Institution: University of Exeter

Unit of Assessment: Clinical Medicine

Title of case study: The plastics chemical Bisphenol A and its potential human health effects

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

Research by Professors David Melzer and Tamara Galloway on the bioactivity of Bisphenol A (BPA) an oestrogenic chemical widely used in plastics, has influenced public policy on an international scale and led to improvements in human health. They demonstrated that BPA is active in the human body at commonly experienced concentrations and that higher exposures are associated with hormonal imbalance and coronary artery disease. The outcomes have stimulated policy debate and led to a reappraisal of the environmental risks associated with BPA exposure. Regulatory authorities across the world are now committed to reducing BPA residues in food and beverages.

2. Underpinning research (indicative maximum 500 words)

Bisphenol A, a synthetic oestrogen, is added to polycarbonate plastics and resins, from where it leaches into food and beverages and is readily ingested by humans. It is then absorbed from the gut, processed in the liver, circulated in the blood and excreted in the urine. By contrast, BPA is excreted in the bile of laboratory rodents, with little entering the peripheral circulation. Hence, animal models have proved unreliable as a means to understand the disposition of BPA in humans, despite the use of a variety of animal strains coupled with varying exposure routes and dosing regimens. In humans, 95% of the US population has detectable urinary BPA and, in a programme of epidemiological and human cell model analyses, Melzer & Galloway demonstrated that circulating BPA may be more bioactive than was previously thought and is associated with hormonal imbalance and coronary heart disease. They have:

- Conducted the first cross-sectional associations between BPA concentrations and adult diseases in a representative sample of the US population - NHANES study, published in the Journal of the American Medical Association in 2008 [1].
- Performed the first replication study of these findings, confirming that BPA exposure is associated with an elevated risk of coronary artery disease [2;3].
- Undertaken the first prospective study, showing that higher urinary BPA concentrations predict onset of coronary heart disease in apparently healthy adults in Norfolk, UK; thereby, augmenting any existing risk factors [4].
- Shown that these associations were specific to angiographically defined coronary artery narrowings, in patients from Papworth Hospital, Cambridgeshire UK [2].
- Shown for the first time that men with higher concentrations of BPA have higher testosterone concentrations [5]
- Shown for the first time that expression of BPA target genes is altered in association with higher BPA concentrations, with the first evidence that BPA might activate the alternative oestrogen receptor (ESRRA), a key controller of energy metabolism [6]
- Obtained the first evidence that human cell models are responsive to BPA exposure at extremely low concentrations relative to human exposures (in progress)

Throughout the course of their research, Melzer and Galloway have been careful to note that definitive experimental proof of the adverse effects of BPA in humans cannot be obtained.

Nevertheless, they have been instrumental in providing a solid body of underpinning evidence which questions the safety of this environmental pollutant in human populations.

All of the work was developed and led in the University of Exeter by Melzer (Professor of Epidemiology and Public Health; appointed 2005) and Galloway (Professor of Toxicology; appointed 2007). The gene expression studies were undertaken in collaboration with Dr Lorna Harries, Senior Lecturer, University of Exeter Medical School.

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

Evidence of the quality of the research is provided via a selection of highly-cited, peer reviewed, publications and by the award of external grant support.

1. Lang IA, Galloway TS, Scarlett A, Henley W, Depledge M, Wallace RB, Melzer D (2008) Association of urinary Bisphenol A concentration with medical disorders and laboratory abnormalities in adults. *Journal of the American Medical Association* 300(11) 1303-1310 (495 citations to Oct 2013) accompanying editorial *JAMA* 300: 1353-1355; media summary http://pubs.ama-assn.org/media/2008jer/0916.dtl#vnrscript)

2. Melzer D, Gates P, Osborn NJ, Henley WE, Cipelli R, Young A, Money C, McCormack P, Schofield P, Mosedale D, Grainger D, Galloway TS. Urinary bisphenol a concentration and angiography-defined coronary artery stenosis. PLoS One. 2012;7(8):e43378. (9 citations to Oct 2013).

