Toxicology in Denmark, 21+22 April 2022, University of Copenhagen, Center of Science and Society, Kommunehospitalet, Gammeltoftgade 35.0.12. Contact for participation: Lisbeth E. Knudsen liek@sund.ku.dk.

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Program

Thursday 21.4.2022
Lunch and registration 12-12.30.

Theme: Who are toxicologists in DK, what are their tasks, educational backgrounds and perspectives – limited minutes for all please also present 1 page abstract by 11st April for distribution prior to the meeting. Presentations (8 min each)

12.30-13.30 Governmental institutions Chair Eva Bonefeld Jørgensen:
Danish Environmental Protection Agency, Chemicals Division, Magnus Løfstedt
Danish Environmental Protection Agency, Pesticides & Biocides Division, Charlotta A. Wallensten
Danish Medicines Agency, Louise F.S. Lauritsen: *Toxicology in daily work and future*
Danish Veterinary and Food Administration: Mette Holm and Jeanette Søgaard Nielsen
Danish Working Environment Authority: Flemming Ingerslev
Clinical Pharmacology, RegionH, Kim Dalhoff
Clinical Occupational/Environmental Health Holbæk, Paula Hammer

13.30-15.00 Private companies/industries Chair Gunnar Toft:
Novo Nordisk A/S, Alan Christensen: *Working as a Toxicologist at Novo Nordisk*.
Lundbeck, Allan Dahl Rasmussen, Karina Bernholm: *Ongoing activities and perspectives*
Scantox, Mikkel Lykke: *Ongoing activities and perspectives*
Leo-Pharma, Klaus Rytved: *Ongoing activities and perspectives*
NOVOZYMES, Denisa Cupi: *Ongoing activities and perspectives*
3Rs Management&Consulting, Erwin Roggen: *Ongoing activities and perspectives*
FORCE Technology, Pia Bruun Poulsen: *Toxicology in risk assessments of consumer products*
DHI, Poul Bo Larsen, Brian Svend Nielsen: *Regulatory toxicology and course activities*
Independent toxicology and preclinical advisor Mette Due Theilade (no abstract): *Juvenile animals and pediatric investigation plans*

15.00-15.30 Coffee break

15.30 -16.00 Nordic Universities/research centers Chair Lisbeth E. Knudsen:
Lisbeth E. Knudsen, University of Copenhagen: *The Nordic questionnaire and the Danish replies*
Hubert Dirven, Norwegian Institute of Public Health, Norway: *Ongoing activities in Norway* and *Perspectives for toxicology at the NIPH.*
Matti Viluksela, Finland: Mapping the competence situation and needs in Finland

16.15 -18.00 Danish Universities/research centers Chair Ulla Vogel:

National Research Center for the Working Environment, Karin Sørig Hougaard: *Ongoing activities and perspectives for toxicology at the institution*
Experimental Pharmacology and Toxicology, UCPH University of Copenhagen, Pernille Tveden: *Ongoing activities and perspectives for toxicology at the institution* Department of Public Health Line Mathiesen *Ongoing activities and perspectives for toxicology at the institution*
Toxicology and Drug Metabolism Group UCPH Bjarne Styrishave, *Ongoing activities and perspectives for toxicology at the institution*
University of Southern Denmark, Helle Raun Andersen, Philippe Grandjean: *Ongoing activities and perspectives for toxicology at the institution, DK and globally*
Aarhus University, Eva Bonefeld-Jørgensen: *Ongoing activities and perspectives for toxicology at the institution*
CEHOS, Anna Maria Andersson: *Ongoing activities and perspectives for toxicology at the institution*

18.00-19.00 Glass of Wine

Friday 22.4.2022

9.00-10.30 DTU and European/global initiatives (8min each) Chair Karin Sørig Hougaard
DTU Food: Anne Marie Vinggaard, *Research in the Cell Toxicology team*
Terje Svingen, DTU Food: *Research in the Research group on Molecular and Reproductive toxicology*
Susanne Hougaard Bennekou, DTU Food: *Research in Research group on chemical risk assessment and GMO*
Sofie Christiansen, DTU Food: *OECD, AOP, IATA and consultancy work*
University of Copenhagen: Lisbeth E. Knudsen, *3Rs and use of human tissue*
Aarhus University: Eva Bonefeld Jørgensen, *Why is it important to be member of the "European Society of Toxicology"*
National Research Center for the Working Environment Ulla Vogel, *ERT certification*
National Research Center for the Working Environment Ulla Vogel *Board of Health –scientific advisory committee*

10.30-11.00 Coffee and Group Picture

11.00-12.30: PARC – Partnership for the Assessment of Risks from Chemicals – Update and the bridging to HBM4EU Chair Anne-Marie Vinggaard
HBM4EU in Denmark **-** Anna Maria Andersson Region H, Katrin Vorkamp, AU, Lisbeth E. Knudsen, UCPH
PARC Norway – Hubert Dirven
Organisation of the Partnership for Assessment of Risks from Chemicals (PARC) in Denmark, Ditte Secher Paludan MST, Anna Maria Andersson Region H, Susanne Hougaard from DTU, and Coming Aarhus University activities in the PARC Project Eva Bonefeld-Jørgensen AU

12.30-13.00 Summary and recommendations for toxicology in the future Chair Lisbeth E. Knudsen

The future of toxicology in Denmark and the Nordic countries, can toxicology be organized in a different way, how can we collaborate better, how can toxicological methods be used in the health care system, opportunities for increased collaboration across traditional toxicology and the clinic etc.

13.00-14.00 Lunch and goodbye

Governmental institutions in Denmark

Danish Environmental Protection Agency, Chemicals Division

Magnus Buhl Løfstedt, Lykke Boysen**,** Danish Environmental Protection Agency, Chemicals Division

Introduction to organisation
The Chemicals Division in the Danish Environmental Protection Agency (DEPA) is responsible for monitoring compliance with different chemical regulations in relation to industrial use of chemicals and chemicals in consumer products. This includes REACH, CLP, Toys Directive, Cosmetics Regulation, PIC, ROHS, Lead, F-gasses, etc. Furthermore, the DEPA is responsible for a number of other activities such as conducting surveys and assessments of chemicals in consumer products, deriving quality criteria for water, soil and air, development of test and non-test methods, and coordination of research centers.

Toxicology at your institutions
Toxicologists in the Chemicals Division are involved in hazard and risk assessments of chemical substances. This involves e.g. EU harmonized classification under CLP, nomination of substances of very high concern (SVHC) under REACH, restriction proposals under REACH, derivation of quality criteria for drinking water, risk assessments of consumer products, screening to identify substances of potential concern, etc. Approximately half of the 25 employees in the division are involved with toxicology. The typical educational background for the toxicologists are pharmacy, biology, veterinary medicine, biomedicine or chemical engineering. Approximately one third of the toxicologists have a PhD while the rest holds a master degree.

Prospects/future plans/collaborations
Formalized cooperations are in place under the cooperation agreements between the DEPA and the Technical University of Denmark and Aarhus University (DCE), respectively. Furthermore, the DEPA coordinates two research centers on endocrine disruptors (CeHoS) and allergy (VFA). Finally, the DEPA will be coordinating Danish activities under the EU research program PARC with participation from a number of Danish research institutions.

References
https://mst.dk/service/om-miljoestyrelsen/organisation/miljoestyrelsens-enheder/kemikalier/
http://cehos.dk
https://dce.au.dk/
https://www.videncenterforallergi.dk/
https://www.dtu.dk/Samarbejde/raadgivning/ministerier-og-styrelser/rammeaftale-mfvm

Danish Environmental Protection Agency, Pesticides & Biocides Division

Charlotta Wallensten, Danish Environmental Protection Agency, Pesticides & Biocides Division

Introduction to organisation
The Pesticides & Biocides Division in the Danish Environmental Protection Agency (DEPA) is the responsible competent authority when it comes to evaluating pesticides and biocidal products in Denmark when it comes to human health, environment, efficacy, and physiochemical properties. Furthermore, the DEPA is responsible for implementing regulations regarding the use of pesticides and biocides.

Toxicology at your institutions
Toxicologists in the Pesticides & Biocides Division are responsible for hazard and risk assessments of pesticide and biocidal active substances and products. This involves working with European colleagues using harmonized guidelines for making both risk and exposure assessments of the products and determining safe use.

There are 20 employees in the division are involved with toxicology and human health risk assessments. The typical educational background for the toxicologists are pharmacy, biology, veterinary medicine, biomedicine, or chemical engineering. Approximately one third of the toxicologists have a PhD while the rest holds a master degree.

Prospects/future plans/collaborations
Formalized cooperation is in place with the Danish Veterinary and Food administration, who together with expert assistance from DTU perform dietary risk assessments and assess maximum residue limits.
Expert collaborations are also in place with DTU regarding assessment of microbiological pesticides and specialized parts of some active substance evaluations, for instance endocrine disrupting properties.
The Pesticide and biocide research program is still an intrinsic part of the national action plans for pesticides and biocides in 2022-2026, and the knowledge acquired through the program is integrated in the regulation whenever possible.

References
https://mst.dk/service/om-miljoestyrelsen/organisation/miljoestyrelsens-enheder/pesticider-biocider/
https://eng.mst.dk/chemicals/pesticides/grant-programmes/the-pesticide-reseach-programme/
https://www.dtu.dk/Samarbejde/raadgivning/ministerier-og-styrelser/rammeaftale-mfvm

Danish Medicines Agency

Louise F. S. Bang-Lauritsen, Danish Medicines Agency

Introduction to company/institute
The Danish Medicines Agency (DKMA) is responsible for approval and control of medicinal products and medicinal manufacturers on the Danish market, surveillance of side effects, approval of clinical trials, decisions on reimbursement of medicines, as well as supervision of medical equipment available in Denmark and monitoring of serious incidents with medical equipment. Further, DKMA appoints pharmacists, organizes the pharmacy structure, and supervises pharmacies and retailers.

We have toxicologists/nonclinical assessors in the section for Toxicology and Pharmacokinetics as well as in the clinical trial section, both of which are located in Quality Assessment & Clinical Trials Unit. The Danish medicines agency strives to be a fantastic workplace for approximately 630 employees.

Toxicology at your institutions
At the Danish Medicines Agency, toxicology is part of our nonclinical assessments supporting marketing authorizations and clinical trials, for both human and animals. In the nonclinical part of the dossier in a marketing authorisation application, numerous studies on pharmacology, pharmacokinetics and toxicology are submitted, in order to establish the proof of concept, animal pharmacokinetics and target organs of toxicity. Quality aspects of the medicine under investigation as well as clinical trial results and the proposed indication and wording of SmPC and patient information leaflets are also assessed. Toxicology may also be part of the surveillance of side effects, in order to ascertain if nonclinical studies can help clarify unwanted effects observed after marketing of a medicinal product.

Prospects/future plans/collaborations
Through collaboration with EMA, the Danish Medicines agency have members in e.g. the Nonclinical Working Group and the 3R Working Group, where guidelines regarding regulatory toxicology and the ethical use of animals in medicine testing are drafted. These working groups are currently being restructured by EMA in order to facilitate and streamline the organization. Through EMA, contributions to ICH-collaboration are also an option. An example of this is the recent update to ICH S5 (R3) on reproductive toxicology where scenarios were included to inform which animal studies may be reduced or replaced by alternative assays. Another example is ICH S1 which is also under revision in order to specify in which cases two-year carcinogenicity studies may be waived.

