Radiation Protection Research programme

Department of Health

Prepared by

Radiation, Chemical and Environmental Hazards Branch, Department of Health

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Introduction

The Department of Health Radiation Protection Research (RPR) programme

The RPR is a programme of research into the health effects of exposure to ionising radiation and to electromagnetic fields. There is a separate, specific research programme into the possible health effects from mobile phones and base stations known as the Mobile Telecommunications Health Protection Research (MTHR) programme. Information on the MTHR programme can be found on the MTHR website. (http://www.mthr.org.uk/) Hence the RPR will not consider health effects associated with the operations of telecommunications systems.

The Radiation Protection Research programme was originally run under the auspices of the old Department of Energy. It was transferred to the Department of Health and Social Security in the summer of 1987 and has subsequently passed to the Department of Health (DH). In 2005 the management of the programme was delegated to the Health Protection Agency although DH retains responsibility for the research strategy and the budgetary requirements of the programme. The purpose of the programme is to help guide Government policy in the field of radiation protection.

The RPR programme is a rolling programme but works within a research strategy which operates over a three year period. After each three year period the strategy is reviewed by senior scientists and medical practitioners independent of both Government and industry. This ensures that the strategy continues to be relevant to the changing requirements in the field of radiation protection. The last review took place in December 2005. Following this a new research strategy was drawn up in 2006 and agreed in the light of that review. The current strategy is available on this web site.

For further information contact Kerry Broom at the Health Protection Agency at the following e-mail address:
kerry.broom@hpa.org.uk

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Department of Health Radiation Protection Research strategy

Strategy on research into health effects of ionising radiation, non-ionising radiation, specifically electromagnetic fields (excluding telecommunications) and pulsed ultrasound.

1. Introduction

The Department of Health (DH) has a programme of research into the health effects of exposure to ionising radiation and to electromagnetic fields called the Radiation Protection Research (RPR) programme. Research is commissioned on the basis of competitive tender with the specific objective of informing the development of DH policy. Projects commissioned will be those where the result of the research can be clearly linked to a specific policy need. Generally, they should be such that there will be a clear outcome that directly affects the development or implementation of policy.

This document outlines the RPR programme strategy and indicates areas of research currently of interest to the Department.

There is a separate, specific Government research programme into the possible health effects from mobile phones and emerging communications technology as recommended by the Independent Expert Group on Mobile Phones. It is intended that the RPR research programme and the Mobile Telecommunications Health Research Programme will be complementary. The RPR programme will not consider health effects associated with the operation of telecommunications systems.

2. Main issues of public health importance within the scope of the RPR programme

2.1 Ionising radiation

Both natural and man-made sources of ionising radiation contribute to human exposure and can constitute a hazard for human health. Exposure of the population to natural radiation is to some extent unavoidable and medical exposure of the patient during diagnosis and therapy is now an indispensable part of modern medicine. The exposure of workers, and to a smaller extent of the public, to low levels of radiation from nuclear energy production and other industrial uses of ionising radiation have become an integral part of industrialised society. The public often perceives the use of radiation technologies, especially those in nuclear energy, with concern and anxiety about potential health hazards, although average exposure to man made radiation is a small fraction of that to natural radiation.

The highest exposures from ionising radiation are from radon, a naturally occurring decay product of uranium found in all soils, and exposures from medical sources used either for diagnostic or treatment purposes. Although medical exposures should be of net benefit to the patient, the possible risks also need to be investigated. Uncertainty remains about the magnitude of the risks from low doses and at low rates of exposure particularly from inhaled or ingested sources (often known as internal sources).

There is ample evidence that most organs and tissues of the body are at increased risk of cancer after substantial doses of ionising radiation, and it seems likely there is some increase in the risk from any dose however small. Studies done on human populations who have received unusual and well-documented exposure (eg, survivors from the atomic bombs at Hiroshima and Nagasaki, and populations exposed to medical and industrial sources of ionising radiation) have been used to derive quantitative estimates of risks. Current risk estimates from the International Commission on Radiological Protection (ICRP), based on a linear extrapolation of high dose risk to low dose exposures levels, suggest that approximately 4 to 5 fatal cancers per hundred persons and two non-fatal cases per hundred persons result from each sievert of exposure of ionising radiation. The National Radiological Protection Board (NRPB) have calculated that for a UK population of 57 million and an annual average exposure of 2.5 millisieverts, about 6,500 fatal cancers could be caused by radiation each year and about a further 3,000 or so non-fatal ones. The total number of deaths recorded in the UK each year is about 650,000, of which about 160,000 are due to cancer. Thus, ionising radiation is estimated to be responsible for about one per cent of all deaths and about four per cent of deaths due to cancer. The greatest contribution to these estimates is that from exposure to natural radioactivity from radon and some of this exposure is remediable by making structural changes in houses and other buildings.

These estimates of a substantial mortality are generally accepted but in very recent years some countries have argued for a downward revision of these risks. However, in the UK, they are not currently subject to any general, significant academic challenge for downward revision. Public fear of radiation exposure, however, currently exceeds that which might be reasonable on the basis of these estimates. Some of this fear arises from the observations of childhood leukaemia ‘clusters’ in the vicinity of some nuclear installations. The presence of these ‘clusters’ suggests that local risks could be greater than accepted estimates for reasons that are, at present, not understood. The possibility of such a risk is therefore of concern to both the Government and to the public.

Although much is known about the quantitative effects of exposure to ionising radiation, considerable uncertainties remain about the health effects at low doses. For example, the duration of the increased risk following exposure, the effect of different dose rates on the subsequent risk, and the risk due to the interaction of radiation and other carcinogens. Such information would permit further optimisation of remedial measures to reduce exposure and minimise the health risks.

The Department of the Environment, Food and Rural Affairs (Defra) is undertaking a radon measurement programme to identify homes where exposure exceeds the acceptable level. Further work on possible risk factors associated with radon exposure would assist in focusing further action on the groups most at risk.

Public concern about possible health effects from nuclear plants still remains. This area has been addressed by the Committee on Medical Aspects of Radiation in the Environment (COMARE), who have reiterated support for the programme and helped to shape the detailed research needs.

