Section A

Institution: Durham University

Unit of Assessment: Unit 10: Mathematical Sciences

Title of case study: Quantifying Uncertainty in Risk Assessment for Food Safety

Period when the underpinning research was undertaken: Between 2005 and 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:**
Peter Craig	Professor of Statistics	September 1989 to present

Period when the claimed impact occurred: August 2013 onwards

Is this case study continued from a case study submitted in 2014? N

Section B

1. Summary of the impact

Since 2005, Craig's research around quantification of uncertainty has had a significant impact in the context of European food safety. Using a range of methods that include statistical modelling and reasoning, Craig has contributed to significant change in the way the European Food Safety Authority (EFSA) addresses uncertainty in its scientific assessments for the EU Commission and member states. Quantifying uncertainty in these assessments plays a critical role in risk management decisions that relate to food production, packaging and consumption; ultimately protecting consumers, animals and the environment from food-related risks. Craig's research has also contributed directly to the treatment of uncertainty in EFSA topic-specific guidance and individual assessments.

2. Underpinning research

Craig is a statistician who works mostly from the Bayesian subjectivist viewpoint on statistics. Craig's research focus is on methodology for quantification of uncertainty in real world problems based on careful application of statistical principles and methodology and in-depth knowledge of applications. Key components are Bayesian random-effects modelling, imprecise probability and expert knowledge elicitation.

For the decade to 2002, Craig worked mostly on statistical methodology for computer models as part of a Durham group specialising in Bayesian emulation of computer models, use of expert knowledge elicitation to quantify expert judgement using probability, and statistical modelling of discrepancies between models and reality. Funding came from EPSRC and oil industry partners. The relevance to the case study is its focus on quantification of uncertainty about the real world based on deterministic and statistical models of data and elicitation of expert judgement using probability, laying the ground for the research and impact reported in the case study.

Since 2005, Craig's research has largely been concerned in one way or another with quantification of uncertainty in relation to risk and benefit assessments in the context of food safety. Much of the research has been conducted with or for EFSA, often as a member of an EFSA working group. This has involved a diverse range of activities and applications; the common thread is quantification of uncertainty using statistical modelling and reasoning. The research has been published in academic journals and by EFSA in its own journal. Examples of relevant academic journal articles are [R1] [R2] and [R3].

Publications in the EFSA journal are of several different kinds: scientific assessments in relation to risk (or sometimes benefit) of potential policy changes/actions, commissioned by EU state risk managers; guidance documents developed to influence the conduct of assessments; scientific opinions combining review of the relevant scientific literature with evaluation of how science can be brought to bear on areas of EFSA activity. Any of these may require development of new methodology or novel analysis and interpretation of data, and this may be included in the main text or appendices of the resulting publication.

Craig's topic-specific research, started in the EFSA context and contributing to impact, includes:

- Bayesian statistical modelling of pesticide residues in food, probabilistic modelling of dietary exposure to pesticides and assessment of cumulative risk from multiple pesticides in human diet (see part 4 of this case study).

- Statistical methods in ecotoxicological risk assessment, beginning with an EFSA Scientific Opinion for aquatic species [R4], and continuing in academic journal articles (for example [R1] and [R2]) and later EFSA scientific opinions for other species groups.
- Statistical analysis and reasoning for dermal exposure to pesticides. The research is contained in [R5], an appendix to the EFSA guidance document, written in collaboration with Dr Guillot of EFSA, and also in the report of an EFSA funded research project investigating the applicability of in silico methods of predicting dermal absorption.

Craig's research on generic methodology and tools for quantifying uncertainty in risk (or benefit) assessments started with research projects ([R3] was one product) funded by the UK Food Standards Agency (UK FSA) and led to membership of the EFSA working group developing a new guidance document on the assessment of uncertainty to cover all areas of EFSA's activity. The first EFSA output was a scientific opinion on the underlying science and principles [R6] which led, after a public consultation phase, to a new guidance document (see part 4 of this case study). The opinion and guidance document provide a coherent approach to uncertainty analysis focussed on the actual uncertainty of conclusions provided to EU risk managers and rooted fundamentally in the subjective Bayesian approach to uncertainty and statistical inference, including generalisation to imprecise probabilities. The opinion and guidance document also include a novel method for applying probability bounds analysis to imprecise probabilities describing both uncertainty and variability, intended to allow assessors to provide useful partial probability statements to risk managers based on extremely limited probability judgements obtained by expert knowledge elicitation. The key principle of the guidance is that the analysis should focus on the uncertainty in conclusions/recommendations provided to decision-makers, i.e. uncertainty about reality rather than uncertainty about parameters in models.

