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

2021/2022 International Scientific Advisory Board Report

Imperial College London

UK Health Security Agency

KING'S College LONDON

MRC Toxicology Unit

UNIVERSITY OF CAMBRIDGE

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List of Abbreviations

ACDP	Academic career development programme
AML	Acute Myeloid Leukaemia
BEED	Breast-milk, Environment, Early-life and Development
BNFL	British Nuclear Fuels Limited
CASH	Clean Air for Southall and Hayes
CNS	Central Nervous system
COMARE	Committee on Medical Aspects of Radiation in the Environment
COMPEAP	Committee on the Medical Effects of Air Pollutants
COSMOS	Cohort Study of Mobile Phone Use and Health
COT	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
CRTH	Chemical Radiation Threats and Hazards
CWA	Chemical warfare agents
DBPs	Disinfection by-products
DOM	Dissolved organic matter
ECRs	Early-career researchers
EDIC	Equality, Diversity and Inclusion Centre
EEH	Environmental Exposure and Health
EVAR	Endovascular aneurysm repair
FCDO	Foreign, Commonwealth and Development Office
HMEs	Homemade explosives
HPRU	Health Protection Research Unit
HRMS	High resolution mass spectrometry
HTA	High toxicity agents
ICL	Imperial College London
ICRP	International Commission on Radiological Protection
ILs	Ionic liquids
IR	Ionising radiation
ISAB	International Scientific Advisory Board
ISoRED	International Society of Radiation Epidemiology and Dosimetry
KCL	King’s College London
KM	Knowledge mobilisation
KMM	KM Manager
LNHL	Leukaemia and Non-Hodgkins Lymphoma
MRC-CEH	MRC Centre for Environment and Health
MVN	Multivariate normal
MWI	Municipal waste incinerator
NDA	Nuclear Decommissioning Authority
NIHR	National Institute for Health Research
NO	Nitric oxide
NRRW	National Registry for Radiation Workers
NTA	Non-Targeted Analysis
OTA	Ochratoxin A
PAS	Passive air sampler

PCBs	Polychlorinated biphenyls
PCDD/Fs	Polychlorinated dibenzo-dioxins/furans
PCIEP	Public and community involvement, engagement and participation
PCOG	Public and Community Oversight Group
PLS	Partial least square
PSRE	Public Sector Research Establishment
PTFE	Polytetrafluoroethylene
RF-EMF	Radiofrequency electromagnetic fields
SAHSU	Small Area Health Statistics Unit
SCAMP	Study of Cognition, Adolescents and Mobile Phones
SGA	Small for gestational age
SVOC	Semi-volatile organic compounds
TEQs	Toxic equivalent quantities
UC	University of Cambridge
UKHSA	UK Health Security Agency
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation
UV	Ultra-violet
UV-A	Ultraviolet A
UV-B	Ultraviolet B
VOC	Volatile organic compounds
YPAN	The Young Persons' Advisory Network

1. OVERVIEW

Mission and vision

The mission of the National Institute for Health Research (NIHR) Health Protection Research Unit in Chemical and Radiation Threats and Hazards (HPRU-CRTH) is to undertake the highest quality research on the health effects of exposures to hazardous chemicals and radiation to improve assessment, management and control of risk to humans. Our aims are to gain new knowledge on the distribution, determinants, mechanisms and pathways linking these exposures to health effects; to advance our understanding of how the everyday and exceptional contact we have with chemicals and radiation leads to ill health; to strengthen the scientific evidence underpinning public health practice and policy in this area.

Our vision is to establish the HPRU-CRTH as a leading resource for knowledge, expertise and training on today's most serious chemical and radiation threats and hazards, producing evidence to ensure effective protection of the population and to mitigate health inequalities from these exposures.

Strategy and objectives

The HPRU-CRTH brings together leading expertise in epidemiology, public health, biology, chemistry, toxicology, statistics and 'omics' technologies. Our multidisciplinary approach will identify markers of exposure and risk based on mechanistic understanding of disease pathogenesis, integrate these into epidemiological studies and investigate novel approaches to risk assessment, mitigation and health protection. Our research programme is organised into four complementary Themes focusing on exposures to priority hazards, including ionising radiation, electromagnetic fields, ultra-violet light, re-developed brownfield sites, neurotoxins and other high-toxicity chemical agents and drinking water contaminants. Priorities are selected to represent areas of scientific uncertainties and policy concern.

Our strategy will be informed by, and remain responsive to, the priority research needs and evidence gaps in the UK identified in partnership with UK Health Security Agency (UKHSA), other public health agencies, our International Scientific Advisory Board (ISAB), Public and Community Oversight Group (PCOG) and local communities. Particular attention will be given to engaging with the diverse range of communities affected by the hazards under study, training the next generation of research leaders in environment and health and to the translation of scientific findings into policy or commercial exploitation.

Progress/achievements in the last year

This report presents how the HPRU-CRTH successfully continues to deliver on its research programme, producing evidence supporting the protection of public health from chemical and radiation hazards. As we move to more normal post-pandemic ways of working, the HPRU-CRTH has strengthened its collaborative working environment between researchers in cross-disciplinary teams from Imperial College London (ICL), UKHSA, King's College London (KCL) and the University of Cambridge (UC). Close working with the NIHR Health Protection Research Unit in Environmental Exposures and Health at Imperial College London (HPRU-EEH) and the MRC Centre for Environment and Health (MRC-CEH) continues, establishing a centre of excellence in the UK with critical mass and international reach in the relevant research areas. This report is in support of our first face-to-face meeting with the ISAB following an online meeting of the HPRU with the ISAB in September 2021.

Leadership, governance and management arrangements

The over-arching governance structure for the HPRU-CRTH was established in Year 1 in partnership with the HPRU-EEH and MRC-CEH, including an Executive Group, the joint Academic Career Development Committee and the Public and Community Involvement Engagement and Participation (PCIEP) Committee. The two external independent advisory groups: the ISAB and PCOG are overseeing HPRU operations while the PCOG is informing development of the PCIEP strategy.

Changes to CRTH leadership during the last year:

1. Dr Liz Ainsbury has taken over the lead of Theme I and of Projects Theme 1: Project 2 (T1:P2) and T1:P4 following Dr Ken Raj's departure from UKHSA.
2. Dr Tim Marczylo is now sole lead for T4: P2 following the departure of Dr Sam Collins from UKHSA.

3. Dr Eduardo Pombo Seleiro left the post of CRTH Scientific Manager in January 2022. Ms Anastasia Ioakeimidou commenced in the post of CRTH Scientific Manager in June 2022.

Significant developments in implementing the strategy for the Unit

There have been no major changes to our overall research strategy. Work continues to strengthen the research network between UKHSA and academic partners and we are working in close collaboration with the HPRU-EEH.

There was one change to Theme I medium-term objectives: Addition of new work on radiation effects in the lens to T1:P2, reflecting a priority research area identified by the International Commission on Radiation Protection.

Projects in Themes III and IV changed focus:

- T3:P3 – Delays in recruiting a PhD student meant a change in plan to conduct a population-level analysis with sampling carried out under Theme I;
- T3:P5C – work for milestone 2 (M2) is now focused on investigation of the toxicity, including genotoxicity, of herbicide active ingredients and their commercial formulations;
- T4:P1.M1&M2 – research planned on nitric oxide and NOx was dropped due to the impact of the COVID-19 pandemic limiting access to laboratory facilities.

Collaboration continues across all Themes with regular meetings to foster the development of multidisciplinary, multi-partner research teams. In particular, there is collaboration between T2:P3 (Biomarkers of potential chemical exposures in populations living in new housing developments built on brownfield sites), which will complement the activities in T3:P3 (Exposures and health effects near brownfield sites), as well as providing samples relevant to T4:P3 (Detection of Highly Toxic Agents (HTAs) in water).

Top three achievements during 2021-2022

1. T3:P4: Homemade threat agents in wastewater
   We have identified chemical substances found in homemade explosives (HMEs) as part of wastewater analysis for explosives manufacture monitoring, which could only have taken place with NIHR funding. The resultant new database and tools are being used by Government and the intelligence community for the interception of threats in this area.

2. T2:P3 Identification of brownfield sites
   We have completed identification of brownfield sites to facilitate identification of biomarkers of potential chemical exposures in populations living on new housing estates built on such sites. This closely involves local community stakeholders, from the initial planning stages, making this an excellent example of co-production.

3. T2:P1: Contribution to new European Society for Vascular Surgery guidelines for radiation protection for vascular operators and patients.
   This work has drawn both on HPRU expertise and members of the PCOG for a chapter on patient experiences. The anticipated impact is improved radiation practice in vascular settings across Europe and beyond.

Significant challenges in delivering the work programme during 2021-2022

The disruption caused by the COVID-19 pandemic continued to affect the ability to work, particularly for laboratory-based research projects and affected recruitment, but we have not encountered other significant challenges during Year 2. We have largely addressed short-term impacts caused by delays to data access, technical/equipment issues, and staffing shortages, by adjusting recruitment or scientific plans whilst remaining in scope of overall objectives. Our medium and long-term objectives remain on target.

2. RESEARCH THEMES

Theme I – Adverse outcome pathways and exposure-response relationships for ionising and non-ionising radiation

Theme Leads – Liz Ainsbury (UKHSA) and Mireille Toledano (ICL)

Theme I Overview

Human exposures to ionising and non-ionising radiations are ubiquitous. They include natural and man-made sources of ionising radiation, radiofrequency electromagnetic fields (RF-EMF) from telecommunications, and ultra-violet (UV) and visible light exposures (both indoors and outdoors). There is greater awareness in society of the increasing exposure to EMFs, and concerns that they may be a potential cause of ill-health. Research projects in this Theme address the potential health effects - good or bad - of the most prevalent electromagnetic waves that humans are exposed to, including both ionising and non-ionising radiations, the latter including sunlight, mobile phone and radio waves.

Our strategy is to gain improved understanding of these exposures and their effects on health through both epidemiological and mechanistic investigations. Research topics include quantifying cancer risk of populations living near nuclear installations, effects of ionising radiation exposure on circulatory disease and age-related pathologies, health impact of mobile telecommunications usage and assessing the risks and benefits of UV and light exposures on health. We will undertake studies to quantify population and age- and sex-related variation in response.

Objectives

- *Short term:* To update estimates of cancer risks among children living near nuclear installations; to establish human cell models to investigate effects of individual variation, age-at-exposure and cell type, and epigenetic ageing, from ionising radiation exposure; to establish cell-based assays to determine UV and light impacts on cardiometabolic risk using surrogate assays.
- *Medium term:* To obtain quantitative data on the impacts of age-at-exposure and inter-individual variation on IR responses related to circulatory disease and ageing; to improve quantification of possible health impact of mobile telecommunications usage; to improve the evidence base for advice on 'damaging' vs 'healthy' levels of UV/sunlight exposure.
- *Long term:* To describe non-mutational mechanisms of ionising radiation action and identify biomarkers, to understand population variation in response to ionising radiation; to provide clear evidence on the harms, or lack thereof, due to RF-EMF exposure; to provide evidence to refine policy in relation to UV and light exposure.

Progress against objectives

- *Short-term objectives:* The short-term objectives are complete, including surveillance of childhood cancer work (P1), establishment of cellular models to assess cardiovascular responses (P2), data sharing agreements for the large P3 cohorts, and extensive data on nitric acid production in response to UVA and broad-spectrum solar radiation.
- *Medium-term objectives:* There has been excellent progress on medium-term objectives. For P1, publication is expected soon. For P2, age at exposure and circulatory disease has yielded some interesting data, which are being prepared for publication. For the work on the lens, this is a new programme for 2022 onwards, but the experimental work has been initiated. For P3, data sharing agreements are in place, which means fuller analysis can continue apace, and for P4, further work to expand the UV programme and consider the public health impact is progressing well.
- *Long-term objectives:* We are on track to complete the longer-term objectives. This Theme will contribute clear progress both in terms of scientific understanding of the mechanisms and effects of radiation exposure, and also in terms of public health impact. Improved public health communication (e.g. on UV, and non-ionising RF-EMF exposures) and other interventions (based on assessed risks) are expected as a result of this work.

Project 1 – Nuclear installations and childhood cancer

Project Lead – Bethan Davies, Paul Elliott, and Mireille Toledano (ICL)
Research Team – Fred Piel, Daniela Fecht, Aina Roca-Barcelo, Anna Freni Sterrantino, and Marta Blangiardo (ICL), Res. Associate TBA

Summary and aims

Committee on Medical Aspects of Radiation in the Environment (COMARE) maintains an active programme of surveillance of the incidence of childhood cancer in populations living close to nuclear installations. SAHSU have undertaken an independent analysis which has been reported to COMARE.

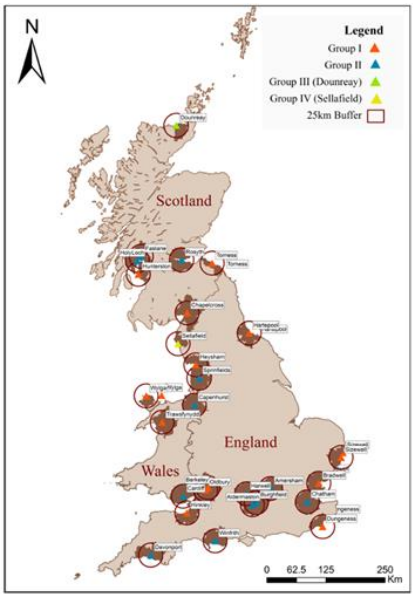
Progress

Background: We present an independent analysis of the contemporary risks of childhood cancer in children living close to nuclear installations.

Methods: We undertook a national retrospective population study in Great Britain, 1995-2016. We used national registry data on incident cases of cancer diagnosed in children under 15 years and categorised them using the International Classification of Childhood Cancer 3rd edition into:

- Leukaemia and Non-Hodgkins Lymphoma (LNHL);
- Central Nervous system (CNS);
- Solid tumours.

We allocated cases to communities within 25km of a nuclear installation or the general population. Nuclear installations were grouped into nuclear power plants (n=13), other nuclear installations (n=13), Sellafield and Dounreay (Figure).



We estimated standardised incidence ratios (SIRs, overall risk) and incidence rate ratios (IRRs, risk by distance) adjusted for community-level deprivation, rural/urban status and population density and performed sensitivity analyses by installation decommissioning status, age and sex.

Conclusions: In this preliminary analysis, we did not find evidence to support an excess risk of childhood cancers (LNHL, CNS or solid tumours) in the population living within 25km of a nuclear installation compared to the rest of the population of Great Britain in the period 1995-2016.

Ethics and data statement: Cancer data can be obtained from the data providers (Public Health England, Welsh Cancer Intelligence and Surveillance Unit and Health Protection Scotland). SAHSU holds approvals both from the London-South East Research Ethics Committee (22/LO/0256) and the Health Research Authority Confidentiality Advisory Group (20/CAG/0028).

Impact

Study has been reported to COMARE; draft manuscript for submission to publication is in process.

Project 2: Ionising radiation adverse outcome pathways for non-cancer disease including circulatory diseases, ageing and cataract

Project Leads – Liz Ainsbury (UKHSA)
Research Team – Christopher Whiteman and Stephen Barnard (UKHSA)

Summary and aims

As two priority research questions under the wider topic of exposure-response relationships for ionising radiation (IR), the key aims are: for circulatory disease, to ascertain whether age (17 to 60 years) at time of exposure is a determinant of an adverse outcome of radiation to the coronary artery, and for radiation cataract, to investigate the role of radiation quality in cataractogenesis.

Selected study – Circulatory disease and aging

Background: The health effects of IR are numerous and work is still ongoing to understand these. In recent years it has become clear from epidemiological as well as from limited mechanistic studies, that cardiovascular effects are associated with radiation exposure. This project seeks to address a key open research question in this area, namely, to obtain quantitative data on the impacts of age-at-exposure and inter-individual variation on IR responses related to circulatory disease and ageing.
Methods: The first part of the project has focused on sourcing, immortalisation and characterisation of human coronary artery endothelial cells from donors of different ages, as well as measurement of radiation-induced adhesiveness and permeability of endothelial cells obtained from these donors.
Results: The initial results from the studies described above are summarised in Figure 1. In brief, age at exposure clearly has an impact on radiation response, but further work is needed.

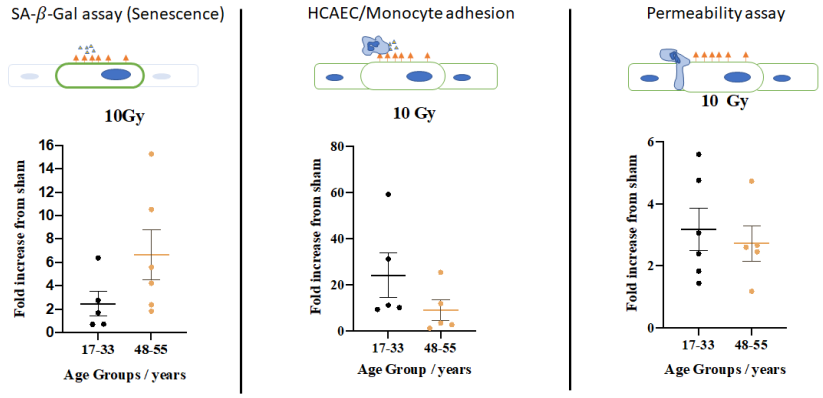


Figure 1. Senescence, adhesion and permeability in human coronary artery endothelial cells.