3. Melzer D, Rice NE, Lewis C, Henley WE, Galloway TS (2010) Association of urinary Bisphenol A concentration with heart disease: Evidence from NHANES 2003/06. *PLoS One* 5(1) e8673 (137 citations to Oct 2013) see also editorials in *Environ. Health Perspect*. 118(3) A116 and *Nature* doi:10.1038/news.2010.7.

4. Melzer D, Osborne NJ, Henley WE, Cipelli R, Young A, Money C, McCormack P, Luben R, Khaw KT, Wareham NJ, Galloway TS. Urinary Bisphenol A concentration and risk of future coronary artery disease in apparently healthy men and women. Circulation. 2012 Mar 27;125(12):1482-1490. (29 citations to Oct 2013).

5. Galloway T, Cipelli R, Guralnik J, Ferrucci L, Bandinelli S, Corsi AM, Money C, McCormack P, Melzer D (2010) Daily Bisphenol A excretion and associations with sex hormone concentrations: results from the InCHIANTI adult population study. *Environ Health Perspect.*118(11):1603-1608 (38 citations to Oct 2013)

6. Melzer D, Harries L, Cipelli R, Henley W, Money C, McCormack P, Young A, Guralnik J, Ferrucci L, Bandinelli S, Corsi AM, Galloway T. Bisphenol A exposure is associated with in-vivo estrogenic gene expression in adults. *Environ Health Perspect*. 2011 Dec;119(12):1788-1793. (16 citations to Oct 2013).

Grants:

1) Chemical Exposure and risk of cardiovascular disease in adults: The “CARDIS” Study; Project grant. Melzer D (PI), Galloway T, plus several collaborators. The British Heart Foundation. Dates: 03/2010 to 03/2012. Total grant: £125000

2) The Role of Bisphenol A In The Development Of Chronic Disease. Project grant APP1022923. Magliano, D (PI) and colleagues, Baker IDI Heart and Diabetes Institute, Australia. Melzer D: PI for Exeter UK work - Aus$250000. National Health and Medical Research Council, Australia. Total Grant Aus$384,000

3) Peninsula Clinical Research Facility 2009-2010 Title: Determination of Bisphenol A

concentrations in clinical samples from the InCHIANTI study. £10000

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

Research undertaken directly by Melzer & Galloway generated the first large scale studies on the human health effects of BPA; one of the most widely used chemicals in the world. This research has combined observational epidemiology with detailed mechanistic studies to provide enhanced research evidence of the human health effects of BPA. They showed that the 25% of the population with the highest exposure to BPA have on average a 1.5-2 fold increased risk of developing heart disease and that this is independent of established risk factors such as smoking, blood lipids or obesity. This research has yielded the following specific identifiable impacts.

International policy debate has been stimulated. Publication of their 2008 paper in JAMA [1] provoked a large number of policy discussion documents such that Melzer & Galloway were invited in person to provide verbal evidence to the FDA Congressional Review of the Safety of BPA, Washington DC (September 2008). Policy papers discussing the results and their impact on legislation and the current advice on tolerable daily intakes were subsequently published in various countries including by the US FDA, European Food Standards Agency, (Statement of the European Food Safety Authority on a Study Associating bisphenol A with Medical Disorders' (EFSA Journal 2008 838:1-3) [a]), the Advisory Board of the German Society of Toxicology and Health Canada amongst others. EFSA issued further debate in the 2010 paper [b] in EFSA Journal 2010 8:9 'Scientific opinion on bisphenol A: evaluation of studies investigating toxicity.'This review highlighted the need for '*additional longitudinal and mechanistic studies'*, which Melzer, Galloway and team have since published [key references 3-6].

International policy has been influenced to restrict the use of BPA in food contact materials. For example, in January 2010, US federal officials at the FDA stated "some concern" about BPA's safety, particularly for infants and young children. The case study research undertaken by Melzer & Galloway [key references 1, 2] was included in the cited evidence. Canada declared BPA a toxin and banned it from baby bottles in 2008, followed by France and Denmark in 2010. Similar restrictions have been instituted across various US states. In July 2012 FDA acknowledged 'substantial uncertainties with respect to the overall interpretation of human health studies and their implications'. and has banned BPA from infant feeding containers. In January 2011, the European Commission adopted Directive 2011/8/EU, prohibiting the use of BPA in infant feeding bottles and has instigated a systematic re-evaluation of research to inform current legislation further.

