSEK	Direct costs kSEK	Total costs kSEK	Direct costs kSEK	Total costs kSEK	Direct costs kSEK	Total costs kSEK	Direct costs kSEK	Total costs kSEK	Direct costs kSEK	Total costs kSEK
1. Salaries (incl. Social fees/LKP)	(%)												
Reseacher NN1 SweTox Reseache Centre, 80%	35,00%	400	540	670	905	670	905	700	945	700	945		0
Reseacher NN2 SweTox Reseache Centre, 80%	35,00%	400	540	670	905	670	905	700	945	700	945		0
Reseacher NN3 SweTox Reseache Centre, 80%	35,00%	400	540	670	905	670	905	700	945	700	945		0
Reseacher NN4 SweTox Reseache Centre, 80%	35,00%	400	540	670	905	670	905	700	945	700	945		0
Reseacher NN5 SweTox Reseache Centre, 80%	35,00%	400	540	670	905	670	905	700	945	700	945		0
Reseacher NN6 SweTox Reseache Centre, 80%	35,00%	400	540	670	905	670	905	700	945	700	945		0
Three visiting scientists (1-2months/year)	35,00%	400	540	400	540	400	540	400	540	400	540		0
Infrastructure support to NN1-NN6 at Gärtuna	35,00%	2000	2700	700	945	700	945	700	945	700	945		0
			0		0		0		0		0		0
Sum salaries:		4800	6480	5120	6912	5120	6912	5300	7155	5300	7155		0
2. Running cost (incl.equipment <500kSEK)	(%)												
Running costs á 200 kSEK per reseacher NN1-NN6	35,00%	600	810	1200	1620	1200	1620	1200	1620	1200	1620		0
Travel/meetings á 50 kSEK per reseacher NN1-NN6	35,00%	200	270	300	405	300	405	300	405	300	405		0
Travel costs Visiting scientists	35,00%	50	68	100	135	100	135	100	135	100	135		0
International EDC cooperation platform, annual meeting	35,00%	300	405	300	405	300	405	200	270	200	270		0
Reseach school	35,00%	400	540	300	405	300	405	300	405	300	405		0
Other costs	35,00%	400	540	85	115	85	115	0	0	0	0		0
start-up costs	35,00%	600	810	0	0	0	0	0	0	0	0		0
			0		0		0		0		0		0
Sum Running costs:		2550	3443	2285	3085	2285	3085	2100	2835	2100	2835		0
3. Equipment depreciation costs													
			0		0		0		0		0		0
4. Premises costs													
			0		0		0		0		0		0
Sum Equipment and Premises costs:		0	0	0	0	0	0	0	0	0	0	0	0
SUM DIRECT COSTS:		7350		7405		7405		7400		7400		0	
AMOUNT APPLIED FOR (incl. Indirect costs):			9923		9997		9997		9990		9990		0

Commentary to budget

The SweTox Research Centre (SweTox RC) is aimed to become a national resource in the area of toxicology-related sciences in Sweden. The present application is one, among others to come. Due to the novelty of SweTox RC, it is not possible to make all the specifications that are commonly requested for research grant applications. However, the motivations that can be presented are given below.

Budget motivations

The budget for EDC-2020 is aimed to cover costs primarily generated at SweTox RC in Södertälje, Gärtuna. This includes firsthand, six positions as researchers that will be announced, two researchers for Spoke 1, due to the breadth of mechanisms and models, and one researcher each for the Spokes 2-5, dealing with bioanalysis, toxicokinetics, respiratory exposures and science to policy, respectively. Since there are several research areas under each spoke it is our aim to announce, under competition, more than one position/spoke to attract the best possible competence for building up the EDC related research at SweTox RC. The exact areas of research, under each spoke, to be announced will be brought forward in an open process, starting with a two day workshop to which all Swedish researchers, from the 10 participating universities and with an interest in EDC-2020 are invited to discuss the development of SweTox RC in general but EDC-2020 in particular. The EDC-2020 management team and the board, in cooperation with the International scientific advisory board, will thoroughly investigate and prioritize which areas of research, within each spoke, to bring forward for open announcements. The six researchers are aimed to be affiliated with senior researchers, active at any of the universities supporting EDC-2020. The researchers will be employed by the university to which the researcher wants to be affiliated.