Conclusions: Further work will include sourcing of a wider range of ages and increasing the number of donors used to look at the atherogenic responses of the cells to IR, investigation of whether the cytokine expression differs after IR exposure depending on the age of the endothelial cell donor, and investigation of the use of senolytics/senomorphics for the modulation of permeability, adhesion, and senescence seen in endothelial cells after IR exposure.

Progress in other project studies/ Other progress

In addition to the above, T1:P2 newly in 2022 includes the milestone M3: Report on the impact of radiation quality on human lens epithelial cell lines in terms of DNA damage, proliferation and morphology. To date, the focus for this work has been on sourcing/establishment of suitable human in vitro cell lines as well as identification of suitable radiation sources. The Milestone is on track for completion in March 2023.

Impact

The long-term objectives for this work are to contribute to understanding of mutational and non-mutational mechanisms of IR action, to better understand population variation in response to IR, as well as to identify biomarkers of the response for cardiovascular disease and cataract. Improved understanding will ultimately contribute to better radiation protection for the UK population.

Publications

A publication on the cardiovascular work is now in preparation.

Project 3 – Health risks associated with mobile phones and police radios

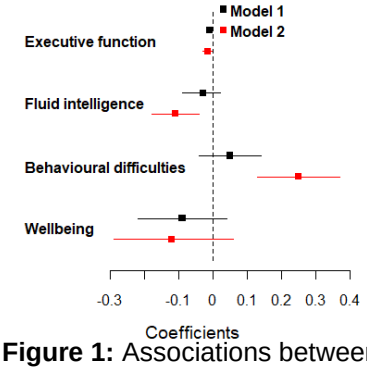
Project Leads –Mireille Toledano and Paul Elliott (ICL)
Research Team – Steven Shen, Rachel Smith, Joel Heller (ICL); Simon Mann (UKHSA)

Summary and aims

Studies on exposure to radiofrequency electromagnetic fields (RF-EMF) emitted by modern mobile communication devices have found no convincing evidence of adverse health effects, however given their almost ubiquitous use it is essential to continue investigation of any potential long-term effects. The aim of this project is to investigate long-term health effects of RF-EMF exposure in some of the largest study cohorts of mobile communications users worldwide.

Selected study – The Study of Cognition, Adolescents and Mobile Phones (SCAMP)

Background: Use of mobile phones by children and young people has increased rapidly over the last decade. Precautionary recommendations to limit children's use of mobile phones (based on concerns about RF-EMF exposures) have not been updated since the Stewart Report of 2000. The SCAMP study aims to investigate the longitudinal associations between use of mobile phones and other wireless devices and neurocognitive and behavioural outcomes during adolescence; specifically, to discern whether any observed associations may be due to RF-EMF exposure to the brain/whole body or digital behaviours regardless of exposure to RF-EMF.
Methods: Between November 2014 and July 2016 (baseline), 6581 Year 7 pupils completed a computerised assessment including questionnaire surveys and a battery of cognitive tests. A total of 4978 pupils completed the follow-up assessment when they were in Year 9/10 between November 2016 and July 2018. Total and organ-specific RF-EMF exposure was estimated using the Integrated Exposure Model. Multi-level linear regression was used to assess the associations between exposure and outcome variables.
Results: RF-EMF exposures to brain and body were associated with lower executive function and fluid intelligence, and greater behavioural difficulties in adolescents. Use of mobile phones and wireless devices excessively was associated with greater behavioural difficulties and lower wellbeing.



Model 1: Exposure at baseline;
Model 2: Average exposure between baseline and follow-up

Adjusted for age, sex, ethnicity, parental occupation, and respective cognitive and behavioural functioning at baseline; School clustering effect was also adjusted

Figure 1: Associations between RF-EMF brain dose and cognitive/behavioural functioning

Conclusions: Our findings suggest potential adverse effect of mobile phone use/RF-EMF exposure on children's cognitive development and behaviours whilst digital behaviours are more strongly related to behavioural functioning and wellbeing than cognitive development.

Progress in other project studies/ Other progress

The Airwave Health Monitoring Study of the British police forces continues to follow up the cohort with respect to use of police radios including linkage to cancer incidence. The COSMOS study is completing analyses of i) brain cancer risk, ii) fertility in relation to use and estimated exposures from mobile phones.

Impact

We anticipate addressing current gaps in scientific evidence and UK policy on children's mobile phone use and health, which will directly inform health policy in England on children's mobile phone use. Our research outputs will also allow review of the current precautionary advice regarding children's mobile phone use, and an update to this advice in the form of new guidelines for young people, and their parents, teachers, and clinicians.

Publications

The primary analyses in SCAMP are now complete, and a manuscript is being drafted.

Project 4 – Potential effects of sunlight on cardiometabolic health

Project Leads – Liz Aisbury and Gareth Hazell (UKHSA)
Research Team – Gareth Hazell and Marina Khazova (UKHSA)

Summary and aims

Epidemiological studies (for example evaluation of sunlight outside of summer months, when the skin is not exposed to sun) suggest sunlight exposure may have beneficial effects on blood pressure. However, problems occur at high dose, most notably skin cancer. This work assesses *in vitro* actual UK sunlight in deriving vaso-protective intermediates, highlighting DNA damaging effects alongside this.

Selected study – Circulatory disease and aging

Background: Ultraviolet A (UV-A) in sunlight may lower blood pressure via enzyme upregulation and breakdown of salts stored within the skin. This study ascertains if it is possible to get a sufficient dose of nitric oxide (NO) from UK sunlight without risk of damage associated with exposure to short wavelength ultraviolet B (UV-B).
Methods: Keratinocytes, endothelial cells and fibroblasts were isolated from neonatal donors, and exposed to actual UK sunlight. This makes the work the first of its kind *in vitro* by not using a simulated light source. Standard gamma-H2AX, and NO assays were carried out as previously described in Hazell et al. 2022. Cell survival assays were carried out alongside to solidify results.
Results: Results are summarised in Figures 1 to 3. In brief, low level UK sunlight exposure at 1 SED (~ 10 min in summer) induced comparable DNA damage to unexposed controls and had no impact on cell survival. Conversely, all doses of sunlight were capable of upregulating NO; surprisingly the biggest elevations in NO were found in non-keratinocyte-based cell lines (not understood to have large stores of salts liberated as NO).

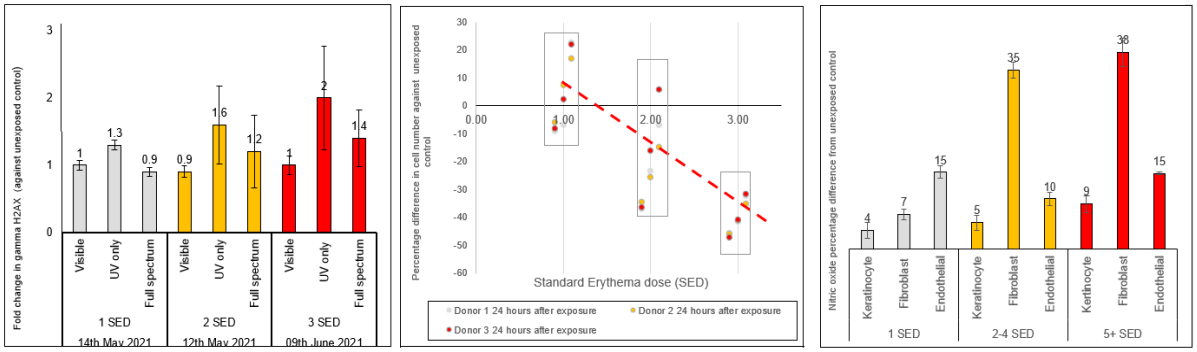


Figure 1-3. DNA damage, cell survival and NO induced following exposures to 1- 5 SED.

Conclusions: UK sunlight could be beneficial to cardiovascular function for the elderly population and others with little adverse effects. Further work is needed, assessing if lower energy UV-A light can induce NO, as here adverse effects are potentially even lower.

Impact

Systemic arterial hypertension is a major risk factor for renal failure, stroke, and peripheral arterial disease, with incidence increasing as we age, this occurs in part due to our body's bioavailability of NO waning in old age. Re-evaluation of health protection policy for at risk demographics may provide benefits and reduce strain on the NHS. Isolation of wavelengths near the visible spectra within a translational light source may also provide additional treatment options.

Publications

Hazell G, Khazova M. UK sunlight exposure friend or foe? 2023– article to be submitted to scientific reports for potential publication, we expect to do this shortly.

Theme II – Biomarkers of exposure, effect and susceptibility to chemical and radiation exposures

Theme Leads – Marc Chadeau-Hyam (ICL) and Christophe Badie (UKHSA)

Theme II Overview

The overarching aim of this Theme is to adopt an exposome-based approach to the characterisation of the effects of exposures to chemicals and radiation. This approach will offer new insights into the internal and molecular response to such exposures and will allow us to: i) identify and validate biomarkers of exposure, early and long-term effects (such as toxicity and carcinogenesis) and susceptibility, ii) identify potential mechanisms involved, and iii) improve our understanding of causal pathways to evaluate their subsequent effects on health and ageing. These studies will use existing large and well-established population, patient and occupational cohort studies, as well as de novo collected biosamples, *in vitro* cell lines and blood samples exposed *ex vivo*. We will apply state-of-the-art 'omics' technologies and develop new statistical approaches to mine these large datasets for early effect biomarkers of chemical and radiation exposures. Further mechanistic investigations will be carried out using causal modelling approaches, as well as cell line experiments.

Objectives

- *Short term:* Recruit one PhD student per project to investigate exposure and effect molecular biomarkers associated with IR, chemical exposures and mixtures, emissions from brownfield sites and early life exposures to a range of chemicals.
- *Medium term:* Characterise a range of exposure and early effect biomarkers for the various exposures above. We will further develop and validate gene expression assays for rapid assessment of exposure in radiation incidents. We will extend the omic/biomarker studies to: i) non-ionising radiation using unique collections of biological samples, omic analyses and police radio and mobile phone use already obtained in the *Airwave* (police cohort) and *SCAMP* (adolescents) studies respectively, ii) to other chemicals (e.g. halogenated compounds).
- *Long term:* Investigate the role of identified biomarkers in biochemical and mechanistic pathways to better understand potential health consequences and validate these hypotheses through linkage to data from other themes and already existing larger (mainly cohort-based) data.

Progress against objectives

- *Short-term objectives:* PhD students on each project have been recruited. For P1, dose details of vascular patients and operators have been received and results of cytogenetic/genetic biomarker responses in vascular operators are to be published shortly. For P2, data inventory is completed, DTA in place. Analyses of biomarkers of exposure to disinfection by-products (DBPs) through swimming in a chlorinated pool are complete (publication in preparation). Validation/extension to exposure to DBPs via drinking water has started. For P3. Brownfield sites identified and local community engaged. For P4, datasets prepared and explored. Analytical plan developed.
- *Medium-term objectives:* P1. The characterisation of exposure and early effect biomarkers. Funding secured for development of new assays for rapid assessment of exposure in radiation incidents. P2. Substantial progress on developing new methodology to integrate multi-omics data to investigate the molecular signatures of complex exposures. Approach successfully applied to pilot data and validation on larger data from exposure to DBPs via drinking water is ongoing. Further development using clustering approaches are also progressing. P3. Study sites identified and progress on testing passive samplers in collaboration with local community. Two publications ahead of schedule. Collaboration with T3:P3. P4. Datasets prepared and on track to analyse preliminary results and publish.
- *Long-term objectives:* We are confident of successful completion of the identification and validation of relevant biomarkers/pathways. There is potential to interrogate biomarkers identified in this Theme in relation to health outcomes by linkage to other projects.

Project 1 – Exposure and risk markers in medical uses of IR

Project Leads – Christophe Badie and Liz Ainsbury (UKHSA); Bijan Modarai and Samantha Terry (KCL)

Research Team – Grainne O'Brien, Lourdes Cruz-Garcia, Jayne Moquet, Mingzhu Sun, Stephen Barnard and Irene MButu-Austin (UKHSA); Tian Yeong (KCL)

Summary and aims

Biological markers of IR response have the potential to contribute to safer use of radiation in clinical practice, including through assessment of individual sensitivity as well as to tailor high-dose treatment. The overall objectives of this project are to develop and validate novel biomarkers of radiation exposure, effect and susceptibility in the context of medical practitioners, in the first instance for those delivering X-ray guided endovascular procedures and their patients, as well as for nuclear medicine technologists.

Selected study – Establishing initial cytogenetic and genetic biomarker responses in vascular operators (Milestone 2-3)

Background:

Aorta is the most common site for aneurysm, especially abdominal aortic aneurysm. Endovascular aneurysm repair (EVAR) involves lining the diseased aorta under X-ray guidance, with lower peri-operative mortality & morbidity compared to open repair. It requires multiple pre-operative CT scans for planning and post-operative scans for surveillance. In case of complex EVAR, doses up to 400mSv can be delivered to the patient. The aims of the project are i) To identify biomarkers of radiation exposure in patients after complex EVAR and associated CT scans; ii) To compare inter-individual radiosensitivity by irradiating patients' blood samples in vitro, and iii) To pilot data linkage study to assess the incidence of cancer in those who had EVAR compared to those who have had open repair.

Methods: Cytogenic analysis and dose assessment will be carried out using the standard dicentric chromosomal assay. Transcriptional gene expression using NanoString nCounter and quantitative multiplex PCR analyses. Gamma H2AX & ATM foci will also be assessed according to newly improved protocols. For part iii), linkage involves formal application for access to NHS Digital.

Results: Patients who had complex EVAR and multiple pre- and post-operative CT scans within the last 12 months have been identified and recruitment for the study started in September 2022. The dicentric chromosomal assay and the flow cytometry technique for gamma H2AX and ATM analyses have been optimised for this study.

Conclusions: Next steps are to test and validate use of transcriptional gene expression and to finalise access to the patient data from NHS Digital. This work is at an early stage, however, it is hoped that the results will ultimately demonstrate the potential to use biomarkers in EVAR patient and vascular operator populations, to support the safer use of IR in these and wider contexts.

Progress in other project studies/ Other progress

- Work ongoing in T2:P1.M2: Establishing doses received by vascular patients and operators.
- T2:P1:M3: Establishing the system to assess cytogenetic and genetic biomarkers in nuclear medicine technologists, the PhD student has received ethical approval to recruit technologists, has optimised the biomarker approaches, and started work on the reference dosimetry aspects.

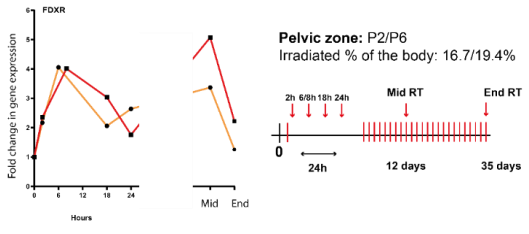


Figure 1: Transcriptional dynamics of DNA damage responsive genes in circulating leukocytes during radiotherapy

Amongst all the genes studied, *FDXR* was the most sensitive and responsive to the very low dose of radiation received by the circulating white blood cell from the localised radiation treatment.

Impact

Ultimately, the new knowledge from these studies will be used to support health decisions by medical professionals, the public and policymakers and allow individual differences in sensitivity to be considered to better protect those at higher risk.

Publications

Paper submitted to the European Journal of Vascular & Endovascular Surgery, with the title "Estimated radiation dose to the operator during endovascular aneurysm repair."

Project 2 – Pathways and biomarkers of mixtures of chemical exposures

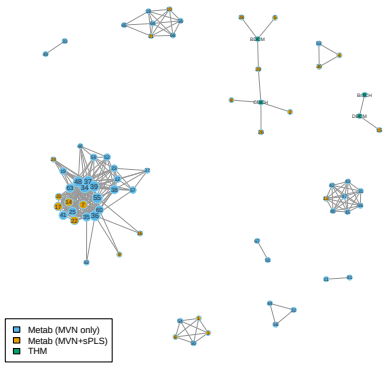
Project Leads – Marc Chadeau-Hyam and Paul Elliott (ICL)
Research Team – Paolo Vineis, Ian Mudway, Sonia Dagnino, Dragana Vuckovic, Leon Barron and Lucas Cheng (ICL)

Summary and aims

This project aims at developing novel approaches to identify molecular markers of complex (multivariate) exposures at multiple molecular levels. Using graphical models, we aim at integrating results obtained at each molecular level to visualise the complex correlations across exposure-associated features to inform on potential pathways affected by these exposures.