References
https://laegemiddelstyrelsen.dk/da/om/
https://www.ema.europa.eu/en/human-regulatory/research-development/ethical-use-animals-medicine-testing
https://ich.org/page/safety-guidelines

Danish Veterinary and Food Administration

Mette Holm and Jeanette Søgaard Nielsen, Danish Veterinary and Food Administration

The Danish Veterinary and Food Administration is the competent authority for risk management of chemicals in food and feed. We regulate unwanted – and sometimes wanted, chemical substances in food and feed. We perform control and inspection at business operators to enforce the legislation and to monitor the content of various substances in food and feed. An important part of the risk management, is to give information and guidelines to business operators about the regulation and how they can reduce the content of unwanted chemical substances in the food they produce, import or trade. We advise the public as well, giving consumers information on how to cook, wrap and eat food, to avoid or reduce the intake of unwanted chemicals from the food.

Food must be safe. This is the overarching requirement in the General Food Law in the EU. For some chemical substances, there are specific maximum legal limits for the concentration in the food. This is for example the case for pesticide residues, environmental contaminants, substances from food contact materials, food additives. For other substances there are guideline values – if the

concentration is below this limit, the food is considered safe. For a large part of the possible chemical substances no limits are set. The safety evaluation has to be performed case by case.

To set legal limits, guideline values or to perform a specific risk assessment we depend on toxicologist. The risk assessment has to be independent from the risk management. In the DFVA we mainly ask the toxicologist and risk assessors at DTU Food for advice and assessments as background for our risk management.

In the future, we expect more coordinated action across the pillars dealing with chemicals in general, chemicals in consumer products and chemicals in food. We welcome the one-substance-one-assessment concept– if the exposure of 'chemical A' from cosmetics or toys is a considered health risk, the same substance in food also has to be looked at and vice versa. Preferably, the risk assessment of 'chemical A' is to take into consideration all possible sources of exposure and the legislation (e.g. authorization, legal limits) should reflect all sources.

Danish Working Environment Authority

Flemming Ingerslev, Special consultant, Ph.D., Office of Chemicals and technique. Danish Working Environment Authority

Introduction to the Agency: The Danish Working Environment Authority (WEA) is an agency under Ministry of Employment. By carrying out inspections at companies, drawing up rules on health and safety at work, and providing information on health and safety at work the WEA contributes to the creation of safe and healthy working conditions at Danish workplaces. The WEA also contributes to ministerial service and is involved in discussions on issues related to the working environment with the social partners.

The Office of chemicals and technique is responsible for the national and EU-regulation related to chemical agents. This covers the general statutory orders on carcinogens, chemicals agents, and occupational exposure levels and a number of specific orders related to chemical agents (e.g., asbestos, mineral wool). The corresponding EU-directives is an additional area of expertise.

Toxicology at your institution: A major work area cover implementation of occupational exposure limits (OEL's) from EU-directives and for some of these a further reduction at national level (chromium 6, diesel engine exhaust, asbestos, etc.). A general review of the Danish list of OELs was initiated in 2018. This activity focuses on assessing whether the limit values on the Danish OEL-list needs update to mirror the current toxicological information sufficiently. Work on OEL's is in close collaboration with the National Research Institute for the Working Environment.

Other activities concerns carcinogens, asbestos, dust, silica dust and other agents of importance for the working environment. Among these, it is important to note process generated agents such as welding fumes, engine exhaust, smoke from fires etc.

Prospects/future plans/collaborations: The WEA will continue the activities described above. This is expected to include negotiations about asbestos on national and EU-level as well as the implementation of the fourth amendment of the directive of carcinogens and mutagens. Further the work on setting new OEL's is expected to be intensified in the coming years.

Department of Clinical Pharmacology (DCP), Region H

Kim Dalhoff, Department of Clinical Pharmacology (DCP), Bispebjerg and Frederiksberg University Hospital (BFH)

Introduction to institute
Clinical toxicology is a substantial part of the functions of DCP/BFH. The department runs – together with two other departments at BBH – the Danish Poison Information Center (DPIC) which opened in 2006.

Toxicology at your institution
DPIC is a national centre which gives advice to the public and to health care staff about acute poisonings including Greenland and The Faroe Islands. DPC is responsible for advice given in relation to acute intake of medicines.

Prospects/future/collaborations
The number of enquiries to the DPIC has increased constantly from 10,000 calls in 2007 to almost 40,000 calls in 2021. In addition to specific patient-related advice we also follow changes in the patterns of poisonings in Denmark. We have numerous collaborators nationwide including Health Care Authorities and physicians treating the poisoned patients. In the future one of our main goals is starting initiatives to prevent poisonings e.g. medication errors in nursing homes.

References
S Bøgevig, LCG Høgberg, KP Dalhoff & OS Mortensen. Status and trends in poisonings in Denmark 2007-2009. Dan Med Bull 58/5 Maj 2011

Toxicology at Danish Departments of Occupational and Environmental Medicine,

Paula E. C. Hammer[1,2], Ann C. Lyngberg[2], Anja J. Huusom[1], Margrethe Bordado Sköld[1], Jakob H. Bønløkke[3], Harald W. Meyer[1], Niels Ebbehøj[2]

[1] Department of Occupational and Environmental Medicine – Bispebjerg/Frederiksberg University Hospital

[2] Department of Occupational and Social Medicine – Holbaek University Hospital

[3] Department of Occupational and Environmental Medicine – Aalborg University Hospital

Introduction to institute
Department of Occupational and Environmental Medicine, Holbaek and Bispebjerg/Frederiksberg University Hospital representing also the Danish Society of Occupational and Environmental Medicine

Toxicology at your institutions
Clinical toxicology has been part of occupational and environmental medicine for centuries.
Due to the multifactorial cause of many diseases Occupational & Environmental Medicine pursue to elucidate the different causes of diseases / health effects. We are interested in identifying attributable risks (the portion of disease rate attributable to specific exposures) and dose-response relationships in order to mitigate and prevent modifiable risks. Therefore, exposure and risk assessment are the core of our medical specialty.

In our daily work we practice clinical toxicology in a broader context regardless the origin of a toxicological exposure being from work or the environment and regardless its health effects being chronic or acute. We asses individual and combined toxicological exposures (such as industrial and household chemicals, PFAS, PCB, asbestos etc.) among individuals, for instance pregnant women and patients with cancer, and among groups for instance workers from specific occupations.
The clinical perspective in toxicology is important because risk is not the same as disease in the same way as exposure is not always the same as risk. In our daily practice we translate research into clinical relevance for our patients.
Furthermore, we practice risk communication specially at both individual and group level translating relative risk into absolute risks.
Adequate risk communication is especially important because risk perception influences behavior in both individual, group and public health level often regardless laws, regulations and expert evaluations. Occupational & Environmental Medicine pursue to provide information without causing inadequate worries and panic and unnecessary costs - for example screening programs that do not (in an evidence-base matter) alter risks or health effects. Furthermore, adequate risk communication contributes to a fruitful collaboration with the media.

Prospects/future plans collaborations
Exposure and risk assessment, risk management and risk communication can be a puzzle, so the right piece at the right moment is crucial to get the right picture and each piece is important. Systematic collaboration can open doors to gather toxicological know-how from different sources (institutions, organizations, companies, authorities, hospitals etc.) so knowledge can be translated into actions benefitting individuals and populations.

Private companies/industries

Novo Nordisk A/S

Alan Christensen
Toxicologist, Principal Scientist, Toxicology Outsourcing Specialist. Novo Nordisk A/S

Introduction to company
Novo Nordisk A/S are a global healthcare company, founded in 1923 and headquartered just outside Copenhagen, Denmark.

Novo Nordisk A/S purpose is to drive change to defeat diabetes and other serious chronic diseases such as obesity, and rare blood and rare endocrine diseases. This is done by pioneering scientific breakthroughs, expanding access to our medicines and working to prevent and ultimately cure the diseases we treat.

Novo Nordisk A/S employ more than 47,000 people in 80 offices around the world.

Toxicology at your institutions
The role as Toxicologist at Novo Nordisk is having the responsibility of performing non-clinical (toxicology) studies supporting the safety assessment of drug candidates throughout development. The role involves extensive interaction with other scientists and clinicians both within and outside the company and internationally, designing and implementing the programs of work necessary to satisfy ethical safety standards internally and for submission to national drug regulatory bodies.

In addition to this also toxicological assessments to Product Supply. As CRO coordinator, also responsible for ensuring high quality and cost effective outsourcing to CROs.

Prospects/future plans/collaborations
In addition to the standard animal toxicity testing as per international guidance, technological advances are changing the ways in which we generate data, analyze and look at these. Submission of large datasets to authorities (SEND) with the possibility to use control data more efficient within a company and sharing externally.

Also in vitro models offer new ways for relevant toxicity testing, which have the potential to reduce the need for animal testing and maybe offer more cost-efficient and timely results. As examples are “organ on a chip” models, use of read-across and use of In Silico testing.

Lundbeck A/S

Karina Bernholm, DVM, MSc App. Tox., Senior Director of Drug Safety.
Allan Dahl Rasmussen, MSc, PhD, DABT, ERT, Director of Regulatory Toxicology & Safety Assessment.
H. Lundbeck A/S

Introduction to company/institute
H. Lundbeck A/S is a pharmaceutical company situated in Valby, that specializes in CNS diseases. Approximately 6000 people work for Lundbeck worldwide and cover both research, development, production and marketing, as well as other functions relevant for an international pharma company.

The company has 2 toxicology departments that house 14 toxicologists.

Toxicology in our departments
The main tasks covered by the 2 departments are:
- Toxicological assessments of compounds potentially entering the development pipeline, using both in silico, in vitro and in vivo models to select the best possible candidates.
- Continuing the toxicological assessment of the compounds that have entered the pipeline with focus on protecting healthy volunteers and patients in clinical trials, bringing the compound safely to the market.
- Support compounds on the market with analysis of incoming data as well as additional toxicology studies and evaluations to support the safety of patients using our compounds worldwide.

The departments also support:
- Environmental assessments of the fate and effects of marketed compounds in the ecosystems.
- Production and other types of handling of compounds by generating data and assessments for work and cleaning instructions.

Prospects/future plans/collaborations
It will continue to be a Lundbeck strategy to employ a diverse group of people originating from the natural sciences to cover the expanding field of toxicology. The group thus hold MSc, DVM and PhD degrees from several areas and come with extensive experience from both academia, public institutions and other pharma companies.

At Lundbeck, toxicologists are encouraged to expand their knowledge by attending conferences, seminars, on-the-job training, etc. Also, time is allocated to work on and obtain additional credentials such as ERT, DABT, MSc MIND, MSC App. Tox., if the toxicologist wishes to do so.

We will continue to be involved in collaborations with consortia such as IMI, IHI and EFPIA as well as working for professional societies within toxicology.

Scantox

Mikkel Lykke, Scantox A/S

Scantox is a pre-clinical research organization (CRO) primarily working within regulatory toxicology. Scantox is GLP and GMP accredited by the Danish Medicines Agency and DANAK. As a CRO we offer a wide range of services within toxicology, pharmacology, pathology and medical devices. At Scantox we work with rodents, rabbits, dogs and minipigs. At Scantox we are well-known for our minipig expertise and are among the global leaders in minipig toxicology.

At Scantox most studies performed is within regulatory toxicology and are performed according to regulatory guidelines e.g. OECD GLP and ICH. Our toxicology studies range from dose range finding studies to chronic 39-week studies and they are used to identify the appropriate dose levels for the subsequent clinical studies. The potential toxicological effects are assessed by clinical evaluation of the animals e.g. body weight and food consumption. Blood samples are collected for clinical pathology and bioanalysis. Additional examinations include electrocardiography and ophthalmoscopy. At the end of the study a histopathologic evaluation is performed to determine any morphological organ changes.
Study Directors (toxicologists) are the main point of contact throughout the study -from writing of the protocol, supervision of study activities until the study report is finalized and archived. The Study

Director is responsible for evaluating the collected data and determining the no-observed-adverse-effect-level (NOAEL).

