NSFT

Norsk Selskap for Farmakologi og Toksikologi
Norwegian Society of Pharmacology and Toxicology

Member of EPHAR, IUPHAR, EUROTOX and IUTOX **www.nsft.net**

Vintermøtet på Beitostølen

2020

Sponsor av NSFTs vintermøte 2020

Norsk Selskap for Farmakologi og Toksikologi

Program

Torsdag 23. januar	
13:00 - 14:30	**Lunsj**
Velkommen *v/ NSFTs leder Mohammad Nouri Sharikabad* Besseggen	
Fellessymposium: ADHD *Møteleder: Mohammad Nouri Sharikabad (FHI)* Besseggen	
14:40 - 15:10	Prenatal toxic exposure and risk of neurodevelopmental disorders – the NeuroTox project *Heidi Aase (Folkehelseinstituttet)*
15:10 - 15:40	Biologiske årsaker til ADHD og nye legemiddeltargets *Jan Haavik (Universitetet i Bergen)*
Pause	
Priser for årets beste artikler **Fellessymposium** *Møteledere*: *Jason Matthews (UiO) / Jenny Lund (UiO)* Besseggen	
16:00 - 16:20	Effect of CYP2D6 Genotype on Exposure and Efficacy of Risperidone and Aripiprazole: A Retrospective, Cohort Study *Robert L Smith (Diakonhjemmet; Årets farmakologiartikkel)*
16:20 - 16:40	Cellulose Nanocrystals Modulate Alveolar Macrophage Phenotype and Phagocytic Function *Johanna Samulin Erdem (STAMI)*
Kaffe	

	Toksikologi: **Polarforskning** *Møteleder*: *Jason Matthews (UiO)* Besseggen 1	**Farmakologi:** **Type 2-diabetes** *Møteleder*: *Jenny Lund (UiO)* Besseggen 2
17:10 - 17:40	Current knowledge of pollutants and their effects in Arctic mammals *Heli Routti (Norwegian Polar Institute)*	Diabetes - ikke bare min skyld. Diagnose og behandling *Per Medbøe Thorsby (OUS)*
17:40 - 18:10	Effects of complex petroleum mixtures to Barents Sea key fishes – recent results on species sensitivity and a novel hypothesis that may lead to a paradigm shift in the field of research *Jasmin Nahrgang (The Artic University of Norway)*	Nye legemiddeltargets i behandling av diabetes *Arild C. Rustan (UiO)*
18:10 - 18:40	The role of the altricial-precocial spectrum for pollutant loads and effects in marine mammal offspring *Bjørn Munro Jensen (NTNU)*	
19:30	**Samling i baren**	
20:00	**Middag**	

Fredag 24. januar

12:30 - 14:00	**Lunsj**

Fellessymposium: Antibiotikaresistens
Møteleder: Mohammad Nouri Sharikabad (Folkehelseinstituttet)
Besseggen

14:00 - 14:30	Tackling AMR - the public health perspective *Jasper Littmann (Folkehelseinstituttet)*
14:30 - 15:00	Optimalisering av antibiotikaforskrivning - Hvordan vil intervensjoner på systemnivå påvirker forskrivning av antibiotika *Hege Salvesen Blix (FHI og UiO)*

Kaffe

Frie foredrag

Toksikologi *Møteleder: Odd Andre Karlsen (UiB)* Besseggen 1		**Farmakologi** *Møteleder:Kristine Hole (Diakonhjemmet)* Besseggen 2	
15:30	Prenatal exposure to metals and associations with ADHD and ASD in children *Thea S. Skogheim (FHI)*	Effect of low calorie diet on the activity of hepatic transporter OATP1B1 in patients with severe obesity *Markus H. Hovd (UiO)*	15:30
15:40	Effects of combined exposure to nicotine and HEMA *Solveig Uvsløkk (NIOM)*	Allosteric enhancement of the natriuretic peptide receptor A with small molecules *Henriette Andresen (UiO/OUS)*	15:40
15:50	Aminated polystyrene nanoparticles affect the early life development and life cycle of the marine copepod Tisbe battagliai: role of surface functionalisation *Anastasia Georgantzopoulou (NIVA)*	Opioider ved behandling av kroniske sterke smerter *Svetlana Skurtveit (FHI/UiO)*	15:50

16:00	Integrated strategy for toxicity prediction and hazard ranking of feed additives and contaminants using (Q)SAR and nontargeted high-resolution mass spectrometry *J.D. Rasinger (IMR)*	The effect of the β2 – adrenergic receptor agonist terbutaline on cultured human myotubes *Christine Skagen (UiO)*	16:00
16:10	Polar cod and Goliat: How an oil spill may affect polar cod reproduction *Leah Catherine Stroplе*	Kombinasjonsbruk av valproat og lamotrigin assosiert med klozapins metabolittmønster *Anh Thu Tran (Diakonhjemmet/UiO)*	16:10
16:20	Adapting a liver slice culture method for ex vivo toxicological studies in arctic and sub-arctic fish species during sampling cruises *Fekadu Yadetie (UiB)*	Electrical pulse stimulation of human primary myotubes affects the protein cargo of extracellular vesicles released to the cell media *Vigdis Aas (OsloMet)*	16:20
16:30	Development of in vitro models to study environmental factors influencing gill epithelial function *Anita Solhaug (VI)*	Identification of new candidate CYP2C19 variants causing ultrarapid metabolism *Line S. Bråten (Diakonhjemmet/OsloMet)*	16:30
Pause			
17:00	A battery of Atlantic cod (Gadus morhua) stress-activated receptors as a bioassay tool to analyse sediment extracts *Siri Øfsthus Goksøyr (UiB)*	Compartmentation of natriuretic peptide signalling – are interacting proteins involved? *Lise Román Moltzau (UiO/OUS)*	17:00
17:10	Biological responses in Atlantic cod (Gadus morhua) exposed to polycyclic aromatic hydrocarbons and perfluoroalkyl substances *Karina Dale (UiB)*	Extrapolating an adult tacrolimus population pharmacokinetic model to pediatric renal transplant recipients *Andrea Storås (UiO)*	17:10
17:20	Expression and localization of the aryl hydrocarbon receptors and cytochrome P450 1A during early development of atlantic cod (*Gadus morhua*) *Libe Aranguren-Abadía (UiB)*	Studies on the cysteine protease legumain in cardiovascular disease *Ngoc Nguyen Lunde (UiO)*	17:20
		Early changes in cardiac performance caused by calcineurin inhibitors – a marker of long-term organ toxicity? *Bernadin Ndongson-Dongmo (UiO/OUS)*	17:30

		DSSLepR rats as a new animal model of heart failure with preserved ejection fraction (HFpEF) for testing new pharmacological treatment strategies *Vladimir Nikolaev Martinov (UiO/OUS)*	17:40
		Identification of a novel polymorphism associated with reduced clozapine concentration in schizophrenia patients – a GWAS adjusting for smoking habits *Robert L. Smith (Diakonhjemmet)*	17:50
		Spatial signaling of cGMP in nanodomains modifies heart function *Kjetil Wessel Andressen (UiO)*	18:00
Pause			
Postervisning (3 min presentasjoner etterfulgt av diskusjon ved postere)			
Toksikologi *Møteleder: Jason Matthews (UiO)* Besseggen 1 (kl. 17:40)		**Farmakologi** *Møteleder: Jenny Lund (UiO)* Besseggen 2 (kl. 18:20)	
– The *in vitro* toxicity of a dental resin monomer varies among different cell culture models *Bergitte P. Olderbø (NIOM)* – Effect of methacrylates and nanoparticles used in dental materials on A549 lung epithelial cells *Svava K. Bjarnadóttir (UiO/NIOM)* – The effect of lipopolysaccharide from E.coli serotypes on interleukin-1β release in RAW 264.7 *Mathias Fon (UiO/NIOM)* – Associations between urine phthalate metabolites and thyroid function in pregnant women and the influence of iodine status *Gro D. Villanger (FHI)* – Exposure assessment of phthalates based on aggregated exposure from food and personal care products: creation of a concentration database *Athanasios Gkrillas (FHI)*		– Poly ADP-ribose polymerase 7 (PARP7) and mono-ADP-ribosylation regulate Estrogen Receptor α (ERα) signaling *Marit Rasmussen (UiO)* – Effekten av høy dose omega-3 fettsyrer på farmakokinetikken til takrolimus og mykofenolat i nyretransplanterte pasienter *Berfin Gence (UiO)* – Effekt av teriparatid på differensiering og regulering av cysteinproteaser i osteoblaster *Nasra Ciyow (UiO)* – Immunsuppressive legemidler og tarmmikrobiomet: farmakokinetikk- og mikrobiomvariasjon og effektforskjeller *Maja Rannem Bilden (UiO)* – Differensiering av RAW264.7 til osteoklaster og karakterisering av cysteinproteaser i osteoklaster *Arthii Mohanachandran (UiO)*	

– Nicotine promote the toxicity of resin-based biomaterials by impairing lysosomal function *Jonas Lundh Berner (UiO/NIOM)* – Results from the Norwegian human biomonitoring study in the EuroMix project: Exposure to the pesticides boscalid and imazalil from the diet in Norway *Friederike Sonnet (FHI)* – Effects of air pollution particles from two tunnels in norway in lung epithelial cells *Tonje Skuland (FHI)* – How much chemicals with PFAS do we use in Norway? A data register study based on data from 2009-2017. *Merete Grung (NIVA)* – Fortsatt målbar radioaktivitet i beitevekster og hjortedyr i Norge etter Tsjernobyl-ulykken *Aksel Bernhoft (VI)* – Mixture effects of benzo[a]pyrene and perfluoroalkyl substances on the aryl hydrocarbon receptor signalling pathway and energy metabolism of Atlantic cod (Gadus morhua) *Torill Horvli (UiB)* – Functional Characterization of Atlantic Cod (Gadus morhua) Peroxisome proliferator-activated receptor alpha 1 and 2 *Kristianne Hjorth Viken (UiB)* – Predicting environmental risks of pharmaceuticals in Norwegian surface water *Samuel A. Welch (NIVA)*	– For høye opioider doser ved behandling av kroniske sterke smerter? *Emilie Elise Heggen (NTNU)* – Effekt av cysteinproteasen legumain på celleviabilitet etter fotodynamisk terapi Kristine Løkke Olsen (UiO/OUS)
Posterdiskusjon	
20:00	**Middag**
22:00 - 22:30	**Kveldsnytt: Pest eller kolera? Hva er verst?** *Siamak Yazdankhah* Besseggen

Lørdag 25. januar

Generalforsamling og årsmøter		
09:00 - 09:30	Årsmøte Seksjon for toksikologi Besseggen 1	Årsmøte Seksjon for farmakologi Besseggen 2
09:30 - 10:30	Generalforsamling Norsk Selskap for Farmakologi og Toksikologi Besseggen 2	
12:30 - 14:00	**Lunsj**	
Beitoforelesningen 2020 (BCPT-sponsored) *Møteleder: Jason Matthews (UiO)* Besseggen		
14:00 - 14:45	Using fish cells to build micro-organs that help us better understand the risk of pharmaceuticals in the environment *Stewart Owen (AstraZeneca)*	
Nordic symposium (BCPT-sponsored) Doping Fellessymposium *Møteleder: Rigmor Solberg (UiO)* Besseggen		
14:50 - 15:20	Beta2-adrenergic agonists - from obesity to athletes *Morten Hostrup (Københavns universitet)*	
Kaffe		
15:50 - 16:20	Doping som etisk dilemma *Sigmund Loland (Norges Idrettshøyskole)*	
16:20 – 16:50	Blood doping in sports – current challenges and ways of detection *Yvette Dehnes (Oslo universitetssykehus)*	
Pause		

	Luftforurensing *Møteleder: Jason Matthews (UiO)* Besseggen 1	**Immunfarmakologi/ nye behandlingsprinsipper** *Møteleder: Helene Dugstad (Novartis)* *Besseggen 2*	
17:10 - 17:40	Health effects of air pollution *Marit Låg (FHI)*	Design of the next generation of biologics *Stian Foss (UiO)*	17:10 - 17:40
17:40 - 18:10	Hvordan jobber myndighetene for trygg utendørsluft i Norge? *Line Merete Karlsøen (Milijødirektoratet)*	Exploiting exosomes as therapeutic delivery vehicles in cancer therapy *Marit Inngjerdingen (UiO)*	17:40 - 18:10
18:10 - 18:40	Verdibasert ventilasjon Inneklima, mennesker og virus – risikovurderinger og tiltak? *Jan Vilhelm Bakke (pensjonert overlege i Arbeidstilsynet)*		
20:00	**Festmiddag**		

Søndag 27. januar

08:00 - 12:00	**Brunsj**

Innholdsfortegnelse

NSFTs vintermøte nr. 48

Norsk Selskap for Farmakologi og Toksikologi (NSFT) har arrangert vintermøter hvert år siden 1973, det vil si at årets møte er nummer 48 i rekken. Selskapets styre gikk i 1972 sterkt inn for å få i gang nasjonale møter, som både kunne bli et kontaktforum og en faglig arena for selskapets voksende antall medlemmer fra de ulike deler av landet.

I det programmet ferdigstilles er det påmeldt 100 deltakere til årets møte (ledsagere og barn ikke inkludert), og det er 20 inviterte foredragsholdere fordelt på 9 symposier. Til sammen er det meldt inn 23 frie foredrag og 19 postere fordelt på farmakologi og toksikologi.

I år har NSFT mottatt økonomisk støtte fra Basic & Clinical Pharmacology & Toxicology (BCPT) for å invitere flere utenlandske foredragsholdere og holde et nordisk symposium. Støtten har også gjort det mulig å opprettholde stipendtildelingen for studenter som presenterer poster eller frie fordrag.

Styret i NSFT takker for året som har gått og håper at deltakerne får både faglig og sosialt påfyll på årets vintermøte.

Vennlig hilsen
Styret

Oversikt over styremedlemmer i NSFT

NSFTs hovedstyre
Leder: Mohammad Nouri Sharikabad
Sekretær: Jan Tore Samuelsen
Kasserer: Kristine Hole
Styremedlem: Maria Hultman
Representant for bedriftsmedlemmer: Helene Dugstad
Representanter fra seksjonsstyrene: Jenny Lund og Jason Matthews
Varamedlemmer: Rigmor Solberg, Birgitte Lyrån og Aina Westrheim Ravna

Seksjon for farmakologi
Leder: Jenny Lund
Styremedlemmer: Lise Román Moltzau, Kristin Nordal, Erlend Johannesen Egeland og Marianne Kristiansen Kringen

Kontaktpersoner for seksjon for farmakologi
Bergen: Jon Andsnes Berg
Trondheim: Ola Dale
Tromsø: Aina Westrheim Ravna

Seksjon for toksikologi
Leder: Jason Matthews
Styremedlemmer: Anita Solhaug, Dag Marcus Eide, Marit Nøst Hegseth, Nina Landvik, Pål Amdal Magnusson, Vibeke Ansteinsson og Odd Andre Karlsen.
Varastyremedlemmer: Vidar Berg og Solveig Føreland.

Velkommen til NSFTs vintermøte 2020

Kjære medlemmer, deltagere og ledsagere. Velkommen til Norsk Selskap for Farmakologi og Toksikologi (NSFT) sitt førtiåttende vintermøte. Vintermøtet er en årlig hovedaktivitet i NSFT og har vært organisert og holdt siden 1973.

Norsk Farmakologisk Selskap ble stiftet i 1936. Etter hvert ble fagområde toksikologi innlemmet og selskapet skiftet navn til NSFT i 1981. Medlemmer i NSFT og deltagere på våre arrangementer dekker mange fagfelt, og arbeider med tema som spenner fra eksperimentell forskning til klinisk arbeid, arbeider i offentlige institusjoner, sykehus, akademia og farmasøytisk industri. NSFT sitt vintermøte er dermed en meget god arena for å treffe kollegaer fra basal og klinisk farmakologi samt human- og miljøtoksikologi og få oppdatering og ikke minst danne nye kontakter på tvers av kompetanse og fagfelt. Vi må erkjenne at NSFT ikke kan konkurrere med store internasjonale kongresser og møter hverken i størrelse eller økonomi. Vi tror likevel at vintermøtene tilbyr et variert og godt faglig program i fine rammer her på fjellet. For å oppnå dette er vi avhengige av våre medlemmers deltagelse og faglig bidrag, noe NSFT setter veldig stor pris på. Jeg vil samtidig bruke anledningen å takke alle styremedlemmer og varamedlemmer. Uten deres innsats gjennom 2019 ville det ikke være mulig å arrangere dette vintermøtet.

Vi har en variert og godt program foran oss med spennende tema som presenteres av veldig gode inviterte foredragsholdere. Muntlige presentasjoner og posterer innfor både farmakologi og toksikologi er som vanlig en sentral og uunnværlig del av dette møtet. Programmet inneholder som vanlig felles sesjoner og separate sesjoner i farmakologi og toksikologi. Utdeling av priser til beste poster og årets artikkel i begge fagfeltene er faste poster i programmet. Med den økonomiske støtten vi mottar fra vår hovedsponsor «Basic and Clinical Pharmacology and Toxicology, BCPT», har vi igjen kunnet arrangere et møte av høy kvalitet. Vi er derfor utrolig glad og takknemlig for at BCPT i år i likhet med mange forhenværende år har støttet oss.

Tradisjonen tro ble Poulssonmedaljen, som har fått sitt navn etter den store norske farmakologen professor Poul Edvard Poulsson (1858- 1935), delt ut den 9. oktober i et flott seminar i Domus Medica, UiO. Poulssonmedaljen 2019 ble tildelt i basalfarmakologi til Professor Muthu Periasamy, UCF College of Medicine, Burnett School of Biomedical Sciences. Prisvinneren hold en meget bra forelesning med tittelen “Futile cycling of SERCA pump in muscle can melt fat and control obesity”. Av andre arrangementer vil jeg nevne følgende. Det ble arrangert en spennende og lærerikt vårmøte i regi av Norsk Farmasøytisk Selskap og farmakologiseksjon i NSFT om nye perorale antikoagulantia NOAKs/DOAKs i mai og en meget vellykket og fullsatt høstmøte i toksikologi om forurensning med per- og poly-fluorerte stoffer, «PFOS og PFAS i Tyrifjorden, kjøkkenet og skiløypa» den 5. november.

Jeg håper at alle får godt faglig utbytte av møtet, og ikke minst hyggelig sosialt samvær med andre møtedeltagere og ledsagere. Det er storslått natur rett utenfor hotellet noe som forhåpentligvis byr på fine turer på beina, ski, eller i slalåmbakken. Hotellet har også fine fasiliteter for svømming, badstue og rekreasjon.

Med ønske om et godt vintermøte og videre et fantastisk 2020 for alle.

Med vennlig hilsen
Mohammad Nouri Sharikabad
Leder, NSFT

Praktisk informasjon

Hotelloversikt

Første gang en er på Beitostølen høyfjellshotell (Radisson Blu Resort Beitostølen) kan det være vanskelig å vite i hvilken retning en skal gå for å få med seg de første foredragene. I år vil alle sesjoner holdes i konferanseavdelingen. Denne finner du i andre etasje. Gå rett fram gjennom glasshallen så finner du rommene Besseggen 1 og Besseggen 2.

Vintermøtet er godkjent som etter- og videreutdanningskurs

Farmasøyters etter- og videreutdanning (FEVU) er et poengsystem for registrering av deltakelse i faglige etterutdanningsaktiviteter. NSFTs vintermøte 2020 tildeles FEVU-poeng. Farmasøyter som er medlemmer av Norges Farmaceutiske Forening (NFF) kan selv registrere deltakelse på vintermøtet ved å logge inn på «*Min side*» på www.farmaceutene.no i etterkant av arrangementet. For mer informasjon om FEVU-poeng, se: http://www.farmaceutene.no/fevu-hva-er-det.

NSFT

Norsk Selskap for Farmakologi og Toksikologi

Årsberetning 2019

1. Styrets sammensetning

Generalforsamlingen i NSFT ble holdt 27. januar 2018 på Radisson BLU Resort Beitostølen.

Styrets sammensetning etter valget på generalforsamlingen har vært som følger:
- Leder: Mohammad Nouri Sharikabad (2017-2019. 2019-2021)
- Sekretær: Jan Tore Samuelsen (2016-2018. 2018-2020)
- Kasserer: Kristine Hole (2017-2018. 2018-2020)
- Styremedlem: Maria Hultman (2019-2021)

Vararepresentanter:
- Rigmor Solberg (2018-2020)
- Birgitte Lyrån (2016-2018. 2018-2020)
- Aina Westrheim Ravna (2012-2014, 2014-2016. 2016-2018 og 2018-2020)

Seksjonene har utpekt følgende representanter til styret:
- Toksikologi: Jason Matthews
- Farmakologi: Jenny Lund

Representant for industrien:
- Helene Dugstad (2019-2021)

Valgkomité for 2020:
- Sara Bremer (2018-2020)
- David Eidsvoll (2019-2021)
- Lars Erik Eng Eibak (2019-2021)

Revisor:
- Vigdis Aas (2018-2020)

2. Styrets arbeid

Det har vært avholdt 6 møter i hovedstyret. Deler av styrets arbeid har vært utført via e-post.
Styret har i perioden jobbet med:
- Organisering av NSFTs faglige virksomhet (vår-, høst- og vintermøte)
- Planlegging og organisering av utdeling av Poulssonprisen og pris for beste publikasjon
- Organisering av styrets arbeid og møter
- Rekruttering av nye medlemmer
- Formidling av informasjon på NSFTs nettsider, i nyhetsbrev og via Facebook
- Europeisk registrert toksikolog (ERT)-registreringer
- Finansiering av Selskapets aktiviteter

3. Økonomi

Økonomien til NSFT vurderes som tilfredsstillende. Medlemskontingenten er kr 400,- for vanlige medlemmer og kr 150,- for studenter. Medlemskontingenten for bedriftsmedlemmer er fortsatt kr 3500,-.

NSFT har i 2019 mottatt økonomiske støtte fra Basic & Clinical Pharmacology & Toxicology (BCPT) til NSFTs vintermøte 2019 som gikk til forelesere, da spesielt Beitoforelesningen, Nordisk symposium og støtte til studenter.

For Vintermøtet 2020 er det satt av 10500,- til stipend for studenter som presenterer poster eller fritt foredrag. Stipend, Beitoforelesningen, årets artikkel og Nordisk symposium støttes i år av BCPT.

