Air Pollutant Toxicology Round Table 3rd December 2020

Rebuilding air pollution toxicology research in the UK: A call for action.

A. Introduction

Air pollution is acknowledged as one of the five greatest health risks to humanity worldwide and the single greatest environmental health risk. Both short- and long-term exposure to air pollution can lead to and exacerbate a wide range of diseases effecting almost all organs. Put simply, air pollution is an under-recognised systemic stressor across the life course.

Both short- and long-term exposure to air pollution can lead to and accelerate a wide range of diseases (e.g. cardiovascular diseases and reduced lung function, respiratory infection, and asthma). The World Health Organization (WHO) provides evidence of links between exposure to air pollution and type 2 diabetes, obesity, systemic inflammation, Alzheimer's disease and dementia (https://www.eea.europa.eu/themes/air/health-impacts-of-air-pollution). The International Agency for Research on Cancer has classified air pollution (in particular $PM_{2.5}$) as a leading cause of cancer. A recent global review found that chronic exposure can affect every organ in the body, complicating and exacerbating existing health conditions (https://www.eea.europa.eu/publications/healthy-environment-healthy-lives). Air pollution, both outdoors and indoors, impacts human health from conception to death and, therefore, assessing its impact requires a life-course perspective. Indeed, if epigenetic factors are included then transgenerational influences may operate before conception.

A combination of epidemiology and toxicology is required to understand the consequences of air pollution on human health, and mechanisms for these adverse effects. Toxicology of air pollutants enables causative pathways to be established thereby facilitating decisions over which pollutants and their sources require regulation. Currently, policy measures for air pollutant control cannot be focussed to yield the most cost-effective solutions to minimise impacts upon public health due to a lack of adequate pollutant-specific knowledge of effects. This is especially the case for airborne particles where current regulatory approaches focus on mass concentration rather than their chemical composition or physical properties. Similarly, it is still not clear whether adverse health effects of NO_2 is a consequence of this gas or the co-emitted organic pollutants e.g. from diesel combustion.

There is also the emerging recognition of indoor air pollution about which far less is known when compared with that outdoors. As more attention is being focused to conserve energy to meet climate change objectives, new homes are being "sealed" but with less regard to indoor ventilation and chemical pollutants that may accumulate as a result.

While epidemiology can establish associations between air pollutant exposures and health effects, with this single approach, only pollutant interventions can establish causality. There is therefore a need to be able to better support epidemiological associations with mechanistic work as a stepping-stone to causality and to support interventions. Currently, policy measures for air pollutant control cannot currently be focussed to yield the most cost-effective solutions to minimise impacts upon public health due to a lack of adequate pollutant-specific knowledge of effects (https://www.epa.gov/clean-air-act-overview/air-pollution-current-and-future-challenges). New approaches are needed to research on the health effects of air pollutants; to address questions such as how to distinguish the effects of closely correlated pollutants in epidemiological studies, to investigate which pollutant mixtures that are associated with adverse health and how to differentiate the toxicity of particles of different composition. This is important because it would lead to source identification and control measures. An increased focus on toxicology will unlock these questions, to inform a mechanistic understanding of the adverse effects of air pollution on human health and optimise policy. In marked contrast to the growth of high-quality epidemiology and atmospheric science, where the UK is world leading, our once strong air pollution toxicology research has declined.

This report summarises a round table convened by the Clean Air Champions to address this issue. It is clear that progress cannot be made without enabling actions by those that fund research in the UK. The report begins with recommendations for capacity building and key research priorities. This is followed by a detailed summary of the presentations and discussion from the round table.

B. Summary and Recommendations

Put simply, a lack of modern air pollution toxicology input is holding back the development of air quality polices to protect human health.

