Part A Lessons from health hazards

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2 The precautionary principle and false alarms — lessons learned

Steffen Foss Hansen and Joel A. Tickner

Most of the cases examined in the *Late lessons from early warnings* reports are 'false negatives' — instances where early warnings existed but no preventive actions were taken. In debates surrounding the precautionary principle it is often claimed that widespread application of the principle will lead to a large number of regulatory false positives — over-regulation of minor risks and regulation of non-existent risks, often due to unwarranted public 'fears'. Understanding and learning from past false positives as well as false negatives is essential for improving decision-making about public health and the environment.

This chapter reviews incidents of 'false positives', where government regulation was undertaken based on precaution but later turned out to be unnecessary. In total 88 cases were identified to be alleged false positives, however, following a detailed analysis most of them turned out to be either real risks, or cases where 'the jury is still out', or unregulated alarms, or risk-risk trade-offs, rather than false positives.

The analysis revealed four regulatory false positives: US swine flu, saccharin, food irradiation, and Southern leaf corn blight. Numerous important lessons can be learned from each, although there are few parallels between them in terms of when and why each risk was falsely believed to be real. This is a lesson in itself: each risk is unique, as is the science and politics behind it and hence a flexible approach is therefore needed, adapted to the nature of the problem. The costs of the false positives identified were mainly economic, although the actions taken to address swine flu in 1976 did lead to some unintended deaths and human suffering, and diverted resources from other potentially serious health risks. Determining the net costs of mistaken regulatory action, however, requires a complete assessment of the impacts of the regulation, including the costs and benefits of using alternative technologies and approaches.

Overall, the analysis shows that fear of false positives is misplaced and should not be a rationale for avoiding precautionary actions where warranted. False positives are few and far between as compared to false negatives and carefully designed precautionary actions can stimulate innovation, even if the risk turns out not to be real or as serious as initially feared. There is a need for new approaches to characterising and preventing complex risks that move debate from the 'problem' sphere to the 'solutions' sphere. By learning from the lessons in this chapter, more effective preventive decisions can be made in the future.

The scarcity of genuine false positives compared to the large number of 'mistaken false positives' could partly be the result of a deliberate strategy in risk communication. Several references and leaked documents have shown that some regulated parties have consciously recruited reputable scientists, media experts and politicians to call on if their products are linked to a possible hazard. Manufacturing doubt, disregarding scientific evidence of risks and claiming over-regulation appear to be a deliberate strategy for some industry groups and think tanks to undermine precautionary decision-making.

In debates surrounding the precautionary principle it is often claimed that widespread application of the principle will lead to a large number of regulatory false positives — over-regulation of minor risks and regulation of non-existent risks, often due to unwarranted public 'fears'. Critics of the precautionary principle argue that this means losing economic, environmental and human health benefits associated with the over-regulated activities (Smith, 1997 and 2000; Within Worldwide, 2000; Bate, 2001; Bergkamp, 2002; Sunstein, 2002; Graham, 2004). The literature is replete with case studies in which researchers claim excessive or unnecessary environmental and health regulation (see for instance Claus and Bolander, 1977; Whelan, 1985 and 1993; Bast et al., 1994; Wildavsky, 1995; Lieberman and Kwon, 1998; Sanera and Shaw, 1999; Bailey, 2002).

The case studies in the first volume of *Late lessons from early warnings* (EEA, 2001) were all false negatives, where early warnings existed but no preventive action was taken. In preparing the first volume, the editorial team queried the existence of 'false positives' and invited industry representatives to submit examples of instances where action was taken on the basis of a precautionary approach that turned out to be unnecessary. No suitable examples emerged and the false positive were therefore not addressed. To address this shortfall, the present chapter contains a thorough review of the issue.

2.1 'False alarms', 'regulatory abuse' and 'regulatory false positives'

The terminology regarding false positives varies. Lieberman and Kwon (1998) call their cases of overreaction 'unfounded health scares', whereas others use terms like 'environmental hoaxes and myths' (Martin, 1990), 'eco-myths' (Bailey, 2002), 'regulatory abuse' (Cohen and Giovanetti, 1999) and 'false alarms' (Mazur, 2004). Each of these researchers uses a different set of criteria — often not clearly outlined — to define when such cases of overreaction have occurred.

Most often, the authors cited above have included any case where concerns were raised over the safety of an activity, and where they deem that these concerns were later shown to be unfounded. The mere fact that concerns were raised does not, however, imply that regulatory measures were taken. The present analysis focuses on the extent to which applying the precautionary principle leads to over-regulation and it is therefore important that regulatory measures were actually taken to mitigate the suspected risk as a result of public and scientific concerns. Clearly, concerns raised by the media or public entities can lead to changes in markets or companies ceasing activities because of concerns over, for example, liability. The present chapter focuses, however, on false positives in terms of government regulation.

Similarly, for a case to be classified as a 'false positive', scientific evidence must exist showing that a perceived risk is actually non-existent and this evidence must be generally accepted in the scientific and regulatory communities. Using the Intergovernmental Panel on Climate Change (IPCC) sliding scale for assessing the state of knowledge on climate change (Moss and Schneider, 2000; Table 2.1), we argue that there should at least be a 'high confidence' (67–95 %) in the scientific evidence indicating no harm before a case can reasonably be claimed to be a false positive. This is consistent with the strength of evidence often sought in regulatory policy before preventive actions are taken, and with the classification systems of international bodies. For example, the International Agency for Research on Cancer requires that strict criteria be applied in concluding that there is no evidence of carcinogenicity as it is often difficult to rule out the possibility of effects.

For the purpose of this analysis, regulatory false positives are defined as:

> 'Cases where (i) regulatory authorities suspected that an activity posed a risk, and acted upon this suspected risk by implementing measures aimed at mitigating this risk, and (ii) that there is at least 'high confidence' in the scientific evidence that later became available indicating that the activity regulated did not pose the risk originally suspected' (Hansen et al., 2007a).

Thus, in the absence of preventive regulatory (mandated) action and high confidence in the scientific evidence about an activity's risk, a case

Table 2.1 IPCC scale for assessing the state of knowledge

95–100 %	Very high confidence
67–95 %	High confidence
33–67 %	Medium confidence
5–33 %	Low confidence
0–5 %	Very low confidence

Source: Moss and Schneider, 2000.

cannot be considered a regulatory false positive. All types of regulatory measures — including bans, labelling requirements and restrictions — fall under the definition of preventive measures. Contrastingly, decisions to study a suspected risk further or non-regulatory actions (e.g. including a substance on a list of chemicals of concern) are not considered regulatory measures for the purposes of this chapter, although some might consider government agency programmes or statements to be *de facto* regulation.

2.2 Identifying regulatory false positives

In order to identify regulatory false positives, we followed a two-step approach.

First, we conducted a detailed literature review to identify examples of regulatory false positives in the environmental and human health fields. The search terms used included 'false positives', 'over-regulation', 'health scares' and 'false alarms'. The review involved detailed literature searches and cross-referencing, and scrutiny of relevant websites. We also interviewed experts from academia, industry, non-governmental organisations and independent think tanks. Based on the review, we compiled a list of 88 case studies that claimed to be regulatory false positives (listed in full in Table 2.3 at the end of this chapter). A limited number of references provided the majority of these cases (Mazur, 2004; Wildavsky, 1995; Lieberman and Kwon, 1998; Milloy, 2001).

In the second part of the study, we analysed the literature on each of these examples to determine whether the case could indeed be considered a regulatory false positive. This was assessed based on the definition of a regulatory false positive elaborated in the previous section and current scientific knowledge. The analysis of the literature on each of the examples was performed as follows:

1. first, scientific opinions and reviews conducted by international consensus panels or bodies such as the World Health Organization (WHO), the United Nations Environment Programme (UNEP), European Commission Scientific Committees, and the IPCC, were consulted;

2. if no recent international reviews were available, we consulted up-to-date, recent reviews conducted by national governmental institutions such as the US Food and Drug Administration (FDA), and national environmental protection agencies such as the US National Academy of Sciences or Britain's Royal Society;

3. in cases where neither international nor national reviews were available, we performed literature reviews of peer-reviewed journals.

When reviewing the cases, emphasis was first placed on whether the conclusions reached in the scientific literature and by the different scientific panels and agencies were in conflict. Differing conclusions by various scientific panels, agencies and scientists would tend to lead to dismissing the case as a false positive, whereas consistent conclusions would tend to lead to accepting the case. In cases of conflicting conclusions between different scientific panels, agencies and scientists, however, we investigated the scientific literature to identify possible explanations for those differing viewpoints. If a reasonable explanation was identified to support the claim that a case was a false positive and the explanation was found to be scientifically valid by most scientists (some dissenting scientific views were accepted) in the field, the case was accepted as an authentic false positive.

For each case, we investigated what regulatory action had been taken to mitigate the risk in question, when and why, in order to determine whether the action taken could be considered to be unnecessary or disproportionate. In the event that a case was not considered to be a false positive, which occurred frequently, the reason for this was identified.

2.3 Mistaken false positives

Following a detailed analysis of each of the 88 cases, we developed a series of 'categories' of mistaken false positives including: real risks; 'the jury is still out'; unregulated alarms; 'too narrow a definition of risk' and 'risk-risk trade-offs'. The criteria used to assign cases to each category are set out in Table 2.2, and Hansen et al. (2007a) present additional examples that illustrate the key characteristics of each category.

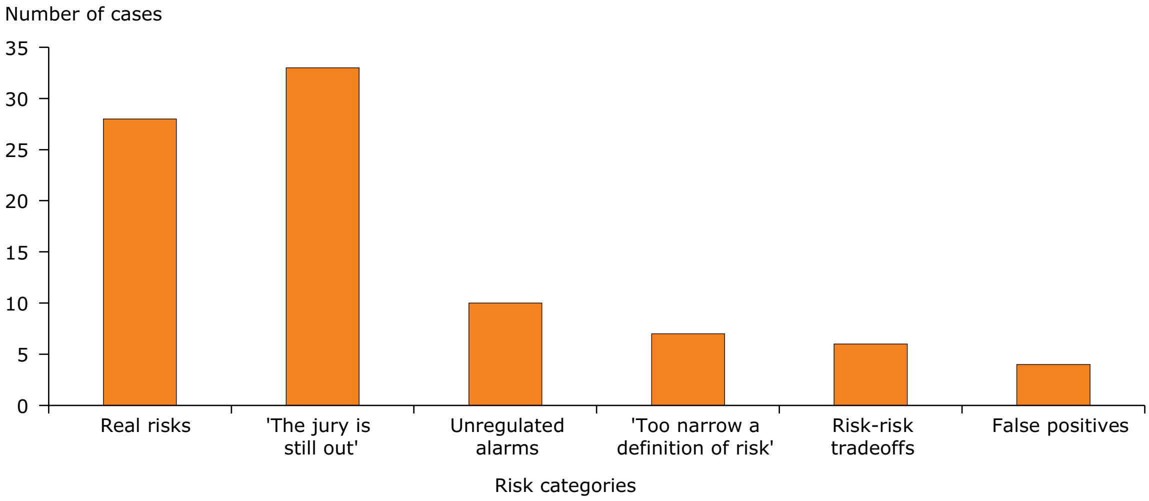
Figure 2.1 presents the distribution of cases in categories of false positives and mistaken false positives.

A detailed written analysis of each case is beyond the scope of this chapter. For a rationale for the categorisation of the cases into false positive and mistaken false positive categories, see Hansen (2004). Below, the categories are summarised.