4. Faglig virksomhet

Vintermøtet

Vintermøtet 2019 ble holdt på Radisson Blu Resort Beitostølen 24. januar – 27. januar. Det var påmeldt 107 deltakere (ledsagere og barn ikke inkludert) og det var invitert 20 foredragsholdere fordelt på 9 symposier. Symposiene hadde følgende hovedtema:

- *Drugs of abuse (felles)*
- *Årets artikkel (Farmakologi & toksikologi, felles)*
- *The dCod 1.0 project: decoding the systems toxicology of Atlantic cod (toksikologi)*
- *Cancer in children; disease, treatment and late effects (farmakologi)*
- *Mikro / Nano (felles)*
- *Science and society – nice to know or need to know? (Beitoforelesningen, felles)*
- *The Immune system: from therapy to toxicology (Nordic symposium, felles)*
- *Hazard and exposure assessments of mixtures of chemicals for human health (toksikologi)*
- *Treatment of psychotic disorders (farmakologi)*

Kveldsnytt, *«Our toxic future - Proxima Centauri next?»*, ble holdt av Dag Markus Eide, Folkehelseinstituttet.

Til sammen var det meldt inn 29 frie foredrag og 19 postere fordelt på farmakologi og toksikologi.

Vårmøter

Nye perorale antikoagulantia (NOAKs)/direktevirkende perorale antikoagulantia (DOAKs): Hvor gode er de egentlig?
Tid og sted: 29. mai 2019, Runde auditorium, Domus Medica (UiO).
Arrangør: NSFT og Norsk Farmasøytisk Selskap

Dioksiner og dioksinlignende PCB i maten vi spiser: Hva er risikoen og helsemessige bekymringer?
Tid og sted: 7. mai 2019, Runde Auditorium, Domus Medica (UiO).
Arrangør: NSFT

Høstmøte

PFOS og PFAS i Tyrifjorden, kjøkkenet og skiløypa
Tid og sted: 5. november 2019, Folkehelseinstituttet, Oslo.
Arrangør: NSFT

Poulssonforelesning og seminar:

Poulssonmedaljen 2019 innen basalfarmakologi ble tildelt Professor Muthu Periasamy ved UCF College of Medicine, Burnett School of Biomedical Sciences, USA. Medaljeoverrekkelsen og Poulssonseminar ble holdt 9. oktober i Lille auditorium, Domus Medica (UiO)
Arrangør: NSFT

NSFTs publikasjonspris
NSFT opprettet i 2014 en ny pris for beste publikasjon fra norske fagmiljøer innen hhv. farmakologi og toksikologi. De første prisene ble delt ut på vintermøtet 2015.

Vinner av årets publikasjonspris innen farmakologi er Robert L Smith (Diakonhjemmet) og medarbeidere for artikkelen *«Effect of CYP2D6 Genotype on Exposure and Efficacy of Risperidone and Aripiprazole: A Retrospective, Cohort Study»*, Lancet Psychiatry, 2019. Styret mottok til sammen 12 nominasjoner innen farmakologi og komiteen for vurderingen av publikasjonene har bestått av Marianne Kristiansen Kringen (Diakonhjemmet), Erlend Johannessen Egeland (UiO) og Mohammad Nouri Sharikabad (FHI).

Vinner av publikasjonsprisen innen toksikologi er Johanna Samulin Erdema (STAMI) for artikkelen *«Cellulose nanocrystals modulate alveolar macrophage phenotype and phagocytic function»*, Biomaterials, 2019. Styret mottok til sammen 11 nominasjoner innen toksikologi, og komiteen for vurderingen har bestått av Jason Matthews (UiO), Vibeke Ansteinsson (TKØ) and Ketil Hylland (UiO).

5. Medlemmer
Selskapet har 306 medlemmer (per 1.1.2020). Av disse har 77 medlemmer oppgitt tilhørighet til farmakologiseksjonen, 144 til toksikologiseksjonen og 34 medlemmer har tilhørighet til begge seksjonene. De resterende medlemmene (51) har ikke valgt seksjonstilhørighet.

Ved utgangen av 2019 hadde 56 % av medlemmene betalt medlemskontingenten for 2019. Dette er en bedring fra 2018 (39 % betalende), men fortsatt er det mange som ikke betaler. Medlemmer uten funksjonell e-postadresse og manglende medlemskontingent fjernes etter hvert fra databasen.

6. Formidling av faglig informasjon i nyhetsbrev og på nettsider
NSFT har i løpet av 2019 sendt ut 8 elektroniske nyhetsbrev til samtlige medlemmer. Nyhetsbrevene inneholder bl.a. informasjon om kommende kurs og arrangementer innen farmakologi og toksikologi. Faglig informasjon har også blitt publisert på NSFTs nettsider og på NSFTs Facebook-side.

7. Toksikologen
Det har ikke vært utgitt nye utgaver av medlemsbladet «Toksikologen» i 2019. Toksikologiseksjonen jobber med å finne en ny form for innholdet.

8. Registreringsordningen for Europeisk-registrerte toksikologer (ERT)
Den norske komiteen for godkjenning av Europeiskregistrerte toksikologer (ERT) har etter Vintermøtet 2019 bestått av: Birgitte Lindeman (leder), Folkehelseinstituttet, Oslo (valgt til 2019); Christine Bjørge, Miljødirektoratet, Oslo (valgt til 2019); Espen Mariussen, Norsk institutt for luftforskning, Kjeller (valgt til 2019); Hege Stubberud, GE Healthcare AS, Lindesnes (valgt til 2020); Åse Krøkje, Norges teknisk-naturvitenskapelige universitet, Trondheim (valgt til 2021); Ketil Hylland, Universitetet i Oslo, Oslo (valgt til 2021); Marie Bjørgan, Yara International ASA, Oslo (valgt til 2021); Elise Rundén-Pran, Norsk institutt for luftforskning, Kjeller (valgt til 2019), Shan Zienolddiny, Statens arbeidsmiljøinstitutt (valgt til 2019).

Informasjon om ERT-ordningen finnes på NSFTs nettsider: http://nsft.net/ert

Oppsummering av ERT-komitéens arbeid i 2019 Komiteen mottok høsten 2019, 7 søknader om førstegangs-registrering som betyr at fjorårets trend med godt tilfang av nye søkere

fortsetter. Det ble levert 5 søknader om re-registrering. Søknadene blir behandlet i ERT-komitéen i januar 2020. Det er per 2019 omtrent 90 registrerte toksikologer på den norske listen. Det var ikke deltagelse fra den norske ERT-komiteen på EUROTOX' ERT-møte i 2019. Den norske ERT-komiteen jobber med utvidelse av informasjon til søkere om registeringsprosedyrene og oppdatering av informasjon på NSFTs hjemmeside.
Vintermøtet 2020

9. Registreringsordning for Europeisk sertifisert farmakolog (EuCP)
En komité bestående av Hege Thoresen (UiO), Harald Thidemann Johansen (UiO), Aina Westrheim Ravna (UiT), Laila Sortvik Nilssen (SLV), Janne K. Sund (NTNU), Siri Amundsen (UNN) og Tone Otterhaug (PCI Biotech) utarbeidet et forslag til nasjonale retningslinjer for EuCP som tilfredsstiller de internasjonale retningslinjene fra The Federation of European Pharmacological Societies (EPHAR). Søknad om å opprette ordningen ble sendt til EPHAR i 2017.

I april 2019 fikk NSFT svar fra EuCP programmet med 6 konkrete punkter som trenger adressering. Kommiteen jobber med å avklare punktene og har som mål å være ferdig med dette i begynnelsen av 2020.

Styret for 2019 takker for seg og ønsker det nye styret lykke til i det videre arbeidet.

Oslo, januar 2020

Mohammad Nouri Sharikabad (leder)
Jan Tore Samuelsen (sekretær)
Kristine Hole (kasserer)
Maria Hultman (styremedlem)
Jenny Lund (leder, Seksjon for farmakologi)
Jason Matthews (leder, Seksjon for toksikologi)
Helene Dugstad (industrirepresentant)
Rigmor Solberg (vara)
Birgitte Lyrån (vara)
Aina Westrheim Ravna (vara)

NSFT

Norsk Selskap for Farmakologi og Toksikologi

Innkalling til generalforsamling i NSFT
Beitostølen, 25. januar 2020, kl. 09:30

DAGSORDEN:

1. Konstituering av generalforsamlingen ved sekretær Jan Tore Samuelsen
    a. Godkjenning av møteinnkalling og dagsorden
    b. Valg av ordstyrer og referent

2. Årsberetning for 2019 - gjennomgang ved Jan Tore Samuelsen

3. Økonomi - gjennomgang ved kasserer Kristine Hole
    a. NSFTs regnskap for 2019 og budsjett for 2020

4. Valg ved valgkomiteen.
    a. Nytt styre
    b. Ny revisor
    c. Ny valgkomité

5. På generalforsamlingen 2019 ble besluttet at NSFT skulle støtte en søknad om å få IATDMCT konferansen til Oslo. Det er nå avgjort at konferansen legges til Oslo i 2023. Stein Bergan gir en kort orientering om veien frem mot 2023 og NSFTs rolle

6. Eventuelt

Oslo, 10. januar 2020
Hovedstyret i NSFT

NSFT

Norsk Selskap for Farmakologi og Toksikologi

Årsberetning 2019 – seksjon for farmakologi

Dette er styrets beretning om aktiviteter i perioden fra 1. februar 2019 til 25. januar 2020. Årsberetningen legges fram for godkjenning på årsmøtet i Seksjon for farmakologi på Beitostølen 25. januar 2020.

Styret har hatt følgende sammensetning:
Leder: Jenny Lund (2019-2021)
Styremedlem: Lise Román Moltzau (2016-2020)
Styremedlem: Kristin Nordal (2016-2020)
Styremedlem: Erlend Johannesen Egeland (2019-2021)
Styremedlem: Marianne Kristiansen Kringen (2019-2021)

Kontaktpersoner utenfor Oslo har vært:
Bergen: Jon Andsnes Berg
Trondheim: Ola Dale
Tromsø: Aina Ravna

Representant for seksjonen i NSFTs hovedstyre har vært Jenny Lund.
Valgkomiteen har bestått av Ida Robertsen, Ingvild Holdø og Sigrid Narum.

Styret har i perioden avholdt 4 styremøter, og har ellers hatt fortløpende kontakt via e-post og telefon om aktuelle saker. Seksjonen har per 1.1.2019 111 medlemmer. Av disse er 34 også medlem av seksjon for toksikologi. Totalt registrerte medlemmer i NSFT er 306.

EPHAR (www.ephar.org)
Neste EACPT-møte:
15th European ISSX (International Society for the Study of Xenobiotics) & EACPT (European Association for Clinical Pharmacology and Therapeutics) Meeting
Geneva, Switzerland, 07.-10. juni 2020
http://www.issxeacpt2020.org

IUPHAR (www.iuphar.org)
Neste IUPHAR-møte:
19th World Congress of Basic and Clinical Pharmacology 2022
Glasgow, Scotland, 16.-22. juli 2022
http://wcp2022.org
NSFT kan ha en representant på generalforsamlingen.

NSFTs publikasjonspris innen farmakologi 2019
Vinner av årets publikasjonspris innen farmakologi er Robert Løvsletten Smith og medarbeidere for artikkelen «Effect of CYP2D6 genotype on exposure and efficacy of risperidone and aripiprazole: a retrospective, cohort study», Lancet Psychiatry, 2019. Styret mottok til sammen 12 nominasjoner innen farmakologi og komiteen for vurderingen av publikasjonene har bestått av Mohammad Nouri Sharikabad (FHI), Marianne Kristiansen Kringen (OUS) og Erlend Johannesen Egeland (SLV).

Begrunnelse:
Prisen for beste publikasjon innen fagfeltet farmakologi går til: Robert Løvsletten Smith og medarbeidere for artikkelen «Effect of CYP2D6 genotype on exposure and efficacy of risperidone and aripiprazole: a retrospective, cohort study». Artikkelen er publisert i det anerkjente tidsskriftet Lancet Psychiatry. Dette er et samarbeidsprosjekt mellom Senter for psykofarmakologi (Diakonhjemmet sykehus), Avdeling for fysiologi og farmakologi (Karolinska Institutet), Farmasøytisk fakultet (Universitetet i Beograd), og Farmasøytisk institutt (Universitetet i Oslo).

Artikkelen viser at behandling med psykosemedisinene risperidon og aripiprazol, som årlig brukes av 15 000 nordmenn, kan forbedres med en enkel gentest av CYP2D6. Minst ett av fire behandlingsavbrudd kan unngås hvis gentesten utføres ved oppstart av medisinering, siden svaret fra gentesten kan brukes til å individualisere dosen i den enkelte pasient. Studien inkluderer mer enn 2500 norske pasienter, og er hittil verdens største innen dette forskningsfeltet.

Publikasjonen er svært godt skrevet, har en klar farmakologisk problemstilling og er basert på internasjonalt samarbeid. Komiteet trekker spesielt frem som positivt at studien er meget omfattende og har direkte klinisk relevans.

Vårmøte
I samarbeid med NFS (Norsk Farmasøytisk Selskap) inviterte seksjonen til Vårmøte med tema ”Nye perorale antikoagulantia (NOAKs)/direktevirkende perorale antikoagulantia (DOAKs): Hvor gode er de egentlig?”, 29. mai 2019 i Runde auditorium, Domus Medica (UiO).

Program

13:00-13:10	Velkommen Jenny Lund (seksjon for farmakologi, NSFT) og Hege Helm (NFS)
13:10-13:40	Hvordan har de etablert seg i klinikken? Sigrun Halvorsen (Oslo Universitetssykehus og Universitetet i Oslo)
13:40-14:10	Hvor effektive er de og hva sier anbefalingene? Steinar Madsen (Statens Legemiddelverk)
14:10-14:40	Pause med lett servering
14:40-15:10	Hvordan monitorere for å sikre god effekt? Erik Koldberg Amundsen (Oslo Universitetssykehus)
15:10-15:40	Er det noen utfordringer? Farmakokinetiske hensyn og potensielle interaksjoner Katrine Eek (RELIS)
15:40-15:55	Spørsmål og diskusjon
15:55-16:00	Oppsummering og slutt Jenny Lund (seksjon for farmakologi, NSFT)

Utdeling av Poulssonmedaljen 2019
Poulssonmedaljen 2019 innen basal farmakologi ble tildelt professor Muthu Periasamy, UCF College of Medicine, Burnett School of Biomedical Sciences, onsdag 9. oktober 2019 i Lille auditorium, Domus Medica, Universitetet i Oslo.

Program

13:00-13:15	Welcome and introduction of the award winner Mohammad Nouri Sharikabad, NSFT Chair
13:15-14:15	The award lecture Futile cycling of SERCA pump in muscle can melt fat and control obesity Professor Muthu Periasamy, UCF College of Medicine
14:15-14:45	Break
14:45-15:10	Remodelling of energy metabolism in human myotubes Professor Arild Rustan, University of Oslo
15:10-15:35	Coupling of PDE3A to SERCA2 in cardiomyocytes – regulation of cardiac contractility and future drug target Associate Professor Magnus Aronsen, University of Oslo
15:35-16:00	Targeting the adrenergic regulation of the SERCA2 complex protects from myocardial ischemia-reperfusion injury Researcher Ana Calejo, University of Oslo

Vintermøtet 2019
Seksjonen har deltatt i utformingen av programmet for NSFTs vintermøte.

Regnskap
Regnskapet for seksjonen har i 2019 vært håndtert sammen med regnskapet for NSFT som helhet. For en formell økonomisk oversikt henvises det derfor til NSFTs regnskap.

Avslutning
Seksjonsstyret for 2019 takker for seg og ønsker det nye styret lykke til med det videre arbeidet.

Lise Román Moltzau Kringen (Styremedlem)	Kristin Nordal (Styremedlem)	Marianne Kristiansen (Styremedlem)

Erlend Johannesen Egeland (Styremedlem)	Jenny Lund (Leder)

NSFT

Norsk Selskap for Farmakologi og Toksikologi

Innkalling til årsmøte i seksjon for farmakologi

NSFT
Beitostølen, 25. januar 2020, kl. 09:00-09:30

DAGSORDEN

1. Konstituering av årsmøtet
    a. Godkjenning av møteinnkalling og dagsorden
    b. Valg av ordstyrer og referent

2. Årsberetning for farmakologiseksjonen 2019

3. Godkjenning av budsjett for seksjon for farmakologi

4. Valg
    a. Nytt styre i farmakologiseksjonen
    b. Ny valgkomité

5. Orienterings- og diskusjonssaker
    a. Vår/høstmøte 2020
    b. Innspill til vintermøte 2021

6. Eventuelt

Oslo, januar 2020
Styret i farmakologiseksjonen, NSFT

NSFT

Norsk Selskap for Farmakologi og Toksikologi

Årsberetning 2019 – seksjon for toksikologi

This is the Toxicology board's report on our activities during the period from 1 February 2019 to 25 January 2020. This annual report is submitted for approval at the annual meeting of the Section for Toxicology at NSFT winter meeting at the Radisson BLU Resort Beitostølen on 25 January 2020.

1. The composition of the board
The board members for the toxicology section in the year 2019 has been as follows:

Leder – Jason Matthews (2019-2021) – UiO, Oslo
Vibeke Ansteinsson, (2019-2021)- TKØ, Oslo,
Anita Solhaug, (2019-2021)- VI, Oslo,
Odd Andre Karlsen (2019-2021) – UiB, Bergen
Marit Nøst Hegseth (2019-2020)- UNN/UiT, Tromsø
Nina Landvik (2018-2020- ikke på valg) – Miljødirektoratet, Oslo
Pål Amdal Magnusson (2018-2020- ikke på valg)- Miljødirektoratet, Oslo
Dag Markus Eide (2019-2021) – FHI, Oslo

Varamedlemmmer:
Solveig Føreland, varamedlem, (2019-2021)- UNN, Tromsø
Vidar Berg-varamedlem (2018-2020)- NMBU, Oslo

Valgkomiteen for 2019: Shan Zienolddiny and Hubert Dirven

2. The work of the board
The board had four meetings and many email communications during the year.

The board's work over the past year:

Jason Matthews participated in the Eurotox 2019 business meeting in Helsinki (September 2019).

Vintermøtet 2019
Pris for beste poster gikk til Silje Modahl Johanson (NMBU) Maternal exposure to a mixture of persistent organic pollutants have long-lasting effects on gut metabolite composition but not on colorectal cancer

Pris for beste frie foredrag gikk til: Karina Dale (UiB) Contaminant accumulation and biological responses in Atlantic cod (*Gadus morhua*) exposed to polycyclic aromatic hydrocarbons and perfluoroalkyl substances.

Alan R Boobis fra Imperial College London holdt Beito-forelesning om Science and society – nice to know or need to know?

Vårmøtet 2019

Dioksiner og dioksinlignende PCB i maten vi spiser: Hva er risikoen og helsemessige bekymringer?

Dioxins and dioxin-like PCBs in the food we eat: What are the risks and health concerns?

When: Tuesday 7th of May, 13:00-16:00
Where: Runde Auditorium R-105, Domus Medica tilbygg UiO

Agenda

13:00 Welcome – Jason Matthews (NSFT)

13:05 **Johan Øvrevik** – Folkehelseinstituttet – Aryl hydrokarbonresptor - nye roller for dioksinreseptoren i sykdomsutvikling

13:35 **Ole Jakob Nøstbakken**, Havforskningsinstituttet – Dioksin og dl-PCB i norsk sjømat

14:05 Coffee break

14:30 **Helle Knutsen**, Folkehelseinstituttet - Dioksiner og DL-PCB er fortsatt en helserisiko: presentasjon av EFSAs nye og syv ganger lavere TWI

15.15 **Aksel Bernhoft**, Veterinærinstituttet - Eksponering av dioksiner og dioksinlike PCB hos dyr og risiko for dyras helse

15.45 Questions/comments
16:00 End of meeting

Comments: Approximately, 40 people attended the spring meeting. Only 20 remained at the end. Disappointingly, few of the attendees were UiO students.

HøstMøtet 2019

PFOS og PFAS i Tyrifjorden, kjøkkenet og skiløypa.
Når: Tirsdag 5. november, 13:00-15:00
Hvor: Folkehelseinstituttet Rom L8 HB 1013 Auditoriet

Agenda

13:00 **Kristine Gutzkow**, Folkehelseinstituttet: Hvor helseskadelig er PFAS PFOA og Teflon? Hvorfor forsvinner det aldri?

13:25 **Eivind Farmen**, Miljødirektoratet: PFAS i Tyrifjorden - vann og fisk en helsetrussel?

13:50 **Jan Lyche**, NMBU: Spor etter fluor i skisporet?

14:00 Kaffe

14:15 **Eleni Papadopoulou,** Folkehelseinstituttet: PFAS and mixture effects on the liver. The Helix multicentre studies.
14:30 **Birgitte Lindeman**, Folkehelseinstituttet: Skismøring - eksponering å bekymre seg for?

14:45 **Berit Granum,** Folkehelseinstituttet: PFAS påvirker immunsystemet vårt. Er det så farlig?

15:00 Spørsmål diskusjon og slutt

Comments: About 50-ersoner deltok på dette vårmøtet. It was also Skype streamed to UiB for about 5-8 people? The skype stream worked, but could be improved.

Nominasjon av NSFT's publikasjonspris innen toksikologi for 2019

Siden 2014 har NSFT tildelt pris for årets beste publikasjon fra norske fagmiljøer innen hhv. farmakologi og toksikologi (akseptert for publikasjon i perioden 1. november året før til 31. oktober inneværende år).

I 2019 har komiteen for vurderingen bestått av Jason Matthews (UiO), Vibeke Ansteinsson (TKØ) and Ketil Hylland (UiO)

Toksikologiseksjonen fikk inn 11 nominasjoner til denne prisen.

Vinner av publikasjonsprisen innen toksikologi er: Johanna Samulin Erdema for artikkelen *«Cellulose nanocrystals modulate alveolar macrophage phenotype and phagocytic function»*. The article was published in the journal Biomaterials and the research was done at the National Institute of Occupational Health (STAMI).

This article investigated the effects of cellulose nanocrystals (CNC) on alveolar macrophage polarization, inflammation and cellular function. CNC is an attractive biomaterial and novel material that is clearly relevant for society and as such there is potential for occupational exposure. However, toxicity data on CNC are lacking. The study found that CNC exposure may result in dysregulation of macrophage activation and function, both of which are critical in inflammatory.

The publication was well-written and included relevant endpoints generated from an impressive amount data. Moreover, the study was comprehensive, well-designed and had clear toxicological and societal relevance.