1. **Mechanisms of toxicity.** Is there one common mechanism which explains effects on multiple health endpoints (such as systemic or local inflammation, oxidative stress, DNA damage) or multiple different mechanisms each elicited by a different component of the air pollution mixture? It is particularly important to focus on the molecular initiating event e.g. receptor interaction and not to just the apical outcome such as cell death which can be the outcome of numerous molecular initiating events.
2. **Better integration of toxicology with epidemiology.** Understanding spatial and temporal changes in air pollution and health. Understanding how susceptibilities such as pre-natal and early life exposures impact on later-life risk of chronic disease. Where there are established biomarkers of exposure, use the exposome concept for exposure measurement and an understanding of toxicological hazard mechanisms to discern risk. Align these data with epidemiological findings or to initiate epidemiology and where possible, integration of source apportionment measures.
3. **Improve *in vitro* and *in vivo* assay systems for the assessment of toxicological hazard**. Develop and refine models to assist in the understanding of mechanistic hazard work based on their capacity to predict acute and chronic clinical responses. This is more challenging for longer-term and low-level exposures. Where necessary, animal studies have a role to play with researchers being encouraged to collectively integrate animal and *in vitro* work.

4. **What factors make an individual particularly susceptible/vulnerable to the effects of air pollutants** ideally using a combined animal and human approach. Application of artificial intelligence, genetic/epigenetic approaches, and novel genetically altered model systems. Input from experts in these diseases, where overlap between effects of pollution and pathomechanisms will open up new avenues for research.
5. **Develop informative biomarkers** and make them specific for particular types of exposure. From this, promote more hypothesis driven research to validate findings from large scale agnostic analysis using multi-omic platforms. Follow up findings from -omics work in other models to confirm the importance of new markers and to place them with adverse outcome pathways contributing to the development of chronic disease.
6. **Ranking of air quality hazards**. Ranking is important for intervention and policy strategies and the protection of health. This has traditionally been done using epidemiology but has limitations. The objective is to use mechanistic information to enhance the accuracy of the ranking, e.g. from agriculture, certain transport (shipping, aviation, underground), wood-stove fumes, non-exhaust traffic pollutants, indoor pollution, in order to design targeted interventions for health improvement.
7. **There is an urgent need for (more) 'freshly collected' particulates** from UK pollution to perform comparative toxicology alongside 'older' PM materials. Suitable amounts need to be collected and stored for toxicology work in multiple laboratories.
8. **Understanding the importance of combination exposures**. Air quality combinations can consist of anthropogenic particles, combustion particles, gases and biologicals (e.g. dust mite, fungal, animal and pollen allergens and infectious agents). Understanding how these interact is important to understand disease mechanisms and for creating effective interventions for improving health. This is difficult to do using an epidemiological approach and requires well understood model systems and an understanding of differential hazards with additive, antagonistic and synergistic effects.
9. **Establish indoor air quality standards and human biomonitoring guidance values for key air pollutants and combinations thereof.** Consider going beyond the concept of personal exposures to "criterion pollutants" (both indoor and outdoor) to a more comprehensive understanding of complex chemical exposures and internal biomarkers of exposure, as the gold standard for assessing environmental xenobiotics. This needs to be based on a mechanistic understanding of pollutant hazard alone, in combination, as well as levels of exposure and target susceptibility.
10. **Address which pharmacological interventions may attenuate the effects of air pollution**. In the longer term the possibility of prophylactic/therapeutic and dietary interventions should not be ruled out, particularly for vulnerable groups or those with unavoidable high exposure to air pollution.

C. Enablers to facilitate new research and capacity building

1. **Move away from descriptive science. The questions are too complex to make firm conclusions from global profiling for example.**

2. **Urgent requirement for a human *in vivo* exposure chamber for trials.**
3. **Identify dedicated funding.** Not just to go to the well-recognised centres but also to bring in new researchers who have different abilities.
4. **Establish a strong core group of scientists from all disciplines.** In doing so, create better communication and understanding between disciplines and focusing on how investigators can work together, rather than focusing on weaknesses of each discipline.
5. **Encourage early career researchers to join and build a future in the area with greater stability.** Consider a specific strand of funding, maybe nested within the Integrated Toxicology Training Partnership (ITTP) studentships (https://www.mrc-tox.cam.ac.uk/postgraduate/ittp-integrative-toxicology-training-partnership)? It would also be helpful to develop conversations with GO-Science on The Government Science and Engineering (GSE) profession gap and also possible links to the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment.
6. **Organise high profile meetings that are co-created with government agencies and the media.**
7. **Create more joined up working/banking/pipeline development for the collection of PM samples from a wide range of sources.**

These priority areas have been identified from a range of topics discussed which are presented below.

