Institution: BRUNEL UNIVERSITY (H0113)

Unit of Assessment: 7 – Earth Systems and Environmental Sciences

Title of case study: Better health and environmental protection from harmful chemical mixtures

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

Hundreds of synthetic chemicals contaminate our food and water. Brunel's research shows harmful cumulative cocktail effects of low levels of contaminants in food and water, previously thought to be safe. The active translation of these results into European chemicals legislation also ensured a sound basis for including multiple chemical exposures in risk assessment. By working with the European Food Safety Authority, we demonstrated a viable approach to grouping chemicals for mixtures risk assessment. Based on our research, a totally new approach to grouping chemicals for mixtures risk assessment has been decided. This will influence maximum residue levels for toxic pesticides in food in Europe leading to better protection of consumers against the increased risks of harm due to multiple pesticide residues present in the majority of food items.

2. Underpinning research (indicative maximum 500 words)

Although chemical exposures of human populations and of wildlife are not to single substances, but to large numbers of chemicals simultaneously, the combined effects of such exposures had rarely been studied. In 1999, **Professors Sumpter and Tyler** (then at Brunel) recognized this major limitation and began to develop experimental strategies (Thorpe 2001, 2003) for assessing the joint toxicity of chemical mixtures in ecotoxicology. In 2001, **Sumpter** began to collaborate on chemical cocktails with Drs Andreas **Kortenkamp and Martin Scholze**, at the School of Pharmacy, University of London in an EU-funded project, ACE (Analysing combination effects of mixtures of estrogenic chemicals in marine and freshwater organisms), led by Professor Sumpter. The ACE project helped create a sound conceptual basis for the assessment of multi-component mixtures using mathematical algorithms to derive prediction curves for combinations which could be used as a benchmark against which synergisms and antagonisms could be evaluated. Subsequently, many observations confirming the predictability of multi-component mixtures were made with *in vitro* assays, but information about mixtures of chemicals in entire organisms was needed to make these ideas more credible in the arena of risk assessment. These concepts and methodologies were further developed in an EU-funded project awarded to Kortenkamp (Eden) in which Sumpter participated. In 2005, **Prof Sumpter**, and **Dr Jayne Brian** published a landmark paper on the effects of five chemicals in fish, showing that the variability normally encountered in an *in vivo* system is no hindrance to predicting mixture effects accurately (Brian et al. 2005). It also demonstrated that taking account of mixture effects provided consistently higher risk estimates than approaches which do not consider combination effects. As a direct result, the idea that mixture effects should be taken into account during chemical risk assessment gained credibility, however, the practicalities of doing so had to be worked out.

A key issue was *which chemicals should be grouped together for chemical risk assessment and which criteria should be used for grouping?*

Established practice was to group together chemicals with very similar structural features and mechanisms. For example, the US EPA currently considers organophosphate pesticides and carbonate pesticides in separate groups, although both types of pesticides essentially work through the same mechanisms, inhibition of acetylcholine esterase. In several key scientific papers and reports, **Prof Kortenkamp's team** (who joined Brunel in July 2011 with **Silva**, **Martin**, **Evans, Orton, Ermler** and **Scholze**) showed that these criteria are too narrow and might lead to underestimations of risks by leaving out chemicals that in reality also contribute to a mixture effect. Several pesticides affecting male sexual development by totally different mechanisms were shown to act together and result in significant mixture effects despite their enormous chemical and mechanistic diversity (Evans et al. 2012, Kortenkamp et al. 2012, Orton et al. 2012, Christiansen et al., 2012). This research was conducted as part of the EU-funded CONTAMED project headed by **Kortenkamp** and had a profound impact on the thinking about grouping criteria for predicting the effects of mixtures of pesticides found in food and water. It led to the realization that grouping

according to chemical structural features and mechanisms would lead to underestimations of risk by ignoring chemicals that in reality also contribute to combination effects.