Table 2.2 Categories of mistaken false positives and criteria for inclusion

	Criterion 1		Criterion 2		Criterion 3	Conclusion
Real risks	Hazard	and	exposure			Not a false positive
'The jury is still out'	Uncertain hazard	or	uncertain exposure	or	disputed evidence	
Unregulated alarms	Alarm raised	and	no action taken			
'Too narrow a definition of risk'	Other hazard	and	exposure			
Risk-risk trade-offs	Target risk	and	countervailing risk	and	action taken	

Figure 2.1 Distribution of 88 proclaimed false positives



2.3.1 *Real risks*

In about one third of the 88 cases proclaimed to be false positives, scientific evidence is available indicating that the activity in question posed a real risk. In these cases, a lack of regulatory intervention could have (and in some cases has) led to adverse effects on human health or the environment.

An example of such a case is acid rain. When exposed to bright sunshine, human emissions of sulphur dioxide and nitrogen oxides can be converted into sulfate and nitrate molecules. These particles can then interact with water vapour to form sulphuric or nitric acids, which return to Earth in rain, snow or fog. Concern was raised in the 1980s that acid rain might injure human health and the environment but according to Bast et al. (1994) and Wildavsky (1995) acid rain poses little or no threat to forests, crops, human health or lakes in America.

In response to the claims about damage caused by acid rain, the US Congress authorised a ten-year research effort called the National Acid Precipitation Assessment Program (NAPAP) (Bast et al., 1994). NAPAP acts as a coordinating office between six federal agencies including the National Oceanic and Atmospheric Administration (NOAA), the Environmental Protection Agency (EPA), and the National Aeronautics and Space Administration (NASA) (NAPAP, 2011).

In 1996 NAPAP published an integrated assessment of costs, benefits and effectiveness of acid rain controls. NAPAP found that, although most forest ecosystems were not then known to be adversely impacted by acid deposition, sulphur and nitrogen deposition had caused adverse impacts on certain highly sensitive forest ecosystems, especially high-elevation spruce-fir forests in the eastern United States. These adverse effects might develop in more forests if deposition levels were not reduced (NAPAP, 1996). Because acid deposition has had adverse impacts on certain highly sensitive forest ecosystems in the eastern United States, this case is considered a real risk. See Semb (2001) for a discussion of sulphur dioxide and acid rain in the European context.

2.3.2 *'The jury is still out'*

In another third of the 88 cases, there is not a 'high confidence' in the scientific evidence of no harm from the activity in question. These could be categorised as cases for which 'the jury is still out' — instances where the scientific data are uncertain or disputed and no final conclusion has yet been reached.

In these cases, lack of evidence of harm has been misinterpreted as evidence of safety. This may be due to numerous factors, including the length of time the hazard has been studied, clear disagreements in the scientific literature, or limited human studies. For example, for the International Agency for Research on Cancer (IARC) to classify a chemical as 'probably not carcinogenic to humans', there is a need for 'strong evidence that it does not cause cancer in humans'. Only one substance has been listed as such.

An example of a case where 'the jury is still out' is the health risks of mobile phones (see also Chapter 21). Lieberman and Kwon (1998) argue that there is no evidence of serious health effects from routine use of cellular phones. Graham (2004) also mentions cell phones and brain cancer as a scare where qualified scientists did not replicate early studies suggesting danger. Several reviews of the scientific literature have been conducted by both international and national bodies such as the UK's Independent Expert Group on Mobile Phones (IEGMP, 2000), the British Medical Association (BMA, 2001), the Health Council of the Netherlands (2002), the Swedish Radiation Protection Authority's Independent Expert Group on Electromagnetic Fields (2003), the UK's National Radiological Protection Board (NRPB, 2003), Sweden's Research Council for Worklife and Social Science (FAS, 2003), WHO (2004) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR, 2009). Although most reviews conclude that cellular phones probably do not constitute a health hazard after less than ten years of use, many still advise a 'precautionary approach' and recommend further research into the long-term effects on health because of the prolonged latency period of many chronic diseases (SCENIHR, 2009; WHO, 2010a and 2010b). A recent book compiling the scientific evidence on cell phone health risks (Davis, 2010), found that the there is strong enough evidence on health risks to warrant immediate action to redesign cell phones to make them safer.

According to the IEGMP (2000), the US FDA (cited in US GAO, 2001), the Danish Health Agency (2000), the Royal Society of Canada (RSC, 1999) and SCENIHR (2009), there is not enough information to conclude that cellular phones are without risk after long-term use (more than 10 years), although research to date does not show that mobile phones have adverse effects after short-term use (less than 10 years).

Several factors make it difficult to draw definitive conclusions from existing studies (US GAO, 2001; SCENIHR, 2009). Existing epidemiological studies on the health effects of radiofrequency in general have focused on short-term exposure of the entire body, not long-term exposure to the head. No studies on mobile and cordless phone use among children and adolescents have been completed so far. Additionally, most research has been conducted on the use of analogue phones instead of digital phones, which have become the standard technology. Finally, most research investigates the health effects at different frequencies than those used in mobile phones, and it is not clear how impacts from one frequency on the radiofrequency spectrum relate to other frequencies (US GAO, 2001; SCENIHR, 2009).

Studies on animal and human cells and tissues have shown that radiofrequency emissions can produce measurable responses, although it is not known whether or not these responses are harmful (Bast et al., 1994; RSC, 1999; ICNIRP, 2001). IEGMP (2000) found evidence to suggest that radiofrequency radiation might influence the ion channels and other membrane proteins of neurons in the brain under normal conditions but the significance of such effects for human health is uncertain. According to the US FDA (cited in US GAO, 2001), one type of test known as the micronucleus assay has shown changes in the genetic material, which is a common precursor to cancer. The US FDA therefore calls for additional research into the safety of mobile phones emissions. Numerous national and international research projects have been initiated across the globe to study the health risks (BMA, 2004).

The IARC has an electromagnetic field (EMF) project under way to coordinate and stimulate research and scientific discussion that can provide the basis for its reviews. IARC (2008) has established a series of multinational case-control studies (known as the Interphone study) that will potentially deliver more conclusive data on the possible health effects of mobile phones than previous research. Several studies from the Interphone study have been published (IARC, 2008) and a majority of these have found no association between cellular phone use and the risk of brain cancer. A number of small, long-term studies did, however, find a slightly increased risk for certain types of brain tumours after long-term use of cellular phones (Lönn et al., 2004 and 2005; Hours et al., 2007; Klaeboe et al., 2007). After pooling data from Nordic countries and the United Kingdom, Lahkola et al. (2007) and Schoemaker et al. (2005) reported finding a significant increased risk of glioma on the side of the head where the tumour developed after at least 10 years of using cellular phones (IARC, 2008). See Chapter 21 on mobile phone use and brain tumour risk for an updated evaluation of this evidence.

There are a number of reasons why this case falls into the category 'the jury is still out'. First, several factors make it hard to evaluate existing epidemiological studies, as previously noted. Second, although the significance for human health is unknown, different effects on cells and tissues have been observed when exposed to radiofrequency radiation. Third, there is a vast amount of research currently under way as a result of lingering scientific concerns and uncertainties.

2.3.3 Unregulated alarms

In a number of cases, a given substance, technology or procedure was proclaimed to be a risk but no regulatory action was ever taken to mitigate it. Concerns could be raised as a result of a scientific study (which later turns out to be a scientific false positive) or public or political concern. Since the cases have not been regulated, they are not considered false positives from a regulatory point of view. Examples of cases that fall into this category include the claimed links between coffee and pancreatic cancer, between fluoridated water and associated health effects, and between the measles-mumps-rubella (MMR) vaccine and autism.

There has been great public concern about the safety of the measles-mumps-rubella (MMR) vaccine since Wakefield et al. (1998) published a small study in *The Lancet* suggesting an association between the vaccine and bowel problems and autism in 12 children. In the study, parents or doctors recalled that the first signs of autism had started within two weeks after the MMR vaccination and the researchers wondered whether these two were connected. They never claimed, however, to have conclusively demonstrated this association (IOM, 2001a). The culprit was suspected to be a vaccine preservative known as thimerosal, which contains mercury (Fields, 2004).

According to Bate (2001), this research made some pressure groups argue that a precautionary approach should be taken and that the vaccines should be withdrawn, which could lead to new disease outbreaks with severe public health consequences. According to Bate (2001) 'Precautionary vaccination propaganda that results in individual and government action harms, and sometimes even kills, children.' Guldberg (2000) calls this case an obvious example of scare-mongering and argues that damage has been done because many parents decided not to take the one-in-a-million chance of a serious reaction to the vaccine. According to Guldberg (2000) this led to falling vaccination rates in the United Kingdom, which could lead to a measles epidemic. Marchant (2003) also mentions the MMR vaccine as a case in which excessive precaution was taken.

Extensive efforts have been made to confirm the findings of Wakefield et al. (1998). A number of small studies have supported the results, whereas a series of large-scale studies have found no association between MMR vaccines and autism (e.g. Taylor et al., 1999; Meldgaard Madsen et al., 2002; DeStefano et al., 2004; Smeeth et al., 2004; Hornig et al., 2008). A number of literature reviews have also been published that have all concluded that the epidemiological evidence does not support the hypothesis of an association between the MMR vaccine and autism. These reviews further conclude that the epidemiological studies that do support an association have significant flaws in their design that limit the validity of their conclusions (CSM, 1999; IOM, 2001a, 2001b and 2004; WHO, 2003a; Parker et al., 2004). In 2004, 10 of the 12 authors of the original article by Wakefield et al. (1998) retracted their support for the findings in the study (Murch et al., 2004).

Despite the public concern about MMR vaccine and actions by many advocacy groups and parents, no regulatory action was ever taken to stop parents from getting their children MMR vaccinated. On the contrary, health agencies all over the world strongly recommended MMR vaccines at the time concerns were raised and still do (NACI, 2003; CDC, 2004; UK Department of Health, 2004; WHO, 2001 and 2003b). Therefore, this case falls into the 'unregulated alarm' category.

It is correct that the controversy about the safety of MMR vaccines led to decreasing numbers of children being vaccinated in the United Kingdom but according to the UK Department of Health (2003) the numbers are increasing again. There has been an outbreak of mumps in England and Wales but the agency has emphasised that this outbreak could not be attributed to the drop in MMR

Photo: © istockphoto/Josef Mohyla

vaccinations caused by fears of a link to autism. The outbreak was actually largely due to young adults that missed out on the MMR programme, which began in 1988 (see Medical News Today, 2004).

2.3.4 *'Too narrow a definition of risk'*

Some cases proclaimed as false positives focus only on one aspect of the potential risks from a hazard. This can happen, for example, when only the human health effects of a particular hazard are examined and not the known environmental effects. Another example could be claims that a given substance is a false positive because it has been shown not to cause one type of cancer, when there is documented evidence that it increases the risk of other kinds of cancer. Examples of cases in this category include the links between hair dyes and certain cancers, and between second-hand smoke and breast cancer.

Nuclear power is another example, with some authors arguing that precautionary decisions to halt nuclear plant construction were not justified by the risks to those living near plants or the risks of accidents at the plants. For example, Graham (2004) notes that on the basis of precautionary considerations there has been a *de facto* moratorium (1) on the construction of new nuclear power plants in the US since the 1979 Three Mile Island incident. As a consequence, he argues that the US has become deeply dependent on fossil fuels for energy and 'now precaution is being invoked as a reason to enact stricter rules on use of fossil fuels'.

Bast et al. (1994) have further argued that the public is overly fearful of nuclear power and has been since the Three Mile Island incident. They further argue that low doses of radiation are not harmful and that nuclear power is a safe and clean technology, although they admit that accidents can happen. More recently, some have argued that nuclear power poses no risk of cancer based on a 2011 UK Committee on Medical Aspects of Radiation in the Environment (COMARE) 30 year study which found no increased risk of leukemia among children in the proximity of nuclear power plants in the United Kingdom (Ross, 2011; COMRE, 2011).

