NIHR
Health Protection Research Unit in Environmental Exposures and Health

2020/21 Annual Report

MRC Centre for Environment & Health
UKRI Medical Research Council
Imperial College London

NIHR | Health Protection Research Unit in Environmental Exposures and Health at Imperial College London

NIHR | Health Protection Research Unit in Chemical and Radiation Threats and Hazards at Imperial College London

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1. OVERVIEW

Mission and vision

Since 2014 the National Institute for Health Research (NIHR) funded Health Protection Research Unit (HPRU) in Health Impact of Environmental Hazards (http://hieh.hpru.nihr.ac.uk/), a partnership between King's College London, Imperial College London and Public Health England / UK Health Security Agency[1] (PHE/UKHSA), has provided high quality scientific evidence to support PHE/UKHSA in implementing effective public health interventions to reduce the burden of ill health resulting from environmental exposures. Following the end of the first round of funding on 31st March 2020, the NIHR awarded the partnership a further 5 years of funding (£4M) to further progress this work under a slightly differentially titled HPRU in Environmental Exposures and Health (EEH) that commenced on 1st April 2020.

The mission of the EEH HPRU remains broadly similar to that of its predecessor which is to undertake the highest quality research on the health effects associated with exposure to a range of environmental pollutants, including those in the ambient and indoor settings.

Strategy and objectives

Air pollution, noise, illicit drugs and tobacco are major underlying causes of chronic diseases while emerging exposures such as microplastics and e-cigarettes pose possible risks to human health. Combined these represent a considerable burden to the NHS and public purse with air pollution and tobacco being responsible for approximately 120,000 premature deaths/year in the UK. Many environmental exposures are ubiquitous and there is potential to reduce morbidity and mortality from disease, increase healthy life expectancy, reduce health inequalities from appropriate interventions and controls and improve understanding of the interactions of genetic and environmental factors through understanding and application of the knowledge gained.

Thus, our aims are to improve the understanding of the distribution, determinants and pathways linking these exposures to health effects, to provide scientific evidence that will impact directly on public health practice and policy, and to train the next generation of research leaders in environment and health.

The research programme is organised into four complementary themes focusing on furthering understanding of the risk of ambient and indoor air pollutants on health, by examining a range of adverse endpoints in specific population subgroups (e.g., adverse birth outcomes and cognitive function in school children) and in specific locations (indoor, homes and offices, transport micro-environments including the London Underground).

In addition, we will look at emerging risks including e-cigarettes, microplastics, illicit, licit and herbal drug use and particles resulting from brake and tyre wear.

To achieve this, we utilise recently improved exposure assessment methods including data geocoding and linkage along with ‘omic’ technologies to produce an integrated approach to environmental health research and risk assessment. This approach, across our themes, allows us to focus activity on the established adverse outcome pathway framework that provides a basis in which to assess the weight of data and identify data gaps on the molecular pathway that links exposures to adverse outcomes at the cell, organ and population level. This framework allows the advancement of knowledge to better inform environment and health policy.

Progress/achievements in the first year

Progress with leadership, governance and management arrangements

We are pleased to report that we have established our leadership, governance and management structure as proposed in our application. Full details of the leadership, governance and management arrangements can be found in Annex 1.

Due to the impact of the SARS-CoV2 pandemic we had to move to an online format of meetings for the Management team and Theme Lead meetings. These have worked well and we have been able to

meet more often than perhaps we would have done face to face, and with less downtime resulting from travel.

Implementation of the research strategy

Beyond the obvious impacts of the pandemic and associated closure of research labs most projects have proceeded, albeit some at a slower pace than initially anticipated, such as our investigations into e-cigarettes, and biomonitoring which suffered some delay through not being able to undertake work in the community. Some of the effort on e-cigarettes has been diverted to understanding the interaction of e-cigarettes and SARS-CoV2 at the level of the infection pathway. The COVID-19 pandemic has raised further public health and environmental questions which we have been able to address such as environmental sampling programmes for the virus in public spaces such as the London transport network as well as the impact(s) of the shutdown periods on air quality in London. The pandemic caused the biomonitoring project in Theme I to be postponed for 1 year as the subcontractor, Health Survey for England, could not complete the trial work required. This project was reprofiled to years 2 and 3 and is now underway. One substantial change to strategy occurred in Theme IV where we replaced a planned body of work on fracking (because of the withdrawal of Government support for fracking within the UK) with a project on the health impacts of perfluorinated compounds. These chemicals are of substantial concern due to their widespread use, presence in the environment, multiple types and recognised hazard. This project dovetails with a surveillance project by the Environment Agency for these perfluorinated chemicals in the environment. The project will strengthen the evidence on the risk of PFAS and other poly-fluorinated chemicals in the environment to human health. This work directly supports a front-line requirement.

In responsive work two projects have been undertaken. The first was funded by Defra on the Tolerability to Residual Hazards Following a Chemical Incident which looked at the level of chemicals that could be tolerated in an environment following a contamination incident taking into account analytical considerations. The second examined the links between air pollution, SARS-CoV2 and lower respiratory infections.

Significant challenges faced during 2020-2021

We have faced some challenges and also experienced some benefits as a direct result of the imposed restrictions resulting from the pandemic. Restricted laboratory access in PHE/UKHSA and Imperial delayed practical work and has resulted in some work being reprofiled to years 2 and 3. There were also some delays due to our inability to fill various PhD posts with suitably qualified students. We anticipate catching up on most of the delays by year 3. For knowledge mobilisation and PCIEP there were also some delays and most of this activity had to be moved on-line which, while successful, took more work. Some events in the PCIEP calendar had to be cancelled such as New Scientist Live. Training events took place online and were arguably as successful, perhaps even more so, than face to face with greater participation. There have therefore been some beneficial learning experiences as a result of our experience with on-line formats.

Top three achievements during Year 1

Considering the various challenges resulting from restrictions due to the pandemic, the HPRU has still managed to achieve a great deal including:

- Completion of two pieces of responsive work detailed above and responses to the pandemic including the effects of public transport use, air pollution and e-cigarette co-exposures.
- Work on birth outcomes, impacts on mental health and dementia, as well as the planned evaluations of the impacts of the introduction of London's Ultra Low Emission Zone, all of which have major public health ramifications.
- Setting up of a bioaerosol surveillance program in collaboration with the Centre for Environment, Health and Sustainability (CEHS) at Leicester University, a recipient of a Health Protection Research Unit Development Award from NIHR (Theme I Project 5).

2. RESEARCH THEMES

During its first year the EEH HPRU's research advanced understanding of the causes and effects of key environmental issues affecting public health. Progress has continued in the second year with more recruitment and the impact of delays caused by the pandemic have been reduced.

Theme I: Assessment of Population Exposures

Theme Leads: Emma Marczylo (PHE/UKHSA) and Benjamin Barratt (ICL)

Theme Overview

Both the Chief Medical Officer's 2017 annual report and the Toxic Chemicals in Everyday Life Inquiry Report by the Environmental Audit Committee (EAC) highlighted the need for robust research to quantify UK exposures to environmental hazards. This Theme combines direct and indirect methods of exposure assessment to improve our exposure knowledge. Human biomonitoring (HBM) and air sampling (both outdoor and indoor) will determine exposures to chemicals, metals, gases, nanoparticles, bioaerosols and e-cigarettes within sample populations. Modelling tools will be developed to predict UK population exposures. Data generated from this Theme will inform the epidemiological, mechanistic and responsive projects across themes 2, 3 and 4.

Aims/Objectives

To advance the understanding of exposures to a range of known and emerging environmental toxicants and support interventions to improve public health by improving risk assessment and management.

- Identify and/or characterise exposures of concern within indoor and outdoor environments, including chemicals, gases, bioaerosols and toxicants released from consumer products.
- Undertake human biomonitoring studies to analyse environmental toxicants from a subset of the Health Survey for England cohort and markers of smoking/vaping within at risk groups including pregnant women and mental health patients.
- Model exposures from indoor environments and consumer products to support improved risk assessments and work within the other themes to provide a better understanding of health effects of environmental exposures.

Project 1: Human Biomonitoring (HBM)

Project Leads: Ovnair Sepai, Lorraine Stewart (PHE/UKHSA) and Leon Barron (ICL)
Research Team: Tim Marczylo (PHE/UKHSA)

Summary and project aims

We are exposed to a mixture of chemicals in our everyday life through the foods we eat, the air we breathe, the consumer products we use and the general environment in which we reside, play, learn and work. HBM is an important tool which enables quantification and assessment of human exposures to potential toxicants through the use of biological samples such as blood, urine, saliva and hair. PHE/UKHSA is the UK lead for the Human Biomonitoring Initiative for Europe (HBM4EU), which involves 30 countries across Europe. Many thousands of chemicals are approved for use within the EU and this work will build on the HBM4EU work to determine background chemical exposure levels within the English population. The project is piloting the inclusion of HBM in Health Survey for England (HSfE), hence this phase will use urine and blood samples from English participants to investigate the body burden with respect to per/poly fluoroalkyl substances, flame retardants, Bisphenols, Phthalates/DINCH and metals (including lead). These chemicals of interest have been identified as priority substances in HBM4EU and by other government departments (OGDs). There are several projects in the CRTH HPRU that would benefit from current exposure data, and we are developing links with Themes 2 and 3.

