Institution: University of Southampton

Unit of Assessment: 01 Clinical Medicine

Title of case study: 01-06 The health effects of air pollution: driving policy and legislative change to improve air quality and protect public health.

Period when the underpinning research was undertaken: 2000 – 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:
Stephen Holgate	Medical Research Council Clinical Professor of Immunopharmacology and Honorary Consultant Physician	November 1975 – present
Susan Wilson	Associate Professor and Head of the Histochemistry Research Unit	January 1989 – present
Donna Davies	Professor of Respiratory Cell and Molecular Biology	May 1985 – present
Matt Loxham	BBSRC Future Leader Fellow	November 2013 – present

Period when the claimed impact occurred: August 2013 – December 2020

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

1. Summary of the impact

Twenty years of respiratory research at the University of Southampton (UoS), which demonstrated direct associations between airway damage and inflammation, and exposure to diesel combustion and ambient particulate matter (PM), nitrogen dioxide (NO_2) and ozone (O_3), has led to significant changes in government legislation, national and regional policy, and public awareness. This body of human mechanistic evidence formed the basis of the landmark Royal College of Physicians 2016 report: *Every Breath We Take: The Lifelong Impact of Air Pollution,* chaired by Professor Stephen Holgate. The report had a sustained impact on parliamentary scrutiny in Westminster, policy actions taken in Whitehall and by city mayors, high-profile legal challenges and advocacy campaigns by professional bodies, all focused on improving air quality for the benefit of public health. This culminated in the UK government's Clean Air Strategy that made a commitment for the UK to meet WHO guidelines on air pollution. The research also altered the course of a historic legal case around the link between air pollution and the death of a young child with asthma.

2. Underpinning research

By the early 2000s, epidemiological studies had established an association between transport-related air pollutants and adverse health (respiratory, cardiovascular and all-cause mortality). However, as Holgate highlighted in a high-profile review article 'Air pollution and health' in *The Lancet* (2002; with Brunekreef, Utrecht University), establishing causality was limited by lack of human toxicological evidence. University of Southampton exposure chamber studies with bronchial lavage and biopsy, followed by immunohistochemistry, addressed this gap. In 2003, two key studies led by Holgate and Wilson uncovered the direct pro-inflammatory effects of fresh diesel exhaust (DEPs) [**3.1**] and ambient air pollution-particles [**3.2**] on human normal and asthmatic airways. Two hours' exposure to DEPs provoked a marked neutrophilic airway inflammatory response that was similar, but less intense, with pollution particles concentrated from ambient air ($PM_{2.5}$).

Previous studies at the University of Southampton had shown short-term inhalation of key traffic-related pollutant NO_2 induced mild airways inflammation, but its longer-term effects were unknown. Research by Holgate and Wilson saw volunteers inhale NO_2 for four hours on four successive days with bronchial biopsies taken before the first and after the last exposure. NO_2 exposure stimulated an increase in airway expression of epithelial pro-allergic/asthmatic cytokines, interleukin (IL) -5 and IL-13, and upregulation of the adhesion molecule, ICAM-1, to promote inflammation [**3.3**]. ICAM-1 is the receptor for the major class of common cold rhinoviruses, explaining why a further study, published in *The Lancet*, found that high personal exposure to NO_2 of asthmatic schoolchildren prior to a viral respiratory infection was associated with greater asthma exacerbations [**3.4**].

These studies made a fundamental contribution to the evidence base that underpinned Holgate's research for the WHO's *Systematic review of health aspects of air pollution in Europe* (2004). As one of ten members of the scientific advisory committee that led the three-year study, Holgate authored the chapter: *Health effects of PM, ozone and nitrogen dioxide*. His findings revealed a considerable health burden at pollutant concentrations previously considered safe and highlighted the negative impact of $PM_{2.5}$, NO_2 and diesel emissions, leading to the WHO revising its air quality guidelines. The report demonstrated the negative impact of poor air quality on lung development in children but identified a need for further research into the role of air pollution in the observed incidence of asthma. A further study by Holgate demonstrated how early life environmental factors like pollutant exposure can affect the expression of genes associated with asthma [**3.5**].