Vintermøtet 2020
Styret har foreslått en del temaer til symposia

- Beito-forelesning – Stewar Owen fra AstraZeneca "Using fish cells to build micro-organs that help us better understand the risk of pharmaceuticals in the environment"
- ADHD
- Polarforskning i toksikologi
- Luftforurensning

Toksikologiseksjonen fikk inn 10 abstrakter for orale presentasjoner og 12 abstrakter for postervisninger til Vintermøtet 2020.

3. Establishment of a «Poulsson» pris in Økotoksikologi. This still needs to be discussed. According to the Poulsson award charter, the award cannot be given to an Økotoksikolog. This still needs to be confirmed. If this is indeed the case, then a new award for outstanding contributions to Økotoksikologi will need to be established.

4. Utgivelse av "TOKSIKOLOGEN"- Toksikologiseksjonens fagtidsskrift. There were no editions of "Toksikologen" produced in 2019. Suggestions from last year's winter meeting were to start a blog or something similar, but unfortunately, nothing has been done to make this happen.

NSFT

Norsk Selskap for Farmakologi og Toksikologi

Innkalling til årsmøte i seksjon for toksikologi

NSFT
Beitostølen, 25. januar 2020, kl. 09:00-09:30

Dagsorden:

1. Konstituering av årsmøtet
   a. Godkjenning av møteinnkalling og dagsorden
   b. Valg av ordstyrer og referent

2. Årsberetning for toksikologiseksjonen 2019. Leder av seksjonen går gjennom årsberetning

3. Valg
   a. Nytt styre i toksikologiseksjonen
   b. Ny valgkomité

4. Etablering av en ærespris (Poulsson-pris) for økotoksikologer

5. Toksikologen – Should it be revived as a blog?

6. Møter 2020 – nye forslag og videreføring av idéer
   a. Vår- og høstmøte 2020 - NETS 2020
   b. Innspill til vintermøte 2021

7. Eventuelt

Oslo, januar 2020
Styret i toksikologiseksjonen NSFT

Inviterte foredrag (IF)

IF-1

Prenatal toxic exposure and risk of neurodevelopmental disorders –the NeuroTox project

Heidi Aase, PhD, PI, Avdelingsdirektør for Barns helse og utvikling, Folkehelseinstituttet

The developing brain is vulnerable to environmental insults, particularly from toxic compounds. The knowledge about adverse effects of toxicants on neurodevelopment is still limited, and consequently it is largely unknown whether exposure to toxicants is a risk factor for neurological and neurodevelopmentaldisorders such as attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), epilepsy and cerebral palsy (CP). These disorders often have profound consequences for the children who are affected, for their families and communities. Treatment can be a great challenge and has a large socio economic cost. The identification of preventablerisk factors, such as hazardous substances in the environment, should therefore be prioritized.In NeuroTox, weinvestigate risk associated with two types of neurotoxicants: (1) perfluoralkyl substances (PFAS), a novel group of persistent organic pollutants that are suspected developmental neurotoxicants, and (2) trace elements and metals with known neurotoxic effects, e.g. mercury, lead, arsenic, cadmium, manganese. These toxicants are present in our environment at levels that may have biological effects, and may be transferred to the fetus via the placenta and disrupt critical periods of brain development. We assess risk for each substance independently, and investigate possible combined effects in a complex mixture approach. Additionally, we investigate if these toxicants indirectly affect neurodevelopment by acting as thyroid hormone disruptors or by modifying epigenetic processes.

A better understanding of the mechanistic pathways linking toxicant exposures to neurodevelopmental disorders and cognitive functions in children will improve our knowledge about the sensitivity of the brainduring perinatal development.In NeuroTox, weutilizethe world’s largest birth cohort; the Norwegian Mother, Fatherand Child Cohort Study (MoBa) and its ongoing sub-studies of ADHD, ASD, epilepsy and CP. Data include questionnaire data and biological samples, clinical assessments, and linkages to the nationwide Norwegian Patient Registry (NPR) and the National screening program for newborn children.The presentation will include a thorough description of the study and some preliminary findings.

IF-2

Biologiske årsaker til ADHD og nye legemiddeltargets

Jan Haavik, Universitetet i Bergen

IF-3

Effect of *CYP2D6* genotype on exposure and efficacy of risperidone and aripiprazole: a retrospective, cohort study

Marin M Jukic[1,2], Robert L Smith[3], Tore Haslemo[3], Espen Molden[3,4], Magnus Ingelman-Sundberg[1]* (*shared seniorship)*

[1]Section of Pharmacogenetics, Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden
[2]Department of Physiology, Faculty of Pharmacy, University of Belgrade, Serbia
[3]Center for Psychopharmacology, Diakonhjemmet Hospital, Oslo, Norway
[4]Department of Pharmaceutical Biosciences, School of Pharmacy, University of Oslo, Norway
Presenting author: Robert L Smith (robert.lovsletten.smith@gmail.com)

Aim
The polymorphic CYP2D6 enzyme metabolises the antipsychotic drugs risperidone and aripiprazole to their active metabolites, 9OH-risperidone and dehydroaripiprazole. The aim of this study was to quantify the effect of *CYP2D6* genetic variability on risperidone and aripiprazole exposure and treatment in a large patient population.

Methods
We retrospectively obtained patient data from a routine therapeutic drug monitoring database at the Center for Psychopharmacology, Diakonhjemmet Hospital, Oslo, Norway, between Jan 1, 2005, and Oct 15, 2018. Individuals included in our analyses were *CYP2D6*-genotyped patients treated with risperidone or aripiprazole. Inclusion criteria for measurement of pharmacokinetic parameters (drug and metabolite serum concentrations) were oral administration of risperidone or aripiprazole, information known about prescribed daily dose and comedications, and aged older than 18 years. Exclusion criteria included polypharmacy with drugs known to be CYP2D6 inhibitors or CYP3A4 inducers or inhibitors. Treatment failure was analysed in all patients treated with risperidone or aripiprazole without these criteria. The first endpoint in our analysis was the metabolism of risperidone to 9OH-risperidone and aripiprazole to dehydroaripiprazole, estimated by the log-transformed ratio between the concentrations of metabolite and parent drug (ie, the metabolic ratio for risperidone [9OH-risperidone]/[risperidone] and the metabolic ratio for aripiprazole [dehydroaripiprazole]/[aripiprazole]). Endpoint two was measurement of drug exposure, quantified by the dose-normalised sum of parent drug and active metabolite serum concentrations (ie, active moiety). The third endpoint of treatment failure was measured as the number of patients switched from risperidone or aripiprazole to another antipsychotic drug within 1 year after the last therapeutic drug monitoring analysis of risperidone or aripiprazole. Patient subgroups were defined by *CYP2D6* genotype-determined metaboliser status: poor metabolisers, intermediate metabolisers, normal metabolisers, and ultrarapid metabolisers. ANOVA was used to assess the differences in metabolic ratios, active moieties, and daily doses between individual metaboliser categories, and risperidone and aripiprazole therapeutic failures were compared by logistic regression using the normal metaboliser subgroup as a reference.

Results
1288 risperidone-treated patients and 1334 aripiprazole-treated patients were included in the study, of whom 725 (56%) risperidone-treated and 890 (67%) aripiprazole-treated patients were eligible for the pharmacokinetic analyses. *CYP2D6* genotype significantly changed risperidone and aripiprazole metabolism resulting in an approximately 1.6-times and 1.4-

times increase in risperidone and aripiprazole active moiety exposure in poor and intermediate metabolisers compared with normal metabolisers, respectively (odds ratios [OR] for the risperidone dose-normalised active moiety concentration 1.568 (95% CI 1.401–1.736) and 1.373 (1.213–1.532); and for the aripiprazole dose-normalised active moiety concentration 1.585 (1.447–1.724) and 1.476 (1.263–1.688) respectively; p<0.0001 for all). Compared with doses for normal metabolisers, clinicians reduced daily doses of risperidone and aripiprazole administered to poor metabolisers by 19% (95% CI 5–35, p=0.010) and 15% (95% CI 1–28, p=0.033) respectively. The incidence of switching from risperidone to another antipsychotic was increased in ultrarapid metabolisers (OR 2.934, 95% CI 1.437–5.989, p=0.003) and poor metabolisers (1.874, 1.128–3.112, p=0.015); by contrast, the incidence of switching from aripiprazole to another antipsychotic was not significantly related to CYP2D6 metaboliser status.

Conclusion
CYP2D6 genotype had a substantial clinical effect on risperidone and aripiprazole exposure and on the therapeutic failure of risperidone. Pre-emptive *CYP2D6* genotyping would be valuable for individualising risperidone and aripiprazole dosing and treatment optimisation.

IF-4

Cellulose Nanocrystals Modulate Alveolar Macrophage Phenotype and Phagocytic Function

Johanna Samulin Erdem, Mayes Alswady-Hoff, Torunn K Ervik, Øivind Skare, Dag G Ellingsen, Shanbeh Zienolddiny
Statens Arbeidsmiljøinstitutt, Oslo

Nanocellulose is a promising bio-nanomaterial with attractive properties suitable for multiple industrial applications. The increased use of nanocellulose may lead to occupational exposure and negative health outcomes. However, knowledge on its health effects is limited, and while nanocellulose exposure may induce acute inflammatory responses in the lung, the underlying mechanisms are unknown. Alveolar macrophages are key cells in alveolar particle clearance. Their activation and function may be affected by various particles. Here, we investigated the uptake of pristine cellulose nanocrystals (CNC), and their effects on alveolar macrophage polarization and biological function. CNC uptake enhanced the secretion of several cytokines but did not on its own induce a complete macrophage polarization. In presence of macrophage activators, such as LPS/IFNG and IL4/IL13, CNC exposure enhanced the expression of M1 phenotype markers and the secretion of pro-inflammatory cytokines and chemokines, while decreasing M2 markers. CNC exposure also affected the function of activated alveolar macrophages resulting in a prominent cytokine burst and altered phagocytic activity. In conclusion, CNC exposure may result in dysregulation of macrophage activation and function that are critical in inflammatory responses in the lung.

IF-5

Current knowledge of pollutants and their effects in Arctic mammals

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Arctic mammals are exposed to a wide range of environmental contaminants, but legacy persistent organic pollutants are still the main compounds, which arctic mammals accumulate and are exposed to. These are dominated by polychlorinated biphenyls, organochlorine pesticides and perfluoroalkyl substances. Several factors including diet, trophic level, habitat use and biotransformation capacity determine inter-species variation in contaminant levels and patterns among arctic mammals. For most legacy POPs that have been banned for decades, concentrations initially declined in arctic mammals, but recently some compounds have remained at constant levels or increased. This is likely related to changes in food webs and mobilization of contaminants from ice and permafrost due to global warming. Numerous studies have investigated potential adverse effects of contaminants in arctic mammals using correlative, in vitro and modelling approaches. However, our understanding of population level risks and effects of contaminants is still very limited.

IF-6

Effects of complex petroleum mixtures to Barents Sea key fishes – recent results on species sensitivity and a novel hypothesis that may lead to a paradigm shift in the field of research

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Climate change and the northward shift of the marginal ice zone may portend a significant expansion of the industrial activities in the coming years. Although technological advances and regulations may help lower the potential impacts of accidental oil spills, their environmental and societal consequences can be tremendous and long-lasting. A large number of studies document the high toxicity of crude oil to fishes, and in particular to early life stages. Here, I will present the work conducted in the past years to elucidate the effects of crude oil to both adults and early life stages of a key Arctic species, the polar cod (*Boreogadus saida*). I will further contrast the findings with the recent work on the commercially important capelin (*Mallotus villosus)*, that also has distinct life history traits. Polycyclic aromatic hydrocarbons are believed to be the major causative agents to fish early life stages toxicity when exposed to petroleum related mixtures. I will discuss this currently accepted understanding based on the past 20 years of research and propose an alternative hypothesis.

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IF-7

The role of the altricial-precocial spectrum for pollutant loads and effects in marine mammal offspring

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Offspring of marine mammals are exposed to maternally transferred persistent organic pollutants (POPs) both *in utero* and *post-partum* through mothers milk. However, the maternal transfer differ between these two exposure routes, causing exposure of offspring to differential toxic compounds *in utero* and during suckling. Since different POPs have differing modes-of-action, effects following exposure *in utero* and via mothers milk most likely differ. Precocial and altricial mammals differ significantly in their development *in utero*. Offspring of precocial mammals are well-developed when born, having received energy and nutrients for development *in utero*. In contrast, altricial species are dependent on a high *post-partum* parental investment, the mothers milk providing energy and nutrients for offspring development. We hypothesized that the exposure of offspring to specific POPs caused by maternal transfer differ between precocial and altricial speciess. This was tested by retrieving literature data on maternal transfer of polychlorinated biphenyls (PCBs) and their hydroxylated metabolites (OH-PCBs) and per- and polyfluoroalkyl substances (PFAS) in hooded seals (*Cystophora cristata*) and polar bears (*Ursus maritimus*), which have a highly precocial and highly altricial development, respectively. The results showed that maternal transfer of the proteinophilic PFASs was significantly higher in offspring of the precocial hooded seal than in offspring of the altricial polar bear. In contrast, the maternal transfer of lipophilic PCBs was significantly higher in the offspring of the altricial polar bear than in the precocial hooded seal. Exposure to PFASs have been linked to adverse health outcomes in mammals, and in particular immunosuppressive effects in young developing mammals. Our findings indicate that increased pup-mortality associated with adverse health effects of *in utero* derived PFASs could play a role in the dramatic population decline reported in hooded seals off the coast of East-Greenland.

IF-8

Diabetes – ikke bare min skyld?

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Diabetes er en av de vanligste endokrine tilstander med stor forekomst i alle land. Både type 1 og 2 diabetes er karakterisert av en absolutt eller relativ insulinmangel. Felles for alle diabetessykdommene er at blodsukkeret stiger og det er i hovedsak dette som fører til sykdommenes komplikasjoner. Årsakene til blodsukkerstigningen er sammensatt. Fortsatt er det sannsynligvis ca 50 -100 000 personer i Norge med uoppdaget diabetes.
Det er godt kjent at overspising og lite fysisk aktivitet fører til overvekt og at dette igjen kan lede til livsstilssykdommer som type 2 diabetes. Samtidig har det vært kjent, blant annet gjennom tvillingstudier, at disse tilsandende også har en betydelig arvelig komponent; både sosial arv, som det å vokse opp i samme miljø i en familie og ren genetisk arv, det man arver ved å ha felles arvestoff. Arv som risikofaktor har vært underkommunisert for disse hyppige tilstandene.

Den arvelige sårbarheten til type 1 diabetes er i gener som styrer immunforsvaret (HLA), mens den arvelige sårbarheten ved type 2 diabetes, overraskende nok, i all hovedsak i gener som styrer den insulinproduserende beta-cellen og ikke overvekt. Skulle overvekt vært årsak til sykdommen, ville man forventet at den arvelige årsaken også var i gener som hadde med overvekt og insulinresistens og gjøre.

Behandlingen av diabetes retter seg i all hovedsak mot å forebygge sykdomskomplikasjoner av kronisk forhøyet blodsukker. Dette er i hovedsak sykdommer som skyldes skader i blodkar. Sykdommer assosiert med skader i små blodkar er nyre-, nerve- og øyesykdommer. Hjerte/kar sykdom, slag og amputasjoner er forårsaket av skade i store blodkar. Det er ofte kombinasjonen av høyt blodsukker, forstyret blodfett og høy blodtrykk som er årsak til sykdommene og det er behandling av disse årsakene som står sentralt i behandlingen av diabetes.
Behandlingen blir derfor med mange medikamentgrupper samtidig og det er ønskelig med polyfarmasi. Det er vist at god kontroll på blodsukker, blodtrykk og blodlipider i kombinasjon, reduserer senkomplikasjoner og tidlig død med opp til 50%. Det kan se ut til at god behandling av blodtrykk og lipidsenking er det aller viktigste.

Mål din egene diabetesrisiko:

Risikofaktor	**Svar**	**Risikoskår**
Diabetes i slekten	Nei	0
	Førstegrads slektning	5
	I slekten	3
Alder (år)	< 45	0
	45-54	2
	>55	3
BMI (kg/m^2)	<25	0
	25-30	1
	>30	3
Livmål (cm)	<94 menn, <80 kvinner	0
	94-101 menn, 80-87 kvinner	3
	>102 menn, >88 kvinner	4
Bruk av blodtrykksmedisin	Nei	0
	Ja	2
Tidligere forhøyet blodsukker	Nei	0
	Ja	5
Fysisk aktivitet < 30 min om dagen	Nei	0
	Ja	2
Daglig inntak av frukt og grønnsaker	Nei	1
	Ja	0

Tab 1. En risikoskår på >9 gir ca. 10-15% risiko for diabetes de neste 10 år. Etter: J. Lindström og J. Tuomilehto, Diabetes Care, 26, 3, 2003, 725-30

IF-9

Nye mulige legemiddelmål for behandling av type 2-diabetes?

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Ulike nyere legemiddelmål (targets) for behandling av type 2-diabetes vil bli gjennomgått, både nåværende og mulige nye legemiddelmål. Virkningsmekanismer og effekter av nyere antidiabetika slik som *GLP-1 analoger, DPP4-hemmere og SGLT2-hemmere* vil bli gjennomgått. Det vil videre fokuseres på nye mulige legemiddelmål slik som enzymer, transportmekanismer og signalsystemer som kan påvirke glukosemetabolismen og energiomsetningen i gunstig retning, inklusive energiforbruket og kroppsvekten. Sentrale organer for regulering av energiomsetningen hvor legemidler kan utøve sin effekt vil fortrinnsvis være pankreas, lever, skjelettmuskel, fettvev og nyre.

IF-10

Tackling antimicrobial resistance – the public health perspective

Jasper Littmann, Folkehelseinstituttet

Antimicrobial Resistance (AMR) is a threat to global health and will likely increase significantly over the course of the coming decades. AMR undermines many of the foundations of our health care system, by making bacterial infections more difficult, or impossible to treat, and by reducing the effectiveness of antibiotic prophylaxis, which has enabled us to safely perform a wide range of invasive surgical procedures.
It is estimated that AMR already kills more than 700.000 people annually today, and this number is projected to grow more than ten-fold until 2050, unless drastic action is taken. This presentation will outline the need for and required scope of a coordinated and intersectorial response. To this end, it will characterise the emergence of AMR as a health systems failure across three dimensions: first, a lack of innovation, second, a lack of access to effective antibiotics, and third a failure to conserve the effectiveness of existing antibiotics through rational use.
Developing a successful policy response to the mounting challenge that AMR presents will therefore require simultaneous action within these three fields. At the same time, it will be important to adapt policies to regional differences, since AMR impacts societies, health systems and populations differently, and consequently represents not one universal challenge, but rather a broad spectrum of policy problems.

IF-11

Appropriate prescribing of antibiotics - can national interventions promote responsible antibiotic prescribing in humans?

Hege Salvesen Blix, Department Drug Statistics, Norwegian Institute of Public Health and Department of Pharmacy, University of Oslo

Antimicrobial resistance (AMR) is an urgent global public health problem. Antibiotic use is a main risk factor for AMR, hence, unnecessary and excessive use of broad spectrum antibiotics should be avoided. There is a global call for national and international initiatives to curb overuse and misuse of antibiotics. However, the impact of initiatives will differ according to culture and type of health system and health settings. Different interventions and impact of nationally interventions aiming to reduce inappropriate antibiotic use in humans must target both prescribers and users. Prescribing in primary care should focus on whether or not to use antibiotics, in hospitals the focus should be choosing appropriate treatment and narrow-spectrum treatment.
The Norwegian national strategy for combating AMR and national action plan have shown to be effective, in humans, animals and in the environment. Focusing on the use in humans, many interventions have been implemented and are still on-going – nationally as well as in primary care, nursing homes and in hospitals. Multi-faceted interventions combining surveillance, audit and feedback and educational efforts seem to be very effective to reduce antibiotic use and have moved national antibiotic use towards more narrow spectrum antibiotics. However, there is still a need to focus on patient safety, targeted treatment and special needs in different population groups. Moreover, more research is needed to assess the different antibiotic stewardship interventions, and to explore barriers to implementation.

References
Usage of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Norway. 2018: Tromsø / Oslo. 2019 p. ISSN: 1502-2307 (print) / 1890-9965 (electronic).
The Norwegian National Strategy Against Antibiotic Resistance 2015-2020 https://www.regjeringen.no/no/dokumenter/nasjonal-strategi-mot-antibiotikaresistens-2015-2020/id2424598/

IF-12

Using fish cells to build micro-organs that help us better understand the risk of pharmaceuticals in the environment

Stewart Owen, Astra Zeneca

Fish cell culture has a history stretching 60 years, but in the last decade we have learnt to re-build 3-dimensional micro organoids that better represent an intact fish. We can use these integrated tissue models to both reduce the number of fish used in the laboratory, but more importantly answer questions that were not easy with living animals. We have developed a range of organs and co-culture models. This approach represents better science, and over the next six years of a European Union Collaboration across public and private partners it will help us prioritise which medicines represent the greatest risk to the aquatic environment.

Dr Stewart Owen is the Principal Environmental Scientist at AstraZeneca and an Honorary Associate Professor, University of Exeter.

IF-13

Beta2-adrenergic agonists - from obesity to athletes

Morten Hostrup, Københavns universitet

IF-14

Doping as an ethical dilemma

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Research question
Doping, or the use of bio-medical means and methods to enhance athletic performance, represents a complex, ethical dilemma. Why is doping banned in sport?

Methods
This is a study in practical philosophy in which arguments are presented and weighed within a systematic and critical *pro et contra* framework.

Results
Arguments from fairness and health are dissected and criticized. Facts alone are not sufficient to justify a ban. I argue that a ban on doping depends upon interpretations of the value of sport. I propose one specific interpretation within which fairness and health arguments regain meaning and relevance. I discuss as well the fragility of the doping ban and the possibility of other normative sport interpretations.

Conclusion
Doping is banned in sport based upon a specific interpretation of the value of sport.

