Institution: University of Dundee

Unit of Assessment: 5: Biological Sciences

Title of case study: Impact of research on cyanobacterial toxins on governmental and regulatory authority guidelines on water safety.

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

Cyanobacteria (blue-green algae) occur globally and produce a wide range of potent toxins (cyanotoxins) that can be among the most hazardous natural products in aquatic environments. Research by the University of Dundee uncovered the biochemical mechanism of action of the microcystin family of cyanotoxins, which resulted in the development of new cyanotoxin detection and analytical methods, and demonstrated the health risks of cyanotoxins. This body of research has had a direct impact on several governmental and regulatory authority guidelines on water safety, resulting in the implementation of procedures to reduce the risks presented by cyanotoxins to water-users.

2. Underpinning research (indicative maximum 500 words)

Surveys in different parts of the world have found that 45-90% of blooms of blue-green algae produce toxins. These include hepato-, neuro-, and cytotoxins, carcinogens and tumour promoters. Since the early 1980s, the University of Dundee has worked to elucidate the health hazards of cyanobacterial toxins and develop new methods for their analysis and detection (including Refs 1-6). In 1990, **Prof Carol MacKintosh** (Programme Leader at the MRC Protein Phosphorylation Unit) together with **Prof Geoff Codd FRSE** (Professor of Microbiology at College of Life Sciences from 1972-2010) discovered that microcystin-LR, a potent hepatotoxin produced by cyanobacteria, inhibited protein phosphatases 1 (PP1) and 2A (PP2A) (FEBS Lett, *264*,187-192). This has become one of the most highly cited papers in this field (739 citations at November 2013).

Documented incidents on human and animal health in the late eighties/early nineties following exposure to cyanobacterial blooms caused increasing public concern. Suitable analytical techniques for drinking water analysis were not available and there was insufficient toxicological data to set health-based guidelines or standards for drinking water in the UK. In 1994, Prof Codd developed a new and rapid methodology based on high-performance liquid chromatography to analyse cyanobacterial microcystins in raw and treated waters (1). At the same time, Prof MacKintosh and colleagues dissected the biochemical mechanism of microcystin binding to phosphatases (2,3). Prof MacKintosh then collaborated with Thames Water Utilities to develop and use new methods for detection of cyanobacterial toxins based on protein phosphatase assays.

Before 1998, cyanobacteria were known to have caused deaths in livestock, domestic animals and wildlife; however evidence concerning the risk to humans of cyanotoxin exposure via drinking water, accidental ingestion or recreational contact, was mostly circumstantial (4). Dundee researchers helped to highlight the public health dangers of cyanotoxins. In 1997, MacKintosh and colleagues demonstrated that there were significant levels of microcystin and cyanobacteria in Irish lakes (5). A key report by Codd in the Lancet in 1998 revealed that the death of 60 patients in a haemodialysis unit in Caruaru, north-east Brazil, could be attributed to exposure to highly toxic microcystins in the water supply from a lake with massive growth of cyanobacteria (6). This report had far reaching public health implications and resulted in recognition that haemodialysis represented a high-risk exposure route for poisoning by cyanobacterial toxins and suggested that water used for dialysis required special processing. Moreover, the Dundee discovery that microcystin binds covalently to protein phosphatases (3) explained why hepatic levels of free toxin were lower than expected in post-mortem analyses in the Brazilian case, and in suspected cases of microcystin poisoning in animals. The Dundee findings that microcystin shares the same binding site as the tumour promoter okadaic acid highlighted that management strategies should be set to prevent chronic exposure to low doses of microcystin.

Continuing research from Dundee researchers has helped determine procedures for the risk management of cyanobacterial toxins, including derivation of tolerable daily intakes and guideline values for the cyanobacterial toxins in drinking water, and for toxigenic cyanobacteria in bathing waters.

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

1. Lawton, L.A., Edwards, C. and **Codd, G.A.** (1994) Extraction and high-performance liquid chromatographic method for the determination of microcystins in raw and treated waters. Analyst *119*, 1525-1530. (doi:10.1039/AN9941901525) (Citations 348, Scopus Nov 2013).

2. Moorhead G., MacKintosh R.W., Morrice N., Gallagher T. & **MacKintosh C**. (1994) Purification of type 1 protein (serine/threonine) phosphatases by microcystin-Sepharose affinity chromatography. FEBS Lett. *356*, 46-50. (doi:10.1016/0014-5793(94)01232-6) (Citations 123, Scopus Nov 2013).