Selected study – Multi-omic signature of exposure to DBPs (Milestone 2-3)

Background: Disinfection by-products (DBPs) are a complex mixture of halogenated organic compounds present in drinking and swimming pool water. Although several epidemiological studies have established their association with adverse health outcomes such as bladder cancer, their mode of action and the downstream molecular consequences of the exposure to mixtures of DBPs remain uncertain. In this study, we adopt an integrative approach to identify molecular signatures of exposures to mixtures of DBPs in participants exposed while swimming in a chlorinated pool.
Methods: In PISCINA-II study, metabolomics and proteomics in serum were measured along with levels of DBPs in exhaled breath in 60 individuals before and after swimming. Pre-processing of High resolution mass spectrometry (HRMS) data from PISCINA-II study was customised to maximise coverage of halogenated compounds. Multivariate normal (MVN) and sparse partial least square (PLS) models were used to identify metabolomic features associated with DBP exposures. Conditional correlation networks were constructed to visualise and understand the complex correlation structures amongst the DBP-associated metabolic, and (pre-selected) proteomics features.
Results: 187 metabolic features were identified to be associated with at least one DBP exposure in univariate models. Of these, 95 metabolic features were selected as jointly associated with DBP mixture using the multi-block sPLS approach. Conditional independence networks showed that these features were clustered in several modules, which were differentially associated with each individual exposure (Figure 1). Networks combining metabolic features and proteins identified multi-omic modules, which may represent different pathways affected by exposure to DBP.



Conclusions: Our approach based on customised data reprocessing combined with stability selection allowed the identification of novel metabolomic signatures of exposure to DBP mixtures. The use of targeted conditional correlation networks offers views into the functional proximity of these (multi-omic) signatures of exposure to DBP. These may inform on the underlying molecular pathways.

Figure 1: Conditional independence network for the (N=187) metabolic features associated with exposure to DBPs. Features associated only using univariate MVN models are in blue. Those jointly associated with exposure to DBP in the sparse Partial Least Square (sPLS) model (all also identified in the MVN model) are in orange. The conditional correlation network includes exposure to four assayed disinfection by-products (trihalomethanes, THM, in green).

Progress in other project studies/ Other progress

- Validation in the MCC cohort (DBP exposure via drinking water): explore the relationship between identified omics markers and exposures at lower doses and extend these analyses to drinking water exposures
- Application of these approaches to the Oxford Street study (exposure to air pollution)
- Use similar approach to investigate breast milk biomarkers of air pollutants (T2:P4)

Contributions

This work has been presented as a poster at ISEE, 2022.

Publications

Publications are in preparation on the PISCINA analysis and on the Oxford Street analyses.

Project 3 – Biomarkers of potential chemical exposures in populations living in new housing developments built on brownfield sites

Project Leads – Ian Mudway and Bethan Davies (ICL)
Research Team – Leon Barron, Stephanie Wright and Holly Walder (ICL)

Summary and aims

The urgent need for affordable housing in the UK has driven the exploitation of brownfield sites. This has resulted in considerable public concern, but to date there is limited data on the likely residual chemical exposures of populations at these locations. These issues are compounded by the fact that many of the developments are in inner city areas with multiple potential sources. In this project we aim to address this knowledge gap by monitoring a broad range of pollutants at selected brownfield sites where there is significant or planned housing development. This surveillance work will be complemented by personal and environmental monitoring of populations living at varying distance from these locations using novel passive absorption badges to capture exposures to volatile organic compounds (VOC) and semi-volatile organic compounds (SVOC), with a focus on vulnerable groups.

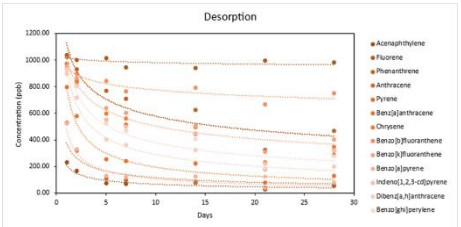
Progress

Background: There are concerns that populations living near to ex-industrial sites are exposed to contaminants, especially during remediation. This research attempts to address this concern by deploying a novel passive air sampler (PAS) to quantify potential exposures.

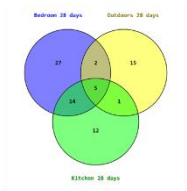
Methods: We have developed a polytetrafluoroethylene (PTFE) passive sampler that houses five sorbent discs (Figure (a)). After method optimisation, two sorbents were chosen, a liquid Tenax TA®-coated PALLFLEX® Emfab filter and polydimethylsiloxane (silicone) that together cover the chemical space for SVOC and VOC compounds. Detailed optimisation experiments were performed to establish the adsorption and desorption kinetics of the passive samples over periods of 24-hours to 28-days, both under controlled laboratory conditions and within real-world indoor and outdoor environments. Following periods of exposure sorbents are solvent extracted and analysed using gas chromatography with mass spectrometry (GC-MS) performed on a Rxi – 624Sil MS capillary column, splitless mode and 20 mins run time (QP 2020 NX Shimadzu). The resultant extracts were then analysed using an untargeted method, with compound identification confirmed using reference libraries.

Results: i) Following the spiking of the sorbents with a mixture of SVOCs at r.t.p we observed significant variation in compound loss, between 0% to 58% loss in the first 24hrs to 8% to 95% loss after 28 days reflecting compound volatility (Fig (b)). ii) When sorbents were exposed over a 28-day period at a roadside location a constant rate of SVOC accumulation was apparent over a 7-day period, after which losses due to desorption were apparent. These data therefore demonstrate that under outdoor conditions sampling over 1-week is not recommended. iii) Following weekly deployments of the PASs over a month within (bedroom and kitchen) and outside an urban house we were able to discriminate numerous VOCs and SVOC, including fragrance compounds (such as tridecylaldehyde), flavouring agents (such as Cuminaldehyde and Isoamyl salicylate) and plasticizers (such as Phthalic acid, diisobutyl ester), - see inset Figure (c).

(a) PTFE passive sampler



(b) SVOC and VOC desorption kinetics under controlled environmental conditions



(c) Venn diagram of the number of identified SVOCs and VOCs after 28-days deployment indoors and outdoors.

Conclusions: This study highlights both the utility and specific limitations of passive samplers for field deployment. The new PAS are now ready for deployment around identified brownfield sites.

Impact

- Development of a novel low-cost passive sampler for environmental and personal monitoring.
- Meetings with the Clean Air for Southall and Hayes (CASH) campaign to inform the development of a passive monitoring campaign.

Publications

Walder H, Dack S, Mudway, I. Assessing the health impacts of redeveloping and remediating sites of former manufactured gasworks in local populations: a review. **In progress.**

Project 4 – Biomarkers of early-life exposures and neurodevelopmental outcomes

Project Lead – Mireille Toledano and Paul Elliott (ICL)
Research Team – Ruth Parsons (ICL) and Ovnair Sepai (UKHSA)

Summary and aims

Incinerators produce toxic emissions and these lead to widespread UK population exposure. There is potential for prenatal exposure to pollutants from these emissions to alter the incidence of some birth outcomes in the UK. We aim to use this biomonitoring study to examine the concentrations of incinerator related pollutants in breast milk and link concentrations to additional participant information and outcomes.

Selected study – Exploratory analyses of BEED participants

Progress

Background: Breast milk, Environment, Early life and Development (BEED) is a cross-sectional biomonitoring study established to examine human milk pollutant concentrations of participants living near municipal waste incinerators (MWIs) in the UK.
Methods: Primiparous women residing within 20km of three MWIs in the UK were recruited between 2013 and 2015 to provide expressed milk samples (about 30ml) and socio-economic, occupational, and dietary data. The milk samples were analysed for 29 dioxin congeners (17 polychlorinated dibenzo-dioxins/furans (PCDD/Fs) and 12 polychlorinated biphenyls (PCBs)), 42 heavy metals and metabolites.
Results: 584 participants were recruited, 69% were aged between 30 and 39 years, 88% were White ethnicity and 79% had a degree level qualification. Residential proximity to an MWI was not associated with toxic equivalent quantities (TEQs) of PCDD/Fs or PCBs. Maternal age was associated with PCDD/Fs and PCB TEQs (Figure 1) and older participants had a higher contribution of the most toxic congener (TCDD).
Conclusions: PCDD/F and PCB TEQs were not associated with residential proximity to MWI but were associated with maternal age. Total milk PCDD/F concentrations were higher than what is considered safe by the World Health Organisation. Future analyses will be used to examine milk concentrations of heavy metal and metabolomic profiles.

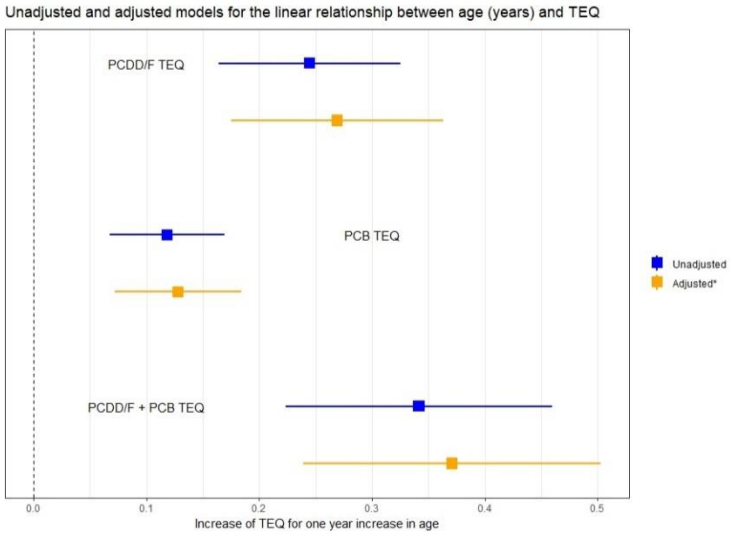


*Figure 1: Plot of the estimated increase in TEQ for one year increase in age with 95% confidence intervals. *Fully adjusted models were adjusted for the body mass index, qualification level and ethnicity of the mother.*

Impact

Presentation of the BEED study in PCIEP Public Involvement Meeting with the aim of gauging public concern around the health impacts of MWI and the cost (in terms of time and burden to the participants) to benefit ratio of resurveying the participants for cognitive development of their children. There was overwhelming support for this resurveying from the panel, with interest in the published results being presented in layman's terms and disseminated to the BEED participants and wider population.

Theme III – *In vitro* testing and integration with epidemiological data

Theme Leads – David Phillips (KCL) and Richard Haylock (UKHSA)

Theme III Overview

This Theme exploits our collective expertise in mechanisms of toxicity and carcinogenesis of environmental toxicants, their bioavailability, biological consequences of DNA damage and health effects of exposure to ionising radiation and toxic chemicals. It addresses questions on the origins of mutations in human tumours and the role of the gut microbiome in toxicity of environmental pollutants. It uses state-of-the-art *in vitro* mammalian and bacterial cell systems and high throughput analyses to obtain insights and apply biomarkers (including those identified in Theme II), to epidemiological studies of health effects of exposure to ionising radiation and toxic chemicals.

Objectives

- *Short term:* To establish two PhD studentships (Projects 3, 4); to collect cohort samples from people occupationally exposed to radiation and from residents living near brownfield sites.
- *Medium term:* To establish the capacity of 3D human tissue organoids and gut bacteria to metabolically activate toxic chemicals and define their utilities as in vitro test systems.
- *Long term:* To define with whole genome sequencing the mutational signatures of environmental carcinogens and compare them with signatures in human tumours; to broaden our understanding of the toxic effects of food-borne pollutants and suggest new avenues for their detoxification via microbiome modulation; to identify biomarkers of occupational radiation exposure and quantify health effects of living on or near brownfield sites.

Progress against objectives

- *Short-term objectives:* For P1, a post-doctoral scientist was recruited instead of a PhD student. P3 is yet to recruit a PhD candidate due to several unsuccessful recruitment rounds. The plan is now to conduct a population-level analysis; sampling will be conducted as part of Theme 1.
- *Medium-term objectives:* Good progress in toxicological characterisation of human tissue organoids, with 1 review article published and 2 research manuscripts submitted. Work on brownfield sites (P3) - all such sites in the country identified (see T2:P3). In P5, we have established a panel of ~100 gut bacterial strains that are phylogenetically and metabolically representative of the healthy human microbiota. Methods to assess their biotransformation capabilities are being established, both experimentally and computationally.
- *Long-term objectives:* WGS of mutated organoids treated with a catalogue of environmental and chemotherapeutic agents currently in progress. Biomarker work falls under Theme 1, with the emphasis on establishing population health effects from brownfield sites. We have mapped a network of individual bacteria - compound interactions for 20 gut bacteria and >2k food-borne compounds (drugs, pesticides and other pollutants). These are revealing a bi-directional network of drug-bacteria interactions that can be leveraged to identify potential mitigation pathways.

Project 1 – Mutagenesis and toxicology in 3D cell systems

Project Leads – David Phillips (KCL) and Christophe Badie (UKHSA)
Research Team – David Phillips (KCL), Jill Kucab, Halh-Al-Serori, Rebekah Beck, Angela Caipa Garcia (PhD student), Christophe Badie (UKHSA)

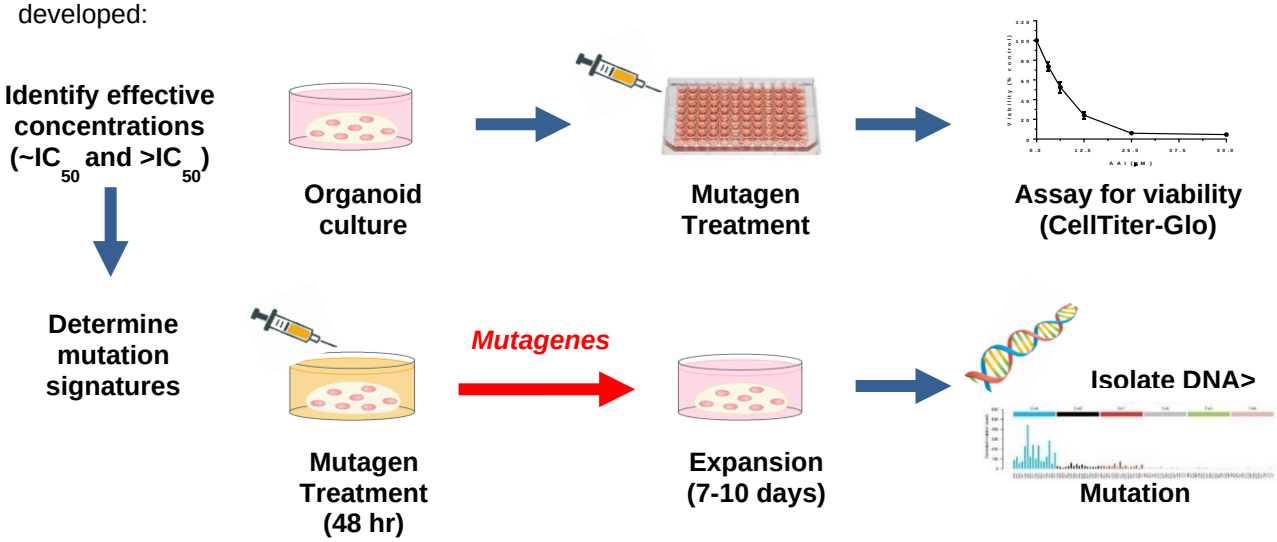
Summary and aims

To use normal human tissue organoids to explore the mutagenesis and toxicology of environmental toxicants and chemotherapeutic agents; obtain mutational signatures by whole genome duplex sequencing and compare with mutations in human tumours; to undertake similar analysis of genetic and epigenetic changes in DNA samples from patients diagnosed with therapy related second cancers, such as acute myeloid leukaemia.

Selected study – Mutational signatures of chemotherapeutic and environmental agents in human tissue organoids

Background: Human tumours contain multiple mutations, the nature of which offers clues to the aetiology of cancer. We are investigating human tissue organoids as a 3D model system for treatment with potential carcinogens in order to generate mutational signatures and compare these with those in human tumours and thereby identify causes of cancer.

Methods: A protocol for generating mutational signatures in human tissue organoids has been developed:



Results: We have established the ability of five human tissue organoids to metabolically activate carcinogens (2 manuscripts submitted for publication). Mutational signatures of 4 carcinogens (aristolochic acid, benzo[a]pyrene, aflatoxin B1, PhIP) in 5 tissues (colon, stomach, kidney, pancreas, liver) have been determined. The signatures of a further 16 environmental agents and 30 chemotherapeutic agents in gastric organoids are currently being extracted and a number of key correlations with the COSMIC signatures (https://cancer.sanger.ac.uk/cosmic) extracted from human tumours have been observed.

Conclusions: Human tissue organoids can activate environmental carcinogens and have considerable potential in toxicology and mutagenesis for providing an in vitro system that has greater physiological relevance to in vivo characteristics and conditions than widely used 2D monocultures.

Publications

A review article on organoids for genetic toxicology has been published. 2 manuscripts resulting from our studies on carcinogen activation have been submitted. A paper on DNA methylation in AML has been submitted.
An abstract submitted to the European Radiation Protection Week in Estoril was selected for oral presentation.

Project 2 – Occupational exposure to ionising radiation

Project Leads – Richard Haylock and Liz Ainsbury (UKHSA)
Research Team – Catherine Smith, Jayne Moquet, Mingzhu Sun, Stephen Barnard and Wei Zhang (UKHSA)

Summary and aims

UKHSA has over many years conducted epidemiological analyses of the health of the UK radiation workforce based on the National Registry for Radiation Workers (NRRW) and are internationally recognised as experts in analysis of biological samples for radiation dosimetry and research purposes. For a few individuals in the NRRW cohort, biological samples have been collected in the context of a study of the ex- British Nuclear Fuels Limited (BNFL) workforce. These samples offer the opportunity to test new methods of biomarker analysis as well as to demonstrate that linkage of samples and occupational data to the NRRW could improve radiation health risk assessment in the long term.