The future plans for Scantox are to grow the company organically to be able to service clients with a full pre-IND package which also include genetic toxicology. We will continue to expand our panel of biomarkers as well as digitization within histopathology by using a new slide scanner.

Predictive toxicology at LEO Pharma

Klaus Rytved, PhD. ERT, Principal Scientist. Mikael Egebjerg, PhD. ERT, Senior Scientist. Janne Koch, PhD, Manager.

Introduction LEO Pharma
LEO Pharma is a mid-sized pharmaceutical company focusing on medical dermatology. We seek to develop systemic treatments of skin diseases using small molecules. This includes new drug modalities such as protein-protein interaction modulators (PPIm) and targeted protein degraders (PROTACs).

Toxicology at LEO Pharma
The predictive toxicology team at LEO is responsible for safety assessment of new targets, in silico, vitro and in vivo toxicity profiling of small molecules and selection of candidate molecules to be profiled in the regulatory GLP toxicity studies.
We subcontract the majority of the in vitro toxicity studies to CROs. This includes off target screening, genetic toxicology, cytotoxicity etc.
In our in-house facilities, we can conduct rodent toxicity studies up to 2 weeks of duration.

Future plans
In the predictive tox team we seek to follow the latest development in the field.
In vitro toxicity testing is transforming from testing in 2D cultures (monolayers) to 3D cultures (spheroids) and micro physiological systems. We are evaluating these systems with the purpose of implementing 3D in vitro toxicity screening for most in vitro tox endpoints.
We are currently evaluating new approaches to in silico assessment of chemical structures to aid the selection of the best molecules to be synthesized and tested.
In our animal facilities we are continuously working to improve animal welfare as for instance performing CMS (capillary micro sampling) in mice and rats. This technique makes is possible to take up to eight blood samples per animal with 24 hours thereby avoiding the use of satellite animals in the tox studies, and therefore the CMS technique is both at refinement and reduction initiative.

Novozymes A/S

Denisa Cupi, PhD, Novozymes A/S

Introduction to company/institute
Novozymes is the world leader in biological solutions, providing a wide range of enzymes, microorganisms, technical and digital solutions, which help our customers produce more from less. Novozymes was named most innovative company in Denmark by the European Patents Office. The main business areas are ‘Household Care’, ‘Grain & Tech Processing’, ‘Bioenergy’, ‘Food, Beverages and Human Health’, and ‘Agriculture, Animal Health and Nutrition’. Some of the strategic highlights at Novozymes have been investing in advanced protein solutions, strengthening the BioHealth

business (with pre- and probiotics), increasing ethanol production efficiency, novel enzyme-based crop protection solutions, among other things.

Toxicology at your institutions
We are a group of toxicologists providing support to the entire organization related to toxicology and ecotoxicology and general safety assessment of Novozymes products. Since Novozymes has a broad range of business areas and industries, various toxicological and ecotoxicological tests are performed as per requirements of each industry, and internal safety requirements.
Novozymes has Science Ethics Committees to ensure that Novozymes projects always are in compliance with high ethical standards. All studies involving laboratory animals or human trial subjects must be reviewed and approved by SEC prior to initiation.

Prospects/future plans/collaborations
Novozymes' purpose looks ahead to what we can achieve together with customers, consumers, governments, academia and others around us in terms of finding the sustainable answers that our world needs. Novozymes has a very active involvement with trade organizations (e.g. AMFEP). Novozymes toxicologists are open to collaborating with external colleagues on expanding the network, sparring on toxicological issues, discuss on how to best implement new guidelines, new testing strategies for replacing the use of animals, etc.

3Rs Management&Consulting

Erwin Roggen, 3Rs Management and Consulting ApS

Introduction to company: 3Rs Management and Consulting ApS (2009) is a non-profit initiative promoting implementation and application of promising mechanism-based novel approach methods (NAMs) by industry and regulatory authorities in the areas of skin, respiratory and food sensitization, as well as systemic repeated dose toxicity. The company is co-founder of SenzaGen AB (2011) (S), specialized in cell-based solutions to identify sensitizers, including proteins, based on key events of AOPs for skin and lung sensitization, and ToxGenSolutions BV (2015) (NL) aiming at human relevant peripheral biomarkersreflecting key processes of pathology leading to neurodegeneration, immunosuppression and carcinogenesis that are affected by environmental and systemic risk factors.

Toxicity assessment is based on the mechanistic information captured in (q)AOPs and AOP networks. NAMs that reflect key events (KEs) affected by (environmental) chemicals are used to assess the potential of the chemical to deteriorate physiological processes into pathology. The applied NAMs include *in silico* (RASAR, Toxicokinetics), *in vitro* (2D, 3D), machine learning and artificial intelligence-based approaches. The toxicity endpoints of interest include skin, respiratory and food sensitization, neurodegeneration (current focus on late-onset Alzheimer's disease), immunosuppression, carcinogenesis and systemic repeated dose toxicity.

Prospects/future plans/collaborations: (1) ***'Full validation of a microRNA profile'*** capable of identifying individuals at risk for progressing into late-onset Alzheimer's disease. The profile is based on mechanistic data reflecting normal physiology, pathology and chemical neurotoxicity. This project is supported by EuroStars (3 years) and is a collaboration with TAmiRNA (AU) and OPTOI (I). (2) Development of a ***'Probabilistic Risk Assessment'*** tool for systemic repeated dose toxicity in the context of the Horizon2020 project ONTOX (ONTOX project (ontox-project.eu)) (5 years). (3) ***'New Generation Health Care'*** project aiming at preventing disease by timely diagnosis of individuals at risk for progressing into disease with focus on the impact of environmental chemicals on health

while taking into account gender differences. The project partners as well as funding resources are being identified. Anticipated start date: early 2023.

References:

2017: Application of the AOP concept to structure the available *in vivo* and *in vitro* mechanistic data for allergic sensitization to food proteins (https://doi.org/10.1186/s13601.017.0152.0)
2017: An AOP for sensitization of the respiratory tract by LMW chemicals: Building evidence to support the utility of *in vitro* and *in silico* methods in a regulatory context (https://doi.org/10.1089/aivt.2017.0010)
2019: Applying the AOP for food sensitization to support *in vitro* testing strategies (https://doi.org/10.1016/j.tifs.2019.01.014)
2021: A tau-driven AOP blueprint toward memory loss in sporadic (late onset) Alzheimer's disease with plausible MIE plug-ins for environmental neurotoxicants (https://doi.org/10.3233/JAD-201418) 2022: Sporadic Alzheimer's disease and neurotoxicity-related microRNAs affecting KEs of the tau- driven AOP toward memory loss (https://doi.org/10.3233/JAD-215434)
2022: Building a network of AOPs linked to the tau-driven AOP toward memory loss (JAD – accepted) 2022: ''In Litero" Screening: Retrospective Evaluation of Clinical Evidence to Establish a Reference List of Human Chemical Respiratory Sensitizers (Frontiers – in review).

FORCE Technology

Pia Brunn Poulsen, FORCE Technology

Introduction to company/institute

FORCE Technology is an international technology consultancy and service company. Based in Scandinavia, FORCE Technology makes a global footprint. With a strong infrastructure of facilities and skill sets, we advice and service our clients globally in the energy and environment industries, the electronics industry, the lifescience industry, the food industry, the oil and gas industry, and in the maritime industry, among others. FORCE Technology is government approved (is one of the large GTS Institutes in Denmark) and dedicated to develop and use technologies and new knowledge for the benefit of companies and the society as a whole. FORCE Technology has existed since 1940 and employs today about 1,100 employees.

Toxicology at your institutions

Toxicology is not a research discipline at FORCE Technology. FORCE Technology is a user of toxicology and of risk assessment. FORCE Technology is using risk assessment qualifications in combination with our expertise in chemical analysis for private customers and in surveys contracted by the Danish Environmental Protection Agency under the program "Survey on chemicals in consumer products" (Danish EPA, 2022). FORCE Technology has for the almost 20 years been involved in different surveys on chemicals in different consumer products, where a risk assessment of identified chemical substances has been carried out, as well as chemical analysis of different consumer products. The latest (published) project FORCE Technology has been involved in has been "Survey and risk assessment of chemicals in textile face masks" (Poulsen, Knudsen et al., 2021), where a risk assessment of antimony and formaldehyde identified in textile face masks was carried out in cooperation with Lisbeth E. Knudsen (University of Copenhagen).

Prospects/future plans/collaborations

Only a limited number of private companies is involved in risk assessment for the Danish EPA surveys. The number has been decreasing the last couple of years and limits the number of advisors/tenderers for the Danish EPA consumer projects. More collaborations are needed in this area.
The consultancy tasks carried out by FORCE Technology for private customers, have in recent years demonstrated new product types, which in combination with a circular economy in a globalized

world, result in products produced in recycled materials. This introduces new toxicological concerns in some business areas and underlines the need for toxicological expertise and collaboration between experts in this field.

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DHI, Industry – Environment & Toxicology

Poul Bo Larsen & Brian Svend Nielsen, Industry, Environment and Toxicology: DHI A/S

Introduction to company/institute

DHI, Industry – Environment & Toxicology Eighteen employees within toxicology and ecotoxicology.

Services: Consultancy within regulatory toxicology - Risk/ safety assessment of chemical substances for both environment and health.
Sectors: EU authorities, Chemical Industry, Production Industry, Medical Device and Pharmaceutical sector, Food Industry

Toxicology at your institutions

Focus on regulatory requirement and how to justify and comply.
Data gap analysis; alternatives, in silico models, testing strategy; test design; generation of data; risk /safety assessment.
Courses/ webinars in toxicology and regulatory issues on chemical safety assessment (e.g. whit-in REACH; Biocide regulation, Medical device regulation, Food regulation)

Prospects/future plans/collaborations

Collaboration with e.g.: Danish EPA, ECHA; Dansk Standard; TI, Force, NFA, Dansk Miljøanalyse, DTU Food, Medicoindustrien
Development of further partnership to complement our services.
Further development of courses/ seminars in toxicology and safety/ risk assessment within different regulatory areas.

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Mette Due Theilade, PIP Adviser

Mette Due Theilade is an independent consultant specialised in nonclinical development, paediatric investigation plans and gene therapy.
The path to establishing her own business has been through employments in regulatory agencies and pharmaceutical industry, where she has worked with different aspects of these three main areas.
Becoming an independent consultant made it possible to combine these areas of interest to work on assignments covering several of them. For instance, paediatric investigation plans demand an evaluation of the need for and design of juvenile animal studies, and furthermore, some of these plans are concerning development of new gene therapies.

Collaborations take place through a network of colleagues within these different fields, and through affiliations with small or larger companies and consultancy agencies.

Nordic Universities/research centers

Mapping the competence situation and needs for chemical risk analysis and safety in the Nordic countries

Lisbeth E. Knudsen, UCPH Denmark
Hubert Dirven, NIPH Norway
Matti Viluksela, Finland
Hrönn Ólína Jörundsdóttir - MAST
Åke Bergman, Orebro University, Sweden

Introduction
As active in the area of Chemical Risk Analysis (Risk assessment and Risk communication) of chemicals, we are concerned that our five Nordic countries within some years will not be able to meet societal demands for highly educated and well-trained professionals to contribute with high-quality knowledge in the governmental, private and non-governmental sectors. The concern is further pronounced as such competence needs will become even more demanding as the European Commission Green Deal initiatives are to be managed. The prevention of health hazards from chemicals is high on the political agenda through, among others, the Chemicals Strategy for Sustainability, and the EU Action Plan: Towards Zero Pollution for Air, Water, and Soil

The process of the mapping is as follows:
Step 1. National users of toxicology in government and private industries are kindly asked to fill in the electronic questionnaire and return it, according to the instructions in the questionnaire. Universities will be approached separately through interviews and emails in order to collect their view on the risk analysis competence provision task.
Step 2. (OPTIONAL) For those responding to the questionnaire who wants to have direct contact with the project group for clarifications purposes or for expanding their input, will be contacted after we have received such a request from you. Please respond to your national contact point for this survey.
Step 3. A report will be prepared for the Nordics based on the responses we have received.
Final steps. Launching the results of the mapping (digitally) and approaching our Nordic governments and other relevant decision-makers. The result of the mapping will be presented to the European Commission

The human toxicology environment in Norway

Hubert Dirven and Birgitte Lindeman. Department for Chemical Toxicology, Division of Climate and Environmental Health at the Norwegian Institute of Public Health.

