Institution: University of Exeter

Unit of Assessment: Biological Sciences

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

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

Professor Tamara Galloway's research has identified for the first time associations between exposure to one of the world's most widely used chemicals, bisphenol A (BPA), and an elevated risk of developing cardiovascular disease (CVD), the leading cause of death globally. Specifically the 25% of individuals with highest urinary BPA levels, compared to the 25% with the lowest levels, have a 1.5-2 fold increased risk of developing CVD. This finding has influenced international policy debate and resulted in restrictions on the use of BPA in food contact materials, and is stimulating industry investment into safer chemical alternatives. Furthermore it has raised public awareness of the associated health risks.

2. Underpinning research (indicative maximum 500 words)

Research in the Galloway laboratory is aimed at understanding the biological effects of environmental chemicals on human and wild populations. She is particularly interested in ebndocrine disruptors. Bisphenol A (BPA) is a synthetic estrogen used as a monomer in the synthesis of polycarbonate plastics and the epoxy resins used to line cans. Exposure to BPA occurs mainly when people eat or drink BPA-contaminated food and drinks, with additional exposure routes from dental sealants, BPA-coated paper and household dusts. Biomonitoring studies by Galloway's team have shown that >95% of the population is exposed to BPA [1]. Linking increased BPA exposure to elevated disease incidence is, however, controversial: animal and laboratory studies consistently report adverse health effects at concentrations well below the recommended tolerable daily intake, but data on human health have previously been lacking. Work in the Galloway group has addressed this lack of human health-related data.

In 2008, Galloway (Biosciences, joined Exeter 2007) and Melzer (Medical School, joined Exeter 2005) examined data from the US National Health and Nutrition Examination Survey (NHANES) 2003-2004 which measured, for the first time, urinary BPA concentrations in 1455 people. They found that elevated urinary BPA concentrations were significantly associated with cardiovascular diagnoses (CVD), diabetes and clinically abnormal concentrations of key liver enzymes. The results showed that the quarter of the population with the highest concentrations of BPA metabolites in their urine were more than twice as likely to report having heart disease and diabetes than those in the lowest quarter. Associations were independent of classical risk factors for heart disease, including obesity, smoking and blood lipids [1].

A single cross-sectional observational study cannot by itself prove causality, and further research by the team has strengthened causal inference by replicating the findings. They have also studied associations over time and explored biological mechanism. Galloway showed, for instance, in 2010 that urinary BPA concentrations were again (and independently) associated with heart disease [2]. This makes chance an unlikely explanation of the findings. Longitudinal studies, funded by the British Heart Foundation, involving 758 heart disease patients and 861 control group patients confirmed that BPA exposure preceded disease progression by up to 10 years [3]. This finding is important in determining that reverse causation is not occuring. Most recently, the team showed that exposure to BPA was asssociated with narrowing of the arteries, based on a study of patients whose CVD had been precisely diagnosed by angiogram, considered a gold standard method for determining vessel thickness. This provides further evidence of the specificity of the assocation and points towards a potential mechanism [4]. These studies have firmly established that increased BPA exposure results in elevated CVD.

To investigate the effect of BPA on hormone levels, the researchers studied 715 adult men and found that exposure to BPA was associated with changes in circulating testosterone concentrations [5], whilst examination of *in vivo* gene expression patterns in the men's circulating

blood cells showed significant alterations in the expression of estrogen responsive genes [6]. These results are consistent, prehaps unsurprisingly as BPA is a synthetic estrogen, with BPA acting as a endocrine disruptor.

Overall, this research shows a significant increase in the risks of developing CVD associated with elevated exposure to BPA. There was roughly a 1.5-2 fold increase in risk across all studies, which was independent of other common risk factors. Since over 95% of the population has measurable BPA metabolites in their urine and given that CVD is the leading cause of morbidity and death globally, this research has been of wide impact and public and industry interest.

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

Evidence of the quality of the research: this work has been published in high quality peer reviewed journals and has attracted significant external grant funding.

1. Lang I A, **Galloway T S**, 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 300:1303-1310 (Faculty of 1000 highly commended)

2. Melzer D, Rice N E, Lewis C, Henley W E, **Galloway T S** (2010) Association of urinary Bisphenol A concentration with heart disease: Evidence from NHANES 2003/06. PLoS One 5(1) e8673

3. Melzer D M, Osborne N, Henley W E, Cipelli R, Young A, Money C, McCormack P, Luben R, Kay-Tee Khaw KT, Wareham N J. **Galloway TS** (2012) Urinary Bisphenol A concentration and risk of future coronary artery disease in apparently health men and women. Circulation 125:1482-1490

4. Melzer D, Gates P, Osborn N J, Henley W E, Cipelli R, et al. **Galloway TS**(2012) Urinary Bisphenol A Concentration and Angiography-Defined Coronary Artery Stenosis. PLoS ONE 7(8): e43378. doi:10.1371/journal.pone.0043378

5. **Galloway T S,** Cipelli R, Guralnik J, Ferrucci L, Bandinelli S, Corsi A M, Money C, McCormack P, Melzer D (2010) Daily Bisphenol A excretion and associations with sex hormone concentrations: results from the InCHIANTI adult population study. Environmental Health Perspectives 118:1603-8