Challenges to be addressed

The data generated from this work will be used to initiate an evolving database of chemical exposures in the English population, addressing the former CMO's recommendation (refer to Annual Report published in March 2018) to *create an English health biomonitoring dataset to indicate human exposure*

to pollutants and health outcomes. Such a database will: 1) greatly enhance PHE/UKHSA's ability to undertake more comprehensive risk assessments during major incidents such as Grenfell in the future; 2) facilitate our understanding of the burden of disease and economic costs due to chemical exposure, thereby enabling the UK Government to develop and implement evidence-based policy to improve and protect public health; 3) help to address the target of "managing exposure to chemicals" in the 25 Year Environment Plan (YEP); and 4) contribute to the monitoring and evaluation of the success of the UK Chemical Strategy.

Year 1 progress and outputs

Note: COVID restrictions delayed the start of the pilot study.

Milestone 1: Engage with NatCen to select a subset of the English cohort recruited to participate in the Health Survey for England (HSfE), and undertake a pilot study to test questionnaire & sampling protocols – Ethical approval for the inclusion of the HBM module in HSfE has been obtained; nurse's questionnaires, online questionnaires and participants leaflets have been finalised; participants for the pilot study have been identified; and preparation of the sampling material is almost complete.
Milestone 2: Identify UK relevant priority toxicants, develop analytical methods and SOPs utilising UKHSA and ICL laboratories – new researcher (PHE/UKHSA) recruited (Mar 2021); priority toxicant lists developed, and UKHSA and ICL labs coordinating method/SOP development.
Milestone 3: Updated questionnaire and SOPs for HBM – Completed.

Future direction and objectives

- Arrange visits to PHE/UKHSA and Imperial analytical laboratories to further exchange knowledge and develop analytical capabilities at both institutions (this is underway).
- Develop a secure database to host the information collated from this work, which will be readily searchable for incident response, government chemical policy development, scientific research and horizon scanning.
- Explore the potential of biomarkers of effects for priority toxicants to better facilitate linking exposures and outcomes, linking with CRTH HPRU.
- Submit the European Partnership for the Assessment of Risks from Chemicals (PARC) project application for EU funding to undertake a second round of sample collection and hopefully include children, who are more susceptible to the effects of chemical exposures (completed).
- Continue to work with OGDs to identify policy relevant areas of work and seek to attract further funding to address these knowledge gaps.

Project 2: Biomarkers in smoking and vaping populations

Project Leads: Tim Marczylo (PHE/UKHSA) and Debbie Robson (KCL)
Research Team: Ann McNeill, Eve Taylor (KCL), Adam Laycock (PHE/UKHSA)

Summary and project aims

In collaboration with KCL, PHE/UKHSA has developed a policy on e-cigarette use for tobacco harm reduction. This project will address some outstanding safety and behavioural issues associated with e-cigarette use in three at-risk populations: 1) pregnant women, 2) vape shop workers and 3) mental health patients. Characterisation of exposures from e-cigarette use in such vulnerable populations will inform policy and smoking cessation strategies in these populations.

Challenges to be addressed

The potential impact of e-cigarette use compared to tobacco cigarette smoking and the other main harm reduction product nicotine replacement therapy (NRT) on pregnancy remains unknown. A cross-sectional study will determine levels of toxicant markers from different chemical classes in the first trimester of pregnancy including e-cigarette-only, NRT only, smokers, non-smokers/non-vapers and dual user groups. Vape shop workers have been identified as vulnerable because they are often both heavy vapers and exposed to second-hand e-cigarette aerosols within their workplace. A pilot study will determine toxicant biomarker concentrations in these workers. Mental health patients have a far greater incidence of smoking compared with the general public, which contributes to the reduced life expectancy in this population. Few studies have been undertaken to help mental health patients quit

smoking. A pilot study will evaluate the feasibility of e-cigarettes for smoking cessation in such groups and examine for the presence of toxicant biomarkers.

Year 1 progress and outputs

Note: COVID restrictions delayed work, however, milestones remain achievable provided recruitment recommences as planned.

Milestone 1: Recruit and collect samples for mental health patient study and quantify smoking-related biomarkers (Q3 Y2) – PhD student recruited (Oct 2020); clinicians engaged; ethics approved and recruitment will begin once COVID restrictions are lifted; literature review of smoking/vaping-related biomarkers underway to identify those for analysis.
Milestone 2: Quantify smoking-related biomarkers in pregnancy study and submit for publication (Q4 Y2) – Recruitment and sample collection completed; insufficient NRT volunteers to complete group; samples at PHE/UKHSA ready for analyses.

Future direction and objectives

- Submit literature review and pregnancy and mental health patient studies for publication.
- Continue to liaise with the Tobacco Control Programme to inform policy and smoking cessation strategies, particularly within vulnerable populations.
- Apply for additional funding to conduct full studies to follow on from the pilot studies.
- Feed relevant data into the mechanistic e-cigarette work within Theme 3.

Note: The pandemic has restricted the use of vape shops, as well as the recruitment of vape shop workers. Thus, this aspect of the study is on hold until it becomes clear if vape shop culture will return to what it was pre-COVID and vape shop workers remain a vulnerable group.

Project 3: Acute carbon monoxide (CO) exposure

Project Leads: Tim Marczylo (PHE/UKHSA) and Ian Mudway (ICL)
Research Team: Sameirah Macchiarulo (PHE/UKHSA)

Brief summary and aims

Acute CO poisoning is associated with lasting neurotoxicological effects. This Gas Safety Trust funded EDCO study is using patients attending Emergency Departments with symptoms typical of CO exposure to determine exposure prevalence. Untargeted metabolomics will be undertaken to identify better biomarkers of CO exposure. This project will inform policies to mitigate health impacts.

Challenges to be addressed

This project addresses concerns that incidences of CO exposure are poorly diagnosed and consequently under-reported. The study took pace in 4 UK A&E departments using the COMA acronym (Cohabitees also affected, symptoms subside when Outdoors, whether gas boilers have been adequately Maintained and whether there is a functioning CO Alarm present and has it been triggered).

Year 1 progress and outputs

Milestone 1: Complete analysis of plasma samples for smoking status (cotinine) and submit for publication (Q4 Y2) – *Completed.*
Milestone 2: Conduct a non-targeted investigation to identify potential biomarkers of CO exposure in non-smokers and submit for publication (Q4 Y2) – *On-track.*

Future direction and objectives

Once both milestones are completed, we will collaborate with Theme II (Project 4) to translate findings to health studies.

Project 4: Assessing (nano-)particle exposures from consumer products including those using advanced materials

Project Leads: Matthew Wright (PHE/UKHSA) and Ian Mudway (ICL)
Research Team: Adam Laycock, Alison Buckley, Rachel Smith (PHE/UKHSA), Steph Wright (ICL)

Brief summary and aims

Domestic access to consumer products using advanced materials, especially nanomaterials, increases the potential for inhalation exposures to materials with ill-defined hazard profiles. The characteristics of aerosols produced by these materials are not well understood. The objective of this project is to measure the concentrations, chemical content, temporal and size distributions of these aerosols to estimate indoor exposures to inform risk assessments.

Challenges to be addressed

Although there has been some previous work examining inhalation exposures from the use of nanoparticle-containing or 'nano-enabled' consumer products, the rapidly developing market and paucity of relevant information (including market penetration, usage patterns, material/product composition etc.) makes estimating real-world exposures, and hence informing risk assessments, very challenging. This project aims to identify the most important products falling within this broad definition; assess their relevance from a human health perspective with a focus on inhalation exposure; and to gather, via experimental and modelling work as well as data from the literature, the information required to ultimately perform more rigorous exposure and risk assessments for these products, providing context for these exposures within the wider framework of indoor air pollution.

Year 1 progress and outputs

Milestone 1: Review literature and investigate the UK/online market to identify novel nano-containing products, product classes, advanced materials and nanomaterial compositions of interest, and submit results for publication (Q4 Y2) – Updated survey of the UK market for consumer products containing nanomaterials with potential for inhalation exposure during use completed (building on knowledge from the previous HPRU); colloidal spay products and 'nano-enabled' hairdryers identified and samples for characterisation acquired.
Milestone 2: Develop (or identify) suitable facilities and experimental protocols to 'scale-up' from 'small box' aerosol studies to larger chambers and produce outline plan to generate aerosol emission data to be utilised in indoor exposure modelling (Q4 Y2) – Characterisation in our small chamber exposure system will use aerosol size and concentration measurement instrumentation with samples to be collected for offline chemical analysis. This information should allow an 'emission factor' to be estimated for each product, enabling quantitative linkage between these small-scale laboratory studies and 'real-world' use scenario – On-track.
Milestone 3: In collaboration with Theme I Project 6, identify potential approaches to link laboratory studies to realistic exposure estimates for the indoor environment (Q4 Y2) – *On-track*.

Future direction and objectives

- Focus on 'advanced materials' – undertake review of literature, databases, market and ongoing review activities (e.g. OECD horizon-scanning projects) to identify novel product classes and/or nanomaterial compositions of interest, with the ultimate aim of estimating exposures via the inhalation (or other) route(s) and informing risk assessment. A 'watching brief' will be maintained on already-identified product classes to ensure changes in the market and/or regulation of certain product classes or constituents are reflected in future experimental work and exposure/risk assessments.
- Develop, and feed relevant data into, mechanistic work within Theme 3.

