

Annex 1 – Author biographies ⁽¹⁾

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Jeroen Aerts is a professor in the area of risk management, climate change and water resources management. His research activities include a vast number of international climate and water resources and risk management projects in global river basins and coastal cities. These projects mainly focus on water related to issues as disaster management, insurance arrangements, poverty and vulnerability reduction, decision analyses and risk management strategies. He is coordinator of the adaptation and research program as part of the Dutch 'Climate changes Spatial Planning' initiative and co-founder of the connecting delta cities network.

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Maria Albin is associate professor with the Section of Occupational and Environmental Medicine, Department of Laboratory Medicine, and also senior consultant at Skåne University Hospital. She coordinates the excellence centre METALUND, focused on the effects of different environmental factors on diseases and disorders of major concern for public health. Her research interests are directed towards occupational epidemiology, at the crossroads with toxicology, and towards environmental epidemiology (traffic noise, airways disease, green environments).

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Mikael Skou Andersen is an environmental economist and policy analyst of the European Environment Agency. He is also for more than 10 years a professor in Environmental Policy Analysis at Aarhus University, Denmark, from where he is currently on leave. He has covered a broad field of environmental research with special emphasis on economic instruments, external costs of pollution and EU environmental policy.

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Iulie Aslaksen is an ecological economist and senior researcher in the Research Department of Statistics Norway since 1981. Her fields of expertise include ecological economics, biodiversity policy, sustainable development indicators, precautionary perspectives, and connecting ecological and feminist economics. She has recently been project leader for an interdisciplinary project on sustainable development indicators (SDI) in the context of the precautionary principle.

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Keith Beven is Distinguished Professor of Hydrology at Lancaster University and visiting professor at Uppsala University and EPFL, Lausanne. He is well known for his work in distributed rainfall-runoff modelling, including the development of TOPMODEL. He is the instigator of the Generalised Likelihood Uncertainty Estimation (GLUE) methodology. Professor Beven is one of the most highly cited hydrologists and recipient of awards from the American Geophysical Union, European Geosciences Union and International Association of Hydrological Sciences.

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Eula Bingham began her career at the University of Cincinnati School of Medicine in 1961 as a researcher who did pioneering work on chemical carcinogens. She served as a scientific and policy advisor for the National Institute for Occupational Safety and Health from 1972 to 1976, in the Department of Labor as an advisor on coke oven emissions and carcinogens (1973–1975), in the National Academy of Sciences' Lead in Paint Commission (1974–1975), in the Food

and Drug Administration and in the Environmental Protection Agency (1976–1977). President Jimmy Carter appointed her Director of OSHA, and she served through his administration. She later served as Vice President and University Dean for Graduate Studies and Research at the University of Cincinnati (1982–1990), and as a distinguished professor of environmental health at the University of Cincinnati.

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Prof Riana Bornman is an extraordinary professor and head of Andrology in the Department of Urology as well as an extraordinary professor in Environmental Health at the School of Health Systems and Public Health at University of Pretoria, South Africa. Prof Bornman's area of expertise centres on the adverse health effects of the use of DDT as a pesticide. Since 2008 Prof Bornman has acted as temporary adviser to the Stockholm Convention on Persistent Organic Pollutants (WHO/UNEP) and to the World Health Organization (WHO) Consultation on DDT Hazard Assessment. She is a Working Member of the Group of the UNEP/WHO effort to update the endocrine disrupter chemical (EDC) document of 2002.

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Michael Carlberg obtained his MSc in Statistics in 1997 and has since then worked as a statistician at the University Hospital in Örebro, Sweden. He has been working together with Lennart Hardell on several projects over the years and has been a co-author of 50 peer-reviewed publications including recent studies of cellular and cordless telephones and the risk for brain tumours.

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Masazumi Harada, MD, PhD, graduated from Kumamoto University School of Medicine. While working as a psychiatrist, he was involved in the study of Minamata disease throughout his career and is the author of the book 'Minamata disease' which gives a thorough account of the incident from the first outbreak to lawsuits. Professor Harada testified frequently in the Minamata disease court cases as well as in other environmental and occupational disease cases. His research areas include the congenital Minamata disease, fetal toxicology, environmental and occupational toxicology and epidemiology. Dr. Harada sadly passed away in June 2012.

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Professor McGlade became Executive Director of the European Environment Agency on 1 June 2003; she is on leave from University College London where she is a Professor in the Mathematics department. Prior to this she held academic and government positions in Europe and North America, focusing her research on spatial data analysis and informatics, climate change, scenario development and the international politics of the environment and natural resources.

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David Ozonoff is Professor of Environmental Health at the Boston University School of Public Health. He was the founding Chair of the Department of Environmental Health, a position he occupied from 1977 to 2003. His current research centers on community health effects of toxic exposures, especially from hazardous waste sites; the mathematical foundations of epidemiology; and the use of scientific evidence in court. Prof. Ozonoff has been principal or co-investigator of several major studies of waste sites and has been Director of the Superfund Basic Research Program—a multidisciplinary effort, funded by the National Institute of Environmental Health Sciences for the last 16 years.

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Annex 2 – An overview of *Late lessons from early warnings: the precautionary principle 1896–2000 vol. 1*

Volume 1 of *Late lessons from early warnings* was published in 2001. The rationale behind the report was that science's growing powers of innovation seem to be outstripping its ability to predict the consequences of its applications, while the scale of human interventions in nature increases the chances that any hazardous impacts could be serious and global. The report therefore aimed to take stock of past experiences and identify lessons on how we can adapt to these changes, particularly in terms of providing information and identifying early warnings.

The lessons of history have rarely been used in trying to manage current and future risks. In volume 1 of *Late lessons from early warnings*, fourteen case studies were chosen where sufficient is now known about their impacts to draw

conclusions about how well they were addressed by governments and civil society. Such conclusions were based on 'the spirit of the times' and not on the luxury of hindsight. The authors, all experts in their particular field of environmental, occupational and consumer hazards, were asked to identify the dates of early warnings, to analyse how the information was used or not used in reducing hazards, and to describe the resulting costs, benefits and lessons for the future.

This annex summarises the fourteen cases studies included in *Late lessons from early warnings: the precautionary principle 1896–2000*. The full report is available at: <http://www.eea.europa.eu/publications/late-lessons-2001>. A free printed copy can be ordered from the EU Bookshop: <http://bookshop.europa.eu>.

Table A2.1 Case studies in *Late lessons from early warnings: the precautionary principle 1896–2000*

Case study	Date of first early warning	Date of effective risk reduction action	Years of substantial inaction
Fisheries: taking stock	1376	1995–2008 'responsible' management (which is not very effective)	Hundreds
Radiation: early warnings, late effects	1896	1961–1996 UK and other countries, then EU laws.	65
Benzene: occupational setting	1897	1978 benzene voluntarily withdrawn from most US consumer products.	81
Asbestos: from 'magic' to malevolent material	1898	1999 EU ban by 2005	101
PCBs and the precautionary principle	1899	1970–1980s: EU and US restrictions, phase out by 2010	c. 100
Halocarbons, the ozone layer and the precautionary principle	1974	1987–2010 global ban on CFCs and other ozone depleters	10–30
DES: long-term consequences of pre-natal exposure	1938	1971–1985 US, EU, global ban	30–50
Antimicrobials as growth promoters: resistance to common sense	1969	1999 EU ban	30
SO ₂ : from protection of human lungs to remote lake restoration	1952 (lung) 1968 (lakes)	1979–2001 increasing EU and other restrictions leading to c. 90 % reduction on 1975 levels by 2010	25–55
MTBE in petrol as a substitute for lead	1960 taste/ odour/ persistence in water	2000 undesirable in Denmark and California, permitted elsewhere	40+
Great Lakes contamination	1962/1963	1970s DDT banned in North America and the EU. Debates continue about persistent health damaging pollution	45+
TBT antifoulants: a tale of ships, snails and imposex	1976–1981 French oyster beds collapse	1982–1987 French, UK then north-east Atlantic ban; 2008 global ban	5–30
Beef hormones as growth promoters	1972/1973 oestrogen effects on wildlife	1988 EU ban, US continues	16+
Mad cow disease — reassurances undermined precaution	1979–1986	1989 partial; 1996 total ban	10–17

Source: Gee, 2009.

Fisheries: taking stock

Malcolm MacGarvin

Measures to secure sustainable fishing have been known for centuries. However, when industrial fishing intensified in the second half of the 20th century pressure on fish stocks increased dramatically. Necessary safety margins were

underestimated, bringing, for example, North Sea herring to the brink of collapse by the 1970s.

The chapter analyses different approaches to managing stocks in Canada, the US and the EU. It also evaluated the implications of international documents introducing the term 'precautionary approach' to fisheries.

Table A2.2 Fisheries – early warnings and actions

Early fisheries in the United Kingdom	
1376–1377	Setting up a committee is the answer of the English parliament to a call for precautionary actions in fishing by controlling the mesh of the nets
1866–1893	Following uncertainty about the consequences of fisheries growth official enquiries take place, but no action is taken
Sardine fisheries in California	
Mid-1920s	Californian sardine fisheries scientists call for precaution and research
1942	Continuous inaction leads to the collapse of the sardine stock (signs of recovery only in mid-1980s)
Northern cod fisheries in Canada	
Late 1970s	Canada starts managing the northern cod fisheries up to 200 nautical miles, claiming it is doing so cautiously
1986	Keats Report commissioned by inshore fishers indicates severe underestimation of the fishing pressure
1988	Alverson Report, prepared by fishery scientists, states that consistent overestimation of the stock size leads to overfishing
1989	A new government assessment recommends that the offshore catch should be halved
1990	A new independent assessment, the Harris Report, confirms overfishing
1992	The stock collapses and a moratorium is imposed
1999	Restart of the northern cod fisheries at low levels, but dissidents state it is not low enough
General fisheries	
1990s	The ecosystem approach slowly settles in fisheries management procedures
1995	FAO Code of Conduct for Responsible Fisheries and the UN Agreement on Straddling Fish Stocks and Highly Migratory Fish Stocks are negotiated and published
2001	European Commission Green Paper on the future of the Common Fisheries Policy
2001	Positive changes are occurring, but are they happening fast enough to avoid further collapses?

Radiation: early warnings; late effects

Barrie Lambert

This case study analyses the development of radiation and radium protection over more than 100 years. Although injuries and fatalities caused by radiation were acknowledged as early as 1896, the serious consequences of widespread use of radiation were not recognised. Absence of an agreed unit to measure radiation made the introduction of effective standards of protection difficult. In the 1930s–1950s there were still many examples of ill-conceived

use of radiation e.g. for fitting children's shoes, the treatment of ringworm and removal of hair.

