ANNEX 5.2.2 – NERC/MRC Discussion Document

ANNEX 2

Discussion Document for NERC & MRC: - Joint Environment & Human Health Programme – Phase II

Section I –E&HH Programme Achievements & Key Successes to Date

The Joint Environment & Human Health Programme has succeeded in bringing together many scientists from a broad range of environmental and biomedical backgrounds in order to address critical questions on health issues that are linked or believed to be linked to the natural environment. Many of these questions relate to complex issues such as the environmental biology and geochemistry of soils and how these influence the transport, accessibility and bioavailability of chemical pollutants and infectivity of pathogens. The dispersion of harmful particles in the atmosphere is another area of major concern where the E&HH Programme is breaking new ground on how the chemical and physical properties of such particles influence their environmental behaviour and may govern their toxicity and resultant pathological reactions induced following inhalation. Again this has required the formation of interdisciplinary teams of materials scientists, surface and environmental chemists, geochemists, environmental and human toxicologists, food scientists, veterinary scientists, pathologists, epidemiologists, geographers, social scientists, economists and atmospheric modellers. Working groups and workshops have identified potential health problems concerning the transport and emergence of pathogenic human viruses associated with food and water.

Some specific examples are presented below to illustrate why the problems being addressed by this programme, can only be addressed by multi- and interdisciplinary groups of scientists working together in cohesive collaborative projects.

1. Evidence for a specific lung fluid protein causing agglomeration of inhaled ultrafine particles thus modifying their biological behaviour and reactivity in the lungs (NE/E009395/1). This project brings together environmental chemists, material and medical scientists in order to understand how the fluids in the lung can modify the biological reactivity and pathogenesis of airborne nanoparticles.

2. Demonstration of the toxicity of silver nanoparticles in human food-chain model including invertebrates, fish and mammals (NE/E008232/1). The project draws on the combined expertise of environmental chemists, ecotoxicologists, cellular toxicologists and animal and clinical pathologists, as well as health scientists working together to identify the behaviour of nanomaterials in the natural environment and how these may impact on human health through the human food-chain.

3. Demonstration of bacterial endotoxin associated with airborne particles produced by commercial composting, which have detrimental biological effects on an *in vitro* cell-based model of the lung (NE/E008534/1). This project underlines the problem of how coatings of biological origin may affect the harmful biological reactivity of micro- and nano-scale particles. The research involves the physical behaviour of the airborne compost particles, the potential toxicity of biogenic toxins of bacterial and fungal origin and investigation of inflammatory and pathological reactions induced in an *in vitro* experimental model of lung tissue. The project has been dependant on the successful collaboration of environmental scientists (waste management and risk assessment), microbiologists and biomedical scientists.

4. A Report to Defra and HPA on the environmental pathways for exposure to pathogenic viruses and emerging viral problems (e.g., from farm animals and global transport of food products from industrial organic farms in China, Mexico and California). Identification of current knowledge gaps regarding transmission of viruses through the environment and food (NE/E009026/1). This project brought together a wide range of medical and environmental virologists and microbiologists, food and public health scientists, and epidemiologists.

5. Data analysis is currently underway in the UK on soil and blood samples from a field study in Malawi on the effects of micronutrient depleted soils (e.g., selenium) on maternal health and postnatal development. (NE/E008313/1). This is undoubtedly the most logistically challenging project supported by the E&HH programme, involving soil geochemists, healthcare workers and biomedical scientists working together under very difficult social and cultural conditions in central Africa.

6. Development of a robust analytical system for the assessment of the bioaccessibility of arsenic and polycyclic aromatic hydrocarbons (PAHs) in a simulated human gut environment (NE/E008844/1). This has resulted in the development of a patentable test kit. The experimental model of the human digestive tract has provided a novel way of testing the behaviour of harmful toxic environmental contaminants is influenced by the complex interactions between the gut chemistry and microbiology. This project has also demonstrated the detrimental impact of PAHs on the microbial flora from the human gut.