Progress

Background: This project will scope the feasibility of wider prospective sample collection with a view to identifying and integrating novel prognostic biomarker information to improve health risk estimation in support of UK radiological protection practices.

Methods: In the first instance, traditional cytogenetic and novel transcriptional analyses are applied to a subsection of samples from 30 individuals from low, intermediate and high dose groups of former Sellafield workers. At the same time, analysis of the occupational health data is being carried out to inform the biomarker responses, and linkage to NRRW is being tested.

Results: The study is still in progress so while data are being generated no scientific results are yet available. However, M1 has been completed: The agreement of the Nuclear Decommissioning Authority (NDA) was obtained for a proof-of-concept molecular epidemiology study using the retained former Sellafield worker biological samples, towards collation of evidence in support of UK radiological protection practises, and ethical approval is in place.

Conclusions: The next milestones are focused on collection of the data as proof of concept of the utility of biomarkers in these samples in support of the epidemiological linkage. This is a long-term ambition, however, the work is progressing well towards collation of evidence in support of improved UK radiological protection practises.

Impact

This proof-of-concept project will inform on the viability for cytogenetic and genetic biomarker analysis in support of radiation risk assessment and health protection. If these techniques are shown to be viable then this work will provide the evidence to justify a much larger study based on the collection of new blood samples from current radiation workers. This would be a much longer-term project but which would eventually enable collection of sufficient data to allow the meaningful linkage between the biomarker results and epidemiological and occupational health data stored about radiation workers in the NRRW. Results of such a study would be of interest to UNSCEAR and ICRP review evidence and provide recommendations for radiation protection around the world.

Project 3 – Exposures and health effects near brownfield sites

Project Leads – Daniela Fecht (ICL) and Robie Kamanyire (UKHSA)
Research Team – Daniela Fecht, Bethan Davies, Weiyi Wang, Ian Mudway (ICL); Robie Kamanyire, Sarah Dack, PhD student TBA (UKHSA)

Summary and aims

To respond to the growing housing need and protect the countryside from development, brownfield sites are increasingly being targeted for housing redevelopment. Little evidence exists on potential health effects from living on or around brownfield sites, in relation to their previous use, although risk assessment is generally used to assess a site based on soil data and probable health outcomes. This project aims to synthesise the existing evidence and conduct an epidemiological analysis to quantify potential adverse health outcomes in populations living near brownfield sites and assess inequalities in exposure and health effects.

Selected study – Brownfield sites and health: a systematic review of the literature (Milestone 3)

Background: Brownfield sites refer to land previously used for industrial or commercial purposes, but has subsequently become vacant or derelict. Brownfield sites are increasingly being targeted for housing redevelopment. Depending on the previous use, however, they might pose potential risks to the health of residents on or in the vicinity of redeveloped sites. This review synthesised the empirical evidence on the associations between brownfield sites and health.
Methods: We systematically searched EMBASE, MEDLINE, Global Health, Web of Science, Scopus and GreenFile using a study protocol registered on PROSPERO (CRD42022286826). The search strategy combined the keywords “brownfield” and its interchangeable terms such as “previously developed land”, and any health outcomes. Study quality was assessed based on the Newcastle-Ottawa Scale.
Results: Of the 1,987 records retrieved, 6 studies met the inclusion criteria, with 5 cross-sectional studies (3 of which were small-area analyses) and 1 longitudinal study. There was considerable heterogeneity in the exposure metrics and health outcomes being assessed. All studies found significant associations of brownfields proximity or density with at least one health outcome, including self-reported general health, premature mortality, birth defects, serum metal levels and accelerated immune aging.
Conclusions: Brownfield sites can potentially adversely affect the health of nearby residents. The epidemiological evidence on health effects associated with brownfield sites in local communities, however, remain inconclusive and limited. Further studies are required to strengthen the evidence base to inform future housing policies and urban planning.

Progress in other project studies/ Other progress

In preparation for the epidemiological analysis, we have identified ~27,600 brownfield sites in England using information from Local Authorities as part of the Brownfield Land Register (M2). We are currently developing the methodology to identify previous use with relevance to health, making use of Point of Interests and supervised classification of Google Street View images (M4), see Figure 1. We are also in the process of securing access to relevant health outcome data including all cause and cause-specific hospital admissions and birth outcomes including birth weight and pre-term births from SAHSU (M5).

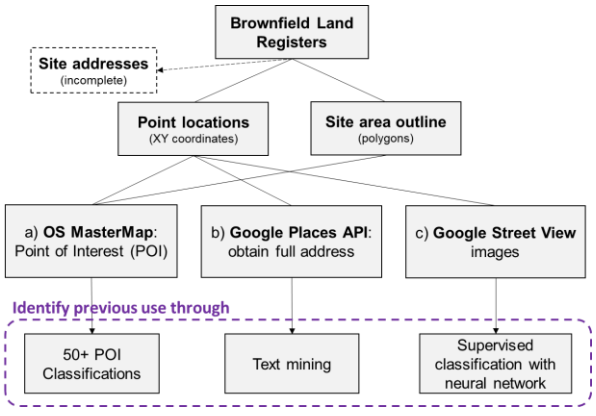


Figure 1. Identification of brownfield sites

Impact/Contributions/Publications

We presented our proposed methodology to identify previous use of brownfield sites at the UK Exposure Science Meeting, 4th & 5th October 2022, University of Leicester.
The systematic review of the literature has been drafted and will be submitted in December 2022.

Project 4 – Gut microbiome mediation of toxicity of environmental pollutants

Project Leads – Anne Willis and Kiran Patil (UC)
Research Team – Anna Lindell (UC)

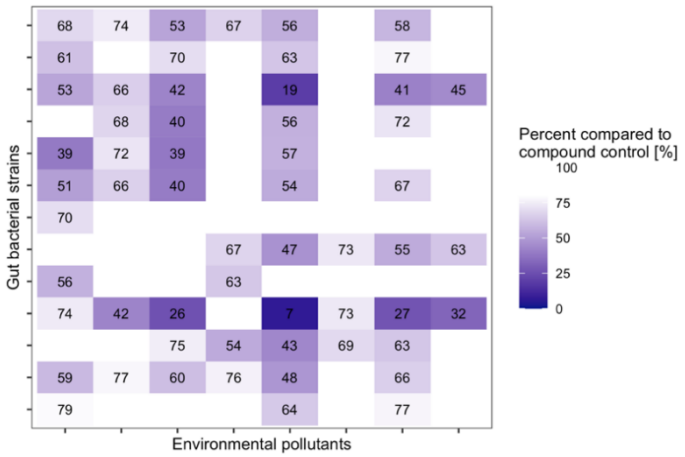
Summary and aims

The overall goal of this project is to discover reciprocal interactions between commonly encountered environmental pollutants such as pesticides and human gut bacteria, and to identify the underlying mechanisms of these interactions. We have charted an interaction network between commensal gut bacteria and pollutants at large scale providing insights into hitherto unknown adverse outcome pathways.

Selected study – Bioaccumulation of pollutants by human gut bacteria

Background: The gut microbiome is exposed to various pollutants via food and drink. While the effect on the microbiota could increase the risk of, for example, metabolic diseases, certain bacteria might aid in detoxifying these compounds.

Methods: We assembled a library of >1200 environmental pollutants. spanning various classes of common pollutants (pesticides, food contact material chemicals etc.). To date, 23 phylogenetically and metabolically representative gut bacterial strains have been screened against >1200 compounds. Further, 55 xenobiotics have been tested for biodegradation/bioaccumulation by gut bacteria using mass-spectrometry assays.



Results: Several pollutants were found to be inhibitory to gut bacterial growth, many with specific activity, while a few showed surprisingly broad-spectrum activity. We also identified novel biodegrading and bio-accumulating bacteria with potential detoxification applications (Figure 1).

Figure 1. Abundant gut bacteria bioaccumulate / biodegrade common environmental pollutants.

Conclusions: Our screen has provided, to the best of our knowledge, the largest network of gut bacteria – pollutant interactions. The pollutant exposure is thus likely to be an important contributing factor underlying microbiome variation and dynamics as well as a factor in kinetics and dynamics of pollutants in the body.

Other parts of the project

We are working towards gaining molecular insights into the bacteria-pollutant and pollutant-bacteria interactions and collaborating with other labs to validate our findings under in vivo settings.

Impact

The results will improve our understanding of how the gut microbiota contributes to the adverse effects of pollutant exposure. This will help better assess safe exposure limits and may provide a means to detoxify certain environmental pollutants.

Publications

Publication of the experimental data will be likely in 2023.

Project 5 – Pesticide toxicity

Summary and project aims

This project combines three ongoing studies by groups associated with the HPRU-CRTH funded from external sources, that have a common aim of improving our understanding of the bio-availability and effects of exposures to pesticides and related pollutants through the respiratory and intestinal routes.

Project P5A – Respiratory bioavailability

Project Lead – Ian Mudway (ICL)
Research Team – Ian Mudway (ICL); Ben Forbes and Zachary Enlo-Scott (KCL)

Summary and aims

Current European regulatory guidelines do not exploit emerging *in vitro* toxicity models and make the unvalidated assumption that 100% of the inhaled pesticide is absorbed into systemic circulation, in stark contrast to oral or dermal routes of exposure, which use established evidence-based *in vitro* and *in silico* methods, in addition to *in vivo* models. Data-driven approaches for predicting toxicity and estimating respiratory bioavailability based on experimental evidence are therefore urgently needed and have important implications for future risk assessments.

Progress

Background: There is a need to develop *in vitro* models that can be exploited to determine the bioavailability and local toxicity of inhaled pesticides to inform hazard and risk assessments, both with respect to occupational exposures, but also of bystander populations near agricultural land.
Methods: Different *in vitro* models were assessed and optimised to study the local toxicity, transepithelial permeability and potential in situ metabolism of unintentionally inhaled pesticides. Cell lines tested included the nasally derived RPMI-2650, bronchially derived BEAS-2B, 16HBE14o-, Calu-3 and alveolar derived cell lines A549 and TT1. These were tested for their suitability to assess the cytotoxicity of 9 different pesticides with varying physicochemical properties and modes of action. Standard markers for xenobiotic metabolism (by CYP1A1, 1A2, 2B6, 3A4, 3A5, NQO1 and GST) and permeability within the respiratory tract, highlighted Calu-3 as the most suitable model. Additionally, lipid-based permeability models such as PAMPA and lung lipid extract were found to be complementary and were included in further experiments.
Results: Following model optimisation, the in vitro ADME properties of the 3 fungicides azoxystrobin, chlorothalonil and propiconazole were tested, revealing significant differences for transepithelial permeability, airway surface liquid binding and plasma protein binding, based on the physicochemical properties of the fungicides. These *in vitro* data were then combined with *in silico* modelling to predict the bioavailability of the respective fungicides for a range of occupational exposure scenarios, highlighting toxicokinetic differences dependent on regional deposition within the respiratory tract and the influence of physicochemical properties of the fungicide. In all realistic exposure scenarios respiratory bioavailability was less than 100%, due to regional aerosol deposition and the interplay between transepithelial permeability and non-absorptive clearance.
Conclusions: This study highlights that *in vitro* data combined with an *in silico* approach has the potential to improve predictions of respiratory toxicity and bioavailability and optimise future occupational and population risk assessments for respiratory exposure to xenobiotics.

Impact

Completion of PhD thesis: Enlo-Scott Z. Understanding local respiratory toxicity and bioavailability of inhaled pesticides in an occupational exposure setting. 2022.

Publications

Enlo-Scott, Z., Mudway, IS., and Forbes, B., 2022. Comparison of permeability, drug metabolism and sensitivity to toxicity in human respiratory epithelial cell lines, for the risk assessment of inhaled xenobiotics. (In preparation)

Project P5B – Unravelling system-wide biomolecular interactions of food-borne pollutants

Project Lead – Kiran Patil and Anne Willis (UC)
Research Team – Nonantzin Beristain, James Thaventhiran, Luis Martins, Marion MacFarlane (UC)

Summary and aims

This sub-project (funded by the MRC Toxicology Unit in Cambridge) aims to examine how environmental pollutants impact cell physiology and suggest potential targets towards mitigation, by large-scale profiling of the effects of hundreds of common food-borne pollutants (pesticides, herbicides, and veterinary medicines) using a multi-scale bioassay approach.

Selected study – Bioactivity of pollutants on human cell lines

Background: The adverse outcome pathways following pollutant exposure are only sparsely known. Identification of the molecular mechanisms involved in pollutant-cell interactions are crucial to assessing the health risks.
Methods: We have established bioactivity assays – cell viability, oxidative stress, mitochondrial stress, and ER stress – using three different cell lines. Pilot screen using a library of circa 80 compounds is completed and data analysis is ongoing.
Results: The results indicate cell-type specificity of pollutant effect on cell viability and stress.
Conclusions: Impact of environmental pollutants on human cells needs to be assessed across multiple cell lines and at exposure relevant concentrations.

Other parts of the project

Proteomics and metabolomics assays are being developed to identify molecular targets of the pollutants. The project is carried out in close alignment with Theme III: Project 4 (gut bacteria – pollutant interactions). We aim at integrating the results to gain a holistic view on adverse outcome pathways linked to pollutant exposure.

Impact

The results will improve our understanding of molecular mechanisms involved in pollutant toxicity.

Publications

Publication of the experimental data will be likely in 2023.

Project P5C – Identifying the effects of pesticides on intestinal permeability and gut-bacterial dysbiosis

Project Lead – Michael Antoniou (KCL)
Research Team – Scarlett Ferguson (PhD Student) and Robin Mesnage (KCL)

Summary and aims

Commercial pesticide formulations consist of an "active ingredient" and co-formulants. Although known to be toxic, co-formulants are listed as "inert" and are paid little or no attention during regulatory risk assessment. The primary aim of this project was to compare the toxicity between herbicide active ingredients and a corresponding typical commercial formulation, which are most used in the UK. We focused on carcinogenic and gut microbiome outcome measures.

Selected study: **Cytotoxicity mechanisms of eight major UK herbicide active ingredients in comparison to their commercial formulations,** Scarlett Ferguson, Robin Mesnage and Michael N Antoniou, *submitted for publication.*

Background: This study compared the toxicity of 8 major UK herbicides namely glyphosate, dicamba, 2,4-D, fluroxypyr, quizalofop-p-ethyl, pendimethalin, propyzamide and metazachlor with typical commercial formulation.
Methods: Human hepatocyte HepG2 and immortalised fibroblast cells were treated with herbicide active ingredients and their representative commercial formulation.
Results: Formulations were more toxic than the active ingredients alone in both cell lines. Metazachlor and its formulation Sultan50C had similar cytotoxicity profiles but Sultan50C resulted in significant membrane disruption compared to the active ingredient. Generation of reactive oxygen species was detected for glyphosate, fluroxypyr, pendimethalin, quizalofop-p-ethyl, the formulation of 2,4-D (Anti-Liserons), and dicamba and its formulation Hunter. Testing of quizalofop-p-ethyl and its formulation Targa Super in the ToxTracker carcinogenicity assay system revealed that both products induced oxidative stress and an unfolded protein response.
Conclusions: our results add to the growing body of evidence which demonstrate that both commercial pesticide formulations as well as active ingredients need to be risk assessed to inform appropriate regulation and better public and environmental protection.

Progress in other project studies/ Other progress

The surfactant co-formulant POEA in the glyphosate-based herbicide RangerPro but not glyphosate alone causes necrosis in Caco-2 and HepG2 human cell lines and ER stress in the ToxTracker assay

Mesnage R, Ferguson S, Brandsma I, Moelijker N, Zhang G, Mazzacuva F, Caldwell A, Halket J, Antoniou MN (2022) *Food Chem Toxicol*., **168**: 113380.
Background: The most toxic pesticide co-formulant is polyoxyethylene tallow amine (POEA) known as POE-15 tallow amine (POE-15), which is still widely used especially in the USA.
Methods: Mass spectrometry was used to assess the presence of POEA/POE-15 in the glyphosate-based herbicide RangerPro. Cytotoxicity assays were undertaken in human intestinal epithelial Caco-2 and hepatocyte HepG2 cell lines. Carcinogenicity was assessed using the ToxTracker assay system.
Results: RangerPro and POE-15 were far more cytotoxic than glyphosate alone. RangerPro and POE-15 but not glyphosate caused cell necrosis in both cell lines, and that glyphosate and RangerPro but not POE-15 caused oxidative stress in HepG2 cells. Tests in the ToxTracker carcinogenicity assay system showed RangerPro and POE-15 but not glyphosate give rise to ER stress. **Conclusion:** the toxicity resulting from RangerPro exposure involves ER stress caused by POE-15, along with oxidative stress caused by glyphosate.

Impact

The above studies reinforce the need to test both commercial formulations and active ingredients of commercial pesticides to inform appropriate regulation and better public and environmental protection.