6. Melzer D, Harries L, Cipelli R, Henley W, Money C, McCormack P, Young A, Guralnik J, Ferruci L, Bandinelli S, Corsi A M, **Galloway T S**. (2011) Bisphenol A Exposure is Associated with In-Vivo Estrogenic Gene Expression in Adults. Environmental Health Perspectives 119:1788-1793 (Faculty of 1000 highly commended)

Grant support related to this research:

7. Peninsula Clinical Research Facility 2009-2010: 'Determination of bisphenol A concentrations in clinical samples from the InChianti study'. £10,000

8. British Heart Foundation 2010-2012: 'Chemical exposure and risk of cardiovascular disease in adults: The CARDIS study'. Ref PG/09/07. £119,500

9. National Health and Medical Research Council, Australia 2012-2015 (Co-I with Baker IDI Heart and Diabetes Institute). 'The role of Bisphenol A in the development of chronic disease'. NHMRC Project – APP1022923 360,000 Australian dollars = £180,000 to Exeter

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

The research directly undertaken by Galloway and colleagues generated the first large-scale studies on the human health effects of BPA. This demonstrated that the 25% of the population with the highest exposure to BPA had on average a 1.5-2 fold increased risk for developing heart disease. This finding has had a direct impact on governmental policy, raised public awareness of the health risks associated with environmental chemicals and has increased industrial interest in safer alternatives. It has had the following specific identifiable impacts:

International policy debate has been stimulated. Publication of the 2008 paper in *JAMA* [1] provoked a large number of policy discussion documents and Galloway and Melzer were invited in person to provide oral evidence to the Food and Drug Administration's (FDA) Congressional Review of the Safety of BPA (Washington, September 2008). Policy papers discussing Galloway's results and their impact on legislation and the current advice on tolerable daily intakes have been published by the US FDA (section 5; source 1), European Food Standards Agency (EFSA) (section 5; source 2, 3), the Advisory Board of the German Society of Toxicology (section 5; source 4) and have been highlighted in policy maker briefings to the US congress (section 5; source 5).

International policy changes to restrict the use of BPA in food contact materials internationally have been directly influenced by the research. In January 2010, federal officials at the FDA stated "some concern" about BPA's safety, particularly for infants and young children. This research [1, 2] was included in the cited evidence (section 5; source 1). 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 by EFSA to inform current legislation further.

Public awareness of health risks associated with plastics additives has been raised through public debate and critical media reviews. There are over 3000 items of editorial and commentary material discussing the research described here in the international peer reviewed literature, international media, popular scientific press, podcasts, popular journals e.g. *Marie Claire, Men's Health, Women's Health, National Geographic, Elle, BBC Food Magazine* and newspapers e.g. *The Independent, Times, Daily Mail, New York Times & USA Today* (section 5; sources 6-8). Galloway has appeared in a German TV documentary by '3sat Nano' (the German equivalent to *Tomorrow's World*), which featured this research and was broadcast to a target audience across Europe of >6 million. The research also features in an online popular science blog from the BBC (section 5; source 5), featuring an interview with Galloway.

Industry investment 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 (section 5; source 9). BPA is the leading end-use segment for the phenol market and drives the phenol market globally. Demand for BPA in 2010 was 2,761,915 metric tonnes, generating revenue of £4.4 billion per annum. The intensive green chemistry approaches that have been stimulated to meet this market need are summarised in (section 5; source 10), with much interest in 2,2,4,4-tetramethyl-1,3-cyclobutanediol (TMCD) which is used to make a copolyester marketed as Tritan (Eastman Chemicals).

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

Policy change/debate

1) Update on Bisphenol A for Use in Food Contact Applications, U.S. Food and Drug Administration. January 2010 . http://www.fda.gov/downloads/NewsEvents/PublicHealthFocus/UCM197778.pdf

2) EFSA Journal 2008:838 p1-3. 'Statement of the European Food Safety Authority on a study

associating bisphenol A with medical disorders'. References Galloway p.3 http://www.efsa.europa.eu/en/scdocs/doc/cef_ej838_statement_bpa_medical_disorders_en.pdf

3) 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 Galloway p.85 and p.86.http://www.efsa.europa.eu/it/scdocs/doc/1829.pdf

4) Critical evaluation of key evidence on the human health hazards of exposure to bisohenol A. Hengstler JG, Foth H, Gebel T, Kramer P-J, Lillenblum W, Schweinfurth H, Volkel W, Wollin K-M & Gundert-Remy U. (2011) Crit Rev Toxicol 41:263-291.

5) Congressional review services. Bisphenol A (BPA) in Plastics and Possible Human Health Effects. L. Schierow and S Lister 2010 http://www.fas.org/sgp/crs/misc/RS22869.pdf

Public interest

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

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

8) 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

Industry investment

9) 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**.

10) No clear winners yet in the race to find non-BPA replacements' Chemistry and Engineering News vol 91: (6) pp24-25 '