7. Development of screening tests for MRSA in the agricultural environment (NE/E008054/1). MRSA is no longer just a problem in the hospital environment. MRSA and other drug-resistant microbes are present in the natural environment with the attendant concerns about the transfer of the genes conferring drug-resistance to other species of bacteria. This project brought together microbial ecologists and clinical microbiologists in order to address the health risks posed by the widespread presence of MRSA in the environment, where it is associated with pig herds, bovine milk and faeces. Dairy products have also been implicated as reservoirs of MRSA in Europe.

8. Human disease causing bacteria can survive inside nematode worms and are protected from the action of chemical sanitiser treatment (NE/E009085/1). Food-borne diseases are a significant public health problem where pathogens such as *Salmonella* occurring in the soil can interact with other organisms such as free-living helminth worms (nematodes). This project involved the collaborative efforts of epidemiologists, helminthologists, microbiologists and veterinary scientists who have demonstrated that *Salmonella* ingested by the worms can survive and be returned to the environment in a viable and infective state. The inference is that soil nematodes can provide a protective micro-environment for human pathogens with health implications for the persistence of such pathogens in the soil.

9. A book is due to be published in October indicating that the health benefits of organic foods are probably over-rated, and that in some cases they may pose a greater health risk than normal foods (NE/E008399/1). This project dealt with a complicated set of potentially interacting factors including soil science, pesticide toxicology, biogenic fungal toxins and infectious pathogens, as well as the nutritional composition of the foods in question. A two-day International Workshop involving over 80 participants from a wide-range of disciplines, including soil and food science, environmental toxicology and microbiology, nutritional and clinical physiology and public health, specifically addressed these problems.

10. Substantial progress has been achieved towards deriving a summary measure of multiple environmental deprivation at small area level, akin to the measures of multiple socioeconomic deprivation used by health researchers from many disciplinary backgrounds (NE/E0087201). The key achievements have been to i) systematically identify which elements of physical environment should be included in the measure, ii) compile appropriate environmental data for the whole UK, iii) produce several different versions of the measure iv) discover independent associations between the measures and variation in all cause and cause specific mortality, and v) begin to examine the interaction between social and physical environments on health inequalities in the UK. This project involves collaborations between epidemiologists, public health scientists, health geographers and environmental scientists.

Many of the Exploratory Study awards are still ongoing since a number of these did not start until earlier this year. It is anticipated that these will produce exciting new data and insights into many of the issues and gaps identified in **Section II** below. The Network, Working Groups and Workshops have also served to highlight and refine the issues and gaps described below.

The overall research progress has been excellent with many exciting developments highlighting new avenues for future investigation as indicated above. Fortunately, there have been few problems in the implementation of the programme, which given its complexity is perhaps surprising, but nonetheless serves to underline the dedication, skill, ingenuity and resourcefulness of the many scientists involved. Where problems have arisen, they have largely been limited to logistical and staffing issues. The need to await decisions by University Ethics Committees has also resulted in a few delays; but this is understandable given the multi-institutional nature of many of the Projects.

Finally, the establishment of new active research links between many of the projects funded by the Joint E&HH Programme is helping to build a cohesive community of research scientists with both UK and international linkages. Feedback from the researchers themselves has strongly indicated that the interfacial nature of much of the research has resulted in exciting and challenging projects with a lot of intellectual cross-fertilisation and the spawning of new collaborations involving existing and proposed future projects. To try and identify which has been the most successful matching of disciplines is very difficult, and probably impossible at this stage of the Programme, given the huge range of disciplines involved and the very high quality of the research that has been and is being generated.

Section II – Issues and Questions Arising from the E&HH Programme

Exposure to Toxic Contaminants and Pathogens

1. Pathways of exposure – environmental modification of colloids, particles and chemicals – coating of particles with biogenic materials. How does this affect their biological reactivity?

2. Complexity of the soil environmental interfaces – how does this affect the transport and bioaccessibility of contaminant chemicals and pathogens?

3. What is the relative health significance of chemical (including biogenics and novel xenobiotics) and pathogen exposure pathways for food, air, soil and water?

4. Is environmental exposure to toxic contaminants and pathogens – beneficial or harmful? Low level exposures of both chemicals and pathogens may be beneficial by stimulating the body's defensive systems – biphasic effects (hormesis).