The researchers we have in mind for employment should have their postdoctoral studies behind them and they must have shown good progress after they defended their PhD thesis. The budget is set with a plain salary (80%) of 45 kSEK/month, at start. The researchers are aimed to work and use the infrastructure at SweTox RC SweTox RC in Gärtuna. The infrastructural support is prioritized for technical and laboratory assistance to promote the research projects. For this a sum of 2000 kSEK is applied for the first year, to allow the researchers to obtain particular support in the start. Infrastructural support is budgeted for each of the consecutive years but at a lower level per year. Each one of the researchers is also given a budget for running costs and travel, to promote their scientific development. The other 20% is aimed to be covered by university funding for university related activities.

Additional costs are related to salaries internationally outstanding experts that will be invited as part of the international EDC cooperation platform. The invited experts are planned to be invited to work at SweTox RC and together with the host universities for 1-2 months per year. These highly competent persons will be involved in the educational program under the national research school. In addition to their salary costs there is a cost related to travel expenses as specified in the budget.

The funding of the national research school is covered by cooperation between the universities and the SweTox RC. Therefore only a minor proportion of the full costs for the research school is applied for herein (Appendix B1). The total cost for this has been calculated to approx. 4000 kSEK.

Over-head is set to 35% of all funding to cover both the university mutual costs and to contribute to the premises costs. Since ten universities are applying together it is not possible to make any further specification since the systems varies between universities and there are differences between departments within the same university.

Other funding

The SweTox Research Centre is in a wider perspective also financially supported by a grant from Knut and Alice Wallenberg foundation and by Karolinska Institutet. The project will also benefit from ongoing EDC related projects currently running at each of the ten universities, see Table below.

Major EDC-related projects presently being run at the applying universities/institutes

Univ. location	Funding source	Project title	Project period	Total grant (kSEK)	Principal investigator (PI) and collaborators
GU	FORMAS	Novel instruments for effect-based assessment of chemical pollution in coastal ecosystems (NICE).	2011-16	25 000	Thomas Backhaus (PI)
GU	FORMAS	Linking chemical pollution to the health status of coastal fish	2013-16	8 000	Lars Förlin (PI)
KI	AZ-KAW	An integrated approach to disease understanding and the development of predictive models in asthma, allergies and COPD	2013-17	35 000	S-E Dahlén
KI	Formas	Delineating Molecular Mechanisms Underlying Epigenetic Modulation of Endocrine Disruptive Compounds	2013-17	3 587	Joëlle Rüegg (PI)
KI	EU FP7	FORMAMP: Inhalation of antibacterial peptides	2013-17	3 000	Per Gerde
LiU UU		Does Developmental exposure to Bisphenol A induce bone and adipose tissue disturbances?	2013-15	7 350	Helen Karlsson Monica Lind (PI)
LiU	VR	Alternative ex-corpore testing of chemicals and drug candidates	2012-14	3 295	Heriberto Rodriguez-Martinez
LU	Formas	Levels of phthalates, perfluorinated compounds, persistent organochoride compounds, and the changes in these levels during pregnancy and the relationship with reproductive effects	2010-13	3 570	Bo Jönsson
LU	Formas	Assessment of pesticide-related health risks in pregnant women and their newborn living in banana producing areas in Costa Rica - analysis of biomarkers of exposure, response and susceptibility	2011-13	3 500	Christian Lindh
LU	EU	Clear - Climate Change, Environmental Contaminants and Reproductive Health	2009-13	20 450 7 600 (LU)	Jens P. Bonde (CPH) Bo A. Jönsson (LU)
SLU UU	Formas	Integrated chemical and toxicological methods for early detection of hazardous chemicals in drinking water	1013-16	16 000	Karin Wiberg (PI)Agneta Oskarsson; Björn Hellman
SU SLU UmU	Formas	Mixture assessment of Endocrine Disrupting Compounds (EDC) with emphasis on thyroidogenicity - using cats as model for human indoor exposure	2012-16	20 040	Åke Bergman (PI) Leif Norrgren Patrik Andersson
SU UU UmU	Mistra	MistraPharma - Identification and Reduction of Environmental Risks Caused by Human Pharmaceuticals	2008-15	96 000	Christina Rudén Ingvar Brandt Mats Tysklind
UmU	Formas	Novel Strategies to Reduce Diffuse Emissions of Micropollutants from On-Site Sewage Facilities	2013-17	15 985	Patrik Andersson
UU	Formas	Cyanobacterial toxins: Hazards and risks to brain development and function in mammals, birds and fish	2011-13	6 375	Eva Brittebo
OrU	EU	Clean Sea: Tools, Innovation and Applications: Monitoring and Modeling	2013-15	5 889	Bert van Bavel