2.2 Non-ionising radiation - electromagnetic fields

Exposure to electromagnetic fields (EMFs) is ever-present in modern society. There has been public concern about electric and magnetic fields from power lines for many decades, but the evidence for adverse health effects at exposure levels below safety guidelines remains equivocal. Most epidemiological studies have considered exposures to magnetic fields, and there remains the possibility that there are health effects (in particular an enhanced risk of childhood leukaemia) at exposures levels toward the upper range of those encountered by the public. There have also been concerns about exposures to power-frequency electric fields, for which there are fewer data on health effects. There is also comparatively little published information on the biological and health effects of transient power frequency fields that might be encountered by the public, for example in trains.

There is already a substantial body of evidence about the biological and health effects of radiofrequency (RF) fields, and particular recent specific public concern about fields from telecommunications systems will be addressed in the Mobile Telecommunications and Health Research (MTHR) programme. However the public are exposed to radiofrequency fields from other sources such as radio broadcast, antitheft and radar systems. The main areas of research that might be addressed as part of the RPR programme relate to the possibility of biological or health effects occurring below safety guideline levels. In 2004, the National Radiological Protection Board (NRPB) adopted the guidelines of the International Commission on Non-Ionizing Radiation Protection (ICNIRP) that have lower levels for the public than for workers. The rationale for this 2-tier approach is that there may be particularly susceptible individuals in the general population. The presence and degree of any such susceptibility are topics that might be addressed under the RPR programme.

2.3 Non-ionising radiation - pulsed and transient RF fields

There has been interest in possible health effects of public exposures to pulsed and transient RF fields other than from mobile telephone systems, for example ultra-wide band radars and anti-theft devices. Under the wing of its International Electromagnetic Fields Project the World Health Organisation (WHO) has held scientific meetings on this subject as has the European COST 281 programme. COST stands for ‘European Cooperation in the Field of Scientific and Technical Research’. There are questions relating to dosimetry, epidemiology and basic biology that might be addressed under the RPR programme.

Another area which has been prioritised by WHO and COST is that of possible health effects of public exposures to intermediate frequencies (100 kHz – 10 MHz) from security systems, electrified transport and AM radio transmitters. The basic biology that underlies the exposure guidelines does not address this frequency range specifically; guidelines have generally been set by extrapolation from higher and lower frequencies. There is scope for research into the dosimetry, epidemiology and basic biology of intermediate frequency fields to be undertaken within the RPR programme. The development of exposure metrics for RF and EMF epidemiology and the dosimetry of experimental systems is a WHO priority and could be supported under the RPR Programme.

2.4 Non-ionising radiation - pulsed ultrasound

From 2006 the RPR programme will also fund research into ultrasound as part of its new role in medical radiation protection research (see 5.3 below). The advent of new ultrasound equipment and techniques has prompted users and the authorities to question the relevance of the basis on which existing guidelines were drawn up. From 2005, the Health Protection Agency's (HPA) Radiation Protection Division has responsibility for advising on ultrasound safety. HPA initiated scoping discussions that have indicated a need for new work in this area and HPA held an international meeting in October 2005 in order to determine the key issues that will need to be addressed by research. In the period addressed by this research strategy we will be considering applications on the potential health effects of ultrasound exposures.

3. Policy Questions

The main policy questions that need to be addressed are:

3.1 Ionising radiation

How can the characteristics of ionising radiation affect health risk? To what extent are radiation quality, dose rate, micro-distribution and energy important factors in determining the risk following exposure to a particular type of radiation such as alpha particles?

What tissues are relevant to radiation-induced health detriment? Will these vary during the different stages of biological development and does the variation depend on radiation type?

Can radiation-induced health effects be clearly distinguished?

To what extent are health effects from internal radiation quantitatively or qualitatively different to those from external radiation?

Can it be determined whether radiation damage is non-linear at low doses and low dose rates?

3.2 Electromagnetic fields

Is there any risk to health from EMF exposure of the public arising from the use of shop, library and airport security systems, from the operation of power lines, from electrified transport systems, from radio and TV broadcast or from ultrawideband radars?

What, if any, are the characteristics of exposure which may result in a risk to human health?

Is there a real public health benefit to having lower exposure guidelines for the public than for workers?

3.3 At risk groups

Who is most at risk?

Are there sub-populations with undue susceptibility to radiation?

Are there critical groups, stages or times for exposure such as the foetus or early childhood? Are there sub groups of the population exposed to higher levels of radioactivity or EMF?

3.4 Risk perception and communication

Public perception of risk is sometimes different from the perception of experts and people make their own judgement of risks and benefits. For example, it is widely believed there is a far greater risk from emissions from nuclear plants than from radon and medical diagnostic exposures. It might be that such a perception leads to a reduced take-up of radon measurement programmes and may make people fail to appreciate the importance of taking remedial action to reduce radon levels. For a public health policy such as radiation protection to be effective it needs to enjoy public support and understanding.

To what extent does the public perception of risk differ from that of experts in the fields of ionising radiation protection and EMF? To what extent does the source of information determine the public perception of trust?

How can the public's radiation and EMF concerns be addressed effectively?

Different perceptions of level of risk can also lead to an imbalance of priorities when compared with other important public health risks, eg, other carcinogens, (including smoking, CHD rates; accidents). There are various ways that comparisons can be made and messages can be communicated. To what extent is this subject-dependent? To what extent can this be quantified?

4. Current research

The DH RPR programme's main priorities since its inception have been to follow up the Independent Advisory Group chaired by Sir Douglas Black (Black Committee report 1984) and COMARE recommendations to investigate uncertainties in the radiological impact from

environmental radiation. Although complete, this work often addressed local rather than general problems, which still require further investigation. In addition, in response to a COMARE recommendation, further work was commissioned through the Co-ordinating Committee on Health Aspects of Radiation Research (CCHARR) to look at risks to the offspring from parental occupational exposure to ionising radiation. These studies have now been completed and have led to a greater understanding of preconceptional effects, but have raised the possibility that changes occurring within the uterus may be of importance.

Other work examined problems relating to radon exposure and the related topics of the effect of different types of radiation exposure at low doses and low dose rates. This work has suggested novel methods of exposure to natural radionuclides, which should be clarified.

From 1996 onwards, the RPR programme funded research into electromagnetic field health effects and risk perception. The EMF part of the United Kingdom Childhood Cancer Study was funded in part under the RPR Programme; this was a large-scale investigation which has made an important contribution to scientific knowledge.