These insights informed Holgate's research contributions to the Committee on the Medical Effects of Air Pollutants (COMEAP, government advisory body) and, as expert panel chair, to Defra's air quality standards; Holgate oversaw the development of Defra's UK Daily Air Quality Index in 2011. They informed Holgate's research contribution to the WHO's *Review of evidence on health aspects of air pollution* (2013), a technical study in which new evidence demonstrated that decisive policy actions were needed to protect health. Concurrent studies by Davies and Holgate showed inflammation resulted from toxic damage to the airway epithelium with release of epithelial proinflammatory mediators and growth factors [**3.6**]. This toxicological understanding contributed to an assessment of ultrafine particles ($PM_{0.1}$) as newly identified air toxicants by Holgate, and particulates from underground railways [**3.7**], led by Loxham and Davies. In 2016, Holgate led the publication of a Royal College of Physicians (RCP) systematic review *Every breath we take: the lifelong impact of air pollution*. It was the first research to attribute ~40,000 UK deaths each year to exposure to air pollution. The findings were published in the RCP's peer-reviewed journal *Clinical Medicine* [**3.8**]. A later study, led by the University of Southampton, was the first to evaluate the very long-term (60 years) mortality resulting from air pollution experienced in early life – in this case demonstrating a link between existing health effects and coal-based pollution in the 1950s [**3.9**].

Taken as a combined body of research over two decades, these studies provided the necessary mechanistic underpinning of epidemiological evidence linking air pollutants at ambient levels to adverse respiratory health and lung disease, with diesel emissions being especially problematic.

3. References to the research

3.1 Holgate ST, Sandström T, Frew AJ, Stenfors N, Nördenhall C, Salvi S, Blomberg A, Helleday R, Söderberg M. Health effects of acute exposure to air pollution. Part I: Healthy and asthmatic subjects exposed to diesel exhaust. Res Rep Health Eff Inst. 2003; 112: 1-30; discussion 51-67. https://pubmed.ncbi.nlm.nih.gov/14738208

3.2 Holgate ST, Devlin RB, Wilson SJ, Frew AJ. Health effects of acute exposure to air pollution. Part II: Healthy subjects exposed to concentrated ambient particles. Res Rep Health Eff Inst. 2003; 112: 31-50; discussion 51-67. https://pubmed.ncbi.nlm.nih.gov/14738209

3.3 Pathmanathan S, Krishna MT, Blomberg A, Helleday R, Kelly FJ, Sandström T, Holgate ST, Wilson SJ, Frew AJ. Repeated daily exposure to 2 ppm nitrogen dioxide upregulates the expression of IL-5, IL-10, IL-13, and ICAM-1 in the bronchial epithelium of healthy human airways. Occup Environ Med. 2003; 60: 892-6. https://doi.org/10.1136/oem.60.11.892

3.4 Chauhan AJ, Inskip HM, Linaker CH, Smith S, Schreiber J, Johnston SL, Holgate ST. Personal exposure to nitrogen dioxide (NO_2) and the severity of virus-induced asthma in children. Lancet. 2003; 361: 1939-44. https://doi.org/10.1016/S0140-6736(03)13582-9

3.5 Holgate ST, Davies DE, Powell RM, Howarth PH, Haitchi HM, Holloway JW. Local genetic and environmental factors in asthma disease pathogenesis: chronicity and persistence mechanisms. European Respiratory Journal 2007; 29: 793-803. https://doi.org/10.1183/09031936.00087506

3.6 Parnia S, Hamilton LM, Puddicombe SM, Holgate ST, Frew AJ, Davies DE. Autocrine ligands of the epithelial growth factor receptor mediate inflammatory responses to diesel exhaust particles. Respir Res. 2014; 15: 22. https://doi.org/10.1186/1465-9921-15-22

3.7 Matthew Loxham, Matthew J. Cooper, Miriam E. Gerlofs-Nijland, Flemming R. Cassee, Donna E. Davies, Martin R. Palmer, and Damon A. H. Teagle. Physicochemical characterization of

airborne particulate matter at a mainline underground railway station. *Environmental Science & Technology*. 2013. *47* (8), 3614-3622 https://doi.org/10.1021/es304481m