In summary, Craig's research has focussed on statistical tools for quantification of uncertainty in risk assessments with a particular emphasis on issues relevant to food safety.

3. References to the research

R1. Craig, P.S., Hickey, G.L., Luttik, R. and Hart, A. (2012), Species non-exchangeability in probabilistic ecotoxicological risk assessment. Journal of the Royal Statistical Society: Series A (Statistics in Society), 175: 243-262. https://doi.org/10.1111/j.1467-985X.2011.00716.x

R2. Hickey, G.L., Craig, P.S., Luttik, R. and de Zwart, D. (2012), On the quantification of intertest variability in ecotoxicity data with application to species sensitivity distributions. Environmental Toxicology and Chemistry, 31: 1903-1910. https://doi.org/10.1002/etc.1891

R3. Boobis A, Flari V, Gosling JP, Hart A, Craig P, Rushton L& Idahosa-Taylor E (2013). Interpretation of the margin of exposure for genotoxic carcinogens – Elicitation of expert knowledge about the form of the dose response curve at human relevant exposures. *Food and Chemical Toxicology*, **57**, pp 106-118. https://doi.org/10.1016/j.fct.2013.03.003

R4. EFSA (2005). Opinion of the Scientific Panel on Plant health, Plant protection products and their Residues on a request from EFSA related to the assessment of the acute and chronic risk to aquatic organisms with regard to the possibility of lowering the uncertainty factor if additional species were tested**.** *EFSA Journal,* **301***,* pp1--59. https://doi.org/10.2903/j.efsa.2006.301

R5. Appendix B — Statistical Analysis of EFSA (European Food Safety Authority), Buist, H, Craig, P, Dewhurst, I, Hougaard Bennekou, S, Kneuer, C, Machera, K, Pieper, C, Court Marques, D, Guillot, G, Ruffo, F and Chiusolo, A, 2017. Guidance on dermal absorption. *EFSA Journal* 2017; 15(6):4873, 60 pp https://doi.org/10.2903/j.efsa.2017.4873

R6. EFSA Scientific Committee, Benford, D, Halldorsson, T, Jeger, MJ, Knutsen, HK, More, S, Naegeli, H, Noteborn, H, Ockleford, C, Ricci, A, Rychen, G, Schlatter, JR, Silano, V, Solecki, R, Turck, D, Younes, M, Craig, P, Hart, A, Von Goetz, N, Koutsoumanis, K, Mortensen, A, Ossendorp, B, Germini, A, Martino, L, Merten, C, Mosbach-Schulz, O, Smith, A and Hardy, A, 2018. Scientific Opinion on the principles and methods behind EFSA's Guidance on Uncertainty Analysis in Scientific Assessment. *EFSA Journal* 2018;16(1):5122, 235 pp. https://doi.org/10.2903/j.efsa.2018.5122

*Scientific opinion [**R4**], including the technical appendix, was part of Durham's RAE 2008 submission. It is known that it was rated at least two star by the RAE panel as all articles in the submission received at least two stars. In a testimonial for RAE 2008, Professor Hardy (then Chair of EFSA's Plant Protection Products and their Residues Panel) wrote "Dr Craig was an ad hoc expert advising the PPR panel of EFSA. He was sole author of the technical statistical appendix, contributed most of the statistical methodology (including all of section 5 other than 5.2.2) and was substantially involved in writing the main text of the opinion". The research combined mathematics, statistical modelling and data analysis to show, for risk assessment for the ecotoxicological effects of pesticides on aquatic species, the potential benefit to both risk managers and applicants for pesticide registration of encouraging the testing of more species than required in legislation by adjusting the statistical calculation used. It also showed how to improve the stability of a standard method by using Bayesian hierarchical modelling.*

***[R1]** and **[R2]** are journal articles expanding on issues in relation to ecotoxicological risk assessment: non-exchangeability of species identified and partially addressed in **[R4]** and intertest variability which had previously been omitted from consideration.*

***[R5]** details data analyses, statistical modelling and statistical predictions intended to support the setting in the guidance document of default values to be used in the absence of in vitro data. The appendix also provides data analysis to support the method proposed in the guidance for addressing uncertainty due to limited sample size for in vitro data.*

***[R3]** exemplifies the use of expert knowledge elicitation in the context of assessing uncertainty about the risk from exposure to genotoxic carcinogens.*

***[R6]** surveys the science required for uncertainty analysis, bringing it together in an approach containing several novel elements: emphasis on overall uncertainty of conclusions and recommendations, use of imprecise probability theory as a key mathematical and practical tool, probability bounds analysis for simple analysis of uncertainty about outputs of models combining variable quantities. In a testimonial for REF 2021, Professor Hardy (Chair of EFSA Scientific Committee at the time of developing **[R6]** and the guidance on uncertainty) confirmed that Craig was the primary provider of input on mathematical and statistical methodology and the principles behind use of probability and imprecise probability to quantify expert judgement, the lead drafting author for quantitative sections of **[R6]** including appendices, and the sole drafting author for Appendix B.13 Probability Bounds Analysis.*