In the 1950s Alice Stewart was instrumental in collecting evidence linking radiology during pregnancy to leukaemia in children. Although controversial at first, her work along with that of other researchers eventually lead the way for the principles of justification, optimisation and dose limitations aimed at protecting patients as well as radiologists. Similar concerns are now being expressed at the frequent over-exposure to radiation from CT scans.

Table A2.3 Radiation — early warnings and actions

1896	Injuries from exposure to X-rays noted by Edison, Tesla and Grubbe
1899	John Dennis, New York journalist, campaigns for licensing of radiologists and warns of harm from X-rays
1904	Death of Edison's assistant from complications arising from severe X-ray radiodermatitis
1904	William Rollins, Harvard dentist/doctor, publishes many warnings on X-ray hazards, and recommendations on prevention for radiologists and patients, including pregnant women
1913	First published rules of voluntary radiological protection by German Radiological Society
1924	New York dentist, Theodore Blum, identifies 'radium jaw' in radium dial painters: but wrongly attributes this to phosphorous
1925–1929	Harrison Martland, New Jersey pathologist, identifies radium as the cause of the jawbone cancers in the dial painters studied
1928	Establishment of the International X-ray and Radium Protection Committee: which later became the International Committee on Radiological Protection (ICRP)
1934	Reports by Colwell and Russ, on the death of more than 200 radiologists from radiation-induced cancers
1949	ICRP concludes that there is no dose threshold for radiation-induced cancer and optimisation of all exposures is crucial
1958	Alice Stewart reports that 'low dose' X-rays to pregnant women can cause leukaemia in their children. Not generally accepted until the 1970s
1961	The United Kingdom publishes regulations covering the use of radioactive substances
1977	ICRP updates its radiation protection recommendations and links dose limits to risk
1988	Regulations covering radiation doses to patients produced in the United Kingdom
1990–1997	NRPB reports 20 % of medical X-rays are probably clinically unhelpful; that 50 % of the collective dose to patients could be avoided; and that individual doses for the same X-ray vary by 100x between hospitals
1990	ICRP concludes in Publication 60 that the risk of radiation-induced cancer is 4–5 times greater than estimated in 1977 — reduces the occupational dose limit to 20mSv per year
1996	EU Directive on Ionising Radiations based on ICRP 60 which will be mandatory on Member States

Benzene: an historical perspective on the American and European occupational setting

Peter F. Infante

Despite early knowledge that benzene is poisonous to bone marrow, it was used as a solvent in the rubber industry from 1910 and later expanded into

many other industries. This was accompanied by reports of benzene-induced leukaemia as well as other cancers and non-cancer diseases. Exposure recommendations were set slowly and remained at high levels for many years. From the 1970s the benzene industry began to attack the science demonstrating its harm. This contributed to delays in government action and in identifying safer threshold limit values on occupational exposures.

Table A2.4 Benzene – early warnings and actions

1897	Santessen report on observed aplastic anaemia in Sweden and other reports show that benzene is a powerful bone marrow poison
1926	Greenburg and colleagues observe abnormally low white blood cell counts in benzene workers
1928	Dolore and Borgomano publish the first case of benzene-induced leukaemia
1939	A number of investigators recommend the substitution of benzene with other solvents, but this was not implemented
1946	American Conference of Governmental Industrial Hygienists (ACGIH) recommends a limit of 100 ppm for benzene exposure, even though some cases of benzene poisoning were associated with levels of 25 ppm and 10 ppm
1947	Recommended value reduced to 50 ppm
1948	Further reduced to 35 ppm
1948	American Petroleum Institute (API) concludes that the only absolutely safe level is zero, but recommends 50 ppm or less
1957	ACGIH lowers recommended exposure to 25 ppm
1950s–1960s	Obvious lack of precaution for workers exposed to benzene in many parts of the world with fatal consequences
1977	Infante et al. publish the first cohort study of workers linking benzene exposure directly to leukaemia
1977	Based on these results, the US Department of Labor wants to reduce exposure to 1 ppm, but is challenged in the courts by API
1978	Benzene was voluntarily withdrawn from consumer products in the United States of America
1980	US Supreme Court issues the Benzene Decision severely limiting regulatory actions
1987	New benzene standard of 1 ppm. This 10-year delay caused more than 200 deaths in the United States
1996	Studies showing benzene-related diseases from 1 ppm level of exposure
2001	Petrol contains benzene, giving public exposure risk

Asbestos: from 'magic' to malevolent mineral

David Gee and Morris Greenberg

Asbestos became increasingly popular among manufacturers and builders in the late 19th century because of its sound absorption and its resistance to fire, heat, electrical and chemical damage. A severe downside, however, was the risk for workers in the mining and production industries, as exposure to asbestos dust proved to cause the lung disease asbestosis and cancer. With an average latent

period of 20–40 years from first exposure to cancer outbreak, it took a long time before the seriousness of the problems were recognised, although inspectors had warned about the risks as early as 1898.

From 1959 a third asbestos-induced disease, mesothelioma cancer, was identified. It is this cancer that is now causing the bulk of current and future harm from asbestos, including some 400 000 expected deaths in Europe over the next three decades.

Table A2.5 Asbestos – early warnings and actions

1898	UK Factory Inspector Lucy Deane warns of harmful and 'evil' effects of asbestos dust
1906	French factory report of 50 deaths in female asbestos textile workers and recommendation of controls
1911	'Reasonable grounds' for suspicion, from experiments with rats, that asbestos dust is harmful
1911 and 1917	UK Factory Department finds insufficient evidence to justify further actions
1918	US insurers refuse cover to asbestos workers due to assumptions about injurious conditions in the industry
1930	UK Merewether Report finds 66 % of long-term workers in Rochdale factory with asbestosis
1931	UK Asbestos Regulations specify dust control in manufacturing only and compensation for asbestosis, but this is poorly implemented
1935–1949	Lung cancer cases reported in asbestos manufacturing workers
1955	Doll establishes high lung cancer risk in Rochdale asbestos workers
1959–1960	Mesothelioma cancer in workers and public identified in South Africa
1962/1964	Mesothelioma cancer identified in asbestos workers, in neighbourhood 'bystanders' and in relatives, in the United Kingdom and the United States, amongst others
1969	UK Asbestos Regulations improve controls, but ignore users and cancers
1982–1989	UK media, trade union and other pressure provokes tightening of asbestos controls on users and producers, and stimulates substitutes
1998–1999	EU and France ban all forms of asbestos
2000–2001	WTO upholds EU/French bans against Canadian appeal

PCBs and the precautionary principle

Janna G. Koppe and Jane Keys

PCBs were primarily used in the electrical industry where they facilitated smaller, lighter, and what were thought to be safer, equipment. Use subsequently expanded to many other industries. Within the electrical industry, adverse effects on workers such as a painful disfiguring skin disease,

chloracne, and severe liver damage, were already well known in the 1930s. From the 1960s findings emerged of PCBs in the tissues of wildlife causing infertility and severe damage to animals. Later PCB contamination of human breast milk was found and studies showed effects of endocrine disruption. Prohibition only happened gradually with each government action taken on the basis of a high level of scientific proof.

Table A2.6 PCB – early warnings and actions

1899	Chloracne identified in workers in chlorinated organic industry
1929	Mass production of PCBs for commercial use begins
1936	More workers affected by chloracne and liver damage
1937	Chloracne and liver damage observed in experiments with rats. Results did not gain attention from policymakers but both labour regulators and manufacturers were made aware of the concerns surrounding PCBs
1966	Jensen discovers unknown molecules in sea eagles in Sweden — only in 1969 was he able to demonstrate that they were PCBs
1968	Poisoning of 1 800 people who had ingested PCB-contaminated rice oil in Japan gives rise to a new Japanese word: Yusho — rice oil disease, and to the first well-publicised warning that PCBs are harmful to humans
1970s	High levels of PCBs found in infertile seals of three different species
1972	Sweden bans 'open' uses of PCBs
1976	Toxic Substances Control Act (United States) — PCBs to be used only in a 'totally enclosed manner'
1979	2 000 people again poisoned, in Taiwan, by polluted rice oil. Follow-up research showed that 25 % of children born of poisoned mothers died before the age of four years
1980s	Evidence of PCB contamination of breast milk
1990s	PCBs associated with IQ and brain effects in children exposed in utero to mothers' PCB-contaminated diets. Fetotoxicity represents a new paradigm for toxicology
1996	EU directive to eliminate PCBs, with phase-out by 2010
1999	Chicken food contaminated with PCBs is found in Belgium

Halocarbons, the ozone layer and the precautionary principle

Joe Farman

CFCs came into industrial use in the 1930s as refrigerants and their use increased during the Second World War when widespread use of aerosol sprays commenced. The ozone layer had been discovered at that time and variations in the amount of ozone measured. Concerns linking human activities to the ozone layer did not arise before the

1970s. Five reports from the World Meteorological Organization published in the period 1985–1999 concluded that halocarbons were beyond reasonable doubt responsible for damage to the ozone layer. When phasing out CFCs they were largely replaced by HCFCs (ozone depleting substances, but less harmful than CFCs) and HFCs (with zero ozone depletion but powerful greenhouse gases). The political process failed to stimulate more radical changes towards halocarbon-free and energy-efficient technology.

Table A2.7 Halocarbons – early warnings and actions

1907	Laboratory experiments by Weigert on the decomposition of ozone photosensitised by chlorine
1934	Ditto by Norrish and Neville
1973	Global survey of CFCs by Lovelock et al. showing their distribution in the atmosphere worldwide
1974	Molina and Rowland publish their theoretical arguments that CFCs would be destroying the ozone layer
1977	United States bans CFCs in aerosols based on 'reasonable expectation' of damage, followed by Canada, Norway and Sweden
1977	Research-oriented 'world plan of action on the ozone layer' agreed, overseen by UNEP
1980	European decision restricting use of CFCs in aerosols, but rising use in refrigerators, etc. marginalises this restriction
1985	UNEP Vienna Convention for the protection of the ozone layer agrees research, monitoring, information exchange and restrictions if and when justified
1985	Farman, Gardiner and Shanklin publish results showing hole in ozone layer over Antarctica
1987	Montreal Protocol on protection of the ozone layer is signed, with phasing out of ozone depleting substances for both developed and developing countries within different timescales
1990s	Increasing finance to developing countries to help them reduce their dependence on ozone depleting substances
1997	Amendments to the Montreal Protocol in order to restore levels of chlorine by 2050–2060
1999	Beijing Declaration calling for efforts to stop illegal trade in ozone depleting substances

The DES story: long-term consequences of prenatal exposure

Dolores Ibarreta and Shanna H. Swan

In 1970 seven young women were diagnosed with a rare vaginal cancer in the US. Studies in the following years linked these and other cases to consumption of DES (a synthetic oestrogen diethylstilboestrol) by the patients' mothers during

pregnancy. DES had been prescribed to pregnant women from 1947 in the belief that it prevented miscarriages. Prescription continued even though trials in the 1950s established the ineffectiveness of DES in preventing miscarriages. The cancer findings forced scientists to abandon their commonly held view of the foetal environment as a safe place, protected by the placental 'barrier' and replace it with an understanding of the extreme vulnerability of the developing foetus.