Publications

Mesnage R, Calatayud M, Duysburgh C, Mazorati M and Antoniou MN (2022). Alterations in infant gut microbiome composition and metabolism after exposure to glyphosate and Roundup and/or a spore-based formulation using the *SHIME*® technology. *Gut Microbiome,* **3**: E6

Mesnage R, Bowyer RCE, El Balkhi S et al. (2022) Impacts of dietary exposure to pesticides on faecal microbiome metabolism in adult twins. *Environ Health*, **21**: 46.

Theme IV – Neurotoxins & high toxicity agents (HTA)

Theme Leads – Nora Bourbia (UKHSA) and Tom Welton (ICL)

Theme IV Overview

This theme aims to increase our understanding of significant chemical hazards to human health, ranging from household pollutants to toxic industrial chemicals and chemical warfare agents (CWA). In brief, the cycle of environmental toxic agents starts from: i) its presence in the environment, ii) its direct contact with humans, iii) its absorption by the body followed by the physiological process of its toxicity, and iv) its clearance from the body. The research in this Theme focuses on elucidating presence in the environment, the mechanisms of action, impact at the cellular level, defining decontamination protocols and developing novel routes to decomposition/disruption. A key aspect is the impact of such chemicals on humans, and how to decontaminate or alleviate exposure.

Objectives

- *Short term*: Recruit PhD students to Projects 2, 3 and 4 to conduct literature reviews and identification of simulants/development of analytical methods.
- *Medium term*: Determine the cellular uptake of neurotoxins and impact of household mould; develop analytical methods for highly toxic agents (HTA)/CWA simulant quantitation; investigate solvation and decomposition of CWA simulants; survey HTAs in UK drinking/waste waters.
- *Long term*: Human decontamination studies; urine analysis for quantification of HTA exposure; testing *in-silico* novel ionic liquids (ILs) with simulants and CWAs. Develop a tool kit to assess the potential of environmental agents to induce cellular phenotypes similar to those found in persons with neurodegenerative disorders.

Progress against objectives

- *Short-term objectives:* Recruitment of all PhD students is complete and studies have started. Training of PhDs in specialist techniques is progressing well. Submission of a manuscript proposing appropriate novel chemical simulants has been completed. Other literature reviews are on track.
- *Medium-term objectives:* For P1, assessment of the household mould mycotoxin Ochratoxin on brain cell and cytotoxicity is reaching an end with a manuscript in preparation. For P2, method development is getting back on track after COVID-19 delays. For P3, analytical method development and preliminary dataset for 100 HTAs is underway. For P4 initial studies of hydrolysis of CWA simulants are underway.
- *Long-term objectives:* The excellent progress in the medium-term objectives means we are on track to complete the longer-term objectives. For P1, identifying an emerging mycotoxin of interest has been done and the investigation on whether this emerging mycotoxin of interest can have an impact on brain functions and neurodegenerative disorders has started.

Project 1 – Novel screens for environmental neurotoxins

Project Lead – Nora Bourbia (UKHSA)
Research Team – Nora Bourbia and Sean Gettings (UKHSA)

Summary and aims

Most brain disorders and diseases are multifactorial with environmental factors being part of the cause of the disease/disorders. Our aim is to investigate whether exposure to common environmental agents, such as mycotoxins, can affect brain function, and especially whether they can induce cellular phenotypes similar to those found in human neurodegenerative diseases.

Selected study – *In vitro* exposure to Ochratoxin A alters the expression of genes associated with Parkinson's diseases (T4.P1.M2)

Background: Ochratoxin A (OTA) is a common crop, food and drink contaminant. Despite readily crossing the blood-brain barrier, the role of OTA in neurodegenerative diseases is not understood. This study investigated whether chronic OTA exposure acts as an environmental hazard linked to Parkinson's disease.
Methods: Undifferentiated SH-SY5Y cells, previously used as a Parkinson's disease model, were used to investigate the effect of OTA on the expression of genes associated with neuronal health (*BAX*, *P53* and *BDNF*) and neurodegenerative disease (*MAPT* and *TPPP*). SH-SY5Y cells were exposed to 1µM or 1nM OTA for 1-2 days or 2fM and 2pM OTA for 2, 5 or 11 days. Cells were then harvested and pelleted for RNA extraction, followed by cDNA conversion for rt-qPCR to quantify gene expression.
Results: Exposing cells to 1µM OTA reduced *P53*, *MAPT*, and *BAX* expression at days 1 and 2. The expression of *BDNF* and *TPPP* were significantly reduced at day 1 yet significantly increase at day 2. SH-SY5Y cells exposed to a 1nM OTA were observed to have a significant reduction in *BAX* and *P53* only. After 11 days 2fM OTA did not alter gene expression, although 2pM OTA reduced *BDNF* expression.
Conclusions: An acute (1µM) OTA dose altered expression of Parkinson's disease markers, reducing *MAPT* expression, while increasing *TPPP* expression. A realistic (2fM) OTA dose did not alter gene expression and so may not trigger Parkinson's disease. However, *BDNF* downregulation followed chronic exposure to a high OTA dose (2pM), potentially causing adverse effects on neuronal health.

Progress in other project studies/ Other progress

Two new milestones have been added to the T4P1:

- Development of a toolkit to assess whether environmental agents can induce similar cellular phenotypes found in human with neurodegenerative diseases (T4.P1.M3 - March 2024)
- Investigate whether the emerging mycotoxin beauvericin can induce common cellular phenotypes of neurodegenerative disease (T4.P1.M5 - March 2023).

Impact

We are contributing to understanding whether our current long-term exposure to mycotoxins could negatively impact brain function, and especially whether mycotoxins could trigger the on-set of neurodegenerative diseases. Understanding environmental factors of brain diseases/disorders will ultimately contribute to better protection for the UK population.

Publications

- Abstract: The impact of ochratoxin A on the expression of genes associated with neurodegenerative diseases. FENs 2022, (Paris, France). Poster
- Manuscript in preparation ready to be submitted for peer-review by end of November 2022 (T4.P1.M4).

Project 2 – Identification and validation of novel simulants of CWAs and toxic industrial chemicals

Project Leads – Tim Marczylo (UKHSA)
Research Team – Tim Marczylo, Tom James (UKHSA – PhD student), Haydn Cole (UKHSA); Tom Welton (ICL)

Summary and aims

Mass casualty decontamination protocols in the UK are well established but are based upon evidence from a few simulants with similar physicochemical characteristics.
We will identify novel simulants with diverse physicochemical characteristics and investigate decontamination of a selection of these using protocols based on UK best practice. Additionally, we will determine whether water-based decontamination increases systemic exposure, 'the wash-in effect'.

Systematic reviews – (T4.P2.M1 and M2)

Background: Chemical simulants are used in human trials of mass decontamination to determine the efficacy of decontamination interventions against more toxic agents. Historically, simulants have been surrogates of specific agents (e.g. methyl salicylate is a simulant for sulphur mustard) and do not model most toxic industrial chemicals.
Skin decontamination interventions may increase dermal absorption, a phenomenon known as the wash-in effect. where the act of decontamination enhances dermal penetration of toxicants increasing potential morbidity and mortality. However, the wash-in effect is seldom investigated within the context of mass casualty decontamination and the real-life consequences are therefore poorly understood.
Methods: Two literature reviews were conducted: One to identify chemicals that had been previously tested on human volunteers and that represent diverse physicochemical characteristics to create a repository for chemical simulants; the other to review the existing literature on the wash-in effect.

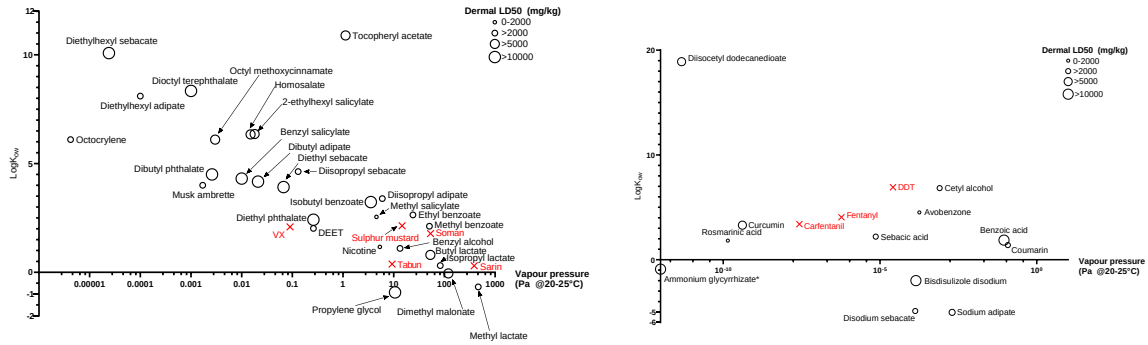


Figure 1. Physicochemical properties of potential simulants Left: room temperature liquids, Right: solids.

Results: Of the 171 unique chemicals identified 77 were discounted for reasons of toxicity, 40 were deemed suitable for use and a further 54 were possible simulants but would require further research. Suitable simulants included both solids and liquid chemicals spanning a wide range of physicochemical properties including molecular weight, logK_{ow}, vapour pressure and solubility.
Eighteen wash-in studies were identified, and 6 mechanisms proposed for the wash-in effect, skin hydration, physical effects (spreading, mechanical disruption), surfactant effects, pH effects, physicochemical effects, and in vitro artefacts.

Conclusions: We identified 40 physicochemically diverse simulants suitable for human volunteer decontamination studies. We identified 6 potential mechanisms behind the wash-in effect to inform our human trials.

Impact

Thus far we are keeping relevant government departments updated upon progress of this project and will continue to do so as the project develops including whether UK decontamination protocols will require adaptation to be suitable for physicochemically diverse chemicals.

Project 3 – Detection of Highly Toxic Agents (HTAs) in water

Project Lead – Leon Barron (ICL)
Research Team – Leon Barron, Paolo Vineis, and Davide Ciccarelli (ICL); Tim Marczylo (UKHSA)

Summary and aims

Identification of new highly toxic agents (HTAs) in drinking water such as disinfectant by-products, perfluorinated chemicals, pharmaceuticals, pesticides, plastics, etc., remains a significant challenge. The aim of this project is to develop new analytical capability to characterise and classify new HTAs in UK municipal, well and bottled drinking waters and assess their potential risks for human exposure.

Selected study – Non-targeted analysis of organic acids in water by strong anion exchange SPE and mixed-mode LC-HRMS. (Milestones 3 and 4)

Background: Non-Targeted Analysis (NTA) in water aims theoretically at detecting all substances contained in a sample. The scientific community is placing an increasing attention on the importance of extending the scope of sample preparation and/or chromatographic methods to very polar compounds. The vast majority of published NTA methods for water samples employ a single extract in which all sample components are concentrated. However, co-elution during liquid chromatography-electrospray ionization-mass spectrometry analysis generates signal suppression and increases the complexity of mass spectra.

Methods: Using solid-phase extraction and a mixed-mode anion exchange-reversed-phase chromatographic column to help provide this selectivity, a selection of 23 highly toxic acidic substances were used to develop a suitable qualitative analytical method for application to drinking water. The data processing workflow for wider application to NTA was tailored to exclude features generated by sample preparation, instrument and dissolved organic matter (DOM). The developed method was then applied to suspect screening and NTA of HTAs in several samples of UK municipal drinking water.

Results: With average recoveries of 88%, low-mid ng/L concentration level sensitivity was achieved for all compounds and to within 5 ppm mass inaccuracy. The novel DOM filter proved to reduce on average 19% of remaining features, decreasing the chance of false positive results and workload. Several novel disinfection by-products with significant predicted toxicity were found in drinking water.

Conclusions: Overall, this method represents an efficient means to recover, detect and identify anionic species at very low concentrations in water matrices in comparison to existing qualitative methods.

Progress in other project studies/ Other progress

- Synthesis and purification of four halogenated hydroxycyclopentanediones (HCDs) for structure confirmation and preliminary in-vitro toxicity study (Milestone 5): synthesis and semi-preparative liquid chromatography currently being optimised. Dibromo and tribromo-hydroxycyclopentenedione to be purified shortly for structure confirmation by NMR. Preliminary toxicity test to be conducted with Prof David Phillips.
- Survey of approximatively 120 samples of municipal water for quantitative analysis of selected compounds (Milestone 6): survey design currently in development.

Impact/ Publications

A preprint of the analytical workflow for analysis of acidic substances was published as a pre-print “An improved non-target analysis and suspect screening workflow for organic acid contaminants in drinking water”, Davide Ciccarelli, Tim Marczylo, Paolo Vineis and Leon Barron
https://doi.org/10.26434/chemrxiv-2022-df8gb-v2

Project 4 – Ionic liquids for the clearance of neurotoxins and other highly toxic chemicals from the environment

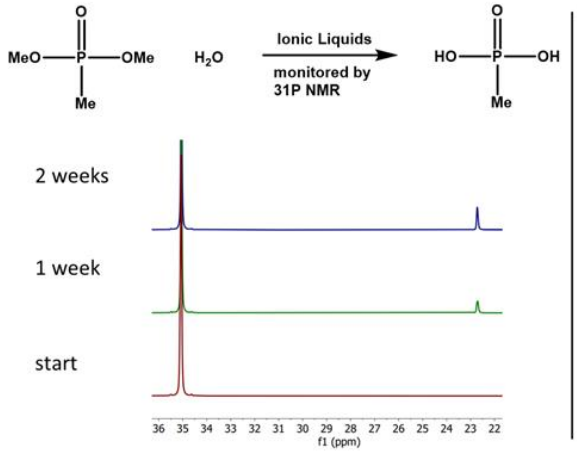
Project Leads – Tom Welton (ICL) and Patricia Hunt (ICL/Victoria University of Wellington), Charles Romain (ICL)
Research Team – Gavin Smith (ICL)

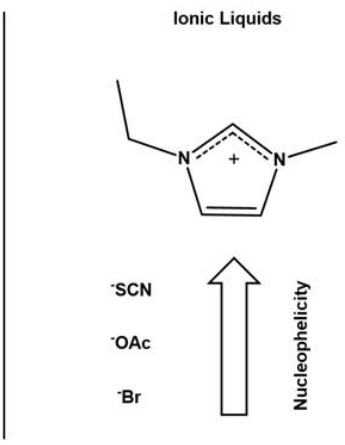
Summary and aims

The aim of the project is to use the ability of ionic liquids (ILs) to affect the rates of reactions to develop systems for the decomposition of chemical warfare agents (CWAs). We are using a combination of theoretical and experimental approaches to understand the effects of ionic liquids on relevant reactions, such as hydrolysis or oxidation. This will then be applied to the decomposition of CWAs and their mimics.

Selected study – Hydrolysis of CWA mimics (Milestone 5)

Background: One established method to decompose CWAs is by hydrolysis. It is already known the addition of either nucleophiles or bases can increase hydrolysis rates. A variety of ILs with varying basicity and nucleophilicity were synthesised and tested for the hydrolysis of CWA mimics.
Methods: Hydrolysis was tracked by ^{31}P NMR. Reactions were monitored periodically for 2 weeks.
Results: Preliminary screening of ILs has been performed and show increased rate of hydrolysis in ILs compared to water. Testing of specific anions with varying nucleophilicity and basicity appear to show a corelation between basicity of the IL and the increase in hydrolysis rate.





Solvent	Conversion [% per week]
[C2C1im] [Br]	<1
[C2C1im] [SCN]	1-2
[C2C1im] [OAc]	8
Water	<1

Conclusions: the results show that ILs can give a significant increase in hydrolysis rate of dimethymethylphosphate (CWA mimic) compared to just water. This increase appears to be mostly driven by basicity not nucleophilicity. Hence, adding nucleophilic catalysts may be able to give rise to a double effect of basicity from the ionic liquid, coupled with nucleophilicity from the catalyst.

Progress in other project studies/ Other progress

- T4, P4, M1: Literature review of known decomposition methods and entraining effect of Ionic liquids has been completed
- T4.P3.M3: Introduction to computation techniques has been completed. Training calculations were performed on known cope and Claisen rearrangements from literature so comparison could be made with experimental data in the literature. This work has been mostly completed and is currently being written up
- T4.P3.M3 Introduction to experimental techniques for IL synthesis and analytical characterisation, and introduction to computational techniques have been completed. The techniques learned were used to synthesis the ILs tested in T4.P3.M3 (see results above)

Impact

The need to find ways to safely destroy CWAs is self-evident and has been a long-term aim of practitioners. The ability of ILs to supress vapour formation of the CWAs (M1) together with their ability to accelerate the decomposition of the CWAs (M5) is pointing to us being able to achieve this.

Project 5 – Identification of illegal threat manufacturing activity via wastewater markers (*ThreatMARK*)

Project Leads – Keng Tiong Ng and Leon Barron (ICL)
Research Team – Tom B (Centre for the Protection of National Infrastructure), Peter Thompson (National Physics Laboratory)

Summary and aims

This is an externally funded project by the Royal Academy of Engineering and associated with the HPRU-CRTH. The aim of this work is to develop new detection capabilities and identify threat markers to monitor the synthesis of "homemade" threats via wastewater analysis. To achieve this, the project utilises the latest analytical instruments and *in silico* AI-assisted technologies. A new database of the chemical composition of several high-priority homemade explosives and potential markers has been compiled and provided to the UK Intelligence Community for intelligence purposes to intercept threats.