Toxicologists are employed in different sectors in Norway. Both ecotoxicologists and human toxicologists are employed in industry, in government, at universities and at research institutes.

There are large oil and chemical industries in Norway like Equinor, Aker BP, YARA, and Norsk Hydro where there is a need for toxicological competencies. There is no longer a large pharmaceutical industry in Norway, like Nycomed Imaging in the past, with in-house toxicology expertise, but there are a large number of small to medium (bio) pharmaceutical industries with is a need for toxicological competence like Bayer Algeta, Vistin Pharma, Photocure, Aker Biomarine, GE Healthcare and others.

Toxicologists are also employed at regional and national authorities. The two most important national regulatory agencies regarding chemicals are the Norwegian Environment Agency (Miljødirektoratet) and the Norwegian Food Safety Authority (Mattilsynet). Medicinal drugs and medical devices are the responsibility of the Norwegian Medicines Agency. Norway is an EEA country and follows the EU regulation on chemicals and pharmaceuticals as set by the European Commission.

At a number of universities in Norway it is possible to take a MSc or PhD education in toxicology. There is a large focus on ecotoxicology at universities like the Norwegian University of Life Sciences (NMBU), University of Bergen, Norwegian University of Science and Technology (NTNU), University of Oslo (UiO) and others. The number of universities that provide human toxicology courses is more limited with UiO and NTNU in Trondheim as the most important players. The number of professors at universities with a specialization in human toxicology is very limited.

A lot of toxicology advice to the government and European organisations is provided by research institutes. Some of these institutes are mainly paid by the government, like the National Institute of Public Health (NIPH), the National Institute of Occupational Health (STAMI) and the Norwegian Veterinary Institute (NVI) and others. Research at these institutes is mainly financed by competitive grants. Other institutes like the Norwegian Institute of Air Research (NILU) and The Norwegian Institute of Water Research (NIVA) are with respect to funding more dependent on contract research.

Because of the lack of dedicated research programs in the Norwegian Research Council the number of awarded research programs in the area of human toxicology in the last 7 years is almost zero.

Recruitment of toxicologists with a PhD degree to the area of human toxicology is under pressure. Both the Norwegian Society for Pharmacology and Toxicology (NSFT) as well as the Norwegian Scientific Council on Human Toxicology (Fagrådet for humantoksikologi) have tried to put this topic on the agenda, so far without measurable success.

Toxicology at the Norwegian Institute of Public Health (Folkehelseinstituttet)

Hubert Dirven, Department for Chemical Toxicology, Division of Climate and Environmental Health at the Norwegian Institute of Public Health.

The Norwegian institute of Public Health is a knowledge provider to the Norwegian government and is placed directly under the Ministry of Health and Care Services. The institute is maintaining several health registries like for example the Mother, Father and Child study (MoBa) and biobanks. The

knowledge-based advice is supported by a large research portfolio, that is mainly financed by EU programs like Horizon 2020 and Horizon Europe.

Most of the toxicology activities are placed in the division of Climate and Environmental Health (headed by Dr Ågot Aakra). There are 3 departments in this division: Air quality and Noise headed by Dr Kristin Bjerve Gützkow, Food safety headed by Dr Cathrine Thomsen and Chemical Toxicology headed by Dr Hubert Dirven. Currently 72 people are employed in the division, including PhD students and postdocs. There are approximately 25 toxicologists with a Dr degree employed, which makes NIPH the largest human toxicology group in Norway.

All researchers in the department work up to 50% with advisory work for the Norwegian food safety Authority (Mattilsynet) and the Norwegian Environment Agency (Miljødirektoratet). The Environment Agency is competent authority for REACH chemicals. Members of the department are active in EFSA panels, in the Scientific Committee for Consumer Safety, the Norwegian committee for Food Safety and the Environment and OECD working groups. Currently the staff in the department is involved in the general PFAS restriction, in the evaluation of 160 EOGRT studies as initiated by ECHA, in safety assessment of chemicals in toys and in read-across activities for ECHA.

Human biomonitoring, neural development toxicity, immunotoxicology and inhalation toxicology are focus areas for the division within toxicology. Both epidemiological competence and well-equipped laboratory facilities are available to perform research. The department is participating in a large number of EU projects like:

- **Athlete** (874583) and **Eximious** (814707), both are exposome projects
- **ONTOX** (963845) on the use and development of New Approach Methods for the risk assessment of chemicals
- **POLYRISK** (964766), studying the exposure and effects of nano- and microplastics on human health
- **Ultrhas** (9553909, studying the health effects of ultrafine particles produced by engines
- **HBM4EU** (733032), European biomonitoring initiative
- **Partnership for the Assessment of Risk from Chemicals** (PARC). NIPH is both grant signatory and participating mainly in WP4 (biomonitoring), WP5 (hazard assessment) and WP6 (risk assessment)

The division is also participating in the Center of Excellence CERAD to study the effect of low doses of radiation on human health.

Finland: Competences and needs

Mapping the competence situation and needs for chemical risk analysis and safety in the Nordic countries: Preliminary results from Finland

Matti Viluksela, University of Eastern Finland (UEF) and Finnish Institute for Health and Welfare (THL), Finland
Lisbeth E. Knudsen, University of Copenhagen (UCPH), Denmark
Jaana Rysä, University of Eastern Finland (UEF), Finland
Kimmo Peltonen, Finnish Safety and Chemicals Agency (TUKES), Finland
Hubert Dirven, Norwegian Institute of Public Health (FHI), Norway
Hrönn Ólína Jörundsdóttir, Icelandic Food and Veterinary Authority (MAST), Iceland - MAST
Åke Bergman, Stockholm University (SU) and Örebro University, Sweden

Mapping of the competence situation and needs in Finland was carried out using an electronic questionnaire as described by Knudsen et al. (Ibid.). Number of responses was 13 out of 50 (26%) of which 4 represented research institutes, 5 national authorities, 2 industry/businesses and 2 consultants. Most (84.6%) of the respondent organizations has currently a need for hiring competent personnel, mainly toxicologists, and most of them (93.7%) find it necessary to train their new personnel due to limited expertise in the beginning. In general, there is a need for toxicologists both at MSc and PhD level, and most candidates lack sufficient experience in risk assessment. There is a need for specialists in general toxicology, occupational toxicology and industrial hygiene, regulatory toxicology and ecotoxicology, environmental toxicology, and risk assessment. Importantly, it has been very challenging to recruit medical doctors with interest in clinical toxicology. This is likely due to the lack of subspecialty training in clinical toxicology in Finland, and the fact that there is currently no professorship in clinical toxicology.

Respondents found it necessary to strengthen both national and joint Nordic educational efforts to optimize the number of competent experts in the field of chemical risk analysis. The Nordic training cooperation could include joint Nordic training courses and workshops in toxicology and risk assessment (e.g. by NIVA, NKE), student exchange programs and postgraduate training. A directory of Nordic experts with information on the field of their expertise was considered useful. It was also proposed that an organization like the former Nordic School of Public Health should be established.

Danish Universities/research centers

National Research Centre for the Working Environment

Karin Sørig Hougaard[1,2], Jorid Sørli[1], Anne Thoustrup Saber[1], Marie Frederiksen[1], Jakob Klenø Nøjgaard[1], Niels Hadrup[1,3], Keld Alstrup Jensen[1], Ulla Vogel[1,3]

[1]National Research Centre for the Working Environment, [2]Section of Environmental Health, Department of Public Health, University of Copenhagen, [3]DTU Food, Technical University of Denmark,

Det Nationale Forskningscenter for Arbejdsmiljø (NFA)
(National Research Centre for the Working Environment (NRCWE))
NFA is a government research institute under the Danish Ministry of Employment. It's goal is to generate and disseminate knowledge contributing to a safe, healthy work environment in accordance with the technical and social developments in the Danish society. The annual budget is 13 million EUR and the total staff amounts to approx. 130. Occupational nanosafety and chemical working conditions constitute one of NFA's five strategic research areas. Website: www.nfa.dk.

Toxicology at the NFA
At the NFA, we prioritize research on substances and materials produced and used in high volumes and/or identified to be highly toxic as well as emerging chemical risks. During the last decade, we have had strategic focus on the risks associated with exposure to manufactured nanomaterials, especially following exposure via the airways. Recently, we expanded the strategic focus to also include other particulates and VOCs as well as exposure via skin. Our research projects include epidemiological, biomonitoring, animal and in vitro studies (cellular as well as acellular setups). Our entire research portfolio covers the full cycle from substance identification, testing and measurement methods, release and exposure assessment, hazard identification by testing of toxicity to full assessment and management of risks. The toxicological research mainly focuses on cancer, cardiovascular disease, reproductive and developmental toxicity, and acute lung toxicity end-points. We also endeavour into understanding toxicological mechanisms and establishment of molecular initiating events and adverse outcome pathways and alternative test methods. NFA acts as advisor to the Working Environment Authority and generate documentation for health-based occupational exposure limits for the Working Environment Authority. Results from this work recently served as basis for lowering of the occupational exposure limits for chromium VI, asbestos and diesel engine exhaust. Funding is achieved from several sources, including EU, with FFIKA (Focused Research Effort on Chemicals in the Working Environment) from the Danish Government, as the overarching project.

A main goal is to contribute to create knowledge and improve regulation of the chemical work environment. The number of different chemicals and particulates is extremely high, precluding adequate toxicological testing of chemicals on an individual basis. Our work to delineate mechanisms-of-action and development of Adverse Outcome pathways (AOPWiki) can help to speed up the assessment process. Among other methods, we highlight development of the "artificial lung" (a constrained drop surfactometer), exposure- and biomonitoring in diverse occupational settings and the use of Danish health registers and cohorts to identify health risks related to occupational exposures, e.g. autoimmune diseases, infertility and adverse pregnancy outcomes.

Experimental Pharmacology and Toxicology, UCPH

Pernille Tveden-Nyborg and Jens Lykkesfeldt,
Experimental Pharmacology and Toxicology; Department of Veterinary and Animal Sciences; Faculty of Health and Medical Science; University of Copenhagen.

Introduction to company/institute
Department of Veterinary and Animal Sciences at UCPH provides Denmark with skilled candidates within veterinary medicine and animal science and creates new knowledge in food safety, antibiotic resistance, animal models and welfare, immune system and lifestyle diseases. The department covers a wide spectrum of animal and human disease biology in close collaboration with other departments at the University of Copenhagen. We are among world leading within fields such as cell pathology, host-agent interactions, food safety and health in developing countries. The department comprises 8 sections with a total of about 400 employees.