IF-15

Blood doping in sports – Current challenges and ways of detection

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Doping and its detection has been a challenge in sports for decades, and the development of new or more sensitive methods in doping analysis is often followed up by new strategies from the cheats on how to pass a doping test. Detection of blood doping has been particularly difficult. Already decades ago, it was well known that elite athletes were cheating with blood transfusions and recombinant erythropoietin (EPO), while doping control suffered from the lack of direct tests for detection. With the arrival of the EPO-test (by IEF-PAGE) 20 years ago, it was for the first time possible to sanction the cheats. The direct EPO-test led to a resurgence of blood transfusions amongst cheating athletes. A test for detection of homologous blood doping was developed, and the practice of autologous blood doping increased as a result. The Athlete Biological Passport and its Haematological Module was introduced 10 years ago and is still the only way to – indirectly – detect autologous transfusions. The Biological Passport remains a very important tool in doping control today, where atypical passports will be followed up with targeted tests and/or additional analyses. The EPO-test itself has meanwhile been significantly improved, both in terms of sensitivity and efficiency. The last few years we have also seen the use of substances, so-called HIF-stabilizers, that increase the endogenous synthesis of EPO by preventing degradation of the hypoxia-inducible factor (HIF) 1α. An overview of the current challenges of blood doping we face today and how these are dealt with in doping control will be presented.

IF-16

Health effects of air pollution with focus on particular matter

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Ambient air pollution is among the leading environmental health risk factors, estimated to cause approximately four million deaths globally, and 1500 premature deaths in Norway. Exposure to particular matter (PM) with an aerodynamic diameter of 2.5 µm and less ($PM_{2.5}$) is known to have vascular and respiratory effects. Some of the strongest causal associations have been reported between $PM_{2.5}$ and vascular effects leading to ischemia, myocardial infarction, stroke, and development or exacerbation of adverse respiratory outcomes including respiratory infections, asthma, chronic obstructive pulmonary disease (COPD) and lung cancer. To estimate burden of disease of $PM_{2.5}$ both exposure of the population, a concentration-response function and register data with death and diseases in the population have to be included. In our new web side, "Air quality in Norway", which is an air quality forecast with public information, the population-weighted exposure is possible to elucidate for all the local councils.

Mass of size fractions of PM is normally linked to health effects and used in regulatory policy against air pollution. However, size, shape, structure, surface reactivity and lipophilic and hydrophilic chemicals attached to particles have all been found to be important for biological reactivity and health outcomes. PM might be produced in various processes and represent variable entities with highly source-dependent properties, such as PM from exhaust and wear of road pavement, tires and brakes. Combustion PM from exhaust and wood burning typically consists of a carbon core in the ultrafine size range (< 100 nm), and contains mixtures of organic chemicals adhered to the surface. Whereas, abrasion/wear particles can be in all size fractions from coarse to ultrafine with a core of minerals, metals or rubber. These very different PMs might also induce different types of health effects. However, upon using epidemiological studies it is difficult to discriminate the observed health effects of PM to specific PM components. Therefore, mechanistic understanding of processes leading to diseases by the different PM components is important to establish causal relationships.

IF-17

Hvordan jobber myndighetene for trygg utendørsluft i Norge?

Line Merete Karlsøen, Miljødirektoratet

Luftforurensning er skadelig for helsa. Årlig dør tre til fire millioner mennesker for tidlig i verden grunnet luftforurensning, mens rundt 1000 mennesker dør for tidlig i Norge. Mange flere opplever forverret sykdom og helseplager.

Vi har lovverk som skal beskytte oss mot dette, og i Norge er kommunen forurensningsmyndighet for lokal luftkvalitet.

Luftsamarbeidet, som består av fem statlige aktører, har utviklet en varslingstjeneste kalt Luftkvalitet i Norge (https://luftkvalitet.miljostatus.no) hvor alle kan sjekke luftkvaliteten i dag og i morgen, hvor som helst i landet til enhver tid. Og få helseråd. En tjeneste for fagbrukere med luftkvalitetskart, befolkningseksponering med mer for alle kommunene i landet er også rundt hjørnet. Disse tjenestene setter brukeren i sentrum og er fundert på, blant annet, mengder med toksikologisk forskning.

Velkommen til et luftig, men likevel innholdsrikt foredrag om forvaltningen av den lokale utendørslufta i Norge!"

IF-18

Verdibasert ventilasjon bygd på HealthVent og EUs normer for luftkvalitet inne og ute

Jan Vilhelm Bakke, Phd, overlege, spesialist i arbeidsmedisin.

Carrer et al 2018 har foreslått nye helsebaserte ventilasjonskrav med en grunnventilasjon på 4l/s/person. De skal avløse dagens høyere krav som er basert på opplevd luftkvalitet (sensorisk basert). Eksperimenter i klimakammer undervurderte effekt av lav luftfuktighet som på våre breddegrader er et stort problem om vinteren. Det slår særlig ut på smitterisiko for influensasykdom. Fall i utetemperatur og damptrykk kommer før inkubasjonstiden for de årlige influensaepidemiene (Jaakkola et al 2014, Sundell et al 2016). Humant rhino- og enterovirus synes uavhengig av klimatiske forhold.
Sykehusene anses som «verstingen» med hensyn til «tørr luft» med dels svært høye ventilasjonsrater og for høye lufttemperaturer kombinert med opphopning av særlig sårbare pasientgrupper. Forebyggende tiltak kan omfatte:

1. Utetemperaturjusterte temperatur- og ventilasjonskrav. I første omgang også effekter av nye ventilasjonskrav fra EU i Health Vent (Carrer et al 2018).
2. Lavere lufthastigheter ned mot 0,05 m/s i oppvarmingssesongen. Økende lufthastigheter 0,07 – 0,15 m/s gir ikke opplevelse av «trekk», men av redusert temperatur (Bakke et al2008).
3. Befuktning når helt nødvendig, kun der det trengs og med den mengden som er nødvendig. Det trengs eventuelt «idiotsikre» installasjoner som er lett å drifte.

Diakonhjemmet instrumenterer nå et nytt helsebygg slik at det vil kunne styre og dokumentere ventilasjonsforholdene. Det kan gi bedre underlag for å evaluere effekter at ulike betingelser.

Snart 40 års systematisk arbeid med «air quality guidelines» (IAQ 2000 og 2006, EU-index 2005 og 2010) gir ikke grunnlag for å operere med andre krav inne enn ute.

De enkelte land må selv utvikle sine ventilasjonskrav så langt det er mulig. Det er behov for

- Grundige tverr- og flerfaglige risikovurderinger og kartlegging av forskningsbehov.
- Implementering og evaluering av kunnskapsbaserte tiltak og løsninger.
- Etablering og finansiering av tverr- og flerfaglig kunnskapsutvikling, forskning og evaluering av tiltak.

Interessante samarbeidspartnere er

- Byggforsk/ Best Vent/ Oslo Met.
- Folkehelseinstituttet, (inneklima og helse, smittevern virus).
- Diakonhjemmet sykehus og Bygg og Eiendom i Helse Sør-Øst.
- Avdeling for smittevern i Helse Sør-Øst.

IF-19

Design of the next generation of biologics

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The half-life of the two most abundant proteins in blood, immunoglobulin G (IgG) and serum albumin, is extraordinary and roughly 3 weeks in humans. This phenomenon secures a broad biodistribution throughout the body of both molecules. The long half-life has made IgG the natural choice for engineering of antibody-based therapeutics, while albumin is increasingly used as a fusion partner or carrier of drugs. Remarkably, the half-life of these two unrelated proteins has been shown to be prolonged by a cellular recycling pathway mediated by a common cell-bound receptor named the neonatal Fc receptor (FcRn). I will discuss how we combine structural and biochemical analyses with cellular and in vivo studies to gain in-depth molecular insights that guide design of novel albumin and antibody molecules with improved functions that may translate into the next-generation of biologics.

IF-20

Exploiting exosomes as therapeutic delivery vehicles in cancer therapy

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Problemstilling
A challenge in nanomedicine is the development of safe and non-immunogenetic delivery vehicles. Exosomes are promising natural nanodelivery vehicles of drugs. Enclosed in exosomes, chemicals and bio-molecules are protected from elimination, and can therefore more effectively reach their site of action. Exosomes are shown to optimally fuse with target cells in acidic environments, such as within tumor microenvironments. To explore the potential of natural exosomes in tumor therapy, we utilize exosomes derived from natural killer (NK) cells. NK cells are increasingly exploited in immunotherapeutic therapies against cancers, due to their broad recognition of stress-induced self proteins on surface of cancer cells. Thus, NK cells are not limited to specific tumor antigens (neoantigens), but can react in a more broad manner. Using NK cell-derived exosomes (NK-exosomes), we will be able to generate exosomes displaying a broad targeting repertoire towards cancer cells, without the drawback of cancer cell mediated immune suppression. Moreover, NK-cell derived exosomes may naturally contain cytolytic cargo that can be used to eradicate cancer cells.

Metode
NK cell-derived exosomes are isolated from primary human NK cell cultures, or from the NK cell line NKL. Expression of cytolytic proteins and exosomal markers is analysed by western blotting, and killing ability investigated using in vitro 2D and 3D tumor models.

Resultater
We have established a protocol to generate NK-cell exosomes, and shown that they contain cytolytic proteins commonly used to kill cancer cells. Cytokine activation of NK cells lead to increased accumulation of cytolytic proteins within NK-cell derived exosomes. We are currently testing their ability to infiltrate and kill colorectal adenocarcinoma spheroids.

Frie foredrag

De frie foredragene er på 10 minutter hver, hvorav 8 minutter er til foredraget og 2 minutter er til spørsmål og diskusjon.

NSFTs pris for beste frie foredrag 2020
En priskomité vil vurdere alle bidrag og finne en vinner innen henholdsvis farmakologi og toksikologi. Hver vinner får tildelt diplom og en vandreplakett under festmiddagen lørdag 25. januar.

Vinnere av pris for beste frie foredrag 2019:

- Toksikologi:
  Karina Dale (UiB): Contaminant accumulation and biological responses in Atlantic cod (Gadus morhua) exposed to polycyclic aromatic hydrocarbons and perfluoroalkyl substances
- Farmakologi:
  Rolf Klaasen (OUS): Tacrolimus concentrations measured in capillary micro samples

Frie foredrag i toksikologi (TF)

TF-1 Toksikologi

Prenatal exposure to metals and associations with ADHD and ASD in children

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Research aim
The aim of this study is to investigate the associations between prenatal exposure to toxic and essential metals and attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) in children.

Methods
This study included 470 ADHD cases, 397 ASD cases and 1060 controls, whose mothers participated in the Norwegian Mother, Father and Child Cohort Study (MoBa). Cases in MoBa were identified through linkage with the Norwegian Patient Registry. Prenatal levels of metals were measured in maternal blood at week 17 of gestation and included seven toxic/non-essential metals: lead (Pb), mercury (Hg), arsenic (As), cadmium (Cd), molybdenum (Mo), cesium (Cs), and cobalt (Co) and five essential metals: manganese (Mn), selenium (Se), zinc (Zn), magnesium (Mg), and copper (Cu). Multivariable adjusted logistic regression models were used to examine associations between levels of the metals categorized into quartiles with ADHD and ASD diagnoses as outcomes.

Results
The results showed a monotonic increase in risk of ASD with increasing Cu levels, with significant results in quartiles 2, 3 and 4 [OR = 1.57 (CI: 1.07, 2.30); OR = 2.58 (CI: 1.77, 3.76); OR = 3.69 (CI: 2.53, 5.36)] compared to quartile 1 (reference). Similar patterns of increasing risks were found for Se, Mg and Mo with significant results in the fourth quartiles. For As, there was an increased risk of ASD, with a slightly decreasing pattern, with significant results in quartiles 2, 3 and 4 [OR = 2.65 (CI: 1.81, 3.87); OR = 2.48 (CI: 1.68, 3.67); OR = 2.14 (CI: 1.43, 3.21)]. The results showed an elevated risk of ADHD with increasing Cd exposure with a monotonic dose response pattern, where the fourth quartile was significant [OR = 1.68 (CI: 1.17, 2.42)]. For Pb, Cu and Mg, there seemed to be non-linear dose-response relationships, with increased risk of ADHD at low and high exposure level, although only the fourth quartile of Mg was significant.

Conclusion
Our study showed that prenatal exposure to several metals (Cu, As, Se, Mg and Mo) were associated with 1.6 to 3.7 times increased risk of ASD in children where the most notable association was with Cu. Furthermore, prenatal Cd exposure was associated with 1.7 times increase risk of ADHD in the child. The metal exposures in the present study are line with results from previous studies of pregnant women in Norway and Europe, indicating that even population levels of these metals may have a negative impact on neurodevelopment. The results warrant further investigation and replication in order to gain more information about safe exposure levels for fetal neurodevelopment.

TF-2 Toksikologi

Effects of combined exposure to nicotine and HEMA

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Introduction

Nicotine containing products such as nicotine lozenges, gums, sprays and snus gives a direct exposure of nicotine to oral cells and tissues. The health effects of nicotine are suggested to depend primarily on interaction with cholinergic receptors. However, nicotine is also known to affect lysosomes directly. In cellular degradation pathways, such as phagocytosis and autophagy, these organelles are essential.

The monomer 2-hydroxyethylmethacrylate (HEMA) is known to leak into the oral cavity of the patient during and after treatment with resin-based materials. HEMA has a cytotoxic potential *in vitro*. It is suggested that cellular defence against HEMA-induced damage involves autophagy. Hence, impairment of lysosomal function by nicotine could disturb this important defense mechanism. Based on this knowledge, we hypothesize that nicotine exposure increases the toxicity of HEMA by reducing the autophagic capacity.

Methods

For this in *vitro* study, a human tongue squamous carcinoma cell line (PE/CA-PJ49) was used as a model for oral exposure. Cells were cultured and exposed to HEMA (2 mM) and nicotine (5-10 mM) individually and in combination. The effects of nicotine were compared to the effects of an inhibitor of lysosomal activity (Bafilomycin; 10 nM). Cell viability was measured using the MTT assay. Cellular level of p62/SQSTM1 (p62; a marker of autophagic flux) was measured by western blotting. IncuCyte, a real-time live cell imaging system, was used to monitor cell morphology and mobility (scratch wound migration assay).

Results

When exposed to both HEMA and nicotine for 24 h, the viability of PJ49 cells dropped significantly compared to individual exposures. The p62 levels increased similarly when cells were exposed to nicotine and Bafilomycin. This level increased further when HEMA was added to the exposure mix. HEMA alone also increase p62 levels, but to a smaller extent. Visible morphological changes were seen rapidly (minutes) after exposure to nicotine. Combined exposure with HEMA did not alter this effect. No visible changes were seen in cells exposed to HEMA alone. Individual exposure to nicotine and HEMA had no/minor measurable effect in the wound healing assay while the combined exposure resulted in almost total inhibition cell migration.

Conclusion

This study showed effects of combined exposure to nicotine and HEMA that was not observed in individual exposure experiments. Although the results support the hypothesized interaction with autophagy, more experiments are needed to verify this possible consequence of nicotine exposure.

Aminated polystyrene nanoparticles affect the early life development and life cycle of the marine copepod *Tisbe battagliai*: role of surface functionalisation

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Plastics are prolific environmental contaminants, widely distributed and identified in marine and freshwater ecosystems. Although much attention has been paid on the occurrence and effects of micro-scale plastics, much less is known on the behavior and potential impacts of nanosized plastic particles that can result from progressive fragmentation of larger plastics. The aim of this study is to better understand the behavior, uptake and long-term effects of nanosized polystyrene particles and assess the uptake and subsequent developmental and life cycle effects on the marine harpacticoid copepod *Tisbe battagliai*.
Methods: Spherical polystyrene and polystyrene carboxylated, aminated nanoparticles (PS, PS-COOH, PS-NH_2 NPs 50 nm, Phosphorex Inc, Sigma-Aldrich) and their fluorescent counterparts were used. The size (hydrodynamic diameter) and surface charge (zeta potential) of the particles in MilliQ water and natural filtered seawater (0.22 μm) during exposure were characterized with dynamic light scattering (DLS) and Laser Doppler Micro-electrophoresis (NanoZSP, Malvern Instruments Ltd, UK). Size and particle number of the stock plastic NP solutions were also assessed with nanoparticle tracking analysis (NTA, Malvern Instruments Ltd, UK). *T. battagliai* nauplii (<10h post-release) were exposed to increasing concentrations of the particles for 6 days and the developmental rate was assessed. At the end of the exposure period the animals were transferred in clean seawater and the further development was followed until the appearance of gravid females. The time to the appearance of the first gravid female, the sex ratio of F0 generation, number of gravid and non-ovigerous females and the reproductive output per gravid female was assessed. The localization of the particles in the animals was studied by confocal microscopy.
Results: All particles remained stable over 72h in MilliQ water. Both PS and PS-COOH formed aggregates in the microscale in seawater reaching 5771±1455 nm and 3288±157.4 nm, respectively while PS-NH_2, appeared to be more stable with aggregate sizes of ~ 133 nm. PS and PS-COOH particles had a negative charge with the highest negative charge being demonstrated for PS (-58.9±0.56). A concentration-dependent effect on the developmental rate of nauplii upon exposure to PS-NH_2 (EC_{50} 4.3 mg/L) and PS-COOH (EC_{50} 10 mg/L) was observed (Figure 2). At a concentration of 10 mg/L PS-NH_2 a complete inhibition of development and subsequent mortality was observed. The further development of the copepodids until sexual maturity, mating and reproduction was studied. Early life exposure of *T. battagliai* to PS-NH_2 particles led to a 42% increase in the number of females compared to control while an increase in the presence of non-ovigerous/unfertilized females was also observed accompanied by a significant decrease in the number of offspring per gravid female at the highest concentration of 5 mg/L PS-NH_2.
Conclusion: Early life exposure to cationic polystyrene particles can impact the development and reproductive success of the animals, leading to increased presence of non-ovigerous/unfertilized females and decreased fecundity. The current results suggest potential ecological implications as early life stages of organisms with important functions are impacted that could affect population stability. Further mechanistic studies are needed for the elucidation of particle interaction or associated chemicals with the specific cells/organs (ovary/diverticula, developing oocytes).

Integrated strategy for toxicity prediction and hazard ranking of feed additives and contaminants using (Q)SAR and nontargeted high-resolution mass spectrometry

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Background
The lack of experimental data for an increasing number of chemicals calls for more efficient screening strategies for hazard identification and prioritization for feed and food safety risks assessments (Rasinger et al., 2018). High throughput non-targeted high-resolution mass spectrometry (HRMS) in combination with computational *in silico* models predicting metabolic fates of chemicals and providing data on their physicochemical and toxicological characteristics can contribute to fill current data gaps. Here we present a case study using the antioxidant feed additive ethoxyquin (EQ; 6-Ethoxy-2,2,4-trimethyl-1,2-dihydroquinoline) as an example.

Methods
Using high-resolution mass spectrometry (HRMS) 27 EQ transformation products (TP) were identified in oxidation experiments. Moreover, 25 of these were positively identified in fish feed and 24 in fish fillets from EQ exposure experiments (Merel et al., 2019). Based on the HRMS data, (Q)SAR analyses were performed to *in silico* predict genotoxic and cancerogenic effects. Five (Q)SAR tools were used for the prediction of mutagenicity and three tools for carcinogenicity predictions. Following an approach described in Frenzel et al. (2017), model specific outputs were converted into numeric values (ranging from 0 to 1), which for further interpretation, were classified into three categories: (i) compounds considered mutagenic (carcinogenic) with a high probability, (ii) compounds for which reliable predictions cannot be made, and (iii) compounds considered non-mutagenic (non-carcinogenic).

Results
Except for EQ TP predicted to be non-mutagenic or non-carcinogenic, *in silico* toxicity predictions made by the different (Q)SAR tools used were inconsistent. Therefore, instead of direct comparison of (Q)SAR outputs published earlier (Van Bossuyt et al. 2017) fuzzy analytical hierarchy process (AHP) modelling was applied; a multiple criteria decision-making (MCDM) tool in risk assessment, which aims to settle conflicts between practical demand and scientific decision making. This allowed for the creation of a hazard priority rank of EQ TP based on the combination of both analytical occurrence data and the conflicting output of several different (Q)SAR models.

Conclusion
We demonstrate how high-resolution mass spectrometry and computational *in silico* analyses can be combined to detect and prioritize chemical hazards in feed and food according to their occurrence and predicted toxicities.

Referanser
Frenzel F. et al., Arch Toxicol. (2017)
Merel S. et al., Food Chem. (2019)
Rasinger J.D. et al., EFSA Journ. (2018)
Van Bossuyt M. et al., Food Chem. Toxicol. (2017)

TF-5 Toksikologi

Polar cod and Goliat: How an oil spill may affect polar cod reproduction

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Background

Declining sea-ice abundance in the Arctic has expanded the potential for oil exploration and increased the associated risk of an oil spill in these pristine regions, especially during the dark period of the year [1]. Polar cod, a key arctic fish species, spawns during polar night [2], making them potentially sensitive to reproductive effects in the case an oil spill. Polar cod may also be vulnerable during this period due to lower food availability and low energy reserves, which are primarily allocated for reproduction [3]. In the current *in vivo* study, the sensitivity of polar cod to an oil spill was assessed by exposing wild-caught polar cod to the water-soluble fraction (WSF) of crude oil along with different food regimes over their spawning period.

Methods

Polar cod (*Boreogadus saida*) were exposed to the WSF of Goliat crude oil via a gravel column system from December (pre-spawning) to April (post-spawning). This set-up simulated the natural weathering and degradation of the crude oil over time [4]. Fish were exposed to either control (0 ng/L) or the WSF of crude oil (12.5 ng/L, sum PAH). These groups were further subdivided into low feed (1.5% somatic weight) and high feed (4% somatic weight) groups in order to assess the effect of variable food availability. During the experiment, samples were taken at the start (mid-December, Day 0), at spawning (late January, day 47), and at post-spawning (April, day 131). Samples taken at these timepoints were analysed for sublethal reproductive effects on plasma hormone levels (T, 11kt and estradiol), gene expression of genes related to steroidogenesis (estrogen receptor and vitellogenin), and gonadal maturation stages (staging and Weibel-grid analysis).

Results

The WSF exposure caused a significant induction of biotransformation enzyme, *cyp1a*, in male and female Polar cod during spawning and post-spawning, i.e. 131 days after the exposure began. A trend of lower levels of 11-kt testosterone in exposed males compared to control, was observed at spawning. However, no trend was observed in testosterone levels in the same spawning males.

Conclusion

Preliminary results of *cyp1a* induction suggest chronic exposure of polar cod to the WSF of crude oil over the experimental period. On-going analyses indicate that the WSF exposure may cause alterations in some aspects of polar cod reproduction. These results will be presented and discussed.

The study was part of the Nansen Legacy program, funded by the Norwegian Research Council (project no. 276730). [1] Harsem et al. 2011; [2] Hop and Gjøsæter 2013; [3] Hop et al. 1995; [4] Carls et al. 1999.