4. Details of the impact

The impact of Craig's work should be seen in the context of the critical role played by the European Food Safety Authority (EFSA), the European Union (EU) agency established in 2001 by the European Parliament and Council to develop and manage risk assessment policy in the EU regarding food and animal feed safety. EFSA's scientific advice helps to protect consumers, animals and the environment from food-related risks. EFSA publications are used as the basis for policy making and implementation by the European Commission and Parliament and by individual EU member states. By contributing to a step-change in the way that EFSA addresses uncertainty, Craig's research is crucial to decisions that have serious consequences for the health of people, animals and the environment.

In food safety risk assessment, scientists must assess the safety of a new food, pesticide or food-borne bacteria. As evidence or knowledge is always incomplete, it is important to explain how uncertainty may affect conclusions and the implications for decision-making. In quantifying these uncertainties, Craig's methodology and tools have significantly improved EFSA's assessments of risk and benefit in relation to food production, packaging and consumption.

<u>Impact in the area of pesticide registration</u>

One EFSA role is overall supervision of EU risk assessment for pesticides. In that role, EFSA produces and publishes risk assessment peer reviews of individual pesticides which support decisions made by individual EU member states in response to applications from the pesticide industry for authorisation for use. Risk assessment for pesticides covers the risk to humans from eating food containing pesticides, the risk to humans from exposure via the skin (for example when spraying pesticides or working with plants which have been sprayed) and the risk to other species exposed due to the use of pesticides in agricultural production.

In the period for consideration of impact for REF 2021, the ecotoxicology sections of EFSA peer review reports for 5 pesticides used the geometric mean approach proposed and justified in [R4]. For example, [E1] refined the acute risk assessment for fish species in this way for the pesticide acrinathrin. The benefit of the geometric mean approach was that applicants for authorisation were encouraged to provide test results for more species than required by legislation. Previously the test result for the most sensitive species would be used and this was effectively a disincentive to test additional species. The benefit for applicants of the changed approach was knowledge that the geometric mean would be used, thereby making authorisation more likely, while the reliability of the assessment benefited from the greater knowledge provided by additional test results

The EFSA 2018 [E5] guidance document on dermal absorption (for pesticides) made two changes to guidance on the basis of research reported in Appendix B: (i) to the calculation to allow for uncertainty about absorption on the basis of limited in vitro data; (ii) to the default values to be used in the absence of in vitro data for the pesticide to address the uncertainty arising from the absence of the data. The first of these changes means that uncertainty due to limited sample size is now taken properly into account in the assessment and the second means that the new default values are based on a transparent analysis of a large dataset taking into account uncertainty about absorption for an untested pesticide. In May 2018, the EU Standing Committee on Plants, Animals, Food and Feed recommended [E6] that the guidance be used, from August 2018, by applicants for authorisation and by EU members states in peer reviews of pesticides. The result is improved treatment of uncertainty and greater transparency about the basis for decisions.

Uncertainty across EFSA

Guidance document [E2] provides explicit direction on how to carry out uncertainty analysis in scientific assessments. The guidance was adopted by the EFSA Scientific Committee in December 2017 [E3a] and is applicable to all areas of EFSA's work [E3b]. The most significant new feature of this guidance is the requirement that assessors should assess the overall impact of uncertainty on conclusions and that they should express the uncertainty using the mathematical language of probability. This new approach is fundamentally rooted in the subjectivist view of probability and associated methodology, areas of Craig's research expertise. During development of the guidance, Craig was one of two lead drafting authors and had responsibility for the quantitative sections [E3b].

Following the adoption of the guidance, EFSA created a standing cross-cutting Working Group (WG) on Uncertainty [E4] and Craig has been a member since its inception. As well as experts in uncertainty, the cross-cutting WG has members from four of EFSA's eight Scientific Panels and is mandated to support the Panels in applying the guidance in their outputs. Examples of EFSA outputs following the new guidance and containing substantial uncertainty analysis are:

- the scientific opinion of the EFSA Panel on Nutrition, Novel Foods and Food Allergens on dietary reference values for sodium [E7], produced at the request of the European Commission. Sodium is an important element in human diet but also a source of health risk, and both risk and benefit are uncertain. The scientific opinion provides a transparent account and quantification of uncertainties affecting the conclusions as required by [E2].
- the EFSA Panel on Plant Health Guidance on quantitative pest risk assessment [E9] which is used routinely by the Panel in subsequent assessments of risk of entry, spread and consequent environmental and economic damage for plant and plant-based pests.
- The scientific opinion of the EFSA Panel on Biological Hazards on control options for Campylobacter in broilers at primary production [E10], produced at the request of the European Commission. Campylobacter is a significant contributor to food-poisoning resulting from consumption of contaminated poultry.
- EFSA Scientific Reports on cumulative risk from presence of multiple pesticides in human diet, produced by EFSA in the context of the EU regulations requiring that (a) decisions about the maximum levels permitted in food should take into account cumulative effects as and when methods for doing so become available and (b) pesticides should have no harmful effects – including cumulative effects – on humans. The first such report is [E8]. Previously, risk to consumers from the presence of pesticide residues in food was only

assessed substance by substance despite the possibility of multiple substances contributing cumulatively to a particular harmful effect.

Uncertainty assessment requires expert training both for assessors and for decision-makers who use assessments. To support implementation of the uncertainty guidance, EFSA commissioned a series of training courses (for example [E11]). Craig was one of two tutors who prepared and delivered the training for four courses on general application of the guidance, delivered to EFSA scientific staff and external members of the ten scientific panels, and three courses each tailored to the needs of a single scientific panel and attended by all panel members and staff from related EFSA units. Each 1.5-2 day course was attended by 25-30 scientists full-time. Craig was a facilitator at a two-day 2017 EFSA workshop reviewing 13 case studies covering a wide range of EFSA activities and conducted during a one-year trial period for the draft guidance. Participants were relevant risk managers (decision-makers) from the European Commission and the scientific experts who worked on each case study.

Further impacts derive from the influence of EFSA outputs on other international groups involved in food safety, e.g. the US Environmental Protection Agency, the Organisation for Economic Cooperation and Development (OECD), the Joint Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) Meeting on Pesticide Residues, and the WHO. During the period for consideration of impact for REF 2021 and following from his work with EFSA: (i) Craig joined an OECD working group on international harmonisation in relation to dermal absorption of chemicals; (ii) Craig delivered training on uncertainty to the EU Joint Research Centre, the EU Scientific Committee on Health Environment and Emerging Risks, the UK Food Standards Agency and Finland's food safety agency EVIRA.

5. Sources to corroborate the impact

E1. European Food Safety Authority, 2013. Conclusion on the peer review of the pesticide risk assessment of the active substance acrinathrin. *EFSA Journal* 2013; 11(12):3469, 82 pp. https://doi.org/10.2903/j.efsa.2013.3469.

E2. EFSA (European Food Safety Authority) Scientific Committee et al, 2018. Guidance on Uncertainty Analysis in Scientific Assessments. *EFSA Journal* 2018;16(1):5123, 39 pp. https://doi.org/10.2903/j.efsa.2018.5123

E3. Evidence in relation to [E2]: (a) minutes of EFSA Scientific Committee recording adoption of the guidance; (b) testimonial letter from Professor Tony Hardy confirming Craig's role in the development of [E2] and [R6].

E4. https://www.efsa.europa.eu/sites/default/files/event/2020/98th-plenary-meeting-scientific-committee-minutes.pdf

E5. EFSA (European Food Safety Authority) et al, 2017. Guidance on dermal absorption. *EFSA Journal* 2017; 15(6):4873, 60 pp. https://doi.org/10.2903/j.efsa.2017.4873

E6. EFSA (European Food Safety Authority) et al, 2018. Technical report on the outcome of the pesticides peer review meeting on general recurring issues in mammalian toxicology. *EFSA supporting publication* 2018: 15(9):EN-1485. 11 pp. https://doi.org/10.2903/sp.efsa.2018.EN-1485

E7. EFSA (European Food Safety Authority) et al, 2019. Scientific Opinion on the dietary reference values for sodium. *EFSA Journal* 2019;17(9):5778, 191 pp. https://www.efsa.europa.eu/en/efsajournal/pub/5778

E8. EFSA (European Food Safety Authority) et al, 2020. Scientific report on the cumulative dietary risk characterisation of pesticides that have chronic effects on the thyroid. *EFSA Journal* 2020;18(4):6088, 71 pp. https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2020.6088

E9. EFSA (European Food Safety Authority) et al, 2018. Guidance on quantitative pest risk assessment. *EFSA Journal* 2018;16(8):5350, 86 pp. https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2018.5350

E10. EFSA (European Food Safety Authority) et al, 2020. Update and review of control options for Campylobacter in broilers at primary production. *EFSA Journal* 2020;18(4):6090, 89 pp. https://www.efsa.europa.eu/en/efsajournal/pub/6090

E11. https://www.efsa.europa.eu/en/supporting/pub/en-1346