Toxicology at your institutions
The department is responsible for teaching pharmacology and toxicology as part of the curriculum for students enrolled in the veterinary medicine, animal science, human nutrition and biotechnology study programs on both bachelor and masters level. Particularly for the veterinary masters' education, toxicology is a defined part of the Biomedicine Differentiation aimed at students with a particular interest in pursuing a career within biomedical research. Toxicology projects are also part of proposals for bachelor and master theses. Not a main feature of the course plan, toxicology is part of the PhD courses on in vivo pharmacology, laboratory animal science and laboratory animal pathology. Teaching includes lecturers from academia as well as external partners situated in the pharmaceutical industry and from ministerial offices, when relevant. Lecturers also contribute chapters on toxicology to text books, e.g. for laboratory animal science, and publish research findings in peer-reviewed journals targeting toxicology. In this way, toxicology is recognized as its own field, combining knowledge of basic principles with practical and clinical applications and research outlook within veterinary and translational science.

Prospects/future plans/collaborations
Ongoing plans include efforts to maintain the visibility of toxicology, enabling students to gain an interest in the field and appreciate the values of toxicological investigations. In addition, efforts are made to ensure that lecturers remain updated, e.g. through attendance to toxicology meetings and through individual research projects and collaborations with the pharmaceutical industry.

Toxicology and Drug Metabolism Group,

Bjarne Styrishave, Department of Pharmacy, Toxicology and Drug Metabolism Group, Faculty of Health and Medical Sciences, University of Copenhagen

Introduction to organisation
The Toxicology and Drug Metabolism Group, Dept. of Pharmacy, performs experimental research revealing the toxicological, metabolic and endocrine effects of xenobiotics, especially pharmaceuticals, with the aim of assessing their risks to humans and biota. We apply various *in vitro, ex vivo and in vivo* assays and advanced analytical techniques, such as LC-MS and mass spectrometry imaging. The group consists of 4 scientific staff members, 2 lab technicians, 2 postdocs, 4 phd students and 11 master students.

Toxicology at your institutions
The Toxicology and Drug Metabolism Group is responsible for teaching the course in Toxicology and Drug Safety, a 7.5 ECTS, 7th semester Master course, mandatory for all pharmacist students. The course has 180-220 students. The group also train approximately 10 master thesis students within the area of drug toxicology each year.

Prospects/future plans/collaborations
Our goal is to elucidate side effects on growth and reproduction associated with drugs use, in order to improve treatment regimens and drug design. The research group has world leading expertise in effects of drugs, and metabolites on endocrine systems. Using advanced analytical chemistry we investigate all major drug classes on the Danish market to unravel any unintentional effects that these drugs and their metabolites may have on the endocrine system. Together with our national and international partners we investigate the mechanisms by which drugs interact with mammalian endocrinology, to provide better drugs for the general population. We also perform mass spectrometry imaging studies of drug and metabolites in samples from laboratory animals and in clinical samples, providing information on whether a drug reaches the target and where it is metabolized. The distribution of a drug in an entire animal or the permeation through skin or the intestine is of importance in pharmaceutical development.

Department of Public Health, University of Copenhagen

Line Mathiesen, Martin Roursgaard, Peter Møller, Lisbeth E. Knudsen

Introduction to the Department of Public Health, Section of Environmental health
The research is focused on the interaction between environmental factors and vulnerability, including groups such as the fetus, children and the elderly. The principal emphasis is on the development of:
Molecular and functional assessment of exposure, susceptibility and effects

- Experimental in vitro and in vivo model systems
- Alternatives to animal experimentation

applied in the study of:

- Health effects on children and pregnant women of exposure to chemical agents
- Health effects of particles produced by atmospheric pollution and nanotechnology

Toxicology at our unit
Toxicology is the major activity in the Molecular Epidemiology and Toxicology Group where experimental models are the tools of choice for the hazard assessment of contemporary exposures. Our research focuses on mechanisms of action of environmental agents, using cell cultures, experimental laboratory models and controlled human exposures. The research strives to use experimental models to reduce or replace animal experiments.
The participation in the Human Biomonitoring for Europe (HBM4EU) program implies use of toxicological data in design and interpretation of results from human biomonitoring activities

Prospects/future plans/collaborations
Whilst the majority of the Department of Public Health conducts “dry” research we also have a strong lab focused on biological effects of pollution as well as clinical specialities (General practice, Social medicine and Work and Environmental medicine). This gives us unique opportunities within research,

teaching and societal impact. However, we need to strengthen the links between the clinical groups, which are not physically co-located with the Department. Likewise, we should strengthen links with external core wet collaborators and multiple groups at hospitals across Copenhagen and Zealand.

References:
Placenta Perfusionsprojekt – Københavns Universitet (ku.dk)
https://www.hbm4eu.eu/about-us/about-hbm4eu/

Environmental Medicine, University of Southern Denmark

Helle Raun Andersen, Philippe Grandjean, Environmental Medicine, University of Southern Denmark

Toxicology at your institution
SDU Environmental Medicine focuses on the long-term adverse effects associated with early-life exposures to environmental chemicals, such as PFAS and pesticides. Because of the intense developmental processes and the substantial maturation of organ functions happening prenatally and during early childhood, this life stage is particularly vulnerable to adverse effects from toxicants. Further, as these processes cannot be repeated, the adverse impacts may be difficult to compensate and may be lasting. The SDU team has therefore focused on prospective birth cohorts, at first inorganic lead, then methylmercury, followed by a variety of halogenated substances, especially the PFASs as well as non-persistent substances including some currently used pesticides. Given that exposure levels may change substantially during early life, sometimes impacted by the duration of breastfeeding, efforts have concentrated on obtaining biological samples that reflect vulnerable ages, e.g., umbilical cord blood. In some cases, where blood samples were missing, serum concentrations have been estimated. Cumulated evidence shows that cross-sectional studies likely underestimate exposure-related effects and that exposure profiles may be needed for proper risk assessment.

Prospects/future plans/collaborations
In collaboration with Pál Weihe, Faroese Hospital System, the sixth Faroese birth cohort is currently being formed, and a new cohort will also be recruited in Odense to supplement the Odense Child Cohort. These cohorts will be followed with more detailed exposure monitoring, and older cohorts will be examined in further detail to reveal long-term consequences of exposures incurred during early life. These efforts aim at providing more complete documentation of the adverse health consequences of the exposures.

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Department of Public Health, Aarhus University.

Eva Cecilie Bonefeld-Jørgensen, Maria Wielsøe, Manhai Long, Vivi Schlünssen, Department of Public Health, Aarhus University.

ONGOING ACTIVITIES AND PERSPECTIVES FOR TOXICOLOGY AT THE INSTITUTION.

The Department of Public Health at Aarhus University is a part of the Faculty of Health at Aarhus University including five departments focusing health science, clinical science & health education. The Department of Public Health include 13 research units of which especially two units (i, ii) focus on public health risk upon exposures to environmental and occupational chemicals and organic compounds.
i. The Centre for Arctic Health & Molecular Epidemiology (CAHME), Aarhus University, Center director Professor Eva Cecilie Bonefeld-Jørgensen is key national member of the AMAP Human Health Assessment Group.
ii. The Research unit 'Environment, Work and Health' (EWH), Research Unit head Professor Torben Sigsgaard, being a part of the Danish Ramazzini Center.

Toxicology at Centre for Arctic Health & Molecular Epidemiology (CAHME)

The CAHME focuses on human exposure to environmental chemicals, including **endocrine disruptive compounds,** and health effects on the **reproductive-, immune-, and neuro-endocrine systems**. Our research include human biomonitoring, epidemiological and **molecular toxicological** methods.
The research projects includes development of new biomarkers of exposure and effect with a focus on real-life chemical exposure mixtures. We have developed unique experimental methods to extract real-life chemical mixtures from biological matrixes and assess the combined effects in *in vitro* cell based assays. In addition, we have established laboratory methods to assess steroid and other nuclear receptor activities, oxidative stress factors, apoptosis/DNA repair, gene expressions, genetic variations, etc.
Examples of current CAHME project activities with toxicological aspects:

- *HBM4EU* - WP13 (Exposure Health relations) and WP14 (Effect biomarkers).
    - Several literature review related to PFAS exposure, including possible effect biomarkers, disruption of thyroid homeostasis, and possible mechanisms underlying the association with birth weight
    - Epidemiological study on PFAS exposure and disruption of thyroid homeostasis in pregnant women
    - Experimental study of extraction of real-life chemical mixtures from placentas and assessment of receptor activities
- *The Greenlandic ACCEPT birth cohort and follow-up.* The cohort was established in 2010-2015 and recently follow-up in 2019-20 with the overall objective to assess lifestyle, food intake, and environmental chemical exposures in the Inuit population and to investigate related health effects. We have published regional food intake, chemical blood concentrations of pregnant women and both parents at follow-up, and effects of prenatal exposures on birth outcomes and child development.
- In future projects, we will follow-up ACCEPT to explore associations between prenatal exposures, child development, and health outcomes e.g. infection frequencies. We also plan to measure new chemical groups such as phthalates, where only limited exposure information is available for the Greenlandic population.
- Exposure to persistent organic pollutants and risk of allergy and asthma among seafood processing workers in Greenland in collaboration with Clinical Associate Professor Jakob Bønløkke, Aalborg University Hospital.

Toxicology at the Research unit 'Environment, Work and Health' (EWH)

The EWH research unit focus on the impact of environmental chemical and organic factors on allergy and respiratory diseases including occupational exposures. EWH partners include researchers from other universities and medical clinicians from departments for pulmonary and occupational medicine, who bring up clinical issues that help to define and develop new research areas. The research has a strong end-user focus, with emphasis on transforming its findings into real benefits for the groups exposed to the adverse environmental conditions. That is why research projects often have an advisory group composed of key stakeholders, including ministries and labor-market organizations.

Examples of current EWH project activities with toxicological aspects:

- Participation in CEEH – the interdisciplinary Centre for Energy, Environment and Health.
- Numerous studies of acute toxicity. Conducted in the unit's advanced climate chamber, enabling scientists to directly examine inflammation in the respiratory tract after a subject's controlled exposure to environmental pollutants, indoor contaminants, air pollution and pollen.
- Leadership of CISBO – the interdisciplinary Centre for Indoor Air and Health in Dwellings, under the auspices of Real-Dania Research
- The SUS project, studying exposures and indoor heath in farm buildings, has catalogued data on 2,400 young farmers over a period of 15 years.
- A study of potential links between wood dust and the development of respiratory diseases among 2,000 workers in the furniture industry.
- Participating as WP lead in the EU Horizon projects: SPRINT who aim to assess impacts of Plant Protection Products on environment and human health, and EPHOR on the working life exposome (https://www.ephor-project.eu/).

Prospects/future plans/collaborations

AU-PH is also part of the PARC project starting on 1st May, 2022, and will contribute to activities related to human biomonitoring, effect biomarkers, mixture effects, development of AOPs and occupational studies in WP4, WP5, and WP6. The activities are described further in the presentation on 22nd April: COMING AARHUS UNIVERSITY ACTIVITIES IN THE PARC PROJECT

Centre on Endocrine Disruptors (CEHOS)

Senior researcher Anna-Maria Andersson, Dept. of Growth and Reproduction, Rigshospitalet. Leader of Centre on Endocrine Disruptors

Introduction to institute

Centre on Endocrine Disrupters (CEHOS) is an interdisciplinary scientific collaboration without walls between the research groups at Dept. of Growth and Reproduction at Copenhagen University Hospital (Rigshospitalet), DTU-FOOD at the Technical University of Denmark, and Dept. of Biology at the University of Southern Denmark. The Centre refers directly to the Chemical Unit of the Danish Environment Protection Agency (DK-EPA).

Centre on Endocrine Disrupters was first established in December 2008 on a 1-year grant on the national financial bill as the result of a political initiative. Since then it has been on the financial bill as an action under the Danish Action Plans on Chemicals 2010-2013, 2014-2017, and 2018-2021. Continuation of the Centre in 2022-2025 has been negotiated as part of the new Danish Action plan on chemicals 2022-2025. The contractual paperwork between the DK-EPA and the Centre management for this new 4-year period is currently being prepared.