Potential effects of mobile phone signals on aspects of human reaction time and memory in rodents were investigated under the RPR programme, as a response to increased public concern about new communications technologies. The results of these studies were considered by the Independent Expert Group on Mobile Phones, whose report (available at www.iegmp.org.uk) recommended a range of precautionary actions for the use of mobile telephone technologies, including the setting up of the Mobile Telecommunications and Health Research programme.

From 2006 the RPR programme will also fund research into medical radiation protection measures (to include ultrasound – see 2.4 above).

Funding for the maintenance of whole body monitoring equipment at Newcastle General Hospital used in research studies has been ongoing since April 2004.

5. Priority questions for research under the 2006 programme

5.1 Ionising radiation

There are clear health risks associated with exposure to ionising radiation. Priority questions for the current research programme include the following:

i) To what extent do different health risks (both qualitatively and quantitatively) arise from exposure to radiation of different quality?

ii) Measurement and assessment of target tissues. What are the most sensitive tissues in the different periods of biological development and do they vary with radiation type?

iii) Can studies be undertaken to define the genetic factors that underlie differences in individual sensitivity to radiation exposure?

iv) Do genetic instability, minisatellite and microsatellite mutations and the bystander effect contribute a significant health detriment? Are initial energy loss events amplified by time and untargeted genes to produce effects with significant health implications?

v) Effects of radioactivity within the uterus, do they contribute to future cancer risk?

vi) Mechanistic or epidemiological studies of the interaction between radiation and other environmental and/or infectious agents. Are the studies methodologically feasible?

vii) To what extent are health effects from internal radiation quantitatively or qualitatively different to those from external radiation and to what extent do they depend on the microscopic distributions of different distributions of different internal emitters?

viii) How large are the uncertainties relating to the calculations of risk from individual internal radiation emitters?

ix) Are the implications of microdosimetric factors clearly understood in relation to radiation damage arising from internal emitters?

x) What is the impact on health risks of dose rate, energy and quality of ionising radiation, through internal and external exposure and the appropriateness of ‘equivalent dose’ and ‘effective dose’ as measures of representing these risks, particularly when humans are subject to different types of ionising radiations in combination?

5.2 Electromagnetic fields

These priorities reflect areas of research where there are unanswered health questions, as well as public concerns.

xi) Power-frequency fields, particularly electric fields and transient fields

xii) Health effects of public exposures to pulsed and transient RF fields (excluding telecommunications)

xiii) Health effects of public exposures to intermediate frequencies from security systems, broadcast transmitters and electrified transport.

xiv) Development of exposure metrics for RF epidemiology and for dosimetry of experimental systems (excluding telecommunications).

5.3 Medical irradiation practice

xv) Are there medically exposed populations (to both ionising and non-ionising radiation) whose study could provide answers to the questions posed in 5.1 and 5.2 above?

xvi) Are the risks from pulsed ultrasound, at current or projected power levels, sufficiently well understood to cover possible risks from all current UK practices?

xvii) Are the risks assessments of exposure to magnetic fields (static and switched), as for example, generated in Magnetic Resonance Imaging sufficiently robust or is further research required?

6. Co-ordination of research

Some parts of the work described above might be appropriate for funding by the Medical Research Council or for the Economic and Social Research Council. Other organisations active in this area include the cancer charities and the HPA. The DH's research programme is intended to complement these other activities and there is continuing liaison between these bodies and international activities to ensure efficient use of resources. In addition, the programme will generally expect adherence to the WHO research quality criteria for EMF projects, which may be found using the link below.
(http://www.who.int/peh-emf/research/agenda/en/index2.html)

7. Administrative arrangements

DH commissions, by competitive tender, a programme of inter-related research projects covering the areas identified in this strategy document. Those who wish to bid for funding of projects under this scheme may initially be asked to submit outline proposals to the Department using the application form provided. These outline proposals will be scrutinised and subject to peer-review to determine their scientific quality, relevance and value for money, in accordance with the DH Research Governance Framework for Health and Social Care (http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4108962

Applicants whose proposals meet the DH's strategic objectives and research quality criteria will be invited, without commitment, to submit formal full applications. Dialogue with applicants to develop and optimise certain types of proposal might be required at this stage.

It is a condition of research contracts that research is conducted in accordance with the DH Research Governance Framework for Health and Social Care and, where relevant, also in accordance with the DH Governance arrangements for NHS research Ethics Committees (http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4005727).

If a contract to undertake research under the RPR programme is offered, DH's research management procedures and conditions will be explained fully. However, it should be noted that

publication of results in peer reviewed journals is expected both during and at the end of each project.

In the event of any animals being used in research, all requirements of the Animals (Scientific Procedures) Act 1986 must be followed. In addition, both the DH's Research Governance Framework for Health and Social Care, and Home Office advice on the ethical review process in relation to this Act must be effective and in operation.

DH's Research Governance Framework states that:
'When undertaking research which could involve the use of animals, three principles should be followed:
- replacement of animals by non-animal methods wherever possible;
- reduction of numbers to the minimum necessary to obtain valid results where replacement is not possible; and
- refinement of all procedures to minimise adverse effects.

Wherever possible, alternatives such as cells, tissues, computers, bacteria and plants must be used instead. When animal use is unavoidable, there are strict controls enforced by the Home Office. Before a researcher can use animals, a series of special licences must be obtained. Primates are only to be used if less advanced animals could not provide the information. Researchers must have the necessary skills, training and experience, and the research laboratory must have the facilities to care for the animals properly. The highest standards of animal husbandry and welfare under veterinary supervision must be maintained and an ethical review process must operate in accordance with the Home Office requirements.'