D. Background and Context

An informative Royal Society Workshop, *Research priorities in air pollution and health: recommendations* was held on 14th and 15th September 2020 (Appendix 1). This discussed new approaches to research on the health effects of air pollutants, to address questions such as how to distinguish the effects of closely correlated pollutants in epidemiological studies and how to differentiate the toxicity of particles of different composition or from different sources a series of key conclusions emerged, most notably the need for further investment in air pollutant toxicology. As in other fields of toxicology the UK has been at the forefront in developing and supporting this speciality, but in recent years this has declined https://pubs.rsc.org/am/content/articlepdf/2019/tx/c9tx00063a. This is especially the case for air pollution. The reason for this is likely to be multifactorial, but the net result is a workforce that is limited and fragmented. This is in marked contrast to the growth of high-quality epidemiology and atmospheric science, in which the UK are world leaders (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/832948/annual-report-of-the-chief-medical-officer-2019.pdf).
Flowing from the conclusions of the RS Air Pollution Workshop (which extended beyond toxicology research) and the Road Map that the Clean Air Champions undertook in 2020 (https://www.ukcleanair.org/wp-content/uploads/sites/361/2020/09/A-UK-research-roadmap-for-clean-air-summary.pdf), it became clear that a more in depth analysis of the air pollution toxicological landscape in the UK was required with a view to both current and future needs to inform improved policy. This review was especially timely following the UK's exit from the European Union since the UK now has the opportunity to set its own air quality policies (https://uk-air.defra.gov.uk/air-pollution/uk-eu-policy-context and https://airqualitynews.com/2020/10/12/protecting-air-quality-after-brexit/).

Following the Royal Society Workshop, a preliminary paper on this topic was prepared by the late Martin Williams summarising the Clean Air Champions views (*Thoughts from the Clean Air Champions on Research Priorities following the Royal Society Meeting 14-15 September 2020*) and is included as Appendix 2.

Jointly coordinated by Dr Graham Campbell, Programme Manager of the Molecular and Cellular Medicine Board of the Medical Research Council and with the Clean Air Champions (Professor Sir Stephen Holgate, Professor Martin Williams and Dr Jenny Baverstock), a Round Table Discussion involving a wide range of air pollution toxicology researchers and those with wider interests in the field, took place by Zoom on December 3rd 2020. Attendees were asked to prepare short answers to the following questions: 1) What do you see as the top three problems; 2) What do you consider are the top five research areas and experimental approaches to the problem?; 3) What are the three main enablers that we could do as a community to build back toxicology as a strong research field?; 4) What are your top three enablers to build capacity building for early career researchers?; 5) Which are the organisations to raise concerns about toxicology with, to seek possible additional funding?; and 6) Could you provide your top three to five priorities in air pollution toxicology?

After participants gave brief presentations, there was extensive discussion. This was then captured in subsequent brief text provided by participants. In distilling the conclusions from this event, several major themes emerged. Since there was some overlap in the responses, these have been grouped for simplicity. Under each of these are subheadings listed according to the priorities suggested.

E. Approach

1. **Current research in this area at present lacks novelty and innovation and experimental approaches being used are often not informative.**
    a. Toxicology is often a work package in a multi-disciplinary grant, rather than a being a central focus of a large grant that brings different toxicological groups/methods together (important for funding sufficient staff to do a decent body of practical toxicology work).
    b. There is a problem with intellectual and logistical cooperation across disciplines. Getting to grips with PM toxicology spans many disciplines, from atmospheric chemistry and "measurement science" through analytical chemistry, cell and molecular biology, and clinical medicine, and others besides.
    c. Analytical methodologies are needed to advance microplastic toxicology.
    d. Develop *in silico* modelling *and* artificial intelligence approaches exploiting current data sets.
    e. For some studies to be hypothesis free (e.g. 'omics approach) to generate reliable markers of exposure to identify and monitor air pollution exposure (exposome).
    f. Use the more sophisticated biologically relevant *in vitro* models (e.g. organoids, multi-cell models and use human cells) and animal models (e.g. humanised animal exposure models) to address hypotheses that arise from both epidemiology and toxicology.