In fact, concerns about at least two other types of issues need to be considered in discussions about risks from nuclear plants: the cost of nuclear-generated electricity and radioactive waste. Before considering them, however, it is worth asking whether the risks to those living near nuclear plants are, indeed, insufficient to justify a precautionary moratorium. There is little doubt, for example, that a major reactor accident could release large amounts of radiation into the environment, as was demonstrated during the nuclear disasters at Chernobyl, Ukraine, in 1986 and more recently at Fukushima, Japan, in 2011. Dispute seems to centre on the likelihood of such an event and there seems to be a significant disagreement between expert and lay perceptions of risk.

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(1) Since the moratorium has only been *de facto*, this case can also be discounted as a regulatory false positive because it constitutes an 'unregulated alarm'.

In 1975, the Rasmussen report assessed reactor safety in US commercial nuclear power plants. It found that the probability of having an accident like the Three Mile Island is anywhere from 1 in 250 to 1 in 25 000 reactor-years. These estimates did not take (among other factors) the possibility of human errors into consideration. US Nuclear Regulatory Commission data indicate that there is a 50 % chance of another accident occurring equal in size to Three Mile Island or larger (Shrader-Frechette, 1993).

These findings suggest that a precautionary moratorium on plant construction based on concerns about accidents and radiation leaks alone might not have been irrational. As noted, however, other factors played a role, including concerns about financial risks. Orders to construct nuclear plants had begun to decline sharply even before the Three Mile Island accident. By September 1974, 57 of 191 nuclear plants under construction, under licensing review, on order, or announced by utilities had been delayed by a year or more and a few had been cancelled altogether. Fourteen months later, 122 of the 191 projects had been deferred and nine had been cancelled. Between 1975 and 1978, US utilities ordered only 11 nuclear units. Utilities cut back on both coal and nuclear projects, but the blow fell disproportionately on builders of nuclear units because of higher capital costs (Walker, 2004). This was only partly due to public opposition.

The energy crisis of the early seventies sharply and quickly drove up the price of oil and other fuels that utilities purchased to run their plants. This again drained their financial resources. Adding to this, the serious problem of inflation greatly increased the cost of borrowing money for plant construction. An economic slump and increasing unemployment also curtailed demand for electricity, which grew at a substantially slower rate than experts had anticipated (Walker, 2004). As Giere (1991) states 'The accidents at Three Mile Island and Chernobyl dramatised the dangers of nuclear power, but the immediate cause of the demise of the nuclear power industry in the United States has been economic'. Supporting Giere's statement, the costs of nuclear-generated electricity quadrupled in the 1980s alone, and 2001 data from the US Department of Energy show that nuclear fission is more expensive per kilowatt-hour than coal, natural gas, wind, and solar thermal (Shrader-Frechette, 1993). According to Shrader-Frechette (2003) this is just another reason that no new nuclear plant has been ordered since the seventies.

In addition to accidents, radiation leaks and doubts about the financial viability of nuclear power, concerns also focused on the risks associated with radioactive waste produced as a by-product of power generation. During the 1980s radioactive waste doubled and there is still controversy surrounding how to deal with it. Although large-scale nuclear accidents might be rare, several accidents have occurred at nuclear storage facilities causing the death of hundreds of people. Clean-ups will cost hundreds of billions of dollars (Shrader-Frechette, 1993).

The example of nuclear power demonstrates that in assessing whether a decision is based on a false perception of risk, it is essential to examine all the factors motivating that decision. In this case, claims that the US moratorium represents (*de facto*) over-regulation based on disproportionate fears about accidents and radiation leaks do not bear up to scrutiny.

2.3.5 Risk-risk trade-offs

Risk-risk trade-offs can be defined as cases where efforts to combat a 'target risk' of concern unintentionally create 'countervailing risks' (also known as 'side-effects' or 'unintended consequences') (Graham and Wiener, 1995). Addressing risk-risk trade-offs (ensuring that regulatory actions do not create new risks) is an important concern in regulatory policy and several authors have written about this subject (see Tickner and Gouveia-Vigeant, 2005). The situation differs, however, from precautionary over-regulation.

One example of such a case is the use of nitrites in meat preservation. Nitrites have been used to cure meat, such as bacon, ham, hot dogs and other sausages, for several centuries. Besides enhancing colour and flavour, nitrites inhibit the growth of *Clostridium botulinum* and other toxins. *Clostridium botulinum* causes botulism, a rare but often fatal form of food poisoning (McCutcheon, 1984). Since 1899 there have been only seven outbreaks of botulism poisoning in commercially cured meat products in the US and Canada, resulting in nine deaths. The excellent safety record of cured meat has been largely attributed to the use of nitrites (Pierson and Smoot, 1982).

In the late 1970s there was a discussion about whether or not to ban nitrites in the US. Concerns were raised after scientists found that nitrites react in the body with other food agents to form nitrosamines, which are known carcinogens (IPCS, 1978). Since attempts to discover a single alternative preservative with all the properties of nitrites have been unsuccessful, banning nitrites could result in a risk-risk trade-off between the risk of nitrosamine-induced cancers and increased risk of botulism. This argument was used by the US Food and Drug Administration (FDA) and the US Department of Agriculture (USDA) and as a result nitrites were not banned (Wildavsky, 1995; Lieberman and Kwon, 1998).

Lieberman and Kwon (1998) have described the arguments against nitrites as one of the 'greatest unfounded health scares of recent times' fuelled by application of the precautionary principle. But the fact that a ban on nitrites could itself have created certain risks is not evidence that concerns about nitrites were unfounded. Indeed, the measured response of government and the food industry that ensued looks like smart management of risks, rather than over-regulation.

In 1978 the USDA required that the level of nitrite be reduced and that nitrite be used in combination with sodium ascorbate or erythorbate. Sodium ascorbate (vitamin C) or erythorbate (chemically similar to vitamin C) block or inhibit the formation of nitrosamines from nitrite (Institute of Food Technologists, 1998). The USDA took forceful steps to ensure that bacon was in compliance with the new regulations and began an extensive three-phase monitoring programme. The intent of the programme was not to stop bacon production but rather to produce bacon according to the new requirements. Plants in violation of the requirements were allowed to correct their procedures to reduce nitrosamines, and USDA offered technical assistance to plants with potential problems. The food industry responded by tightening its own quality control and nearly all bacon was free from confirmable levels of nitrosamines within one year of the start of the three-phase monitoring programme (McCutcheon, 1984).

Beyond bacon, the food industry generally made substantial changes to the cured meat manufacturing process. It stopped using sodium nitrate in major meat processes; it reduced the use of nitrite in the processing of cured meats; and it increased the use of ascorbate and erythorbate in the curing process. As a result, the food industry was able to eliminate the addition of nitrite to foods, reducing residual nitrite levels in cured meat products five-fold without compromising antibotulinal effects. Today the average level of residual nitrite is one-fifth of the amount present 20 years ago (Institute of Food Technologists, 1998). Indeed, there is a growing market for non-preserved meats due to concerns about the health implications of nitrites and antibiotics in traditional processed meats with no known safety implications to date.

2.4 Identified false positives

Of 88 cases of alleged over-regulation, only four cases fulfilled the definition of a regulatory false positive (Hansen et al., 2007a). These are the cases of:

- **Southern corn leaf blight:** the US Department of Agriculture decision in 1971 to plant more corn in the mistaken anticipation that Southern corn leaf blight would return and destroy a large part of the harvest (Lawless, 1977; Mazur, 2004; Hansen 2004);
- **saccharin:** the 1977 decision requiring saccharin to be labelled in the US because it was believed to be a human carcinogen;
- **swine flu:** the US Department of Health, Education, and Welfare decision in 1976 to mass immunise the entire American population in the mistaken anticipation of a return of swine flu (US GAO, 1977; Neustadt and Fineberg, 1978);
- **food irradiation impacts on consumer health:** the reluctance of the US Food and Drug Administration to allow food irradiation that could help reduce a large number of food pathogens and increase shelf life (WHO, 1981; 1999; SCF, 2003).

The latter two cases are presented below in greater detail. An in-depth analysis of the first two cases can be found in Hansen (2004). In the discussion that follows, however, all four cases are referred to in drawing policy relevant lessons for decision-makers.

Each case was analysed in order to understand:

- when and why precautionary regulatory action was taken;
- when and why it was realised that this precautionary action was unnecessary;
- what the resulting cost and benefits were.

These factors are emphasised differently in each of the cases, as each has a unique historical and scientific basis. Literature is very scarce on Southern corn leaf blight, which makes it impossible to analyse and answer all of the questions in depth.

2.5 Swine flu

In late January 1976, twelve soldiers at Fort Dix in New Jersey became sick with an upper respiratory infection. One of the soldiers died after participating in a forced march. The cause of the infection was a new strain of the flu virus dubbed 'swine flu', which was antigenetically similar to the Spanish flu that had caused 40–50 million deaths worldwide in 1918–1919 (US GAO, 1977; Potter, 1998; Reid et al., 1999). Influenza epidemics result in about three to five million cases of severe illness annually and about 250 000 to 500 000 deaths, primarily among the elderly (WHO, 2010c).

Photo: © istockphoto/Sean Locke

US President Ford decided to immunise the entire American population against swine flu, dedicating USD 135 million to the production of vaccines (US GAO, 1977). The immunisation programme suffered a number of setbacks in the implementation phase, however, and only 40 million Americans (out of 200 million) were inoculated. The widespread swine flu outbreak feared by decision-makers never occurred. On this basis, the mass immunisation program appears to have been unnecessary.

2.5.1 Responses to early warnings

The initial outbreak at Fort Dix was taken very seriously by the Center for Disease Control (CDC) and other agencies for a number of reasons. Among them:

- Scientists had observed that when a new strain of the flu emerged, it would typically appear in low levels towards the end of a flu season — just as swine flu did at Fort Dix — and then return in epidemic proportions the following flu season.
- A hypothesis at the time suggested that major flu epidemics took place at regular intervals of eleven years. Because the US had experienced epidemics in 1946, 1957 and 1968, it seemed plausible that a new one would occur in 1977.
- Another theory suggested that virulent flu strains recycled themselves at intervals of sixty or seventy years. Almost sixty years had elapsed since the Spanish flu epidemic of 1918–1919 and it seemed reasonable that the swine flu virus was in the process of re-emerging.
- A new strain of flu virus had never before appeared without it leading to a major epidemic (Boffey, 1976; Colin, 1976; USDHEW, 1976; Neustadt and Fineberg, 1978; Wecht, 1979; Silverstein, 1978; Bernstein, 1985).

Knowing this, government officials held a series of emergency meetings and decided that the CDC should begin preparing to produce large amounts of swine flu antibodies. Special attention was paid to informing the public to prevent the media portraying the Fort Dix outbreak as a 'gloom and doom' scenario (Neustadt and Fineberg, 1978; Silverstein, 1978).

Little new information on the Fort Dix outbreak was available when the CDC's Advisory Committee on Immunization Practices (ACIP) held its annual meeting in March, 1976 to review the vaccine recommendations for the next flu season. Most of the participants were in favour of recommending mass production of swine flu vaccine and inoculation of the American population as soon as possible.

One member of ACIP suggested producing the vaccine and then stockpiling it until a clearer signal of a flu pandemic emerged. According to the records, he felt that one should always be careful about putting foreign material into the human body, especially when the number of bodies approached 200 million (Neustadt and Fineberg, 1978; Silverstein, 1978). According to the minutes of the meeting, the possibility of stockpiling vaccines was never really discussed. According to some experts (Wecht, 1979), however, the option was discussed by Dr Sencer, Director of the CDC, and a few other committee members during one of the breaks of the meeting. They did not consider the option viable due to the amount of time required to distribute and administer the vaccines. Too many people could get sick and perhaps die in the time it would take for the vaccine to find its way through the delivery pipeline. The basis for not discussing this option openly during the ACIP meeting was later attributed by some to Dr Sencer's eagerness to act immediately (US GAO, 1977; Neustadt and Fineberg, 1978; Silverstein, 1978; Bernstein, 1985).

