Institution: The University of Edinburgh

Unit of Assessment: 1

Title of case study: O: Making technological advancement safer by defining the specific attributes of carbon nanofibres that are detrimental to human health

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

Impact: Influencing industry, governmental policy, insurance industry policy and public awareness/engagement.

Significance: By establishing the actual risks posed by specific carbon nanotubes (CNT), UK Health and Safety Executive (HSE) guidance and workplace guidance and industry was influenced internationally.

Beneficiaries: CNT industry and users, governments and policy-makers, the HSE and its international equivalents, the public.

Attribution: Donaldson and colleagues (UoE) published the first demonstrations of potential CNT toxicity.

Reach: Global media coverage, encompassing UK, Europe, USA and India. Results considered by national and international policy-making bodies, for example, House of Lords Science and Technology committee, US National Institute for Occupational Safety and Health.

2. Underpinning research (indicative maximum 500 words)

Over the last decade, there has been a great deal of investment in R&D and increasing production of nanoparticles including nanofibres; however, despite concerns over health effects, relatively little effort or funding had been directed towards assessing their safety. Responding to this deficit, and based on his experience with asbestos and coalmine dust, Professor Ken Donaldson (Professor of Respiratory Toxicology, UoE, 2002–2013; now Emeritus) established a programme in 2006 to address the possible dangers of these new materials.

Donaldson's intention was to relate structure to toxicity, and was therefore relevant to both known and untested nanofibres. Drawing on the comparison with asbestos, the focus was on pleural effects because mesothelioma, a pleural cancer, is uniquely associated with asbestos exposure. Fibre length plays a crucial role in the harmfulness of a fibre so, to investigate whether length was related to toxicity, Donaldson compared different lengths of carbon nanotubes (CNT) in a mouse peritoneal model. Only those CNT that comprised long (>~10 µm) individual fibres were pathogenic, whilst those that were compact (agglomerated) and short were rapidly cleared and did not cause appreciable inflammation or fibrosis. At the same mass dose, the effects seen were significantly greater that those observed with long asbestos fibres; thus, long-fibre CNT could cause mesothelioma. With internal and external collaborators, Donaldson published the findings in Nature Nanotechnology (impact factor 31.17) in 2008 [3.1].

In subsequent studies, Donaldson demonstrated the same length dependence for inflammation and fibrosis for nickel nanowires [3.2], and also, following direct delivery of CNT into the pleural cavity of mice, the most common site of mesothelioma development [3.3]. Long, but not short CNT introduced into the airways caused pleural inflammation; thus, the same effects were seen using a physiological route of delivery [3.4].

These early results led to the publication by Donaldson of a highly accessed article (15,775 times) outlining the potential risks of fibrous nanomaterials and routes of safe-by-design particles [3.5].

By fully exploiting nanomaterials' variety and ability to generate materials to exacting

specifications, Donaldson investigated a large panel of different fibres, demonstrating that the length-dependent effect was not material-specific. Silver nanowires in well-defined length classes, plus a wide range of nanofibres, were used to show that the threshold length for retention and pathogenesis in the pleural space was 5 µm [3.6]. This has great significance for understanding and controlling the risk from asbestos and other existing fibres, and for the safe-by-design development of new nanofibres.

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

3.1 Poland C, Duffin R, Kinloch I,…Donaldson K. Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study. Nat Nanotechnol. 2008;3:423–8. DOI: 10.1038/nnano.2008.111.

3.2 Poland C, Byrne F, Cho W,…Donaldson K. Length dependent pathogenic effects of nickel oxide nanowires in the lungs and the peritoneal cavity. Nanotoxicology. 2012;6:899–911. DOI: 10.3109/17435390.2011.626535.

3.3 Murphy F, Poland C, Duffin R,…Donaldson K. Length-dependent retention of carbon nanotubes in the pleural space of mice initiates sustained inflammation and progressive fibrosis on the parietal pleura. Am J Pathol. 2011;178:2587–600. DOI: 10.1016/j.ajpath.2011.02.040.

3.4 Murphy F, Poland C, Duffin R, Donaldson K. Length-dependent pleural inflammation and parietal pleural responses after deposition of carbon nanotubes in the pulmonary airspaces of mice. Nanotoxicology. 2013;7:1157–67. DOI: 10.3109/17435390.2012.713527.

3.5 Donaldson K, Murphy F, Duffin R, Poland C. Asbestos, carbon nanotubes and the pleural mesothelium: a review and the hypothesis regarding the role of long fibre retention in the parietal pleura, inflammation and mesothelioma. Part Fibre Toxicol. 2010;7:5. DOI: 10.1186/1743-8977-7-5.

3.6 Schinwald A, Murphy F, Prina-Mello A,…Donaldson K. The threshold length for fiber-induced acute pleural inflammation: shedding light on the early events in asbestos-induced mesothelioma. Toxicol Sci. 2012;128:461–70. DOI: 10.1093/toxsci/kfs171.

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

Pathways to impact

It was clear that the linkage of a new widely-used material to a mechanism of toxicity might spark an unbalanced response and result in damage to UK and worldwide industry and wealth creation. Therefore, Donaldson took a considered and multi-faceted approach to dissemination of the findings to government, industry and the public. He and colleagues informed and presented the findings to the UK Health and Safety Executive (HSE), the UK Department for Environment, Food and Rural Affairs and the Nanotechnology Industry Association (NIA) prior to publication of the Nature Nanotechnology paper [3.1]; consequently the NIA informed its members and developed a proportionate public response.