Table A2.8 DES – early warnings and actions

1938	DES synthesised
1938	First report of increased cancer incidence in animals after DES administration
1939	First report of DES administered to patients
1942	Approval of DES by the American Council of Pharmacy and Chemistry
1942	First report of DES used for prevention of abortion
1947	US Food and Drug Administration (FDA) approves DES for the treatment of threatened or habitual abortion
1948	Use of DES increases following publication of large-scale study in the US
1953	First large placebo-controlled randomised trial shows DES ineffective in the prevention of miscarriage
1970	Published report of seven cases of vaginal clear-cell adenocarcinoma in young women
April 1971	Prenatal DES exposure is linked to vaginal clear-cell adenocarcinoma
November 1971	FDA withdraws approval of DES for use by pregnant women
1972	Registry of Clear-Cell Adenocarcinoma of the Genital Tract in Young Females is established
1978	Reanalysis of 1953 Dieckmann data shows that DES actually increased the risk of miscarriage and other adverse pregnancy outcomes
1985	Last reported use of DES by pregnant women world-wide

Antimicrobials as growth promoters: resistance to common sense

Lars-Erik Edqvist and Knud Børge Pedersen

Antimicrobials are defined as substances of natural, semisynthetic or synthetic origin that kill or inhibit the growth of microorganisms. Growth promoting properties of antimicrobial agents in farm animals were discovered in the late 1940s, resulting in e.g. faster growth of chicken, improved egg

production in laying hens and increased milk yields in dairy cows. Bacteria exposed to antimicrobials can, however, develop resistance to them with possible effects on human health. The number of independent scientific studies of this issue was relatively small compared to the number of studies supported by the pharmaceutical industry. The number of independent studies only increased when the resistance associated with using additives in animal feed was made clear.

Table A2.9 Antimicrobials as growth promoters – early warnings and actions

1945	Alexander Flemming warns against misuse of penicillin as 'microbes are educated to resist'
1950s	Antibiotic resistance widely recognised – vertical transmission
1960s	Horizontal transmission recognised
1969	Swann Committee recommends severe restrictions on antimicrobials in animal feed
1970s	Most Swann recommendations initially implemented in the United Kingdom and EU
1975	Swann recommendations are relaxed: tolysin and spiramycin still permitted as growth promoters as human equivalents; vancomycin comes into use
1977	Swedish Agriculture Board considers potential risk of antibiotic resistance, but concludes it is negligible
1984	Swedish farmers ask for government ban on antimicrobials in animal feed because of health and consumer concerns
1985	Swedish ban on grounds of antibiotic resistance in animals and 'uncertain' long-term effects
1997	Swedish report concludes that risk of antibiotic resistance in humans is 'far from negligible'
1997	WHO scientific meeting concludes that it is 'essential to replace growth promoting antimicrobials'
1998	EU bans four antimicrobials in animal feed as 'precautionary' measure
1999	EU Scientific Steering Committee recommends phase-out of antimicrobials that may be used in human/animal therapy
1999	Pharmaceutical industry opposes EU bans and takes EU to the European Court; judgement expected end 2001 (*)
2000	WHO recommends ban on antimicrobials as growth promoters if used in human therapy and in absence of risk-based evaluation

Note: (*) EU won the case against Pfizer Animal Health (Pfizer Animal Health SA v Council of the European Union, judgment available at: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:61999A0013:EN:HTML>).

Sulphur dioxide: from protection of human lungs to remote lake restoration

Arne Semb

Dense smog over London in 1952 and 1962 drew attention to air pollution and its severe health impacts. Measures were slowly taken to reduce the emission of sulphur dioxide (SO₂) but increasing

energy consumption in the 1960s resulted in large emission increases. Studies of precipitation introduced the concept of 'acid rain' and determined the long-range impact of emissions. Its harmful effects on forests and fish drew attention to the need for transnational cooperation. In Europe, this was extremely difficult during the Cold War period but progress in reducing SO₂ emissions were achieved during the 1980s and 90s.

Table A2.10 Sulphur dioxide – early warnings and actions

1952	A dense smog kills more than 2 000 people in London
1952	The Beaver Report prepared by a parliamentary commission proposes modest remedies
1962	Second smog incident kills 800 people in London
1968	Acidification of precipitation and rivers in Sweden is linked to sulphur dioxide emissions in other countries
Late 1960s	An OECD Air Management Sector Group is set up, contributing to solving air problems
1972	Further evidence of acidification of Swedish lakes presented to the UN environment conference, Stockholm
1972	OECD acid rain study is launched
1972	OECD programme on long-range transport of air pollutants is launched
1977	OECD report is published, determining the relationship between emissions and depositions of sulphur compounds
1979	Convention on Long-range Transboundary Air Pollution (LRTAP Convention) is agreed
1979	WHO recommends air quality guidelines, setting a standard for the pollution abatement work in Europe
1980s	Forest death from 'acid rain' in Germany, Poland, Czechoslovakia and North America
1985	LRTAP Convention protocol agrees 30 % reduction in sulphur emissions
1988	The EU directive on large combustion plants is published, and amended in 1988. These were very efficiently used by Germany against the British opposition to emission controls
1994	Second sulphur protocol, based on the critical load concept that had already been mapped all over Europe

MTBE in petrol as a substitute for lead

Martin Kraye von Krauss and Poul Harremoës

The toxic effects of lead have been well-known for centuries (as noted in Chapter 3 on lead in petrol). Following debate about the hazards of using lead as an anti-knocking agent in petrol in the 1960s, the petrochemical industry chose MTBE as a substitute. In around 1990 concerns arose as studies identified

MTBE contamination of groundwater, which rendered large water reserves useless and thereby put pressure on supplies in many areas. Suspicions were also raised that MTBE causes asthma, cancer and endocrine disruption.

The chapter examines the extent to which it would have been possible to foresee undesirable properties of MTBE at the time of its introduction.

Table A2.11 MTBE in petrol – early warnings and actions

1954	First scientific paper demonstrates low biodegradability of the ether family in water
1960	Information about taste and odour in water and low biodegradability available in textbook
1990	First indications of the potential for groundwater pollution with MTBE at laboratory scale
1990	Significant increase in use of MTBE in the United States due to amendments to the Clean Air Act
1990	Comprehensive investigations of carcinogenicity initiated in the 1990s
1995	MTBE detected in wells that supplied drinking water in Santa Monica, California. These had to be closed and the city lost 71 % of its local water supply
1996	Concerns become widespread following a US Geological Survey report
1997	Field studies demonstrate that MTBE is highly soluble, mobile and persistent and therefore a potential risk to groundwater
1998	A Danish EPA report acknowledges that the government was informed in 1990 that MTBE might give rise to groundwater problems and presents an action plan for MTBE remediation and risk reduction
1999	California recommends removal of MTBE from petrol as soon as possible, but not later than end 2002
2000	Indications that MTBE might be linked to asthma in some US cities
2000	Indications that MTBE might be an endocrine disrupter
2000	US EPA announces that steps will be taken to significantly reduce or eliminate MTBE as a petrol additive
2000	Danish EPA places MTBE on its list of undesirable substances
2001	EU reports on analysis of risks and risk reduction related to MTBE. European Chemicals Bureau decides that MTBE should not be classified as a carcinogen
2001	The debate goes on

The precautionary principle and early warnings of chemical contamination of the Great Lakes

Michael Gilbertson

The Great Lakes on the border between the US and Canada have been subject to comprehensive pollution for decades. In 1972, the two governments responded to findings of organochlorine compounds

in wildlife with the Great Lakes Water Quality Agreement and prohibitions of DDT and other substances. In the 1980s, however, the political climate changed and statements about the effects of persistent toxic substances on wildlife and humans were met with scepticism and demands for proof of a causal relationship before appropriating funds for remedial works. Decades later the efforts to clean up the area continue.

Table A2.12 Great Lakes contamination — early warnings and actions

1962	<i>Silent spring</i> by Rachel Carson is the significant early warning of the effects of organochlorine pesticides on fish and wildlife as well as the threat of cancer in humans
1963	First observation of changes in eggshell quality on Pigeon Island in Lake Ontario
1966	Hickey et al. publish the first analytical results of the presence of organochlorine compounds in organisms in the Great Lakes
1969	DDT and related pesticides are banned in Canada
1972	DDT is banned in the United States (dieldrin is banned in 1973) and gradual improvements in wildlife begin in the Great Lakes
1974	Concerns of possible effects of organochlorine compounds on human health
1978	Association of incidence of diseases (high rates of birth defects, miscarriages, cancers, etc.) in Love Canal, Niagara Falls with the disposal of toxic wastes (including dioxin) denied by Hooker Chemical Company
1978	Renegotiation of the Great Lakes Water Quality Agreement, including a precautionary policy, but it is not properly implemented
1980	President's Emergency Declaration moves 900 families from the hazardous Love Canal area
1984	Studies show that, at birth, infants exposed to high levels of PCBs (maternal consumption of Lake Michigan contaminated fish) weighed less and had smaller heads
1996	Studies of Lake Ontario affected children published that observed same behavioural effects as in affected children from Lake Michigan
2000	The specific relationship between behavioural anomalies and prenatal exposures to the highly chlorinated biphenyls is determined
2000	Reluctance to undertake costly remedial actions even after causal relationship is proven

Tributyltin (TBT) antifoulants: a tale of ships, snails and imposex

David Santillo, Paul Johnston and William J. Langston

Preventing plants and animals from growing on and fouling hulls has a huge effect on the fuel consumption of boats. TBT marine paint was introduced in the late 1960s and the first incidents

of imposex in gastropods were discovered in France in 1970. It was not until early 1980s, however, that analytical techniques were sensitive enough to identify TBT as the agent responsible for sex reversals in oysters and snails caused by disruption to the endocrine system. This case study analyses the process leading up to the prohibition of TBT for vessels under 25 metres and subsequently for all vessels.