TF-6 Økotoksikologi

Adapting a liver slice culture method for ex vivo toxicological studies in arctic and sub arctic fish species during sampling cruises

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Background

The arctic region can be susceptible to effects of pollution from sources such as northward expanding petroleum related activities and long-range transport of pollutants. The Arctic marine environment is characterized by a high seasonality in light and food availability and strongly influenced by global warming, which might influence effects of pollutants in organisms. Toxicological investigations and development of methodologies for future environmental monitoring of arctic fish are therefore warranted. The aim of this work is to demonstrate the use of *ex vivo* liver slice culture method to investigate transcriptome responses to Benzo[a]pyrene (BaP) in key arctic fish species during research cruises.

Methods

We used a precision-cut liver slice culture method developed for Atlantic cod (*Gadus morhua*) (Eide et al., 2014) and adapted the protocol for use in a wide range of species including small fish. On board R/V Kronprins Haakon of the Q3-2019 Nansen Legacy cruise, we developed liver slice culture from four key arctic and sub-arctic fish species, Atlantic cod, capelin (*Mallotus villosus*), polar cod (*Boreogadus saida*) and long rough dab (*Hippoglossoides platessoides*). The liver slice cultures were exposed to BaP, a ubiquitous environmental pollutant, also found in crude oil. Samples were harvested for transcriptomics (qPCR and RNA-seq) and other analyses.

Results

The precision-cut liver slice method (Eide et al., 2014) was adapted for flexible and higher throughput experiments with diverse fish species including small fish such as polar cod. Liver slicing and exposure studies were successfully performed on board R/V Kronprins Haakon. The first results show that BaP induced *cyp1a* gene expression in a dose-dependent manner in slice culture from all the fish sampled. Results from ongoing transcriptomics analysis will be presented.

Conclusions

We successfully performed liver slice culture and exposure experiments using diverse fish species, demonstrating that *ex vivo* experiments can be performed during field studies and sampling campaigns. This technique will be especially valuable to study species that are not available in the laboratory, or that are difficult to transport to the laboratory from the field.

The study was funded by the Research Council of Norway, projects Nansen Legacy (276730), dCod 1.0 (248840) and the iCod 2.0 (244564).

Reference

Eide M, Karlsen OA, Kryvi H, Olsvik PA, Goksøyr A. Precision-cut liver slices of Atlantic cod (Gadus morhua): an in vitro system for studying the effects of environmental contaminants. Aquat Toxicol. 2014. 153:110-5.

Development of in vitro models to study environmental factors influencing gill epithelial function

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Issue

To replace, refine and reduce (3R) the numbers of fish used in gill-focused research, an effective *in vitro* model that mimics features of the gill barrier is required. A gill epithelial cell line from trout (RTgill-W1, ATCC CRL2523), has over several years been extensively used in research and a close correlation between RTgill-W1 cytotoxicity and acute fish toxicity has been demonstrated. RT-gillW1 has also been verified as a standard for determination of acute toxicity of water samples and chemicals (ISO21115:2019). In order to study differences between species and to avoid inter-species extrapolation, researchers at the Norwegian Veterinary Institute have established promising epithelial gill cell lines from Atlantic salmon (ASG10) and Lumpfish (LG-1). With a co-operation between the two projects, GILLMODEL[1] (ASG10) and BIO-direct[2] (LG-1), we aim to characterize the two cell lines, for use in research in a similar way as RT-gillW1 has been used.

Methods

1) Transcriptomic analysis and transfection optimization **2)** Analysis of the proteome, detoxification enzymes and transport proteins, and heterogeneity of the cell line **3)** Fresh and seawater adaptation, co-culture establishment and translocation studies with microplastics and viruses **4)** Test bioassay systems on relevant exposures known to impair water quality in farming situations and testing of water samples from aquaculture facilities.

Results

ASG10 and LG-1 grown on transwell inserts were able to polarize and generate tight junctions, measured by an increased transepithelial electrical resistance (TEER). Furthermore, expression of ZO-1 and cytokeratin supports that they are of epithelial origin. The cell lines did not stain positive for neither chloride cells nor goblet cells. Detoxification capabilities were investigated (LC-MS/MS, EROD) and phase I and II enzymes were found to be inducible. Furthermore, when comparing the ASG10 and RTgill-W1 towards the cytotoxicity induced by rotenone, differences regarding toxicity and expression of glutathione were detected.

Conclusion

The ASG10 and LG-1 cell lines are promising *in vitro* models that may be used to test environmental factors influencing functions such as cell viability and epithelial barrier integrity.

1. Development of *in vitro* model to study environmental factors influencing the gill epithelial function (GILLMODEL), NFR294876
2. Biomarkers and bioassays for veterinary research and diagnostics (BIO-direct), strategic initiative of the Norwegian Veterinary Institute, www.vetinst.no

TF-8 Toksikologi

A battery of Atlantic cod (*Gadus morhua*) stress-activated receptors as a bioassay tool to analyse sediment extracts

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Sediments are a major depot for many persistent contaminants introduced from sewage discharges, runoff from roads, accidental oil spills, etc., which can lead to adverse outcomes in organisms living, spawning and feeding in the area. Atlantic cod (*Gadus morhua*) is commonly used as sentinel species in marine environmental monitoring due to its distribution along the coast of the North Atlantic Ocean, which makes it susceptible to pollution from coastlines and open sea. It is a benthopelagic fish meaning that it is living close to and feeding off the seafloor. In the dCod 1.0 project, we have developed a luciferase reporter gene-based bioassay battery, consisting of eight stress-activated receptors cloned from Atlantic cod, to investigate sediment sample extracts. The tested extracts are a collection of seven sediments taken around Bergen area, four sediments from the Boknafjord, close to Stavanger, and untreated and treated drill cuttings from off-shore activities.

The Atlantic cod aryl hydrocarbon receptors 1a and 2a (gmAhr1a and gmAhr2a), peroxisome proliferator-activated receptors alpha 1 and alpha 2 (gmPpara1 and gmPpara2), estrogen receptor alpha (gmEra), androgen receptor alpha (gmAra), and vitamin D receptors alpha and beta (gmVdra and gmVdrb), were used in a luciferase reporter gene assays to investigate the sediment extracts ability to transactivate these receptors. In addition, PLHC-1 cells and RTgill-W1 cells were used to investigate cell viability, the generation of reactive oxygen-species (ROS), and 7-ethoxyresorufun-O-deethylase (EROD) activity, to analyse the metabolic impairment, detect oxidative stress, and the induction of the biotransformation gene, CYP1A, respectively.

All tested sediment samples were able to transactivate both Ahr receptors, including the reference station, indicating the presence of Ahr agonists at various levels. The sediment extract from the inner harbor (Vågen) of Bergen was able to transactivate the entire battery of receptors, promote oxidative stress, metabolic impairment, and induce CYP1A activity, demonstrating a more complex contaminant situation. Chemical analyses of the sediment extracts showed PAH concentrations in line with the activation of the Ahr-signalling pathway.

This study demonstrated the usefulness of using a panel of *in vitro* bioassays to screen sediment samples for contaminant profiles. The use of gene-reporter assays based on stress-activated receptors from Atlantic cod can provide relevant results for environmental risk assessment.

The study was funded as part of the dCod 1.0 project under the Digital Life Norway program, financed by the Norwegian Research Council (project no. 248840).

TF-9 Økotoksikologi

Biological responses in Atlantic cod (*Gadus morhua*) exposed to polycyclic aromatic hydrocarbons and perfluoroalkyl substances

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Background and aim

Studying effects of environmental contaminants in mixtures is crucial to understand their toxic behavior in the environment. The objective of the present study was to investigate biological responses of mixtures of six polycyclic aromatic hydrocarbons (PAHs) and/or four perfluoroalkyl substances (PFASs), at low, environmentally relevant (L) or high (H=20xL) doses, in juvenile Atlantic cod (Gadus morhua).

Methods

We performed a two-week in vivo experiment, with intraperitoneal injections of farmed juvenile cod at day 0 and day 7. In total, 10 groups, each consisting of 21-22 fish were included in the experiment, with two control groups, separate groups of PAH mix (L, H) and PFAS mix (L, H), and four groups combining PAH and PFAS mixes (L/L, H/L, L/H, H/H). To assess chemical accumulation, PFAS concentrations were determined in cod liver, and concentrations of PAH metabolites were determined in bile. Biological effects were investigated by measuring biomarkers at transcript and protein levels in cod liver, in addition the lipidome and the proteome were evaluated.

Results

Chemical analyses showed significantly higher concentrations of PAHs and PFASs in cod tissues for H groups compared to control and L groups. Significant effects of PAH and/or PFAS exposure were observed on hepatosomatic index, antioxidant enzyme activities and the liver lipidome. Proteomics results are currently being analysed and will be presented.

Conclusion

In summary, contaminants accumulation and effects on processes related to growth, oxidative stress and lipid metabolism were observed in Atlantic cod, demonstrating biological effects of PAH and PFAS mixtures, both alone and combined. We are currently investigating responses of single compounds using precision-cut liver slices.

The study was funded by dCod 1.0 (Project no. 248840), a project linked to Center for Digital Life Norway (DLN), financed by the Research Council of Norway (NFR).

TF-10 Økotoksikologi

EXPRESSION AND LOCALIZATION OF THE ARYL HYDROCARBON RECEPTORS AND CYTOCHROME P450 1A DURING EARLY DEVELOPMENT OF ATLANTIC COD (*GADUS MORHUA*)

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Problemstilling
The aryl hydrocarbon receptor (Ahr) is a ligand-activated transcription factor involved in the regulation of genes important for the biotransformation of xenobiotics. Different environmental pollutants, such as polycyclic aromatic hydrocarbons, dioxins, and dioxin-like polychlorinated biphenyls, are known to act as agonists of Ahr. It has been demonstrated that the Ahr2 subtype is the main protein involved in mediating the toxicity of these compounds in most teleost species, but it is also involved in the nervous system development during early life stages. The role of Ahr1 is less clear, and it has been hypothesized that Ahr1 has both a role in toxicity and a possible physiological role during embryonic development. Atlantic cod (*Gadus morhua*) has emerged as a model species within environmental toxicology during the last years, and recently the Atlantic cod Ahr1a and Ahr2a receptors were characterized. However, it has not yet been elucidated if there is a functional specialization of these paralogous genes in this species.

Metode
Atlantic cod embryos (5 dpf) were continuously exposed to the Ahr agonist, benzo[a]pyrene (B[a]P), using a passive-dosing system until three days post hatching. Expression of *ahr1a*, *ahr2a*, *cyp1a1* and *ahrrb* was assessed in embryos (8 dpf and 10 dpf) and larvae (3 dph) with quantitative real-time PCR analyses (qPCR), while *in situ* hybridization was used to assess the localization of expression of *ahr1a*, *ahr2a* and *cyp1a1*.

Resultater
There was an increased *cyp1a1* expression in B[a]P-exposed eggs at all developmental stages, and differences in localization of *ahr2a* and *cyp1a1* transcripts between B[a]P-exposed eggs and controls occurred already at 8 dpf. Importantly, expression of *ahr1a* was mainly localized in the eye of embryos, whereas a co-localization of gene expression was observed between *ahr2a* and *cyp1a1*, especially at 3 dph.

Konklusjon
The co-localization of *ahr2a* and *cyp1a1* transcripts suggests that Ahr2 has a major role in regulating the transcription of biotransformation genes in Atlantic cod. The presence of *ahr1a* in the eye of embryos, and of *ahr2a* in the jaws, fins and nose of larvae, further indicate evolved roles in both eye and nervous system development during early life stages.

Frie foredrag farmakologi (FF)

FF1 Klinisk farmakologi

Effect of low calorie diet on the activity of hepatic transporter OATP1B1 in patients with severe obesity

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Background
Obesity is global health issue, with a rapidly increasing prevalence. Morbid obesity is associated with a range of physical and psychological comorbidities that often requires medical intervention. Diet with subsequent weight loss may lead to changes in individual pharmacokinetic parameters, but the underlying mechanisms are not fully understood. The aim of this work is to investigate the effect of a low-calorie diet on the activity of the hepatic uptake transporter OATP1B1.

Method
Rosuvastatin was used as a probe substance for the hepatic uptake-transporter OATP1B1. Three 24-hour pharmacokinetic investigations were performed over the course of the study; at baseline, after three weeks of low-calorie diet (<1200 kcal/day), and after six weeks of very low-calorie diet (<800 kcal/day). Sampling occurred at 0.25, 0.5, 1, 1.5, 2, 3, 4, 4.25, 4.5, 5, 5.5, 6, 8, 10, 12, 23 and 24 hours after administration of 20 mg Rosuvastatin. A population pharmacokinetic model was develop to characterize individual pharmacokinetic parameters at each visit.

Results and discussion
Forty patients with a mean body mass index at baseline of 39.5 ± 7.3 were included. Of these, 37 participated in three full pharmacokinetic investigations.

Further results will be presented at the conference.

Allosteric enhancement of the natriuretic peptide receptor A with small molecules

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Introduction
The natriuretic peptide system (NP) plays an important role in regulating cardiovascular and renal homeostasis. Atrial NP (ANP) and brain type NP (BNP) activate NP receptor (NPR)-A and C-type NP (CNP) activates NPR-B. NPRs are membrane bound guanylyl cyclases (GCs) that catalyse the production of cGMP upon activation. We have previously found small molecular allosteric enhancers of NPR-A that showed selectivity towards NPR-A with no effects towards NPR-B. These molecules enhanced the efficacy of ANP and BNP, while having no effect on their own. In order to optimize our compounds further, we need to understand how they enhance the NP-mediated cGMP production and where they work on NPR-A.

Method
Chimeric NPR-A/NPR-B receptors and point mutations were constructed using In-Fusion HD plus cloning kit. The molecules ability to modulate the efficacy of BNP and CNP in chimeric or mutated receptors were investigated in transiently transfected cells and the cGMP production was measured using AlphaScreen assay for cGMP. Radioligand binding assays were performed in whole cells and membranes from NPR-A expressing cells. Modulation of the enzyme activity of the GC was investigated in substrate-velocity assays in membranes from NPR-A expressing cells and cGMP production was measured by ELISA.

Results
With chimeric NPR-A/NPR-B receptors where the whole extracellular or intracellular domains were swapped between the receptors, the ability of the molecules to enhance the BNP- or CNP-mediated cGMP production followed the intracellular and not the extracellular domain, indicating interaction of the molecules with the intracellular domain. Further studies showed that our molecules most likely bind to a region within the intracellular kinase homology domain in NPR-A. In contrast to effects observed using whole cells, none of the compounds were able to increase the guanylyl cyclase activity in substrate-velocity assays or in cGMP assays using broken cells. Similarly, none of the compounds modulated affinity in membrane preparations, but increased the overall binding of ANP to NPR-A in whole cell binding assays by increasing Bmax.

Conclusion
We propose an allosteric binding site on the kinase homology domain in NPR-A and our findings suggests a mechanism of action that requires cell integrity.

FF3 Klinisk farmakologi

Opioider ved behandling av kroniske sterke smerter

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Problemstilling
I 2008 ble det innført en ordning i Blåreseptforskriften slik at pasienter med kroniske sterke smerter kunne få refusjon for smertestillende legemidler på blå resept. For vanedannende smertestillende legemidler, som for eksempel opioider, måtte legen søke om individuell refusjon. Da ordningen ble innført var det kun spesialister som kunne starte behandling med opioider. I 2016 ble blåreseptforskriften endret slik at også fastlegene kunne initiere søknad om individuell refusjon og forskrive opioider på blå resept til pasienter med kroniske sterke smerter.
Vi har sett nærmere på utviklingen i bruk av smertestillende legemidder (opioid og ikke – opioid) og langvaring bruk av opioider på blå resept i perioden 2009-2018.

Metode
Vi har brukt data fra Reseptregisteret som inneholder informasjon om alle legemidler som er forskrevet og utlevert til pasienter utenfor institusjon.

Resultater
Antall og andel pasienter som får minst ett smertestillende legemiddel (opioid og ikke opioid) på blå resept har økt i den voksne befolkningen etter at blåreseptforskriften ble endret og i 2018 var det totalt
233 157 pasienter (5,5 %) som fikk smertestillende legemidler på blå resept. Det første smertestillende legemiddelet på blå resept var for de fleste paracetamol.
Det har også vært en økning i totalt antall pasienter som får opioider for kroniske sterke smerter på blå resept, både blant kvinner og menn, siden ordningen ble innført i 2008. I 2018 var det totalt rundt 0,41 % av den voksne befolkningen som fikk opioider på blå resept for kroniske sterke smerter. Dette tilsvarer 17 383 pasienter. Etter 2016, da fastlegene fikk mulighet til å initiere behandling av opioider på blå resept, ser vi at forskrivningsmønsteret endres; flere pasienter fikk forskrevet opioider og flere fikk tramadol som sitt første opioid enn tidligere.
En høy andel av de som starter med opioider på blå resept blir langvarige brukere. Over 50 % fortsetter med opioider i ni påfølgende år.

Konklusjon
Vi har observert en økning i antall og andel pasienter som får smertestillende på blå resept både når det gjelder alle smertestillende legemidler samlet og når vi studerer opioidene for seg. Denne gradvise økningen er forventet, siden det tar tid før slike ordninger blir kjent og fullt implementert. Økningen i antall opioidbrukere er ikke i seg selv foruroligende. Langvarig behandling med opioider kan være bekymringsfullt og må ses i lys av at kunnskapsgrunnlaget for nytten av slik behandling er svakt.

The effect of the β2 – adrenergic receptor agonist terbutaline on cultured human myotubes

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Stimulation of the β-adrenergic receptors has shown to stimulate glucose uptake as well as an hypertrophic effect in rodent skeletal muscle cells. It is also reported changes in fatty acid metabolism, protein synthesis and mitochondrial biogenesis. In clinical studies, daily treatment with β_2 agonists caused alternations in exercise-induced adaptions in skeletal muscle (Hostrup *et. al,* 2018). Our group has previously reported that an *in vitro* model of exercise using chronic, low-frequency electric pulse stimulation (EPS) to mimic exercise increases glucose uptake and fatty acid oxidation in human skeletal muscle cell (Nikolić *et. al*, 2017. and Feng *et. al,* 2015). With this model it is possible to study the effects of treatment with the β-AR agonist terbutaline and exercise *in vitro.*

Myoblasts from satellite cells isolated from muscle biopsies from healthy donors were cultured and differentiated into myotubes. The cells were treated with terbutaline for 4 or 96 h and/or without EPS (single, bipolar pulses of 2 ms, with 10 V and 1 Hz) for 24 h. Glucose uptake was studied using [^{14}C]deoxy-D-glucose. Gene expression was measured by PCR to study the changes in genes related to hypertrophy and mitochondrial biogenesis. Protein synthesis was studied by looking at the incorporation of [^{14}C]leucine for 6 or 24 h.

Chronic and acute stimulation of the β-AR by terbutaline increased deoxyglucose uptake *in vivo*. Preliminary results indicated that chronic incubation with terbutaline changed the mRNA levels of hypertrophy-related genes such as MMP-2, MMP-9 and FOXO1, and increased [^{14}C]leucine incorporation. Ongoing studies combine EPS with β-AR stimulation to explore the possible additive effects on hypertrophy and mitochondrial biogenesis.

Feng YZ, et. al, 2015, Am J Physiol Cell Physiol 308(7): p. C548-56.
Hostrup M, et. al, 2018, J Physiol 596(2): p. 231-252.
Hostrup M, et. al, 2018, The Journal of Physiology 596(17): p. 4121-4139.
Nikolić N, et.al, 2017, PLOS ONE 7(3): p. e33203.

Kombinasjonsbruk av valproat og lamotrigin assosiert med klozapins metabolittmønster.

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Problemstilling
Klozapin er det mest effektive legemidlet for behandling av schizofreni, men kan gi alvorlige bivirkninger som agranulocytose og tonisk-kloniske anfall. Kombinasjonsbehandling med valproat er aktuelt hos pasienter med schizoaffektiv lidelse eller anfallsrisiko. Oppstart av valproat hos klozapinbehandlede pasienter er rapportert å medføre agranulocytose. Dette kan potensielt skyldes at valproat reduserer nivå av den aktive metabolitten N-desmetylklozapin, men mekansimen bak dette er ukjent. Hensikten med denne studien er derfor å undersøke hvordan kombinasjonsbruk av valproat påvirker metabolittmønsteret til klozapin.

Metode
I studien ble det hentet ut UPLC-MS/MS-spektra fra prøveanalyser ved Senter for Psykofarmakologi, Diakonhjemmet sykehus. Totalt ble det hentet ut analyseresultater fra 35 pasienter med enten klozapinbruker alene (n=15), kombinasjonsbruker av klozapin med valproat (n=14) eller kombinasjonsbruker av klozapin med lamotrigin (n=6). Informasjon om retensjonstid, toppenes høyde og areal ble benyttet som grunnlag for semikvantitativ bestemmelse av relativ mengde klozapinmetabolitter (klozapin/metabolitt MS/MS-signal). Gjennomsnittsverdier og standardavvik ble beregnet for de ulike metabolitt-ratioene (metabolitt/klozapin) og sammenlignet mellom de ulike undergruppene av pasienter.

Resultater
De foreløpige resultatene indikerer at mengden N-desmetylklozapin blir redusert ved kombinasjonsbruk av klozapin sammen med valproat (metabolitt forhold 0,349 ved klozapin vs. 0,210 ved valproat vs. 0,367 ved lamotrigin). Videre ble det observert nærmere en dobling av den ene glukuronidmetabolitten av klozapin blant kombinasjonsbrukere av valproat (metabolittforhold $1{,}72 \times 10^{-3}$) sammenlignet klozapinbrukere uten valproat ($9{,}11 \times 10^{-4}$). Samtidig var metabolitt-forholdet av en annen glukuronidmetabolitt redusert med omlag 80 % hos valproatbrukere ($1{,}33 \times 10^{-4}$) sammenlignet klozapinbrukere uten valproat ($5{,}37 \times 10^{-4}$).

Konklusjon
De preliminære resultatene indikerer at kombinasjonsbehandling med valproat påvirker flere metabolismeveier av klozapin, inkludert glukuronidering. I hvilken grad endringen i metabolittmønster er av klinisk betydning for toleransen av klozapin må undersøkes nærmere hos pasienter som opplever bvirkningsreaksjoner under kombinasjonsbehandling med valproat.

Electrical pulse stimulation of human primary myotubes affects the protein cargo of extracellular vesicles released to the cell media.

