Institution: University of Birmingham

Unit of Assessment: A1

Title of case study: Changing European Commission policy in relation to biocides as agents driving antibiotic resistance

1. Summary of the impact

Antibiotic resistance has become one of the great challenges to human health in the 21st century with increasing numbers of isolates of many pathogenic bacteria being resistant to front line, therapeutic antibiotics. Recent evidence has suggested that antibiotic resistance can be selected by exposure to biocides, which are commonly used as disinfectants and preservatives.

Research at the University of Birmingham has shown the common mechanistic links between antibiotic and triclosan (a commonly used biocide) resistance. This research was used by the European Commission as evidence to support two reports published in 2009 and 2010 to inform opinions as to the safety of biocide use. These reports recommended specific new research avenues be funded and that possible selection of antibiotic resistance by biocides is a valid concern and were used as part of the evidence base in preparation of a new law which has come in to force across the European Union.

Biocide use and sales in Europe have been controlled by the Biocidal Products Directive since 1998. This legislation has been superseded by the EU Biocides Regulation (published May 2012, legally binding from September 2013). This new legislation now includes a requirement for new biocides to be demonstrated not to select resistance to themselves or antibiotics in target organisms before achieving registration; this addition was informed by University of Birmingham research. This will prevent biocides entering the environment that exert a selective pressure and favour the emergence of mutant bacteria with increased biocide and antibiotic resistance. Thus the research described has had an impact on **policy debate** and the introduction of **new legislation**.

2. Underpinning research

In recent years there has been an increase in the use of biocides in industrial, clinical and domestic applications, this increased usage has prompted concerns that biocide exposure may lead to biocide resistance, which as a result of common mechanisms of resistance, will also select for mutant bacteria which are cross-resistant to antibiotics. There is a global reliance on the use of antibiotics to treat bacterial infections and the emergence of new resistant strains presents a real global health concern.

Research conducted at the University of Birmingham by Professor Laura Piddock (at Uob since 1987) and Dr Mark Webber (Senior Research Fellow, at UoB since 2001)) aimed to investigate the common mechanistic links between resistance to the commonly used biocide, triclosan and antibiotic resistance. The research started in 2003, initially as part of two collaborative projects funded by Defra (2003-2007, OD2010: £433,925) between the University of Birmingham (Prof **Laura Piddock**), Bristol University (Prof Tom Humphrey) and the Animal Health Veterinary Laboratories Agency (Prof Martin Woodward) and subsequently continuing at Birmingham alone as the focus of a BBSRC David Phillips fellowship (2007-2011, BB/D020476/1: £451,049) and BBSRC project grant (2009-2012, BB/G012016/1: £522,284) awarded to Dr **Mark Webber** and continuing to the present.

Using *Salmonella* as a model food borne pathogen, the research demonstrated that exposure to common household biocides does select for mutant bacterial strains, which demonstrate cross resistance to antibiotics. Novel mechanisms of biocide resistance were identified and the mutant strains were found not to be severely compromised in their fitness, for example triclosan resistant *Salmonella* were able to survive in a chick colonisation model in competition with parent strains throughout a 28 day experiment [1-4]. As a result such mutants present a credible risk of surviving in the food chain once selected and indeed are indistinguishable from antibiotic resistant isolates recovered from patients. Human infection with resistant bacterial strains is known to be associated with higher chances of mortality, morbidity and increased lengths of time in hospital, with resistant Salmonella strains being associated with a three fold higher risk of severe illness or death than drug sensitive strains. Proteomic and transcriptomic investigations of resistant mutants identified novel changes to core metabolism in mutants which are relevant to antibiotic resistance, for example triclosan resistant mutants were found to have up-regulated a network of proteins involved in

production of fatty acids in order to bypass the metabolic block of the drug [5, 6]. This research has already resulted in nine publications in internationally recognised microbiology journals (an average impact factor of 4.93 and an average of 25 citations per publication from a total of 221 as of March 2013).

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

1. Bailey AM, Constantinidou C Ivens A, Garvey MI, **Webber MA** Coldham, NG Hobman J, Wain J, Woodward MJ, **Piddock**, **LJV**. Exposure of *Escherichia coli* and *Salmonella enterica* serovar Typhimurium to triclosan induces a species-specific response, including drug detoxification. *J Antimicrob Chemother*. 2009 64(5):973-985*. DOI 10.1093/jac/dkp320*
2. **Webber MA**, Randall LP, Cooles S, Woodward MJ, **Piddock LJ**. Triclosan resistance in *Salmonella enterica* serovar Typhimurium. *J Antimicrob Chemother*. 2008 62(1):83-91. *DOI 10.1093/jac/dkn137*
3. Randall LP, Cooles SW, Coldham NG, Penuela EG, Mott AC, Woodward MJ, **Piddock LJ**, **Webber MA**. Commonly used farm disinfectants can select for mutant *Salmonella enterica* serovar typhimurium with decreased susceptibility to biocides and antibiotics. *J. Antimicrob Chemother*. 2007;60(6):1273-80. *DOI 10.1093/jac/dkm359*
4. Karatzas KA, **Webber MA**, Jorgensen F, Woodward MJ, **Piddock LJ**, Humphrey TJ. Prolonged treatment of *Salmonella enterica* serovar Typhimurium with commercial disinfectants selects for multiple antibiotic resistance, increased efflux and reduced invasiveness. *J Antimicrob Chemother*. 2007;60(5):947-55. *DOI: 10.1093/jac/dkm314*
5. **Webber MA**, Coldham NG, Woodward MJ, **Piddock LJ**. Proteomic analysis of triclosan resistance in *Salmonella enterica* serovar Typhimurium. *J Antimicrob Chemother*. 2008 62(1):92-7. *In REF2*
6. Karatzas KA, Randall LP, **Webber M**, **Piddock LJ**, Humphrey TJ, Woodward MJ, Coldham NG. Phenotypic and proteomic characterization of multiply antibiotic-resistant variants of *Salmonella enterica* serovar Typhimurium selected following exposure to disinfectants. *Appl Environ Microbiol*. 2008;74(5):1508-16. *DOI 10.1128/AEM.01931-07*