Novel Biomarkers

1. Biomarkers of exposure and harmful effect – need to distinguish between complex interactions resulting from exposure to mixtures of chemicals and combinations of chemical, pathogens and physical/nutritional stressors.

2. In biphasic responses, biomarkers of exposure may be expressed during the beneficial non-pathogenic region of the response curve (i.e., hormetic beta-curve). We need to be able to determine whether biomarkers of exposure are indicating pathology or not.

3. Requirement for biomarkers for hormesis – antioxidant defences, heat-shock proteins (*hsp*'s & *hsc*'s, Sirtuin 1 – SIRT 1, etc).

4. Requirement for pathology biomarkers – proteomics?

5. How can we effectively distinguish synergistic and antagonistic interactions in a complex environment?

Gaps Highlighted by the E&HH Programme Projects

1. Improved epidemiological modelling and identification of problems on a geographical scale.

2. How can we quantitatively incorporate uncertainty in assessing hazard and risk?

3. Numerical and Computational Toxicology & Ecotoxicology – conceptual modelling, QSAR modelling, numerical model development and validation, co-evolution of modelling and empirical investigation. How can modelling contribute to evaluation of risk and development of predictive models for impact on human health?

4. Can we interpret stress and disease (including ageing) as a loss of biological complexity? The influence of environmental factors on protein-protein interactions (protein interactomics) and the loss of effective protein-protein interactions and failure to effectively remove damaged proteins and aggregates needs to be assessed since these molecular dysfunctions contribute to ageing and a number of pathologies.

5. How does speciation of chemicals and nano- and micro-particulate material affect their biological reactivity and toxicology?

6. Can QSAR modelling be applied to particulate material?

7. Are interactions between environmental agents and epigenetic processes significant in rapid adaptation to pathogens and toxic materials?

8. Aggregation of particles – how does this affect uptake and toxicity along the foodchain?

9. Do nanoparticles act as Trojan Horses for bringing conventional toxins such as the pesticide Diuron, polycyclic aromatic hydrocarbons (PAHs) and iron into the body (e.g., lungs and digestive tract)? Iron for instance will promote ROS (reactive oxygen species) production.

Gaps highlighted by the Wider Environment & Health Community

1. What are the health consequences of photo-oxidation of biogenic and contaminant chemicals and particles in the natural environment?

2. Can plastic degradation particles concentrate and transport lipophilic contaminants and persistent organic pollutants (POPs)?

3. Are there thresholds or biphasic responses for biological effects of environmental radioactivity?

4. Can we clearly identify environmental reservoirs of contaminants and pathogens?

5. Emergent viral diseases – what is the realistic risk of a human pandemic of bird flu if for example there is transfer of the virulent genes from the H5 strain to the more widespread and H2 and H9 types of the virus which can be contagious in humans?

6. What environmental pathways contribute to the spread of intractable mycobacterial diseases such as tuberculosis?

7. What are the risks from the next generation non-passive nanomaterials – nano-biotech synthetic biological products such as DNA scaffold devices, rosette carbon

nanotubes, self-assembling nano-devices including artificial viruses (i.e., replicators), engineered RNA-based cellular computers and supramolecular cellular components (e.g., ribosomes and receptors)?

8. Can some endocrine disruptors (e.g., xenoestrogens, POP's - including brominated flame retardents and bisphenol A) also act as obesogens and possibly trigger type 2 diabetes?

9. Are there more ***prion*** diseases out there in the wildlife and do they pose a threat to humans?

10. Environmental agents acting during pregnancy have been implicated in developmental abnormalities. Do environmental triggers such as exposure to viruses or environmental pollutants apply to conditions such as autism?

11. How widespread in invertebrate Phyla are novel anti-bacterial and anti-viral agents produced by lower organisms (e.g., anti- MRSA, - *Clostridium difficile* and - *E. coli* peptide (s) produced by insect larvae; Prof N Ratcliffe, U. Swansea)?

12. Can lower organisms including invertebrates and fish be used as surrogates for investigating environmental linkages with genetic and epigenetic aspects of human disease processes?

13. Does the oceanic dissolved organic carbon (DOC) of largely viral origin (estimated to be 97-98%) have any biological reactivity and are there health risks or benefits?

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