Project 5: Bioaerosol quantitation and effects

Project Leads: Pippa Douglas, Emma Marczylo (PHE/UKHSA) and Fred Piel (ICL)
Research Team: Sameirah Macchiarulo (PHE/UKHSA), Muhammed Saleem Khan (ICL)

Brief summary and aims

Previous HPRU studies indicated a need for improved bioaerosol exposure assessment, particularly bioaerosol dispersion models to replace distance as a proxy of exposure, and studies that combine exposure and health outcomes. Fungi are of particular interest as they are present in both outdoor and indoor air and are associated with asthma, allergies and complications in other respiratory diseases. This project will use molecular techniques, including metabarcoding, to better characterise the fungal composition of bioaerosol exposures within different environments; perform epidemiological studies with better measures models of bioaerosol exposure and determine cellular responses to fungal bioaerosols *in vitro*.

Challenges to be addressed

Bioaerosols, including fungal spores, their fragments and/or by-products, are being increasingly recognised as components of both outdoor and indoor environments that can impact health. Unlike the majority of other air pollutants, they can offer health benefits, since diverse biological exposures in early life help shape development of a functional immune system. The challenge is understanding which components in what contexts induce benefits *vs* harms. In order to do this, we need to better characterise what we are exposed to in different environments, the cellular responses to bioaerosol exposures, and associations between specific exposures and outcomes.

Year 1 progress and outputs

Milestone 1: Review the literature on the cellular responses to fungal exposures and submit for publication (Q3 Y2) - New researcher (PHE/UKHSA) recruited (Jan 2021); preliminary review of literature identified knowledge gaps and more focussed search terms.
Milestone 2: Set up and test bioaerosol sampling equipment at UKHSA and ICL and collect daily air samples over the course of 12 months at both UKHSA and ICL, and in collaboration with HPRU at UoL (Q4 Y2) – sampling equipment up and running at UKHSA and UoL; delayed by restricted building access at ICL.
Milestone 3: Perform an epidemiological study to explore associations between living near to anthropogenic sources of bioaerosols and cystic fibrosis outcomes and submit for publication (Q4 Y2) – study complete and currently being drafted for submission.
*Additional publication on the fungal composition of soils from different urban greenspaces accepted.

Future direction and objectives

- Set up cell models of the upper and lower epithelia of the respiratory tract to explore knowledge gaps in the cellular responses to fungal exposures identified from the literature review in collaboration with Theme 3.
- Characterise bioaerosols collected from different environments, including composting sites and the London Underground (the latter in collaboration with Theme 2).
- Hold bioaerosol focused meeting between PHE/UKHSA, the University of Leicester and Imperial College to discuss areas for collaboration and applications for joint funding.

Project 6: Indoor air pollution

Project Leads: Sani Dimitroulopoulou (PHE/UKHSA) and Ben Barratt (ICL)
Research Team: Tim Marczylo, Christina Mitsakou, Stephanie Osborne, Charlotte Landeg-Cox (PHE/UKHSA), PhD student (ICL)

Brief summary and aims

Indoor air contains particulates, bioaerosols and chemicals that can adversely impact human health. This project will develop a microenvironmental exposure model to predict indoor concentrations of volatile organic compounds (VOCs) and semi volatile organic compounds (SVOCs) in the home environment. Predicted exposures will be compared with experimental indoor VOC and SVOC

measurements for validation. The validation of the modelling tool will be achieved through our HPRU collaboration with the UKRI-funded WellHome project, which will carry out indoor air quality monitoring in 100 homes in West London. PCIEP methods will be used to research public perceptions of exposures and evaluate effective methods to communicate risk.

Challenges to be addressed

Previous studies have identified VOCs and SVOCs in the indoor environment, as being of particular public health concern, however, the lack of documented indoor emission properties for many chemicals as well as the limited data on human exposure routes lead to uncertainties in estimating the associated health risk. The modelling work aims to simulate exposures of different population groups to organic compounds emitted from consumer products in the home.

Year 1 progress and outputs

Milestone 1: Rapid review of VOC and SVOC modelling tools (Q3 Y1) – Completed.
Milestone 2: Complete review of VOC and SVOCs in homes and submit for publication. (Q4 Y2) – Review of VOC sources, concentrations and health impacts in homes has almost finished and drafting of paper will follow; SVOC review has begun.
Milestone 3: Develop a microenvironmental/exposure model for VOCs/SVOCs (Q4 Y2) – VOC equations identified; SVOC modelling has started; PhD studentship re-advertised following unsuccessful initial recruitment.

Future direction and objectives

- Continue with existing milestones.
- Evaluate model performance and refine in collaboration with work in Theme 2.
- Assess risk from exposure to VOCs/SVOCs in homes and submit for publication.
- Explore public perceptions of indoor air pollution and evaluate methods to communicate risk.

Theme II – Air pollution and health

Theme Leads: Heather Walton, Ian Mudway (ICL) and Helen Crabbe (PHE/UKHSA)

Theme Overview

Substantial evidence links air pollution to health impacts at concentrations commonly encountered in the UK. Data is robust for the impacts of fine particulate matter ($PM_{2.5}$) on cardiorespiratory diseases, but emerging evidence has demonstrated associations with adverse birth outcomes, sub-optimal developmental trajectories in children, the early aetiology of disease, impacts on mental health and dementia. If these observations can be shown to be robust and underpinned by causal pathways, they imply a substantial additional burden on population health, experienced across the life course. Addressing the evidence of the impact of air pollution on these emerging areas is the key aim of Theme II. We will do this by understanding the totality of air pollution exposures across the indoor to outdoor continuum in collaboration with Themes I and III.

Aims/Objectives

Over the first two years of the HPRU the major ***short-term*** aims of Theme II are to deliver an updated meta-analysis on the effects of air pollutants on a range of birth outcomes and to extend work examining the links between long-term exposures to air pollution and dementia in support of COMEAP ongoing work in these areas. Through the ***medium-term*** we plan to extend the work on the neurological impacts of air pollution to a wider range of mental health endpoints and to improve exposure assessment, through the development of an integrated indoor exposure model, the development of a national model for ambient metals and an improved understanding in exposures in transport microenvironments. Over the ***longer-term***, we plan to extend work to look at the impact of cognition, across the life-course and to evaluate how changes in pollution exposures resulting from the introduction of Clean Air Zones, impact on a range of health and adverse physiological endpoints. We also plan throughout the lifetime of the HPRU to address the relative hazard of $PM_{2.5}$, primary combustion derived PM and NO_2, using both statistical and biomarker-based approaches.

Project 1: Air pollution and adverse birth outcomes

Project Leads: Rachel B. Smith and Heather Walton (ICL), Pippa Douglas (PHE/UKHSA)
Research Leads: Klea Katsouyanni, Sean Beevers, Mireille Toledano, Bethan Davies (ICL), Valentina Guercio, Karen Exley, (PHE/UKHSA)

Brief summary and aims

Evidence on the impacts of air pollution on birth outcomes is accumulating, but results are inconclusive. Existing meta-analyses are now out of date, often of poor quality and the literature base has expanded rapidly in recent years. An updated meta-analysis is urgently required to inform policy in this emerging area.

Challenges to be addressed

Quantification of the adverse birth outcomes associated with long-term exposures to air pollutants and exposures during pregnancy.

Year 1 progress and outputs

Milestone 1: A master's student has completed a metanalysis of the literature associating $PM_{2.5}$ exposures to term low birth weight (TLBW). An extension of this work is ongoing covering associations with PM_{10}, NO_2 and O_3.

Milestone 2*:* Work is continuing to evaluate the evidence on birth outcomes for COMEAP (report being finalised). To support and extend this activity a PhD student has been appointed to investigate the relationship between air pollution and preterm birth.

Future direction and objectives:

Milestone 3: Work investigating the impact of the ULEZ on birth outcomes, linked to the MRC funded Public Health Impacts of UK's Clean Air Zones project (PHICAZ), will be ongoing over the next year, focusing on the identification of suitable health data sets and linkage to modelled pollutant data.
Milestone 4: Update the TLBW meta-analysis. Publication of the updated metanalysis outlined in M1.

Project 2: Air pollution – impacts on the brain across the life course

Project Leads: Ian Mudway (ICL) and Valentina Guercio (PHE/UKHSA)
Research Team: Sean Beevers, Dave Green, Mireille Toledano, Klea Katsouyanni, Dylan Wood, PhD student (ICL), Tony Fletcher, (PHE/UKHSA)

Brief summary and aims

The impact of air pollution on dementia incidence has been identified as a priority area of research by COMEAP. There is a need to understand the impact of long-term exposures and the underlying causal mechanisms of dementia risk. Impacts on early life cognitive development and mental health into adulthood have also been highlighted. Project 2 will address the neurological impacts of air pollution across the life course, also exploring how air pollution mitigation measures impact on cognition and mental health endpoints, either reflecting planned interventions, such as London's Ultra Low Emission Zone (ULEZ), or unplanned natural experiments, such as the impact of COVID-19 pandemic lockdown on air quality.

Challenges to be addressed

Establishing the impacts of long-term air pollution exposures on a range of neurological endpoints across the life course.

Year 1 progress and outputs

Milestone 1: Appoint a PhD student to expand the modelling capacity within Theme II to include metal exposures, across the UK population for linkage to their neurotoxicological effects. This post has been advertised twice, but we have not identified a suitable candidate. The position will be readvertised in September 2021.