4. Details of the impact

Antibiotic resistance is a global issue, with the number of pathogenic bacteria being resistant to front line, therapeutic antibiotics increasing. A recent report by the UK Chief Medical Officer (Annual Report March 2013) detailed that that infections cost the UK economy over £30 billion per year in economic cost and antibiotic resistance significantly increased mortality rates (to ~30% for infections with resistant bacteria compared with 15% for infection with drug susceptible strains), over half the ~5000 UK deaths from sepsis each year caused by *E. coli* are a result of infection with multiply resistant strains. The US Centres for Disease Control and Prevention has recently estimated infections with resistant organisms to cause over 2 million illnesses in the US per annum with over 23000 deaths resulting. These figures demonstrate the global nature of the problem and the impact in developed countries, the situation is worse in the developing world. With the increasing demand for biocide based antibacterial and preservative products, the risk of the emergence of new resistant strains has increased. The work described above has had an impact on the development of **European policy** and has informed the drafting of **new legislation** governing the licensing of biocidal products across the European union.

The research described above by Professor Laura Piddock and Dr Mark Webber at the University of Birmingham provided a scientific and mechanistic insight into how biocide exposure can select antibiotic resistance, proved that common mechanisms of resistance are relevant to both biocides and antibiotics and that mutants selected after biocide exposure are fit in animal models. The research also identified significant gaps in the current knowledge base regarding the mechanisms by which bacteria respond to biocides and commonalities with response to antibiotics, as well as a dearth of data on biocide tolerance in clinical and environmental isolates of pathogenic species. The impact from these findings was the provision of significant new information for policy makers and opinion leaders to formulate opinions as to the safe use of biocides and recommendations for future research priorities at a European level (1). This report gave a series of recommendations including instigation of research programmes to develop surveillance programmes to identify levels of biocide tolerance, develop standards for testing of the propensity of

biocides to select for resistance and to monitor biocide production and environmental accumulation levels.

The research was directly and exclusively quoted in 2010 in the EC Scientific Committee on Consumer Safety 'Preliminary opinion on triclosan': *'the identification of mechanisms of microbial resistance including genomic and proteomic aspects, is commendable and should be extended to other biocides'* (2).

The research has not only helped to shape EU opinion but also influenced changes to the law governing the use of biocides. The new 'EU biocides regulation (No 528/2012)' (3) was released in 2012 and became legally binding across the EU from 2013. This includes requirements for any new biocidal product to demonstrate that it does not select resistance to itself or target organisms before it can be registered and used in any formulations. This legislation supersedes the previous 'Biocidal products directive'. In the UK alone 652 biocidal products are currently licensed under the previous directive, as detailed on the Health and Safety Executive website of licensed biocides (4). The new regulations influenced by this work will apply to at least this number of products in a growing market. The research described was highlighted in a report published in October 2013 on antibiotic resistance in the environment (5), which was prepared for the Houses of Parliament by the Parliamentary Office of Science and Technology.

All biocidal products now submitted for regulatory approval required to be allowed to be sold in the European Union must now have been demonstrated not to select resistance to themselves or other antimicrobials, this will prevent biocides being used that provide a selective pressure that can drive antibiotic resistance. Whilst the new legislation has only been legally binding since September 2013 the German federal bureau for risk management (BfR) recommended a ban on triclosan in 2009 (6) in all non-medical contexts, the BfR ruling relied heavily on the report mentioned above from the EC Scientific Committee on Consumer Safety 'Preliminary opinion on triclosan' to form a basis for its decision which in turn used research from Birmingham to shape its conclusions. The EU in turn imposed a similar ban across Europe in 2010 in response to the BfR recommendation and a petition from Ciba (the manufacturer of triclosan) to remove triclosan from the approved list of biocidal products (this ban was over-ruled in 2012 after appeal from users of triclosan due to procedural problems with the original ruling, further legal consideration is pending at the time of submission).

The work was disseminated by publication in international peer reviewed journals, conference presentations and informal discussion with government agencies e.g. quarterly meetings with colleagues at DEFRA.

5. Sources to corroborate the impact

1. SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks), Assessment of the Antibiotic Resistance Effects of Biocides. European Commission; 19 January 2009 http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_021.pdf (cited on p52 and on 86)
2. SCCS (Scientific Committee on Consumer Safety), Preliminary opinion on triclosan (antimicrobial resistance). European Commission; 23 March, 2010 http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_013.pdf (cited on p 50 and 2x on 55)
3. Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:167:FULL:EN:PDF
4. http://webcommunities.hse.gov.uk/connect.ti/pesticides/viewdatastore?dsid=6020&adv=S
5. http://www.parliament.uk/documents/POST/postpn446_Antibiotic-resistance-in-the-environmentreferences.pdf
6. Bfr opinion #031/2009, 12 June 2009. Bfr supports ban on triclosan in food contact materials. http://www.bfr.bund.de/cm/349/bfr_supports_ban_on_triclosan_in_food_contact_materials.pdf