Lead researchers, durations and costs of RPR projects

Table of RPR projects, duration and cost

17 September 2008

Project reference	Lead researcher	Project title	Research institution	Start date	Completion date	Total cost
RRX 107	Dr John Hunt	The human body retention time of organically bound tritium: a study of an internal radiation emitter relevant to an at-risk group	Centre for Environment, Fisheries and Aquascience	01/01/2007	30/11/2008	£42,220
RRX 108	Professor Sarah Darby	Studies of ionising radiation and risk of heart disease	University of Oxford	01/01/2007	31/12/2009	£449,162
RRX 109	Professor Eric Wright	Mechanisms and genetics of radiation induced in vivo bystander signalling	University of Dundee	01/02/2007	31/01/2010	£360,017
RRX 110	Dr G. Malcolm Taylor	A case-control comparison of germ line mini satellite mutation frequency in childhood leukaemia	University of Manchester	01/07/2007	31/08/2009	£301,497
RRX 111	Dr Christophe Badie	Assessment of the heritability of human cellular radiosensitivity	Health Protection Agency	01/04/2007	31/03/2010	£132,051
RRX 112	Professor Eric Wright	Interactions between radiation, inflammation and environmental carcinogens	University of Dundee	01/04/2007	31/03/2010	£388,093
RRX 113	Mr Adam Shaw	Neonatal transcranial ultrasound - thermal hazard and risk assessment	National Physical Laboratory	02/04/2007	01/10/2009	£203,035
RRX 114	Dr Kai Rothkamm	A cytogenetic assessment of the impact of long term exposure to chemical agents on radiation responses	Health Protection Agency	01/05/2007	30/04/2010	£199,737
RRX 115	Dr Rhona Anderson	Chromosomal damage in normal human lung cells after exposure to low doses of ionizing radiation	Brunel University	01/05/2007	30/04/2010	£374,569

Table of RPR projects, duration and cost (continued)

17 September 2008

Project reference	Lead researcher	Project title	Research institution	Start date	Completion date	Total cost
RRX 116	Professor Penny Jeggo	Application of gamma-H2AX foci analysis to monitor double strand break induction and repair in cells and tissues	University of Sussex	01/04/2007	31/03/2010	£347,481
RRX 117	Dr Janet Tawn	Characterisation of chromosome damage induced in vitro by alpha irradiation and identification of potential markers of in vivo exposure	Westlakes Research Limited	01/04/2007	31/03/2010	£274,958
RRX 118	Mr Michael Gillies	A comparison of the cancer mortality and cancer registration experience of radiation workers exposed to external radiation only with workers additionally exposed to plutonium, uranium or tritium or a combination of these radionuclides	Westlakes Research Limited	01/04/2007	31/03/2010	£67,088
RRX 119	Dr Mark Pearce	Long-term sequelae of radiation exposure due to computed tomography in childhood	Newcastle University	01/04/2007	31/03/2010	£358,292
RRX 120	Dr Rob Mairs	Investigation of genotoxic effects of ELF-EMF radiation utilising microsatellite sequences	University of Glasgow	01/11/2007	31/10/2010	£381,641
RRX 121	Dr Wooter Poortinga	Awareness and perceptions of the risk of exposure to radon in homes: a population based approach to examine the impacts of local radon policies, trust and social capital	Cardiff University	01/09/2007	28/02/2010	£327,698
RRX 122	Dr John Harrison	Uncertainty in dose coefficients for radionuclide ingestion and inhalation	Health Protection Agency	01/04/2008	31/03/2011	£50,011
RRX 123	Dr Mike Murphy	Updated investigations of cancer excesses in the vicinity of Seascale and Dounreay	University of Oxford	01/07/2007	31/03/2009	£246,325
						£4,503,875

Table of earlier RPR projects, duration and cost

17 September 2008

Project reference	Lead researcher	Project title	Research institution	Start date	Completion date	Total cost
RRX 46b	Gerald Draper	Childhood cancer and EMF exposure from power lines	University of Oxford	01/10/1997	31/03/2009	£36,718.
RRX 84	Gerald Draper	Linkage study of childhood cancer in the offspring of female radiation workers	University of Oxford	01/10/2002	30/06/2008	£102,227
RRX 101	Kate Carr	Doses and damages to organs following intestinal uptake and distribution of microparticles	University of Oxford	01/10/2002	30/09/2009	£334,526
RRX 106	Paul Elliott	Adult cancers near overhead powerlines	Imperial College London	01/04/2005	30/06/2008*	£7,000**
* finish dates may change from those given.						
** The figure given (£7000) is DH funding. RRX 106 is also in receipt of £99,840 funding from the Energy Networks Association.						

Details of RPR projects

Project RRX 107 The human body retention time of organically bound tritium: a study of an internal radiation emitter relevant to an at-risk group

G.J. HUNT and T.A. BAILEY
Centre for Environment, Fisheries and Aquaculture Science,
Lowestoft, Suffolk NR33 0HT

Tritium in the environment of the UK is due to both natural sources and to discharges of radioactive wastes from nuclear, radiochemical, weapons, medical and research facilities. Although radiation doses to the UK public as a result of these sources are low[1], there are uncertainties in the dose coefficient to calculate the dose from eating foodstuffs, particularly for the component of organically bound tritium (OBT)[2]. A component to that uncertainty is the body retention time. In reports this has been expressed as 'half time' retention in the body and refers to the number of days after eating the foodstuff when half of the tritium still remains in the body. A recent study extrapolating from results in rats[3] has suggested that retention of OBT in humans has a 70% component of 10 days half time and a 30% component of 100 days half time, compared with data from ICRP (ICRP, 1993) of 50% 10 days and 50% 40 days.

This study will aim to investigate body retention of OBT in human volunteers. The foodstuff under study is sole from Cardiff Bay, an area labelled by authorised discharges of tritium from the GE Healthcare plant at Whitchurch, Cardiff. Much of the tritium discharged is in the form of OBT. Samples of sole have been obtained from a suitable local supplier; about 600g of sole were eaten by each of 5 volunteers over a period of 1-2 days. Replicate subsamples are being analysed for total tritium and OBT to estimate the amounts consumed. Volunteers are providing 24-hour samples of urine for 3 days prior to consumption and for 7 days afterwards, then for periods of 3 days around day 12, 20, 28, 40, 60, 100, 150 days. Analyses of urine are being carried out for tritiated water and OBT. Excretion curves will be plotted over time to investigate body retention times, and conclusions drawn relevant to calculation of the dose coefficient. The data will be written up for publication in a scientific journal.

References:

[1]RIFE, 2006. Radioactivity in food and the environment, 2005. Environment Agency, Environment and Heritage Service, Food Standards Agency, Scottish environment Protection Agency. RIFE-11, 271 pages.

[2]Harrison, J.D., Khursheed, A., and Lambert, B.E., 2002. Uncertainties in dose coefficients for intakes of tritiated water and organically bound forms of tritium by members of the public. Rad Prot Dosim 98 (3) 299-311.