Milestone 2: Undertake an assessment of biomarkers of systemic oxidative stress and neuro-inflammation in the MRC-funded Cognitive Development in the Urban Environment study, linking biomarker concentrations to estimates of short-term exposures in air pollutants using models enhanced to reflect indoor and outdoor exposures.

Milestone 3: Contributions to the forthcoming COMEAP report on air pollution and dementia, as well as the NERC scoping review on the intersection between environmental science and mental health research (https://valuing-nature.net/sites/default/files/documents/VNP27-EnvSciMenHealthReview-A4-88pp%20reduced.pdf). We have completed analysis of the association between traffic-related air pollution with common mental disorders and mental health service use (inpatient days, inpatient events, community mental health team (CMHT) days and CMHT events, cognitive decline, and incident dementia. This work has been supported by linkage of air pollution models to the South East London Community Health Study (SELCoH) study examining common mental disorders, based on a random household survey in Lambeth and Southwark. Results published (doi: 10.1007/s00127-020-01966-x). Linkage of air pollution models to the Clinical Record Interactive Search (CRIS) system at the NIHR Maudsley Biomedical Research Centre has also allowed a retrospective cohort study of case-registry data to examine associations from first contact with psychotic and mood with inpatient days and community mental health service events recorded over 1 and 7-year follow-up periods. Results published (DOI: https://doi.org/10.1192/bjp.2021.119). Work has also been completed examining the associations between incident dementia and cognitive decline in the age population using the English Longitudinal Study of Ageing (ELSA) cohort, with publications planned for year 2. In addition, we have published an analysis of the association between air pollution and adolescent conduct problems in urban children (doi: DOI: 10.1007/s00127-021-02097-7) and produced an updated systemic review on the air pollution and dementia (DOI: 10.1159/000515394).

Milestone 4: In year 1 we obtained funding from The Bart's charity (https://bartslifesciences.org/new-research-to-study-impact-of-air-pollution-on-childrens-brain-development-and-mental-health/) to include cognitive function testing in primary school aged children within the NIHR funded Children's Health in London and Luton (CHILL) cohort. As of the end of the 2020/21 academic year, cognitive function tests had been performed on 1288 children across 51 schools, with additional data on mental health collected using the Revised Child Anxiety and Depression Scale (RCADS) and strengths and difficulties questionnaire (SDQ). We are working with the 'Born in Bradford study' to ensure wider integration of our findings into other relevant cohorts. Repeat cognition tests will be performed next year and we have worked with QMUL's Centre of the Cell to design in school teaching sessions on air pollution and cognition that will be performed alongside this assessment.

Future direction and objectives

- Publication of papers arising out of the work outlined in milestones 1, 2 and 3.
- Seeking additional funding to support extension of our work on the CRIS data base, to consider service use over the periods of the ULEZ introduction and the lockdown periods during the pandemic and to allow linkage to other cohorts addressing adolescent mental health.
- To promote stronger linkages with Theme III we have recently received funding from NERC UKRI to explore the mechanistic basis for the neurological associations observed in the epidemiological literature: Hazard Identification Platform to Assess the Health Impacts associated with Indoor and Outdoor Air Pollutant Exposures: (https://gtr.ukri.org/projects?ref=NE%2FW00206X%2F1).

Project 3. Indoor exposures and health

Project Leads: Ben Barratt (ICL) and Helen Crabbe (PHE/UKHSA)
Research Team: Fred Piel (ICL) Giovanni Leonardi, (PHE/UKHSA)

Brief summary and aims

Indoor air exposure models for studies of population health effects have been developed which include built environment characteristics, analysis of exposure measurement error, and measures of population movements (time activity patterns and population estimates). We will develop an integrated exposure model based on the above elements, for indoor air pollutants, namely CO and emerging chemicals (VOCs). The application of such models can be validated with measurements and then applied to

epidemiological analyses, building on previous CO work. As this project is dependent on outputs from other projects underway, notably Theme I Project 6, activities in the first two years will focus on preparation and review of existing resources, with fieldwork and analysis following in Years 3-5.

Challenges to be addressed

An improved understanding of population exposures across the indoor and outdoor continuum to support health evaluations.

Progress and outputs:

Milestone 1: A review has been undertaken to identify suitable public health and exposure datasets for integration with enhanced indoor exposure models. Additional funding to support this work was obtained as part of the UKRI Strategic Priorities Fund: West London Healthy Home and Environment Study (WellHome - https://gtr.ukri.org/projects?ref=NE%2FW002116%2F1). This activity will also be supported by ongoing work funded by NERC as part of the APEx project (An Air Pollution Exposure model to integrate protection of vulnerable groups into the UK Clean Air Programme - http://gotw.nerc.ac.uk/list_full.asp?pcode=NE%2FT001887%2F1&cookieConsent=A)

Future direction and objectives

Milestone 2: Test available CO and VOC sensors for evaluation fieldwork.
Milestone 3: A systematic review of published studies that evaluate indoor exposure models relevant to CO and VOCs in health studies.

Project 4. Exposures in transport microenvironments and their impact on health

Project Leads: Dave Green (ICL) and Emma Marczylo (PHE/UKHSA)
Research Team: Rudy Sinharay, Ian Mudway, Ben Barratt (ICL)

Brief summary and aims

This project will quantify exposures to primary particulate matter (from vehicular combustion and abrasion processes) and co-pollutant gases in transport microenvironments and assess their impact on health and acute adverse biological responses. It will initiate work investigating the acute effects of air pollution on the London Underground in sensitive sub-populations, as well as expand on previous personal monitoring studies highlighting the high exposures to diesel fumes experienced by professional drivers.

Challenges to be addressed

Quantifying pollutant exposures and health impacts associated with high pollutant transport microenvironments.

Progress and outputs:

Milestone 1: We have published a review examining the exposure of professional drivers to diesel exhaust fumes (https://doi.org/10.1007/s11869-021-01048-0). In addition, we have published a series of papers examining exposures in drivers as part of the Institution of Occupational Safety and Health (IOSH) funded Driver Diesel Exposure Mitigation Study (DEMiSt) (DOI: 10.1016/j.envint.2021.106532; DOI: 10.1016/j.envres.2021.110736; doi.org/10.3390/atmos11070749). The data arising from these studies, including recommendations for reducing occupational exposures to diesel in drivers have now been integrated into IOSH's *"No Time To Lose"* campaign to reduce occupational cancer, ensuring their dissemination to a wide international audience. The IOSH final report is available: https://iosh.com/media/8902/the-driver-diesel-exposure-mitigation-study-full-report.pdf, with the co-designed education materials also online: https://www.notimetolose.org.uk/free-resources/diesel-pack-taster/. The DEMiSt data are currently used as part of the USA Health Effects Institute funded study*," Investigating the consequences of Measurement Error of gradually more sophisticated long-term personal exposure models in assessing health effects: the LOndon Study (MELONS)*", to support the development of sophisticated exposure models that take account of the mobility of the population (https://www.healtheffects.org/research/ongoing-research/investigating-consequences-measurement-error-gradually-more-sophisticated).

Milestone 2: Ethics has been obtained for a human exposure study, using patients with COPD, on the London underground. This study will perform real time measurements of pollutant exposure and relate them to a range of short term systemic and respiratory physiologic and biochemical endpoints. This work is funded by the MRC, https://gtr.ukri.org/projects?ref=MR%2FS035613%2F1

Milestone 3: Funding obtained from TfL to investigate sickness absences in London Underground workers in relation to their role and likely pollutant exposures.

Milestone 4: Characterisation of air pollution within the London Underground and its impact on commuters, vulnerable groups, and tube workers. Platform monitoring established, with initial deployment at Hampstead Northern Line platform between May – June 21. Measurements now include ozone and PM10 sampling onto sterile filters for determination of airborne microbiota.

Future direction and objectives

- Recruitment of COPD patients for the MRC-funded Underground study has started (Aug 2021) and will be ongoing whilst permissions are sought for the Underground exposures, which have been delayed due to COVID-19 restrictions on the network.
- Publish a paper on airway metals deposition in individuals on tube platforms by the close of the second year of the HPRU.
- Whilst the DEMiSt study has completed, we are currently seeking funds to extend this work to examine in vehicle exposures amongst drivers of diesel and electric vehicles.

Project 5: Disentangling effects of NO_2 and $PM_{2.5}$ in time-series analysis

Project Leads: Dave Green (ICL) and Emma Marczylo (PHE/UKHSA)
Research Team: Heather Walton, Klea Katsouyanni, Dimitris Evangelopoulos, PhD student (ICL) Karen, Exley, Helen Crabbe (PHE/UKHSA)

Brief summary and aims

Effects of NO_2 and $PM_{2.5}$ are difficult to disentangle but in recent years, with the introduction of particle traps, the ratio of NO_2 and $PM_{2.5}$ has been changing. If the associations for NO_2 are an indicator for particulate matter, rather than a direct effect, the changing ratio should lead to a change in the time-series coefficient for NO_2. The ratios with $PM_{2.5}$ components may also have changed in different ways e.g. ultrafine particles dropped sharply with lowering sulphur content in fuel. This project complements the project on comparative toxicological potency of NO_2 and PM in Theme III and extends previous HPRU work on measurement error and multi-pollutant models for NO_2 and $PM_{2.5}$. This project will dovetail with Theme III Project 5 which is undertaking a similar laboratory-based study.

Challenges to be addressed

The relative hazard of NO2, PM2.5 and primary combustion derived particles

Progress and outputs

A PhD student to take forward this activity had been appointed but they subsequently withdrew.