Figures and a table referred to in the project description, Encl. A

Figure J1. The SweTox Research Centre is aimed to become a Swedish national resource in the area of toxicology-related sciences (TRS). Presently 10 Swedish universities are supporting this effort, and likewise co-applicants for the present project, EDC-2020, for funding from the Research Council Formas. The universities are Gothenburg University (GU), Karolinska Institutet (KI), Royal institute of Technology (KTH), Linköping University (LiU), Lund University (LU), Swedish University of Agricultural Sciences (SLU), Stockholm University (SU), Umeå University (UmU), Uppsala University (UU) and Örebro University (OrU). The SweTox Research Centre is constructed to include a variety of projects, presently one on "Drug related toxicology" is funded from KAW, while other ellipses are still empty.

EDC-2020 relies on toxicology-related sciences, an international EDC cooperation platform and a national research school as shown in the figure and further elaborated on in Encl. A.

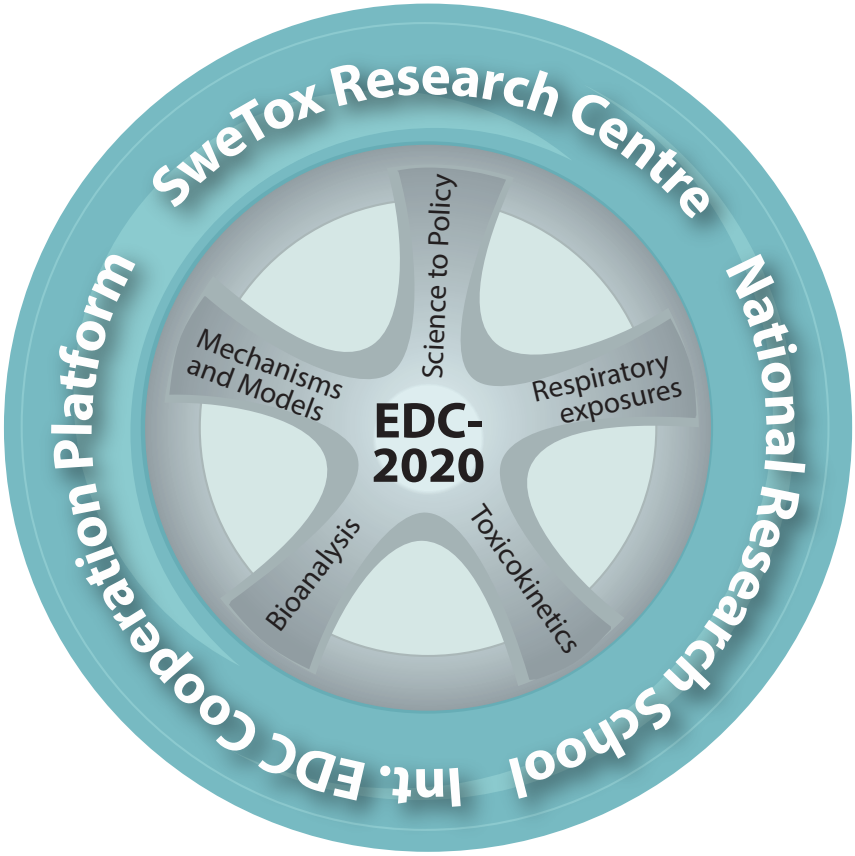

Figure J2 – The Wheel. This figure interlink the different parts of EDC-2020, i.e. the collaboration with SweTox Research Centre as a whole (cf. Figure J1). The academic deep EDC competences from the 10 universities are making up the five spokes, interlinking these spokes through the rim and adding thereto the international EDC cooperation platform and the national research school. The spokes are: #1: Mechanisms and models; #2. Bioanalysis; #3. Toxicokinetics; #4. Respiratory exposures and #5. Science to policy.