3.8 Holgate ST. 'Every breath we take: the lifelong impact of air pollution' - a call for action. *Clinical Medicine*. 2017. 17(1):8-12. https://doi.org/10.7861/clinmedicine.17-1-8

3.9 Phillips DIW, Osmond C, Southall H, Aucott P, Jones, A, Holgate ST. Evaluating the long-term consequences of air pollution in early life: geographical correlations between coal consumption in 1951/1952 and current mortality in England and Wales. *BMJ* Open. 2018. 8:e018231. https://doi.org/10.1136/bmjopen-2017-018231

Related awards:

- Royal College of Physicians President's Medal awarded to Holgate in 2018 for his research into the health effects of air pollution.
- Holgate appointed as the UKRI Clean Air Champion in 2019.
- Faculty of Public Health's Bazalgette Professorship – Champion of Evidence Award awarded to Holgate in 2020.
- Holgate received a Knighthood in the Queen's Birthday Honours List for services to medical research in October 2020.

4. Details of the impact

The University of Southampton's respiratory research has had an instrumental impact on public policy debates around air quality, underpinning evidence-based advocacy by professional organisations for urgent action, leading to significant changes to government policy and legislation and providing crucial evidence for a High Court ruling on the death of a child with asthma.

In October 2013, the RCP President invited Holgate to chair a two-year systematic review of evidence of the health effects of air pollution and make recommendations for action. Holgate's appointment was made '*on the basis of his published research over the previous decade evidencing the health effects across the lifecourse of nitrogen dioxide from diesel exhaust emissions, and the acute impact of air pollution on adults and children with asthma and other chronic respiratory conditions*' [**5.1**]. Alongside this role, Holgate was appointed as the RCP's Special Adviser on air quality in September 2016 '*as a result of his published studies that demonstrated the negative health consequences of exposure to nitrogen dioxide, ozone and particulate matter even at ambient levels*' [**5.1**]. In February 2016, Holgate led the publication of the landmark report *Every breath we take* (EBWT)*: the lifelong impact of air pollution* [**5.2**], authoring the preface and the resulting peer-reviewed journal article [**3.8**]. University of Southampton research made '*a fundamental contribution*' [**5.1**] to the evidence base that underpinned Chapter 3: *In the beginning: protecting our future generations*, Chapter 4: *Health effects of air pollution over our lifetime* and Chapter 5: *Our vulnerable groups*. Holgate's co-authored COMEAP reports and WHO 2013 technical report were also cited throughout. EBWT was the first review to conclude that ~40,000 UK deaths each year are attributable to outdoor air pollution with an annual cost to the UK economy of >GBP20 billion. It identified 14 calls to action.

The *EBWT* report was covered by all national media outlets and websites of professional bodies (e.g. nhs.uk), reaching an audience of more than 100 million people in its first month [**5.3**]. An accompanying editorial in *The Lancet* called the report '*one of the clearest calls to action to advance the UK's environment health*' [**5.4**]. On 16 March 2016, Leader of the Opposition Jeremy Corbyn cited the report's findings in Prime Minister's Questions to challenge the Government's record on air pollution [**5.5**]. The report has continued to be cited in national media reports on air quality through to the end of the impact period and has had a transformational effect in increasing awareness and raising the policy profile of air pollution as a cause of adverse health. The report page on the RCP website has had more than 81,000 views [**5.1**]. The RCP President said: '*His (Holgate's) 2016 report proved to be magisterial and as important in the battle against pollution and climate change as the College report Smoking and Health in 1962, and a worthy successor to it* [**5.1**].'