Future direction and objectives

The studentship will be readvertised in September 2021 for a January 2022 start.

Theme III - Biomarkers of exposure and effect

Theme Leads: Catherine Hawrylowicz (KCL) and Martin Leonard (PHE/UKHSA)

Theme overview

Research in this Theme will use a 'whole systems' approach to study the mechanistic pathways linking ambient air pollution exposure to disease outcomes. It will involve metabolic phenotyping technologies (metabolomics) that are powerful tools to capture information on a range of toxicological and disease processes. As exhaust emission controls take effect, non-exhaust emissions from brakes and tyres are

drawing increasing attention. Research on the health impacts of these emissions will provide information requested by COMEAP. This year a UK coroner's report for the first-time cited Air Pollution as a significant contributory factor to both the induction and exacerbations of asthma that caused a child's death. Theme III will also focus on understanding the mechanistic linkage between air pollution and asthma. Finally, our work on e-cigarettes and advanced materials will fulfil PHE/UKHSA requirements in these important areas.

Aims/Objectives

- Identify biomarkers following acute exposure to different air pollutants and define whether they discriminate between different sources.
- Examine non-exhaust PM emissions (brake, tyre and road wear) for toxicological impact in the lung and investigate the relative toxicities of exhaust PM and NO2.
- Investigate different air pollutant components for their influence on asthma and mechanisms of allergy?
- Determine the relative toxicities of e-cigarette components?

Project 1 - Understanding key molecular events following fibre and combustion particle pollutant exposure

Project Leads: Frank Kelly, Paul Elliott, Ian Mudway (ICL), Liza Selly, Anne Willis (UoC)
Research Team: Yiqun Han, Hanbin Zhang, Queenie Chan (ICL)

Brief summary and aims

There is an incomplete understanding of the initial biochemical and physiological disturbances related to pollutant exposure that drive the causal adverse outcome pathways to disease and disease exacerbation. These pathway data are necessary to strengthen the causal basis for the epidemiological findings of an association between air pollution and disease outcomes and disease interventions. We will use multivariate metabolic phenotyping to discover novel blood-based markers of air pollution exposures and discern causal pathways (asbestos, diesel exhaust, wood smoke).

Challenges to be addressed

- Objective 1: From appropriate epidemiological studies obtain biomarker information for the association between air pollution and disease outcomes and disease interventions.
- Objective 2: Identification of pathways that are disrupted by wood smoke exposure in human bronchial tissue and publish findings.
- Objective 3: Publish manuscript detailing potential mechanisms of aviation UFP toxicity as established via human urinary metabolomics.

Year 1 Progress and outputs

Objective 1: Delayed due to COVID restrictions. Blood plasma samples from diesel, biodiesel and woodsmoke human exposures now undergoing metabolomic and lipidomic analysis. DNA samples have been collected for epigenetic analysis as part of the DREaM study. Air quality models to support linkage of the observed methylation patterns for 2018 and 2019 are now available.
Objective 2: Bronchial lavage and bronchial biopsy samples collected after air and woodsmoke challenge from the University of Umea have been transferred to UoC for analysis. A workflow for preparing bronchial wash for proteomic analysis has been optimised and is awaiting preliminary mass spectrometry profiling results. Library preparation is underway for RNA extracted from bronchial biopsies. Dendritic, neutrophil and lymphocyte responses to urban and rural samples (the latter reflecting crop burning) from Thailand currently being analysed as part of a British Council funded study.
Objective 3: Publish manuscript detailing potential mechanisms of aviation UFP toxicity as established via human urinary metabolomics (Q2, Y2). Results presented to Dutch parliament and published: https://doi.org/10.1016/j.ijheh.2021.113803

Future direction and objectives

The objectives remain unchanged as detailed above and will be progressed further over the coming year.

Project 2 - Health Effects of non-combustion particles

Project Leads: Ian Mudway (ICL), Liza Selly, Adam Boies (UoC)
Research Team: Marion MacFarlane, PhD student (UoC), Rachel Smith (PHE/UKHSA)

Brief summary and aims

Changes in the traffic fleet are leading to alterations in the types of airborne particles. To date, the major public health focus has been on exhaust particles. As these decrease, focus is changing to particles from tyre, brake, and road wear. These particles are generated from both electric and combustion vehicles and they have a different composition from combustion particles and thus may have different health effects. This project will use *in vitro* models to examine the effects of non-exhaust particles on pulmonary immunity, with focus on macrophage and dendritic cell function.

Challenges to be addressed

- Objective 1: Establish doses of non-combustion derived PM which adversely impact innate immune function, including the inhibition of bacterial phagocytosis by macrophages, assess the mechanisms of inhibition of bacterial phagocytosis and publish findings.
- Objective 2: Examine the mechanisms (focus on metals and oxidative stress) of immunotoxicity of coarse mode PM constituents derived from brake wear (Cu, Sb and Ba), general metal abrasion (Fe, Mn and V) and road dust re-suspension (Ca) on the activation of airway immune cells in comparison to ambient $PM_{2.5}$ and PM_{10} and publish findings.
- Objective 3: Publish peer review article synthesising toxicological and epidemiological evidence on the potential adverse effects of non-exhaust PM.

Year 1 Progress and outputs

Objective 1: Ongoing. *In vitro* work with brake abrasion dust ongoing. Proteomic analysis of RAW 264.7 following low dose exposure to brake dust (6 µg/ml) shows onset of responses associated with altered metal homeostasis and disruption of ETC, NFkB signalling, altered transcriptional and translational control and cell cycle arrest. 2D-TEM indicates that pseudopodia formation is impaired in brake dust treated cells during *S. aureus* infection. Response validation in the presence of metal chelators and NAC is underway as well as transcriptomic analysis.
Objective 2: Ongoing. Work on dendritic cell responses complete. Papers being drafted for submission by the end of Q2.
Objective 3: Ongoing. Work on a review on the epidemiological and toxicological evidence on the potential adverse effects of non-exhaust PM is ongoing, review of literature complete and first draft being amended.

Future direction and objectives

The objectives remain unchanged as detailed above and will be progressed further over the coming year.

Project 3 - The role of the AhR in Asthma

Project Leads: Kasia Hawrylowicz (KCL), Ian Mudway (ICL), Rachel Smith, Martin Leonard, Tim Gant (PHE/UKHSA)
Research Team: Research Associate (PHE/UKSHA)

Brief summary and aims

To test a range of PM samples for their effects in humans to understand components that drive inappropriate inflammatory responses and how this relates to allergy and asthma impact. This will be associated with PM compositional data in order to identify relevant signalling pathways and explore potential mediators that may mitigate detrimental PM effects.

Challenges to be addressed

- Objective 1: Update our literature review on immune studies of real-world PM effects on various cell types and relevant signalling pathways and publish.
- Objective 2: Establish *in vitro* single cell types (BECs, neutrophils, dendritic cells, monocytes/macrophages) and co-culture systems to assess the impact of different PM samples

(including different biodiesel exhaust materials) to influence inflammatory responses (activation markers, soluble mediator release) and gene expression.
- Objective 3: Establish role of AhR and other signalling pathways, identified in M2, using specific inhibitors, antagonists etc. in in-vitro models and publish results. (Q2 Y2). Pending recruitment of a PhD student.

Year 1 Progress and outputs

(Note: Progress constrained by COVID restrictions, delayed by approximately 6 months).

Objective 1: Review published. doi: 10.1016/j.freeradbiomed.2020.01.179
Objective 2: Protocols have been established and cultures of primary airway epithelial and monocyte derived immune cells have commenced. Training of new staff member at PHE/UKHSA has also been carried out to progress this work. Biodiesel and fossil exhaust particulate material has been collected. At KCL, dendritic cell pre-treatment with London-derived PM_{10} and $PM_{2.5}$ samples was shown to induce a pro-inflammatory Th17 response, which is associated with severe and treatment refractory asthma.
Objective 3: A role of the AhR pathway in the DC-induced pro-inflammatory Th17 response is indicated by upregulation of AhR expression by T cells, as well as inhibition of T cell proliferation and expression of Th17-associated cytokines in the presence of an AhR antagonist (CH223191).

Future direction and objectives

The objectives remain unchanged and will be progressed further over the coming year.

Project 4 - E-cigarette toxicity and health effects from second-hand exposures

Project Leads: Tim Marczylo, Matthew Wright (PHE/UKHSA), Ann McNeill (KCL)
Research Team: PhD Student (PHE/UKHSA), Joseph Levermore (ICL), P

Brief summary and aims

Knowledge gaps exist around the toxicity of e-cigarette components, especially around flavour chemicals that are considered as safe based only on oral toxicology data. Toxicity to human airway cells will be investigated by combining air-liquid interface exposure and high-throughput toxicity screening assays. This work will be undertaken by a PHE/UKHSA funded PhD student. Additional studies will evaluate the contributions of e-cigarette device characteristics (coil age, temperature settings, coil resistance etc.) and ageing to aerosol characteristics. Characterisation will include analysis of aerosol (number concentration and size distribution) and determining the concentrations of nicotine, VOCs, metals and flavour compounds in air and deposited on surfaces. Using these analyses estimate theoretical quantities and location of aerosol deposited within the lung.