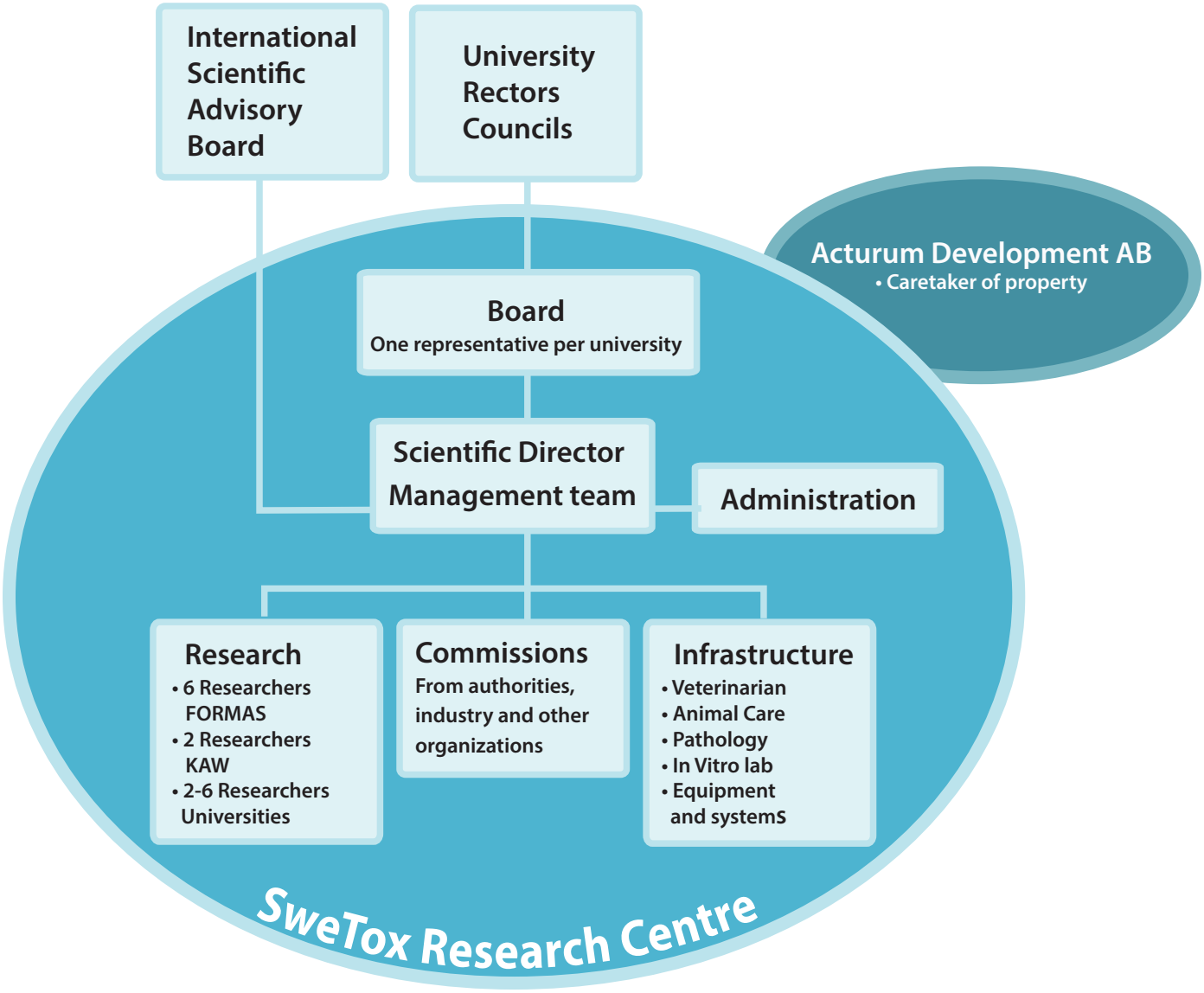

Figure J3. SweTox Research Centre organization scheme

Table J1. This table is aimed to visualize the main areas in which the 10 universities, applying for support (cf. Figure J1), have extensive expertise and for which in kind contributions will be given to the EDC-2020.

Spoke	Area of research	GU	KI	KTH	LiU	LU	SLU	SU	UmU	UU	OrU
Spoke 1	Mechanisms and models	X	X	X	X	X	X	X	X	X	X
Spoke 2	Bioanalysis	X	X	X	X	X	X	X	X	X	X
Spoke 3	Toxicokinetics	X	X	X		X	X	X		X	
Spoke 4	Respiratory exposures	X	X		X	X		X	X		
Spoke 5	Science to policy	X	X		X	X	X	X		X	

The Gärtuna facility - Infrastructure and Competences

Facility

The Gärtuna facility that housed the previous AstraZeneca Safety Assessment organization was vacated at the end of 2012. The facility (around 20.000 sqm) contains state of the art laboratories in which all forms of toxicology studies necessary to support the safety assessment of drug candidates were performed. These included genetic toxicology, molecular toxicology, immune toxicology, bioanalysis, clinical chemistry, pathology, reproduction toxicology, all types of in vivo studies in rodents and dogs, inhalation toxicology and safety Pharmacology. The facility had GLP accreditation. It is important to stress that these are the same requirements that will be needed for advanced risk assessment of actual and potential environmental pollutants in general and for EDCs, more specifically.

SweTox Infrastructure