g. Better linking of *in vitro* studies with *in vivo* (e.g. animal models) across to population-based epidemiology – e.g. exposure doses that have "real world" relevance.
h. Improvement of population level biomonitoring, not only for health protection, but to ensure policy is supported by evidence using more mechanistic areas.
i. There is an issue with toxicology having focused more on the apical outcome such as disease and not at the level of the molecular initiating event. Understanding the latter is more important for the design of policy and intervention to improve health.

2. **Epidemiologists need to work together with toxicologists.**
    a. To design toxicological experiments that provide solutions for policymakers. This would involve multidisciplinary work with epidemiologists, atmospheric scientists as well as the policy community. Air pollution toxicology can sometimes be considered to be an after-thought to epidemiology, rather than given an equal weighting with recognition that they address different facets of the same question.
    b. Relating the epidemiological findings with mechanistic toxicology to then address the problems relating to e.g. exposure dose, toxic mechanisms, interactions with disease and duration of exposure.
    c. Incorporation of mechanistic investigations within prospective epidemiological studies. Collaborative research to bring together the mechanistic toxicologists (*in vitro* and *in vivo*) and the epidemiologists to make the most use of materials and samples across the air pollution community.
3. **Lack of toxicological expertise**. Lack of toxicology training and funding in the UK is a real problem. Currently, only a few academic groups are working on mechanistic toxicology (in particular, mechanisms of air pollution toxicology e.g. MRC Toxicology Unit, Cambridge; PHE Toxicology Department; Harwell Science Campus, Oxfordshire; MRC-PHE Centre for Environment and Health, IC, London; University/BHF Centre for Cardiovascular Science, University of Edinburgh).
4. **Collaboration between UK air pollution groups is not as good as it should be**. There is reasonable collaboration across disciplines in large consortium projects, but not between groups that specialise in toxicological aspects of air pollution. Is there enough networking within the toxicology community in the UK and lack of multidisciplinary networking of toxicologists, chemists, epidemiologists and healthcare? At air pollution meetings, the measurement/atmospheric science generally predominates.
5. **Insufficient and insufficiently targeted funding** to undertake substantial toxicological investigations with respect to air pollution.

F. Improved Methodology

1. **Consensus and equivalence between different aero-toxicity assays**.
    a. Lack of standardisation and agreement of outputs across the field.
    b. Lack of mechanistic understanding in human relevant models and lack of models able to deal with low level and chronic exposure – limitations of *in vitro*/animal models.
    c. Need for studies of different pollutants/types of PM in the same experimental systems (as part of the same study) to inform consideration of causality and differential toxicity.

d. Develop high throughput screening assays and models (and maybe even *in situ* methods for monitoring) for rapid screening for results from *in vitro* assays which read across to *in vivo* animal effects.
e. Application of laboratory based genetic studies in cell culture and animal models to identify toxic mechanisms and susceptibility factors.

2. Lack of *in vivo* challenge facilities

a. In contrast to other countries that lead in air pollutant research (the Netherlands, others?), there is no dedicated UK chamber exposure facility for humans. This means that it is difficult to study exposures in a controlled manner *in vivo*.
b. *In vivo* exposure studies should be designed for maximal use of samples/tissue for data analyses.
c. Standardised aerosols are required for reproducible *in vivo* exposures. For this, new methods of generating aerosols are needed. Some innovative projects exist to generate standardised aerosols to test instrumentation (e.g. at NPL). Such generators could be coupled with a chamber giving far more exposure options beyond simply running a diesel engine. The European Aerotox project (https://www.euramet.org/research-innovation/search-research-projects/details/?tx_eurametctcp_project[project]=1622) is looking to see how these standardised aerosol generators could be used in toxicological studies.
d. Controlled exposures of humans, lab animals and *in vitro* systems, combining batteries of techniques and disciplines to make best use of each individual study to address mechanistic questions with respect to multiple endpoints/disciplines. It is essential to have the ability to carry out human and animal exposure studies.
e. Move to establish more human exposure challenge laboratories and link these up with each other and with the wider research community to utilise the materials and samples for analytical studies.

