Institution: Oxford Brookes University

Unit of Assessment: 5 - Biological Sciences

Title of case study: Low-dose radiation exposure and its implications on health risk assessment policy in the UK and globally

1. Summary of the impact (indicative maximum 100 words)

Kadhim's research at Oxford Brookes University into the 'non-targeted effects' of radiation has had extensive conceptual impact leading to reconsideration of the recommended dose limits permissible in both clinical and environmental contexts. Her research has been referenced by major international bodies such as UNSCEAR (United Nations) and has led to her advisory role to UK Government Departments through the Committee on Medical Aspects of Radiation. Her contribution to the 2013 report to the Department of Health has already impacted health risk assessment and clinical radiotherapy through its recommendations for new lower thresholds of dose levels to protect patient health. This has already contributed to changes in the clinical practice guidelines on low-dose radiation usage for CT scans.

2. Underpinning research (indicative maximum 500 words)

Since the discovery of X-rays researchers in the radiation biology field have, for over a century, developed their understanding of biological effects of ionizing radiation through an intuitive paradigm, in which the magnitude of the effect was proportional to absorbed radiation energy. This evolving knowledge was expressed eloquently in a mathematical model known as target theory. Accordingly, it has been accepted that the adverse effects of ionizing radiation, such as mutation and carcinogenesis, are caused solely by damage in the DNA of cells absorbing radiation energy, and that the consequences of such damage are expressed in cells surviving radiation. However, pioneering work undertaken by Kadhim and colleagues at MRC Harwell established a new paradigm called "Non-Targeted Effects (NTE) of radiation exposure". NTE are characterised by cellular responses arising in non-targeted cells, i.e. cells that although not directly exposed ionizing radiation were exposed to molecular factors in extracellular fluids, either released by irradiated cells or created by irradiation of extracellular fluid. The NTE paradigm adds a new dimension to radiobiology, as summarised in [1].

Kadhim's group (including Irons, Chapman, Bowler, Al-Mayah & Bright) relocated to Oxford Brookes University in 2007 and continued with their work to establish the mechanisms and parameters of this new radiation response. Their results have had a major influence in changing the conventional model of a hit-effect relationship for radiation, moving away from a paradigm in which radiation energy must be deposited in the nucleus in order to produce a biological effect, to a new paradigm that incorporates radiation's non-targeted effects. These NTE have their basis in active cellular processes initiated by ionizing radiation and perpetuated with time. They manifest principally as genomic instability (GI) and bystander effects (BE) in non-irradiated neighbouring cells. As a key NTE, GI has profound implications for human health including radiation risk estimation, radiotherapy, the progression of normal cells/tissue to a malignancy, and possibly premature ageing.

This work, supported by US Department of Energy (DoE) in 2010 , demonstrated for the first time the existence of intra-individual variation in the level of GI induction under bystander conditions [2&3]. This suggested that inter-cellular communication within the bystander cell population may be critical for the increase in cellular damage. This finding has important consequences for the role of *in vivo* bystander responses, whereby in addition to dose, cell context and genetic predisposition at time of exposure and communication after exposure determine the final biological effect of radiation. It has been shown that some individuals' are more sensitive to radiation than others and thus has implications for environmental dosimetry and radiotherapy [2]. The DoE subsequently highlighted Kadhim's work on their own website.

The group also investigated the mechanistic link between GI in the progeny of irradiated and bystander populations using chromosome damage, total DNA analysis, and several relevant communication molecules, all of which are important manifestations of radiation-induced genomic instability and cancer, to identify the nature of the communication between irradiated and non-irradiated cells. Results identified:

1- TNF-α is predominantly associated with GI initiation in irradiated human endothelial

cells [3],

2- Molecules encapsulated in exosomes play a significant role in NTE [4]

3- Genetic- and dose-specific differences in radiation induced signalling such as TNF-α and Tumour Growth Factor- β[5]. Thus a potential mechanism for inhibition of the damaging effects from these molecules during and after irradiation was revealed and importantly can be used in radiotherapy.

Additionally, through funding from the EU-funded *NOTE* project, the Kadhim group identified important mechanisms for radiation-induced NTE including; DNA nonhomologous end-joining [6], as well as involvement of mitochondrial DNA in direct and non-targeted cellular effects of low dose ionizing radiation [7].

3. References to the research (indicative maximum of six references)

[1] Kadhim, M., Salomaa S. et.al. (2013) Non-targeted effects of ionising radiation—Implications for low dose risk *Mutation Research* 752(2) 84–98, doi: 10.1016/j.mrrev.2012.12.001
This is the final outcome of the NOTE project, which Kadhim led the authorship with contributions from all other work package leaders.

[2] Kadhim, M.A., et al. (2010) Genomic instability after targeted irradiation of human lymphocytes: evidence for inter-individual differences under bystander conditions. *Mutation Research* 688(1-2) 91-94, doi: 10.1016/j.mrfmmm.2010.03.013. Funded by US Dept. of Energy and was designed and supervised by Kadhim.

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[3] Natarajan, M., et al. (2007) Oxidative Stress Signaling: A Potential Mediator of Tumor Necrosis Factor-α Induced Genomic Instability in primary Vascular Endothelial Cells. *The British Journal of Radiology*, 80 (1) S13-22, doi: 10.1259/bjr/15316848
Funded by the US Dept. of Energy, experimentally, Kadhim and Natarajan contributed equally to all aspects of this study.