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Background
Regular physical activity is important for prevention, reduction and treatment of chronic diseases such as obesity, type 2 diabetes and cardiovascular diseases. During exercise, contracting skeletal muscles release molecules into the blood stream. These humoral factors include myokines and extracellular vesicles (EVs) that can communicate with other organs and mediate beneficial effects of exercise. EVs are nano-sized particles that contain bioactive molecules like proteins, lipids, and nucleic acids. In the present study, we have examined how electrical pulse stimulation of human myotubes, a model of exercise, affected the cargo of EVs released to the cell media.

Methods
Chronic low frequency electrical pulse stimulation (EPS) was applied to human primary myotubes for 24 h, and EVs were collected from cell media 24 h thereafter. EV subtypes (exosomes and microvesicles) were isolated by a combination of centrifugation and filtration techniques, and concentration and size of EVs were characterized by nanoparticle tracking analysis (NTA). Expression of EV-specific surface markers was examined by flow cytometry. Protein content was assessed by proteomic analysis (LC-MS/MS), and microRNA by real time RT-qPCR. Interleukin-6 (IL-6) was detected by ELISA.

Results
Muscle contraction (physical activity) was confirmed by a 23 % increase in production of interleukin-6. The concentration and size of EVs produced by the myotubes were unaffected by EPS. Likewise was the expression of the EV-specific surface markers CD63 and CD81 unchanged by EPS. The protein content of exosomes and microvesicles was clearly different. Totally, exosomes contained 1105 proteins, of which 921 were common for cells exposed to EPS and control cells. The microvesicles contained 1473 proteins, and of these 1377 were common for cells exposed to EPS and control cells. EPS significantly increased the expression of 41 proteins and decreased the expression of 16 proteins in microvesicles, whereas EPS increased the expression of 51 proteins and decreased 24 proteins in exosomes. Ingenuity pathway analysis (IPA) revealed that pathways involved in cell growth and protein synthesis were the most affected by EPS. There was no detectable effect of EPS on the content of selected muscle-specific microRNAs (myo-miRs) (miR-1-3p, miR-133a, and miR-206) in exosomes.

Conclusion
Human primary myotubes are able to produce extracellular vesicles (EVs), both exosomes and microvesicles. Electrical pulse stimulation clearly affected the protein content of both exosomes and microvesicles, although size and concentration of EVs were unchanged.

Identification of new candidate *CYP2C19* variants causing ultrarapid metabolism

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Objectives
Our hypothesis is that previously unknown *CYP2C19* metabolizer variants, beside the well-known *CYP2C19*17*-allele, can cause ultrarapid metabolism of drugs metabolized by the CYP2C19 enzyme. The aim of this study was therefore to sequence patients with *CYP2C19 *1/*1* genotype and with ultrarapid phenotype to identify novel gene variants that causes ultrarapid metabolism in these patients.

Methods
Patients who had been *CYP2C19* genotyped and had serum concentration measurements of escitalopram were retrospectively retrieved from the therapeutic drug monitoring (TDM) database at Center for Psychopharmacology, Diakonhjemmet Hospital. Inclusion criteria were a *CYP2C19 *1/*1* genotype, ultrarapid metabolizer phenotype of escitalopram, information about the prescribed escitalopram dose on the requisition forms, and blood sampling for escitalopram TDM 10-30 hours after the last dose intake. A large portion of the *CYP2C19* promoter was sequenced to identify candidate variants for further analyses on a large patient material. Combined haplotypes for the selected candidate variants were determined using PHASE software. Frequencies of the estimated haplotypes for patients with dose-adjusted serum concentrations (C/D ratios) below the reference area for escitalopram were assessed.

Results
Overall, the *CYP2C19* promoter of 30 patients was sequenced and four variants were selected as candidate variants for downstream analyses in a total of 380 patients. Statistical analyses revealed 4 distinct haplotypes that were characterized further. Two of these haplotypes seem to be overrepresented in patients with C/D-ratios below the therapeutic reference area. More detailed results will be presented at the conference.

Conclusion
This study supports our hypothesis that previously unknown *CYP2C19* variants can cause ultrarapid metabolism of drugs metabolized by the CYP2C19 enzyme.

Compartmentation of natriuretic peptide signalling – are interacting proteins involved?

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Background and aims
Natriuretic peptides (NPs) have lately received much attention as potential heart failure therapy. However, the direct cardiac effects are still elusive. Recently, we found that the natriuretic peptides CNP and BNP, both increasing cGMP, affected contractility differently in both normal and failing hearts. CNP, activating the NPR-B receptor, affected contractility both alone and in the presence of cAMP signaling. This was not shared by the NPR-A agonist, BNP, which had no effect on contractility. This strikingly different response to NPR-A and NPR-B stimulation raised the question as to how these responses are compartmented. In this project we wanted to elucidate a potential role of interacting proteins in regulating the response to NPR-A and NPR-B stimulation.

Methods
Interacting proteins of the NPRs were identified by pull-down followed by mass spectrometry (MS). Samples for MS and western analysis were prepared using left ventricular cardiomyocytes infected with adeno virus encoding the intracellular part of either NPR-A or NPR-B, tagged with GFP. NPR-A/B and their interacting proteins were pulled down using GFP-trap assay. cGMP measurements were performed in extracts from ventricular cardiomyocytes from rat or cytohesin-knock out mice. On-cell western and peptide array assays were performed in HEK293 cells or HEK293 cell lysates.

Results
More than 100 proteins were identified as potential interacting proteins of the NPRs. After evaluation of proteins binding to NPR-A and NPR-B , cytohesin-1, a guanine nucleotide exchange factor for ADP-ribosylation factors (ARF-GEFs) were confirmed to interact with intracellular part of NPR-A both from MS analysis and western analysis. This interaction was further confirmed in peptide array assays. Inhibitors of the cytohesin signaling pathway, SecinH3 (cytohesin inhibitor), Pit-1 (PIP3 antagonist) and NAV2729 (ARF6 inhibitor), affected the cGMP levels after BNP and CNP stimulation differently. SecinH3 increased the cGMP levels induced by BNP through the NPR-A, whereas it reduced cGMP levels induced by CNP through the NPR-B.

Conclusion
Cytohesin-1 was identified as an interacting protein of the NPR-A. Our results indicate a potential role for cytohesins in the regulation of the cGMP-mediated signaling of natriuretic peptides in the heart.

Extrapolating an adult tacrolimus population pharmacokinetic model to pediatric renal transplant recipients

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Introduction
Tacrolimus is one of the most frequently used immunosuppressive drugs following solid organ transplantation. The drug exhibits high inter- and intraindividual pharmacokinetic (PK) variability and is classified as a narrow therapeutic index drug. Consequently, therapeutic drug monitoring is mandatory to personalize dosing [1]. Population PK models are able to accurately predict the systemic exposure following drug administration in an individual patient. There is a lack of such models for tacrolimus in the pediatric transplant population [1]. The aim is to evaluate whether an improved existing adult tacrolimus population PK model may adequately predict tacrolimus concentrations in pediatric transplant recipients.

Method
Rich data (more than 3 samples in a dose interval) from adult transplant recipients treated at Oslo University Hospital, Rikshospitalet, was used for improving an existing adult non-parametric population model for tacrolimus [2]. Trough and 3-point PK data from pediatric patients will be used for model evaluation.

Results
In the adult population PK model, *CYP3A5* genotype, day after transplantation, tacrolimus formulation, body size and hematocrit were included as covariates. The results from model evaluation in the pediatric population will be presented at the meeting.

Conclusion
The conclusion of this study will be presented at the meeting.

Referanser
1. *Brunet, M et al, Ther Drug Monit 2019; 41: 261-307*
2. *Åsberg, A et al. Transplant Int 2013; 26(12): 1198-207*

Studies on the cysteine protease legumain in cardiovascular disease

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Background and aims
Cardiovascular disease (CVD) is responsible for high mortality and morbidity world-wide. A major cause of CVD is atherosclerosis, and this progressive inflammatory process results in the development and growth of complex atherosclerotic lesions known as plaques, leading to acute cardiovascular events like myocardial infarction and stroke. Proteases, especially matrix metalloproteases, secreted by immune cells have been implicated in CVD, whereas other proteases, e.g. the cysteine protease legumain, have been less studied. This study aims to shed light on the role of legumain in CVD.

Methods
Circulating levels of legumain in plasma/serum of several CVD patient cohorts or released mediators from platelets or macrophages were assessed by enzyme-linked-immunosorbent assays. Quantitative PCR and immunoblotting were used to study expression, while localization was visualized by immunohistochemistry.

Results
Increased levels of legumain were found in plasma and plaques from patients with carotid atherosclerosis compared to healthy controls. In symptomatic carotid plaques and in samples from both coronary and intracerebral thrombi obtained at the site of vascular occlusion, legumain was co-localized with macrophages and in the same regions as platelets. Patients with an acute cardiovascular event had significantly higher circulating legumain before and immediately after percutaneous coronary intervention compared with healthy controls, and high levels were associated with improved outcome. In vitro, legumain was shown to be present in and released from platelets upon activation, and circulating legumain levels was correlated with markers of platelet activation. Also, THP-1 macrophages exposed to releasate from activated platelets showed increased legumain expression. Interestingly, legumain also promoted development of anti-inflammatory macrophages.

Conclusion
Our data demonstrate for the first time that legumain is upregulated during acute cardiovascular events and is associated with improved outcome.

Early changes in cardiac performance caused by calcineurin inhibitors – a marker of long-term organ toxicity?

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Problem
The calcineurin inhibitors (CNI) cyclosporine and tacrolimus are the basis of most immunosuppressive protocols for prevention of graft rejection following organ transplantation, as well as treatment of various autoimmune diseases. But CNI therapies are also known to ultimately damage the organs they are intended to protect, as well as other organs (long-term treatment failure), making their use tolerated mainly due to their impressive ability to improve short-term outcomes. Because early detection of adverse effect of drugs is important to prevent the end-stage failure, this study aimed to evaluate a possible causal relationship between early cardiac dysfunction during CNI therapy and organs toxicities.

Results
Cardiac output (CO) was significantly reduced (~30%) in mice 5h after CNI injection indicating an early effect of CNI on cardiac performance. This reduction of cardiac performance was associated with cardiac contractility reduction, but also by the reduction of end-diastolic volume (EDV), potentially due to intravascular volume depletion as shown by the volume expansion test. The histological analysis of organs from mice treated similarly with CNI revealed a higher level of cell death/stress and infiltration of neutrophils. The plasma level of LDH and the skeletal muscle level of lactate was higher in mice treated with CNI, suggesting a likely reduced oxygen delivery that could be explained by lower CO. Interestingly, the contractility and the CO after the same treatment in Knock-in mice with inhibited enzymatic function of PI3Kgamma (PI3Kgamma "kinase dead"), and in mice treated simultaneously with PI3Kgamma selective inhibitor were preserved. Concomitantly, the level of plasma LDH, skeletal muscle lactate and the tissue damage was limited in those mice.

Conclusion
So far, our study suggests the early left ventricular dysfunction and cardiac output assessment as potential tools (markers) to evaluate the risk of CNI-related organ toxicities and addresses a call for more investigations.

FF12 Basal farmakologi

DSSLepR rats as a new animal model of heart failure with preserved ejection fraction (HFpEF) for testing new pharmacological treatment strategies

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Heart failure (HF) represents a major societal and personal burden, with prevalence estimated at 1-2% in the general population and increasing with age to about 10%. Furthermore, life expectancy is dramatically shortened for those affected. Several advances have been made in the understanding and treatment of the most studied form of HF, called HF with reduced ejection fraction (HFrEF), formerly also known as systolic HF. However, almost 50% of HF patients suffer from HF with preserved ejection fraction (HFpEF), also known as diastolic HF, which remains poorly understood and lacks effective treatment options. The main problem in HFpEF is a stiff or non-compliant heart, often characterised by concentric remodelling, resulting in a small ventricular lumen causing reduced ventricular filling and thus reduced cardiac output despite preserved ejection fraction. Research on HFpEF has been hampered by the lack of good animal models.

Therefore, we are currently breeding and characterising a new rat model, which combines the two main triggers of HFpEF, hypertension and metabolic syndrome. The model is obtained by cross-breeding Dahl salt-sensitive (DSS) rats (prone to hypertension) with leptin resistant (LepR) Zucker rats (prone to metabolic syndrome due to a missense mutation in the leptin receptor gene). The new rat model, designated DSSLepR rats, is currently in the final stage of breeding in our facility and we are characterising the rats with respect to cardiac and haemodynamic parametres.

Specificly, DSSLepR rats were obtained by initial crossbreeding of male lean Zucker rats, heterozygous (fa/+) for the fa allele causing leptin resistance (LepR) with a female Dahl salt sensitive (DSS) rat, followed by multiple rounds (9-13) of back-crossing to ensure a stable genetic background of DSS with heterozygosity of the fa allele. Mating of such heterozygotes yields three genotypes but only two phenotypes: homozygous (fa/fa) obese, heterozygous (fa/+) lean and homozygous (+/+) lean, in the ratio of 1:2:1. Rats are now evaluated after 9 rounds of crossbreeding. The $Lepr^{fa}$ zygosity was evaluated by genotyping. The homozygous (fa/fa) obese animals are about 30% heavier than their heterozygous (fa/+) lean littermate controls at 5 weeks of age, increasing to about 80% at week 10, and display cardiac ventricular hypertrophy, assessed by transthoracic echocardiography.

In addition to further characterisation, future studies will focus upon investigating the effects of neurohumoral regulation in hearts with diastolic dysfunction and HFpEF. The long-term objective is to utilise this rat model to study factors that lead to HFpEF development and to develop new pharmacological therapy for HFpEF.

Identification of a novel polymorphism associated with reduced clozapine concentration in schizophrenia patients – a GWAS adjusting for smoking habits

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Aim
Clozapine (CLZ) is the superior antipsychotic drug for treatment of schizophrenia, but exhibits an extensive interpatient pharmacokinetic variability. Here, we conducted a genome-wide association study (GWAS) of CLZ serum concentration adjusting for known smoking habits, which is a major non-genetic factor reducing CLZ levels.

Method
The study included 484 patients with 10,283 steady-state serum concentrations of CLZ and *N*-desmethylclozapine, prescribed dosing, co-medications and known smoking habits (n=422; 9,284 serum samples) from a therapeutic drug monitoring (TDM) service. The GWAS analyses were performed with and without smoking habits as covariate, where possible hits were assessed in relation to the CLZ therapeutic concentration range (300-2500 nmol/L).

Results
Our smoking-independent analysis of *N*-desmethylclozapine serum concentration and the CLZ-to-*N*-desmethylclozapine ratio replicated the previously identified locus on chromosome 4. After adjusting for smoking habits in patients confirmed as 'smokers' (61%) or 'non-smokers' (39%), a novel variant (rs28379954) within the gene encoding the nuclear factor 1 B-type (*NFIB*) was significantly associated with reduced CLZ serum concentration ($p=1.68x10^{-8}$, beta=-0.376; minor allele frequency: 4.1%; explained variance: 7.63%; confirmed by Taqman genotyping). The fraction of CLZ TDM samples below the therapeutic concentration range was significantly higher in carriers vs. non-carriers of the rs28379954 minor allele [12.0% (95%CI: 9.4-14.7) vs. 6.2% (95%CI: 5.7-6.8), $p<0.001$].

Conclusion
We identified a novel variant in the *NFIB* gene associated with reduced CLZ levels and increased risk of subtherapeutic serum concentrations. This warrants testing of clinical relevance of screening for the gene-variant, and the biological mechanisms of NFIB involvement in CLZ pharmacokinetics should be clarified in experimental studies.

FF14 Basal farmakologi

Spatial signaling of cGMP in nanodomains modifies heart function

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The natriuretic peptide receptors A and B (GC-A and GC-B) are transmembrane guanylyl cyclases stimulated by natriuretic peptides. Activation of GC-A by atrial natriuretic peptide (ANP) or brain natriuretic peptide (BNP) or activation of GC-B by C -type natriuretic peptide (CNP) regulates cardiovascular function through production of cGMP. In the heart, CNP-stimulation causes a lusitropic and negative inotropic response. Despite similar increases in cGMP, these effects are not mimicked by BNP or ANP. Thus, the mechanisms of the differential cGMP signaling and receptor compartmentation remain unclear.

Here, we develop novel fluorescence resonance energy transfer (FRET)-based biosensors for cGMP to detect low (nM) or high (µM) concentrations of cGMP in cardiac myocytes. To detect cGMP in different nanodomains, we targeted these biosensors to proteins that regulate contractility (inotropic response), diastolic relaxation and mitochondrial activity.

We show that GC-A and GC-B increase cGMP differentially in several nanodomains in cardiomyocytes. In addition, by combining scanning ion conductance microscopy (SICM), FRET and local receptor stimulation, we demonstrate that GC-B both in the transverse tubules (T-tubules) and on the cell crests increases cGMP similarly near both troponin I and phospholamban. Also, the phosphodiesterases PDE2 and PDE3 constrained GC-B signaling in both compartments. In ventricular strips, stimulating GC-B, but not GC-A, induced a lusitropic response that was enhanced by inhibition of either PDE2 or PDE3, and a negative inotropic response.

These results provide a basis for understanding how natriuretic peptide signaling in the heart regulates contractile responses.

Postere

Toksikologi
Postere henges opp på anvist plass i **Besseggen 1.** Postervisningen ledes av: Jason Matthews (UiO).

Farmakologi
Postere henges opp på anvist plass i **Beseggen 2.** Postervisningen ledes av: Jenny Lund (UiO)

Hver poster får plass tilsvarende en plakat på rundt 80 x 120 cm (bredde x høyde). Alle postere må henges opp med tape. Tape vil bli lagt ut ved de merkede plassene.

Presentasjon
Posterpresentasjonene skjer som en 3-minutters PowerPoint-presentasjon med 3-4 lysbilder, hvorav ett tittellysbilde. Unngå bruk av animasjoner.
Pek på hovedpoengene og få frem:

- Problemstilling
- Hvordan studien er utført
- Hovedfunn
- Konklusjon

Ta opp hovedtrekkene og unngå detaljer. Dette er ikke et vanlig foredrag og målet er at tilskuerne skal få lyst til å studere posteren nærmere etterpå. Postersesjonen avsluttes med en fri posterdiskusjon. Her går man tilbake til de enkelte posterne og utfolder seg sammen med spesielt interesserte.

For postere inne toksikologi er det ingen PowerPoint-presentasjon, bare diskusjon ved posterne

NSFTs posterpris 2020
En posterpriskomité vil vurdere alle bidrag og finne en vinner innen henholdsvis toksikologi og farmakologi. Hver vinner får tildelt diplom og en vandreplakett under festmiddagen lørdag 25. januar.

Posterprisvinnere fra 2019:
Toksikologi:
Silje Modahl Johanson (NMBU): Maternal exposure to a mixture of persistent organic pollutants have long-lasting effects on gut metabolite composition but not on colorectal cancer
Farmakologi:
Henriette Andresen (UiO): A search for an allosteric binding site on the natriuretic peptide receptor A

Postere i toksikologi (TP)

TP-1 Toksikologi

The *in vitro* toxicity of a dental resin monomer varies among different cell culture models

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Introduction
In vitro cytotoxicity tests are routinely carried out during biocompatibility evaluation of medical devices. By using immortalized cell lines, such tests become relatively simple, fast to perform and easy to get reproducible and standardized results. However, a wide range of cell lines is available and various protocols describe the use of specific cell types without a decent reason for their choice. Cell lines that are commonly used for toxicity studies differ both in source (species and organ) and how they have become immortalized (e.g. cancer cells and virus transfected cells). Based on this, it can be assumed that they differ in many properties, including their capacity to handle different substances and exposure scenarios. Hence, we hypothesize that results obtained by *in vitro* cytotoxicity tests depend strongly on the chosen cell line.

Methods
In this study, we have compared how four commonly used cell lines respond to 2-hydroxyethylmethacrylate (HEMA) exposure. HEMA is a resin-based biomaterial used in dentistry, among others. The four cell types tested were: 1) A549 cells (human, alveolar carcinoma), 2) BEAS-2B cells (human normal bronchial epithelium, SV40 transformed), 3) RAW 264.7 cells (murine, macrophage-like, Abelson leukemia virus transformed) and 4) L929 cells (murine, fibroblast). All cell lines were exposed to 1-8 mM HEMA (a methacrylate monomer that both dental personnel and dental patients are exposed to during treatment). The endpoints used to measure cellular responses to HEMA were 1) viability (MTT assay), 2) cell death analyses (fluorescence microscopy of Hoechst/propidium iodide stained cells) and 3) cell growth pattern (flow cytometry of DAPI-stained cells).

Results
The relative viability (% viable cells compared to unexposed cell culture) after 24 h HEMA exposure (8 mM) varied from 86 % (L929 cells) to 32 % (RAW 264.7 cells). Similarly, the portion of dead cells varied from 4 % (L929 cells) to 72 % (RAW 264.7 cells). HEMA also caused altered cell growth pattern in some of the cell lines. In A549 cells, an increased portion of cells in S-phase was measured, while a decreased portion of cells in S-phase was observed in RAW 264.7 cells. No significant difference was measured in exposed BEAS-2B and L929 cells.

Conclusion
In summary, our results show that the outcome of an *in vitro* cytotoxicity test depend strongly on the cell line used.

Keywords: cell lines, biocompatibility, HEMA

Effect of methacrylates and nanoparticles used in dental materials on A549 lung epithelial cells

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Background
Polymer based dental materials are widely used in modern dentistry. These materials are classified as resin-based composites, constituting a filling agent (nano- to micro sized silica) embedded in an organic polymer matrix that is made from polymerized methacrylate monomers. During treatment, both dental personnel and dental patients are exposed to methacrylate monomers and filler particles. Knowledge regarding how this combination exposure impacts the health is limited.

HEMA is a commonly used monomer in dental resins, and has been shown to have a toxic potential in vitro. At moderate HEMA levels, lysosomal degradation by autophagy seems to serve as an important defense mechanism in exposed cells. It is suggested that nanoparticles have an impact on lysosomal function. This master thesis focus on lysosome function and autophagy capacity in cells exposed to nanoparticles and HEMA. The aim is to explore the hypothesis that nanoparticles reduce autophagic capacity in exposed cells and thereby increase the toxic potential of HEMA.

Methods
A549 cells, a human lung adenocarcinoma cell line, was used as a model for lung exposure. Cells were exposed to HEMA (1-8 mM) and silica nanoparticles (SiNP; 3-25 µg/) at different concentrations. The MTT-assay was used to measure cell viability after various exposures. Western Blotting was used to measure levels of proteins related to autophagy.