Based on the ACIP recommendations, Dr Sencer prepared a memorandum presenting the pros and cons of four courses of action:

1. No action: leave it to private drug manufacturers to produce vaccines in response to their estimates of demand, and let consumers make their own decisions on whether to get vaccinated.

2. Minimum response: the federal government would advise the drug industry to produce sufficient vaccine to immunise the general population and would undertake a public awareness programme.

3. Government programme: the federal government would advise vaccine manufacturers to embark on full scale production with the expectation of a federal government purchase of up to 200 million doses. The health authorities would carry out an immunisation programme designed to reach 100 % of the population.

4. Combined approach: the federal government would advise vaccine manufacturers to embark on full-scale production and purchase 200 million doses. However, they would leave it to state health agencies to develop plans for immunisation (USDHEW, 1976).

The memorandum recommended the 'combined approach' for a number of reasons. Previous experiences with widespread flu pandemics in 1957 and 1968 indicated that the vaccine should be produced, distributed and administered as fast as possible. In 1957 the flu outbreak came earlier than expected and only about a quarter of the vaccine doses were administered before massive outbreaks occurred, and ultimately only about half of the doses were administrated. Efforts to contain the flu pandemic of 1968 were hampered by the fact that it was realised too late that a new strain of flu had appeared, rendering vaccines in use ineffective.

A combined approach was considered to be the only way to immunise the whole population successfully before the next flu season. Furthermore full public funding was the only means of ensuring the availability of vaccines to all citizens. The cost of approximately USD 135 million would be small in comparison with the human and economic costs of past pandemics (USDHEW, 1976; Wade, 1976; Neustadt and Fineberg, 1978; Dowdle, 1997). The 1957 and 1968 pandemics caused about 45 and 50 million cases of influenza and resulted in the loss of about 70 000 and 33 000 lives, respectively. The total economic cost due to death and disease, health care costs and loss of productivity was USD 7 billion in 1957 and USD 3.9 billion in 1968 (US GAO, 1977; Silverstein, 1978; Bernstein, 1985).

The White House Office of Management and Budget (OMB) prepared a briefing paper for President Ford. It raised three main questions, relating to the probability that swine flu would reappear, the seriousness of the epidemic should it come, and whether the scientific community fully agreed with the recommendation made in Dr Sencer's memorandum (Neustadt and Fineberg, 1978; Silverstein, 1978).

Before announcing his decision on 24 March, President Ford requested a meeting with the nation's top influenza and public health experts. Many of the scientists at the meeting thought that the vaccine was safe, that there was little to lose and that it was 'better to be safe than sorry' (Neustadt and Fineberg, 1978). Consequently, the experts voted unanimously in favour of proceeding with the immunisation campaign. Immediately after the meeting, President Ford requested Congress to appropriate USD 135 million for producing vaccines to inoculate the entire US population (US GAO, 1977; Neustadt and Fineberg, 1978; Bernstein, 1985). Later the President stated:

> 'I think you ought to gamble on the side of caution. I would rather be ahead of the curve than behind it' (Neustadt and Fineberg, 1978).

Congress approved the funds with little debate, and the final bill was signed some four months after the initial outbreak of swine flu at Fort Dix (Neustadt and Fineberg, 1978; Silverstein, 1978; Reitze, 1986).

There are some indications that the consultation process leading up to President Ford's decision did not give proper attention to alternative options and dissenting opinions. Many of the scientists consulted by President Ford noted that the discussions felt *pro forma* and that President Ford seemed already to have reached a decision (Boffey, 1976; Silverstein, 1978).

There was little doubt that Congress would respond positively to the President's request to appropriate money for producing vaccines in the face of unknown dangers (Silverstein, 1978). However, Bernstein (1985) argues that the hearings in Congress were carefully staged and that dissent was excluded. Only a few voices questioned the programme during hearings in the House of Representatives. For instance consumer advocate Ralph Nader's Health Research Group claimed that everyone was being overly alarmist, and hinted at some sort of federal-scientific plot to waste taxpayers' money. Democratic congressmen Henry Waxman of California and Andrew Maguire of New Jersey also spoke critically, implying that a potential 'rip-off' might be in the making, giving huge profits to the vaccine manufacturers (Silverstein, 1978; Garrett, 1994).

Two studies had also become available, indicating that the swine flu virus was not as virulent as had been feared. In England, Beare and Craig (1976) had injected six volunteers with the virus and only four had developed minor symptoms. They concluded that the virus was not especially contagious, a pandemic was very unlikely, and mass immunisation was unnecessary.

These results were supported by a study in the US on monkeys, which suggested that the virus would cause only a 'mild disease' (Silverstein, 1981; Neustadt and Fineberg, 1978; Edsall, 1979). According to *Medical World News* (1977), the results of the British study were known to the programme scientists, and according to Dr Sencer the programme was reconsidered three times: after the field trials; just before the President's push for money; and finally when the programme was suspended (Neustadt and Fineberg, 1978).

2.5.2 Evidence of a false positive

Although the mass immunization programme got off to a good start, the programme soon ran into a series of setbacks that delayed the inoculation process. Eventually, concerns over a possible link between the swine flu vaccination and an outbreak of a rare neurological disease, Guillain-Barré Syndrome (GBS), led the CDC to suspend the programme after only a fraction of the vaccine had been administered. By mid-December 1976, the CDC had received reports of 107 cases of GBS, including six deaths. The evidence indicated that the incidence of the disease was higher in the part of the population that had received the swine flu vaccine (one case in 100 000–200 000) compared to those who had not (one case in more than a million). An option was left open to resume immunisation if the swine flu pandemic in fact occurred in the US but swine flu did not reappear anywhere in the world during the winter of 1976–1977. The media's verdict on the swine flu immunisation programme was harsh, and allegations of incompetence and mismanagement of public funds were common (Neustadt and Fineberg, 1978; Silverstein, 1978; Dowdle, 1997; Reitze, 1986).

2.5.3 Costs and benefits

Besides the non-monetary costs in life and personal injuries due to the vaccine's side effects, the US Department of Health, Education and Welfare spent over USD 100 million on the mass immunisation programme, and state and local agencies are estimated to have spent USD 24 million (US GAO, 1977; Silverstein, 1978). In addition to these direct costs, the federal government had to pay settlements and legal fees related to the over 4 100 lawsuits that followed in the wake of the immunisation programme. Most of these lawsuits either alleged that the swine flu vaccine had caused GBS, or that it was responsible for various other illnesses including rheumatoid arthritis and multiple sclerosis. The indemnities paid by the government totalled USD 83 million which, when added to the administrative and legal costs associated with the law suits, probably equalled the USD 100 million spent directly on the immunisation programme (Kurland et al., 1984; Reitze, 1986; Christoffel and Teret, 1991).

On a positive note, much was learned about the preparation, standardisation and administration of vaccines, as well as adverse reactions, whole and split vaccines and the adjustment of dosage according to age. Besides these benefits, some of the more puzzling findings from previous vaccine studies were clarified (Dowdle, 1997). After the events of 1976, research was initiated on the causes and possible treatment of GBS in medical institutions throughout the US (Silverstein, 1978), and a nationwide disease surveillance system was established (Neustadt and Fineberg, 1978).

2.6 Food irradiation and consumer health

Food irradiation was first applied on strawberries in Sweden in 1916 and the first patents were taken on this technology in 1921 in the US. Three kinds of radiation are typically used to sterilise food: gamma rays, X-rays and electron beams. And there are three main purposes for irradiating food: killing insects and other pests in grain, fruit, and spices; delaying ripening of fruit and vegetables; and reducing bacterial contamination of meat, chicken, seafood and spices (SOU, 1983; MAFF, 1986; WHO, 1981, 1999; SCF, 2003).

Gamma irradiation uses radioactive elements, whereas X-rays and electronic beams use ordinary electricity. However, all three perform a similar function (Environmental Nutrition, 2000; Pothisiri et al., 1991; WHO, 1993). Over the years, the FDA has issued a number of clearances to use this technology on food but in the late 1960s concerns were raised about the safety of food irradiation and no additional approvals were given for the next twenty years. At the beginning of the 1980s, the FDA authorised irradiation for several different kinds of foods, despite consumer reluctance to buy irradiated food (Meeker-Lowry and Ferrara, 1996; Adams, 2000). Consumer resistance is seen by many as the main reason why food irradiation is not widely applied (Thorne et al., 1991).

The failure of regulatory agencies to approve and accept food irradiation, despite evidence of its safety for consumers, constitutes a false positive. Similar evidence of safety was not identified for either the potential risks to worker health and safety from irradiating food, or the potential increased threat of terrorism that could follow from implementing large-scale food irradiation. Since these concerns cannot be ruled out, the perspective of this case is limited to consumer health.

2.6.1 Responses to early warnings

Serious progress in developing food irradiation technology first began in the 1950s when President Eisenhower announced his 'Atoms for Peace' programme, and extensive research and funding went into food irradiation from the US Department of Defence. Irradiation was approved for use in inhibiting potato sprouting and disinfecting wheat in 1963. Irradiation of can-packed bacon was approved in 1963 but this permission was subsequently withdrawn in 1968, after a review of the research found adverse effects in animals fed irradiated food, such as fewer surviving offspring (Webb et al., 1987).

2.6.2 Evidence of a false positive

Several international and national committees have evaluated the safety and 'wholesomeness' of food irradiation since the beginning of the 1980s, and all have concluded that irradiated foods are safe for consumers (SOU, 1983; MAFF, 1986; WHO, 1981, 1999; SCF, 1998, 2003; US FDA, 1986; NFA, 1986). However, this has not led to a general acceptance of food irradiation, and a variety of concerns have been raised through the years.

One of these concerns is about so-called radiolytic products, which form in irradiated food. Some of these radiolytic products are unique for irradiation (SOU, 1983; US FDA, 1986). Opponents of food irradiation argue that some of these chemical changes are known to be mutagenic and carcinogenic, and that free radicals — believed to be cancer promoters — are produced during irradiation (Webb et al., 1987; Public Citizen and Grace, 2002; Epstein, 2002).

Numerous toxicity studies have been performed on a range of animals, using a wide variety of different kinds of irradiated food, and examining different doses and endpoints. According to the World Health Organization, these studies have not provided evidence of harmful effects (WHO, 1981, 1994 and 1999). A number of highly controversial studies have indicated changes in the number of polyploid cells in rats, monkeys and even malnourished Indian children fed freshly irradiated wheat (US FDA, 1986; WHO, 1994; Thayer, 1990; Vijayalaxmi and Rao, 1976; Bhaskaram and Sadasivan, 1975; Vijaylaxmi, 1975 and 1978). The WHO (1994) states, however, that 'No effects were seen showing any consistent pattern or trend, and the studies were overwhelmingly negative indicating that the consumption of irradiated food … had no toxicological effect'.

The WHO (1981, 1994 and 1999) and a British Government Advisory Committee on Irradiated and Novel Foods (MAFF, 1986) concluded that virtually all the radiolytic products found in both low- and high-dose irradiated food were either naturally present in food or produced in thermally processed food. In the US, radiation doses of up to 1 kilogray (kGy) have been approved on the basis that the concentration of radiolytic products is too small to be of toxicological significance (US FDA, 1986).