The main purpose of the Centre is to build and gather new knowledge on human health effects of endocrine disrupters with the focus on providing information requested for the preventive work of the regulatory authorities. It is also a task of the Centre to point out important knowledge gaps and provide recommendations for future knowledge building initiatives. According to this, the main activities of the Centre are:

- Planning and coordination of studies related to endocrine disrupting chemicals (EDCs); i.e. investigation of mechanisms of endocrine disruption in laboratory models and health-exposure associations related to exposure to EDCs in humans, human biomonitoring of exposure to EDCs, identification of new (cross-species) effect biomarkers related to endocrine disruption, and development and optimization of test methods for the identification of EDCs.
- Scientific counselling of the authorities on matters related to EDCs
- Information to the authorities about new relevant national and international knowledge on EDCs
- Coordination of the Copenhagen Workshops on Endocrine Disrupters (COW)
- Organisation of annual educational information meeting to raise the awareness of endocrine disruption from chemicals in the environment

Some projects carried out in the Centre are partner initiated, while some are requested by the DK-EPA.

Toxicology at your institution

Partner-initiated projects carried out in the Centre are in most cases addons to ongoing research at the institutions of the three partners. At Dept. of Growth and Reproduction focus is on human studies including HBM and epidemiological studies but also in vitro models using human tissues. DTU-FOOD has expertise in animal- and in vitro models for EDC mechanisms, especially related to reproduction, and while Dept. of Biology have expertise in ecotoxicology, they also use this for developing non-mammalian test-systems for EDCs effects with relevance also for humans.

Prospects/future plans/collaborations

We look forward to the next 4-year period of CEHOS. All three partners in CEHOS will also be involved in PARC and there is great overlap between the work that has and will be carried out in CEHOS2022-2025 and several aims of PARC. Thus, work on understanding EDC mechanisms and developing AOPs will continue in CEHOS and feed into PARC as will human biomonitoring and human studies on links between exposure to EDCs and health.

References

CEHOS.dk (website in Danish)

Cell Toxicology team, DTU FOOD

Anne Marie Vinggaard, Cell Toxicology team, DTU FOOD

The Cell Toxicology team conducts research centered on the use of New Approach Methodologies (NAM) for assessing human safety to chemical exposures. Our research activities, which are funded by national or EU grants, cover the use or development of NAMs for next generation risk-assessment of chemicals.

We are currently:

- Coordinating the GreenDeal H2020 project PANORAMIX (2021-2025) dealing with adverse health effects of chemical mixtures and development of tools to implement mixture risk assessment

- Contributing to HBM4EU (2017-2022) and PARC (2022-2029), which are EU Joint programs dealing with human biomonitoring and chemical risk assessment within EU. Our PARC projects deal with development of IATA to detect endocrine disrupting chemicals and chemical mixture effects
- Partner in 'Safewater' (2021-2024) funded by the Danish Research Council, in which we are investigating Danish drinking water for contaminants
- Partner in 'PYT' (2021-2023) funded by the Pesticide Research program HBM4EU, in which we focus on adverse effects of pyrethroids
- Leading 'PluriLum' (2022-2023) funded by the Danish 3R Center, in which we develop a stem-cell based model for developmental toxicity

Research in the Research group on Molecular and Reproductive toxicology

Terje Svingen, DTU Food, National Food Institute, Technical University of Denmark

The Research Group for Molecular and Reproductive Toxicology studies how environmental chemicals can disrupt normal development and cause disease. The group has a particular focus on endocrine disruptors and how exposure to these can cause reproductive or cognitive disorders. The goal is to safeguard human health by improving chemical safety testing and risk assessment.

The group is currently involved in two EURION H2020 projects on endocrine disruption. FREIA examines how environmental chemicals can interfere with women's reproductive health and how regulators can better protect women against harmful chemicals. ATHENA focuses on better screening methods for chemical substances that affect the production and function of thyroid hormones, with one overarching aim of protecting brain development. The group is also active in PARC, with a project under WP5a (human health) looking further into multi-organ effects on endocrine disruptors to elaborate more fit-for-purpose chemical testing strategies.

Other active projects include ToAD: "Better tools for assessing endocrine disrupting properties of biocides and pesticides" under the Danish EPA's crop protection research program, with a focus on improving EU legislation that requires that all biocides and pesticides be thoroughly tested for endocrine disrupting effects. The group is also partner in the Danish Centre for Endocrine Disruptors (CeHoS) aiming at characterizing mechanisms of action for endocrine disruption alongside identifying chemicals with endocrine disrupting properties.

The Research Group for Chemical Risk Assessment and GMO

Susanne Hougaard Bennekou: DTU, FOOD

The Research Group for Chemical Risk Assessment and GMO conducts risk assessments related to the presence of chemicals as well as genetically modified organisms, GMO, in food and the environment. The work is carried out primarily for national and international authorities. The focus is on using the most relevant, evidence-based methods. The group stays up-to-date with best practice through participation in a number of Danish and international forums like the OECD, numerous EFSA scientific panels and working groups and EFSA procurements.

Research activities are in the area of developing new approach methodologies (NAM) in the context of next generation risk-assessment strategies within H2020-funded projects. More specifically the group has strong expertise in QSARs – the Danish QSAR database (http://qsar.food.dtu.dk/), NAM-based read-across, Integrated Approach to Testing and Assessment (IATA) and use of in vitro data for developmental neurotoxicity.

OECD, AOP, IATA and consultancy work

Sofie Christiansen, DTU Food, National Food Institute, Technical University of Denmark

The Organisation for Economic Co-operation and Development (OECD)'s Test Guideline Programme, TGP, develops internationally recognized standard test methods for safety testing of chemicals. Senior researcher Sofie Christiansen from the National Food Institute has been one of TGP's two national coordinators in Denmark since 2010, while the other coordinator is a staff member from the Danish Environmental Protection Agency.

In the last few years, we have been leading work under the auspices of TGP aimed at improving several test guidelines. Behind these improvements are many years of research at the National Food Institute, work that has been important for the OECD's acceptance of the changes.

More test guidelines now include an examination of the distance between anus and genitals (anogenital distance) as well as other endocrine sensitive endpoints. The enhanced tests detect more endocrine disrupting substances, thereby providing more knowledge about possible endocrine disrupting effects without using more test animals than is already required.

The OECD Adverse Outcome Pathways (AOPs) Development Programme started in 2012. The framework for systematising adverse effects of chemical exposures and their upstream biomarkers is called AOP. In short, an AOP represents a series of causally linked events following an interaction between a chemical with a biological system that ultimately lead to an adverse outcome (AO). The AOP framework will be briefly described, as well as the use of AOPs in developing Integrated Approaches to Testing and Assessments (IATAs).

The last part of the presentation will give a short glance of our research-based advice/consultancy to the Danish authorities.

European/global initiatives

Human tissue availability for scientific research – A 3R centre in Denmark initiative

Lisbeth E. Knudsen, Institute of Public health, University of Copenhagen
Jan Ottesen, NovoNordic
Peter Bollen, University of Southern Denmark
Birgitte Kousholt, Aarhus University

Introduction
A majority of toxicological studies focus on providing data for human risk assessment. Thus to obtain directly applicable results the request for human tissue availability for scientific research is increasing. In many cases human cells are preferred in cell culture studies and use of human cell tissues in *in vitro* and *ex vivo* studies are increasing.
Biobanking activities provide sources for research activities, however the access to tissue requires a number of steps starting with registries of accessible biobanks and continuing to validation of ethics approvals for secondary uses of tissue, transfer of materials and resolve of IPR issues.

Examples
Skin donation from cosmetic and obesity operations is a common source for studies of skin damage from exposures to e.g. cosmetics and medicines. This is practice in e.g. industries where the donated tissue (surplus skin) is provided from donors consenting to donate and with no access to donor identity at the recipient site. LEO Pharma get blood for in vitro assays from an internal scheme where employees at LEO sign up for a voluntary donor scheme called "Blood for Science" which is of course completely anonymous (personal communication).

Placental perfusion studies of chemical transport across placenta is a well established method providing valuable information related to prenatal exposures. The tissue, which is from healthy non smoking mothers, has to be fresh and donated after informed consent from the mother and the farther. The processing of data is pseudonomised and no personal information reported. (Knudsen 2013). Demonstration of presence of an environmental chemical in cord blood is the ultimate result from placental transfer and supported by human transplacental transport data (Mathiesen et al).

Lung – Sørli et al combined two in vitro models to assess toxicity to the respiratory system; i) a lung surfactant (LS) function assay to assess the acute inhalation toxicity potential, and ii) a cell model with human bronchial epithelial cells to study pro-inflammatory potential and modulation of inflammatory responses.

Human stem cells have major potentials in differentiating into different cells to be included in toxicological testing as eg in (Lautshkce et al) who developed a novel hiPSC-based assay with a standardized readout that may have the potential for higher throughput screening for developmental toxicity.

3R Centre in Denmark initiatives
The Danish 3R centre has the remit amongst other to promote information about replacement initiatives and possibilities as demonstrated in two reports showing lack of knowledge to this R (Nøhr et al and Ditlevsen et al). Currenly a project collecting information about use of human tissue in combination or as substitute to animal studies is established by the Danish 3R centre, arising from collaboration with the Netherlands National Committee for the protection of animals used for scientific purposes (NCad). The first step is to analyse how the 12 of the by now 28 financially

supported projects within the 3R centre makes use of human tissue and how these projects promote further use.
Inventories of biobanks in DK and EU:
At Statens Serum Institute in Denmark they host a number of biobanks with a total of 24 mill samples https://www.danishnationalbiobank.com/ . The Danish Biobank Register provides researchers with an overview of biological material in biobanks participating in the initiative. https://biobanks.dk/
At university and hospital departments a number of research biobanks are stored. These are registered at the sites to ensure GDPR compliance etc. A comprehensive analysis of the entire biobank area solicited by the Ministry of Health and Danish Regions will soon provide background for a national infrastructure initiative, which should improve overview of and access to human material.

Departments of pathology contain a huge amount of human tissues. In The Netherlands there has been a central platform in which you can find virtually all pathology-samples from the last 50 years. This source is already used by many researchers, but use could still increase (especially by scientist now working with experimental animals)

Such samples may be valuable in animal-free research. Unlike other countries like Switzerland, UK and Sweden there are no established initiatives in DK addressing share of human tissue for use in animal free research.

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IFRO_Report_249.pdf (ku.dk)

Sørli JB, Huang Y, Da Silva E, Hansen JS, Zuo YY, Frederiksen M, Nørgaard AW, Ebbehøj NE, Larsen ST, Hougaard KS. Prediction of acute inhalation toxicity using in vitro lung surfactant inhibition. ALTEX. 2018;35(1):26-36. doi: 10.14573/altex.1705181.

Sørli JB, Låg M, Ekeren L, Perez-Gil J, Haug LS, Da Silva E, Matrod MN, Gützkow KB, Lindeman B. Per- and polyfluoroalkyl substances (PFASs) modify lung surfactant function and pro-inflammatory responses in human bronchial epithelial cells. Toxicol In Vitro. 2020 Feb;62:104656.

European Society of Toxicology (EUROTOX)

Eva Cecilie Bonefeld-Jørgensen, Public Health, Aarhus University, Denmark. President of DSTF.

Introduction to the EUROTOX Society

EUROTOX is the Federation of European Toxicologists and European Societies of Toxicology, which together groups approximately 6,000 members across Europe and more than 200 individual members from around the world. EUROTOX includes 35 European National Societies of Toxicology. The Danish Society of Toxicology and Pharmacology https://dstf.dk/ is a member of EUROTOX.