Results and discussion
Exposure of the cells to SiNP (24 h) resulted in a dose-dependent viability loss. The level of sequestome 1 (p62/SQSTM-1; an autophagy related protein) increased with increasing SiNP concentration (up to 12,5 µg/ml). The p62 level was decreased after 24 h HEMA exposure compared to control cells. The transcription factor Nrf-2 is an important regulator of p62 synthesis. A549 is defective in Nrf-2 regulation, therefore it is likely that the increase in p62 results from reduced lysosomal degradation and reduced p62 levels is caused by increased degradation/autophagy. Further, observations by phase contrast microscopy showed an increasing degree of vacuolization in cells exposed to increasing SiNP concentrations. A better characterization of these vacuoles is needed.

Conclusion
The results obtained in this study support the hypothesis that SiNPs affect lysosomal degradation pathways. The results also indicate that HEMA causes increased autophagic flux. However, to verify this hypothesis, more experiments are needed.

The effect of lipopolysaccharide from *E.coli* serotypes on interleukin-1β release in RAW 264.7

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Introduction

Lipopolysaccharides (LPS) are components found in the outer membrane of gram-negative bacteria. Toll-like receptor 4 (TLR4) is able to recognize LPS [1], thereby activating downstream signaling that ultimately lead to the production of a wide array of proteins. This include synthesis of interleukin-1β (IL-1β), an important trigger of innate immune response. The methacrylate 2-hydroxyethylmethacrylate (HEMA) is a major component of many resin-based dental biomaterials. *In vitro* studies have shown that HEMA can inhibit LPS induced IL-1β synthesis. Hence, an insufficient immune response to gram-negative bacteria could result in patients that are exposed to components of resin-based biomaterials.
The aim of this study is to design a good model for investigating the effect of HEMA on innate immune responses. Different bacterial species and serotypes differ in LPS composition. Hence, the primary goal of this study is to map possible differences in IL-1β response of LPS from different *E.coli* serotypes.

Methods

The murine macrophage-like cell line RAW 264.7 were exposed to LPS from *E.coli* serotype O26:B6, O55:B5 and O111:B4. The duration for each experiment lasted 24 hours before harvesting the supernatant. Enzyme-linked immunosorbent assay (ELISA) on the supernatant gave the IL-1β levels in each sample. IL-1β for HEMA/LPS experiment was done in the same fashion.
The data were analyzed in R with one-way analysis of variance (ANOVA), followed by multiple comparison test after a significant ANOVA result ($p < 0.05$).

Results

Morphological changes to the RAW 264.7 cells were observed in all samples. IL-1β release increased drastically in RAW 264.7 cells exposed to LPS from *E.coli* serotype O26:B6 when compared to the two other serotypes. Combination exposure to LPS O26:B6 and HEMA reduced IL-1β release in a concentration-dependent manner.

Conclusion

Despite the LPS originating from the same species, the cellular response varies by a large margin between the serotype. HEMA also inhibits the potent IL-1β response from LPS O26:B6. LPS from serotype O26:B6 seems to be a good candidate for investigating HEMA effects on immune responses.

Associations between urine phthalate metabolites and thyroid function in pregnant women and the influence of iodine status

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Research question
Human populations, including susceptible subpopulations such as pregnant women and their foetuses, are continuously exposed to multiple phthalates. Phthalates may affect the thyroid hormone system, causing concern for pregnancy and child health. Our aim was to investigate the associations between phthalate exposure and thyroid function biomarkers during pregnancy, and if the key nutrient for thyroid health, iodine, modifies these relationships.

Methods
The study included pregnant women (N=1072) that were selected from The Norwegian Mother, Father and Child Cohort study (MoBa). We measured concentrations of 12 urinary phthalate metabolites and 5 plasma thyroid function biomarkers around 17 weeks' gestation. We accounted for the phthalate metabolite mixture by factor analyses, ultimately reducing the exposure into two uncorrelated factors. These factors were used as predictors in multivariable adjusted linear regression models with thyroid function biomarkers as the outcomes. Effect modification by habitual dietary iodine intake was also investigated.

Results
Factor 1, which included high loadings for mono-iso-butyl phthalate (MiBP), mono-n-butyl phthalate (MnBP), and monobenzyl phthalate (MBzP), was associated with increased total triiodothyronine (TT3) and free T3 index (fT3i). These associations appeared to be driven primarily by women with low iodine intake (<150 µg/day, ~70% of our sample). In contrast, factor 2, which included high loadings for di-2-ethylhexyl phthalate metabolites (∑DEHP) and di-iso-nonyl phthalate metabolites (∑DiNP), was associated with a decrease in TT3 and fT3i, which appeared fairly uniform across iodine intake categories.

Conclusion
We find that phthalate exposure is associated with thyroid function in mid-pregnancy among Norwegian women, and that iodine intake, which is essential for thyroid health, could influence some of these relationships. This highlights the importance of investigating the role of iodine in future studies as well as linking our findings to pregnancy and child health outcomes.

Exposure assessment of phthalates based on aggregated exposure from food and personal care products: creation of a concentration database

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Phthalates are diesters of phthalic acid and have been widely used as plasticizers in PVC plastics in order to increase their flexibility. They are also used as excipients in pharmaceuticals and personal care products (PCPs) as; emulsifying agents, solvents, etc. Phthalates can migrate into the air, water, foodstuff and humans can be exposed via multiple pathways such as dermal, oral and inhalation. There is evidence that phthalates can induce reproductive and developmental toxicity not only in experimental animals but also in humans through disruption of estrogenic activity.

A two-day biomonitoring study (BM) was performed to study the aggregated exposure to chemicals, including phthalates, from foods and PCPs. The study was funded by the EuroMix project (Horizon 2020). The aim of this study is to collect information on the occurrence levels of the most important phthalates in foods and PCPs and perform not only an individual exposure estimate but also compare these with the measured concentrations in urine from the BM study.

A systematic literature search was performed for the identification and selection of relevant studies reporting phthalates (DEHP, DiNP, DEP, DnBP, BBP and DINCH) concentrations in foods and PCPs from 2008 to present. This chemical concentration data will be combined with foods consumed and PCP use from the diaries to calculate the aggregate exposure to the aforementioned phthalates. The aggregate exposure will be estimated both via deterministic (mean, median) and probabilistic methods like Monte Carlo Risk assessment (MCRA) software and/or custom-made R scripts, and compared with individual biomonitoring data.

For the concentration database, there were 4330 papers identified from the literature and the most studied phthalates were DBP, DEHP and DEP. The studies were screened based on pre-defined selection criteria and 141 papers have been selected. Currently the extraction of the data is ongoing. From the BM study the main contributors to the mean dietary DEHP exposure are milk and dairy products, with a contribution of 69.3 % and 62.8 % of the total exposure for males and females respectively. The highest exposure from PCPs was due to DEHP in deodorants with a 79% and a 53% contribution, for males and females respectively. For females a relatively high contribution was also observed from body lotion (33 %) and from perfume (9%).

References

Hubinger, J. C., 2010. A survey of phthalate esters in consumer cosmetic products. J Cosmet Sci. 61, 457-65.

Lyche, J. L., et al., 2009. Reproductive and Developmental Toxicity of Phthalates. Journal of Toxicology and Environmental Health, Part B. 12, 225-249.

Husøy, T., Andreassen, M., Hjertholm, H., Carlsen, M.H., Norberg, N., Sprong, C., Papadopoulou, E., Sakhi, A.K., Sabaredzovic, A., Dirven, H.A.A.M., 2019. The Norwegian biomonitoring study from the EU project EuroMix: Levels of phenols and phthalates in 24-hour urine samples and exposure sources from food and personal care products. Environment international 132, 105103.

Nicotine promote the toxicity of resin-based biomaterials by impairing lysosomal function

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Background
Tobacco products as well as nicotine containing replacements contain relatively high levels of nicotine. Although most research on cellular effects of nicotine has focused on receptor-mediated effects, the reported lysosomotropic property of nicotine could be of importance for an observed interaction with autophagy. The resin monomer 2-hydroxyethylmethacrylate (HEMA) is known to leak after dental treatment with HEMA containing materials. Studies have shown that cells defend themselves against HEMA exposure by increasing their autophagy capacity, a cellular function that depends on the lysosomes. The aim of this study was to elucidate the effect of combined exposure of nicotine and HEMA with special focus on lysosomes and autophagy.

Method
The human bronchial epithelial cell line BEAS 2B was exposed to HEMA (0-2 mM), nicotine (0-10 mM) or both in combination. MTT assay was used to measure cell viability. Western blotting was used to quantify the autophagy related protein p62/SQSTM1 (p62).

Results
Shortly after initiation of nicotine exposure we observed morphological changes in the cells. In line with the previously reported lysosomotropic effect, vacuolization was one major visible change. Cells exposed to nicotine also showed significant increased p62 levels. During autophagy, p62 is degraded in the lysosomes. Hence, increased p62 level may indicate reduced autophagic flux. The p62 level increased further when HEMA was added to the exposure mixture.

Conclusion
We show that nicotine affects bronchial epithelial cell morphology. The results further support that nicotine inhibit lysosome function and autophagic flux and that combined exposures to HEMA and nicotine cause synergistic toxicity.

Keywords: Nicotine, HEMA, autophagy, lysosome

Results from the Norwegian human biomonitoring study in the EuroMix project: Exposure to the pesticides boscalid and imazalil from the diet in Norway

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Background
The fungicides boscalid and imazalil were among the most frequently detected pesticides in the residues monitoring programs 2013-2017 in Norway.
The aim of the present study was to estimate the daily intake of these two pesticides and compare with measured concentrations in 24 h urine samples.

Methods
A human biomonitoring study was performed to study the exposure to chemicals present in food and personal care products (PCPs). In two 24 h periods two-three weeks apart, 144 participants (100 women and 44 men) kept detailed weighted food diaries and PCP diaries and collected all urine excreted. Individual-specific consumption data from both 24 h periods were used to estimate boscalid and imazalil exposure deterministically. A sensitive ultra-performance liquid chromatography coupled to tandem mass spectrometry (UPLC-MS-MS) method was developed to measure the boscalid metabolite 2-chloro-N-(4'-chloro-5-hydroxybiphenyl-2-yl)nicotinamide (M510F01) and imazalil in the 24 h urine pools collected at Day 1.

Results
Overall, the estimated dietary exposure of boscalid and imazalil was comparable between males and females. In the lower bound exposure scenarios, the estimated dietary exposure of boscalid ranged from 0-0.9 µg/kg bw/day and the estimated exposure of imazalil ranged from 0-0.81 µg/kg bw/day.
In 99 % of samples M510F01was detected in concentrations from 0.04-15.03 ng/ml. There was a statistically significant difference between genders ($P<0.0001$) with a median concentration of 0.98 ng/ml for females, and 0.46 ng/ml for males. Imazalil was detected in 1 % of the samples. One of the reasons for the low detection of imazalil could be the choice of the chosen urinary biomarker. Comparisons with estimated exposure levels for both boscalid and imazalil will be presented.

Conclusion
Widespread human exposure to the fungicide boscalid as measured by one of its metabolites in urine samples was observed.

Effects of air pollution particles from two tunnels in Norway in lung epithelial cells

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Introduction

Traffic is a major source to urban air pollution and represents a large environmental health problem. Traffic pollution comprises a mixture of gases and particulate matter (PM) from exhaust and wear of road pavement, tires and brakes. From a regulatory view, the main pollution issues related to vehicle traffic in Nordic countries are high levels of coarse mineral-rich wear PM from the road pavement due to use of studded tires in the winter, and exhaust PM from diesel vehicles. In this study we compared three fractions of particles sampled in two tunnels in Norway; coarse, fine and ultrafine. The coarse fraction ($PM_{10-2.5}$) of road dust consists mainly of mineral particles from asphalt, whereas the fine ($PM_{2.5-0.18}$) and ultrafine ($PM_{0.18}$) fractions consists mainly of combustion-derived particles. The tunnels were paved with different stone-types. Collection of the particles were taken before and after sweeping of the tunnels. Our hypothesis was that two different stone-types induce pro-inflammatory responses with different potency. Furthermore, that the coarse fraction induces higher responses than fine and ultrafine fractions.

Methods

The coarse, fine and ultrafine PM were collected in two different tunnels (Hell and Marienborg) using a high volume sampler on three different filters. The PMs were sampled both from wet and dry road surface. The PMs were extracted from the filters with methanol before an evaporation of the methanol. The filters were weighted before and after sampling, and the weights of the PMs were determined. Human bronchial epithelial cells (HBEC-3KT) were exposed to the PMs for 20 h using submerged conditions. Cell-death and increase of the pro-inflammatory cytokine CXCL-8 were determined by Alamar blue and ELISA, respectively. The PM oxidant capacity was measured acellular by Electro Paramagnetic Resonance.

Results

There was collected more PM per hour in the Hell Tunnel than in Marienborg, with largest amount of the coarse fractions and least of the ultrafine fraction. Sweeping of the tunnels relatively, little influenced the amount of PMs. Exposure to the HBEC-3KT cells revealed that the coarse fraction gave almost the same cytokine release independent of the tunnel/stone-type and also independent of dry versus wet conditions. Furthermore, the fine fraction was more potent in the Marienborg than the Hell tunnel. The wet ultrafine fraction from the Marienborg tunnel was much more potent than wet ultrafine PM from Hell. The dry ultrafine fractions from the two tunnels induced approximately similar responses.

Conclusion

The coarse fractions from the two tunnels induced similar pro-inflammatory responses, suggesting that the different stone type was of minor importance. The fine fractions from Marienborg were more potent than from the Hell tunnel. For the ultrafine fraction, the responses were dependent on the humidity during the PM sampling.

How much chemicals with PFAS do we use in Norway? A data register study based on data from 2009-2017.

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A data register study was performed to identify the amounts of PFAS in chemicals imported to Norway during 2009-2017. The Product Register in Norway is the Norwegian authorities' official register of chemicals imported and produced in Norway. According to legislation, manufacturers or importers who produce and/or place on the market 100 kg/y or more of a chemical classified as hazardous are obliged to submit a declaration to the Product Register. The data from the years 2009-2017 was searched for substances from PFAS on the OECD list and on the KEMI list (short chain PFAS).

During the period, 72 CAS from the OECD list and 5 from the KEMI list was used in products in Norway. Most of the PFAS were telomers, sulfonyls precursors or polymers. The tonnages imported (since Norway has no production) were between 15-28 tons/y and was 249 tons in the period. During the years, the amount of telomers was highest (150 tons), but also the amounts of polymers, short chain PFAS and precursors were high (51, 26 and 16 tons respectively). Since 2014, the yearly percentage of use of telomers have decreased from >75 to 25% of yearly import, while the use of polymers, short chain PFAS and precursors have increased.

A telomer with chain length of 6 was the PFAS used in highest amount (110 tons) in the period for fire-fighting purposes, followed by PTFE (49 tons) used in very different products such as e.g. paint, reducing friction, lubricant and more. A silicon with 9 Fluor atoms was used as a defoamer by the oil industry. The use of PFAS compounds was quite diverse, but fire-fighting purposes was using most PFAS (130 tons). However, more than 71 tons of PFAS in the period was used in paint, as defoamers, friction reducers and paper industry (each group >14 tons). In the period the yearly percentage of PFAS used for fire-fighting purposes has been reduced (>50% to 25%) while other uses have increased.

We believe that the amounts that we have reported are minimum data since Norway currently do not have an obligation to declare PFAS to the product register. We recommend Norwegian authorities to amend legislation to include such obligation in line with Sweden.
Our conclusions are that the Product Registry is a very useful tool showing that PFASs are used in high amounts. Fire-fighting purposes has been the major use, but PFAS compounds used for other purposes are increasing.

Fortsatt målbar radioaktivitet i beitevekster og hjortedyr i Norge etter Tsjernobyl-ulykken

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Problemstilling
Siden Tsjernobyl-ulykken i april 1986 har man i Norge vært oppmerksom på at radioaktive isotoper kan tas opp i planter og sopp og videre til beitende dyr, og at dette kan medføre forhøyete nivåer av radioaktivitet i mat fra deler av landet. Den radioaktive isotopen som fortsatt er målbar, er cesium-137 (Cs-137) med en halveringstid på 30 år. I kroppen distribueres det meste av cesium til muskulaturen før det skilles ut i urin og avføring, samt i melk. Den biologiske halveringstiden av cesium i dyr er ca. 3 uker. Veterinærinstituttet har de senere årene vært involvert i radioaktivitetsmåling i mat og fôr som et ledd i myndighetenes ønske om overvåking og beredskap på området.

Metode
I en pilotundersøkelse ble utvalgte beitevekster (smylegress, blåbærlyng, steinsopp og blek piggsopp) samlet inn fra ulike steder i landet for å kunne se på variasjon av radioaktivitetsnivå mellom geografiske områder og mellom vekstene. Kjøttprøver fra hjortedyr (villrein, elg og hjort) ble samlet inn fra Nordfjella der det var lett tilgang på prøvemateriale i forbindelse med nedfellingen av villreinen på grunn av skrantesjuke høsten 2017, for å se på om det var forskjeller i radioaktivitetsnivå mellom artene, kjønn og aldersgrupper, samt om nivået endret seg gjennom høstfellingen. Prøvene ble analysert gammaspektrometrisk med natriumjodid (NaI) scintillasjonsdetektor for måling av Cs-137.

Resultater
Prøvene av beitevekster viste at piggsopp hadde høyere innhold av Cs-137 enn de andre vekstene som ikke viste sikre forskjeller. Målingene av kjøtt fra hjortedyra viste høyere nivå av Cs-137 i villrein enn i elg og hjort som ikke hadde forskjellig nivå. Voksne hanndyr hadde lavere Cs-137-nivå enn hunndyra, noe som antakelig kan forklares med at fellingen foregikk i brunsttida og at hanndyra da ikke tar seg tid til spise. Det var ikke endring i dyras radioaktivitetsnivå gjennom høstfellingen, noe som sannsynligvis har sammenheng med lite sopp i Sør-Norge høsten 2017. Alle prøvene av beitevekster og hjortedyr i dette materialet hadde lavere nivå av radioaktivitet enn den generelle grenseverdien på 600 Bq/kg som gjelder for mat.

Konklusjon
Pilotstudien av beitevekster fra ulike deler av landet og studien av kjøtt fra hjortedyr fra Nordfjella viste målbar radioaktivitet, men betryggende lavt nivå i relasjon til både dyras og menneskers helse.

Mixture effects of benzo[a]pyrene and perfluoroalkyl substances on the aryl hydrocarbon receptor signalling pathway and energy metabolism of Atlantic cod (*Gadus morhua*)

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Background and aim

Polycyclic aromatic hydrocarbons (PAHs) and perfluoroalkyl substances (PFAS) are two classes of environmental contaminants that are widely detected in marine organisms. Among the PAHs found in the environment, benzo[a]pyrene (BaP) is among the most characterized one and has shown to induce *cyp1a* activity. Previous research has suggested that PFASs can modulate the uptake and toxicity of other chemicals (Keiter et al., 2016). As most contaminants are present in mixtures in the environment, it is essential to understand their combined effects. The aim of this project is to study toxicological effects in Atlantic cod after exposure to BaP and PFASs, focusing on changes in gene expression levels. Genes involved in the energy metabolism and the biotransformation of xenobiotics will be especially targeted. BaP is known to be a strong inducer of the aryl hydrocarbon receptor (Ahr) signalling pathway, and PFOS and PFOA have previously shown to increase the activity of mouse and human PPARα and PPARβ, which are receptors involved in controlling the energy homeostasis (Takacs and Abbott, 2007).

Methods

Liver from juvenile Atlantic cod (*Gadus morhua*) was used to make precision cut liver slices (PCLS, Eide et al., 2014) before exposing them to three different PFASs, both as single compounds (PFOA, PFOS and PFNA) and in mixtures. The slices were also exposed to the PFASs in combination with BaP to assess if any cocktail effects between the two different classes of pollutants could be revealed. Cytotoxicity was monitored by using the MTT assay, and expression of the genes *cyp1a*, *acox1*, *acly*, and *ahrrb* was quantified using quantitative real time polymerase chain reaction (qPCR).

Results

The viability of the liver slices did not change during the different exposure regimes. BaP induced *cyp1a* and *ahrrb* expression, and we observed a trend that the expression of these genes was further enhanced by co-exposure to PFASs, both single compounds and in mixture. Expression of *acox1* and *acly* also showed a tendency of increased expression by both individual- and combined PFAS exposure.

Conclusion

The results indicate that the PFASs used in this experiment could enhance the toxicity of BaP through the induction of *cyp1a* and *ahrrb*. The effects of BaP and PFASs will be further investigated using the luciferase reporter gene assay to study Ahr receptor activation.

The work is a part of the project “dCod 1.0; decoding the systems toxicology of Atlantic cod” funded by the Research Council of Norway (NFR, Project no. 248840).

References

Keiter et al., 2016. Science of the total Environment. 548–549, 317–324
Takacs, M. L. and Abbott B. D., 2007.Toxicological Sciences. 108-117

Functional Characterization of Atlantic Cod (*Gadus morhua*) Peroxisome proliferator-activated receptor alpha 1 and 2

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The peroxisome proliferator-activated receptors (PPAR) are ligand-activated transcription factors, and members of the superfamily of nuclear receptors (NR). The PPAR subfamily (NR1C) consists of three members: PPARA, PPARB/D and PPARG. The three subtypes have distinct roles in the regulation of the energy metabolism, and differ in their tissue specific expression, ligand specificity, and target genes. Atlantic cod (*Gadus morhua*) has four different Ppars; gmPpara1, gmPpara2, gmPparb and gmPparg. It has been demonstrated that gmPpara1 can be activated by some exogenous compounds, including the PPARA model-agonist WY-14643, and the perfluoroalkyl substances (PFAS) PFHxA, PFOA, PFNA, and PFHxS. Although gmPpara2 also are responsive to WY-14643, this subtype is not activated by any of the PFASs. When aligning the gmPpara1 protein sequence with gmPpara2 and hsPPARA, an insertion of 14 amino acids in hinge region of the gmPpara2 receptor is observed. Also, two of the amino acids important for coordinating WY-14643 in a second allosteric binding site differ in gmPpara2 compared to both gmPpara1 and the human ortholog. We hypothesize that these differences cause the observed discrepancies in the activation profiles of gmPpara1 and gmPpara2.
In this study, gmPpara2 were mutated to remove the insertion absent in gmPpara1 and hsPPARA. Additionally, the amino acids important for ligand binding were replaced to make gmPpara2 mutants more similar to gmPpara1 and hsPPARA. Luciferase-based reporter gene assays with the constructed gmPpara2 mutants and native gmPparas will be used to see how these introduced changes affect ligand-binding and receptor activation. This will also possibly aid the identification of the amino acids important for ligand recognition and binding.
To produce the different mutants of gmPpara2, site directed mutagenesis (SDM) was performed with either the Q5 SDM Kit from New England BioLabs or the QuickChange Multi SDM kit from Agilent Technologies. For studying ligand activation of the gmPpar receptors, a luciferase reporter gene assay (LRA) will be used. In this assay COS-7 cells are co-transfected with an effector plasmid containing the ligand-binding domain (LBD) of gmPparas fused to the GAL4-DNA binding domain (DBD), and a GAL4-UAS-based reporter plasmid containing the luciferase gene. Then the cells are exposed to test compounds, and the activation of the receptors is measured as luciferase activity, quantified by the amount of light emitted when luciferin is oxidized to oxyluciferin.