3. What are the effects of chronic exposure to air pollution, and how can we study this?

a. Lack of modelling long term chronic and low-level exposures – dose relevance. Understanding of hazard in toxicology studies tends to rely on short-term, higher-level exposures because of model limitations, time or cost. These are difficult to extrapolate to chronic long-term effects, particularly of low-level exposures. This makes linkage of toxicology to population level health impacts particularly challenging. Fundamental to addressing this key issue is an improved understanding of extrapolation of data from short-term hazard exposures to longer-term effects. This requires a mechanistic understanding, particularly at the level of dose response (see d.), and mechanistically linked biomarkers to support epidemiology in human populations. This should include biomarkers of genetic sensitivity and historical exposure e.g.: epigenetic as they have the potential to reveal component-specific mechanistic pathways, that have overlap with those known to contribute to apical outcomes such as cell stress and organism disease.
b. It is important to define susceptible groups, particularly genetic susceptibility from population-based epidemiology. Genetic susceptibility can inform on mechanistic toxicology and these can be linked back to experimental animal models and more appropriate models used, e.g.: genetically modified. Here, there is real potential to exploit existing national longitudinal cohort resources and/or explore whether a

new national effort for these types of investigation is required, rather than the "bolt on approach" to previous cohort investments.

c. Studies linking biomarkers of exposure, effect and susceptibility to clinically relevant health endpoints, including chronic disease would provide novel mechanistic insights.
d. Studies are required with multiple doses to characterise the dose-response relationship and inform risk assessment.
e. Modelling long term exposure in cells and computational models would enhance linkage of mechanisms/biomarkers to relevant health end points.

4. **What are the best endpoints for such studies?**
    a. Oxidative potential offers a relatively simple, relatively high-throughput measure. A greater understanding of the role of oxidative potential in mechanistic air pollution toxicology is urgently required. *In vitro* models can be misleading as they are under a high oxidative potential which may not be relevant to disease. Furthermore, oxidative stress is a feature of disease but may not be the cause of that disease, i.e. is consequential. Mechanisms such as the activation of toll-like receptor signalling pathways may be much more important and specific for initiating disease. These mechanisms are all underexplored in respect of air pollution and the result is a fallback on oxidative potential without a clear understanding of the link to apical end points. Where oxidation is considered as a mechanistic pathway there is a need to understand if this is global or more likely at specific proteins e.g. transporters and where these are temporally located in the lung in respect of exposure. Further research may reveal other undiscovered and important mechanistic endpoints which offer either more biologically relevant readouts or the ability for faster, higher throughput screens
5. **How does air pollution interact with disease?**
    a. Is it simply that pollution induces oxidative stress and inflammation, which can lead to increased incidence and exacerbation, or are there other, more subtle, or perhaps disease/PM component specific effects which are important (see 4a.)?
    b. Air pollution has been cited as the top 'non-communicable' environmental health issue, but we need to be able to determine the best way not just to reduce air pollution, but to understand how air pollution causes long-term and short-term health effects. It is important to fully understand this at a mechanistic level to support interventions. There is a balance in economic impact, climate change and health in respect of air pollution interventions. This balance can only be realistically achieved through an understanding of mechanisms.
    c. There are specific fields where there is a need for mechanistic insight. These include air pollution in asthma exacerbation, long term neurological effects, transmission of nano particles to the brain, mechanisms by which heart rate variability is affected.
    d. A better insight of how air pollution causes/exacerbates disease may lead to a better ability to predict such effects in the future, especially where specific to certain pollution components.
6. **Develop novel/rapid/sensitive biomarkers of exposure and early markers of effect.**
    a. No single air pollutant is responsible for a specific health effect. There are interactions between complex pollutant mixtures, not only between the conventional criterion pollutants but also with allergens and infectious agents. As

stated above this requires exposure and effects biomarkers to uncover interacting and convergent mechanisms (exposome). Such studies are highly susceptible to multiple testing errors. They require external validation, as well as experimental confirmation of the significance of the pathways identified. These types of investigation need to be much more tightly aligned with traditional cell biology/toxicology approaches.