Table A2.13 TBT – early warnings and actions

Early 1970s	Rapid increase in the use of TBT antifouling paints on vessels of all sizes and first reports of imposex in marine snails (Blaber, 1970; Smith, 1971)
1976–81	Repeated failure of larval settlement leads to near collapse of oyster fishery, Arcachon Bay, France
1982	France introduces legislation prohibiting the use of TBT paints on small vessels
1985	First controls introduced in United Kingdom limiting concentrations of TBT in paints
1986	Bryan et al. (1986) report widespread imposex in dogwhelks on southern coast of United Kingdom, linked to TBT
January 1987	United Kingdom announces further restrictions on TBT content of applied antifouling paint
May 1987	United Kingdom introduces ban on retail sale of TBT paint for use on vessels < 25 m and on fish cages
June 1987	PARCOM Recommendation 87/1 calls for similar ban over entire convention area (Northeast Atlantic)
1988	United States introduces restrictions. Waldock et al. (1988) highlight significance of inputs from shipyards
1989	Restrictions introduced in Canada, Australia and New Zealand
1991	Harmonised ban on retail sale of TBT paint introduced at European Union level
1994	Early reports of imposex in whelks from offshore areas of North Sea linked to shipping activity
1995	Ministerial declaration of fourth North Sea conference (Esbjerg) commits to working for global phase-out of TBT paint within IMO
1997	Concept of global phase out of organotin containing paints agreed at MEPC's 40th session
1998	Draft mandatory regulations aimed at such a phase-out adopted. OSPAR (Convention for the Protection of the Marine Environment of the Northeast Atlantic) prioritises organotins for action to cease all releases. Cessation of all releases of organotins to marine environment, under OSPAR's hazardous substances strategy in 2020
November 1999	Deadlines for phase-out adopted under IMO Assembly Resolution A.895(21)
2001	Text of International Convention on the Control of Harmful Anti-fouling Systems to be finalised. In 2003 worldwide prohibition on new application of organotin antifoulants to all vessels and in 2008 the existing organotin antifouling coatings will be replaced on all vessels worldwide

Hormones as growth promoters: the precautionary principle or a political risk assessment?

Jim W. Bridges and Olga Bridges

Oestrogen and androgen hormones have been used as growth promoters to increase meat production since the 1940s, with diethylstilboestrol (DES) being the favoured growth promoter for cattle, sheep and poultry in many countries. In the early 1970s concerns about safety were raised as DES was

confirmed to be a human carcinogen. Although expert scientific committees concluded that growth hormones were safe to use, the EU banned several hormones as growth promoters within Member States in 1988 and later extended this to imports as well. This can be seen as an early example of application of the precautionary principle.

The case study discusses the approach of the European Commission and the legal and financial implications of the trade restrictions in the World Trade Organization context.

Table A2.14 Hormones as growth promoters – early warnings and actions

1970s	Concerns about growth promoters' safety, as DES confirmed a human carcinogen
1972	Peakal publishes that DES likely to affect a wide range of species in the environment (wildlife) but this was ignored until the late 1980s
1972	DES banned as a hormone growth promoter in the United States
1974	Use of DES reinstated in the United States
1976	US Food and Drug Administration (FDA) sets the minimum detectable level of DES
1979	DES banned again on the grounds of the impossibility of identifying levels below which it would not be carcinogenic
1982	EU expert working group (Lamming Committee) concludes that some growth promoters are safe
1985	First EU ban is adopted, ignoring results from the Lamming Committee because the scope of their assessments had not been broad enough
1987	Lamming Committee disbanded by EU and their results were not published
1988	Ban of several growth promoters throughout the EU based on uncertainty of their effects on humans
1988	WHO/FAO Joint Expert Committee on Food, using standard risk assessments, reaches same conclusions as Lamming Committee
1989	EU ban extended to other growth promoters and to imports from third world countries
1989	Pimenta Report finds illegal use of growth promoters in some Member States
1989–1996	USA takes unilateral retaliatory measures on EC exports
1995	European Commission organises an international conference on growth promoters and meat production where uncertainties remain regarding effects on the immune system, endocrine system and cancer
1999	The EU Scientific Committee on Veterinary Measures Relating to Public Health publishes a report concluding that no threshold levels can be defined for six growth promoters
2000	International workshop on hormones and endocrine disrupters in food and water confirms impacts on the environment (wildlife) of veterinary drugs
2001	EU still suffers from sanction to its exports of around EUR 160 million per year

Mad cow disease 1980s–2000: how reassurances undermined precaution

Patrick van Zwanenberg and Erik Millstone

With the first case of an infected animal acknowledged in 1986, BSE (popularly known as mad cow disease) evolved into a serious crisis in the United Kingdom. The source of the epidemic was suspected to be animal slaughterhouse wastes recycled in animal feed, which was infected with

scrapie. A decade later, suspicions that BSE might transmit to humans in the form of Creutzfeld-Jakob disease were confirmed.

This case study analyses the decisions of action and inaction taken by policymakers when weighing human health and financial consequences. The lack of precautionary measures and information to the public about the risks contributed to prolonging the crisis and the collapse of public trust in scientists and governments.

Table A2.15 Mad cow disease — early warnings and actions

Mid-1970s	The United States of America bans scrapie-infected sheep and goat meats from cattle food chain
1979	UK Royal Commission on Environmental Pollution recognises risks of pathogens in animal feed and recommends minimum processing standards in rendering industries
1986	First cases of bovine spongiform encephalopathy (BSE) are officially acknowledged
1988	First documented official acknowledgement that BSE may be transmissible to humans
1988	Southwood Committee is set up and recommends that clinically affected cattle should not go into human and animal food
1989	Ruminant feed ban, slaughter and destruction of affected cattle and specified bovine offal (SBO) ban
1995	Almost 50 % of the abattoirs checked are found to be failing to comply with the SBO ban
1995	Evidence that BSE may cause Creutzfeldt-Jakob disease (CJD)
1996	At last, experiments start to see whether cattle fed on rations deliberately infected with scrapie would get BSE
1996	BSE crisis, after a new variant of CJD emerged in the United Kingdom and consuming BSE contaminated food was considered the most probable cause
1998–2000	The Phillips Inquiry takes place and its 16-volume report is published. Its conclusions do not seem sufficiently rigorous on judging government actions over time. These conclusions state that appropriate policy decisions had been taken, although not always timely, or adequately implemented or enforced

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Annex 3 – An update of some case studies from *Late lessons from early warnings: the precautionary principle 1896–2000 vol. 1*

Introduction

During the preparation of Volume 2 of *Late lessons from early warnings* it became clear that there had been some important developments in several of the earlier case study chapters which perhaps merited a brief update.

It was a step too far to ask for Volume 1 authors to provide comprehensive updates of their chapters. However, we did manage to get the following short updates focusing on the most important developments in some of the case studies since 2001.

For a few subjects the case study authors had subsequently died or could not be contacted. However, some issues were clearly of increasing importance or there had been a very significant legal development and we found other experts to briefly provide an update on these chapters.

The updates also include one contribution, to the fisheries chapter, from another expert who is not the chapter author but, in our view, has provided a different and new early warning, about the health benefits of farmed fish, which we thought was in the spirit of the Late Lessons project, especially as it has been greeted in some quarters an 'inconvenient truth'.

These selective chapter updates illustrate the nature and extent of continuing damage to ecosystems and people since Volume 1 (EEA, 2001) such as the breast cancer now arising in the daughters of the mothers who took the pregnancy pill, DES, and who survived the vaginal cancer of their twenties. Together these updates illustrate an important lesson of Volume 2 of *Late lessons from early warnings*, namely that for most of the harmful agents described in the case studies, their capacity to harm expands over time from that which generated the first 'early warnings' to other kinds of harm and which is often caused by levels of exposure that were previously considered 'safe'.

All case studies referred to in this annex can be found in:

EEA, 2001, *Late lessons from early warnings: the precautionary principle 1896–2000*, Environmental issue report No 22, European Environment Agency.

Fisheries/aquaculture: emerging challenges

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(Original case study *Fisheries: taking stock* by Malcolm MacGarvin)

Aquaculture supplies more than half of the total fish and shellfish for human consumption, and aquaculture's pressure on forage fisheries has been a source of intense debate (Naylor et al., 2009). Research on the health benefits of seafood, especially fatty fish and their long-chain n-3 polyunsaturated fatty acids (omega-3), started decades ago, and a protective effect on cardiovascular disease was reported (Kromhout et al., 1985). More recently, several studies found that the consumption of fish could induce a higher risk for type 2 diabetes (Zhou et al., 2012). In one study, four servings of fish per week was associated with a 49 % increased risk of type 2 diabetes (Djousse et al., 2011). The cardiac protective effects of omega-3 have also seriously been questioned (Rizos et al., 2012; Saravanan et al., 2010) and a possible link between omega-3 and prostate cancer has even been reported (Dahm et al., 2012). Two main factors may help us to better understand these recent findings: the presence of environmental pollutants and the new nutritional value of fish.

Environmental pollutants

There is evidence that the health outcomes of fatty fish are reduced by the presence of persistent organic pollutants (POPs), which are hazardous chemicals highly resistant to degradation. In 2010, it was documented that rats fed fish oil extracted from farmed Atlantic salmon developed multiple disorders associated with type 2 diabetes as well as obesity. On the other hand, when the same salmon oil was purified for POPs, animals were protected from these disorders (Ruzzin et al., 2010). Later, mice fed commercially available farmed Atlantic salmon fillet were found to develop severe metabolic dysfunctions mimicking those present in diabetes, obesity and fatty liver disease. When less POPs were present in farmed salmon fillet, animals exhibited better metabolic profile (Ibrahim et al., 2011). In concert, these data demonstrate that background levels of POPs, which many people consider to be at safe levels, can fully abolish the potential health benefits of fish nutrients. These findings are also consistent with the emerging view that POPs are

contributors to the epidemic of type 2 diabetes (Alonso-Magdalena et al., 2011; Neel and Sargis, 2011; UNEP and WHO, 2013).

Nutritional value of fish

The rapid growth of aquaculture production and the limited marine resources have led to important changes for farmed fish. The traditional fishmeal and fish oil present in aquafeeds (food given to farmed fish) have been largely replaced by vegetable oil and protein. Important financial resources have been used to select the best vegetable ingredients to maximize the growth and health of farmed fish. As a consequence, the nutritional value of farmed fish has significantly changed. For example, the ratio of eicosapentaenoic acid (EPA) (20:5n3) and docosahexaenoic acid (DHA) (22:6n3) to n-6 PUFAs has, between 2005 to 2009, decreased by about 50 % in farmed Atlantic salmon (NIFES), one of the most consumed fishes worldwide. Yet, the impact of this reduction in the more nutritious EPA and DHA has not been researched, but it is likely to have significantly reduced the health benefits of farmed fish.

In conclusion, there is 'early warnings' evidence that the health benefits of seafood and fish may be over-estimated. The presence of environmental pollutants in marine food in the EU is still poorly regulated compared with other dietary products. For instance, organochlorine pesticides, some polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs) and perfluorinated compounds (PFCs) are still unregulated in seafood intended for human consumption (Ruzzin, 2012). In addition, the common use of vegetable ingredients in farmed fish food introduces new hazardous chemicals that may threaten human health. There is therefore urgent need to better control the levels of environmental pollutants in seafood, and to document the human health impacts of the current farmed fish. Ignoring these issues may have important public health consequences.