Challenges addressed

- Objective 1: Establish protocol for conducting laboratory studies of aerosol characteristics generated by e-cigarettes with different device characteristics and publish data.
- Objective 2: Write a review of e-cigarette flavour toxicity and publish manuscript.
- Objective 3: Conduct laboratory studies to determine the effects of coil ageing on toxicant generation and aerosol characteristics.
- Objective 4: Establish high-throughput *in vitro* toxicity screening of flavoured e-liquids (aerosol condensates) in human airway epithelial cells.

Year 1 Progress and outputs

(Note: Progress has been severely hampered by COVID. Limited progress made on Objectives 1+3 because of restricted access to facilities to conduct these studies. Plans in place to accelerate work and catchup in years 2&3).

Objective 1: Complete.
Objective 2: Ongoing. Well underway with comments now on third draft
Objective 4: Ongoing. Making good progress with high-throughput methods established for cell counting, cytotoxicity and viability. The majority of flavour categories have been investigated and we are now incorporating nicotine to investigate any synergistic effects.

Future direction and objectives

The objectives remain unchanged as detailed above and will be progressed further over the coming year.

Project 5 - Improved *in vitro* systems for evaluating and comparing inhalation toxicity of air pollutants including NO2 and PM

Project Leads: Rachel Smith, Martin Leonard (PHE/UKHSA), Heather Walton (ICL)
Research Team: Chang Guo, Alison Buckley, Postdoc (PHE/UKHSA)

Brief summary and aims

Build on previous HPRU networks, capitalising on the novel systems developed in the toxicological assessment of particulates and *in vitro* cell systems to investigate the mechanistic basis of the adverse health effects of combustion derived particulates and NO2, that are currently ill-understood and difficult to separate in epidemiological studies. These novel systems have many advantages in terms of achieving more realistic exposure modalities (e.g. ALI aerosol exposure) and biological relevance (e.g. co-culture models). Comparative toxicology using these approaches will allow measured/considered judgement on the plausibility and likely size of possible mechanistic effects, to include lung inflammation, oxidative stress, aging, carcinogenicity potential and innate immunity governing adaptive immune responses to allergens. The initial part of this project will focus on establishing, characterising and validating the laboratory conditions for such combinatorial experiments to take place.

Challenges to be addressed

- Objective 1: Commence a literature review focussed on toxicological assessments and models used to examine pollutant mixtures and gases such as PM and NO2 in respiratory disease including allergy and asthma.
- Objective 2: Establish *in vitro* systems to carry out exposures of pollutant gases, allergens and particulates alone and in combination. Establish methods of analysis (standard biochemical and high content approaches) to maximise mechanistic information that can be gathered from molecular endpoint analysis.
- Objective 3: Complete pilot cell exposure studies investigating acute effects of NO2 and combustion derived PM on cellular homeostasis.

Year 1 Progress and outputs

(Note: Progress constrained by COVID restrictions introducing a delay of approximately 6 months).

Objective 1: This is in the planning stage and will be progressed over the coming year
Objective 2: PHE/UKHSA capital funding successfully acquired for exposure system development, components received and in process of system set-up.
Objective 3: Primary airway epithelial ALI cultures have been established for use in the gaseous exposure system.

Future direction and objectives

The objectives remain unchanged and will be progressed further over the coming year.

Project 6 – Use of improved *in vitro* systems to evaluate the mechanisms of toxicity and their relative significance for realistic inhalation exposures to advanced materials including nanomaterials

Project Leads: Rachel Smith and Martin Leonard (PHE/UKHSA), Stephanie Wright (ICL)
Research Team: Chang Guo, Alison Buckley (PHE/UKHSA), Stephanie Wright (ICL)

Brief summary and aims

Uncertainties remain about the potential health impact of nanomaterials and other advanced materials, especially at environmentally relevant levels. This work commenced in the previous HPRU and the intention is to extend this. Using established cellular models and exposure systems further advanced

under Project 5, the size of possible mechanistic effects, to include lung inflammation, oxidative stress, aging, carcinogenicity potential and innate immunity governing adaptive immune responses to allergens, in response to a number of relevant materials will be evaluated. Attempts to classify materials into response type groups will be made to assist in supporting future read-across approaches for regulatory control. With its focus on mechanistic toxicity and inhaled materials the project has many synergies with projects in Theme III and will have useful input on materials and exposure levels from Theme I Project 4.

Challenges to be addressed

- Objective 1: Complete characterisation of the exposure system for cerium dioxide nanoparticles (CeO2NP) and *in vitro* exposure studies and publish findings.
- Objective 2: Complete characterisation of the exposure system for additional material nanoparticles and *in vitro* exposure toxicity studies and publish findings.

Year 1 Progress and outputs

(Note: Progress constrained by COVID restrictions and consumable supply issues introducing a delay of approximately 6 months).

Objective 1: Ongoing. Characterisation of aerosol exposure air liquid interface system completed for CeO2 nanoparticle deposition using ICP-MS and laser ablation ICP-MS, defining conditions for homogeneous exposure, and baseline characterisation of cellular toxicity effects of air flows and other system characterisation commenced.
Objective 2: Work on this objective has been delayed as indicated above.

Future direction and objectives

The objectives remain unchanged as detailed above and will be progressed further over the coming year.

Theme IV: Emerging Environmental Issues and Preparedness

Theme Leads: Tim Marczylo (PHE/UKHSA), Stephanie Wright (ICL)

Theme overview and objectives

Theme IV has a diverse portfolio of projects under the umbrella of emerging hazards and preparedness and aims to address current issues of public concern. Across the theme projects there is an initial focus on information gathering and the writing of reviews to identify key knowledge gaps that will drive the latter stages of this theme. This theme also includes a 20% responsive research capacity which may be utilised to respond quickly to any novel emerging issues. We have replaced a planned body of work on fracking because of the withdrawal of Government support for fracking within the UK and a new project on the health impacts of perfluorinated compounds has been included as a response to concerns raised by Defra and the Environment Agency. The objectives of this theme include gaining a better understanding of:

1. The human health impacts from exposures to perfluorinated chemicals.
2. Develop methods to assess emissions from waste fires and biomass-fuelled power stations.
3. Toxicity of microplastics in *in vitro* respiratory and intestinal models.
4. The effects of environmental exposures on fertility.
5. Using quantification of emerging environmental hazards with an initial focus on fentanyl as a mechanism for emergency preparedness.

Project 1: Human health impacts from exposures to perfluorinated chemicals

Project Leads: Robie Kamanyire, Ovnair Sepai (PHE/UKHSA), Fred Piel (ICL)
Research Team: Leon Barron, Brandon Parkes (ICL)

Summary and aims

Perfluoroalkyls and polyfluoroalkyls (PFAS) are a large class of anthropogenic chemicals, consisting of around 4000 individual compounds that repel water and oils and have been used in a wide range of surface coatings from cooking utensils, food packaging to clothing, furniture and carpets. PFAS are persistent in the environment and some are bio-accumulative. There is limited data on the toxicity for most PFAS and exposure. This project will address this emerging issue.
This project aims to Identify the main UK PFAS chemicals of concern in collaboration with Defra and Environment Agency. Publish a paper on the PFAS, or other poly-fluorinated chemicals, of concern relevant to the UK. Use this knowledge base to review pathways of toxicity of these chemicals to identify those of highest relevance/concern to human health and submit a manuscript for publication.

Challenges to be addressed

To identify the most relevant PFAS for potential detrimental health effects in the UK advising regulators to enable appropriate legislation.

Progress and outputs

As yet, no-one has been recruited to undertake this project.

Future direction and objections

Recruit RA to undertake this work

Project 2: Microplastic toxicity in human *in vitro* models

Project Leads: Stephanie Wright, Frank Kelly (ICL), Tim Gant, Tim Marczylo, Rachel Smith, Matthew Wright (PHE/UKHSA), Marion MacFarlane (UoC)
Research Team: Joseph Levermore(ICL), Lorna Jones, Emma Marczylo, Sameirah Macchiarulo (PHE/UKHSA),

Brief summary and aims

Microplastic particles are a complex pollutant arising from the photochemical degradation and/or mechanical abrasion of plastic materials, including synthetic textiles, throughout their life cycle. Recent discoveries of the contamination of food, drinking water, dust and air by these particles has raised concern for public exposure and subsequent impacts on health, but there is a lack of quantitative data on exposure and hazard due to the infancy of this emerging field. This project aims to characterise and quantify the local toxicity of fully characterised microplastic particles at points of first contact using models for the human airway and intestinal barrier.

Challenges to be addressed

Microplastic particles vary greatly in terms of size, chemical structure and composition however research into their toxicity to-date has largely focused on polystyrene beads, for which the application to environmental microplastic particles is uncertain. We are fabricating microplastic materials from common environmental polymer materials which will be fully characterised by polymer/purity, chemical impurities, additives, size distribution and morphology.
Microplastic particles present a mixture of: poorly soluble low toxicity polymeric particles that can additionally contain/adsorb a plethora of monomers, oligomers, chemical additives, and ambient pollutants. The challenge is to interpret their toxicity in respect of particle, chemical and mixture effects.

Progress and outputs

A literature review on microplastic oral toxicity is in preparation for publication.

Three intestinal cultures of increasing complexity - an epithelial monoculture (Caco2), a mucus-secreting co-culture (HT29-MTX), and a mucus-secreting triple culture with M-cell-like cells – have been established and are being assessed.
The fabrication of reference material is underway and funding to fabricate a national repository of reference material for use in toxicity studies has been secured (~100K). Methods for characterising chemical additives and impurities is being developed using py-GCxGC TOF MS.
In vitro dose-response experiments using Raw 267.4 macrophage-like cells are underway, comparing the effect of different microplastic and non-plastic (cellulose) particles on cytotoxicity and soluble mediator release.