b. Discerning which components of the air pollution mix are responsible for adverse health effects e.g. respiratory, neurological etc. is a substantial challenge but one that must be tackled to improve health policies. For instance, are some communities experiencing air mixtures [$\mu g/m^3$] that are more toxic than others?
c. What is the spatial and temporal distribution of air toxicity?

G. Sources of pollutants and differential effects

1. **It is critical to assess the toxicology of the air pollution that will be encountered in the future as the emissions profile changes.**
   a. We still do not know what the most toxic components of air pollution are. The challenge here is the availability of source samples of different types of particles. Toxicology requires far greater quantities of these particles than would be required, and routinely collected, for chemical analyses. Samples are needed of modern primary pollutants and secondary particulates.
   b. To address this shortfall, there is a need for a standardised particulate sample repository. This should be a collection of fresh, UK-relevant, PM samples with different characteristics (size, morphology, composition etc.) in sufficient quantities, that these can be shared between different interests for use in different models. This needs to be maintained and updated for new emerging pollutants for example for microplastic particles for which there are currently no standard samples.
   c. Need to understand what components of particles cause their deleterious effects and then put this into the context of all the components of pollution i.e. not just particles. Starting with single compounds/particles and then increasing the level of complexity. Potential for linking here with occupational exposure scenarios where there may be especially prominent exposures to specific components of interest, albeit at higher concentrations than population exposures.
   d. Are particles of the same material but of different sizes are similarly hazardous?

H. Enablers that could build back air pollutant toxicology as a strong research field

1. **Establish a population level human biomonitoring platform.**

2. **Invest in the development of biomarkers:**
   a. Incorporate early markers of disease.
   b. Develop screening methods to generate data which feeds into more targeted studies.
   c. Include evaluation of mixtures.

3. **Invest in analytical capability and capacity, including quality assurance schemes.**

4. **Build better networks within the current toxicology community**.
    a. Essential to coordinate this with other groups involved in toxicology e.g. the British Toxicology Society, Pharma etc.
    b. Organise a knowledge exchange meeting to discuss this with stakeholders. Stronger connections between atmospheric scientists that understand sources, toxicologists and epidemiologists. The recent Nature paper (*Daellenbach KR et al. Sources of particulate-matter air pollution and its oxidative potential in Europe. Nature. 2020 Nov; 587(7834): 369-370*) owes its success to connecting the first two. There is a need to understand further the role of oxidative potential in causing disease.
    c. Be advocates for the need for fundamental toxicological research/incremental science and the need to fund it. Use success stories and case studies.