Others have argued, however, that irradiated food has never been rigorously tested (Bloomfield and Webb, 1990). It was originally thought that the radiolytic compounds could and should be tested according to the accepted protocols for food additives. This would require, however, that all of the chemicals be identified, isolated and fed separately to laboratory animals. Because of the difficulties of isolating and purifying the numerous radiolytic products, this approach is simply impossible (Bloomfield and Webb, 1990; WHO, 1994). Attempts to apply a safety margin by giving animals food irradiated at high radiation doses were also unsuccessful because the animals simply refused to eat the unpalatable food (US FDA, 1986; Bloomfield and Webb, 1990). Because of these problems testing has been done without safety margins, which may miss underlying or long-term safety hazards, according to Webb et al. (1987).

Concerns have also been raised that food irradiation could benefit irradiation-resistant bacteria, which would then grow exponentially after the food has been irradiated. It has been argued that the consequences of this are unknown (Murray, 1990; Tritsch, 2000). However, the WHO (1981, 1994 and 1999), MAFF (1986) and the Scientific Committee on Food (SCF) (2003) have all found no evidence of selective destruction and potential development of mutations. On the contrary both the WHO (1994) and the SCF (2003) state that irradiation has been found to cause loss of virulence and infectivity, as mutants are usually less competitive and less adapted.

Discussion about the safety of food irradiation has focused in particular on the chemical class of cyclobutanones and the question of whether or not they are carcinogens (Public Citizen and Grace, 2002; Epstein, 2002). Cyclobutanones are created only when fat-containing food is radiated (Delincée and Pool-Zobel, 1998; Delincée et al., 2002). Reports by both the FDA and the WHO have been criticised heavily for ignoring the issue of cyclobutanones (Public Citizen and Grace, 2002; Epstein, 2002). Concern was originally raised after studies by Delincée and Pool-Zobel (1999) and Delincée et al. (1999) found that 2-Dodecylcyclobutanone (DCB) was genotoxic. The identity and purity of the compound had not been verified prior to the studies, however, which the authors argue cast doubts on the results originally obtained (Delincée and Pool-Zobel, 1998).

A further concern relates to reducing the nutritional value of foods. Irradiation treatment does not significantly alter the nutrient value and digestibility of fatty acids and macronutrients, such as proteins, fats and carbohydrates (MAFF, 1986; WHO, 1981, 1999; Bloomfield and Webb, 1990) but loss of micronutrients does increase with radiation doses. The rate of loss differs substantially depending on the food and nutrients. Therefore these losses must be assessed for each food and for each vitamin specifically. According to the WHO (1981), thiamine (B1) is the only vitamin that should be considered in terms of dietary intake because it is radiation sensitive and the main sources of thiamine in the diet (e.g. pork) are candidates for high-dose irradiation.

In 1981, the World Health Organization (WHO) conducted a review of the studies performed with doses below 10 kGy and found that irradiated food has been conclusively demonstrated to be safe from the standpoint of toxicological, nutritional or microbiological risks to human health. This document has later been described as the culmination and turning point in the scientific evaluation of the safety of irradiated foods (WHO, 1993; 1994; Urbain, 1993). Following this report, the FDA began a systematic review of the over 400 toxicological studies on mice, rats, dogs, pigs and monkeys available up to 1982. Only five studies were considered to have been properly conducted in accordance with 1980 toxicological standards and were able to stand alone in support of safety (US FDA, 1986; WHO, 1994). Despite several years of consumer reluctance to eat irradiated food, the FDA decided to allow irradiation of spices and seasonings in 1983 while requiring that irradiated whole foods be labelled as such. Since then the FDA has further allowed irradiation of fruits, vegetables, pork, poultry, red meat and eggs (Meeker-Lowry and Ferrara, 1996; Webb et al., 1987; US FDA, 1997; USDA, 1999a, 1999b; Epstein and Hauter, 2001).

2.6.3 *Costs and benefits*

Complete estimates of cost and benefits of irradiated food are not available. The costs of food-borne diseases in health and economic terms, and the potential role of food irradiation in reducing those costs, are not well documented (WHO, 1993). Robert and Murrell (1993) estimated that the economic losses in the US from food-borne pathogenic diseases are up to USD 5.3 billion annually. A number of factors affect these cost estimates, however, such as the number of estimated cases and estimated deaths, the severity of the illness and the type of food-borne disease (Todd, 1993). Cost-benefit estimates done by the US Department of Agriculture indicate that the benefits would be likely to exceed costs by a ratio of 2.2–2.8 to 1 and that the irradiation of just 10 % of poultry production would produce annual savings in the US of up to USD 50 million (WHO, 1993).

Several cost-benefit analyses have assessed the feasibility of using irradiation in developing countries. Most have indicated large potential benefits, especially with regard to increased shelf life and reduced post-harvest losses (Grünewald, 1973; Al-Bachir et al., 1993; Kahn, 1993; Moretti, 1993; Neketsia-Tabire et al., 1993). A number of challenges would have to be addressed, however, before developing countries can benefit from food irradiation. For the technology to be used efficiently requires, for instance, that the necessary infrastructure be established (WHO, 1993; Hackwood, 1991).

One of the frequently cited benefits of food irradiation is that it reduces the use of chemicals, for example use of ethylene dibromide in controlling insects and mould infestation in grain (WHO, 1993; Grünewald, 1973; Piccioni, 1987). The plausibility of this argument is, however, unclear (Webb et al., 1987; EC, 2002a and 2002b; Piccioni, 1987).

Nestlé (2007) has voiced concerns that extensive irradiation could reduce attention to the sources of pathogenic contamination of food and primary prevention. On the other hand, it could be argued that public reluctance to accept food irradiation may actually focus greater attention on improved sanitation in manufacturing and food preparation. It is unclear, however, whether or not this has been the case.

2.7 Discussion

This chapter aims to identify false positives and investigate lessons that could be learned to improve future decision-making — to minimise both false positives and false negatives. In this final section, we discuss the results of our analysis, focusing on:

1. when and why precautionary regulatory action was taken;

2. when and why it was realised that this precautionary action was unnecessary;

3. the resulting cost and benefits.

Finally, we discuss what lessons can be learned about false positives, why we were only able to identify four false positives, and the policy implications of our analysis.

2.7.1 *False positives and early warnings*

There are few parallels between the four cases in terms of when and why each perceived risk was falsely believed to be real. This is a lesson in itself: each risk is unique, as is the science and politics behind it. A flexible approach to science and policy is therefore needed, adapted to the nature of the problem.

In the swine flu case, concern was mainly raised because an 'early warning' of an outbreak fitted perfectly into three widely held theories about influenza cycles. Perhaps too much faith was placed on the ability of science to foresee the impending outbreak in this case. Even with hindsight, however, it is not at all obvious that the decision to mass immunise the American population was the wrong decision or an over-reaction considering the scientific understanding at the time and the stakes involved. Much contemporary scientific knowledge indicated that swine flu could return and had it done so it could potentially have killed millions. Even with the benefit of current knowledge, the science behind predicting flu epidemics remains very uncertain. One lesson from this case could be the need to be open to dissenting opinions and to discuss their validity before making decisions. Swine flu did not return and this was recognised almost immediately after the flu season, reducing the negative impact of this false positive.

In the case of saccharin, concern was triggered by new scientific knowledge indicating that saccharin causes bladder cancer in rats. There is now a general scientific consensus that saccharin does not have the same effect on humans, although some minority opinions still exist. While it proved unnecessary, it would be wrong to say that the decision to label saccharin as a cause of cancer in laboratory animals was unjustified at the time preventive action was taken. For instance there is no way decision-makers could have known that rats would be the only species in which saccharin causes bladder cancer. Nor could they have known that scientific evidence would emerge indicating that the mechanisms by which it operates in rats appear to be irrelevant in humans. Only the often slow evolution of our scientific understanding gave decision-makers reasons to eliminate the labelling requirements for saccharin.

In both of these cases, it was virtually impossible for scientists, regulatory agencies or decision-makers to know or foresee that the potential risk was not real. The mechanism by which saccharin causes cancer in rats is so specific to this one laboratory animal that no one could have known that it would be irrelevant for humans; even today these mechanisms are disputed. Similarly, no one could know whether the swine flu would reappear or was smouldering in sub-clinical form in the public and would return in epidemic proportions when the flu season began.

The situation was similar with respect to Southern corn leaf blight (SCLB). In that case, the USDA correctly anticipated that the SCLB would return but could not have anticipated that it would not have the same devastating effect as the year before, probably due to a change in weather conditions.

Food irradiation stands out because the publication of a WHO review of existing literature in 1981 created a general consensus regarding the safety of the technology. Even before that, the WHO and others had endorsed and used food irradiation and there had been general consensus about its safety for some time. Nevertheless, the decision to withdraw permission to irradiate can-packed bacon seems completely reasonable in view of the fact that studies had found adverse effects in animals fed irradiated food. At that time there was a serious need for scientific studies investigating the safety of food irradiation.

It is also noteworthy that the false positive of food irradiation had little impact on consumers because alternatives were available to achieve the same outcome, such as improved sanitation in the manufacturing processes and good hygiene. Hence it seems that the availability of alternatives can minimise the total impact of a false positive.

2.7.2 *The costs of false positives*

The costs of the false positives identified were mainly economic, although the actions taken to address swine flu did lead to some unintended deaths and human suffering, and diverted resources from other potentially serious health risks. Clearly, however, determining the **net costs** of mistaken regulatory action requires a complete assessment of the positive and negative impacts of the regulation, including the costs and benefits of using alternative technologies and approaches.

The case of irradiation illustrates this point. There is no doubt that society could benefit substantially from preventing the numbers of food-borne illnesses but it is not obvious that food irradiation is the right answer. An alternative could be improving animal welfare to reduce pathogenic contamination, improving sanitation and conditions in manufacturing processes, and good hygiene (which manufacturers and governments should already be enforcing). Indeed, food irradiation provides an obvious opportunity to cover bad practices. Poor hygiene practices in food production have been widely documented (Webb et al., 1987; Bloomfield and Webb, 1990; Epstein and Hauter, 2001). And since existing regulations and requirements should guarantee that the public receives safe food even without the use of irradiation, the public would have no immediate benefit from food irradiation but would suffer the adverse health impacts if any existed (Tritsch, 2000; Begley and Roberts, 2002). Addressing the root causes of pathogenic contamination in food supply would probably lead to more sustainable prevention actions.

2.7.3 *The precautionary principle, science and technological innovation*

Opponents of the precautionary principle often argue that the principle stifles technological innovation (e.g. Wildavsky, 1995; Mazur, 2004). It appears, however, that the four false positives identified actually sparked innovation within industry and within government.

Innovation experts have noted that regulation may result in technological innovation because stringent regulations indirectly cause dramatic changes in technology and often allow new firms or entrants, thereby displacing dominant technologies (Ashford et al., 1985; Ashford, 1993; Porter, 1991). This phenomenon can be observed in the case of saccharin, whose existence was a major deterrent to the development of other, more costly non-caloric sweeteners.

The mistaken actions to address swine flu likewise resulted in an unprecedented nationwide disease surveillance programme and the government learned how to mobilise resources quickly in the face of an apparent public health threat (Reitze, 1986). Such knowledge is particularly important in the context of new concerns related to bioterrorism.

In all the four cases, regulatory action indirectly sparked a large amount of research in previously unexplored fields of science. Saccharin and food irradiation are often mentioned as being some of the most tested hazards ever, and the swine flu case generated new and far better understanding of GBS — a disease that was previously little understood. The SCLB case sparked research concerning gene diversity and gene vulnerability.

Hrudey and Leiss (2003) state that:

> 'If a hazard is important enough to invoke precaution as a justification to prioritise action, it must also be important enough to understand better'.

This definitely seems to have been the case in these four cases.

2.7.4 Why so few false positives?

Given the vast amount of literature raising concerns that precautionary and preventive policies lead to false positives, it is surprising that so few were identified.