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

Thorpe, K. L., Hutchinson, T. H., Hetheridge, M. J., Scholze, M., Sumpter, J. P., & Tyler, C. R. 2001, "Assessing the biological potency of binary mixtures of environmental estrogens using vitellogenin induction in juvenile rainbow trout (*Oncorhynchus mykiss*)" *Environmental Science and Technology* 35; 2476-2481. http://dx.doi.org/10.1021/es001767u (155 citations)

Thorpe, K. L., Cummings, R. I., Hutchinson, T. H., Scholze, M., Brighty, G., Sumpter, J. P., & Tyler, C. R. 2003, "Relative potencies and combination effects of steroidalestrogens in fish", *Environmental Science and Technology* 37; 1142-1149. http://dx.doi.org/10.1021/es0201348 (260 citations)

Brian, JV., Harris, CA., Scholze, M., Backhaus, T., Booy, P., Lamoree, M., Pojana, G., Jonkers, N., Runnalls, T., Bonfà, A., Marcomini, A. and Sumpter, JP., 2005, "Accurate prediction of the response of freshwater fish to a mixture of estrogenic chemicals", *Environmental Health Perspectives* 113; 721- 728. http://dx.doi.org/10.1021/es0201348 (180 citations)

Christiansen, S., Kortenkamp, A., Axelstad, M., Boberg, J., Scholze, M., Rosenskjold Jacobsen, P., Faust, M., Lichtensteiger, W., Schlumpf, M., Burdorf, A., Hass, U. (2012) "Mixtures of endocrine disrupting contaminants modelled on human high end exposures – an exploratory study in rats." *International Journal of Andrology* 35; 303-316 http://dx.doi.org/10.1111/j.1365-2605.2011.01242.x (5 citations)

Evans, R., Scholze, M., Kortenkamp, A. (2012) "Additive mixture effects of estrogenic chemicals in human cell-based assays can be influenced by inclusion of chemicals with differing effect profiles" *PloS* 7 (8) e43606 http://dx.doi.org/10.1371/journal.pone.0043606 Published: AUG 17 2012 (2 citations)

Kortenkamp A, Evans R, Faust M, Kalberlah F, Scholze M, Schumacher-Wolz U (2012). "Investigation of the state of the science on combined actions of chemicals in food through dissimilar modes of action and proposal for science-based approach for performing related cumulative risk assessment". Supporting publications 2012:EN-232. http://www.efsa.europa.eu/en/supporting/pub/232e.htm

Orton, F., Rosivatz, E., Scholze, M., Kortenkamp, A. (2012) "Competitive androgen receptor antagonism as a factor determining the predictability of mixture effects of widely used pesticides." *Environmental Health Perspectives* 120; 1578-1584. http://dx.doi.org/10.1289/ehp.1205391 (0 citations)

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

Although the experimental mixtures work conducted by **Kortenkamp, Sumpter** and co-workers raised the profile of the topic, the scientific findings in and of themselves could not open up avenues for improvements of chemical risk assessment and regulation. To achieve this, translational work in the appropriate political context in the European Union was necessary.

Kortenkamp was actively involved in this translation and a State of the Art report on Mixture Toxicology for the European Commission (published whilst Kortenkamp was at the London School of Pharmacy) had considerable impact. It cited the work carried out by **Sumpter, Brian, Tyler and Thorpe** (Brunel staff and students at the time the research was carried out) as "*Ecotoxicology that has played an important role in advancing mixture toxicology, with human and mammalian toxicology slowly catching up" (Kortenkamp et al, 2009)*. Several recent pieces of European chemicals legislation now require consideration of mixture effects, including the Plant Protection Product Regulation, PPPR (1107/2009) and the Biocidal Products Regulation (EU 528/2012), REACH, the Water Framework Directive, and the Cosmetics Directive. In the Water Framework

Directive, it states that mixtures can be considered when their qualitative and quantitative composition is well described and that the concentration addition concept defined by Brunel's researchers can be used as a default for setting quality standards. Indeed, it is now unanimously agreed that for chemical mixtures, a classical tiered approach should be used and that the concept of concentration addition (CA) described by Brunel researchers is a suitable approach for the first tier assessment.

Implementation of legislation is a separate step, requiring a framework and a methodology, that has still not been taken for the Water Framework Directive, the PPPR, the Biocidal Products Regulation or REACH, albeit there have been many calls for action. For pesticides and biocides, the European Commission mandated the European Food Safety Authority (EFSA) with working out the details for considering combination effects during the setting of maximum residue levels in food items.