Conclusions
Eight different mutants were successfully cloned and verified with DNA sequencing. Preliminary results have demonstrated that all the constructed gmPpara2 mutants can be activated by WY-14643. We are currently progressing with LRAs to compare potencies and efficacies between gmPpara2 mutants, native gmPpara2, and gmPpara1 in more detail.

Acknowledgement
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TP-13 Økotoksikologi

Predicting environmental risks of pharmaceuticals in Norwegian surface water

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Problem
Pharmaceuticals have attracted much recent attention as 'pollutants of emerging concern'. However, the large-scale measurement of pharmaceuticals in the environment remains difficult due to their diversity and wide range of potential metabolites. Present day environmental risk assessment of pharmaceuticals often relies on environmental concentrations predicted from maximum daily dose and the proportion of a population using a drug. However, in Norway, where high-quality sales records are maintained, it is possible to predict environmental concentrations at a higher level of specificity.

Method
We are working as part of ECORISK2050, a large Innovative Training Network analysing and addressing future risks of chemicals, to refine a predictive model of environmental concentrations of pharmaceuticals in Norwegian freshwaters, from sales data maintained by the Norwegian Institute of Public Health. The aquatic concentrations (predicted environmental concentration, PECs) will later be used to calculate the environmental risk by comparison with predicted no-effect concentrations (PNECs). Once we have fully completed my implementation of this model, we will apply it to NIPH sales data for the years 1995 – 2019, allowing me to retrospectively calculate Risk Quotients for pharmaceuticals in Norwegian freshwaters for this period.

Results
With this data, we hope to predict future scenarios of pharmaceutical use, and develop a list of priority substances that will pose the greatest risk to Norwegian fresh and marine waters over the next three decades. Beyond prioritisation, we will also compare predictions and measure concentrations in Norwegian cities with and without waste water treatment to assess the effectiveness of current techniques.

Conclusion
Finally, I intend to recreate my risk assessment pipeline in a Bayesian context, using Bayesian networks to allow me to quantify uncertainty introduced during the risk assessment process.

Postere i farmakologi (FP)

FP1 Basal farmakologi

Poly ADP-ribose polymerase 7 (PARP7) and mono-ADP-ribosylation regulate Estrogen Receptor α (ERα) signaling

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Background
Breast cancer is the most common cancer in women, and is a serious global health concern. In Norway, breast cancer accounts for 20% of all female cancers and 1/12 women develop the disease before the age of 75. The growth of approximately 70% of breast cancers depends on estrogen and a functional estrogen receptor α (ERα). ER□ is the dominant regulator of estrogen action in breast tissue and mammary development, and the principal therapeutic target for breast cancer treatment. A better understanding of ERα signaling and identification of new proteins and mechanisms that regulate ER could lead to improved treatments for diseases, such as breast cancer. We have previously reported that PARP7, a mono-ADP-ribosyltransferase, acts as a transcriptional co-regulator factor, but its role in ERα signalling is unknown. Here we investigate a novel interplay between PARP7 and ERα in breast cancer cells.

Methods
MCF-7 wild-type and MCF-7 PARP7 knockout cells created by CRISPR-Cas9 gene editing were used in gene expression and western blotting analyses. We also performed ADP-ribosylation assays *in vitro* and identified mono-ADP-ribosylated peptides by mass spectrometry.

Results
CRISPR-mediated PARP7 knockout *in vitro* revealed increased mRNA expression levels of ERα target genes, whereas overexpression of PARP7 decreased ERα levels and activity. Gene expression and ChIP studies revealed that PARP7 mRNA levels were regulated by ERs, and that ERα was recruited to *PARP7*. PARP7 mono-ADP-ribosylated ER□, an affect that was increased in the presence of estrogen. Mass spectrometry studies identified multiple peptides in the N-terminal portion of ERα that were mono-ADP-ribosylated. Based on these findings, we propose a mechanism of action where TIPARP mono-ADP-ribosylates ERα leading to reduced ERα activity.

Conclusion
Taken together, these data illustrate the importance of PARP7 and mono-ADP-ribosylation in the regulation of ERα activity and breast cancer proliferation, suggesting that PARP7 may represent a new therapeutic option for the treatment of this disease.

FP2 Klinisk farmakologi

Effekten av høy dose omega-3 fettsyrer på farmakokinetikken til takrolimus og mykofenolat i nyretransplanterte pasienter

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Bakgrunn
Takrolimus og mykofenolat er en viktig del av den livslange immunosuppressive behandlingen etter en nyretransplantasjon. Målet med behandlingen er å redusere forekomst og alvorlighetsgrad av avstøtning, og riktig plasmakonsentrasjon av legemidlene er avgjørende for effekt. Takrolimus vis er stor farmakokinetisk variasjon, og har smalt terapeutisk vindu. Legemiddelet doseres individuelt, og dosering styres av blodkonsentrasjonsmålinger. Tilskudd av høydose omega-3-fettsyrer kan være gunstig ved nyretransplantasjon. En nyere studie har vist økt overlevelse hos nyretransplanterte pasienter med høyt omega-3-fettsyre konsentrasjon i blodet. I denne studien (AdvaOmega studien) skal effekten av høy dose omega-3 fettsyrer på farmakokinetikken til takrolimus (Advagraf®) og mykofenolat (CellCept®) undersøkes.

Metode
Femten stabile nyretransplanterte som ble behandlet med takrolimus (Advagraf®), mykofenolat og prednisolon ble inkludert i studien. To 8-timers farmakokinetiske undersøkelser ble gjennomført før og etter en 4-ukers behandling med høy dose omega-3. Blodprøver ble tatt 0,15, 0,5, 1, 1,5, 2, 3, 4, 6, og 8 timer etter inntak av takrolimus og mykofenolat. Standard non-kompartment metoder ble brukt for å beregne farmakokinetiske parametere og bioekvivalenskriteriene til EMA ble brukt for å vurdere en mulig farmakokinetisk interaksjon mellom de immunsuppressive legemidlene og omega-3. Takrolimuskonsentrasjoner ble bestemt med en validert UPLC-MS/MS metode. Bioanalytisk metode for bestemmelse av mykofenolat er under utvikling.

Resultat og konklusjon
Tolv nyretransplanterte pasienter med en gjennomsnittsalder på 62 ± 28 år fullførte studien. Foreløpige resultater indikerer at omega-3 tilskudd øker systemisk eksponering av takrolimus med 15 ± 22 %, Det har også blitt utviklet en metode for å måle mykofenolat i plasmaprøver. Denne metoden er under validering og videre arbeid skal bestemme om høy dose omega-3 også påvirker systemisk eksponering av mykofenolat.

Effekt av teriparatid på differensiering og regulering av cysteinproteaser i osteoblaster

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Problemstilling

Osteoporose er en sykdom i skjelettet hvor nedbrytningen går raskere enn nydannelsen av bein. De viktigste cellene som inngår i beinhomeostasen er osteoklaster som bryter ned bein og osteoblaster (OB) som bygger opp bein. Osteoporose kan oppstå ved forskjellige tilstander som skyldes hormonmangel og paratyroideahormon (PTH) er kjent for å regulere beinhomeostasen. Høyt nivå av PTH akselerer beintap, mens lave doser PTH gitt intermitterende kan øke beinmassen. Teriparatid (PTH1-34) brukes som beinformasjonsstimulerende legemiddel ved osteoporose. Den beinoppbyggende effekten av teriparatid blir formidlet av G-proteinavhengig PTH-reseptor-1 i cellemembranen hos OB. Teriparatid øker antall OB og stimulerer beindannelse ved aktivering av eksisterende OB, økt differensiering av stamceller i beinmargen og redusert OB apoptose.

Vår forskningsgruppe har nylig vist at cysteinproteasen legumain (asparaginyl endopeptidase, AEP) hemmer differensiering av stamceller til osteoblaster og *in vivo* beindannelse. Det er ikke kjent om teriparatid har effekt på legumain (eller andre cysteinproteaser) under differensiering av stamceller til osteoblaster. Det var derfor interessant å studere hvilke cellulære effekter teriparatid har på uttrykk, aktivitet og sekresjon av legumain under differensiering av stamceller til osteoblaster.

Metoder

Humane BMSC («bone marrow-derived multipotent stromal (skeletal or mesenchymal) stem cells») stabilt transfektert med katalytisk subenhet av human telomerase reverstranskriptase, ble benyttet som cellemodell. Cellene ble dyrket i 3, 7, og 10 dager i osteblast-induksjonsmedium og behandlet med teriparatid (0, 5, 10, 20, 50 og 100 nM). Sekresjon av legumain til kondisjonert medium ble analysert ved ELISA. Alkalisk fosfataseaktivitet og matriksmineralisering ble målt som markører for osteoblastdifferensiering. Videre ble legumain- og cathepsin B-aktivitet analysert i cellelysat ved spalting av spesifikke fluorescerende peptidsubstrater og proteinuttrykk målt ved immunoblotting.

Resultater

Foreløpige resultater har vist at teriparatid stimulerer osteoblastdifferensiering ved å øke ALP-aktiviteten, men har ingen effekt på beinmineraliseringen i forhold til kontrollceller i løpet av 10 dager. Det var ingen signifikant endring i legumain- eller cathepsinaktivitet eller proteinuttrykk etter behandling med teriparatid i 3, 7 eller 10 dager, og det var heller ingen effekt på legumainsekresjon til kondisjonert medium.

Konklusjon

Foreløpige data har vist at behandling med teriparatid stimulerer differensiering av stamceller til osteoblaster ved å øke aktiviteten av osteoblastmarkøren ALP. Behandling med teriparatid har ingen signifikant effekt på aktivitet eller proteinuttrykk av cysteinproteasene legumain og cathepsin B.

FP4 Klinisk farmakologi

Immunsuppressive legemidler og tarmmikrobiomet: farmakokinetikk- og mikrobiomvariasjon og effektforskjeller

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Problemstilling

Nyretransplanterte trenger livslang immunsuppressiv behandling. Den moderne immunsuppressive behandlingen innebærer en kombinasjon av takrolimus (Tac), prednisolon og mykofenolatmofetil (MMF). Grunnet smale terapeutiske vinduer og stor farmakokinetisk variabilitet benyttes terapeutisk legemiddelmonitorering (TDM) for å justere dosene slik at den systemiske eksponeringen er innenfor de terapeutiske vinduene. Ved å benytte populasjonsfarmakokinetiske modeller kan areal-under-plasmakurve (AUC) predikeres ut fra noen få konsentrasjonsmålinger, dette kan gi en besparelse i både tid og kostnader, og øke måloppnåelsen av TDM.

Etter oral administrering av MMF sees en sekundær topp i plasmakonsentrasjonskurven grunnet enterohepatisk resirkulering. Tarmmikrobiomet er en av årsakene til den enterohepatiske resirkuleringen. Immunsuppressive legemidler endrer mikrobiomet til de transplanterte pasientene, men i hvilken grad det endres er uvisst. Hovedformålet med studien er å undersøke sammenhengen mellom variasjon i mikrobiomet og 12-timers MMF farmakokinetikk. Det skal også utvikles en farmakokinetisk populasjonsmodell for MMF hos nyretransplanterte pasienter.

Metode

En 12-timers farmakokinetikk (PK) undersøkelse av både MMF og Tac vil bli gjort 3-8 uker og 1 år etter nyretransplantasjon. For pasienter som får nyre fra levende donor vil en PK-undersøkelse før transplantasjon utføres i tillegg. Feces prøver vil bli samlet inn før transplantasjon, 1 uke etter transplantasjon og ved 12-timers PK-undersøkelsene. Det skal inkluderes 100 pasienter.

Resultater og konklusjon

Så langt har 5 pasienter gjennomført en PK-undersøkelse 3-6 uker etter transplantasjon.

Videre studier vil vise sammenhengen mellom variasjon i mikrobiomet og 12-timers MMF farmakokinetikk.

Differensiering av RAW264.7 til osteoklaster og karakterisering av cysteinproteaser i osteoklaster

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Problemstilling

Osteoporose er en sykdomstilstand der beinhomeostasen er i ubalanse, hvor beinnedbrytningen ved osteoklaster er større enn beinoppbyggingen ved osteoblaster. Osteoklaster er multinukleære celler som differensierer fra monocytter. Osteoklaster resorberer mineralisert beinvev blant annet ved utskillelse av cysteinproteaser (f.eks. cathepsin K) og matriksmetalloproteaser (f.eks. MMP-9). Det er tidligere rapportert at det C-terminale fragmentet av prolegumain hemmer beinresorpsjonen, men mekanismen er uklar. I dette prosjektet studeres uttrykk og aktivitet av cysteinproteaser (legumain, cathepsin K) og deres endogene inhibitor cystatin E/M under osteoklastdifferensiering. I tillegg studeres effekt av tilsatt prolegumain og cystatin E/M på differensieringen.

Metoder

Cellelinjen RAW264.7 er makrofager fra mus og ble benyttet til osteoklastdifferensiering. Cellene ble stimulert med RANKL (0, 10, 35 og 50 ng/ml) i 6 dager før cellene ble høstet. For studier av tilsatt prolegumain og cystatin E/M under differensiering ble cellene stimulert med kondisjonert medium de 3 siste dagene av differensieringen. Kondisjonerte medier med høyt innhold av prolegumain eller cystatin E/M ble høstet fra henholdsvis M38L-celler (overuttrykker legumain) eller M4C-celler (overuttrykker cystatin E/M). Cellelysater ble brukt til måling av totalproteinkonsentrasjon, legumainaktivitet, cathepsin K-aktivitet og immunoblotting. Legumainaktivitet ble målt ved spalting av et spesifikt fluorescerende peptidsubstrat. Et spesifikt peptidsubstrat for cathepsin K var ikke tilgjengelig og aktiviteten ble derfor estimert ved hjelp av odanacatib, en selektiv cathepsin K inhibitor. «Tartrate-resistant acid phosphatase» (TRAP)-farging ble brukt som markør for påvisning av osteoklaster ved lysmikroskopi.

Resultater

Foreløpige resultater viste at RANKL-stimulering av RAW264,7 ga differensiering til osteoklaster ved TRAP-farging. Det ble observert en reduksjon i legumainaktivitet, men økt ekspresjon av cathepsin K i differensierte osteoklaster. Behandling med prolegumain eller cystatin E/M under differensieringen ga ingen endring i differensiering til osteoklaster. En målemetode for estimering av cathepsin K-aktivitet ble etablert og validert.

Konklusjon

Preliminære analyser har vist RANKL-stimulert differensiering av RAW264,7 makrofager til osteoklaster. Osteoklastene uttrykte mer cathepsin K, men hadde lavere legumainaktiviteten enn makrofager. Tilsetting av prolegumain eller cystatin E/M påvirket ikke differensieringen av osteoklaster.

FP6 Klinisk farmakologi

For høye opioider doser ved behandling av kroniske sterke smerter?

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Problemstilling

I 2008 ble det gjort endringer i blåreseptordningen slik at pasienter med kroniske smerter kunne få forskrevet smertestillende legemidler av spesialist gjennom blåreseptordningen. I 2016 ble blåreseptforskriften endret slik at også fastlegene kunne initiere søknad om individuell refusjon og forskrive opioider på blå resept til pasienter med kroniske sterke smerter. Fastleger kan søke om individuell refusjon for opioider for behandling med opptil 100 mg orale morfinekvivalenter (OMEQ) per dag. Leger ved tverrfaglige smerte-klinikker kan søke om å forskrive daglige mengder over dette, med et øvre tak på 300 mg orale morfinekvivalenter. I Reseptregistret registreres mengde utlevert i definerte døgndoser (DDD). Siden man ikke kan anta at DDD som er fastsatt for de ulike opioidene representerer ekvianalgetiske doser, har vi omregnet volum solgt i DDD til OMEQ. Omregning til OMEQ gjør det mulig å studere samlet utlevert opioid mengde. OMEQ baserer seg på kunnskap om ekvianalgetiske doser ved ulike administrasjonsformer for de ulike opioidene.
Vi har sett nærmere på andel pasienter som fikk opioider på blå resept (-71) som fikk høyere doser enn 300 mg orale morfinekvivalenter per dag.

Metode

Vi har brukt data fra Reseptregisteret som inneholder informasjon om alle legemidler som er forskrevet og utlevert til pasienter utenfor institusjon. Først har vi estimert antall pasienter som fikk høyere doser enn 300 mg orale morfinekvivalenter per dag. Basert på kunnskapen om hva som er de mest brukte opioider har vi estimert morfinekvivalenter basert på total mengde utlevert i antall DDD for alle opioider i fire ulike tenkte situasjoner: 1.alle pasienter brukte bare oksykodon 2.alle pasienter brukte bare tramadol 3.alle pasienter brukte bare transdermal buprenorfin (plaster) 4.Vi antar at 1/3 av mengden brukt opioid var oksykodon, 1/3 tramadol og 1/3 buprenorfin. I omregningen fra DDD til morfinekvivalenter ble det benyttet følgende ekvianalgetiske ratioer oksykodon: 1,6 tramadol: 0,10 buprenorfin:100. I nye analyser vil vi også på individ nivå beregne antall pasienter med slike høye doser. Disse skal sammenlignes med estimatene.

Resultater

I 2018 var det 13 083 pasienter som fikk utlevert opioider på blå resept (refusjonspunkt -71) som også hadde fått dette i 2017. Vi estimerte at omkring 2 % av disse kan ha brukt høyere doser enn den høyeste daglige dosen det er anbefalt at spesialisert forskriver. Dette tilsvarer i underkant av 300 pasienter i 2018. Når vi i tillegg tok hensyn til hvor mye opioid disse pasientene fikk på hvit resept, anslår vi at omkring 4 % av pasientene totalt kan ha fått mer enn 300 mg morfinekvivalenter. Dette tilsvarer i underkant av 550 pasienter.

Konklusjon

Vi har estimert at i 2018 kan i underkant av 300 pasienter ha fått utlevert doser høyere enn 300 mg orale morfinekvivalenter per dag på blå resept og i underkant av 550 pasienter dersom vi i tillegg legger til mengde opioid som pasientene fikk på hvit resept. Hvordan estimatene stemmer med beregninger på individnivå vil bli presentert på poster.

FP7 Basalfarmakologi

Effekt av cysteinproteasen legumain på celleviabilitet etter fotodynamisk terapi

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Problemstilling

Legumain (asparaginyl endopeptidase, AEP) er en lysosomal cysteinprotease som er vist å spille en rolle ved kreftutvikling. Økt forekomst av legumain i svulster assosieres med raskere vekst og økt metastasering. Cystatin E/M, en endogen hemmer av legumain, omtales som en tumorsuppressor. Blokkering av cystatin E/M fører til økt metastasering, blant annet ved brystkreft. Fotodynamisk terapi (PDT) er en behandling ved kreft som baserer seg på at en fotosensitizer vil akkumulere i tumorvev, aktiveres ved lyseksponering og fører til celledød. Enkelte fotosensitizere akkumulerer i endocyttiske vesikler som skades etter lysbehandling. Forskningsgruppen har preliminære data som kan tyde på at legumain påvirker celleviabiliteten, og det er av interesse å undersøke hvordan legumain og cystatin E/M påvirker celleviabilitet etter PDT.

Metoder

Cellelinjene HEK293 og SKOV-3 ble benyttet. HEK293 er humane embryonale nyreepitelceller, og SKOV-3 celler er epitelceller fra adenokarsinom i eggstokk. Cellene ble sådd ut og eksponert for 75 % v/v kondisjonert medium med høyt innhold av prolegumain eller cystatin E/M fra henholdsvis M38L-celler (overuttrykker legumain) eller M4C-celler (overuttrykker cystatin E/M). Cellene ble lysert etter 48 timer og internalisering av prolegumain og cystatin E/M ble målt i cellelysatene ved legumainaktivitetsmåling og immunoblotting. For PDT ble cellene i de siste 18 timene eksponert for fotosensitizeren $TPCS_{2a}$. Deretter ble cellene vasket 2 ganger med PBS, før belysning med blått lys (435 nm). Celleviabiliteten ble målt ved hjelp av MTT-assay 48 timer etter lyseksponeringen.

Resultater

Det ble bekreftet at HEK293 tar opp prolegumain (56 kDa) fra mediet og prosesserer proformen til moden legumain (36 kDa). Redusert prosessering av prolegumain og lavere aktivitet av legumain hos celler eksponert for M4C, tyder på internalisering av cystatin E/M. Enzymaktivitetsmålinger viste at internalisering av prolegumain ga økt legumainaktivitet, mens internalisering av cystatin E/M ga redusert legumainaktivitet. Resultater fra SKOV-3 celler tyder på mer begrenset internalisering av både prolegumain og cystatin E/M, og at prosesseringen av prolegumain til aktiv form skjer i mindre grad i disse cellene sammenlignet med HEK293. Aktivitetsmålinger av SKOV-3 cellelysat viste lavere legumainaktivitet i celler eksponert for cystatin E/M, mens ingen forskjell i aktivitet vises i celler eksponert for prolegumain. Foreløpige resultater fra PDT behandling viser ingen signifikant forskjell i overlevelsen mellom celler eksponert for prolegumain eller cystatin E/M sammenlignet med kontroll.

Konklusjon

Foreløpige data tyder ikke på at cysteinproteasen legumain eller den endogene hemmeren cystatin E/M påvirker celleviabiliteten av verken HEK293 eller SKOV-3 celler etter fotodynamisk terapi.

Stipendmottakere 2020

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Nasra Ciyow
Svava Bjarnadottir
Torill Horvli

Mottakere av stipend må sende kontonummer og adresse til nsft@nsft.net innen 15. februar 2020.