[3]Environment Agency, 2005. Doses from the consumption of Cardiff Bay flounder containing organically bound tritium. EA report (22pages).

Project RRX 108 Studies of ionising radiation and risk of heart disease

S. DARBY, P. McGALE, D. HERMANS, M. PARKIN, R. PETO, K. RAHIMI, C. TAYLOR, Y. WANG
Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), University of Oxford.
with collaborators in several dozen countries.

This project will extend current knowledge about radiation-induced heart disease. It will provide insight into the magnitude, aetiology and timing of the risk; into the nature of the dose-response relationship; and into the variation in risk with age at exposure, smoking status, prior heart disease and other factors.

The project will be conducted in women irradiated for breast cancer, who receive a wide variety of cardiac doses. Randomised controlled trials in such women have already demonstrated a risk of radiation-induced heart disease, and have found that the risk of death from radiation-induced heart disease is greater than the risk of death from radiation-induced second cancer.

The project has three components:

Firstly a cohort study of mortality including at least 1 million women identified via about 100 cancer registries in all five continents, and followed for up to 30 years.

Secondly a study of heart disease incidence including at least 100,000 women in Australia, Denmark, Finland, Italy, Scotland, and Sweden, and followed for up to 30 years.

Thirdly a case-case study in Sweden and Denmark based on 1500 women who have developed heart disease after radiotherapy for breast cancer. Detailed documentation of each woman's radiotherapy will be obtained and quantitative measures of cardiac dose derived using modern radiotherapy planning techniques. The hospital cardiology notes for each woman will be reviewed, providing insight into the relationship between the location of cardiac damage and spatial distribution of radiation dose to the heart.

Project RRX 109 Mechanisms and genetics of radiation induced in vivo bystander signalling

E. WRIGHT, S. LORIMORE, P. COATES
University of Dundee Medical School

Chromosome aberrations, gene mutations and cell death induced by ionizing radiation are conventionally attributed to the DNA being irreversibly changed immediately after exposure, either during the processing and enzymatic repair of the damage or during DNA replication. As malignancy is generally regarded as being initiated by a gene mutation or a chromosomal aberration, the initiating lesion for malignant transformation has been similarly attributed to DNA damage in a directly irradiated cell. Recently, the view that radiation-induced deposition of energy in the nucleus of an irradiated cell leads to all the adverse consequences of radiation exposure has been challenged by observations in which effects of ionising radiation are demonstrated in cells that are not themselves irradiated but are the descendants of irradiated cells (radiation-induced genomic instability) or cells that have communicated with irradiated cells (radiation-induced bystander effects). Radiation-induced genomic instability is characterized by a number of delayed adverse responses including chromosomal abnormalities, gene mutations and cell death days and months post-exposure. Similar effects, as well as responses that may be regarded as protective, have been attributed to bystander mechanisms. These, so called, non-targeted effects have implications for understanding the mechanisms of radiation-induced DNA damage and malignant transformation. Our previous research has highlighted the inter-relationship of these non-targeted effects in irradiated haemopoietic tissues. In this project, we propose to investigate the cellular interactions (bystander effects) that contribute to an in vivo genotype-dependent instability phenotype. The bystander signals in the bone marrow microenvironment and the cellular source of signals will be characterised; the type and levels of cellular responses to such signals will be determined and the signalling pathways in the responder cells investigated.

Project RRX 110 A case-control comparison of germ line minisatellite mutation frequency in childhood leukaemia

G. M. TAYLOR
Cancer Immunogenetics Laboratory, School of Cancer Sciences, University of Manchester, at St Marys Hospital, Manchester, M13 0JH, UK

Evidence of clustering of childhood leukaemia cases in the village of Seascale in the vicinity of the Sellafield nuclear installation has been interpreted, controversially, to suggest that the exposure of parents preconceptionally to ionising radiation may increase the risk of leukaemia in their children. However, there is no direct evidence linking parental preconceptional irradiation (PPI) exposure to the development of childhood leukaemia, and furthermore, the existence of a mechanism by which a radiation-induced mutation in a parental germ cell can cause leukaemia in the next generation has been challenged on the grounds that such mutations occur too infrequently to account for the Seascale cluster. Nonetheless, recent research has suggested that unusual genetic mechanisms may exist by which the exposure of germ cells to radiation could give rise to changes that can destabilise the genome sufficiently to increase the risk of leukaemia in offspring inheriting such mutations. One such change involves the development of mutations in tandemly repeated DNA loci known as minisatellites, at a critical stage of parental gametic development. Although there is no evidence at present that minisatellite mutations directly cause leukaemia, they may act as a useful surrogate for radiation effects associated with the risk of childhood leukaemia. In order to examine whether minisatellite mutations are associated with an increased risk of childhood leukaemia, we are carrying out a comprehensive study of germline mutation rates in five minisatellite loci in 200 children with leukaemia, in comparison with 200 control children. Our aim is to determine whether there is a significantly increased mutation rate in leukaemia case children compared with controls that would justify further studies exploring the mechanisms involved.

Project RRX 111 Assessment of the heritability of human cellular radiosensitivity

C. BADIE and S. BOUFFLER
Centre for Radiation, Chemical and Environmental Hazards, Radiation Protection Division, Health Protection Agency

In general, radiation protection standards treat all individuals within populations equally. However, there is increasing evidence that genetics can influence an individual's health risk. For example, a risk of breast and other common cancers is significantly affected by genetic factors. Thus it is important that sound understanding is obtained of the range of human radiosensitivity and the extent to which genetic factors contribute to the variation.
In this project, the contribution of genetics to human cellular radiosensitivity will be assessed by completion of a 50 twin pair study of cell cycle and apoptotic responses to x-irradiation. The mechanisms contributing to variation in response will be examined by quantitative Polymerase Chain Reaction (PCR) analysis of genes regulating major damage response pathways (cell cycle arrest, apoptosis, mitotic catastrophe). Comparison of cycle, apoptotic and specific gene responses in monozygotic and dizygotic twin pairs will be carried out. Assessment of heritability will be made using the techniques of co-variance and structural equation modelling (in collaboration with Prof Jaakko Kaprio in Finland). With a view to extending the twin approach we will additionally develop high throughput multiwell plate-based assays for cellular radiosensitivity specifically to examine variation and genetics of specific pathways contributing to radiosensitivity initially focusing on apoptosis, DNA double strand break repair. The proposed work addresses directly one of the priority questions identified in the DH 2005 Radiation Protection Research Programme: Can studies be undertaken to define the genetic factors that underlie differences in individual sensitivity to radiation exposure?
This study will inform considerations of the most appropriate approach to radiation protection of populations incorporating innate variation in sensitivity and therefore risk. This applies not only to environmental exposures but also to medical exposures where severe reactions to radiotherapy are frequently observed complications. The work will contribute to policy decisions on how populations are best protected from radiation exposures.

