

Institution: University of Exeter
Unit of Assessment: Earth Systems and Environmental Sciences (UoA7)
Title of case study: Bisphenol A and its potential human health effects
<p>1. Summary of the impact (indicative maximum 100 words)</p> <p>Research by Professors Tamara Galloway, David Melzer, and Michael Depledge at Exeter identified, for the first time, associations between exposure to the widespread environmental contaminant bisphenol A (BPA) and changing incidences of disease. The research showed that higher exposures to BPA are associated with an increased risk of cardiovascular disease and hormonal changes. The research has influenced policy development worldwide, raised public awareness of environmental chemical health risks, stimulated public debate and critical media analysis, and is stimulating enhanced public, policy-maker and business interest in anthropogenic chemicals in the environment and their implications for human health.</p>
<p>2. Underpinning research (indicative maximum 500 words)</p> <p>Bisphenol A (BPA) is one of the world's highest production volume plastic chemicals, with a global demand of greater than 6 million tonnes per annum. This monomer is used in the synthesis of polycarbonate plastics and the epoxy resins lining tinned food. BPA escapes from packaging into food, dust, soil, and water. Careless disposal of consumer products and packaging has resulted in BPA contaminating ecosystems worldwide. Indeed, it is detectable in >95% of the human population [1].</p> <p>In 2008, Profs Galloway (Biosciences), Melzer, and Depledge (Medical School) examined data from the US National Health and Nutrition Examination Survey (NHANES) which, for the first time, measured urinary BPA in a representative sample of the US population [1]. Higher urinary BPA concentrations were associated with increased incidences of cardiovascular disease (CVD), diabetes, and clinically abnormal liver enzymes. The results showed that the quarter of the population with the highest concentrations of BPA metabolites in their urine was more than twice as likely to report having heart disease and diabetes compared with the lowest quarter. In 2012, the findings relating to CVD were replicated [2], making it highly unlikely that this was a chance finding.</p> <p>The team studied the specificity and timing of these associations by carrying out the largest international biomonitoring studies to be undertaken for BPA, funded by the British Heart Association [3]. On-line solid-phase extraction coupled with high performance liquid chromatography isotope dilution mass spectroscopy was used to accurately quantify BPA and its major metabolites BPA-glucuronide and sulphonate in urine samples. The team conducted a longitudinal study of 3900 CVD patients and their controls, which showed that BPA exposure precedes disease progression by up to 10 years. They additionally explored the toxicological mechanism of BPA in men and women whose CVD had been precisely diagnosed by angiogram (considered a gold standard method for determining vessel thickness), to show that BPA exposure is specifically associated with narrowing of the arteries [4].</p> <p>The team also studied the effects of BPA on circulating hormone levels and showed that exposure to BPA was associated with changes in testosterone concentrations in a further 400 adult men [5], with changes in the expression of hormone receptors detectable <i>in vivo</i> [6] and <i>in vitro</i> (paper in press in <i>Reproduction</i>, October 2013). These results are consistent with BPA acting as an environmental endocrine disruptor.</p> <p>The scientists are currently working with colleagues in Australia, with funding from the Australian Medical Research Council, studying associations between diabetes and exposure to BPA and phthalates. Phthalates are plasticising additives that have become ubiquitous environment contaminants.</p>

Impact case study (REF3b)

Additional University of Exeter staff involved: Dr Ceri Lewis, Dr Nicholas Osborne, Dr Riccardo Cipelli, Professor Lora Fleming.

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

Key references to research that underpins the impact described in this case study:

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(11): 1303-1310. #
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. doi:10.1371/journal.pone.0008673. #
3. Melzer D M, Osborne N, Henley W E, Cipelli R, Young A, Money C, McCormack P, Luben R, Kay-Tee Khaw K T, Wareham N J. Galloway T S (2012) Urinary Bisphenol A concentration and risk of future coronary artery disease in apparently healthy men and women. *Circulation* 125: 1482-1490.
4. Melzer D M, Gates P, Osborne N J, Henley WE, Cipelli R, Young A, Money C, McCormack P, Schofield P, Mosedale D, Grainger D, Galloway T S (2012) Urinary Bisphenol A concentration and angiography-defined coronary artery stenosis. *PLoS One* 7(8): e43378. doi:10.1371/journal.pone.004337.
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 (11): 1603-8. #
6. Melzer D, Harries L, Cipelli R, Henley W, Money C, McCormack P, Young A, Guralnik J, Ferrucci L, Bandinelli S, Corsi A M, Galloway, T S (2011) Bisphenol A exposure is associated with *in vivo* gene expression in adults. *Environmental Health Perspectives* 119 (12): 1788-1793.

References that best indicate the quality of the underpinning research.