Clearly, interpreting scientific literature includes some level of subjectivity. Employing the definitions used in this study, different researchers might come up with slightly different categorisations of the 88 cases reviewed and the number of false positives could differ from analysis to analysis. But other studies might also adopt different definitions. For example, some analysts might argue that the concept of a false positive includes situations where an agency conducts a high-profile investigation, makes a public statement or runs an advocacy campaign and this results in concerns that lead to unnecessary actions.

Analysts may also vary in their interpretation of the difference between categories such as 'the jury is still out' and 'false positive', as well as in terms of the types of evidence they review and how they value uncertainties. The science informs decisions about whether a risk is real or not (does it cross some threshold of 'acceptable risk'?). But these are partly policy judgements, based on considerations such as levels of uncertainty and the economic consequences of acting or not acting.

Similarly, the question of whether a regulation is excessive to address a certain risk is a controversial and highly subjective question and difficult to characterise. For example, in current science-policy debates some scientists argue that precautionary regulation of phthalates in children's products or bisphenol-A (BPA) in items that come into contact with food may represent 'over-regulation' based on current understanding. Assessing politically defined 'safe' levels of exposure is incredibly complex given the subtle nature of many product-based exposures, lack of understanding of cumulative and interactive exposures, limited information about exposure pathways and human epidemiological data, and inadequate understanding about critical windows of vulnerability. Given significant uncertainties in such cases, a qualitative synthesis that considers the totality of the evidence of potential exposure (from body burden studies), hazard information, and information on potentially safer alternatives, may be the soundest approach to science for addressing complex risks and sufficient to spur innovation in safer materials (Sarewitz, et al., 2010).

To address concerns about subjectivity, we have attempted in this chapter to make our categorisation and evaluation as transparent as possible so that other researchers can repeat the analysis with these or other cases. Given the large number of cases examined, however, we feel confident in our core findings: that many of the cases identified as false positives are in fact 'mistaken false positives' and that the number of genuine regulatory false positives identified in the literature is small. Cox (2007) and Hansen et al. (2007b) discuss this issue in more detail. In examining the regulatory landscape, the analysis also suggests that common concerns about over-regulation are not justified, based on empirical evidence. As such, a more nuanced approach to policy analysis is needed.

The scarcity of genuine false positives compared to the large number of 'mistaken false positives' could also be the result of a deliberate strategy in risk communication. Several references and leaked documents (e.g. Martin, 2003) have shown that some regulated parties have consciously recruited reputable scientists, media experts and politicians to call on if their products are linked to a possible hazard. As an automatic response or first barrier of defence, these experts are then sent to different news sources to denounce any risk or to manufacture uncertainty about the risk, regardless of whether the risk is real or not (Barnes and Bero, 1998; Rampton and Stauber, 2001; Michaels, 2005). Manufacturing doubt, disregarding scientific evidence of risks and claiming over-regulation appear to be a deliberate strategy for some industry groups and think tanks to undermine precautionary decision-making.

A complementary explanation could be that current decision-making processes in public health and environmental regulation have focused on minimising false positives, which increases the probability of false negatives. Shrader-Frechette (1991) argues that this preference for false negatives arises because it appears to be more consistent with scientific practice. Furthermore, many risk assessments and impact analyses are conducted by those with a vested interest in a particular technology. In such cases, Shrader-Frechette argues that assessors typically underestimate risk probabilities at least in part because it is difficult to identify all hazards and because unidentified risks are usually assumed to be zero.

According to Ozonoff and Boden (1987), institutional reasons also explain why agencies tend to favour not responding to identified effects. First, acknowledging an effect means that the public would expect the agency to do something and might even accuse the agency of not doing enough about the situation in the first place. Second, the solutions to the problem often conflict with other interests, such as economic development. Third, agencies know that affected industries may challenge the agency, accusing it of creating hysteria or negatively impacting business (Ozonoff and Boden, 1987).

In addition to the scientific and political reasons limiting false positives, several aspects of legal and regulatory decision-making in the US and EU, such as judicial review or cost-benefit analysis, greatly influence the steps that agencies must fulfil before taking precautionary actions and how much precaution can be applied. The slow pace of the regulatory process often precludes swift precautionary action on uncertain hazards, unless they pose imminent risks of severe harm. The pace is determined both by regulatory requirements and, especially in the US, by court interpretations of federal policies. The regulatory process has become more rigid and burdensome since the 1970s, leading to the 'ossification' of rule-making (McGarity, 1990).

While avoiding false positives is important, we believe that too little attention is being paid to avoiding false negatives in regulatory decision-making. Decision-makers often worry about taking too much precaution but seem to lack similar concerns about not taking enough. This tendency has developed despite evidence that the costs of not taking precautionary action are substantial — both economically and socially (e.g. EEA, 2001) and despite the many identified benefits of preventive regulation with regards to health, safety and the environment (Ashford, 1993; Ackerman and Heinzerling, 2004). Furthermore, compared to false negatives, the impact of false positives may be more short term (over-regulation can be quickly caught) and affect a relatively small number of actors.

A decision to act on limited knowledge about a hazard may ultimately turn out to have been due to a false positive. But if it spurs innovations, stimulates new economic forces, and raises awareness about sustainability then it may still be judged to have been worthwhile. As a result, there is a need to develop more nuanced policy analysis methods that give equal weight to avoiding both false negatives and false positives. Combining a more precautionary approach with proper assessment of impacts and alternatives in a more flexible management process could minimise the number of false positives and negatives and maximise society's benefits from false positives.

2.7.5 Lessons learned

Understanding and learning from past mistakes is essential for improving decision-making about public health and the environment. Numerous important lessons can be learned from each of the false positives identified. Some are specific to the case and cannot easily be transferred to other risk situations. The focus here is on experience that is applicable to other cases and can be generalised. These lessons are important to avoid both false positives and false negatives.

Lesson 1: the cases of swine flu and saccharin show how important it is to **be open and honest about disagreement and not suggest that there is consensus when there is not**. Even though scientists and others might think that reaching consensus is a goal in itself, disagreement can help provide the decision-maker with a broad picture of alternative explanations of the science, what is at stake and which options and alternatives are available before making a decision.

Lesson 2: following on the previous lesson, it is important to **be transparent about what is known or not known and about uncertainties and make sure that these are apparent in communication** between scientists, regulatory authorities, politicians and the public. Alternative courses of action should be considered with an open mind and limits should not be placed on the range of alternatives in advance.

Lesson 3: the cases of food irradiation and saccharin indicate that **the availability of options minimises the total impact of false positives**. An alternatives assessment that considers the pros and cons of other courses of action (including no action) is critical to avoid risk-risk trade-offs. To reduce the potential negative impact of committing false positives, adequate resources should be made available to consider alternative courses of action. In conducting assessments attention must be paid to defining 'safer' alternatives.

Lesson 4: **particular care is needed when introducing a new substance or technology at a large scale** because of the risk of 'unknown unknowns'. In two of the four cases (swine flu and Southern leaf corn blight), the precautionary action initially taken had unintended consequences because of events that could not have been anticipated and had severe consequences because of its widespread application.

Lesson 5: **initiating and funding research to increase understanding and reduce uncertainties should supplement other risk-reducing regulatory measures** and not be seen as a regulatory measure in itself. In none of the cases could more scientific research have prevented the false positives from happening; indeed, in some of the cases too much trust was put on the capability of science to demonstrate effects.

Lesson 6: **precautionary actions (both necessary and unnecessary) can lead to innovation in science, policy and technology**. Decision-makers should take this into consideration when they consider regulating a potentially harmful technology and choose regulatory measures that can spark innovation even if the precautionary action proves unnecessary.

Lesson 7: it is necessary to **be flexible in decision-making processes**. The decision-making process should be designed with re-evaluation as a key component, so that decisions can be altered in the light of new knowledge. It is also important that the regulators are prepared to alter their initial decisions about risks.

In conclusion, the analysis has shown that fear of false positives should not be a rationale for avoiding precautionary actions where warranted. False positives are few and far between as compared to false negatives and carefully designed precautionary actions can stimulate innovation, even if the risk turns out not to be real or as serious as initially feared. Overall, the analysis has demonstrated the need for new approaches to characterising and preventing complex risks that move debate from the 'problem' sphere to the 'solutions' sphere (Sarewitz, et al., 2010). By learning from the lessons above, more effective preventive decisions can be made in the future.

Table 2.3 Overview — the 88 case studies claimed to be regulatory false positives

	Subject	**Risk category**
1	Acid rain (Bast et al., 1994, Wildavsky, 1995)	Real risk
2	Acrylamide (Löfstedt, 2003)	'The jury is still out'
3	Aflatoxins (Majone, 2002)	Real risk
4	Agent Orange (Milloy, 2001)	Real risk
5	Air pollution in the USA (Whelan, 1993)	Real risk
6	Alar (Fumento, 1990; Wildavsky, 1995; Lieberman and Kwon, 1998)	Risk-risk trade-off
7	Amalgam dental fillings (Lieberman and Kwon, 1998)	Unregulated alarm
8	Antibiotics cause breast cancer (Kava et al., 2004)	'The jury is still out'
9	Asbestos in hair dryers (Lieberman and Kwon, 1998)	Unregulated alarm
10	Asbestos in schools (Lieberman and Kwon, 1998)	Real risk
11	BAM (From, 2004)	'The jury is still out'
12	Ban of Coca Cola (Whelan, 1999)	'The jury is still out'
13	Bendectin (Marchant, 2003)	Unregulated alarm
14	Benzene in Perrier Water (Lieberman and Kwon, 1998)	Real risk
15	Bovine Somatotropin (bST) (Lieberman and Kwon, 1998)	'The jury is still out'
16	Breast implants (Fumento, 1996; Milloy, 2001)	'The jury is still out'
17	BSE and vCJD (Adams, 2000)	'The jury is still out'
18	Busy streets and childhood cancer (Milloy, 2001)	'The jury is still out'
19	Cellular phones (Lieberman and Kwon, 1998; Graham, 2004)	'The jury is still out'
20	Cheeseburgers and Cardiovascular Disease (Kava et al., 2004)	'Too narrow a definition of risk'
21	Chemical Mace (Mazur, 2004)	Unregulated alarm
22	Chemicals in cosmetics (Kava et al., 2004)	'The jury is still out'
23	Chlormequat and Cerone (IMV, 2003)	'The jury is still out'
24	Coffee and pancreatic cancer (Lieberman and Kwon, 1998)	Unregulated alarm

Table 2.3 Overview — the 88 case studies claimed to be regulatory false positives (cont.)