Selected study – Database compilation and threat marker identification

Background: 'Homemade' threats like explosives, nerve agents and other highly toxic substances are often manufactured in residential settings, such as kitchens or bathrooms. Reagents and synthesis products are often disposed directly into sewage systems. Municipal wastewater therefore represents a useful resource to monitor such activity within a city in near real-time. Early identification of illicit manufacturing of threat agents is critical for protection of public safety. Therefore, this project aims to identify suitable threat markers for wastewater analysis, serving as a new detection method to identify imminent chemical threat agents that could endanger the public.
Methods: A range of commercial products known to be used in homemade explosives (HMEs) synthesis and HME products was acquired for full impurity profile screening. Advanced analytical instruments and *in silico* AI-assisted technologies were used to identify potential threat markers and their occurrence in wastewater. All HMEs related to chemical substances, including precursors, products, impurities and potential markers were compiled into a database.
Results: Literature reported and experimental identified chemical substances (n=132) including peroxide, nitrated sugars and inorganic explosives related substances have been added to the database. Of these, we identified 20 potential threat markers with low occurrence in wastewater. A rapid wastewater occurrence screening for explosive standards and markers was also developed, Figure 1.

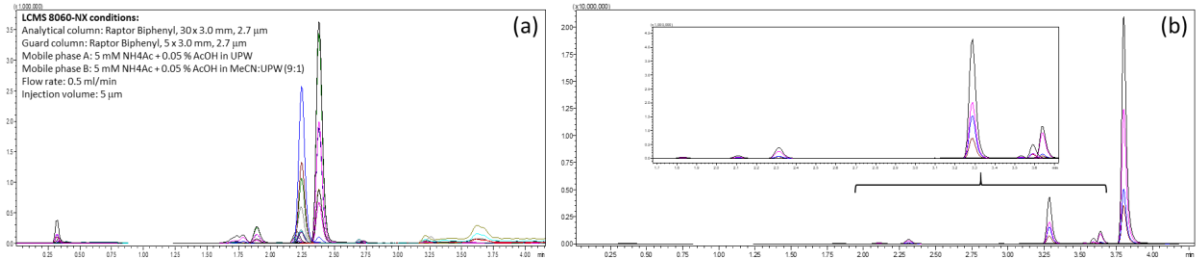


Figure 1. LC-MS/MS chromatograms of spiked HMEs and impurities (a), and spiked explosive standards (b) in wastewater matrix

Conclusions: We show preliminary success in threat markers identification and their application in wastewater analysis as an early warning monitoring tool is still required further investigation to understand their stability and reliability of use to monitor and intercept regional threat activities.

Other parts of the project

This project ended in March 2022. Milestone 1: Database compilation was completed, while milestone 2: publication is underway and expected to finish by December 2022.

Impact

This study can serve as new source of intelligence to be used as an early warning tool by local enforcement to monitor irregular activities. It can be extended to other chemicals to understand the lifestyle, exposure and health status of the community in near real-time. Community groups will benefit from the monitoring and reduce the need for health interventions by identifying threats early.

Publications

Publications in preparation – i) review of explosives ingredients and suitable analytical methods for their measurement; ii) identification of potential novel explosives synthesis markers for wastewater screening

3. ACADEMIC CAREER DEVELOPMENT 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 academic career development programme (ACDP), combining scientific expertise in fundamental toxicological, epidemiological, and environmental research to train the next generation of research leaders in these fields.

Recruitment and appointments

Throughout 2022, our recruitment procedure, based on identifying excellent PhD candidates and early-career researchers (ECRs) through consistent and inclusive processes encouraging diversity and equality, has enabled us to appoint outstanding students and we now have 9 PhD students and 14 ECRs in total to the HPRU-CRTH.

Training activities

We have updated our induction activities: an online induction sessions and a buddy scheme for informal help and support for new starters. Additionally, as pandemic restrictions have eased, we were able to hold a 'Meet Your Buddy' in-person lunch and our default for induction sessions and other activities (below) moving forward will be in-person, unless circumstances change, with option to join online for those unable to travel. We have maintained the ACDP 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. We are also actively promoting participation in NIHR Academy activities. We also facilitate our students and ECRs shadowing senior members of our HPRU in national committees (e.g., COT, COMEAP, COMARE).

Our journal clubs and seminars series, led by ECRs, are ongoing, giving regular opportunities for our PhD students and ECRs to discuss new studies in their field/present their research/ provide exposure to diverse topics. We are continuing to build capacity in quantitative methods through a series of workshops, led by ECRs, combining theory and practical sessions. This year's workshop, on time series analysis, was highly successful in terms of attendance (30 and 70 attendees for theory and practical sessions, respectively) and feedback received.

Our annual training event, held September 2022, was in-person. HPRU PhD students and ECRs gained experience in presenting their research projects as posters, flash oral presentations, or plenary oral presentations to a live audience, with time for questions and discussion. They had the opportunity to network within and beyond their HPRU Theme and Project, and the keynote (Dame Dr Jenny Harries) gave them an insight into the scientific process in government and policy. A talk from the head of the college's Equality, Diversity and Inclusion Centre (EDIC) build further awareness of the importance of EDI in their future research and career. Members of all the other HPRUs were invited to attend and for one of their students present a poster. Furthermore, our PhD students are able to present on the UKHSA PhD students day which brings together all PhD students part of or affiliated with UKHSA including all of those within the HPRUs.

The major update to our training programme, building on the ISAB feedback from last year, is the launch of a more formalised version of the ACDP, starting in October 2022. This will include a schedule of monthly core activities released at the beginning of each academic year; to set expectations in terms of involvement and engagement, and a more systematic approach to feedback and evaluation. This will further improve the structure of our programme and ensure students are equipped with a rounded understanding of environment and health research, and a range of professional skills required for their career progression. The ACDP will include multi-disciplinary core modules, on topics such as risk assessment, toxicity, biostatistics and data science, translation to policy, and career progression. We believe that this will also help increase engagement and involvement of PhD students and ECRs in our ACDP activities and the sense of cohort.

Impact

15 PhD students and ECRs are involved into 14 out the 20 ongoing projects of the HPRU-CRTH, in close partnership with UKHSA. They have contributed to +20 PCIEP events and to 14 publications. They take initiatives to create podcasts (the EnviroHealth podcast) and a sustainability initiative, which

reach far beyond the HPRU.

Future strategy

Over the coming year, we will assess the benefits of the formalised activities outlined above, through feedback and evaluations. The ACDP is increasingly founded on co-design with our students and ECRs being represented on the ACDP Committee; choosing the theme of the workshops; co-organising the journal club and seminar series; designing surveys. We believe the inclusion of students and ECRs in many aspects of the ACDP and beyond is important to their ACD and ensures EDI. We will continue to work with EDIC to further integrate strategic EDI objectives into our training programme. We will continue stimulating ACD interactions with other HPRUs and activities of the NIHR academy. Finally, we will continue building capacity in general quantitative methods, including statistics, big data and coding through dedicated workshops and other ACD activities.

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, our PCIEP Strategy has continued to be informed by the NIHR INVOLVE National Standards for Public Involvement in Research. Over the last year we have demonstrated an ongoing commitment to engaging the public with our research across all themes aiming to embed the UK Standards for Public Involvement. The following highlights how we have been implementing our strategy.

Governance Structures

Our aim is to ensure that the public voice is clearly present in our research management, leadership, and decision-making processes. Our Joint PCIEP Committee continues to meet once in every two months to ensure that PCIEP is firmly embedded in the Unit at a strategic level.

We continue to hold meetings with our Public and Community Oversight Group (PCOG) jointly with the HPRU-EEH and the MRC-CEH. The PCOG appointed a non-professional Chairperson who represents this group in meetings with the leadership team, bringing the public perspective to the highest governance structure of these units.

Various members of our PCOG have been invited to participate in stakeholder groups and liaison committees for various projects associated with our Unit, this to ensure that the public voice is clearly present in our governance structures at all levels.

We will continue to use the UK standards for Public Involvement as a quality benchmark to assess the strengths and weaknesses of our involvement, engagement and participation activities and identify improvements.

Support and Learning

We recognise the importance of providing regular opportunities for researchers to engage and involve members of the public in their research at various stages of the research cycle. To facilitate this, we have conducted regular meetings with our Public and Community Advisory Group (PCOG), our researchers and members of the Executive group. During these meetings, our researchers have had the opportunity to ask our PCOG for advice on various aspects of their research e.g., research plans, protocols, and materials under development.

In December 2021 we announced the first round of our new funding scheme “PCIEP Seed Fund”, a new initiative targeted at early career researchers and PhD students, with the aim of encouraging and enabling early career researchers to develop and deliver new and innovative involvement engagement and participation initiatives. Applicants had the opportunity to submit proposals for a maximum amount of £1000 for public engagement involvement and participation with a broad audience. We received six applications of which three were successful. Our second round for funding will be announced in early December 2022.

We have recently launched our “PCIEP monthly newsletter”, which purpose is to keep our researchers informed on PCIEP training opportunities, activities and events where they can actively engage in PCIEP initiatives, and on updates on policies and guidance related to best PCIEP practice.

Inclusive Opportunities

We have continued to expand the diversity and inclusion in our PCIEP activities by using various networks and online platforms to engage with hard-to-reach groups (e.g., the VOICE Digital Platform and The Young Persons’ Advisory Network (YPAN). Some of our projects have also adopted community-based approaches to research, actively involving the local community, residents and local ambassadors from various ethnic backgrounds and Socio-Economic status in the designing, implementation, and dissemination of our research protocols.

We are currently in the process of reviewing our PCOG membership with a focus on improving diversity (Objective 4). We will seek to identify relevant lay members of the public, stakeholders, and gatekeeper

organisations to ensure broad representation both within the PCOG and in PCIEP workshops, involvement, and engagement activities. As part of this process, we have held discussions with our PCOG members centred around how can we implement the UK Standards for Public Involvement in Research within our Units/Centre with a focus on inclusive opportunities.

Communications

We have continued to engage with the public in a scientific dialogue related to the issues around chemicals and radiation (Objective 7- PCIEP Strategy). We have been doing this through participation in various large public engagement events showcasing our research as a whole, at local and regional level including the Oxford Science and Ideas Festival (October 2021), the Great Exhibition Road Festival (June 2022), the New Scientist Live North in Manchester (January 2022) and New Scientist Live London (October 2022). Our researchers have also participated in various local community festivals (e.g., local science festivals) and have continued delivering numerous talks and engagement activities to primary and secondary school children. Aside public engagement events, our researchers have also been disseminating their research findings through media interviews, blogs posts and public facing reports.

We have also continued to develop our Unit's website, which serves as a central repository for information about research activities, events, publications, and opportunities for the public to engage with and participate in our research. We use our Twitter account (@HPRU_CRTH) to disseminate our outreach activities, promote our PCIEP opportunities and establish a social media presence.

Capturing and Reporting on Impact

We have continued to capture the impact that our activities have on our lay partners and researchers using 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 (Objective 8- PCIEP Strategy).

Our Researchers have been actively using our public engagement reporting tool for reporting, reflecting and learning (Objective 1- PCIEP Strategy). This tool has allowed 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 to actively contribute to the attainment of our PCIEP strategy objectives.

HPRUs Stand at New Scientist Live, Manchester – March 2022

Great Exhibition Road Festival, London - June 2022

HPRUs Stand at New Scientist Live, London – October 2022

5. KNOWLEDGE MOBILISATION

Knowledge mobilisation (KM) brings together communities, scientists, public health practitioners, decision makers and other stakeholders with an interest in one or more topics, to catalyse change. KM maximizes the impact of health protection research to facilitate effective practice and policy change and improved services for patients and the public.

Capacity building and Training

The KM Manager (KMM) is shared with the HPRU-EEH as well as the Environmental Change HPRU at the London School of Hygiene and Tropical Medicine, allowing efficient knowledge transfer and exchange. The KMM participates in the pan-HPRU KM network to enable shared learning across the HPRUs. Through the network, the KMM developed a training survey to identify priority areas for KM training across all the HPRUs, co-organised a cross HPRU webinar on 'Parliament for researchers' in June 2022 and is co-facilitating a KM workshop at the 2022 UKHSA Conference in October.

KM presentations are given at the Theme meetings, and the KMM participates in both the Joint Academic Career Development Committee and Joint Public and Community Involvement and Engagement and Participation (PCIEP) Committee. A session in the distinguished lecture series on KM and policy translation aims to embed KM in the Joint graduate training programme. Imperial researchers provided a training day to members of the Guy's and St Thomas' Hospital and are now developing a CPD training programme on air pollution and health impacts.

The KMM has been involved with UKHSA internally led knowledge management work, using the HPRUs as Proof of Concept to examine knowledge captured by the HPRUs and to identify knowledge management solutions.

A joint PCIEP and KM Update email has been established to be circulated on approximately monthly basis. The aim of this update email is to share knowledge mobilisation opportunities, to be involved with government consultations or link into other related network events, or training opportunities.
UKHSA has become a Public Sector Research Establishment (PSRE) which contributes to the cross-government Life Sciences Vision. UKHSA is also part of the National Laboratory Alliance which aims to increase organisational effectiveness through knowledge sharing and co-developing capability. As UKHSA enters its second year as an organisation, PSRE links will grow, especially now as UKHSA is eligible for UKRI funding.

Engagement with external stakeholders

The KMM has continued to build relationships and connections with stakeholders across formal/informal and multidisciplinary networks, including those across government (e.g., civil service environment network). Stakeholder mapping will continue to be conducted throughout the HPRU's lifetime. By identifying end-users and other stakeholders at the project and theme level, the HPRU-EEH can map and reach out to facilitate knowledge transfer and identify areas for new work where there are evidence gaps.

Several HPRU members have been successfully elected to the International Commission on Radiation Protection (ICRP) to serve on its Main Commission and its Committees. Members serve on Committee 1 (Radiation Effects) and the Main Commission. The UKHSA lead for the HPRU is the UK representative to the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), appointed by Foreign, Commonwealth and Development Office (FCDO).

Working with the Institution of Environmental Sciences, the work of four HPRUs (CRTH, Environmental Change and Health and the two Environmental Exposures and Health Units) were highlighted in a webinar in February 2022. The MRC Toxicology Unit offered a small number of places to HPRU PhD students on their Integrated Toxicology Partnership Summer School, and three HPRU members gave presentations at the International Society of Radiation Epidemiology and Dosimetry (ISoRED) webinar. A number of UKHSA staff are on the organisational committee for the European Radiation Protection Week in October which involves many stakeholders.

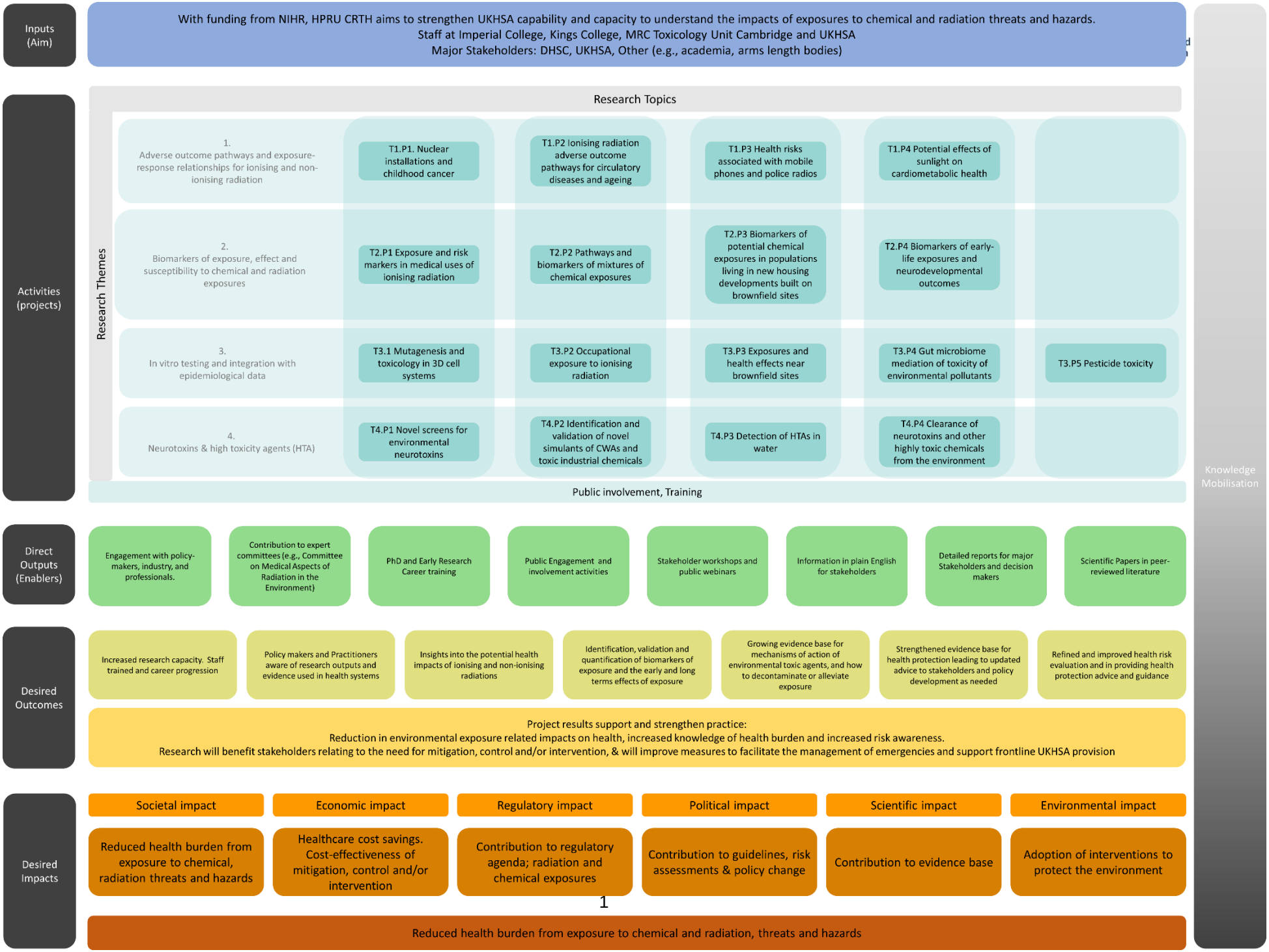
Research into Impact

Theory of change model has been drafted which explanation of how HPRU projects lead to results that leads to impacts (Figure 1)

The KMM regularly attends the Environmental Public Health Practice Board at the UKHSA to ensure dissemination of results to the regional and local Public Health Practice teams. There has been continued representation of HPRU staff on the expert Committee on Medical Aspects of Radiation in the Environment (COMARE). This committee is sponsored and attended by Department of Health & Social Care, Department of Environment and Rural Affairs, Environment Agency etc. Representation allows information flow about current work programmes into the HPRU. The KMM also regularly attends to identify emerging topics. Work from Theme I focussed on childhood cancer and nuclear installations feeds into the work programme of COMARE, and COMARE also retains a watching brief on electromagnetic field exposures such as those from mobile phones in young people in Theme II.