Future direction and objectives

- For the oral exposure route - Establish an *in vitro* alimentary tract model to assess chemical leaching from and degradation of microplastic particles and the effect of the leachables/particles on the intestinal barrier.
- For the air exposure route - Establish cultures of THP-1 and U937 and compare the toxicity of microplastics in these lines to Raw267.4 and determine the relative potency of microplastic particles in ambient PM.

Project 3: Drugs of misuse

Project Leads: Leon Barron (ICL), Tim Marczylo, Tim Gant (PHE/UKHSA)
Research Team: Derryn Grant (ICL), Research Associate (PHE/UKHSA)

Brief summary and project aims

Co-use of fentanyl with heroin substantially increases the risk of overdose and death. Addiction to these prescription opioids is increasing. Fentanyl-related deaths in the UK are relatively rare at around 105 in 2018 when compared with the USA where 55 fentanyl-related deaths/day were reported in 2016. However, there are concerns that incidents in the UK may follow those in USA and this project will investigate the potential use of wastewater sampling to monitor trends in fentanyl use. In addition, fentanyls could potentially be used in a CBRN attack. Establishing capacity through analytical method development for fentanyls and their urinary metabolites at PHE/UKHSA will enable preparedness for such an incident.

The aim is to establish robust analytical techniques for the monitoring of wastewater to detect fentanyls, their metabolites and precursors to enable the rapid detection of any substantive rise in the illegal manufacture and the illicit use of fentanyls in the UK to forewarn against increases in opioid related deaths.

Challenges to be addressed

This project aims to utilise wastewater to enable the identification of changes in trends in use and abuse of fentanyl drugs in the UK. This approach will enable detection of both intentional and non-intentional (when fentanyl is used to adulterate heroin) of fentanyls and may also enable detection and geographical approximation of illegal manufacturing sites for fentanyls.

Progress and outputs

A PhD student (Derryn Grant) was recruited in July 2021 to undertake this project and starts 1st Oct 2021.

Future direction and objectives

- Literature review of usage trends for fentanyl and its analogues and the analytical approaches used for quantitative determination in urine, and wastewater and publication of the findings.
- Subject a range of fentanyl-related substances and their precursors to liver microsomal metabolism, to identify key metabolites for inclusion in wastewater survey.
- Quantitative analytical method development: reoptimize a recently developed method for >100 pharmaceuticals using LC-MS/MS for a suite of prioritised fentanyl-related compounds, identified in Milestone 2 and publication.

- UK-wide wastewater pilot study Utilising samples collected for a nationwide wastewater study in late 2019, and compare these data to that from the USA, Mexico and Colombia for context.

Project 4: Health impact of living near a biomass-fuelled electricity generating installation

Project Leads: Bethan Davies, Fred Piel, Dave Green, Paul Elliott (ICL), Tim Marczylo (PHE/UKHSA)
Research Team: Brandon Parkes (ICL)

Brief summary and aims

The UK is shifting electricity generation towards "renewable" energy sources including biomass. Defra (2017) advise that burning biomass "could have adverse air quality impacts", particularly through PM and NO2 associated health outcomes, including acute exacerbations of asthma and COPD.
We will model the ground-based exposures to air pollutants and investigate potential health impacts near biomass electricity generating installations using spatio-temporal epidemiological methods applied to SAHSU data.

Challenges to be addressed

This project will inform on the potential health impacts on populations living near to biomass electricity generating installation

Progress and outputs

Meetings have been held with the appropriate people at the Environment Agency that has enabled access to inventories of Biomass plants in England, their locations and their generating capacities.

Future direction and objectives

- Literature review of the health impacts of residence in proximity to biomass-fuelled electricity generating installations and publication.
- Identification of biomass-fuelled electricity generating installations in the UK and detail on operation timelines and assessment of population characteristics of people living near and publication.

Project 5: Understanding public exposures to toxicants from waste fires

Project Leads: Alec Dobney, Tim Marczylo, Tim Gant (PHE/UKHSA), Frank Kelly (ICL)
Research Team: Laura Mitchem (PHE/UKHSA)

Brief summary and aims

A current front-line UKHSA issue is understanding the health consequences of waste fires on local populations. Toxicant generation by fires under controlled laboratory conditions is well documented but there is little understanding of the toxicant emissions from waste fire incidents making management challenging.
We will investigate toxicants formed by waste fires to inform the front-line management. In the first year, an evidence review for toxicant generation from waste fires will be conducted and methods to sample and quantify toxicants in air and particulates will be established.

Challenges to be addressed

Improve advice that can be given to the public during and after a waste fire by gaining a better understanding of the harmful exposures generated by different types of waste fires.

Progress and outputs

A systematic review of the literature on toxicants generated during the burning of waste and publication is underway but staff time has been limited due to other commitments.
Analytical methods to quantify some key toxicants (metals PAHs) are established but others to be identified in Deliverable 1 have been delayed.

Future direction and objectives

Evaluate the methods developed for key toxicants in waste fires in a pilot study of a UK waste fire and publication of findings.

Project 6: Air Pollution and infertility

Project Leads: Mireille Toledano, Rachel B. Smith, Sean Beevers, Paul Elliott (ICL), Valentina Guercio, Giovanni Leonardi (PHE/UKHSA)
Research Team: PhD Student (ICL)

Brief summary and aims

The incidence of male and female infertility has increased in recent years. Advanced maternal age is known to be the leading factor responsible but other factors that affect both men and women including air pollution, may contribute. Epidemiological evidence suggests linking exposure to ambient air pollution with fertility disorders in men (i.e. reduced sperm quality) and women (e.g. reduced fecundity demonstrated by time to pregnancy, TTP) is still inconsistent with many study limitations.
We will evaluate the association between exposure to ambient air pollution and reduced fecundity by using UK COSMOS, an ongoing study that provides information on many potential confounding variables.

Challenges to be addressed

Address whether levels of air pollution experienced in the UK contribute to the increasing incidences of male and female infertility

Progress and outputs

As yet a PhD student has not been recruited to this project

Future direction and objectives

- Undertake a critical evaluation of the available epidemiological evidence for the impact of ambient air pollution on fertility disorders in both women and men, to assess state of evidence including mechanistic toxicological pathways and plausibility, identify knowledge gaps and assess whether an updated systematic review/meta-analysis is needed.
- Write analysis plan to investigate the association between exposure to ambient air pollution and TTP in UK COSMOS.
- Dataset preparation and data cleaning of TTP data for subjects included in the UK COSMOS study.
- Publish a report on the state of epidemiological evidence from published systematic reviews/meta-analyses on the relationships between the exposure to ambient air pollution and fertility disorders.

3. TRAINING PROGRAMME

Mission: Our mission is to address the gaps in training available in quantitative data sciences and informatics for the risk assessment of environmental exposures and health impacts. To do this we have established a multidisciplinary doctoral training programme, combining scientific expertise in fundamental toxicological, epidemiological, and environmental research to train the next generation of research leaders in these fields.

Recruitment and appointments: Our recruitment procedure, based on identifying excellent PhD candidates through consistent and inclusive processes encouraging diversity and equality, has enabled us to appoint 3 students and 3 ECRs to the HPRU-EEH. We received applications from 158 candidates, through three competitive rounds of recruitment. Overall, offers were made to 16 candidates (10% success rate).

Training activities: Each of our PhD students are jointly supervised by researchers from the universities and from PHE/UKHSA, to ensure their training reflects both academic and public health perspectives. To support new starters and build a sense of cohort identity, we held two online induction sessions with representatives from all partner institutions. Here, new starters introduced themselves to their peers and were given an overview of the academic career development activities and resources. A buddy scheme was set up, pairing each new PhD student with a current student as a point of contact for informal help and support. We are actively promoting participation in NIHR academy activities, with one of our students attending the NIHR academy training camp in early 2021. Our students and ECRs have also have the opportunity to shadow senior members of our HPRU involved in several national committees (e.g. COT, COMEAP, COMARE).

To promote capacity building and multi-disciplinary career development opportunities, several initiatives have been held jointly with the HPRU-CRTH and the MRC-CEH. These include: creation of a academic career development portal in Microsoft Teams, providing a single point of access to a collection of remote training resources and information on news, events and career opportunities, and a new series of workshops which combine theory and practical sessions to address emerging areas where more capacity is needed (e.g. Machine Learning). EEH HPRU students and ECRs are also invited to attend the journal clubs and seminars series held in the MRC-CEH, providing exposure to diverse topics whilst building their network. All our PhD students primarily based in other institutions have an honorary ICL affiliation so that they can access the wide range of career development opportunities hosted at ICL.

Our annual training event (Mar 29-30 2021), gave our students and ECRs an opportunity to present their research projects as posters or flash oral presentations and to co-chair sessions with some of their peers. Our keynote presentation focused on climate change, an area of development and collaboration for our HPRU. Members of the HPRUs in Environmental Change and Health, in Modelling and Health Economics, and in Respiratory Infections were invited to attend.

An important barrier has been the challenge of interacting, involving and engaging with our cohort of PhD students and ECRs only through online events due to the SARS-CoV-2 pandemic and the uncertainty regarding the length during which restrictions will be in place. Although most of our activities have been highly successful and met our career development objectives. we aim to further increase engagement and involvement of PhD students and ECRs in all our activities.