3. MacKintosh, R.W., Dalby, K.N., Campbell, D.G., Cohen, P.T.W., Cohen, P., **MacKintosh,C.** (1995) The cyanobacterial toxin microcystin binds covalently to cysteine-273 on protein phosphatase 1. FEBS Lett. *371*, 236-240. (doi:10.1016/0014-5793(95)00888-G) (Citations 153, Scopus Nov 2013).

4. **Codd, G.A** (1995) Cyanobacterial toxins: occurrence, properties and biological significance. Water Science and Technology. *32*, 149-156. (doi:10.1016/0273-1223(95)00692-3) (Citations 229, Scopus Nov 2013).

5. Sherlock, I.R., James, K.J., Caudwell, F.B., and **MacKintosh, C.** (1997) First identification of microcystins in Irish lakes aided by a new derivatisation procedure for electrospray mass spectrometric analysis. Nat Toxins *5*, 247-254. (doi:10.1002/(SICI)1522-7189(1997)5:6<247::AID-NT5>3.0.CO;2-N) (Citations 11, Scopus Nov 2013).

6. Pouria, S., de Andrade, A., Barbosa, J., Cavalcanti, R.L., Barreto, V.T.S., Ward, C.J., Preiser, W., Poon, G.K., Neild, G.H. and **Codd, G.A. (**1998) Fatal microcystin intoxication in haemodialysis unit in Caruaru, Brazil. The Lancet *352*, 21-26. (doi:10.1016/S0140-6736(97)12285-1) (Citations 347, Scopus Nov 2013).

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

<u>The beneficiaries</u>

(a) The World Health Organisation (expert opinion that shaped international Guidelines for Drinking Water Quality)
(b) The UK Department of the Environment and Thames Water Utilities Ltd (development and use of phosphatase inhibition assays to monitor cyanotoxin levels in reservoirs and drinking water)
(c) Scottish, US, Canadian, New Zealand, and Australian environmental authorities (expert opinion that shaped guidelines relating to cyanotoxins in recreational and drinking water)
(d) The general public at risk from cyanotoxin exposure in drinking water, dialysis fluid or in lakes and rivers.

<u>Background:</u>
Research by the University of Dundee has had a major impact on the recognition, toxicity-assessment and risk-management of cyanobacterial blooms and cyanotoxins in waterbodies worldwide. This research provided primary guidance in the formulation and adoption of safety plans by several governmental and regulatory authorities for health protection against cyanotoxins in human drinking water supplies, aquaculture and veterinary practice.

<u>Impacts:</u>
In 1999, Professor Codd played a major role in preparing one of the most comprehensive and

highly cited texts in the cyanobacteria field "*Toxic Cyanobacteria in Water: A Guide to their Public Health Consequences, Monitoring and Management*" which was published by the World Health Organization. Professor Codd authored chapters 5, 7, 10, and section 8.5.8 as well as participating in the editorial advisory group. The guide detailed the information needed for protecting drinking-water sources and recreational water bodies from the health hazards caused by cyanobacteria and their toxins. This text was key in the derivation of the World Health Organisation (WHO) guidelines for Drinking Water Quality (1,2). These guidelines, published in 2008 and updated in 2011 (and frequently citing primary research from Professor Codd) are one of the most significant policy documents for the management of water resources (1,2) and represent the current position of "UN-Water", the body that coordinates programmes concerned with water issues amongst the 24 UN agencies.

In addition, Prof MacKintosh was a discussant at the Water Toxins Panel of the Department of the Environment Standing Committee of Analysts (Organic Impurities Working Group) from 1992 to 1996 and was a consultant to Thames Water Utilities Ltd. (1994-1995), advising on use of protein phosphatase assays to detect microcystin in water samples. This resulted in the use of new analytical methods to monitor water safety during a period of microcystic blooming on reservoirs in the Thames area which are still in use today.