HPRU researchers were involved with writing the UNSCEAR 2020/21 Annex C, Biological Mechanisms relevant for the inference of cancer risks from low dose and low dose-rate radiation in December 2021 http://www.unscear.org/docs/publications/2020/UNSCEAR_2020_21_Annex-C.pdf .

Researchers, as well as the Public and Community Oversight Group under Theme II have contributed to the development of new European Society for Vascular Surgery guidelines for radiation protection for vascular operators and patients https://www.sciencedirect.com/science/article/pii/S1078588422005469/pdf?md5=051a89927859acb10bfafe65ba6f6617&pid=1-s2.0-S1078588422005469-main.pdf. This activity was initiated in response to the new EU Basic Safety Standards which came into force in 2018 and relies on the existing clinical links with Kings College. These clinical links include a further two projects examine Exposure and Risk Markers in Medical Uses of ionising radiation.
Work on Bacteria-pollutant interactions under Theme III is under review by Patent attorneys. This indicates the intellectual property potential of the work which will bring added value to the HPRU.


Inputs (Aim)
With funding from NIHR, HPRU CRTH aims to strengthen UKHSA capability and capacity to understand the impacts of exposures to chemical and radiation threats and hazards.
Staff at Imperial College, Kings College, MRC Toxicology Unit Cambridge and UKHSA
Major Stakeholders: DHSC, UKHSA, Other (e.g., academia, arms length bodies)
Activities (projects)
Research Topics
Research Themes
1. Adverse outcome pathways and exposure-response relationships for ionising and non-ionising radiation
T1.P1. Nuclear installations and childhood cancer
T1.P2 Ionising radiation adverse outcome pathways for circulatory diseases and ageing
T1.P3 Health risks associated with mobile phones and police radios
T1.P4 Potential effects of sunlight on cardiometabolic health
2. Biomarkers of exposure, effect and susceptibility to chemical and radiation exposures
T2.P1 Exposure and risk markers in medical uses of ionising radiation
T2.P2 Pathways and biomarkers of mixtures of chemical exposures
T2.P3 Biomarkers of potential chemical exposures in populations living in new housing developments built on brownfield sites
T2.P4 Biomarkers of early-life exposures and neurodevelopmental outcomes
3. In vitro testing and integration with epidemiological data
T3.1 Mutagenesis and toxicology in 3D cell systems
T3.P2 Occupational exposure to ionising radiation
T3.P3 Exposures and health effects near brownfield sites
T3.P4 Gut microbiome mediation of toxicity of environmental pollutants
T3.P5 Pesticide toxicity
4. Neurotoxins & high toxicity agents (HTA)
T4.P1 Novel screens for environmental neurotoxins
T4.P2 Identification and validation of novel simulants of CWAs and toxic industrial chemicals
T4.P3 Detection of HTAs in water
T4.P4 Clearance of neurotoxins and other highly toxic chemicals from the environment
Public involvement, Training
Knowledge Mobilisation
Direct Outputs (Enablers)
Engagement with policy-makers, industry, and professionals.
Contribution to expert committees (e.g., Committee on Medical Aspects of Radiation in the Environment)
PhD and Early Research Career training
Public Engagement and involvement activities
Stakeholder workshops and public webinars
Information in plain English for stakeholders
Detailed reports for major Stakeholders and decision makers
Scientific Papers in peer-reviewed literature
Desired Outcomes
Increased research capacity. Staff trained and career progression
Policy makers and Practitioners aware of research outputs and evidence used in health systems
Insights into the potential health impacts of ionising and non-ionising radiations
Identification, validation and quantification of biomarkers of exposure and the early and long terms effects of exposure
Growing evidence base for mechanisms of action of environmental toxic agents, and how to decontaminate or alleviate exposure
Strengthened evidence base for health protection leading to updated advice to stakeholders and policy development as needed
Refined and improved health risk evaluation and in providing health protection advice and guidance
Project results support and strengthen practice:
Reduction in environmental exposure related impacts on health, increased knowledge of health burden and increased risk awareness.
Research will benefit stakeholders relating to the need for mitigation, control and/or intervention, & will improve measures to facilitate the management of emergencies and support frontline UKHSA provision
Desired Impacts
Societal impact
Economic impact
Regulatory impact
Political impact
Scientific impact
Environmental impact
Reduced health burden from exposure to chemical, radiation threats and hazards
Healthcare cost savings. Cost-effectiveness of mitigation, control and/or intervention
Contribution to regulatory agenda; radiation and chemical exposures
Contribution to guidelines, risk assessments & policy change
Contribution to evidence base
Adoption of interventions to protect the environment
1
Reduced health burden from exposure to chemical and radiation, threats and hazards

6. COLLABORATION WITH OTHER HPRUs

From commencement of the HPRU-CRTH, we established a close partnership with the HPRU-EEH. We set up a common governance and management structures. We established a joint Executive Group, the Academic Career Development, and PCIEP Committees are jointly led and include representatives from all the partners from 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, and to further integrate with the established training programmes at UKHSA and the MRC-CEH.

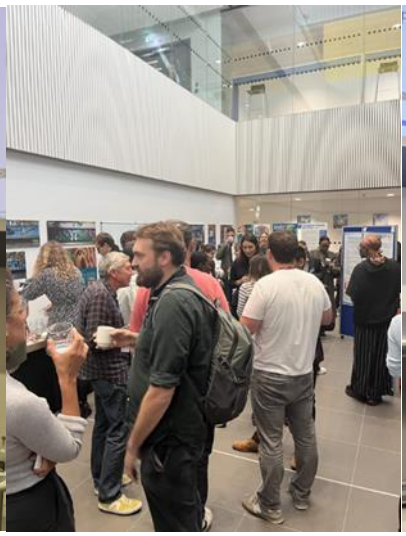
The PCIEP Manager is a member of the Cross-HPRU behavioural science network and is sharing our work and experience in this area.

The early career researchers and PhD students are members of the NIHR Academy, which provides access to a training programme, and all HPRU PhD students and supervisors are invited to the annual UKHSA PhD students' day.

The HPRU-CRTH, 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 Environmental Exposures and Health) are involved in joint public engagement and outreach events for the Imperial Festival.

The KMM has actively participated in the Pan-HPRU Knowledge Mobilisation Network and is the Training Lead within the network. This network has had regular meetings where best practice is discussed and experiences shared. The appointed KMM works across HPRU-CRTH, the HPRU-EEH and the HPRU in Environmental Change and Health facilitating efficient knowledge management, transfer and exchange. A recent piece of joint working between HPRUs involved creating a training survey to identify KM training priorities.

We invited all HPRUs to take part in our 2022 Academic Career Development Programme Annual Day held in September 2022 and we were pleased that we had representation from the HPRUs in Modelling and Health Economics and in Healthcare Associated Infections and Antimicrobial Resistance, with a student from the HPRU in Modelling and Health Economics winning a prize for his poster presentation.




ANNEXES

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ANNEX 1: HPRU-CRTH GOVERNANCE AND MANAGEMENT

HPRU-CRTH Director and UKHSA Lead

Professor Paul Elliott MBBS PhD FRCP FPHM FMedSci CBE - Professor of Epidemiology and Public Health Medicine, School of Public Health, Imperial College London

Professor Paul Elliott joined Imperial College London in 1995 as Chair in Epidemiology and Public Health Medicine. He is Head of the Department of Epidemiology and Biostatistics in the School of Public Health. He is also an honorary clinical consultant in public health medicine at Imperial College Healthcare NHS Trust, academic lead for the Informatics & Biobanking research theme of the Imperial NIHR Biomedical Research Centre and Director of Information Governance for the Imperial Academic Health Sciences Centre. He has been Director of the UK Small Area Health Statistics Unit (SAHSU) since 1991, Director of the MRC Centre for Environment and Health since 2009, and Director of the NIHR Health Protection Unit in Chemical and Radiation Threats and Hazards at Imperial College London since 2020. He is a member of the UK Biobank Strategic Oversight Committee and associate Director of Health Data Research UK-London. His contribution to public health research, most recently in response to the COVID-19 pandemic as director of the REACT surveillance study, was recognised in the award of a CBE in the 2021 Queen's Birthday Honours List.

Dr Simon Bouffler – Deputy Director, Radiation Protection Sciences, UK Health Security Agency

Dr Simon Bouffler trained as a biologist, receiving a BSc and PhD from the University of Southampton and has worked in the radiation protection field for over 25 years. In his role of Deputy Director, Radiation Protection Sciences, he has responsibility for the full range of UKHSA'a radiation protection functions, spanning frontline delivery of the Radiation Protection Advisor service, work related to emergency preparedness and response through to basic research onto radiation dose and risk assessment
He has wide ranging research interests on the mechanisms of radiogenic diseases and on radiation protection. He provided leadership on stakeholder engagement for the EU CONCERT project and is Chair of the MELODI Strategic Research Agenda working group and co-ordinated the RISK-IR project that investigated the effects of ionising radiation, particularly at low doses, on stem cell function. Simon has published extensively on radiation cancer and leukaemia mechanisms, radio-sensitivity, circulatory disease and eye lens sensitivity with over 120 peer reviewed publications.
In addition, he is the UK Representative to the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and a member of the International Commission on Radiological Protection (ICRP) Main Commission. For UNSCEAR he acted as coordinating lead writer for a report on Biological Mechanisms Relevant for the Inference of Cancer Risks from Low-dose and Low Dose-rate Radiation that is expected to be published later in 2021. In 2018, Simon was awarded the Weiss medal by the Association for Radiation Research.

HPRU Leadership Structure

The Joint Executive Group is the senior management, strategy and decision-making forum of the HPRUs in Environmental Exposures and Health and in Chemical and Radiation Threats and Hazards. It comprises the Unit Directors, UK HSA Leads and the HPRU Managers. The Executive Group is responsible for identifying research priorities for the HPRU work programme and ensuring they relate to UK HSA research and policy needs.

The Executive Group is supported by the partner Leads from Kings' College London and the MRC Toxicology Unit at the University of Cambridge, Knowledge Mobilisation Lead, Public and Community Oversight Group Chair, as well as the Theme Leads, Academic Career Development Programme Directors, Knowledge Mobilisation Manager and PCIEP Coordinator.

The Executive Group is also supported by advisory groups and representatives from across the Unit's research areas and core areas of activity, ensuring direct representation of these core areas in the highest governance structure of the Units (see Figure 1 below).

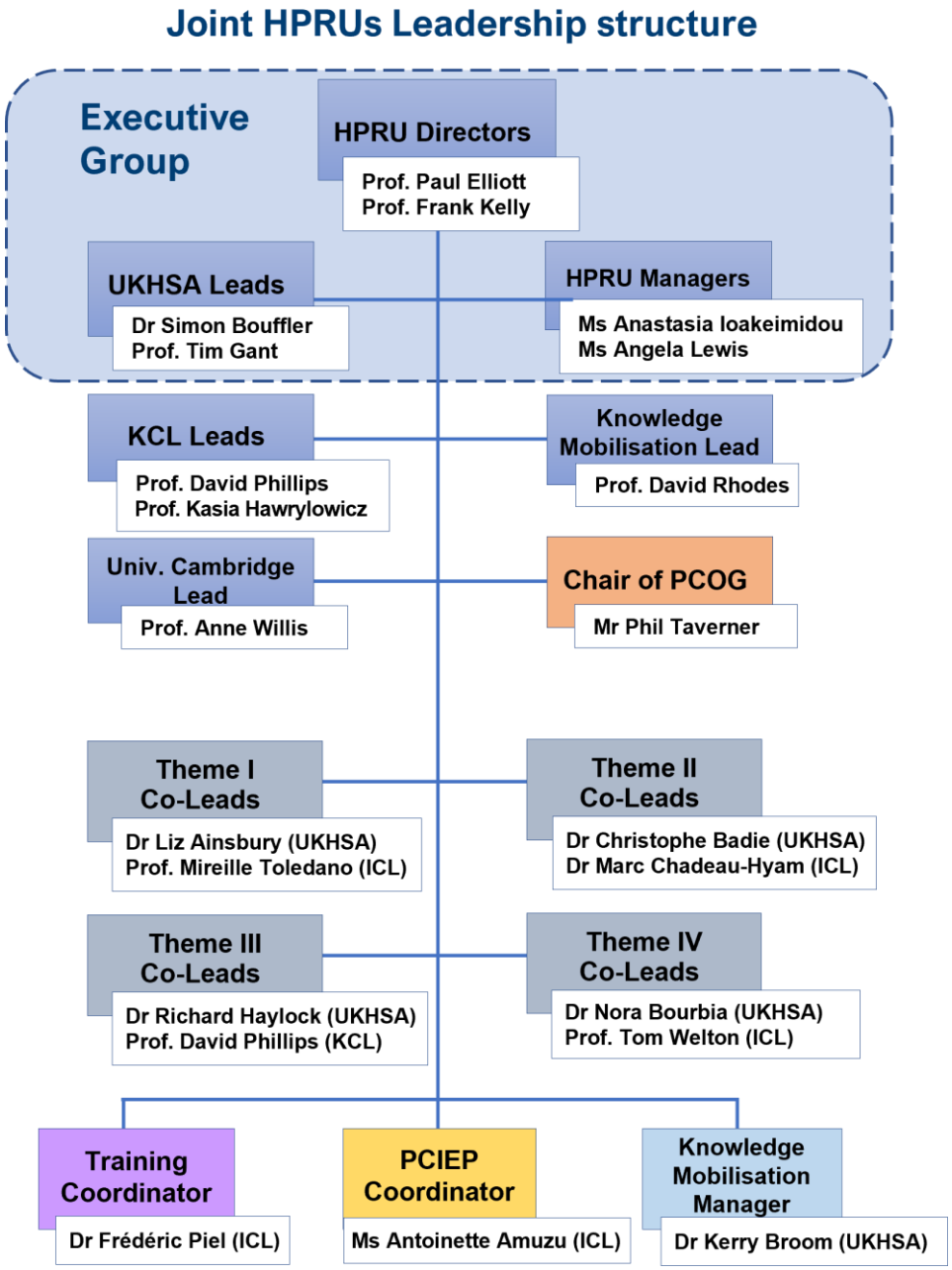

Fig.1 – NIHR HPRU in Chemical and Radiation Threats and Hazards Scientific and Management Structure

International Scientific Advisory Board

The joint International Scientific Advisory Board (ISAB) is an independent group of senior international experts in research on environment and health which acts as a scientific advisory committee, providing feedback and recommendations to the HPRU's Director and UKHSA Lead on the strategic direction and priorities of the HPRU's research and training programmes.

The Chair, membership and terms of reference of the ISAB are agreed between the Directors and UKHSA Leads of the HPRU-CRTH, HPRU-EEH and the Directors of the MRC-CEH.

ISAB Membership

Chair

Professor Jonathan Samet MD, MS
Dean and Prof, Colorado School of Public Health, USA

Key areas of expertise: epidemiology of inhaled pollutants; environmental toxicology; novel methods for *environmental* risk assessment; public health protection with a focus on tobacco control, air pollution, and chronic disease prevention; public health policy.
Short bio of Prof Samet

Members

With special focus on the remit of the NIHR HPRU in Chemical and Radiation Threats and Hazards

Dr Mark P Little
Senior Investigator, Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, USA

Key areas of expertise: radiation epidemiology - ionizing radiation and cancer/ cardiovascular risk; *radiation* biology; modelling of radio-biological processes.
Short bio of Dr Little

Dr Mark R Sambrook
CBR Division, Defence Science and Technology Laboratory, Salisbury, UK

Key areas of expertise: chemistry; detection and decomposition of high-toxicity chemicals/chemical warfare agents.