25	Cyclamates (Lieberman and Kwon, 1998)	'The jury is still out'
26	DDT and malaria (Wildavsky, 1995; Lieberman and Kwon, 1998)	Real risk
27	DEHP (Milloy, 2001)	'The jury is still out'
28	DES in beef (Lieberman and Kwon, 1998)	Real risk
29	Destruction of the ozone layer (Bast et al., 1994)	Real risk
30	Dioxin (Gough, 1994)	Real risk
31	Electric blankets (Lieberman and Kwon, 1998)	'The jury is still out'
32	Electromagnetic fields (Lieberman and Kwon, 1998)	'The jury is still out'
33	Endocrine disrupting chemicals (Maxeiner and Miersch, 1998)	'The jury is still out'
34	Ethylene dibromide (Lieberman and Kwon, 1998)	Risk-risk trade-off
35	Fen-Phen and heart value disease (Milloy, 2001)	Real risk
36	Fluoridated water (Lieberman and Kwon, 1998)	Unregulated alarm
37	Food irradiation (Lieberman and Kwon, 1998)	False positive
38	Formaldehyde (Maxeiner and Miersch, 1998)	Real risk
39	Functional food (Marchant and Mossman, 2002)	'The jury is still out'
40	Genetically modified organisms (Miller and Conko, 2001)	'The jury is still out'
41	Global warming (Bast et al., 1994; Wildavsky, 1995)	Real risk
42	Hair dyes and cancer (Lieberman and Kwon, 1998)	'Too narrow a definition of risk'
43	Homocysteine causing atheroschlerosis (Milloy, 2001)	Real risk
44	Hormone replacement therapy and breast cancer (Milloy, 2001)	Real risk
45	Hypoxia: dead zones in the Gulf of Mexico (Avery, 1999)	Real risk
46	Laundry detergents (Mazur, 2004)	Unregulated alarm
47	Love Canal (Wildavsky, 1995; Lieberman and Kwon, 1998)	Real risk
48	4-MBC in sun-lotion (Politiken, 2001)	Risk-risk trade-off
49	Mercury in fish (Mazur, 2004)	Real risk
50	MMR vaccines (Bate, 2001)	Unregulated alarm
51	Monarch butterfly and Bt corn (Marchant, 2003)	'The jury is still out'
52	Monosodium glutamate (MSG) (Mazur, 2004)	Real risk
53	Nightlights and leukemia (Kava et al., 2004)	'The jury is still out'
54	Nitrilotriacetic acid in detergents (Mazur, 2004)	Risk-risk trade-off
55	Nitrites (Sodium Nitrite) (Lieberman and Kwon, 1998)	Risk-risk trade-off
56	Nuclear power (Bast et al., 1994; Graham, 2004)	'Too narrow a definition of risk'
57	Oral contraceptive pill scare (Adams, 2000)	Real risk
58	Perce in a Harlem school (Lieberman and Kwon, 1998)	'The jury is still out'
59	Pesticides (Whelan, 1993)	Real risk
60	Phenolphthalein (Milloy, 2001)	'The jury is still out'
61	Polybrominated biphenyls (Whelan, 1993)	'The jury is still out'
62	Polychlorinated biphenyls (Whelan, 1993)	Real risk
63	PVC blood bags and cancer (Milloy, 2001)	'The jury is still out'
64	Radon gas in houses poses a health risk (Miloy, 2001)	Real risk
65	Red dye number 2 (Lieberman and Kwon, 1998)	'The jury is still out'
66	Saccharin (Lieberman and Kwon, 1998)	False positive
67	Second hand smoke and breast cancer (Milloy, 2001)	'Too narrow a definition of risk'
68	Second hand smoke and lung cancer (Matthews, 2000)	Real risk
69	Second hand smoke causing hearing problems (Milloy, 2001)	'The jury is still out'
70	Soda causes esophageal cancer (Kava et al., 2004)	'The jury is still out'
71	Spermicides and birth defects (Mills, 1993)	Unregulated alarm
72	Superfund's abandoned hazardous waste sites (Milloy, 2001)	Real risk
73	2,4,5-T (Lieberman and Kwon, 1998)	'The jury is still out'
74	Taconite pollution (Mazur, 2004)	'Too narrow a definition of risk'
75	Teflon causes health problems in humans (Kava et al., 2004)	'The jury is still out'
76	The 'Cranberry Scare' of 1959 (Wildavsky, 1995; Lieberman and Kwon, 1998; Mazur, 2004)	'The jury is still out'
77	The baby bottle scare (Kamrin, 2004)	'The jury is still out'
78	The Dalkon Shield (Milloy, 2001)	Unregulated alarm
79	The Peruvian outbreak of cholera (Bate 2001; Milloy, 2001)	'The jury is still out'
80	The Southern leaf corn blight (Lawless, 1977)	False positive
81	The swine flu (Marchant, 2003)	False positive
82	Three Mile Island (Lieberman and Kwon, 1998; Graham, 2004)	'Too narrow a definition of risk'
83	Times beach, Missouri (Wildavsky, 1995; Lieberman and Kwon, 1998)	Real risk
84	Toxins in breast milk causing harm to babies (Ross, 2004)	Risk-risk trade-off
85	Trichloroethylene (TCE) (Jaeger and Weiss, 1994)	Real risk
86	Tris (Lieberman and Kwon, 1998)	Unregulated alarm
87	Video display terminals (Lieberman and Kwon, 1998)	'Too narrow a definition of risk'
88	Water contamination in Sydney (Clancy, 2000)	Real risk

References

Ackerman, F. and Heinzerling, L., 2004, *Priceless,* The New Press, New York.

Adams P., 2000, 'Where's the beef? An update on meat irradiation in the USA', *Radiation Physics and Chemistry*, (57) 231–233.

Al-Bachir, M., El Den Sharabi, N. and Ayman Midani, M., 1993, *Economic feasibility study of onion and potato irradiation in the Syrian Arab Republic,* Proceedings of an International Symposium on Cost-Benefit Aspects of Food Irradiation Processing, Jointly Organized by the International Atomic Energy Agency, the Food and Agriculture Organization of the United Nations and the World Health Organization and Held in Aix-En-Provence, 1–5 March 1993. Vienna: International Atomic Energy Agency, 159–163.

Ashford, N.A., 1993, 'Understanding technological responses of industrial firms to environmental problems: Implications for government policy', in: Fisher, K., Schot, J.: *Environmental Strategies for Industry: International Perspectives on Research Needs and Policy Implications*, Island Press, pp. 277–307.

Ashford, N.A., Ayers, C. and Stone, R.F., 1985, 'Using regulation to change the market for innovation', *Harvard Environmental Law Review*, (9) 419–466.

Avery, D., 1999, 'Hypoxia: The dead zone lives in Big Government and Bad Science Ten Case Studies' in: Cohen, B.R., Giovanetti, T.A. (eds), *Regulatory Abuse*, Institute for Policy Innovation and Lexington Institute, 9–10.

Bailey, R. (ed.), 2002, *Global Warming and Other Eco-Myths*, Prima Publishing, Roseville, California.

Barnes, D.E. and Bero, L.A., 1998, 'Why review articles on the health effects of passive smoking reach different conclusions', *Journal of the American Medical Association*, (279/19), 1 566–1 570.

Bast, J.L., Hill, P.J. and Rue, R.C., 1994, *Eco-sanity A Common-Sense Guide to Environmentalism*, Madison Books, Maryland.

Bate, R., 2001, *How Precaution Kills: The Demise of DDT and the Resurgence of Malaria*, PRI Luncheon Speech, 25 September 2001 (http://www.pacificresearch.org/press/how-precaution-kills-the-demise-of-ddt-and-the-resurgence-of-malaria) accessed 10 October 2011.

Beare, A.S. and Craig J.W., 1976, 'Virulence for man of a human influenza — a virus antigenically similar to 'classical' swine viruses', *The Lancet*, II: 4.

Begley, S. and Roberts, E., 2002, 'Dishing up gamma rays', *Newsweek*, 27 January, p. 119.

Bergkamp, L., 2002, *Understanding the Precautionary Principle*, Hunton & Williams, Brussels.

Bernstein, B.J., 1985, 'The swine flu immunization program', *Medical Heritage*, (1) 236–266.

Bhaskaram, C. and Sadasivan, G., 1975, 'Effects of feeding irradiated wheat to malnourished children', *American Journal of Nutrition*, (28) 130–135.

Bloomfield, L. and Webb, T., 1990, 'Food Irradiation: A public health issue?', *Journal of Nutritional Medicine*, (1) 75–81.

BMA, 2004, *Mobile phones & health — an update June 2004*, British Medical Association.

BMA, 2001. *Mobile Phones and Health — An Interim Report*, British Medical Association Science Department and the Board of Science and Education (http://bma.eu/images/Mobilephones_tcm27-20881.pdf) accessed 10 October 2011.

Boffey, P., 1976, 'The anatomy of a decision: How the nation declared war on the swine flu', *Science*, (192) 636–641.

CDC, 2004, *FAQs (frequently asked questions) about MMR Vaccine & Autism (Measles, Mumps, and Rubella*), Center for Disease Control (http://www.cdc.gov/vaccines/vpd-vac/combo-vaccines/mmrv/vacopt-faqs-hcp.htm) accessed 10 October 2011.

Christoffel, T. and Teret, S.P., 1991, 'Epidemiology and the Law: Courts and Confidence Intervals', *American Journal of Public Health*, (81) 1 661–1 666.

Clancy, J.L., 2000, 'Sydney's 1998 water quality crisis', *American Water Works Association*, (92) 55–66.

Claus, G. and Bolander, K., 1977, *Ecological Sanity*, David McKay Company, Inc., New York.

Cohen, B.R. and Giovanetti, T.A., 1999, *Big Government and Bad Science Ten Case Studies in Regulatory Abuse*, Institute for Policy Innovation and Lexington Institute.

Colin, N., 1976, 'Behind the politics of influenza', *Nature*, (260) 381–382.

COMARE, 2011, *Fourteenth report — Further consideration of the incidence of childhood leukaemia around nuclear power plants in Great Britain*, Committee on Medical Aspects of Radiation in the Environment, UK Health Protection Agency, London.

Cox, L.A. Jr., 2007, 'Regulatory False Positives: True, False, or Uncertain?', *Risk Analysis*, (27/5) 1 083–1 086.

CSM, 1999, *Report of the working party on MMR vaccine* (http://briandeer.com/wakefield/csm-report.htm) accessed 10 October 2011.

Danish Health Agency, 2000, *Notat om mulige sundhedsrisici ved brug af mobiltelefoner* [In Danish], Sundhedsstyrelsen J.nr./314-6-1999.

Davis, D., 2010, *Disconnect*, Dutton, New York.

Delincée, H., Pool-Zobel, B.L. and Rechkemmer, G., 1999, 'Genotoxicity of 2-dodecylcyclobutanone' in: Knörr M., Ehlermann D.A.E. and Delincée, H. (eds), *Report by the Bundesforschungsanstalt für Ernährung*, BFE-R-99-01, Karlsruhe Bundesforschungsanstalt für Ernährung, (translated from German by Public Citizen, Washington, D.C. February 2001), 1999.

Delincée, H. and Pool-Zobel, B.L., 1998, 'Genotoxic properties of 2-Dodecylcyclobutanone, a compound formed on irradiation of food containing fat', *Radiation Physics and Chemistry*, (52) 39–42.

Delincée, H., Soika, C., Horvatovieh, P., Rechkemmer, G. and Marchioni, E., 2002, 'Genotoxicity of 2-alkylcyclobutanoes, markers for an irradiation treatment in fat-containing food — Part I: Cyto- and genotoxic potential of 2-tetradecylcyclobutanones', *Radiation Physics and Chemistry*, (63) 431–435.

DeStefano, F., Bhasin, T.K., Thompson, W.W., Yeargin-Allsopp, M. and Boyle, C., 2004, 'Age at first measles-mumps-rubella vaccination in children with autism and School-Matched Control Subjects: A Population-Based Study in Metropolitan Atlanta', *Pediatrics*, (113/2) 259–266.

Dowdle, W.R., 1997, 'The 1976 experience', *The Journal of Infectious Diseases*, (176/1) 69–72.

EC, 2002a, Communication from the Commission on Foods and Food Ingredients Authoriszed for treatment with Ionising Radiation in the Community (2001/C 241/03). Official Journal of the European Communities C 241/6–11, 2002. *Consultation Paper Subject: Irradiated food and food ingredients — Commission proposal for completion of the positive list of foodstuffs authorised for treatment with ionising radiation*, 2004 (http://ec.europa.eu/food/fs/sfp/fi01_en.html) accessed 10 October 2011.

EC, 2002b, Report from the Commission on Food Irradiation for the period September 2000 to December 2001. COM (2002) 549 final (2002/ C255/02). Official Journal of the European Communities C 255/2. 23.10.2002.

Edsall, G., 1979, 'Letter to the editor re: The Swine Flu affair decision-making on a slippery disease', *American Journal of Epidemiology*, (110) 522–524.