Grant support related to this research:

- Peninsula Clinical Research Facility 2009-2010: Title: Determination of bisphenol A concentrations in clinical samples from the InChianti study. £10,000
- British Heart Foundation 2010-2012: Title: Chemical exposure and risk of cardiovascular disease in adults: The CARDIS study. Ref PG/09/07. £119,500
- National Health and Medical Research Council, Australia 2012-2015 (Co-I with Baker IDI Heart and Diabetes Institute): Title: The role of Bisphenol A in the development of chronic disease. NHMRC Project – APP1022923. 360,000 Australian dollars

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

Research directly undertaken by Galloway, Melzer, Depledge, and colleagues generated the first large scale studies on the human health effects of BPA, which is one of the most widely used chemicals in the world. Overall, their results indicate that the 25% of the population with the highest exposure to BPA have on average a 1.5-2 fold increased risk for developing heart disease. This research has had identifiable impacts on national and international policy, on public awareness, and on investment in research and development by the plastics industry:

Impact case study (REF3b)**International policy debate**

International policy debate has been stimulated. Publication of the 2008 paper on BPA and CVD in JAMA [1] provoked a large number of policy discussion documents; Galloway and Melzer were invited in person to provide verbal evidence to the FDA Congressional Review of the Safety of BPA, Washington, September 2008. Policy papers discussing these results and their impact on legislation (see below) and the current advice on tolerable daily intakes were published by many countries including: the US FDA; European Food Standards Agency [a]; the Advisory Board of the German Society of Toxicology; and Health Canada. EFSA subsequently issued further scientific opinion and debate on the 2010 paper [b].

Depledge is a member of DEFRA's Hazardous Substances Advisory Committee and is the chair of the EU Science Advisory Group of DG-Research and Innovation and he works with them to explore how other environmental chemicals (perfluorinated, compounds [6], pharmaceutical residues, metals, etc.) might be causing changes in the incidence of various diseases.

International policy change.

The research outlined in Section 2 has directly influenced international policy changes to restrict the use of BPA in food contact materials. In January 2010, federal officials at the FDA stated "some concern" about BPA's safety, particularly for infants and young children. This case study research [key references 1, 2] was included in the cited evidence [c], and there have been associated changes in legislation world-wide. 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 individual US states. In July 2012, the 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 in 2013 has instigated a systematic re-evaluation of research to inform current legislation further.

Public awareness of health risks.

Public awareness of health risks of plastics additives has been raised through public debate and critical media reviews. The research described in Section 2 is described in over 3000 items of editorial and commentary material in the international peer-reviewed literature, international media, newspapers, popular scientific press [d] and podcasts [e], general popular journals such as *Marie Claire*, *Men's Health*, *Women's Health*, *National Geographic*, *Elle*, *BBC Food Magazine*, *National Geographic* [f] and national newspapers such as *The Independent*, *Times*, *Daily Mail*, *New York Times*, *USA Today* [g]. Galloway has appeared in a German TV documentary by '3sat Nano' (the German equivalent to *Tomorrow's World*) featuring this research which was broadcast to a target audience across Europe of more than 6 million. The research also features in an online popular science blog from the BBC featuring an interview with Galloway. The Sunday Times Magazine took up the story by publishing a special feature on Depledge related to the BPA research, but also to the wider issue of how environmental chemicals influence human health [h].

Industry investment in research and development.

In response to the research, 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 [i]. 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 £500,000 per hour. The intensive green chemistry approaches that have been stimulated to meet this market need are summarised in [j], most based on 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**

- a) EFSA Journal 2008:838 p1-3. 'Statement of the European Food Safety Authority on a study associating bisphenol A with medical disorders',
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 ' see pages 54-55, p4 of minority report.
<http://www.efsa.europa.eu/it/scdocs/doc/1829.pdf>
- c) 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>

Raising public awareness

- d) Nature News 'Bisphenol A Link to Heart Disease Confirmed' 13th January 2010
<http://www.nature.com/news/2010/100113/full/news.2010.7.html>
- e) Naked Scientist Podcast 'Pollution and plastics' 26th September 2010
<http://www.thenakedscientists.com/HTML/content/interviews/interview/1275/>
- f) National Geographic's Green Guide Blog 'BPA Linked to Higher Testosterone Levels' 30th August 2010 <http://blogs.nationalgeographic.com/blogs/thegreenguide/2010/08/bpa-linked-to-higher-testoster.html>
- g) USA Today 'Bisphenol A: What you need to know' 27th October 2010
<http://www.usatoday.com/news/health/bpa.htm>
- h) Sunday Times Magazine 'Sugar and spice and all things nasty' 31st July, 2011 featuring M Depledge.

Industry investment

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