Project RRX 112 Interactions between radiation, inflammation and environmental carcinogens

E. WRIGHT, S. LORIMORE, P. COATES
University of Dundee Medical School

The potential for interactive effects of radiation with infection or exposure to other damaging environmental agents has important consequences for human health particularly the incidence of cancer. A major problem with human epidemiological studies is the low incidence of cancers that can be linked to occupational and environmental exposures and the numerous confounding variables of environment and genetics. There is some direct experimental evidence for interactions between radiation and chemicals from animal studies (for instance, irradiation followed by exposure to methyl nitrosourea leads to an elevation in the incidence of leukaemia and changes in the pathology) but with current knowledge, it is unclear whether significant enhancements of tumour incidence would be seen after exposure to combinations of various environmental agents.

In this project, we aim to investigate the feasibility of using surrogate end-points to identify interactions between ionising radiation and chemicals that are carcinogenic or that induce an inflammatory response. To investigate these interactive effects, we aim to test methods that identify the effects of prior exposure to one agent on the cellular responses to subsequent exposure to that or another agent. The general approach will be to assess the ability of tissues to induce appropriate stress responses and to study the amount of DNA damage induced with and without prior exposure. The rationale for the approach is that quantifying DNA damage and damage responses provides a measure of the rate of accumulation of damage. Alterations in damage levels in cells from unexposed compared to previously exposed scenarios would be strong indicators for altered mutagenic rates, with implications for tumourigenic potential.

Project RRX 113 Neonatal transcranial ultrasound – thermal hazard and risk assessment

A. SHAW[1], **B. ZEQIRI**[1], **F. DUCK**[2], **J. OSBORNE**[2].
[1]National Physical Laboratory, [2]Royal United Hospital, Bath

Every year approximately 42,000 premature babies are born in the UK, and transcranial ultrasound is one of the frontline diagnostic tests carried out, yet there is limited information available on the consequences of these exposures.

Ultrasound imaging is extremely widely used in general radiology and has an excellent safety record here. Consequently, it is often assumed that the use of ultrasound is inherently safe. In some circumstances, however, the injudicious use of ultrasound could be a source of hazard: the World Federation for Ultrasound in Medicine and Biology recommendation is that a 4^{o}C increase for 5 minutes or more is potentially hazardous. Recent international standards allow imaging transducers applied to adult skin to produce up to 10^{o}C temperature increase at the skin surface. However, explicit limits for neonatal use are not specified.

The overall aim of this project is to use validated, anatomically relevant phantoms to survey the temperature increase caused by neonatal clinical ultrasound equipment. The equipment will be tested as it is used clinically and the results will provide quantitative, scientific data to inform DH policy in this area. The phantoms may be developed in the future as national or international standards and used to inform purchasing decisions in the NHS.

The project will:

- Summarise available data on current clinical practice.
- Build and validate phantoms.
- Survey transcranial neonatal equipment in clinical use

Project RRX 114 A cytogenetic assessment of the impact of long term exposure to chemical agents on radiation responses.

D. LLOYD, S. BOUFFLER and O. SEPAI (lead is now K. Rothkamm)
Centre for Radiation, Chemical and Environmental Hazards, Radiation Protection Division, Health Protection Agency

Exposure to ionising radiation alone is in practice rare, everybody receives exposures to a complex mixture of chemical and physical agents. Investigations of interactions between different types of agent are important. The aim of the proposed project is to investigate the impact of exposure to certain chemical agents on radiation responses. This will be achieved through the use of in vitro cytogenetic monitoring. Human lymphoblastoid cell lines will be grown in the presence of relatively low levels of chemical genotoxins with different modes of action (e.g. alkylation, bulky adduct formation, reactive oxygen generation) for up to six months. Following chemical exposure, challenge doses of low linear energy transfer (low-LET) ionising radiation will be given. The effects of such treatments will be monitored by the standard cytogenetic methods of dicentric scoring, translocation scoring, micronucleus scoring and chromatid damage scoring. Changes in cell cycling kinetics will be monitored. The exposure regimes are designed to mimic in a very simple way chronic environmental exposure to chemicals followed by radiation exposures as a consequence of medical procedures or accidental exposures. Insights into the importance of considering chemical exposures in predicting radiation effects will be obtained.

Project RRX 115 Chromosomal damage in normal human lung cells after exposure to low doses of ionising radiation

RHONA ANDERSON[1], JOANNA BRIDGER[1] and MARK HILL[2].
[1]Centre for Cell and Chromosome Biology, Division of Biosciences, Brunel University and
[2]MRC Radiation and Genome Stability Unit, Harwell.

Cancer of the lung is the second most common cancer in the UK with around 40,000 new cases diagnosed each year. It has one of the lowest survival outcomes (approximately 6% with a 5 year survival rate) of all cancers, mainly due to limitations in diagnosis at early stages of the disease. Approximately 90% of all lung cancers are attributed to smoking. The remainder are thought to be due to a combination of exposure to other environmental carcinogens including radon gas and its daughter radioisotopes, and as a secondary consequence of radiation therapy for unrelated cancers. As the smoking habits of the UK population decrease in response to public health awareness campaigns and changes in UK law, and the use of radiation as a therapeutic tool increases, then it is likely that the contribution in the causation of lung cancer from non-smoking related carcinogens will increase. Identifying and understanding the carcinogenic mechanisms involved in radiation-induced lung cancer is therefore of great importance. The objective of this study is to characterise chromosomal damage induced in normal human bronchial epithelial cells (HBEpC) after exposure to low doses of high-linear energy transfer (LET) α-particles and low-LET γ-rays to not only investigate chromosome aberration formation within these cells, but with the additional aim of determining whether radiation-induced cellular effects can be mechanistically associated with the pathogenic expression of chromosomal abnormalities in lung carcinoma cells. Chromosome aberrations will be visualised using the technique multiplex fluorescence *in situ* hybridisation (m-FISH) to generate novel data of damage initially induced and also, transmitted in surviving and proliferating HBEpC. This study aims to provide quantitative and qualitative detail on a previously uncharacterized and relevant human cell type that will contribute to current risk estimates for the occurrence of lung cancer after exposure to ionising radiation, particularly at low doses, and which may be of importance in the early stages of the multistage process of carcinogenesis.