Impact on parliamentary debates, advocacy campaigns and legal challenges

In 2017 four House of Commons Select Committees held a joint inquiry into 'Improving Air Quality'. Based on his research and chairing of EBWT, Holgate was invited to provide oral evidence in November 2017. The joint committee's final report, published in March 2018, said there was an '*urgent need*' to '*bring about a step change in how the problem of air quality is tackled*' and that

the Government '*cannot continue to put public health at risk*' [**5.6**]. Holgate's evidence and findings were extensively cited throughout the lead 'Health impacts' chapter (17 citations). The report called for a new clean air act (to enshrine in law the right to breathe clean air), a clean air fund and a national air pollution monitoring programme – all of which reflected the key recommendations of the EBWT report. Shortly afterwards, Holgate chaired a RCP roundtable with ministers for the environment and public health and primary care and published a RCP 'Progress Report' to maintain the momentum for action and reemphasise the EBWT recommendations made two years earlier [**5.7**].

The *EBWT* report, alongside Holgate's expertise and previous research, was used to support three successful legal challenges (2016-2018) by environmental law charity ClientEarth in response to the UK Government breaching EU-level statutory NO_2 limit values. ClientEarth confirmed the report '*provided invaluable evidence to help us hold the UK government and local authorities to account on their legal and moral duty to tackle illegal and harmful levels of air pollution*' and that '*this research-based report helps us … to ensure policy and decision makers respond to this crisis*' [**5.8**]. In 2019 the Times launched its Clean Air for All Campaign with a manifesto that reflected Holgate's EBWT recommendations. Its Environment Editor wrote: '*The RCP report proved to be a very valuable source of authoritative information for The Times's Clean Air for All Campaign. We are very grateful for the work done by you and your colleagues as getting information we can trust has been vital to running this campaign and trying to make a difference on air quality* [**5.9**].'

Holgate also applied his research expertise to the chairing of a further systematic review for the Royal College of Paediatrics and Child Health and RCP: *The inside story: Health effects of indoor air quality on children and young people*, published in January 2020 [**5.10**]. Citing BMJ paper **3.9**, the report highlighted that the cumulative health effects of children's indoor exposures to pollution sources can be wide-ranging, a considerable source of inequality, and in many cases such effects could be reduced with coordinated actions by key stakeholders. It was widely covered in the media, reaching an audience of more than 18 million, and prompted the Local Government Association to call on developers, manufacturers and businesses to do more to tackle indoor air quality. [**5.3**]

Impact on government legislation and national and regional policy decisions

In 2017, Holgate's research expertise was requested for an evaluation of Public Health England (PHE), carried out by The International Association of National Public Health Institutes. Holgate's expertise led to *Recommendation 4: PHE should discuss with partners ways to increase research funding for PHE in critical areas of concern such as air pollution, including expanding PHE's ability to lead research projects and a potential new pool of funds at PHE* [**5.11**]. Holgate has also been an official advisor on PHE steering groups for initiatives such as a study to quantify the potential costs to the NHS and social care system from the health impacts of $PM_{2.5}$ and NO_2, and development of a tool for local authorities that quantifies the number of expected disease cases and costs in their local area.

ClientEarth's three successful legal challenges, supported by EBWT evidence, compelled the Government to publish a more ambitious air pollution plan, which it did in January 2019 through its *Clean Air Strategy 2019*. It named London, Southampton, Birmingham, Leeds and Derby as cities where air quality was the worst in the country and mandated the introduction of local air quality improvement plans. The five cities published new clean air strategies, with each one citing EBWT as evidence to support their actions [**5.12**]. The EBWT evidence that identified the scale of the health impacts from petrol and diesel cars was used by the Mayor of London and other city mayors for the scientific justification of new Low Emission Zones. Holgate advised on the Mayor of London's Clean Air Strategy; City Hall regularly cites EBWT findings and direct insights from Holgate in its statements on improving air quality [**5.13**], including the launch of the world's first Ultra Low Emission Zone in April 2019, which has reduced NO_2 by 44%.