At the end of June 2013, Acturum AB entered an agreement with AstraZeneca to purchase the Gärtuna facility including the majority of the equipment and instrumentation. AstraZeneca also intend to hand over information regarding Standard Operating Procedurs (SOP) and program licenses in order to run these facilities. Acturum AB is going to lease part of the facilities and equipment to SweTox Research Center and other parts to small- medium size companies, with the aim of establishing a creative environment for research in the areas of toxicology and risk assessment.

SweTox competences

SweTox Research Center will require adequate staffing at Gärtuna in order to set up and maintain a facility according to the standards required for research as well as commissions. The recruitment of key staff has been initiated and the infrastructure and competences essential for the establishment and support of the research program presented in this application are expected to be in place and operating by mid 2014. This includes capabilities and competences, included in the proposed budget, for handling of animals and systems/equipment. In addition, together with other available resources of financing, dedicated staff in: **In silico** (molecular modeling etc), **In vitro** (screening, model validation, immunology, etc.), **Bioanalysis** (compound, metabolite and biomarker analysis), **In vivo** (rodent studies), **Pathology** (molecular pathology etc.), **Inhalation** (In vivo and in vitro capabilities), and **DMPK,** are to be recruited.

SweTox Equipment

A majority of the equipment has been retained in the laboratories or placed at nearby locations. The instruments and equipment have been conserved and instructions for start-up are available when to be used again. We project a first year of start-up costs that is in part included in the proposed budget. The remainder of the start-up costs will be paid from already assigned funding.