To this end, the **EFSA Plant Protection Product Regulation (PPR) Panel instituted a working group which Kortenkamp was called to join as an external expert.** The task of this group was to draft a Scientific Opinion of EFSA which was to be adopted by the EFSA PPR Panel. The EFSA working group began by deciding which chemicals should be considered together in mixtures risk assessment, in so-called common assessment groups usually made on the basis of specific criteria regarding common chemical structures and common toxicological mechanisms.

The EFSA working group, however, developed a novel grouping strategy that began not with considerations of mechanisms, but instead using common adverse outcomes as the starting point for creating common assessment groups. Novel grouping criteria, based on the concept of shared toxicity and common adverse outcomes, irrespective of mechanisms, were developed for application to the regulatory framework. With this new grouping approach, all pesticides that affect e.g. the thyroid gland are considered together. The resulting large groupings (around 100 pesticides in the case of the thyroid) can then be broken down into finer groupings, according to additional mechanistic criteria, as and when they become available.

This strategy was chosen with explicit reference to work conducted by Kortenkamp and collaborators (Christiansen et al. 2012, Orton et al. 2012) showing that cocktail effects of chemicals could occur independently of chemical and mechanistic similarity between the ingredients of the cocktail. In June 2013, the EFSA PPR Panel adopted this Scientific Opinion (EFSA 2013, published in July). The adoption process involved rigorous reviews to which **Dr Daniel Pickford** of Brunel's IfE contributed substantially as an EFSA PPR Panel member.

Some of the proposed new assessment groups consist of nearly 100 active pesticidal substances. This marks a radical departure from practice in the USA, where up to now a maximum of 5 pesticides are included in the same assessment group. The novel approach taken by EFSA will set a precedent internationally, not only for pesticides regulation, but for the regulation of chemicals in general.

The Scientific Opinion (EFSA 2013) is shaping profoundly the way in which maximum residue levels for pesticides in food items are set. For the first time, these decisions will be made by taking account of combination effects of pesticides**. In certain cases, maximum residue levels may have to be lowered and this will lead to better protection of consumers from pesticide residues.** In turn, this will reduce total health impacts from pesticide use in Europe (currently estimated at around 2000 disability adjusted life years lost per year) and reduce EU consumer concern regarding pesticide residues (currently the EU barometer states 72% of EU consumers are worried about exposure to pesticide residues). The "knock on" effects internationally, will also lower general public and occupational allowable exposures to pesticides in other countries, such as the USA and Japan.

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

1) Plant Protection Product Regulation, PPPR (1107/2009)

http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:309:0001:0050:EN:PDF

2) Biocidal Products Regulation (EU 528/2012

http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:167:FULL:EN:PDF

3) REACH European Regulation (No 1907/2006)

http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=oj:l:2006:396:0001:0849:en:pdf

4) The Water Framework Directive (No 2000/60/EC)

http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:327:0001:0001:EN:PDF

5) Cosmetics Directive (No 76/768/EEC)

http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31976L0768:EN:NOT

6) EFSA (2013) Scientific opinion on the identification of pesticides to be included in cumulative assessment groups on the basis of their toxicological profile. EFSA Journal; http://www.efsa.europa.eu/en/efsajournal/pub/3293.htm

7) Fantke, P., Rainer, F and Jolliet, O. 2012. Health impact and damage cost assessment of pesticides in Europe Environment International 49 (2012) 9–17

8) **Contactable:**

- Scientific Officer in the European Food Safety Authority (EFSA) Pesticide Unit, Secretary to the Working Group of the Plant Protection Products and their Residues (PPR) Panel that drafted the EFSA (2013) Scientific Opinion
- Toxicologist working for the Danish Environmental Protection Agency, Vice Chair of EFSA's PPR Panel and Chair of the working group that drafted the EFSA (2013) Scientific Opinion.

Both can corroborate the role Kortenkamp played in drafting the Scientific Opinion, as well as the impact of Brunel University's research on the opinion.