Public awareness of health risks has been raised through public debate and critical media reviews [d-j]. There are over 3000 items of editorial and commentary material discussing this work in the international peer reviewed literature, international media, newspapers, specialist scientific and popular press, e.g. national newspapers such as The Independent, Times, Daily Mail, New York Times, popular journals e.g. Marie Claire, Men's Health, Women's Health, National Geographic, Elle, BBC Food Magazine. The research featured in a German TV documentary broadcast to a target audience of >6 million across Europe. The research also features in an online popular science blog and podcast from the BBC: http://www.thenakedscientists.com/HTML/podcasts/show/2010.02.07/; Feb 7th 'Pollution and plastics'.

Industries have invested in research and development of safer chemical alternatives. The 2008 paper [1] is specifically referenced as a major piece of research influencing global market trends in several major market research reports, including 'BPA- A Global Strategic Business Report (c).

BPA is the leading end-use segment for the phenol market and drives the phenol market globally. Demand for BPA in 2010 was in excess of 2.7 million metric tonnes and, despite the health concerns, this figure is predicted to continue to rise to 2018 with increased demand driven especially by markets in the Far East (http://www.prweb.com/releases/bisphenol A_market/phenol_market/prweb10992205.htm). Nevertheless, earlier growth estimates have been

tempered by global health concerns (BPA 2012 World Market Outlook and Forecast to 2017) leading to a concerted effort to develop viable, safer, alternatives by the plasticiser industry. This has spawned a rise in green chemistry approaches and has led to the synthesis and testing of alternative monomers, development of systems to identify endocrine activity in novel materials and promotion of novel polymerisation techniques to reduce unbound residues in polycarbonate.

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

a) EFSA Journal 2008:838 p1-3. 'Statement of the European Food Safety Authority on a study associating bisphenol A with medical disorders'. References Melzer p.3 http://www.efsa.europa.eu/en/scdocs/doc/cef_ej838_statement_bpa_medical_disorders_en.pdf

b) EFSA Journal 2010 8(9) 'Scientific Opinion on Bisphenol A: evaluation of a study investigating its neurodevelopmental toxicity and review of recent scientific literature on its toxicity ' – EFSA Panel on food contact materials, enzymes, flavourings and processing aids '. References Melzer p.85 and p.86.http://www.efsa.europa.eu/it/scdocs/doc/1829.pdf

c) BPA- A Global Strategic Business Report/April 2010/Global Industry Analysts Ltd http://www.strategyr.com/bisphenol_A_market_report.asp. **see section II 10**.

d) Naked Scientist Podcast 'Pollution and plastics' 26th September 2010 http://www.thenakedscientists.com/HTML/podcasts/show/2010.02.07/

e) 'BPA Linked to Higher Testosterone Levels' 30th of August 2010. http://www.webmd.com/news/20100826/stidy-bpa-linked-to-higher-testosterone-levels

f) Bisphenol A Link to Heart Disease Confirmed Nature News. 13th of January 2010 http://www.nature.com/news/2010/100113/full/news.2010.7.html

g) Environmental Health News 'Bisphenol A linked o Diabetes and Heart Disease in Humans' 16th September 2008. http://www.environmentalhealthnews.org/ehs/news/bisphenol-a-linked-to-diabetes-heart-disease-in-humans

h) USA Today 'Bisphenol A 'What You Need to Know'' 27th October 2010 http://www.usatoday.com/news/health/bpa.htm

i) Chemistry World December 2012 p46-49, 'BPA, Friend or Foe?, by Nina Notman, features an interview with Tamara Galloway. http://www.rsc.org/chemistryworld/2012/11/bpa-bisphenol

j) BBC One 'Bang Goes the Theory' Plastics and their environmental and health impacts; to be broadcast Spring 2013. http://www.environmentalhealthnews.org/ehs/news/bisphenol-a-linked-to-diabetes-heart-disease-in-humans