[4] Al-Mayah, A. et al. (2012) Possible role of Exosomes Containing RNA in mediating Non-Targeted Effect of Ionizing Radiation. *Radiation Research* 177(5) 539-545, DOI: 10.1667/RR2868.1
Al-Mayah was a PhD student and the study was fully designed and supervised by Kadhim. All other researchers also Brookes

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[5] Irons, et al, (2012) The effect of genetic background and dose on non-targeted effects of radiation. *International Journal of Radiation Biology* 88(10) 735–742, doi:10.3109/09553002.2012.715793
Irons was part of *NOTE* project as a post-doctoral researcher and the study was fully designed and supervised by Kadhim

[6] Klammer, H.E., et al. (2010) Evidence of an adaptive response targeting DNA nonhomologous endjoining and its transmission to bystander cells. *Cancer Research* 70: (21) 8498-8506, doi: 10.1158/0008-5472.CAN-10-1181
Kadhim's specific contribution to this paper was to contribute to the experiment design and set up, and interpretation of the results and co-authorship of the paper

Submitted to REF2014, Oxford Brookes University, UoA5 - Biological Sciences, REF2, MA Kadhim, Output identifier 7766.

[7] Schilling-Toth, B. et al. (2011) Analysis of the common deletions in the mitochondrial DNA is a sensitive biomarker detecting direct and non-targeted cellular effects of low dose ionizing radiation. *Mutation Research* 716(1-2), 33-39, doi: 10.1016/j.mrfmmm.2011.07.018
Kadhim's specific contribution to this paper was to advise on the design of the experiment and the interpretation of results and co-authorship of the paper

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4. Details of the impact (indicative maximum 750 words)

Risk from low dose ionizing radiation is of major societal concern, as all living things, including humans are exposed continuously to environmental background radiation as well as artificial sources, such as medical equipment for diagnostic and therapeutic purposes. Of particular concern is variability between individual damage and response to radiation (targeted and non-targeted) due to their differing genetic make-up which has implications for environmental risk assessment and therapeutic design.

For risk assessment, a pool of knowledge is always needed to make a societal impact; a change in radiation protection regulation or practise in this case. A single study or a single group cannot make any impact alone but the studies have to be repeated by independent groups. Societal impact requires that the researcher is active in governmental and international committees and working groups.

Prof. Kadhim has had an outstanding contribution on the direction of international research specifically on non-targeted effects. This started from her pioneering observations on genomic instability and bystander effects and contributions to the formulation of a new paradigm of NTE, which has profound implications for radiation protection and therapy.

The global framework for radiation protection leading to the societal impact is based on underpinning science evaluated in 2012 by United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). Kadhim's work on NTE was cited in their White Paper making recommendations to guide their future programme [a]. This White Paper has been used to formulate the principles of protection by the International Commission for Radiation Protection (ICRP) [b] that are then taken up in international standards, such as basic safety standards and national legislation that form the operational framework for radiation practices.

Internationally, Kadhim's research through the pan-European NOTE programme has contributed to the development of recommendations for international decision makers on radiation exposure and the future of radiation biology research. This has taken the form of a position paper from all of the NOTE participants [1] which informs high level discussion at ICRP and UNSCEAR.

In addition to her international reputation, Kadhim's expertise and competence has been recognised by the UK government. In particular she was appointed in 2012 to the Committee on Medical Aspects of Radiation in the Environment (COMARE) [c], which is responsible for advising Government on the health effects of natural and manmade radiation, as well as drafting advice for the general public. Through her work on the COMARE and as a member of the "COMARE Medical Practices Subcommittee (CT)," Kadhim is currently involved in the preparation of a key report to the Department of Health (DoH) concerning radiation doses from Computerised tomography (CT) scanners in the UK. Drawing on the research undertaken by Kadhim referenced above (specifically [1]), this subcommittee report was explicitly tasked with providing:

> 'advice to the DoH on the increased use and the optimisation and justification of CT exposure, with consideration of the potential benefit of practical approaches and supporting initiatives that might result in lower population exposure from the use of diagnostic CT.' [COMARE12-MPSCT-07]

CT is currently the main source of man-made radiation exposure in the western countries and is a major concern for radiation protection. This report makes recommendations for the DoH on clinical guidelines [e], and therefore has profound implications for health and welfare, in the context that clinical and public health guidelines must ensure a fine balance between the beneficial effects of the use of CT in clinics against the potential risk for both patients and clinic operators.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[a] United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2012 white paper 'Biological Mechanisms of Radiation Actions at Low Doses' http://www.unscear.org/docs/reports/Biological_mechanisms_WP_12-57831.pdf

[b] Corroborative statement author 1. Statement from the Chair of International Commission on Radiological Protection (ICRP) Committee 1 on radiation effects. (To corroborate work on NTE of ionizing radiation becoming part of the scientific basis underlying the system of radiation protection by international committees).
[c] COMARE secretariat, http://www.comare.org.uk/comare_members.htm#top
[d] Corroborative statement author 2. Statement from the Chair of the COMARE CT sub-committee
[e] Report from DoH. COMARE12-MPSCT-07 (in pre-submission).