EUROTOX mission is to foster the science and education of toxicology, and influence regulatory and policy frameworks to promote the safety of humans, animals and the environment, and protect global health.

Thus, by the mission of EUROTOX we are scientists working together to debate and promote best practice and understanding within our discipline in a respectful and collegiate manner for the benefit of those communities we serve and represent.

Historically, EUROTOX has its roots in the European Society for the Study of Drug Toxicity, founded 1962 in Zürich. The first annual scientific meeting was held in 1963 in Paris, at which occasion also the Statutes of the new society were adopted. As the Society's interests started to extend into toxicology areas other than drug toxicology, it was decided to change the name into European Society of Toxicology (EST).

There are six EUROTOX subcommittees: Executive, Nomination, Education, Communication, Registration, and Corporate. The subcommittees works professional and gives yearly reports to the Core and Executive committees.

EUROTOX has established five 'Specialty Sections': Carcinogenesis, Immunotoxicology, Eurotox Risk Assessment, In vitro and In silico Toxicology, and Molecular Toxicology. To join any Specialty Section you must be a member of EUROTOX. Membership of EUROTOX includes individual members, corporate program members, and members of societies or affiliated societies that are members of EUROTOX.

EVENTS. In addition to the yearly EUROTOX conference held in different European countries, each third year a conference is held together with the International Union of Toxicology (IUTOX).

National Societies can apply EUROTOX for support to toxicological workshops. Together with other events, the National Toxicological workshops are listed at the EUROTOX website.

EDUCATIONS (EUROTOX Faculty Programme). Part of the mission at EUROTOX is to promote education and training of toxicologists. The EUROTOX Faculty was created to help foster this mission by bringing together experts in toxicology who are willing to offer their expertise to help train the next generation of toxicologists. The aim is to provide a source of volunteer expertise that will be available to help teach EUROTOX courses as and when they are needed across Europe. Currently the EUROTOX Faculty Programme is able to cover the expenses (travel and accommodation) for Faculty members to participate in education courses or training lasting less than one week (7 days).

There are an array of courses organized by EUROTOX with the aim to educate toxicologist to be qualified for the European Registered Toxicologist (ERT) (https://www.eurotox.com/education/)

MEMBERSHIPS (https://www.eurotox.com/membership/). EUROTOX membership can be obtain in one of three ways: 1. Become a member by joining a EUROTOX national member society; 2. Become a EUROTOX Individual Member; 3. Become a Corporate Membership (organizations and private companies).

https://www.eurotox.com/

European Registered Toxicologist in Denmark – how to get the title

Ulla Vogel[1], Anne Marie Vinggaard[2], Alan Christensen[3], Karin Sørig Hougaard[1], Lisbeth E Knudsen[4], Allan Dahl Rasmussen[5], Eva C. Bonefeld-Jørgensen[6]

1. National, Research Centre for the Working Environment, Copenhagen.
2. DTU Food, Technical University of Denmark.
3. Novo Nordisk A/S
4. University of Copenhagen.
5. H. Lundbeck A/S
6. Faculty of Health, Aarhus University, Denmark; President of DSFTM.

The Danish Society for Toxicology and Pharmacology is the Danish section of EUROTOX and IUTOX and hosts the Danish section of European Registered Toxicologists.

According to EUROTOX (https://www.eurotox.com/ert/), the European Register of Toxicologists was established in 1994 and constitutes a list of toxicologists, who excel by high standards of education, skills, experience, and professional standing. Successful applicants, who comply with the requirements defined by EUROTOX and National Societies of Toxicology, are qualified to use the title EUROPEAN REGISTERED TOXICOLOGIST (ERT) with their name.
Registration is performed by a two-step procedure. First, National Registration boards in Europe evaluate applications of candidates according to a consensual process described in the ERT guidelines. Next, EUROTOX will assess the recommendation from the national committee and award the ERT title.

The Danish Society for Toxicology and Pharmacology is responsible for the Danish ERT register, according to the standards set by EUROTOX. As such, the Danish ERT register is a part of the international ERT register. There are at present 32 Danish ERT.

Toxicologists working or living in Denmark are eligible to apply for ERT provided they fulfill the criteria. The ERT certification has to be renewed every 5 years.
Applications is via the DSTF home page: https://dstf.dk/ert-certification/, and it costs 750 DKK, which covers the EUROTOX expenses related to the registration. Application deadlines are April 1 and October 1. The applications are reviewed by the Danish ERT panel.

Guidelines and the criteria for ERT can be found at https://www.eurotox.com/ert/

Danish Health Authority Advisory Scientific Committee on Environmental Health

Ulla Vogel[1] and Hilde Balling[2]

1) National Research Centre for the Working Environment, Copenhagen
2) The Danish Health Authority, Copenhagen

The Advisory Scientific Committee on Environmental Health (Sundhedsstyrelsens Rådgivende Videnskabelige Udvalg for Miljø og Sundhed)– acts as advisor to the Danish Health Authority in relation to environmental and occupational exposure to chemicals and xenobiotics and health. The committee consists of scientists representing universities and government research institutes and representatives from different governmental agencies. The members are appointed for a three-year period at a time.

Members of the committee can be found at
http://miljoogsundhed.sst.dk/omudvalg/medlemmer.html
The committee is the main organizer of ca. 3 dissemination meetings per year, usually one in spring and two in autumn/winter. Information regarding the meetings can be found on the homepage of the Danish Health Authority (https://www.sst.dk/da/Arrangementer/2022/Temadag-og-webinar-om-PFAS). In addition, the Scientific Advisory Committee is responsible for 'Miljø og Sundhed', an ejournal bringing popular scientific articles related to environment and health, http://miljoogsundhed.sst.dk.

Contributions are welcome, and can be sent to Hilde Balling, email HIB@sst.dk. 'Miljø og Sundhed' is published 3 times a year.

Partnership for the Assessment of Risks from Chemicals – Update and the bridging to HBM4EU

Danish National Hub in the HBM4EU project (Human Biomonitoring for EU initiative)

Lisbeth E. Knudsen, Department of Public Health, University of Copenhagen
Anna-Maria Andersson, Department of Growth and Reproduction, Region H
Helle Raun Andersen & Tina Kold Jensen, Department of Environmental Medicine, SDU
Eva Cecilie Bonefeld-Jørgensen and Maria Wielsøe, Department of Public Health (AU-PH), Aarhus University, Aarhus
Katrin Vorkamp, Environmental Science Aarhus University (AU-ENVS), Roskilde.
Anne Marie Vinggaard, DTU Food
Anne T Saber, Ulla B. Vogel, National Research Center of the Working Environment

Introduction HBM4EU is a joint effort of 30 countries, the European Environment Agency and the European Commission, co-funded under Horizon 2020.

The initiative is coordinating and advancing human biomonitoring in Europe. HBM4EU is generating evidence of the actual exposure of citizens to chemicals and the possible health effects in order to support policy making.

Data used and produced under HBM4EU will be made accessible via IPCHEM – the Information Platform for Chemical Monitoring. IPCHEM is the European Commission's reference access point for searching, accessing and retrieving chemical occurrence data collected and managed in Europe.

A network bringing together national HBM activities – National hubs has been formed in all participating countries. In Denmark, the following institutions are represented:

Region H- Rigshospitalet, University of Southern Denmark (SDU), National Research Centre for the Working Environment (NFA), University of Copenhagen (UCPH), Aarhus University (AU), Food Institute (DTU) and participation of Agencies: Environmental Protection Agency (EPA), Food Agency, Labour Inspection, Research and Innovation, Board of Health.

The network met regularly and exchanged information about progress and priorities as well as at the two Nordic meetings for all Nordic HBM4EU hubs, financed by the Nordic Council. 50 participants were present in each of the Nordic workshops, where reports have been published.

Results
Danish participation was the case in all WPs apart from WP3 and Table 1 summarizes the outcome in scientific papers reports etc. The link below provides access to all public HBM4EU documents.
ONLINE LIBRARY – HBM4EU – science and policy for a healthy future

HBM4EU Science Digest by subscribing to the Science Digest Newsletter mailing list.

Impacts of participation for the partners from Denmark

1. Research activities

Major impact on research and education for all partners involved. Active participation in almost all WPs with many publications as well as PhD and post docs employed. Network strengthened

nationally, EU-wise and internationally. Participation in the continuation in PARC welcoming the longer term duration and also with new partners and areas.
More openness and preparedness for participation in EU calls for this kind of research.

2. Ministerial alertness
Use of HBM data in risk assessments, participation in GB.

3. National HBM program/survey
No political and governmental interest in a Danish National HBM program. A Recommendation for National Research Program focused on Environmental Health has been sent to the Board of Health.

4. Public awareness
The public awareness of HBM as a tool in exposure and risk assessment has increased dramatically after PFOS case and drinking water quality discussions.

5. Expectations
The structural and organised approach with common protocols etc has been very well appreciated. Administration heavy.

Table: Overview of Danish contributions to HBM4EU and references *published and planned*.

WP	**DK-tasks**	**Results and References**
WP1: Project coordination and management	Agreement in Consortium on how to handle timely provision of ethics documents	Deliverables of annual ethics reports, and contributions to annual work plans. Legal and ethics Policy paper updated and manuscript in preparation (*Knudsen et al in prep*). UCPH leader of the ethics task 1.5.
WP2: Knowledge Hub	Training	Webinars and courses, with presentations available on internal website. UCPH participated in the Task 2.4
WP3: Internal calls	No DK applications	
WP4: Prioritisation and development of scoping documents	Focus interviews of stakeholders	Danish Ministeries and Agencies have been consulted by the HUB coordinator (UCPH) for specific issues
WP5: Translation of results into policy	Data existing and new from HBM4EU accessible in IPChem. Mixture risk assessment of PFAS	Contributions from RegionH, SDU, UCPH, NRCWE, and DTU. In total 16 Danish studies in IpChem *Louro H et al, Bil W, et al*
WP6: Sustainability and capacity building	Questionnaire and focus interview	Performed in Denmark in 2020 by UCPH and published in *Miljø og Sundhed* (*Knudsen*) and peer reviewed publications *Martisane et al (submitted),Uhl et al (in prep), Ovnair Sepai (in prep)*
WP7: Survey design and fieldwork preparation	Material for communi-cation to participants, including informed consent was developed	Used in Danish aligned studies by Region H and SDU.
WP8: Targeted field work surveys and alignment at EU level	Aligned and new studies. Secondary use of samples, data, and health information	Special attention to exposures to phthalates, BPA, DINCH in aligned studies (RegionH and SDU) as well as DEMOCOPHES study (UCPH)

WP9: Laboratory analysis and quality assurance	Choosing biomarkers and matrices for prioritized compounds, setting up quality assurance and control (QA/QC) standards for chemical analyses, coordinating analyses in HBM4EU. Analysis of samples collected in new aligned HBM studies	Compliance with HBM4EU procedures via Material Transfer Agreements (AU). AU leader of task 9.5. Scientific papers published on most suitable biomarkers, matrices and analytical methods (*Vorkamp et al., 2021*), specific methods for flame retardants (*Hajeb et al., 2022*) as well as the overall QA/QC programme (*Esteban López et al., 2021*). Series of papers produced on QA/QC for prioritized compounds (*Dvorakova et al., 2021; Mol et al., 2022; Nübler et al., 2021; 2022; subm.; Vaccher et al., 2022*). Manuscript in preparation on the analytical phase (*Vorkamp et al., in prep.)*.
WP10: Data management and analysis	Sharing of data via IPCheM,	Major contributions from data owners in aligned studies and DEMOCOPHES study.
WP11: Linking HBM, health studies and registries	Participation in workshops and surveys as well as publications Task leader on T11.1	*Tollonen et al*
WP12: From HBM to exposure	No tasks	
WP13: Establishing exposure-health relationships WP14: Effect biomarkers	Reviewing of existing literature on human exposure, mechanisms, and exposure-health relationships for priority substances.	Literature review on the epidemiological evidence for a relationship between prenatal and postnatal exposure to PFAS, and thyroid function in mothers and/or infants (*Boesen et al,*). Exposure to Persistent Organic Pollutants in Danish pregnant women: hormone levels and fetal growth indices (*Bonefeld-Jørgensen et al in prep*)
	Several tasks	Assessment of chemical mixtures using biomarkers of combined biological activity: A screening study in human placentas (*Rodríguez-Carrillo, el al)* Real-life PFAS mixtures extracted from human placentas and combined estrogen activities *Wielsøe, et al. (in prep)* The use of human biomonitoring in occupational exposure to PAHs: A systematic review of the literature. Silva et al. (in prep)(combined WP8/WP14) Literature review on exposure and biomarkers of effect (BDNF, HDL) and susceptibility. Gundacker et al.)