Other current governmental and regulatory authority guidelines have been heavily influenced by cyanotoxin research at the University of Dundee. These include:

1) Guidance to Public Health and Environmental Health Authorities in Scotland (2012), on risks of cyanobacteria in inland and inshore waters (3). Professor Codd was part of the Working group that prepared this document and the guidance commissioned by the Scottish Government takes account of current WHO guidelines (2).
2) The *Guidelines for Canadian Recreational Water Quality (2012)* (4) is used by provincial and local authorities in Canada and provides advice on the health risks of recreational waters.
3) *Guidelines For Managing Risks in Recreational Water (2008)* (5) is a document produced by the Australian Government for state and territory governments to develop legislation and standards to manage the quality of coastal, estuarine and fresh waters used for recreation.
4) The US Council on Environmental Quality commissioned an Interagency Working Group on Harmful Algal Blooms, Hypoxia, and Human Health to produce a 2008 report assessing the problem of harmful algal blooms in inland waters of the US (6).
5) The US Geological Survey published guidelines in 2008 for the design and sampling for cyanobacterial toxin in lakes and reservoirs (7).
6) The US Environmental Protection Agency published a fact sheet in 2012 (8) providing basic information on human health effects, analytical screening tools, and the effectiveness of various treatment processes to remove or inactivate the three most important cyanotoxins that occur in US water.
7) The New Zealand Ministry for the Environment and Ministry of Health published guidelines in 2009 to promote a unified approach to managing cyanobacterial risk in water used for recreational purposes (9).

The development of microcystin-Sepharose to purify and characterize protein phosphatases and their diverse regulatory subunits by the University of Dundee was adopted by Millipore and this reagent is marketed worldwide. (http://www.millipore.com/catalogue/item/16-147).

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

1. WHO (2008) Guidelines for drinking-water quality, Third edition incorporating the first and second addenda, Volume 1: Recommendations, World Health Organization, Geneva. ISBN: 9789241547611 http://www.who.int/water_sanitation_health/dwq/GDWPRecomdrev1and2.pdf

2. WHO (2011) Guidelines for drinking-water quality, Fourth edition Geneva, Switzerland, World Health Organization. Xiii 541p. ISBN: 9789241548151 http://whqlibdoc.who.int/publications/2011/9789241548151_eng.pdf

3. Scottish Government (2012) Cyanobacteria (Blue-Green Algae) in Inland and Inshore Waters: Assessment and Minimisation of Risks to Public Health. Scottish Government Health & Social Care Directorates. ISBN: 9781780456775. http://www.scotland.gov.uk/Resource/0039/00391470.pdf

4. Health Canada (2012). Guidelines for Canadian Recreational Water Quality, Third Edition. Water, Air and Climate Change Bureau, Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa, Ontario. ISBN: 9781100208923 http://www.hc-sc.gc.ca/ewh-semt/alt_formats/pdf/pubs/water-eau/guide_water-2012-guide_eau/guide_water-2012-guide_eau-eng.pdf

5. Australian Government (2008) Guidelines For Managing Risks in Recreational Water. National Health and Medical Research Council. ISBN Online: 1864962720 http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/eh38.pdf

6. Lopez, C.B., Jewett, E.B., Dortch, Q., Walton, B.T., Hudnell, H.K. (2008). Scientific Assessment of Freshwater harmful Algal Blooms. Interagency Working Group in Harmful Algal Blooms, Hypoxia, and Human Health of the Joint Subcommittee on Ocean Science and Technology. Washington, DC. http://www.whoi.edu/fileserver.do?id=41023&pt=10&p=19132

7. Graham, J.L., Loftin, K.A., Ziegler, A.C., and Meyer, M.T. (2008) Guidelines for design and sampling for cyanobacterial toxin and taste-and-odor studies in lakes and reservoirs: U.S. Geological Survey Scientific Investigations Report 2008–5038, 39 p. http://www.jlakes.org/web/SIR2008-5038.pdf

8. United States Environmental Protection Agency Office of Water 4304T (2012) Cyanobacteria and Cyanotoxins: Information for Drinking Water Systems, EPA-810F11001. http://water.epa.gov/scitech/swguidance/standards/criteria/nutrients/upload/cyanobacteria_factsheet.pdf

9. Ministry for the Environment and Ministry of Health (2009) *New Zealand Guidelines for Cyanobacteria in Recreational Fresh Waters – Interim Guidelines*. Prepared for the Ministry for the Environment and the Ministry of Health by SA Wood, DP Hamilton, WJ Paul, KA Safi and WM Williamson. Wellington: Ministry for the Environment. ISBN: 9780478332490 http://www.mfe.govt.nz/publications/water/guidelines-for-cyanobacteria/nz-guidelines-cyanobacteria-recreational-fresh-waters.pdf