Project RRX 116 Application of gamma-H2AX analysis to monitor double strand break induction and repair in cells and tissues.

P. JEGGO and T. STIFF
Genome Damage and Stability Centre, University of Sussex

DNA double strand breaks (DSBs) represent the major lethal and potentially carcinogenic lesion induced by ionising radiation (IR). DNA is coated with multiple proteins including H2AX, a variant of the histone H2A. An early step in the response to DSB formation is phosphorylation of H2AX in the vicinity of the DSB. Phosphorylated H2AX, termed γ-H2AX, forms around the DSB site and can be visualised as discrete foci by fluorescence microscopy. There is a close 1:1 correlation between γ-H2AX foci and DSBs after IR, providing a highly sensitive assay to monitor DSB formation. The rate of loss γ-H2AX foci allows a sensitive monitor of the rate of DSB repair. This analysis can be carried out in cultured cells but techniques are being developed to monitor γ-H2AX foci in cells and tissues in vivo. We have recently characterised a mouse (LigIV$^{m/m}$) deficient in a protein (DNA ligase IV) required for the major pathway for DSB repair. These tools will be exploited to address priorities of relevance to the Department of Health's Radiation Protection programme. We will (i) establish conditions to monitor γ-H2AX foci in mouse lymphocytes and other tissues to enable us to monitor DSB repair in vivo and to assess DSB repair rates in different tissues (ii) identify a highly sensitive system to monitor DSB induction. Since LigIV$^{m/m}$ cells have slow DSB repair, even low levels of DSBs accumulate and can be quantified. (iii) assess the impact of chronic low dose rate exposure to IR on DSB formation and compare it to the impact of endogenous oxidative damage and iv) assess the sensitivity of the G1/S checkpoint to low IR doses.

Project RRX 117 Characterisation of chromosome damage induced *in vitro* by alpha irradiation and identification of potential markers of *in vivo* exposure

E.J. TAWN[1], **C.A. WHITEHOUSE**[1], **M.A. HILL**[2].
[1]Westlakes Research Institute, Moor Row, Cumbria, CA24 3JY [2]Biophysics Group, MRC Radiation & Genome Stability Unit, Harwell, Oxfordshire, OX11 ORD

A key element in the evaluation of the health risks associated with low dose radiation exposure is the validation and verification of exposure history. The identification of a suitable stable cytogenetic biomarker linked to dose and cancer mechanisms will enhance the power of epidemiological studies of individuals exposed to alpha-irradiation, e.g. radon, plutonium, through improved retrospective dosimetry. It will also provide more relevant data for the derivation of comparative risks of different radiation qualities. The aim of this project is to characterise the cytogenetic damage associated with *in vitro* exposure to alpha irradiation with particular emphasis on the quality and quantity that is likely to be transmitted through cell division to descendant cells.

Lymphocytes will be irradiated in cell stage G_0 with 3.26 MeV alpha-particles at doses in the range of 0 - 1Gy and, for comparison, with X-ray doses of 1.5 and 3Gy X-rays. Cells will be analysed in their first *in vitro* division. In order to characterise the nature of the chromosome damage induced by alpha-irradiation, a multi-colour fluorescence *in situ* hybridisation (mFISH) painting technique will be used to identify individual chromosomes. An additional paint will be applied to enable the identification of the two different chromosome arms. This will allow the detection of stable and unstable chromosome inter-changes involving all chromosomes whilst also enabling the detection of pericentric intra-changes. Dose-response relationships for different aberration types, particularly in stable cells, will be established. The variation in the frequency and distribution of chromosomes aberrations with dose will also be compared to the calculated number of alpha-particle traversals through the nucleus. Identification of possible stable markers for *in vivo* exposure will be tested by studying individuals with known deposits of plutonium.

Project RRX 118 A comparison of the cancer mortality and cancer registration experience of radiation workers exposed to external radiation only with workers additionally exposed to plutonium, uranium or tritium or a combination of these radionuclides.

D. McGEOGHEGAN, K. BINKS, M. GILLIES, S. WHALEY. (lead is M. Gillies)
Westlakes Research Ltd, Moor Row, Cumbria, CA24 3JY

Radiation risk estimates used to set radiation protection standards used in the nuclear industry are based on extrapolation of the dose response curve from high dose and high dose-rate studies. The extrapolation assumes that the dose response is linear and that that there is no dose response at zero dose. The main reason for nuclear worker studies around the world has traditionally been to directly assess the risks of low dose/low dose rate radiation to the workers to ensure that the extrapolation from the high dose studies is valid.

In recent years, attention has focused on the role of internal exposures. Particularly, how does the cancer mortality and cancer registration experience of these workers differ from those of workers only exposed to external radiation and whether such exposures can modify the dose-response curve.

The principal aim of this study is to explore to what extent health effects associated with internal radiation are quantitatively and qualitatively different from those associated only with external radiation. This will be done by directly comparing the cancer mortality and cancer registration experience of workers that have exposure to external radiation with workers who additionally have exposure to plutonium, uranium or tritium or to a combination of these radionuclides. We will also assess to what extent the internal exposure modifies the dose response curve based on workers that have received only external exposures.

Exploratory analyses will include examining Standardised Mortality Ratios and Standardised Incidence Ratios. To reduce the biases associated with the ‘healthy worker’ effect, comparisons also will be made between the workers only exposed to external radiation with workers exposed to different radionuclides and combinations of radionuclides. Poisson regression models will be used to describe excess relative risk and excess absolute risk of the cancer mortality and cancer registration experience associated with the external and organ-specific internal doses.

Project RRX 119 Long-term sequelae of radiation exposure due to computed tomography in childhood.

M. PEARCE[1], L. PARKER[1,2], E. RON[3], A.W. CRAFT[1], K. McHUGH[4], J. SALOTTI[1], D. BRENNER[5], K. PYO KIM[3]

[1]Newcastle University, [2]Dalhousie University, Canada, [3]National Cancer Institute, USA. [4]Great Ormond Street Hospital, London [5]Columbia University, New York.

