Institution: Brunel University London		
Unit of Assessment: 7 – Earth Systems and Environmental Sciences		
Title of case study: Safeguarding against the health effects of chemical cocktails		
Period when the underpinning research was undertaken: 2013 - 2018		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Andreas Kortenkamp	Professor	07/2011-present
John Sumpter	Professor	09/1978-present
Olwenn Martin	Lecturer	08/2011-present
Martin Scholze	Research Fellow	02/2012-present
Sibylle Ermler	Research Fellow	08/2011-present
Period when the claimed impact occurred: 2014 - 2020		
Is this case study continued from a case study submitted in 2014? No		

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

Brunel research has significantly contributed to a major European Union (EU) policy shift towards taking account of chemical cocktails in risk assessment and risk management, away from the traditional focus on single chemical assessments. The new EU Chemical Strategy for Sustainability expresses a commitment to accelerate mixture risk assessments for pesticides and to introduce protective clauses in other chemical regulations. For the first time, this will enable protection of the 445,000,000 EU citizens from mixture risks. Brunel researchers' work on attributing infertility to mixtures of plasticiser chemicals (phthalates) was used by the European Chemicals Agency to support restrictions for mixtures of phthalates in consumer articles which has improved the situation for 400,000 boys at risk from phthalate exposures.

2. Underpinning research (indicative maximum 500 words)

Until about a decade ago, risk assessors and regulators regarded risks from chemical mixtures as negligible, if exposures to all single chemicals in the cocktail were below the levels judged to be safe for each chemical alone. Brunel's research team, namely Kortenkamp, Ermler, Martin, Scholze and Sumpter, has made substantial contributions to building up scientific evidence that challenges this notion. With funding from the European Commission, the UK Food Safety Authority, and the Swedish Foundation for Strategic Environmental Research (MISTRA), the Brunel's team has published more than 30 collaborative experimental papers on this topic in the last 10 years.

The accumulated evidence from this research supports the idea that it is possible to predict the effects of multi-chemical cocktails of hazardous substances when the toxicity of its components is known, assuming additive mixture effects. Because there is an astronomically large number of chemical combinations in real-life mixtures, it is impossible to test all of them. Neither is it necessary. In multiple experimental systems with fish, rodents and cultured cells, the team accurately predicted mixture effects by using the additivity assumption.

Further key insights of Brunel's research are that: (i) the toxicity of a mixture is usually greater than the effect of the most potent single component; (ii) the toxicity of a mixture materialises even when each component is present at levels below those associated with effects (recent example: Ref 1); and (iii) in real world human exposure scenarios only a few chemicals, so-called risk drivers, explain most mixture risks, although exposure is to very large numbers of chemicals (summarised in Ref 2).

Cumulatively, this work demonstrates that a disregard of mixture effects will underestimate chemical risks.

Translation of these insights into better protection against mixture risks will require new policy instruments. The team have shown that the safety margins traditionally introduced to convert single chemical threshold doses estimated in animal experiments into human acceptable exposures do not protect from mixture risks, counter to prevailing risk assessment assumptions (Ref 3). This calls for an additional safety margin, a Mixture Assessment Factor.

The existing provisions for considering mixtures in EU regulations for pesticides and biocides are insufficient for protecting against the risks from multiple chemicals not covered by pesticide and biocide regulations, including food contaminants and industrial chemicals. The Brunel researchers demonstrated that human exposures are typically to mixtures of chemicals that include pesticides, biocides, food contaminants and industrial chemicals, and that toxicity from such mixtures has been shown empirically (Ref 4). However, there is currently no legal mandate to regulate mixtures composed of chemicals beyond biocides and pesticides.

A potential obstacle to utilising existing single chemical toxicity data to anticipate mixture risks without experimental tests by assuming additivity would be the widespread occurrence of stronger than additive mixture effects, synergisms. In the most comprehensive assessment of its kind to date, the team has re-analysed more than 1,200 experiments and concluded that synergisms are rare, supporting the default assumption of additivity (Ref 5).

Kortenkamp has brought the mixture risk assessment perspective to an estimation of the prevalence of male reproductive disorders and associated economic costs in the EU (Ref 6).

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

[1] Thrupp, TJ., Runnalls, TJ., Scholze, M., Kugathas, S., Kortenkamp, A. and Sumpter, JP. (2018) 'The consequences of exposure to mixtures of chemicals: Something from 'nothing' and 'a lot from a little' when fish are exposed to steroid hormones'. *Science of the Total Environment*, 619-620. pp. 1482 - 1492

[2] Kortenkamp, A. and Faust, M. (2018) 'Regulate to reduce chemical mixture risk'. *Science*, 361 (6399). pp. 224 - 226. ISSN: 0036-8075

[3] Martin, O. V., Scholze, M., and Kortenkamp, A. (2013). Dispelling urban myths about default uncertainty factors in chemical risk assessment - Sufficient protection against mixture effects?. *Environmental Health: A Global Access Science Source*, *12*(1). doi:10.1186/1476-069X-12-53