5. **Priority funding**

    a. A joined-up strategy for all UKRI research councils: to provide a dedicated and consolidated research funding for the topic.
    b. Human chamber facility and especially the idea of coupling this with devices that can generate standardised aerosol mixtures. The current technologies can do both fresh and aged/coated/secondary aerosol mixtures.
    c. Establish a strong annual international conference on the topic area – to showcase UK and international cutting-edge science.
    d. Embed toxicology in future cohort/epidemiological studies so it is seen to be an equal partner.
    e. Develop a new three to four-year BSc. In applied molecular toxicology relevant to the environment and therapeutics. Only London Metropolitan has a degree in Toxicology. Also offer placements and projects for MSc courses and dedicated PhD studentships (e.g. enhancing MRC ITTP). Toxicology with Pharmacology was taught at the University of London, School of Pharmacy (SOP) (https://www.ucl.ac.uk/pharmacy/about/history-school#:~:text=1981%20%2D%20New%20BSc%20course&text=However%2C%20in%20the%20late%201990s,Toxicology%20and%20Pharmacology%20was%20abandoned.) which ran from 1981 to the late 1990s. This four-year course was mechanistically orientated with a therapeutic focus taking approximately 60-70% of its input from the Pharmacy course. There is an urgent need for a similar four year an MSc or a BSc joint honours course that additionally includes environmental and regulatory toxicology in additional to therapeutic toxicology with a similar emphasis on mechanisms.
    f. Return of classical toxicological teaching and methodological training to the biomedical curriculum, to increase the availability of candidates for PhD projects and PDRA positions.
    g. When a sizeable animal study is performed, bring together the expertise of different groups to measure a wider range of parameters/organ systems, e.g. by tissues being made available to other groups or researchers can visit other institutes to perform measurements on the same animals. This would avoid two groups carrying out the same exposure and would allow larger group sizes to be used to tackle variability of biological parameters while still reducing animal use overall. It would

also enable toxicological work to target higher impact journals. Consideration of an animal tissue biobank particularly for tissues from long term low-level exposures, or inhalational exposures were there are limited facilities to undertake such work. Biobanking could be a requirement of funding for such studies.

h. Greater availability of funding for smaller toxicological projects (e.g. PhD and short postdoc projects). This would help smaller groups to gain momentum and raise the profile for air pollution work within departments where air pollution can be considered something of a niche interest.
i. Convince the funding agencies that mechanistic toxicology is essential to fund as it is often the only way to understand, manage and solve e.g. environmental challenges.
j. Engage industry in this process and encourage their contribution both financially and through their knowledge base. Communication with industry and those researchers with the best/new and most relevant *in vitro*/*in vivo* models. These maybe outside toxicology e.g. cardio/neuro. Is their sufficient knowledge of the potential models and technology to move the field forward?

I. <u>Funding mechanisms – how do we build a connected interdisciplinary system as a nation – Three suggestions from each attendee?</u>

1. **Understanding how chemicals exert their deleterious effects is a fundamental science.** We need to engage basic scientists in this research area and improve.
2. **Research councils need this to be a priority area for support**.
3. **Need to clearly identify the major toxicological issues** linked to health and the economy.

1. **A centralised exposure and aerosol generation facility**?
2. **Develop a strategic, long-term funding plan** with a clear mechanism for identifying priority areas for research taking into account both policy needs and scientific developments. Ring-fenced, and with enough money to fund ambitious toxicological projects.
3. **A funding model along the lines of the Health Effects Institute in the US** could be considered (part industry, part government funding, with independent oversight; https://www.healtheffects.org/) or the Fraunhofer Institutes in Germany (https://www.fraunhofer.de/en/institutes.html).

1. **Involve the three major employment branches involved, academia, government and industry**.
2. **Get government departments on board**. Government departments have highlighted themselves a lack of toxicological expertise but there is no central focus that is required to drive establishment of more training support.
3. **UKRI MRC and NIHR**. MRC seems the most suitable UKRI research council to take forward air pollution toxicology. Further advantage could be gained with involvement of the NIHR.

1. **Ring-fenced funding for projects** which have to demonstrate true interdisciplinarity.

2. **Funding calls which specify big problems** soluble only with multiple disciplines.
3. **Guaranteed long-term funding of some posts**.

1. **Smaller grants for PhD/PDRA projects** that are co-supervised between 2 or more institutes.
2. **More funding opportunities for toxicology/mechanistic biology as the central theme of grant calls**. Larger collaborative grants focusing on a pressing toxicological question – narrow focus, but sufficient resource to meet the experimental challenge.
3. **Grants dedicated to following-up findings from previous work** and **supporting integration of toxicology and epidemiology findings**.