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Benzene and gasoline: An update on risk of adult and childhood cancers and issues with quantitative risk assessment

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(Original case study *Benzene: an historical perspective on the American and European occupational setting* by Peter F. Infante)

Benzene is the most toxic aromatic hydrocarbon. It has been widely used in the exploitation of oil and in the manufacture and use of chemicals and paints. Significant environmental exposures arise from vehicle exhaust and from gasoline vapors. In the home, exposure to benzene can occur through the use of gasoline as a solvent for cleaning; use of petroleum derived paints and paint products; and from leaking underground gasoline storage tanks (Talbot et al., 2011). See Infante and Bingham (2012) for more detail on sources of environmental benzene exposure.

Since 1897 (LeNoir and Claude, 1897), benzene has been known to cause fatal blood diseases from high exposure levels. Research since then has continued to demonstrate adverse effects on the lymphohematopoietic system, including leukemias and some lymphomas, from lower and lower benzene exposure levels which are now down to average atmospheric exposures that are below 1 ppm.

The vast literature on benzene toxicity now indicates a significantly elevated risk of several types of cancer from benzene exposure including all of the major forms of leukemia, such as acute myelogenous leukemia (AML), acute lymphatic leukemia (ALL), chronic myelogenous leukemia (CML), non-Hodgkin's Lymphoma (NHL), multiple myeloma (MM) and chronic lymphatic leukemia (CLL) (Infante and Bingham, 2012; Infante, 2006; Glass, 2003). Recent studies demonstrate elevated risks of AML and MM associated with average benzene exposure levels below 1 ppm (Kirkeleit et al., 2008; Talbot et al., 2011). These observations of elevated leukemia risk from low level exposure are supported by data demonstrating lower white blood cell counts and damage to hematopoietic stem cells and to leukocytes among workers exposed to benzene down to the lowest levels evaluated (0.1–0.2 ppm) (Lan et al., 2004; Lan et al., 2006; Qu et al., 2002;). The elevated risk of non-Hodgkin's Lymphoma is supported by a large number of experimental studies demonstrating that benzene induces lymphomas, and by current knowledge of the mechanisms of benzene's effect

on human lymphocytes all of which provides a high level of biomedical plausibility supporting a causal relationship between benzene exposure and multiple myeloma, chronic lymphatic leukemia, and lymphomas in general (Infante, 2011; Goldstein, 2009).

Gasoline, a major source of benzene exposure in the workplace and in the environment in general, has been associated with elevated risks of AML and various cytopenias from workplace and residential exposures. These are also the most commonly observed lymphohematopoietic (LHP) diseases among individuals exposed to benzene and may be a reflection of their higher background rates in the populations studied in combination with a relatively shorter latency period and a more potent effect of benzene for these diseases. As the source of high benzene-containing mixtures, e.g. today at least 1–2 %, gasoline should be considered a cause of all lymphohematopoietic cancers associated with benzene exposure to both adults and children (Infante and Bingham, 2012).

Childhood leukemia, both ALL and AML, appears to be significantly elevated in relation to both transplacental and childhood exposures to various sources of benzene exposure as found in gasoline, paint and paint products as well as secondary cigarette smoke. Benzene exposures from these sources were likely to have been well below 1 ppm. For example, children whose mothers were occupationally exposed to benzene or gasoline (Shu et al., 1988), children living in homes where painting occurred during pregnancy (Shu et al., 1999; Schuz et al., 2000; Freedman et al., 2001; Bailey et al., 2011) or children residing near to gasoline stations (Steffen et al., 2004; Brosselin et al., 2009) demonstrate elevated risks of leukemia. Epidemiological observations demonstrating transplacental benzene exposure and elevated risk of leukemia in offspring are supported by experimental studies demonstrating that transplacental benzene exposure induces hematopoietic tumors (Maltoni et al., 1989; Badham, 2010a) and causes oxidative stress in critical embryonic cell signaling pathways involved in normal hematopoiesis (Badham et al., 2010b).

Recent studies indicate that quantitative risk assessments for benzene that extrapolate cancer risk to environmental levels of exposure from data derived from occupational cohorts are likely to underestimate risk by 3- to 9-fold because of more efficient, and alternative, benzene metabolism from exposure levels below 1 ppm (Kim et al., 2006a; Kim et al., 2006b). The major benzene metabolites exhibit a nonlinear dose-response attributable to saturated metabolism of benzene which starts at around 1 ppm. From these results, it was concluded that workers exposed to benzene below 0.1 ppm metabolize benzene to active metabolites about nine times more efficiently, and therefore more adversely than do those more heavily exposed. Other research has shown that humans exposed to ambient air benzene concentrations that are well below 1 ppm also metabolize benzene by a pathway previously unrecognized), with more efficient metabolism than what occurs at concentrations > 1 ppm (Rappaport et al., 2009).

The NIOSH Pliofilm study of the 1970s has since been widely used by government agencies and others to evaluate the cancer dose response relationship between cumulative benzene exposure and leukemia (Infante et al., 1977; White et al., 1982; Rinsky et al., 2002; OSHA, 1987; Paxton et al., 1994; EPA, 1998; IARC, 1982; Silver et al., 2002; Vlaanderen et al., 2010; Vlaanderen et al., 2011). More recent analysis, however, suggests that use of the published data from the Pliofilm cohort to estimate quantitative dose-response for benzene exposure and leukemia will result in an underestimate of leukemia risk by failing to include approximately 4–9 additional leukemia deaths among cohort members over the entire 1950–1996 follow-up period (Infante, 2013a; Infante, 2013b).

Taken together, the new information on benzene metabolism and on the previously missing leukemia deaths in the Pliofilm study indicates that quantitative cancer risk assessments have underestimated cancer risk resulting from environmental benzene exposure levels.

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Asbestos – the campaign for a global ban

Barry Castleman and David Gee

(Original case study *Asbestos: from 'magic' to malevolent mineral* by David Gee and Morris Greenberg)

Several of the harmful agents from both volumes of *Late lessons from early warnings* have been banned or phased out at a global level (TBT, CFCs, leaded petrol), sometimes with essential use exceptions (DDT) and the global treaty to phase out mercury will be signed in Minamata (see Chapter 5) in October 2013. But what of asbestos, banned throughout Europe in 2005?

The World Health Organization (WHO) estimates that, worldwide, at least 107 000 people die each year from occupational exposure to asbestos. Thousands more deaths every year are attributed to non-occupational exposure to asbestos. WHO estimates that 125 million people are exposed to asbestos at work, much of that from installed asbestos materials in buildings and vehicle brakes. The eventual asbestos death toll may reach 5–10 million.

Global asbestos consumption dropped by half from historic levels in the 1990s but has stabilised at around 2 million metric tonnes per year since 2000, with Russia being the leading producer. In 2004, Russia, China, India, Kazakhstan, Thailand and Ukraine together accounted for about three-quarters of world asbestos consumption. Other major consumers of asbestos are Iran, Brazil, Vietnam and Indonesia. Bans in over 50 countries have been offset by dramatically increasing use in China, India and other emerging economies.

National bans on asbestos have been enacted in many countries since 2000 including all countries in the European Union (WHO, 2012), Chile, Argentina, Australia and Japan. In 2006, the International Labour Organization (ILO) and the World Health Organization called for all countries to ban asbestos and developed a program to help countries with national plans for the elimination of asbestos disease. Their assistance enabled Thailand to move toward banning asbestos, during which it was established that the roof for a town house would cost only USD 65 more if it was asbestos-free, adding 0.5 % to the overall cost. However, strong pressure from Russia has held up this progress. (Annex 4 in WHO 2012 contains information about substitutes for asbestos construction materials).

Even in countries where additional asbestos product use is banned there remains a vast tonnage of asbestos-containing material (ACM) in buildings, vehicles and industries. Legislation in some countries requires ACM in buildings to be inventoried so the location and condition of the ACM is determined. When repairs and renovations require the disturbance or replacement of the ACM by safer materials, this has to be done by trained and certified workers following special procedures, using required equipment and taking measures to avoid environmental contamination on-site and during transport and waste disposal.

The European Parliament agreed to a new initiative on removing asbestos from public buildings in the EU which was accepted by a large majority on 13 March 2013. The report called for the removal of asbestos from all public buildings and buildings requiring public access by 2028, an EU-wide model for screening and registration of asbestos, and a roadmap for its removal.

The need for such measures is illustrated in the United Kingdom where, in 2013, the UK Parliament held hearings on asbestos in schools following 139 mesothelioma deaths in school teachers in the last 10 years. 253 teachers have died of mesothelioma since 1980, and the rate per year has risen from 3 in the 1980s to 14 a year in the last decade (Lees, 2013). Children are also at risk from the asbestos exposure in school building material, which is mainly chrysotile (white) but large quantities of amosite (brown) and some crocidolite (blue) (MRC, 1997).

Professor Peto, in his evidence to the UK Committee, stated, following asbestos exposure as a child at school:

'It is reasonable to say that something in the order of 100 to 150 mesothelioma deaths a year in women now could be from asbestos exposure in schools in the 1960s and 1970s, and if levels (asbestos fibre levels) are ten times lower now, then it is reasonable to assume that may go down by a factor of ten in fifty years time... under current conditions there might be 20 or

30 deaths a year in men caused by asbestos exposure in schools...'

There have been successful compensation cases for mesothelioma victims who were exposed as a child at school (UK Supreme Court, 2011).

Asbestos was banned in The Netherlands 20 years ago, but in-place asbestos will give rise to exposures for many years to come. The Health Council of The Netherlands has recommended maximum permissible risk limits of 2 800 chrysotile fibres per cubic metre, 1 300 fibres per cubic metre for mixed exposure to chrysotile and up to 20 % amphibole, and 300 fibres per cubic metre for 100 % amphiboles, as measured with Transmission Electron Microscopy (TEM). These exposure limits are for lifetime environmental exposure. Occupational limits recommended were 2 000, 1 300 and 420 fibres per cubic metre, respectively, for 40 hours/week and 40 years, corresponding to an estimated rate of death from occupational cancer of 4 per 100 000 persons exposed. These values are well below the current Dutch occupational exposure limit for all forms of asbestos, corresponding to 20 000 fibres per cubic metre by TEM (0.01 fibres per cubic centimetre, or equivalently 10 000 fibres per cubic metre measured by phase-contrast microscopic analysis) (GR, 2010).

Transmission electron microscopy is much higher magnification than phase-contrast (optical) microscopy, but mainly because of cost and availability considerations, phase-contrast microscopy has been routinely used in workplace air sampling and therefore in epidemiological studies on dose-response relationships and in regulations. The advantage of TEM is it detects even the smallest asbestos fibres and is considered most appropriate for non-occupational, environmental air sampling.