[4] Evans, RM., Martin, OV., Faust, M. and Kortenkamp, A. (2015) 'Should the scope of human mixture risk assessment span legislative/regulatory silos for chemicals?'. *Science of The Total Environment*, 543 (Pt A). pp. 757 - 764. ISSN: 0048-9697

[5] Martin, O., Scholze, M., Ermler, S., McPhie, J., Bopp, S. K., Kienzler, A., . . . Kortenkamp, A. (2020). Ten years of research on synergisms and antagonisms in chemical mixtures: A systematic review and quantitative reappraisal of mixture studies. *Environment International*, *146*, 106206. doi:10.1016/j.envint.2020.106206

[6] Hauser, R., Skakkebaek, NE., Hass, U., Toppari, J., Juul, A., Andersson, AM., Kortenkamp, A., Heindel, JJ. and Trasande, L. close. (2015) 'Male reproductive disorders, diseases, and costs of exposure to endocrine-disrupting chemicals in the European Union'. *Journal of Clinical Endocrinology and Metabolism*, 100 (4). pp. 1267 - 1277. ISSN: 0021-972X

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

Very few EU chemical regulations currently mandate the consideration of cocktail effects in risk assessment, chief among them the regulations for plant protection products and for biocides. But even here the legal mandates are currently not implemented due to a lack of agreed mixture risk assessment methods (Ref 2). May other chemical regulations relevant to the mixtures issue

currently do not require mixture risk assessments, for example those relevant to food contaminants, food contact materials, industrial emissions and many others.

The new EU Chemical Strategy for Sustainability (S1) acknowledges these regulatory gaps and intends to establish provisions for mixture risk assessment in regulations for all chemicals, not only pesticides and biocides. It commits the EU to accelerate work on pesticides so that existing legal mandates can be implemented in practice. There is also a commitment to introduce Mixture Assessment Factors which will lower exposure limits for chemicals, thereby protecting against mixture risks.

Brunel's work has contributed significantly to this policy shift. A European Commission Staff Working Document (S2) accompanying the Chemical Strategy contains a compilation of recommendations from EU member states, scientists, and other stakeholders (Box 7, p 40) that explicitly references Kortenkamp and Faust (Ref 2). The paper called for the introduction of legal requirements for mixture risk assessment in all relevant regulations, and for a framework to ensure coordination of mixture risk assessment across various regulatory areas.

The Staff Document (p 6) also refers to Brunel's work that exposed the insufficient protection against mixture risks through traditional single chemical safety margins (Ref 3). This supports the idea of introducing additional safety margins leading to lower exposure limits (Mixture Assessment Factors).

To highlight the need for introducing additional regulations that can deal with mixtures composed of chemicals across different regulatory areas (e.g. combinations of plant protection products, biocides, industrial chemicals and pharmaceuticals), the document (p 17) refers to Evans et al. (Ref 4). The paper called for extending the scope of activities across regulatory areas.

In support of making default additivity assumptions in mixture risk assessments based on existing single chemical toxicity data, which will make such assessments feasible in regulatory practice, the document (p 30) cites Brunel researchers' recent systematic review on synergism (Ref 5). This work demonstrated that synergisms are rare and show the usefulness of default additivity assumptions.

In the first example of a regulatory action where the underlying risk assessment considered mixture exposures to several chemicals, the European Chemicals Agency (ECHA) in 2017 introduced restrictions for a group of four phthalates used as plasticisers in consumer articles (S3). When making such restrictions, ECHA is obliged to demonstrate that the envisaged measures have socio-economic benefits by avoiding a minimum number of infertility cases. In making this case, ECHA referred to Brunel's work which showed that infertility attributable to phthalates was close to 9% in 2010 (Ref 6).

ECHA estimated that in 2014 approximately 5% of all newborn boys in the EU (130,000 boys) were at risk through phthalate exposure in prenatal life, and 15.5% of newborn boys (400,000) through direct exposure in postnatal life. On the basis of these statistics, ECHA concluded that without the restrictions for phthalates the exposures to these chemicals would not be adequately controlled.

The prevailing need to better address chemical mixtures in relevant regulations requires the delivery of practicable approaches for the assessment of mixture risks. Kortenkamp made substantial contributions to developing mixture risk assessment guidance by the European Food Safety Authority (EFSA) (More et al. 2019). This guidance (S4) provides a firm basis for procedures of how to assess chemical mixture risks.

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

S1 EU Chemical Strategy towards sustainability, Communication from the European Commission to the European Parliament, the Council, the European Social Committee and the Committee of the Regions, Brussels 14.10.20, https://ec.europa.eu/environment/pdf/chemicals/2020/10/Strategy.pdf

S2 Commission Staff Working Document, Progress report on the assessment and management of combined exposures to multiple chemicals (chemical mixtures) and associated risks https://ec.europa.eu/environment/pdf/chemicals/2020/10/SWD_mixtures.pdf
S3 ECHA 2017 https://echa.europa.eu/documents/10162/e39983ad-1bf6-f402-7992-8a032b5b82aa

S4 More, SJ, Benford D, … Kortenkamp, A, ..et al. (2019) Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals, *EFSA Journal,* 17(3): 5634 https://doi.org/10.2903/j.efsa.2019.5634