1. **We really need joined up systems, and the SPF has been an excellent example of this.** However, working across disciplines still seems to involve unnecessary logistical barriers, and also barriers to interacting with experts in other research areas. Tackling grand challenges by topic, rather than forcing topics into certain artificially constructed silos is very important. In this regard, is it any wonder that the MRC Centre for Environment and Health in London is so prolific, and so productive? I am not sure that UKRI as a whole has performed as hoped in this regard.
2. **Focus on interdisciplinary education at the undergraduate level**. Being conversant in several disciplines, rather than expert in a single one, should be the goal. Languages students generally take more than one language in their degree – the same should be true of scientists and scientific disciplines, which in the modern world are arguably more interconnected than different languages. Again, this will require genuine commitment from Universities, but I think the desire is probably there from the point of view of staff.
3. **An acceptance from funding reviewers (if we must persist with the current form of funding bids) that some aspects of applications may lie outside of their area of expertise, and perhaps a way to allow conversation between reviewers here**. It may be sensible to encourage communication between reviewers at the review stage, so that they can better discuss the aspects of the bid which lie outside their areas. This should lead to more effective, fairer appraisals of a bid, rather than simply ignoring the (potentially important) aspects of a bid outside of their own area.

1. **One way of doing this is to organise high profile meetings that include delegates and sessions with diverse backgrounds** and content, to include "problem solving" workshops. Not unlike the recent Royal Society meeting.
2. **Establish collaborative funding mechanisms** that encourage collaboration across disciplines and enable individuals to work in different institutes, universities, government agencies etc. At the moment, many of us are working in our own bubble. Again, extra resources would be required for this.
3. **With current concerns about the environment inevitably include air pollution, it might be possible to "piggy-back" and add to environmental consortia to increase integration with those working on environmental problems**. Inclusion in their

agendas (research, meetings, strategies etc) will broaden the membership, increase the knowledge base and access to media opportunities.

1. **Network of relevant disciplines**; Targeted workshops linked to priority questions.
2. **Capacity building calls linked to subsequent interdisciplinary research calls to build a network**.
3. **Sufficient funding for ambitious multidisciplinary studies** that complement but do not duplicate, maximise use of samples/tissue collected in animals/humans.

1. **There is a need to ensure funding which would have gone to European research initiatives is drawn down to support UK based research**.
2. **Government apprenticeships**.
3. **Industrial and government placements**.

1. **Fellowships that act to link together different centres of excellence** is an excellent approach and effectively forces integration and collaboration between groups who might overwise play lip service to interdisciplinary. It is also a highly effective way for young researchers interested in interdisciplinary approaches to research questions to build the necessary networks to further their careers. I would include that we need more clinical fellowships in this area.
2. **The NC3Rs have a good model, where they have calls for small scale studies to build networks**, which are then reviewed as a prerequisite for moving onto a full application. There is some potential for the funder, prior to the full application, to suggest the alignment of separate partners from different pilot grants (usually the most successful components) where they think this would strengthen a downstream bid and increase interdisciplinarity.
3. **Need an air pollution toxicology network**. This was not funded in the first wave of network funding. It might seem as though this might simply result in toxicologists talking amongst themselves, but in reality, it would act as a point of contact for other disciplines to interact with the national tox-community.

Round Table Participants:

Prof Roland Wolf, University of Dundee; Dr Gary Fuller, Imperial College London; Dr Alison Gowers, PHE; Prof Frank Kelly, Imperial College London; Prof Tim Gant, PHE/Imperial College London; Prof Roy Harrison, University of Birmingham; Dr Mark Miller, University of Edinburgh; Prof Terry Tetley, Imperial College London; Dr Graham Campbell, Programme Manager for Environmental Health, Pharmacology and Toxicology, MRC; Dr Matthew Loxham, University of Southampton; Prof Anne Willis, Director MRC Toxicology Unit, University of Cambridge; Dr Marion MacFarlane, Deputy Director MRC Toxicology Unit, University of Cambridge; Dr Ovnair Sepai, PHE; Dr Ian Mudway, Imperial College London.

Dr Jenny Baverstock, Prof Stephen Holgate and Dr Gary Fuller as the UKRI Clean Air Champions and coordinated by Mrs Armineh Pogosian.