The World Bank Group (WBG, 2009) published an asbestos guidance note for project officers and international lending institutions advising the use of safer materials in new construction and observance of protective measures when doing repairs and renovations on structures containing asbestos materials. It specifies that:

'the use of ACM should be avoided in new buildings and construction or as a new material in remodelling or renovation activities. Existing facilities with ACM should develop an asbestos management plan that clearly identifies the locations where the ACM is present, its condition (e.g. whether it is in friable form or has the potential to release fibres), procedures for monitoring its condition, procedures to

access the locations where ACM is present to avoid damage, and training of staff who can potentially come into contact with the material to avoid damage and prevent exposure'.

On safer substitutes for asbestos it further notes that: 'Fibre-cement roof panels using polyvinyl alcohol (PVA) or polypropylene combined with cellulose now cost 10–15 % more to manufacture than asbestos-cement (A-C) sheets. Polypropylene-cellulose-cement roofing, a new product, is made at a cost of about 12 % more than A-C roofing and has superior impact resistance. The non-asbestos fiber-cement panels are lighter, less brittle, and have improved nailability over A-C. The increase in the overall cost of building construction that such products represent is to some degree offset by the obviation of special hygiene measures in installation/maintenance/renovation, the lack of a continuing hazard to building workers and occupants, and reduced costs of waste removal and disposal. Micro concrete tiles are cheaper than A-C to produce, and can be made in a basic workshop near the building site with locally available small contractors and materials, lowering transport costs. Compared with A-C pipes, iron pipes can be transported and installed with less difficulty and breakage, take greater compression loading and last longer'.

Some large corporations including Honeywell, Dow, ICI and Unilever have announced that they have global policies of not using asbestos in new construction and observing codes of practice where structures they own contain asbestos and need to be repaired or replaced.

Canada was the world's largest asbestos exporter when it challenged the asbestos ban in France and the EU at the World Trade Organization in 1999 (See the asbestos chapter for a summary of the WTO case, which France and the EU won (EEA, 2001, Ch. 5)). Canada's continuing mining of asbestos, almost all of it for export to India and other Asian countries, has drawn strong opposition from Canadian and other public health authorities and organisations. The Canadian Broadcasting Corporation aired a documentary showing workers picking up bundles of Canadian asbestos loosely in their arms, the dust swirling around their faces, in an Indian asbestos plant (CBC, 2009).

Canada, however, led the opposition to including chrysotile asbestos under the Rotterdam Convention on Prior Informed Consent, a treaty ratified by over 120 countries. The Convention provides that countries

exporting widely banned listed products have to provide pre-export notification of the status of the products and obtain prior informed consent to the transfer before shipping the products. Despite the recommendation of the Convention Chemical Review Committee to add chrysotile to the list of substances covered by the Convention, Canada led opposition from 2004 and in 2011 blocked the addition just after India announced it would drop its opposition. Later in 2011, the last operating asbestos mine in Canada closed.

In mid-2010, the Province of Quebec offered to provide a CAD 58 million loan guarantee to foreign investors, mainly from India, to re-open the giant Jeffrey Mine in the town of Asbestos in Quebec. Unions and opposition political parties as well as the Canadian Cancer Society and leading medical, public health and human rights associations opposed re-opening the mine. A delegation of Asian unionists, asbestos victims and activists came to Quebec to express their opposition. A series of media reports showed that national and regional asbestos trade associations outside Canada closely followed the lines developed by industry defenders in Canada. When the Indo-Canadian businessman who was pushing to re-open the Jeffrey Mine went on a public relations campaign, he was rebuked publicly by the World Health Organization for misrepresenting WHO policy that no exposure for asbestos was free from cancer risk. The deadline for finalising the plan to re-open the Jeffrey Mine was repeatedly postponed following much adverse media coverage in French and English Canada.

At the Canadian Federal level, legislation was advanced by the opposition parties to ban asbestos and provide economic assistance to workers displaced as a result. On 4 September 2012 Quebec's newly elected government cancelled a public loan to the mining company in Asbestos. The Federal authorities in Ottawa have indicated that they will no longer fight international efforts to have Chrysotile declared a hazardous substance under the Rotterdam Convention.

Conferences on asbestos have been important in advancing international cooperation, including several in Europe, e.g. Rome 2006. People from 32 countries attended the conference in Osasco, Brazil in 2000, followed by the first national asbestos bans in South America. Health professionals, unionists and asbestos victims' groups formed the Asian Asbestos Network to assist in efforts to eliminate asbestos hazards and ban new product use. After Brazilian efforts to ban asbestos failed at the Federal level, bans were enacted by some of the country's most populous states; the

Supreme Court agreed in 2008 that the constitution supported the state bans. Court battles followed when labour inspector Fernanda Giannasi blocked shipments of asbestos sacks for export through the port of Santos, in the State of Sao Paulo where asbestos was banned.

Since 2000 unions, community groups and international organisations representing medical and health professionals (such as the Joint Policy Committee of the Societies of Epidemiology (JPC-SE, 2012)) have stepped up efforts to close down the global asbestos trade but the road ahead remains difficult, especially in those remaining countries that still consume much asbestos, particularly India, China and Russia.

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PCBs and the precautionary principle

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(Original case study *PCBs and the precautionary principle* by Janna G. Koppe and Jane Keys)

In the Volume 1 of *Late lessons from early warnings* the PCB story was told until 2000 and it ended with the statement 'the non-application of the precautionary principle has left us with a legacy, the total effects and costs of which can only be guessed at'. In the following period of 2000-2010 parts of the effects on human health and the costs became clearer. Important papers have shown the relation of PCBs with diabetes especially of type 2 diabetes in the last years (Lee et al., 2006). There is a sharp rise in this disease and at the moment 1 million people out of the total population of 17 million in the Netherlands has developed the disease and the same numbers are mentioned. Costs in the Netherlands because of this disease are about EUR 4.5 billion every year.

Scientific understanding has become more sophisticated. And the most important understanding is the process of epigenetic changes. Epigenetics refers to processes that alter the gene expression without changes in DNA sequence. Both DNA hypo- or hypermethylation and changes in histone structure can take place changing the phenotype. Very important are prenatal and early-life environmental factors like PCBs that appear to play a role in the etiology of chronic diseases like diabetes and other chronic diseases. PCBs are causing intra-uterine growth retardation. And at follow-up more obesity is demonstrated (Valvi et al., 2011). An important genetic factor is the Pdx1, a pancreatic and duodenal homeobox 1 transcription factor that is essential for the development and function of the beta-cells in the pancreas. The level of this factor is lower in the intra-uterine growth retarded offspring in a rat model, that also have a reduced beta cell mass and in adult rats that develop diabetes, the Pdx1 expression is permanently silenced. We know that during the Dutch Hunger winter of 1944–1945 more babies were born with intra-uterine growth retardation and at follow-up more obesity in adolescence and more diabetes in adulthood were found with epigenetic changes.

In Slovakia in the Michalovce region a hot spot of PCB intoxication took place. In follow-up studies in

children abnormal gene expressions are found under which the ones important for insulin regulation, mostly causing a reduced activity in relation to PCB exposure. Interestingly in their study authors were able to show in two different groups of children, one group exposed to high levels of PCBs and one group with higher levels of DDT/DDE/HCB that the same 14 genes were epigenetically changed in the same direction. This finding indicates the additive effect of these two well-known groups of environmental toxic chemicals. One of those 14 genes is the TSGA 14 gene that is related to familial autism. And the TSGA gene is mentioned to be related with obesity in mice studies. (Mitra et al., 2012)

Denying toxic effects of PCBs has not only made more people ill, but has also hampered the innovative development to cure the epigenetic changes.

This denial is still taken place inhibiting new innovations and developments.

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Ozone layer update

The following is a summary of *Twenty Questions and Answers About the Ozone Layer: 2006 Update*, Fahey, D.W. (lead author), 2007, World Meteorological Organization, Geneva (<http://www.esrl.noaa.gov/csd/assessments/ozone/2006/report.html>)

(Original case study *Halocarbons, the ozone layer and the precautionary principle* by Joe Farman)

Reactive gases containing chlorine and bromine destroy stratospheric ozone in 'catalytic' cycles made up of two or more separate reactions. As a result, a single chlorine or bromine atom can destroy many hundreds of ozone molecules before it reacts with another gas, breaking the cycle. In this way, a small amount of reactive chlorine or bromine has a large impact on the ozone layer. Certain ozone destruction reactions become most effective in polar regions because the reactive gas chlorine monoxide reaches very high levels there in the late winter/early spring season.

Ozone-depleting gases are present throughout the stratospheric ozone layer because they are transported great distances by atmospheric air motions. The severe depletion of the Antarctic ozone layer known as the 'ozone hole' occurs because of the special weather conditions that exist there and nowhere else on the globe. The very low temperatures of the Antarctic stratosphere create ice clouds called polar stratospheric clouds (PSCs). Special reactions that occur on PSCs and the relative isolation of polar stratospheric air allow chlorine and bromine reactions to produce the ozone hole in Antarctic springtime.

Severe depletion of the Antarctic ozone layer was first observed in the early 1980s. Antarctic ozone depletion is seasonal, occurring primarily in late winter and early spring (August-November). Peak depletion occurs in early October when ozone is often completely destroyed over a range of altitudes, reducing overhead total ozone by as much as two-thirds at some locations. This severe depletion creates the 'ozone hole' in images of Antarctic total ozone made from space. In most years the maximum area of the ozone hole far exceeds the size of the Antarctic continent.

The ozone layer has been depleted gradually since 1980 and now is about an average of 4 % lower over the globe. The average depletion exceeds the natural variability of the ozone layer. The ozone loss is very small near the equator and increases with latitude toward the poles. The larger polar depletion is primarily a result of the late winter/early spring ozone destruction that occurs there each year.

As a result of the Montreal Protocol, the total abundance of ozone-depleting gases in the atmosphere has begun to decrease in recent years. If the nations of the world continue to follow the provisions of the Montreal Protocol, the decrease will continue throughout the 21st century. Some individual gases, such as halons and hydrochlorofluorocarbons (HCFCs), are still increasing in the atmosphere but will begin to decrease in the next decades if compliance with the Protocol continues. Around midcentury, the effective abundance of ozone-depleting gases should fall to values that were present before the Antarctic 'ozone hole' began to form in the early 1980s.

Ultraviolet radiation at the Earth's surface increases as the amount of overhead total ozone decreases, because ozone absorbs ultraviolet radiation from the Sun. Measurements by ground-based instruments and estimates made using satellite data have confirmed that surface ultraviolet radiation has increased in regions where ozone depletion is observed.