		Benzophenone-3: Systematic integrative review of the toxicological and human evidence with meta-analysis of human biomonitoring studies. (*Mustieles et al. in prep*) D15.5 Report on case studies of mixture risk assessments. Manuscript in preparation on mixture effects on antiandrogenic chemicals. *Vinggaard, et al.*
WP15: Mixtures, HBM and human health risk	Case study on mixture effects of antiandrogenic chemicals	
WP16: Emerging chemicals	Effect-directed analysis for guiding identification of emerging chemicals	

References from HBM4EU with Danish contribution

Nordic workshop for scientists and regulatory agencies discussing HBM4EU - the European human biomonitoring initiative 2017http://urn.kb.se/resolve?urn=urn:nbn:se:norden:org:diva-4933
Abstracts from all presentations and small summary of discussions
Nordic workshop for scientists and regulatory agencies discussing HBM4EU 2021
Nordisk Ministerråd - TemaNord2021-528 (norden.org)
Abstracts from all presentations and small summary of discussions
https://www.hbm4eu.eu/work-packages/deliverable-1-5-legal-and-ethics-policy-paper-september-2018/
Presentation of the ethics framework of EU and internationally the organization of ethics in HBM4EU

https://www.hbm4eu.eu/work-packages/deliverable-2-17-second-report-on-the-content-and-use-of-the-online-library/
All official presentations and refernces from the training

https://www.hbm4eu.eu/work-packages/additional-deliverable-4-4-report-of-the-citizens-focus-groups/
Presentation of all performed focusgroup performances with small summary and discussion.

Andersen HR, Dalsager L, Jensen IK, Timmermann CAG, Olesen TS, Trecca F, et al. Prenatal exposure to pyrethroid and organophosphate insecticides and language development at age 20-36 months among children in the Odense Child Cohort. Int J Hyg Environ Health. 2021;235:113755.

Andersen HR, David A, Freire C, Fernándezc MF, D'Cruz SC, Reina-Pérez I, Finie JB, Blaha L. Pyrethroids and developmental neurotoxicity - a systematic review of epidemiological studies and supporting mechanistic evidence (submitted).

Bil W, Govarts E, Zeilmaker MJ, Woutersen M, Bessems J, Mac Y, Mahioutd S, Halldorsson TI, Uhl M, Schoeters G, Santonen T, Vinggaard AM. Approaches to mixture risk assessment of PFASs in the European population based on human hazard and biomonitoring data(submitted).

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Organisation of the Partnership for Assessment of Risks from Chemicals (PARC) in Norway

Hubert Dirven and Cathrine Thomsen. Division of Climate and Environmental Health at the Norwegian Institute of Public Health.

There is a large interest in PARC in the Norwegian research environments. The introduction of New Approach Methods for hazard assessment, biomonitoring and the connection between human

health and the environment are considered vital for a more sustainable use of chemicals and supports the OneHealth concept and the Chemicals Strategy for Sustainability

NIPH has since 2019 participated and contributed to the planning of activities in PARC based on our interests in biomonitoring, hazard assessment, exposure health associations and risk assessment.

For the HBM4EU program, NIPH was grant signatory, national hub coordinator and the only beneficiary. In PARC, NIPH will act as beneficiary (formerly known as grant signatory) and will work with 8 Affiliated Entities. A representative from the Ministry of Health and Care Services will be in the Governance Board (GB) of PARC. We need to assure a good feedback loop between the national hub and the GB representative. In the national hub the Norwegian Environment Agency (Miljødirektoratet) and the Norwegian Food Safety Authority (Mattilsynet) will play an important role to ensure regulatory relevance of proposed activities.

The organisations involved in PARC in Norway are:
Norwegian Institute of Public Health (Folkehelseinstituttet). Beneficiary and task leader in 5.1. The Norwegian Environmental Biobank (Miljøbiobanken) will be part of the PARC human biomonitoring studies.
Norwegian Scientific Committee for Food and Environment (VKM)
National Institute of Occupational Health (STAMI)
Norwegian Institute for Air Research (NILU)
Norwegian Institute for Water Research (NIVA
Norwegian Veterinary Institute (Veterinærinstituttett)
Institute of Marine Research (Havforskningsinstituttet)
Norwegian University of Life sciences (NMBU)
University hospital of North Norway (UNN)

The partners in Norway have reported 1240 Persons Months to PARC with a total budget of 15,7 million Euro for 7 years. With 45% financing by the EU commission, the own contribution by the partners is significant (8.4 million Euro). Discussions with ministries and the Norwegian Research Council were held on options to obtain national funding to cover the own financing contributions, but no solution has been identified so far. For most partners this means that the own contribution must be paid from existing budgets, and this represents in practice a significant problem.

Organisation of the Partnership for Assessment of Risks from Chemicals (PARC) in Denmark

The Danish participation in PARC is organised with the Danish Environmental Protection Agency DK-EPA) as the PARC Grant Signatory and Beneficiary and coordinator of the national activities through the establishment of a national PARC hub. Contact person at DK-EPA and national HUB coordinator for PARC is Ditte Secher Paludan. Magnus Løfstedt from DK-EPA will be representing Denmark as member of both the Grant Signatory Board and the Governing Board of PARC.

Five legal entities are affiliated to DK-EPA and will be active in PARC. These are:

- **University of Copenhagen (UCPH)**, represented by Dept. of Plant and Environmental Sciences (contact person Jan Christensen) – active in WP4 and WP9
- **The Technical University of Denmark (DTU)**, represented by Terje Svingen, Food Institute and Anders Baun, Environment Institute

- **Aarhus University (AU)**, represented by Department of Public Health (AU-PH contact person Eva C. Bonefeld-Jørgensen) – active in WP4, WP5, WP6 and Department of Environmental Science (AU-ENVS contact person Katrin Vorkamp) – active in WP4, WP8 and WP9
- **University of Southern Denmark (SDU)**, represented by Dept. of Biology (contact person Henrik Holbeck) – active in WP5 og WP6
- **The Capital region of Denmark (RegionH)**, represented by Dept. of Growth and Reproduction, Rigshospitalet (contact person Anna-Maria Andersson) – active in WP4 and WP9 and Dept. of Skin and Allergy, Gentofte Hospital (contact person Jeanne Duus Johansen) – active in WP6.

Thus, in total 11 different research departments will be actively involved in the work in PARC.

The Danish national PARC hub will be populated with representatives from DK-EPA and from the above-mentioned research departments that will be active in PARC. In addition, representatives of other relevant Danish agencies: Danish Veterinary and Food Administration, Work Environment in Denmark, and the Danish Health Authority. This will facilitate a knowledge exchange in the national hub between research groups and regulatory authorities, which will play an important role to ensure the regulatory relevance of the ongoing or planned activities.

With 45% financing by the EU commission, the own contribution by the partners is significant. The sources of this co-funding will vary and will for most, if not all, partners involve that the Danish co-funding will be fully or partly paid from their individual own existing budgets. This has most likely limited the Danish involvement in PARC.

Coming Aarhus University activities in the PARC Project

Eva Cecilie Bonefeld-Jørgensen[1], Vivi Schlünssen[1], Maria Wielsøe[1], Manhai Long[1], Katrin Vorkamp[2]

1. Public Health Aarhus University (AU-PH), Bartholin's Allé 2, 8000 Aarhus C;
2. Environmental Science Aarhus University (AU-ENVS), Frederiksborgvej 399, 4000 Roskilde

Introduction to company/institute
1. AU-PH is a department under AU's Faculty of Health at Aarhus University including five departments under which the research units are organized, together with two staff functions and a health science education Centre. At the Department of Public Health (AU-PH), there are 13 research units of which two units participates in the PARC project: "Arctic Health and Molecular Epidemiology" and "Environment, Work and Health". In common for the two units is the research focus on environmental and occupational exposures to chemicals and risk of human health effects.

2. AU-ENVS is an institute under AU's Faculty for Technical Sciences that conducts research and provides research-based advice on all questions related to environmental health. The section Environmental Chemistry & Toxicology focusses on potentially harmful organic chemicals in the environment, including human exposure to these chemicals.

Toxicology at your institutions
1. The AU-PH contribute to PARC with toxicological studies upon environmental and occupational exposure to chemicals assessed on environmental and human samples. The main research focus of the two units are "the impact of lifestyle, genetic makeup on human reproduction and child development and health" and "the impact of environmental factors on allergy and respiratory diseases" conducted by epidemiological and ex vivo/in vitro toxicological studies. The units' long-

term data will allow investigations to disclose whether exposure during gestation or at occupation can lead to diseases later in life

2. The work at AU-ENVS includes the chemical analysis of a wide range of organic contaminants in environmental and human samples, for a better understanding of their fate in the environment and human exposure. The experimental research involving measurements and process studies is typically combined with the modelling of toxicity, often in a risk assessment context.

Prospects/future plans/collaborations

1. In PARC AU-PH are involved in several tasks in WP4, WP5 and WP6.

The contributions of the research unit 'Arctic Health and Molecular Epidemiology' are as follows:

In WP4, we will assist with the selection of effect biomarkers and possibly the analyses of effect biomarkers. Our main contribution in WP4 will be statistical work on mixture analysis (to look into co-occurrence patterns and exposure-effect associations) and exposure-effect associations for health outcome and/or effect biomarker data.

In WP5, we are involved in AOP development based on integration of in vivo and in vitro datasets with focus on endocrine disruption and effect markers. In addition, further development of real-life mixtures extraction of PFAS for measurement of androgen and thyroid activities

In WP6, we will contribute to the mixture project being involved in toxicological grouping of mixtures, assessment of relative potency factors on selected chemicals and mixtures, and observations of real-life mixtures from human biomonitoring studies.

The contributions of the research unit 'Environment, Work and Health' are as follows:

In the occupational surveys of AU-PH in WP4 includes A) Occupational survey in the waste management and B) Setup sentinel surveillance system in their countries.

In the WP6 occupational surveys, AU-PH will contribute to "Aggregate exposure from multiple sources and routes for general population and workers".

2. In PARC, AU-ENVS co-leads the task "Environmental and Multisource Monitoring" together with the French National Institute for Industrial Environment and Risks (INERIS). The task includes 45 European partners and will proceed in close collaboration with e.g. the work packages on Infrastructural and Human Capacities (with regard to quality assurance and control) and FAIR data as well as the sister task "Human Biomonitoring". The first project will focus on per- and polyfluoroalkyl substances (PFAS) and endocrine disrupting compounds in the outdoor environment, also with the purpose of establishing overall structures and processes for the duration of PARC. The project will also be coordinated with interests and activities in the Danish national hub.