With special focus on the remit of the NIHR HPRU in Environmental Exposures and Health

Professor Ana Navas-Acien
Professor of Environmental Health Sciences, Director, Columbia University Superfund Research Program, Columbia Mailman School of Public Health, USA

Key areas of expertise: environmental epidemiology; interaction of environmental exposures with genetic and epigenetic variants.
Short bio of Prof Navas-Acien

Professor Ellen Fritsche
Professor of Environmental Toxicology, University of Dusseldorf, Germany

Key areas of expertise: environmental toxicology, neurotoxicology and developmental neurotoxicity.
Short bio of Prof Fritsche

With special focus on the remit of the MRC Centre for Environment and Health

Professor Daniel Greenbaum
President, Health Effects Institute, Boston, USA

Key areas of expertise: health effects of air pollution; environmental toxicology; development of air quality *management* policies and guidelines in the US and internationally.
Short bio of Prof Greenbaum

Professor Chris Holmes
Chair in Biostatistics, Department of Statistics, University of Oxford

Key areas of expertise: application of computational statistics and statistical machine learning to health research; genomics; metabolomics.
Short bio of Prof Holmes

NIHR / NHS

Professor Stephen Holgate
MRC Clinical Professor of Immunopharmacology at the University of Southampton, UK.

Key areas of expertise: immunology and allergy; respiratory disease and health burden of air pollution.
Short bio of Prof Holgate

ISAB Terms of Reference

The role of the ISAB is to provide independent advice to the Executive Group of the NIHR HPRU-CRTH and NIHR HPRU-EEH, and of the MRC-CEH on the strategic direction and implementation of the research programmes of these units.

Scope and responsibilities:

- Assess the scope, content and quality of the research, training and public engagement activities within the context of the Centre and HPRUs' mission and strategic aims;
- Advise on development of the scientific strategy underpinning the research and training programme, within the context of national/international developments in research on environment and health;
- Advise on the alignment and impact of HPRUs and Centre's outputs in relation to the research and public health priorities of the funding agencies;
- Advise on the appropriate deployment of resources and development of research and training capacity;
- Review the level and range of scientific, educational and public engagement outputs of the HPRUs and Centre in relation to the stated milestones and deliverables;
- Promote relevant contacts with government departments, agencies and other academic groups, nationally and internationally.

ANNEX 2: ACADEMIC CAREER DEVELOPMENT PROGRAMME SUPPLMENTARY INFORMATION

Joint Academic Career Development Committee

The JACD Committee consists of representatives from each of the partners in the two HPRUs and the MRC-CEH, and of the students and early career researchers. Its role is to guide and support the development of a robust multidisciplinary programme for training the next generation of environmental health scientists affiliated with these units.

Joint Academic Career Development Committee Membership

- JACD Programme Director - *Dr Frédéric Piel* (ICL)
- JACD Programme Deputy Director - *Dr Stephanie Wright* (ICL)
- HPRU-CRTH representative - *Dr Liz Ainsbury* (UKHSA)
- HPRU-EEH representative - *Dr Matthew Wright* (UKHSA)
- MRC Tox Unit representative –*Dr Kirsti Hornigold* (University of Cambridge)
- Researchers' Society representative - *Ms Melanie Egli* (ICL)
- HPRU-CRTH & MRC-CEH Scientific Manager – *Ms Anastasia Ioakeimidou* (ICL)
- HPRU-EEH Manager and ERG Associate Director – *Ms Angela Lewis* (ICL)
- MRC-CEH Research Coordinator - *Ms Eno Umoh* (ICL)

Joint Academic Career Development Committee Terms of Reference

The JACD shall conduct its business according to the following terms of reference:

- To support the development of a robust multidisciplinary training programme for the next generation of environmental health scientists affiliated with the HPRUs and MRC Centre.
- To discuss training strategy, training portfolio and early career research experience.
- To receive updates on the Training Programme and monitor progress.
- To regularly engage with affiliated students, early-career researchers, fellows and supervisors.

The Committee shall normally meet every two months either in person or by videoconference. Minutes of the Committee meetings shall be taken in turn by one of the Committee members. Members of the Committee unable to attend a meeting may nominate a replacement providing that the Chair is notified at least a week in advance of the meeting. The Committee may from time to time propose adjustments to its membership. A member of the Committee shall immediately cease its functions if, by notice in writing to the Committee Chair s/he resigns their membership.

ANNEX 3: PUBLIC AND COMMUNITY INVOLVEMENT, ENGAGEMENT AND PARTICIPATION (PCIEP) SUPPLEMENTARY INFORMATION

Joint Public and Community Involvement, Engagement and Participation Committee

The Joint PCIEP Committee consists of representatives from each of the partners in the HPRUs and the MRC Centre, led by the PCIEP Coordinators in the two HPRUs. It is responsible for coordinating and supporting the activities of the Public and Community Oversight Group (PCOG), and for the implementation of the PCIEP strategy and activities, co-developed with the PCOG.

Joint PCIEP Committee Membership

- PCIEP Coordinator, HPRU-CRTH - *Ms Antoinette Amuzu* (ICL)
- PCIEP Coordinator, HPRU-EEH – *Dr Diana Varaden* (ICL)
- MRC-CEH PCIEP Lead – *Dr Ian Mudway* (ICL)
- HPRU-CRTH representative - *Dr Liz Ainsbury* (UKHSA)
- HPRU-EEH representative - *Dr Philippa Douglas* (UKHSA)
- MRC Tox Unit representative - *Dr Liza Selley* (University of Cambridge)
- MRC-CEH & HPRU-CRTH representative - *Dr Bethan Davies* (ICL)
- HPRU-EEH Manager and ERG Associate Director – *Ms Angela Lewis* (ICL)
- HPRU-CRTH & MRC-CEH Scientific Manager – *Ms Anastasia Ioakeimidou* (ICL)

Joint PCIEP Strategy

Please see the Joint PCIEP Strategy document

Public and Community Oversight Group

The new Public and Community Oversight Group (PCOG) has been set up with the aim of advising the HPRU-CRTH, HPRU-EEH and MRC-CEH, ensuring that the public and community voice impacts the research strategies, projects and functions of these units and that our research is accountable, transparent and relevant to the public. The new PCOG benefits from the skills, expertise and experience of over 35 members, including members of the general public, industries, local government, community and patient groups, academics and third sector organisations.

PCOG Membership

Chair

- *Mr Phillip Taverner*

Phil Taverner has a long career in health and social care management and public engagement. He chaired the National Institute for Clinical Excellence (NICE) Committee on Provision of Support for Adult Carers (2017-2020) and is currently a member of a NICE Quality Standards committee, a public member of the Cochrane Airways Priority Setting Group, and a lay reviewer for the British Medical Journal. Previously, he was Assistant Director of an NIHR unit in Southampton (2008-2015), responsible for managing the local Public Health Research programme, and Assistant Director of the National Society for the Prevention of Cruelty to Children in South-East England (2000-2008). He holds a BSc in Sociology with Social Work from the University of Bath.

PCOG Members

– Catherine Sutton	Airborne Allergy Action
– Leigh George	Allergy UK
– Zak Bond	Asthma UK/ British Lung Foundation
– Margaret Jackson	Big Locals
– Stuart Upton	BRE Group
– Professor Andre Ng	British Cardiovascular Society
– Roger Barrowcliff	Clean Air Thinking

PCOG Members (cont.)

– Stewart Martin	COMARE
– Adam Spencer	Communities.gov.uk
– Rebeca Cosgriff	Cystic Fibrosis Trust
– Chris Large	Global Action Plan
– Anna Tarkington	Guy's and St Thomas' Charity
– Jemima Hartshorn	Mums for lungs
– Carol Goodchild	UKHSA Peoples Panel

– John Phipps	UKHSA Peoples Panel
– Robert Goundry	UKHSA Peoples Panel
– Peter Gosling	UKHSA Peoples Panel
– Colette Kelly	UKHSA Peoples Panel
– Ian Wright*	UKHSA Peoples Panel
– Geoff Driver	UKHSA Peoples Panel
– Mike Nielsen	UKHSA Peoples Panel
– Lee White	UKHSA Peoples Panel
– Sahiqa Kauser	UKHSA Peoples Panel
– Andrew Wood	UKHSA Peoples Panel
– Roger Gibb	UKHSA Peoples Panel
– Eve Smyth	UKHSA Peoples Panel
– Salim Vohra	Public Health by Design
– Pete Bryant	Society for Radiological Protection
– Philip Plant	Society of Radiographers
– Andy Cope	Sustrans.org.uk
– Grainne McGill	University of Strathclyde
– Adam Thomas	University of the West of England (Bristol)
– Ruth Morse	University of the West of England (Bristol)
– Isabella Myers	Independent consultant

PCOG Terms of Reference

Please see the PCOG Terms of Reference

ANNEX 4: KNOWLEDGE MOBILISATION SUPPLEMENTARY INFORMATION

Knowledge mobilisation brings together different communities to share knowledge to catalyse change. It is a two-way process which enables advances in health protection research to create benefits for patients and the public by supporting research informed decision-making by policy makers, public health practitioners, the public, and other stakeholders.

Our Knowledge Mobilisation Strategy outlines our approach to promoting the use of the knowledge generated by the HPRU:

- internally, by developing expertise and establishing a culture within the partner organisations that actively seeks to apply the research evidence on chemical and radiation hazards for decision making on public health protection;
- externally, by increasing the understanding of the value of research among those who can use research findings to address the rapidly emerging policy agenda on chemical and radiation risk management.

Please see the HPRU-CRTH Knowledge Mobilisation Strategy

ANNEX 5. HPRU-CRTH PUBLICATIONS

Below is a list of papers published by HPRU-CRTH members from 01 August 2021 to 31 July 2022. All papers that credit the HPRU-CRTH in the affiliations of funder acknowledgements are included.

1. Atchison, C., Pristerà, P., Cooper, E., Papageorgiou, V., Redd, R., Piggin, M., . . . Ward, H. (2021). Usability and acceptability of home-based self-testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies for population surveillance. Clinical Infectious Diseases, 72(9), E384-E393. https://doi.org/10.1093/cid/ciaa1178
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3. Collins, S., Williams, N., Southworth, F., James, T., Davidson, L., Orchard, E., . . . Amlôt, R. (2021). Evaluating the impact of decontamination interventions performed in sequence for mass casualty chemical incidents. Scientific Reports, 11(1) https://doi.org/10.1038/s41598-021-94644-0
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9. Grosso, S., Marini, A., Gyuraszova, K., Voorde, J. V., Sfakianos, A., Garland, G. D., . . . Willis, A. E. (2021). The pathogenesis of mesothelioma is driven by a dysregulated translatome. Nature Communications, 12(1) https://doi.org/10.1038/s41467-021-25173-7
10. James, T., Collins, S., & Marczylo, T. (2021). Identification of novel simulants for toxic industrial chemicals and chemical warfare agents for human decontamination studies: A systematic review and categorisation of physicochemical characteristics. International Journal of Environmental Research and Public Health, 18(16) https://doi.org/10.3390/ijerph18168681
11. James, T., Izon-Cooper, L., Collins, S., Cole, H., & Marczylo, T. (2022). The wash-in effect and its significance for mass casualty decontamination. Journal of Toxicology and Environmental Health - Part B: Critical Reviews, 25(3), 113-134. https://doi.org/10.1080/10937404.2022.2042443
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13. Konstantinoudis, G., Cameletti, M., Gómez-Rubio, V. et al. (2022). Regional excess mortality during the 2020 COVID-19 pandemic in five European countries. Nature Communications, 13, 482. https://doi.org/10.1038/s41467-022-28157-3
14. Lindell, A. E., Zimmermann-Kogadeeva, M., & Patil, K. R. (2022). Multimodal interactions of drugs, natural compounds and pollutants with the gut microbiota. Nature Reviews Microbiology, 20(7), 431-443. https://doi.org/10.1038/s41579-022-00681-5

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16. Rashid, T., Bennett, J., Paciorek, C., Doyle, Y., Pearson-Stuttard, J., Flaxman, S., . . . B., Ezzati, M. (2021). Life expectancy and risk of death in 6791 communities in England from 2002 to 2019: high-resolution spatiotemporal analysis of civil registration data. Lancet Public Health 6: e805–16. https://doi.org/10.1016/S2468-2667(21)00205-X
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ANNEX 6: EXTERNAL FUNDING SECURED

Below is a list of externally funded projects held by HPRU-CRTH PIs that are contributing to the workplan of the HPRU (01 April 2021-31 March 2022)

Funder	Project Long Title	Project Start Date	Project End Date	HPRU PI	HPRU Theme	Total Budget Awarded	Pro-rata in second year
Medical Research Council (MRC)	Centre for Environment and Health	01/06/2019	31/05/2024	Elliott	T1:P1	£1,073,246.00	£231,943.89
Open Philanthropy (Silicon Valley Community Fund)	Epigenetic Ageing	01/12/2019	31/07/2023	Raj	T1:P2	£185,000.00	£50,328.85
Milky Way Research Foundation	Mechanisms of Epigenetic Ageing	01/01/2021	31/12/2023	Raj	T1:P2	£662,434.00	£220,407.66
Department of Health	Revision of Secondary school cohort study of mobile phone use and neurocognitive and behavioural outcomes	01/01/2014	31/12/2021	Toledano	T1:P3	£1,489,700.60	£140,249.15
Medical Research Council (MRC)	Airwave Follow-Up Support (MRC)	01/07/2018	30/06/2023	Elliott	T1:P3	£1,988,965.00	£396,703.16
Medical Research Council (MRC)	SCAMP Wave 2	04/01/2021	03/01/2026	Toledano	T1:P3	£2,449,458.74	£488,549.58
US NIAID/NIH Centers for Medical Counter Measures Against Radiation Consortium (CMCRC)	Projects SORT (Skin biOdosimtry Radiation Transcription) and ROSETTA (Radiation biOdoSimEtry TranscriT vAriants)	01/04/2021	31/03/2022	Badie	T2:P1	£151,700.00	£151,700.00
Commission of the European Communities	EXPANSE: EXposome Powered tools for healthy living in urbAN SEttings (EXPANSE)	01/01/2020	31/12/2024	Chadeau-Hyam	T2:P2	£669,561.25	£133,472.23
Commission of the European Communities	Dynamic longitudinal exposome trajectories in cardiovascular and metabolic non-communicable diseases	01/01/2020	31/12/2024	Chadeau	T2:P2	£569,221.43	£113,470.21
Medical Research Council (MRC)	REACT-GE: Multi-omics to identify biological pathways underlying severity of SARS-CoV-2 infection	15/09/2020	14/06/2021	Elliott	T2:P2	£1,820,765.08	£609,153.02
National Institute for Health Research	REACT Long COVID (REACT-LC)	01/03/2021	28/02/2024	Elliott	T2:P2	£5,448,521.00	£1,812,853.42
Cancer Research UK	Mutographs of Cancer	05/01/2017	31/10/2022	Phillips	T3:P1	£1,031,000.00	£176,604.24
Health Data Research UK	"Modernising public health" research initiative: pan-London Health Data Research UK	01/04/2018	31/03/2023	Elliott	T3:P3	£1,379,510.42	£275,146.19
National Institute of Child Health and Human Development	Improving statistical methods for small area estimates of public health indicators and demographic characteristics.	13/09/2018	31/08/2021	Piel	T3:P3	£340,031.33	£48,037.67
BBSRC-Case studentship with Syngenta	Understanding respiratory transepithelial bioavailability and comparative toxicology for human exposure assessments	01/10/2017	30/09/2021	Mudway	T3:P5A	£104,696.00	£13,122.85

Funder	Project Long Title	Project Start Date	Project End Date	HPRU PI	HPRU Theme	Total Budget Awarded	Pro-rata in second year
Medical Research Council (MRC)	Biomolecular interactions of pollutants	01/01/2021	31/12/2022	Patil	T3:P5B	£250,000.00	£124,828.53
Sustainable Food Alliance (USA)	Identifying the effects of pesticides on intestinal permeability and gut-bacterial dysbiosis	01/10/2020	30/09/2023	Antoniou	T3:P5C	£163,775.00	£54,491.86
National Institute of Health Research	Evaluating and improving the efficacy of Initial and Specialist Operational Response decontamination methods for powders and corrosive substances	01/09/2020	31/08/2022	Collins / Marczylo	T4:P2	£100,000.00	£49,931.41
Royal Academy of Engineering	Identification of illegal threat manufacturing activity via wastewater markers (ThreatMARK)	01/10/2019	10/01/2022	Keng Tiong Ng	T4:P5	£200,000.00	£68.509.62
DSTL	Wastewater Analysis for Narcotics Detection (WAND)	19/02/2021	31/03/2023	Barron	T4:P5	£1,782,000.00	£842,400.00
					TOTAL	**£22,138,391.25**	**£6,262,708.54**