Ozone depletion itself is not the principal cause of climate change. However, because ozone absorbs solar radiation and is a greenhouse gas, ozone changes and climate change are linked in important ways. Stratospheric ozone depletion and increases in global tropospheric ozone that have occurred in recent decades both contribute to climate change. These contributions to climate change are significant but small compared with the total contribution from all other greenhouse gases. Ozone and climate change are indirectly linked because both ozone-depleting gases and substitute gases contribute to climate change.

Substantial recovery of the ozone layer is expected near the middle of the 21st century, assuming global compliance with the Montreal Protocol. Recovery will occur as chlorine- and bromine-containing gases that cause ozone depletion decrease in the coming decades under the provisions of the Protocol. However, the influence of changes in climate and other atmospheric parameters could accelerate or delay ozone recovery, and volcanic eruptions in the next decades could temporarily reduce ozone amounts for several years.

DES: the view from 2013

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(Original case study *The DES story: long-term consequences of prenatal exposure* by Dolores Ibarreta and Shanna H. Swan)

Looking back at 'The DES story: long-term consequences of prenatal exposure', it is now evident that the long-term consequences we wrote about in 2000 were merely the tip of the iceberg. Since then, our understanding of the synthetic oestrogen diethylstilboestrol (DES), now viewed as the archetypical environmental estrogen and endocrine disruptor, has greatly increased. We have a far greater understanding of how DES acts to disrupt fetal reproductive tract development, leading to cancer in rare instances but reproductive dysfunction commonly. DES has been extensively studied in non-human species, and rodents and humans show a remarkable concordance in the outcomes affected (Newbold, 1995). Most dramatically, follow-up studies in DES exposed have shown the impacts of prenatal exposure to be far more extensive and far-reaching than had been anticipated. Perhaps most alarming are data from rodent studies showing that in utero DES exposure causes heritable epigenetic alterations, and recent studies of the DES 'grandchildren' are starting to identify third generation effects in humans.

The DES daughters

Most available data on the long-term effects of prenatal exposure in DES daughters comes from the US, where the National Cancer Institute (NCI) assembled three cohorts with known prenatal DES exposure and suitable unexposed controls. Studies of health outcomes in these cohorts have been published since 2000, most comprehensively in 2011 (Hoover et al., 2011). This latter study, including 4 653 women with documented in utero exposure to DES compared with 1 027 women without, found increased risks of clear-cell adenocarcinoma of the vagina and cervix and 11 other more common adverse health outcomes, including increased risks of infertility and a range of adverse pregnancy outcomes, as well as early menopause and breast cancer in women over the age of 40; hazard ratios ranged from 1.4 to 8.1. For most outcomes, risks among those exposed who showed evidence of vaginal epithelial changes (VEC) at a young age — a marker of higher DES dose and exposure early in gestation — were at far greater risk

than those without VEC. Perhaps most dramatically, the cumulative risks in the VEC group for infertility and preterm birth were 68 % and 41 %, compared to 15 % for both outcomes in the unexposed. Thus, for DES daughters (particularly those with VEC) becoming pregnant at all, maintaining the pregnancy, and delivering a live term baby has proven to be a severe challenge.

The DES sons

Recent studies have confirmed the earlier suggestions of significant reproductive tract damage to DES sons. Male urogenital abnormalities were examined in three US cohorts of DES-exposed sons and suitable controls (Palmer et al., 2009). Significant excess risks were observed for cryptorchidism, epididymal cyst and testicular inflammation/infection. As with the DES daughters, stronger associations were observed for DES exposure that began before the 11th week of pregnancy. A study investigating three endpoints related to testicular dysgenesis syndrome (cryptorchidism, hypospadias and testicular cancer) found doubled risk ratios after DES exposure for all three (Martin et al., 2008).

The DES grandchildren

Children born to DES sons and daughters were survivors of high-risk pregnancies. These DES grandchildren are currently being followed, most extensively in the third generation cohort established by the NCI. Based on the mothers' reports, overall birth defects were elevated in the sons (Odds Ratio (OR) = 1.53; 95 % Confidence Interval (CI) = 1.04, 2.23) and in the daughters (OR = 2.35; 95 % CI = 1.44, 3.82), although the pattern of defects did not resemble those observed in the prenatally exposed men or women (Titus-Ernstoff et al., 2010). Few reproductive tract anomalies were reported, perhaps because most participants had not reached reproductive age. Follow-up of the DES grandchildren is just beginning, and further data is needed to determine whether future generations are affected by ancestral DES exposure.

In conclusion, the tragic DES 'experiment' had consequences even more profound and far-reaching than we predicted in 2000. This is an important lesson when considering synthetic estrogens currently in commerce. For example, Sir Charles Dodds (who synthesized DES) recognized the estrogenicity of bisphenol-A (BPA) in 1930, but following its introduction into plastic in 1940, its use soared, and today 10 billion pounds of BPA are manufactured annually. Exposure by pregnant women is ubiquitous and studies to identify its effects are only now being conducted.

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Antimicrobials as growth promoters

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(Original case study *Antimicrobials as growth promoters: resistance to common sense* by Lars-Erik Edqvist and Knud Børge Pedersen)

Introduction

Edqvist and Pedersen rightly referred to the continued use of antimicrobial drugs as feed additives for animals grown for human consumption as 'resistance to common sense'. Since the publication of the case study, much has been little changed (to quote Edmund Burke) in terms of public policy or drug usage. Those countries that were among the first to adopt bans and restrictions on nontherapeutic uses in agriculture have generated convincing empirical evidence that their actions have not reduced productivity or measurably affected the economics of the food production sector, nor have these bans adversely impacted the health and welfare of animals raised for food. In fact in Denmark and the Netherlands, for example, banning growth-promoting antibiotics (GPA) use has been accompanied by improvements in animal husbandry in part to prevent any impacts of the ban and in part to respond to separate public pressures.

However, these positive steps have been overwhelmed by the failure of major agricultural producing countries to act and by the rapid uptake of the industrial model of food animal production, along with GPA use, by many countries. The US, which has restricted use of only one drug (fluoroquinolones in poultry feed), retains its resistance to change. The US government finally compelled the release of industry data, which showed that nearly 80 % of antimicrobial production is used as feed additives for food animals. With this example, overall drug uses have increased substantially as Brazil, China, and India are now among the top 15 producers of poultry, and China is one of the top producers of swine (OECD-FAO, 2012).

The challenge now is to communicate the evidence for this 'new wave' as they move into global prominence in regional and world markets. The adoption of antimicrobials as feed additives in these and other countries has implications for the health of all. As noted by Thomas O'Brien, the use of antimicrobials anywhere 'can increase resistance to any antimicrobial anywhere else.'

Meanwhile, the crisis in antimicrobial resistance has only grown. Scientists discuss 'the end of the antibiotic era' (Bush et al., 2011) and reports appear in the popular press as well on pathogens with high resistance to multiple classes of antimicrobials. One sign of the importance of drug resistance is the fact that the single most important cause of infectious morbidity and mortality in the US in 2012 is no longer human immunodeficiency virus (HIV) or tuberculosis (TB), but methicillin resistant *Staphylococcus aureus* (MRSA). In the EU, livestock – especially swine and cows – are a major source of human exposures to MRSA. Thus, this is no longer an issue of a failure to heed 'early warnings' but rather a case study of intransigence in the face of overwhelming evidence. To succeed in change requires us to understand the sources and motivations of the continued opposition to ending the use of antimicrobial drugs as animal feed additives.

The global adoption of this practice has implications for the health of all: as stated by Thomas O'Brien (2002), 'use of an antimicrobial anywhere can increase resistance to any antimicrobial anywhere else'.

New evidence

Since the publication of Volume 1 of *Late lessons from early warnings*, evidence has continued to accumulate in two important areas: strengthening the associations between agricultural uses of antimicrobials (AMs) and the selection and spread of multidrug resistant pathogens; and challenging the assumptions that this use is economically important for the food animal production industry.

New evidence on associations between antimicrobials as feed additives and risks for human health

While it was quickly admitted that the use of AMs as feed additives would select for drug resistance in gut bacteria of animals, many industry and government scientists have argued for decades that there is no evidence that this increases risks of drug

resistant infections in human populations. It is increasingly difficult to ignore the overwhelming scientific evidence against this position (Marshall and Levy, 2011).

In conjunction with the removal of AMs from animal feeds in several northern European countries, monitoring programs were initiated to determine if these steps affected the prevalence of drug resistant pathogens carried by food animals, presence on consumer meat and poultry products, and prevalence of resistance in bacteria isolated from human subjects. Data collected in several European countries demonstrated significant reductions in avoparcin resistance in enterococci isolated from animals, consumer food products, and human biosamples over the first three years after removal (reviewed by Marshall and Levy, 2011).

Since 2002, this topic has also been investigated using powerful molecular methods that can demonstrate connections between the sources and transmission pathways that connect herds and flocks to the consumer food supply and to consumers. It is now common to utilize these tools of multilocus genetic sequencing and even whole genome sequencing in studies that test linkages between swine farms and MRSA or poultry houses and *C. difficile*. For the public, used to TV shows like CSI that use similar technologies, this information is readily understandable.

Since Volume 1 of *Late lessons from early warnings*, studies have been conducted in many countries on the prevalence of drug resistant pathogens in the food supply and in farms using the standard industrial model.

These risks are not limited to meat and poultry. Antimicrobials are heavily used in production of fish and shellfish in aquaculture throughout the world. Moreover, since Volume 1 of *Late lessons from early warnings*, we have gained more understanding of the risks of this practice for human health through pathways in addition to food consumption.

One reservoir

Our understanding of microbial resistance has also deepened in the intervening years. We recognize the limitations of the old notion of evaluating the significance of actions that promote selection for resistance on the basis of the clinical importance of the drug and the severity of disease caused by the bug (Silbergeld et al., 2008). Stuart Levy and others had warned against the dangers of this concept in

the early 1970s, based on the well-known ability of bacterial to exchange resistance genes horizontally across many different species and strains but these fundamental events in microbial response to antimicrobial stress (Blazquez et al., 2012) were apparently ignored by regulators and industry in their protection of drug use in animal feeds.

In addition, our awareness has also increased about the environmental impacts of antimicrobial use in food animal production in terms of expanding the resources of resistance available to microbial communities (Davis et al., 2011) and introducing the importance of non-food pathways of exposure for human populations (Feingold et al., 2012).

Economic need for growth promoting antimicrobials

Industry has long argued — since 1947 — and government has long accepted the assumption that GPA use confers important advantages in terms of productivity in food animal production. On that basis, Volume 1 of *Late lessons from early warnings* argued that the case for banning these uses depending upon a risk/benefit balancing. Since that time, evidence has emerged to challenge the nature and extent of any benefits associated with drug use in animal feeds. Review of the early studies submitted in support of the registration by The U.S. Food and Drug Administration (US FDA) of drugs for feed additive use has indicated the limitations of these data. The most persuasive evidence actually comes from two recent industry studies as well as the careful documentation of empirical experience of the industry in Denmark.