Computed tomography (CT) plays an important role in the diagnosis and management of disease and injury. Patients undergoing CT scanning are exposed to relatively higher levels of radiation. In particular, children scanned using CT may have received high doses when compared to those from other diagnostic procedures involving radiation, such as X-rays. The long-term risks of CT are unknown, but children represent a susceptible group for radiation-related cancer. We are conducting a large epidemiological study, in collaboration with the U.S. National Cancer Institute, which provides a unique opportunity to assess the long-term effects of CT scans in children and young adults and to gain more information on a potentially important risk factor for cancer in this population.

We are collecting radiological, clinical and demographic details on 200,000 patients (aged 21 years or less) who had CT scans prior to 2002. This information is obtained from radiology information systems in radiology departments throughout Great Britain and will enable us to describe and evaluate the use of CT exams over the study period.

Patient details will be linked with the National Health Service Central Registry so that cancer and mortality information can be obtained. Patient Information Advisory Group approval was received because it is not feasible to obtain individual level informed consent.

Information on scan details, as well as scan protocols and details of the CT scanner histories in each department is being collected will be used to estimate radiation doses to specific body sites and organs. Additional from to aid the dosimetry process. The calculated doses will be used to estimate cancer and mortality risks.

The study also will be used as the model for a planned international study of the long-term risks associated with CT.

Project RRX 120 Investigation of genotoxic effects of ELF-EMF radiation utilising microsatellite sequences.

R.J. MAIRS, K.M. PRISE and M. BOYD
University of Glasgow

The cancer-causing risk of extremely low frequency electromagnetic fields (ELF EMF), such as those associated with overhead power lines, is uncertain because the analytical methods applied have allowed the examination only of large changes in DNA. We have developed a more sensitive means of detection of DNA damage, involving sequences called microsatellites and minisatellites. These are particularly prone to radiation-induced mutation.

Our research has revealed that exposure of cells to 1 milliTesla (mT) ELF EMF gave rise to a four-fold increase in mutation induction compared with controls, suggesting that ELF EMF is genotoxic.

We are now studying various facets of mutation induction in cellular DNA due to interaction with ELF EMF: the effect of ELF EMF dosage less than 1 mT (occupational and domestic exposure levels); the part played by free radicals in ELF EMF mutagenesis; the comparative mutagenicity of continuous and fractionated ELF EMF exposure.

It is expected that these investigations will provide indicate the mutagenic potential of levels and schedules of ELF EMF exposure similar to those experienced by most of the population.

Project RRX 121 Awareness and perceptions of the risks of exposure to radon in homes: a population based study on the impacts of local radon policies, trust, and social capital

W. POORTINGA, N. PIDGEON, S. LANNON.
Cardiff University

The aim of this project is to inform the development and implementation of the Department of Health (DH) radiation protection policy through a population-based study of people's awareness and perceptions of the risks of radon in the home, and health-protection behaviours to reduce indoor radon levels.

The project will attempt to link people's attitudes and behaviours to the geography of radon occurrence in the area, the history of radon policy and communication initiatives, as well as the socio-economic context. More specifically, the project will examine whether:

- People's awareness and perception of the risks of radon vary according to exposure.
- Recent radon awareness initiatives have an effect on people's radon-related perceptions, awareness, and remedial action.
- The effectiveness of radon policy and communication initiatives is mediated by social factors, such as social capital and trust.

A population-based survey (n=1500) will be organised to assess people's awareness and perceptions of the risks of radon in the home, and health protection (remedial) behaviours to reduce levels of indoor radon gas. Policy interviews will be used to examine the history of radon-related activities in the sampled local authorities. The population-based survey and policy interviews are subsequently combined and analysed using multilevel modelling techniques. Multilevel modelling is a relatively new statistical technique that was developed to analyse clustered, hierarchical or multilayered datasets. The proposed project is innovative in that it combines methodologies from social epidemiology, health services research, social psychology, and the field of risk perception and communication, in order to bring together the risk perception and policy research fields by examining how local radon policies influence people's attitudes and behaviour.

Project RRX 123 Updated investigations of cancer excesses in the vicinity of Seascale and Dounreay.

M.F.G. MURPHY[1], K.J. BUNCH[1], T.J. VINCENT[1], P. McKINNEY[2], R. BLACK[3], K. SMITH[3]
[1]Childhood Cancer Research Group, University of Oxford [2] Paediatric Epidemiology Group, University of Leeds, [3]Information Services Division, Edinburgh

This study will extend earlier investigations into childhood cancer excesses around Seascale and Dounreay by including cancers diagnosed in children born around either nuclear installation from 1950 to 2006 and calculating all age cancer incidence in these individuals to date. Data relating to individuals born around the two installations will be analysed separately but using identical methods. Observed and expected childhood cancers in the cross-sectional populations of relevant ages living in the vicinity of each location over the period will also be calculated.

Approval for this study will be sought from a Multi-Centre Research Ethics Committee, the Patient Information Advisory Group and the Epidemiology and Registry Group of the Childhood Cancer and Leukaemia Group whose members provide much of the data held in the NRCT.

Separate cohorts of individuals born in a specified geographical area around each of the two locations will be assembled. The Seascale cohort will be defined from a data set of Cumbrian births already assembled and covering part of our study period extended by the Office for National Statistics (ONS) to include all births in the area during our study period. The Dounreay cohort will be assembled with data from the General Registrar's Office (GRO) in Scotland. These cohorts will be flagged at ONS or GRO(S) to ascertain the cancers occurring subsequently to members of each cohort, together with the diagnostic type and date of diagnosis for each neoplasm and whether cohort members died or were otherwise lost to follow up. These data will be compared with the corresponding population figures for the equivalent time periods and age groups.

For tumours occurring in children under 15 years of age from 1953 to the present day, more detailed information is held on the National Registry of Childhood Tumours (NRCT) in Oxford. The two birth cohorts will therefore be separately linked to relevant subsets of the NRCT to give a second, independent, estimate of childhood cancer incidence around these two installations. By using multiple sources of childhood cancer ascertainment (ONS, GRO(S), Information Services Division and NRCT records) we can be confident of completeness.