Impact on a landmark legal case on the link between air pollution and the death of a child

Based upon his clinical research in asthma and air pollution, in 2018 Holgate was asked to prepare a report to support the reopening of an inquest into the death of nine-year-old girl Ella Kissi-Debrah from catastrophic asthma in 2013. Lawyers for Ella's family argued that illegal levels of pollution from traffic on London's South Circular Road caused the acute asthma attack that resulted in Ella's death; the first inquest in 2014 did not mention air pollution. Holgate examined Ella's health

records, autopsy report and correlations between neighbourhood air pollutant levels and her admissions to hospital. Citing Southampton research on NO_2, PM and diesel emissions, Holgate was able to incriminate exposure to unlawful levels of air pollution as a major contributory factor to her asthma and cause of death. The new evidence was presented to the Attorney General and the High Court in July 2018 and a new inquest was granted and began in November 2020. Holgate gave oral and written scientific evidence to the new inquest. In December 2020 the coroner made legal history by ruling that air pollution was a cause of Ella's death. Other causes also listed were acute respiratory failure and severe asthma. The ruling was the first of its kind in the UK and received widespread global media attention, the majority of which cited Holgate's evidence to the inquest [**5.14**].

The lawyer for Ella's family confirmed that Holgate's evidence was '*absolutely central to persuading the Attorney General to approve an application to the High Court for the first inquest into Ella's death to be quashed,'* and that his evidence to the new inquest was relied on by the Coroner in reaching his decision. '*The subsequent evidence he gave during the proceedings, meant we were able to demonstrate the fatal role air pollution had in Ella's death. Not only did his research and expertise underpin our argument, but Professor Holgate's presence was of much support to our legal team and the family. The evidence he gave in the inquest was persuasive and relied upon in the Coroner's conclusions*.' [**5.15**] In a letter to Holgate following the ruling, Sadiq Khan, Mayor of London, confirmed Holgate's key role in the proceedings, saying: '*I hope this landmark ruling, which would not have been possible without your report, will provide some comfort and closure to Ella's family.*' [**5.16**]

5. Sources to corroborate the impact

5.1 Corroborating statements from the former and current Presidents of the Royal College of Physicians.

5.2 *Every breath we take: the lifelong impact of air pollution*, RCP 2016: https://www.rcplondon.ac.uk/projects/outputs/every-breath-we-take-lifelong-impact-air-pollution

5.3 Compilation of media and wider online coverage relating to EBWT and Inside Story reports.

5.4 Lancet; Air pollution: consequences and actions for the UK, and beyond. February 27, 2016: Volume 387, Issue 10021, 817 https://doi.org/10.1016/S0140-6736(16)00551-1

5.5 Citations of EBWT report in Prime Minister's Questions, March 16, 2016: https://hansard.parliament.uk/Commons/2016-03-16/debates/16031632000024/Engagements#contribution-0DC88402-A24B-44EB-ADA7-0B4708414B0D

5.6 Improving air quality. Final report by the House of Commons Environment, Food and Rural Affairs, Environmental Audit, Health and Social Care, and Transport Committees: https://publications.parliament.uk/pa/cm201719/cmselect/cmenvfru/433/433.pdf (key pages: 6-9)

5.7 Reducing air pollution in the UK: Progress Report 2018, RCP: https://www.rcplondon.ac.uk/news/reducing-air-pollution-uk-progress-report-2018

5.8 Corroborating statement from environmental law charity ClientEarth.

5.9 Corroborating statement from the Environment Editor at The Times.

5.10 *The inside story: Health effects of indoor air quality on children and young people*, RCPCH 2020: https://www.rcpch.ac.uk/resources/inside-story-health-effects-indoor-air-quality-children-young-people

5.11 Public Health England (PHE) Evaluation and Recommendations: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/661350/PHE-Evaluation_and_Recommendations.pdf

5.12 RAC: Clean Air Zones – what are they and where are they? https://www.rac.co.uk/drive/advice/emissions/clean-air-zones/

5.13 Example public release by Mayor of London citing EBWT and Holgate: https://www.london.gov.uk/press-releases/mayoral/new-report-highlights-findings

5.14 Reporting by The Guardian and Al Jazeera on the coroner's ruling of the death of Ella Kissi-Debrah: https://www.theguardian.com/environment/2020/dec/16/girls-death-contributed-to-by-air-pollution-coroner-rules-in-landmark-case; https://www.aljazeera.com/news/2020/12/16/landmark-ruling-pollution-listed-as-cause-of-death-in-uk-first

5.15 Corroborating statement from the lawyer representing the family of Ella Kissi-Debrah.

5.16 Letter from Sadiq Khan, Mayor of London.