The industry study of poultry production

In 1989, the Perdue Company, one of the oldest and largest poultry integrators in the US, undertook a study of AM efficacy in a major study of their poultry growers in Maryland and North Carolina (Engster et al., 2002). This study has many of the hallmarks of a randomized clinical trial in terms of its size, duration, use of a treatment and control group, and a cross over design. All the outcomes of economic importance were directly measured: growth rate, feed consumption, animal diseases and mortality, as well as acceptability for processing. The only variable in the study was the addition of the standard package of antimicrobial drugs; no other changes were made in animal husbandry, housing conditions, or other practices.

The data as reported by Perdue in its original publication did not indicate major impacts on any parameter of economic importance in comparing production outcome in drug to drug free flocks.

Because the authors did not report data on variance within groups it is not possible to conclude that no effects were observed, but they were certainly relatively small and well below the claims in earlier studies of double digit increases in growth rates. Very importantly, the Perdue study provides no support for the assumption that GPAs reduce diseases or mortality in poultry flocks, as no differences in these variables were found.

We reanalyzed these data to answer an additional question: assuming a significant increase in benefit (improved performance), what was the cost/benefit ratio of antimicrobial use in broiler poultry feeds (Graham et al., 2007). That is, what was the marginal benefit and marginal cost, in monetized variables? Our analysis found that instead of an economic benefit, the use of AMs in animal feeds was actually a net loss for producers. There has been no dispute of this paper in the published literature.

The USDA studies of swine production

The U.S. Department of Agriculture (USDA) has analyzed data from its 2004 survey of swine farmers reporting on drug use and production variables (McBride et al., 2008). These studies are considerably weaker than the Perdue study in that the data are self-reported (not verified) and the participating farmers were not randomly selected. Moreover, the data are basically observational rather than based on a deliberate experiment in which only drug use differed. A 'surprising result', in the words of the authors, was that antimicrobial use was significantly and negatively associated with productivity, in sharp contrast to other factors as carefully managed nutrition that were positively associated with increases in productivity.

How could this be so?

The failure of recent studies as well as the experience of industry in those countries that have banned GPA use to confirm long held assumptions as to the purported benefits of GPA use should cause us to demand a complete re-evaluation of this practice. Until now, the debate has pitted much of the agribusiness sector and many national agricultural ministries against public health practitioners and public health agencies.

None of the early studies was as comprehensive or as systematically designed to incorporate real world conditions as the Perdue study. As recently as 1987, industry was publishing the same inadequate studies to support claims of growth promotion: for example, a study in which groups of 7 new born chicks were tested in a lab for 9 days

(Feighner and Dashkevicz, 1987). It is difficult to infer anything from such a limited test to the real world performance of drugs in large flocks over the lifespan of broilers.

There may be reason to accept the possibility that GPAs once conferred real benefits to industrial food animal production. The early evidence to support drug use came from studies in which antimicrobials were shown to substitute for the so-called 'animal protein factor' to support growth and prolong life among confined species. APF was identified as vitamin B12, and the search for alternatives was mainly driven by the costs of isolating large quantities of this substance back in the 1940s (Stokstad and Jukes, 1959). Since that time methods for synthesis of vitamin B12 have been discovered and implemented. Most animal feeds now contain significant amounts of vitamin B12, which may remove the need for additions of drugs. Additionally, other significant advances in animal breeding, animal husbandry, and feed formulation may have replaced the need for drugs as suggested in the USDA studies (McBride et al., 2008).

Conclusions

The use of antimicrobials in food animal production has very little support in evidence for efficacy and an increasing body of evidence of harm to public health. Since the shoe is clearly now on the other foot, governments and industry have little justification to resist change. This is no longer an issue of 'early warnings in the absence of proof', but rather persistence in a clearly dangerous practice in the absence of benefit.

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A brief comment on MTBE

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(Original case study *MBTE in petrol and as substitute for lead* by Martin Kraymer von Krauss and Poul Harremöes)

Experimental evidence demonstrates that methyl tert-butyl ether (MTBE) is carcinogenic in rats and mice. MTBE is probably carcinogenic for humans; children are particularly at risk; syncancerogenic effects must be taken in consideration. The specific tumors induced by MTBE in the CMCRC/RI experimental model are lymphomas/leukemias in females and testicular tumors. It cannot be ignored that the incidence of lymphomas/leukemias in humans is increasing and that this increase has recently been confined to women (American Cancer Society, 2006; NCI, 2005). Likewise, the rate of testicular cancer has been increasing in many countries (NCI, 2007).

The European Environment Agency calls the case of MTBE one of its *Late lessons from early warnings*, recommending additional research and extreme precaution for use of this persistent chemical (EEA, 2001). While we await new experimental data to better quantify the carcinogenic risks of MTBE, we must recognize the existence of this risk and act accordingly to protect public health.

In the past, our laboratory had different experiences in which its experimental results were ignored for risk assessment, but then confirmed by epidemiology. For example, in 1989 we published the first results showing that formaldehyde is a strong carcinogen for multiple sites, in particular inducing leukemias. In 2009 the IARC Working Group stated that 'there is sufficient evidence in humans for a causal association of formaldehyde with leukaemia' and the overall evaluation is: Formaldehyde is carcinogenic to humans (Group 1) (IARC, 2012). It is very well known that in our body, every molecule of MTBE is transformed in one of formaldehyde.

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Hormones as growth promoters

The following is a personal summary of the report of the WTO Appellate Body in United States, Canada - continued suspension of obligations in the EC – Hormones Dispute (AB-2008-5 and AB-2008-6) by Theofanis Christoforou, Principal Legal Adviser, European Commission.

(Original case study *Hormones as growth promoters: the precautionary principle or a political risk assessment?* by Jim W. Bridgess and Olga Bridges)

The World Trade Organization (WTO) Appellate Body Report ⁽¹⁾ in United States, Canada – continued suspension of obligations in the EC – Hormones Dispute was published on 16 October 2008. In its longest report to date, the Appellate Body reverses most of the conclusions previously reached by the WTO Panel.

In particular, the Appellate Body confirms practically all the SPS (Agreement on the Application of Sanitary and Phytosanitary Measures) related arguments made by the Community on appeal. The Appellate Body found that the panel committed numerous flaws in its analysis including breaching the due process rights of the Community; failing to conduct an objective assessment of the matter and facts before it; incorrectly reversing the burden of proof; failing to apply the correct standard of review under the SPS Agreement; and incorrectly finding that the Community's import ban on hormone treated meat was inconsistent with the SPS Agreement.

With regard to the procedural elements of the case, the Appellate Body report clarifies the existing dispute settlement rules and provides a clear roadmap for resolving implementation disputes. The Appellate Body agrees with the Community on the question which procedure is to be followed when there is a disagreement on the implementation of previous rulings. However, the Appellate Body disagrees with the Community on the question at what point retaliatory sanctions must cease to apply and consequently considers that the United States and Canada did not act in a unilateral manner.

After five years of work, on 14 October 2003, the Parliament and the Council adopted new legislation, Directive 2003/74/EC, which explicitly implemented the recommendations of the Dispute Settlement Body (DSB) of 13 February 1998 in EC – Hormones. After consideration of the new risk assessments, the Directive provides that a definitive prohibition

on the use of oestradiol-17 β is necessary but that the scientific evidence is insufficient to come to a definitive conclusion on the use of testosterone, progesterone, trenbolone acetate, zeranol and melengestrol acetate and that a provisional prohibition on the use of these five hormones is required.

The European Communities communicated the draft and finally adopted measure to the WTO and the United States and Canada and requested them to withdraw the retaliatory sanctions that they had imposed in the meantime. They refused.

Consequently, due to the conduct by the United States and Canada the Community had no option but to bring dispute settlement proceedings against the United States and Canada for violation of the DSU.

The Panel came to contradictory findings and conclusions which all parties appealed.

The SPS analysis

The SPS analysis is a considerable victory to the Community. The Appellate Body agrees with the Community on all essential elements of the case.

The Appellate Body considers that the Panel infringed the Community's due process rights because the appointment and consultation with two scientific experts was likely to affect or give justifiable doubts as to their independence or impartiality. Thus, their appointment and consultation compromised the adjudicative independence and impartiality of the Panel. Consequently, the Panel failed to make an objective assessment of the matter before it in breach of Article 11 of the DSU (in particular paras 481 to 482).

The Appellate Body found that the Panel's interpretation of 'risk assessment' resulted in the

⁽¹⁾ There are formally two reports i.e. AB-2006-5 and AB-2006-6. References are to the paragraphs in Appellate Body report AB-2008-6.

same 'restrictive notion of risk assessment' that the Appellate Body found erroneous in the original EC – Hormones case (in particular para 542). This was due to the Panel's interpretation and application of the SPS Agreement in relation to risk of misuse and abuse in the administration of hormones (paras 543 to 555). The Appellate Body also found that the Panel erred in the allocation of the burden of proof in its assessment of the consistency of Directive 2003/74/EC with Article 5.1 of the SPS Agreement (paras 576 to 584).

The Appellate Body also found that the Panel had incorrectly allocated the burden of proof to the detriment of the Community (paras 716 to 718).

The Appellate Body considered that the Panel failed to conduct an objective assessment of the matter before it, in breach of the SPS Agreement and Article 11 of the DSU, because it went well beyond its role and 'somewhat peremptorily decided what it considered to be the best science, rather than following the more limited exercise that its mandate required' (para 612).

The Appellate Body reverses also the Panel's finding that the Community's provisional ban on meat treated with five specific hormones failed to meet the requirements of Article 5.7 of the SPS Agreement because the relevant scientific evidence was not 'insufficient' within the meaning of the provision.

The Appellate Body considers that the existence of international standards is not dispositive on the sufficiency of the relevant scientific information. The Appellate Body explicitly confirms that a WTO member choosing a higher level of protection than would be achieved by a measure based on international standards is not obliged to frame the scope and methods of its risk assessments in the same manner as the international body that performed the risk assessment underlying the international standards (para 685). The Appellate Body found that the Panel's 'critical mass' standard for determining 'insufficiency' under Article 5.7 of the SPS Agreement was too inflexible (paras 703 to 712).

Overall the Appellate Body's report is a significant victory to the Community in substance and in particular in relation to the SPS Agreement. However, because of the serious flaws in the Panel's analysis and the highly contested facts the Appellate Body could not complete the analysis. Therefore, the confirmation of the consistency of the Community's import ban on hormones treated meat with the WTO rules and the removal of the US and Canadian imposed sanctions will need either an agreement between the parties to the dispute or another round of litigation. Nevertheless, should further litigation become necessary, the Community's position is significantly strengthened following the Appellate Body's report. The SPS findings of the Appellate Body will also be highly relevant for the Community's other SPS disputes.

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