In collaboration with the Science Media Centre (London), Donaldson gave a press conference in May 2008 that was attended by top UK and international science journalists (including the BBC, Times and Guardian). Accompanying statements were provided by the British Lung Foundation and UK academic leaders in the field [5.1]. Craig Poland (technician then PhD candidate, UoE, 2004–2009) presented the findings as an invited speaker at the American Thoracic Society Annual meeting in Toronto (2008).

Impact on society: public engagement and awareness

Donaldson's study achieved widespread global coverage in multiple media forms: newspapers (e.g., Financial Times, New York Times, Agence France Press and Indo-Asian News Service), magazines (e.g., Scientific American), television and internet forums (e.g. BBC News, CBC News Canada, NHS Choices). These increased public awareness and stimulated debate on the risks of CNT, as evidenced by news interest and by prominent citations of the work in high-impact

documents discussing the human health risks of CNT, such as those produced by the US National Institute for Occupational Safety and Health (NIOSH) [5.2] and by Safe Work Australia [5.3].The practical impact of the work is illustrated by the HSE Nanosafety Partnership Group's health and safety guidance document [5.4].

Impact on public policy

In September 2008, an HSE guidance document entitled "Risk Management of Carbon Nanotubes" [5.5], which specifically and solely cited Donaldson's study, was provided to all UK nanotube-related researchers and industries. Later that year, the US Environmental Protection Agency (EPA) formally put manufacturers on notice that it considered CNT to be chemically different from conventional carbon compounds, and potentially subject to regulation as "new" chemicals under the Toxic Substances Control Act [5.6]. Donaldson has frequently been, and continues to be, consulted as an expert in the field of toxicity of nanoparticles: for example, in 2010 to the Science and Technology Committee of the House of Lords [5.7].

Impact on industry/commerce

The results of Donaldson's research were noted by industry with interests in CNT (see NIA response noted above): for example, specifically addressed in a statement submitted to the US Technology Sciences Group by Bayer Material Science AG [5.8]. There have been at least two publications from the legal profession considering the ramifications of the Donaldson study alone [5.9], and its importance was recognised by the insurance company *Lloyds of London*, which awarded Poland a "Science of Risk" prize in November 2010. Concerns within the key insurance industry on the risks of nanotechnology are reflected in the impact of Donaldson's work; the work assisted with actuarial decisions that resulted in the withdrawal of insurance provision for CNT from November 2008 by Continental Western Insurance Group [5.10].

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

5.1 NIA news item "Carbon Nanotube News Travels Fast" (2008) http://www.sciencemediacentre.org/scientists-comment-on-research-into-carbon-nanotubes-as-published-in-nature-nanotechnology-2-2/.

5.2 US National Institute for Occupational Safety and Health, "Occupational Exposure to Carbon Nanotubes and Nanofibers" Publication No. 2013–145 Current Intelligence Bulletin 65 (2013). www.cdc.gov/niosh/docs/2013-145/pdfs/2013-145.pdf.

5.3 Australian Government Department of Health and Ageing. SafeWorkAustralia: "Human Health Hazard Assessment and Classification of Carbon Nanotubes" (2012). *[Available on request.]*

5.4 The UK NanoSafety Partnership Group. "Working Safely with Nanomaterials in Research and Development" (2012). *[Available on request.]*

5.5 HSE "Risk management of carbon nanotubes" (2009). *[Available on request.]* This was reported by The Scotsman on 13 Mar 2009 under the headline "Safety body acts on city experts' work". http://www.scotsman.com/news/safety-body-acts-on-city-experts-work-1-1195142.

5.6 Goodwin Proctor Client Alert "EPA Takes First-Ever Regulatory Actions Aimed at Potential Nanomaterial Risks" (2008). http://www.goodwinprocter.com/~/media/Files/Publications/Newsletters/Client%20Alert/2008/EPA_Takes_First_Ever_Regulatory_Actions_Aimed_at_Potential_Nanomaterial_Risks.ashx.

5.7 House of Lords Science and Technology Committee Minutes of Evidence (2009). http://www.publications.parliament.uk/pa/ld200910/ldselect/ldsctech/22/9050502.htm. *[Memorandum by Donaldson to the Science and Technology Committee Nanotechnologies and Food inquiry.]*

5.8 Technology Science Group Inc. "Multiwalled Carbon Nanotube Toxicity Information" (2008). http://www.epa.gov/oppt/tsca8e/pubs/8ehq/2008/jul08/fyi_0708_01611a.pdf.

5.9 (a) Stimers P. The implications of recent nanomaterials toxicity studies for the nanotech community"; Nanotechnology Law and Business. 2008;5(3):313–8.

http://www.klgates.com/files/Publication/2b1f4c2a-298b-4948-9ce7-69f1396b61ac/Presentation/PublicationAttachment/bbdf8cdc-be42-4fa6-b942-7263b449d0b3/Article_Stimers_Nanotech.pdf.
(b) Monica J Jnr and Monica J. A Nano-Mesothelioma False Alarm. Nanotechnology Law and Business. 2008;5(3):319–33. http://www.nanolawreport.com/5_3_Policy_Ethics_254_1__pdf.pdf.

5.10 Cozzens S and Wetmore J (eds). Nanotechnology and the Challenges of Equity, Equality and Development. Springer London Limited, 2011. http://www.springer.com/social+sciences/book/978-90-481-9614-2. *[Available on request.]*