Impact: One of our students won a writing competition for PHE Day, writing a piece about their project for a lay audience.

Future strategy: Over the coming year, we aim to further advertise and support participation in NIHR academy career development activities, such as SPARC. Second, we want to continue stimulating interactions tailored towards career development with other HPRUs. We started with selected HPRUs (see above) and aim to expand this in the coming year, building on activities of the NIHR academy. Finally, we want to continue building capacity in general quantitative methods, including statistics, big data and coding.

4. PUBLIC AND COMMUNITY INVOLVEMENT, ENGAGEMENT AND PARTICIPATION

Our aim is to engage with and involve the public in a scientific dialogue on environmental health to ensure that the impact of our research extends beyond academic and policy realms and is responsive to the concerns of the public. To this end, we have recently published our Public and Community Involvement Engagement and Participation (PCIEP) strategy developed jointly with the HPRU in Chemical and Radiation Threats and Hazards (CRTH). Our PCIPE Strategy has been informed by the NIHR INVOLVE National Standards for Public Involvement in Research. The following highlights how we have been implementing our strategy.

In our Governance Structures

- We established a joint PCIEP Committee to oversee and advise on the development and implementation of the PCIEP programme.
- Two representatives were identified for each Theme, one from PHE/UKHSA and the other from the partnering universities, to embed PCIPE across the HPRUs. They are responsible for dissemination of PCIEP activities and reporting on progress.
- We established a joint Public and Community Oversight Group (PCOG) with the HPRU-CRTH and the MRC-CEH to advise on the implementation of the PCIEP strategy and on the broader context of the Units' research plans, protocols and materials. We also identified a non-professional PCOG Chairperson who represents this group in the HPRUs Joint Steering Committee meetings, bringing the public perspective to the highest governance structure of these Units.

Working Together

We co-developed the PCIEP Strategy with a group of PCOG members.

Support and Learning

- To build PCIEP capacity and expertise, we are regularly identifying opportunities for training and learning (internally and externally) to share with our researchers and with the PCOG.
- Together with our joint Training & Public Engagement Programme, we conducted sessions with PhD students and Early Career Researchers (ECRs) focusing on the principles and practice of public engagement, highlighting the benefits and rewards of doing public engagement.
- Our PCIEP Coordinator is one of the leaders of the National HPRU Public Patient Involvement and Engagement Network. This has given her the opportunity to share best practice and explore opportunities for collaboration training and funding.

Inclusive Opportunities

We are continually identifying ways to increase diversity and inclusion to allow wider dissemination of information about our research and events to the public and community. We had developed links with various networks and online platforms to engage with difficult to reach groups, e.g., the VOICE Digital Platform and The Young Persons' Advisory Network (YPAN).

Communications

We have been engaging with a variety of audiences through different channels to communicate and to involve the public with our research. This includes the use of media platforms such as our twitter account @HPRU_EEH and our website, and the active participation of many of our researchers in several interviews on newspapers, tv and radio, and as keynote speakers at numerous webinars and workshops.

Capturing and Reporting on Impact

We are working towards embedding PCIEP in our HPRU across all levels with active consultation, collaboration monitoring, reporting, evaluation and learning from the PCIEP activities undertaken in the various research projects. We have been capturing the impact that our activities have on our lay partners and researchers through the use of post event feedback forms. The feedback gathered from the evaluation forms has provided the opportunity for reflection and learning to drive improvement in our future work. We have also developed a public engagement reporting tool for reporting, reflecting and learning. This tool allows us to keep a record of all PCIEP activities undertaken by each of our Themes and to identify which of our themes may need more support in order to actively contribute to the achievement of the strategy objectives.

5. KNOWLEDGE MOBILISATION

Overview

The EEH HPRU recognises the importance of knowledge mobilisation to ensure that funded research is used to benefit health and prosperity. Achieving this is an important goal for both our academic and government partners and aligns well with PHE/UKHSA's remit to provide evidence to inform public health policy, practice and services. This will be achieved in this HPRU by utilising expert knowledge in PHE/UKHSA in the form of Dr David Rhodes, PHE/UKHSA's Director of Environmental Public Health. Dr Rhodes has a background in business development and knowledge management and engages widely across Government and relevant agencies on environmental public health topics. During the first year we recruited a Knowledge Mobilisation Manager, Dr Kerry Broom, to work alongside Dr Rhodes to assist in implementing the knowledge mobilisation activities. This role is shared between the three Environmental HRPUs, (EEH, Chemical and Radiation Threats and Hazards and Environmental Change and Health with an aim to increasing opportunities for impact across the Units. The Knowledge Mobilisation team supports the EEH HPRU to develop and disseminate outputs and assist their transition into application.

Year 1 Progress

Primary stakeholder identification and initial discussions with the Theme Leads have taken place. These discussions identified existing and potential stakeholders, including industry and public liaison activities. These discussions also considered opportunities for interaction with other HPRUs and a number of potential areas of linked interest were identified and are in the process of being followed up; particularly the HPRU in Gastrointestinal Infections and the HPRU in Respiratory Infections relating to Theme IV Project 2 Microplastics and Health. There are existing connections with the Environmental Exposures and Health HPRU. There are also clear links to the UKRI Clean Air Networks in Theme II.

Exploratory discussions have also taken place with the Centre for Environment, Health and Sustainability (CEHS) at Leicester University and areas of potential interest around Bioaerosols and Air Pollution were identified. The Knowledge Mobilisation Manager will continue to liaise with the CEHS to identify areas of mutual benefit. Training on Knowledge Mobilisation to the HPRUs will take place at the September Annual Meeting.

The Knowledge Mobilisation Manager attends the Joint Training Committee Meetings and the Joint Patient and Public Involvement and Engagement Committee meetings. A knowledge mobilisation training session via MS Teams was held for PhD students in July and slides are available on the Teams Training Portal.

The Knowledge Mobilisation Manager attended the Expert Committee on Carcinogenicity as an observer in July to examine the current work programme, meet members and assessors and opportunity to highlight the work of the three environmental HPRUs. There is representation from HPRU staff on the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment. Attendance of the Knowledge Mobilisation Manager as an observer at the Committee on Toxicology and the Committee on Mutagenicity are also planned for the latter half of 2021.

The Knowledge Mobilisation Manager highlighted the work of the three environmental HPRUs at the PHE/UKHSA Environmental Public Health Practice Network in June. Clear areas of interest for PHE/UKHSA were identified for Theme I Population Exposures, and there may also be potential interest with PFAS exposure in Theme II.

The Knowledge Mobilisation Strategy has been developed and published on the HPRU website.

A Science Converge Session was held at PHE/UKHSA CRCE during July to highlight the work of the three environmental HPRUs hosted by CRCE Lead Scientists. Presentations included overviews of the HPRUs and their research.

A section on Knowledge Mobilisation has been published on the HPRU website, and an area within the MS Teams site.

Participation in the pan-HPRU Knowledge Mobilisation network is helping to develop a knowledge mobilisation framework for health protection incorporating learning across KM.

6. COLLABORATION WITH OTHER HPRUs

From commencement of the HPRU-EEH we established a close partnership with the HPRU-CRTH. We set up common governance and management structures. We established a joint Executive Group and Steering Committee, and the Academic Career Development and a PCIEP Committees are jointly led and include representatives from all the partners in both HPRUs. The two external advisory groups, the PCOG and the ISAB, also provide recommendations on the work of both HPRUs.

The joint Academic and Career Development and PCIEP programmes are delivered in a fully integrated way across both HPRUs in order to maximise the use of the available resources and provide a broad range of opportunities for our students, ECRs and more senior researchers. It is our objective to extend the collaboration in these areas to other related HPRUs:

- We invited the NIHR HPRUs in Respiratory Infections, in Modelling and Health Economics and in in Environmental Change and Health (at the London School of Hygiene and Tropical Medicine) to take part in our Inaugural Annual Training Day.

The PCIEP Manager is a member of the Cross-HPRU behavioural science network and is sharing our work and experience in this area.

Together with the other HPRUs hosted at Imperial College (HPRU in Respiratory Infections, HPRU in Healthcare Associated Infections and Antimicrobial Resistance, HPRU in Modelling and Health Economics and HPRU-CRTH) we have been involved in the planning of joint public engagement and outreach events for the next Imperial Festival to be held in late September 2021.

The Knowledge Mobilisation lead has actively participated in the Pan-HPRU Knowledge Mobilisation Network. This network has had regular meetings where best practise is discussed and experiences shared. The Knowledge Mobilisation Manager works across this HPRU, the HPRU-CRTH and the HPRU in Environmental Change and Health facilitating efficient knowledge management, transfer and exchange

Current Collaboration across the HPRU Network
Fungal bioaerosol sampling network in collaboration with the **CEHS at Leicester University** – daily air sampling is being performed at UKHSA and UoL and will shortly commence at ICL. We are exploring the opportunity to form a collaborative network to share data, knowledge and best practice.

Air sampling in transport microenvironments – we are currently exploring opportunities to link with projects involved in characterising exposures in transport microenvironments within the **CEHS at Leicester University** and the **ECH HPRU** with a view to developing collaborative projects and/or mobilising knowledge across multiple HPRUs.

Analysis of fungi and their associated mycotoxins in wastewater – we are discussing options for a pilot study to determine if fungi and/or their mycotoxins can be detected in waste water in collaboration with the **CRTH HPRU**.