EEA, 2001, *Late lessons from early warnings: the precautionary principle 1986–2000*, Environmental issues report No 22, European Environment Agency.

Environmental Nutrition, 2000, 'Electronic irradiation offers food safety without environmental risk', *Environmental Nutrition*, (23) 7.

Epstein, S. and Hauter, W., 2001, 'Preventing pathogenic food poisoning: Sanitation, Not Irradiation', *Environmental and Occupational Health Policy*, (31) 187–192.

Epstein S., 2002, *Food irradiation threatens public health*, National Security Musings, March 11. The Resource Institute for Low Entropy Systems (http://www.riles.org/musings37.htm) accessed 10 October 2011.

FAS, 2003, *Forskning Elöverkänslighet och andra Effeckter av Eletromagnitiska Fält* (in Swedish), Forskningsrådet för Arbeitsliv och Socialvetenskab.

Fields, H., 2004, *Autistic kids. Vaccines with mercury are not shown to cause autism* (http://www.usnews.com/usnews/health/briefs/childrenshealth/hb040907d.htm) accessed 10 October 2011.

From, L., 2004, 'Drikkevand bedre end hidtil antaget' (in Danish), *Morgenavisen Jyllands-Posten*, 30 July: 1, 3.

Fumento, M., 1990, 'The Politics of Cancer Testing', *American Spectator*, (23) 18–24.

Fumento, M. 1996, *Silicone Breast Implants: Why Science has been ignored*, American Council on Science and Health, New York.

Garrett, L., 1994, *A world out of balance*, Farra, Strauss and Giroux, New York.

Giere, R.N., 1991, 'Knowledge, values, and technological decisions: A decision theoretic approach' in: Mayo, D.G. and Hollander, R.D. (eds), *Acceptable Evidence*, Oxford University Press, 183–203.

Gough, M., 1994, 'Dioxin: Perception, estimates and measures' in: Foster, K. R., Bernstein, D. E. and Huber, P. W. (eds) *Phantom Risk*, The MIT Press, 249–278.

Graham, J.D., 2004, *The Perils of the Precautionary Principle: Lessons from the American and European Experience*, Heritage Lecture #818 January 15, The Heritage Foundation.

Graham, J.D. and Wiener, J.B., 1995, *Risk vs. Risk*, Harvard University Press, Cambridge, MA.

Grünewald, T., 1973, *Experience in irradiating potatoes*, Proceedings of a Panel to consider the application of food irradiation in developing countries organized by the Joint FAO/IAEA Division of Atomic Energy in food and agriculture and held in Bombay. 18–22 November 1972. Vienna: International Atomic Energy Agency, 1973, 7–12.

Guldberg, H., 2000, 'Child protection and the precautionary principle' in: Morris, J. (ed.), *Rethinking Risk and the Precautionary Principle*, Butterworth–Heinemann, 127–139.

Hackwood, S., 1991, 'An introduction to the irradiation processing of foods' in: Thorne, S.: *Food Irradiation*, Elsevier Applied Science, v–viii.

Hansen, S.F., 2004, *The Precautionary Principle and Unnecessary Precautionary Action*, Master Thesis, Roskilde University, Denmark (http://rudar.ruc.dk/bitstream/1800/505/1/The_Precautionary_Principle.pdf), accessed 10 October 2011.

Hansen, S.F., Krayer von Krauss, M.P. and Tickner, J.A., 2007a, 'Categorizing Mistaken False Positives in Regulation of Human and Environmental Health', *Risk Analysis*, (27/1) 255–269.

Hansen, S.F., Krayer von Krauss, M.P., Tickner, J.A., 2007b, Response to 'Regulatory False Positives: True, False, or Uncertain?', *Risk Analysis*, (27/5) 1 087–1 089.

Health Council of the Netherlands, 2002, *Mobile telephones: an evaluation of health effects*.

Hornig, M., Briese, T., Buie, T., Bauman, M.L., Lauwers, G., Siemetzki, U., Hummel, K., Rota, P.A., Bellini, W.J., O'Leary, J.J., Sheils, O., Alden, E., Pickering, L. and Lipkin, W.I. , 2008, 'Lack of Association between Measles Virus Vaccine and Autism with Enteropathy: A Case-Control Study', *PLoS ONE*, (3/9) e3140, doi:10.1371/journal.pone.0003140.

Hours, M., Bernard, M., Montestrucq, L., Arslan, M., Bergeret, A., Deltour, I., Cardis, E., 2007, 'Cell Phones and Risk of brain and acoustic nerve tumours: the French INTERPHONE case-control study', *Rev Epidemiol Sante Publique*, (55/5) 321–332.

Hrudey, S.E. and Leiss, W., 2003, 'Risk management and precaution: Insight on the cautious use of evidence', *Environmental Health Perspectives*, (111) 1 577–1 581.

IARC, 2008, *INTERPHONE Study*, Latest Results Update–8 October 2008, International Agency for Research on Cancer, Lyon, France (http://www.iarc.fr/en/research-groups/RAD/Interphone8oct08.pdf) accessed 10 October 2011.

ICNIRP, 2001, 'Review of the Epidemiological Literature on EMF and Health', *Environmental Health Perspectives*, (109/6) 911–933.

IEGMP, 2000, *Mobile Phones and Health*, Independent Expert Group on Mobile Phones, Chilton, National Radiological Protection Board, United Kingdom.

Institute of Food Technologists, 1998, *How and why to use sodium nitrite and nitrate*, document number: 121012637 (http://www.askthemeatman.com/how_and_why_to_use_sodium_nitrite.htm) accessed 10 October 2011.

IOM, 2004, *Immunization Safety Review: Vaccines and Autism*, Immunization Safety Review Committee, National Academy of Sciences, Washington, D.C.

IOM, 2001a, *Immunization Safety Review: Measles-Mumps-Rubella Vaccine and Autism*, National Academy Sciences, Washington, D.C.

IOM, 2001b, *Immunization Safety Review: Thimerosal — Containing Vaccines and Neurodevelopmental Disorders*, Immunization Safety Review Committee, National Academy of Sciences, Washington, D.C.

IPCS, 1978, *Nitrates, nitrites and N-nitroso compounds*, Environmental Health Criteria 5, World Health Organization, Geneva.

IMV, 2003, *Forsigtighedsprincippet i Praksis* (in Danish), Instituttet for Miljøvurdering, Copenhagen, Denmark.

Jaeger, R.J. and Weiss, A.L., 1994, 'Trichloroethylene: Toxicology and epidemiology: A critical review of the literature' in: Foster, K.R., Bernstein, D.E., Huber, P. W. (eds), *Phantom Risk*, The MIT Press, 229–248.

Kamrin, M.A., 2004, 'Bisphenol A: A scientific evaluation', *Medscape General Medicine*, *6*(3), 7.

Kava, R., Stimola, A., Weiser, R. and Mills, L., 2004, *The Top Ten Unfounded Health Scares of 2004*. American Council on Science and Health (http://acsh.org/healthissues/newsID.1007/healthissue_detail.asp) accessed 10 October 2011.

Khan, I., 1993, *Techno-economic evaluation of food irradiation in Pakistan*, Proceedings of an International Symposium on Cost-Benefit Aspects of Food Irradiation Processing, Jointly Organized by the International Atomic Energy Agency, the Food and Agriculture Organization of the United Nations and the World Health Organization and Held in Aix-En-Provence, 1–5 March 1993. International Atomic Energy Agency, Vienna, 155–158.

Klaeboe, L., Blaasaas, K.G. and Tynes, T., 2007, 'Use of mobile phones in Norway and risk of intracranial tumours', *Eur J Cancer Prev.*, (16/2) 158–164.

Kurland, L.T., Molgaard, C.A., Kurland, E.M., Erdtmann, C., Frederick, J., Stebbing, C. and George, E.T., 1984, *Lack of association of swine flu vaccine and rheumatoid arthritis*, Mayo Clinic proceedings, (59) 816–821.

Lahkola, A., Auvinen, A., Raitanen, J., Schoemaker, M.J., Christensen, H.C., Feychting, M., Johansen, C., Klaeboe, L., Lonn, S., Swerdlow, A.J., Tynes, T. and Salminen, T., 2007, 'Mobile phone use and risk of glioma in 5 North European countries', *Int J Cancer*, (120/8) 1 769–1 775.

Lawless, E.W., 1977, *Technology and Social Shock*, Rutgers University Press, New Brunswick/New Jersey.

Lieberman, A.J. and Kwon, S.C., 1998, *Facts Versus Fears: A Review of the Greatest Unfounded Health Scares of Recent Times*, American Council on Science and Health, New York.

Löfstedt, R., 2003, 'Science communication and the Swedish acrylamide "alarm"', *Journal of health communication,* (8) 407–432.

Lönn, S., Ahlbom, A., Hall, P. and Feychting, M., 2004, 'Mobile phone use and the risk of acoustic neuroma', *Epidemiology*, (15) 653–659.

Lönn, S., Ahlbom, A., Hall, P. and Feychting, M., 2005, 'Swedish Interphone Study Group. Long-term mobile phone use and brain tumor risk', *Am J Epidemiol*, (161/6) 526–535.

MAFF, 1986, *Report on The Safety and Wholesomeness of Irradiated Foods*, Ministry of Agriculture, Fisheries and Food, Advisory Committee on Irradiated and Novel Foods, Department of Health and Social Security, Ministry of Agriculture, Fisheries and Food Scottish Home and Health, Department Welsh Office Department of Health and Social Services, Northern Ireland.

Majone, G., 2002, 'What price safety? The precautionary principle and its policy implications', *JCMS,* (40) 89–109.

Marchant, G.E., 2003, 'From general policy to legal rule: Aspirations and limitations of the precautionary principle', *Environmental Health Perspectives*, (111) 1 799–1 803.

Marchant, G.E. and Mossman, K.L., 2002, *Arbitrary and Capricious the Precautionary Principle in European Union Courts,* AEI Press, Washington, D.C.

Martin, C., 2003, 'Chemical industry told to get tough, Lobbyist's memo advises hardball tactics for fighting tighter California regulations', *San Francisco Chronicle*, 21 November 2003.

Martin, N.S., 1990, *Environmental myths and hoaxes the evidence of guilt is insufficient*, speech delivered to B'nai B'rith Hillel Foundation, Houston, Texas, 24 January 1990.

Mazur, A., 2004, *True Warnings and False Alarms — Evaluating Fears about Health Risks of Technology*, 1948–1971, Resources for the Future, Washington, D.C.

Maxeiner, D. and Miersch, M., 1998, *Lexikon Der Öko-Irrtümer (*in German), Eichborn GmbH & Co. Verlag KG, Frankfurt am Main.

McCutcheon, J.W., 1984, 'Nitrosamines in bacon: a case study of balancing risks', *Public Health Rep,* (99/4) 360–364.

McGarity, T.O., 1990, 'Public participation in risk regulation', *Risk* 11 (Spring) (http://law.unh.edu/risk/vol1/spring/mcgarity.htm) accessed 10 October 2011.

Medical News Today, 2004, *Mumps outbreak in England and Wales worst in a decade* (http://www.

medicalnewstoday.com/articles/11613.php) accessed 10 October 2011.

Medical World News, 1977, *Lessons of the swine flu debacle*, 7 March 1977.

Meeker-Lowry, S. and Ferrara, J., 1996, *Meat monopolies dirty meat and the false promises of irradiation*, Food & Water. Inc.

Meldgaard Madsen, K.M., Hviid, A., Vestergaard, M., Schendel, D., Wohlfahrt, J., Thorsen, P., Olsen, J. and Melbye, M., 2002, 'A Population-Based Study of Measles, Mumps, and Rubella Vaccination and Autism', *New England Journal of Medicine,* (347/19) 1 477–1 482.

Michaels, D., 2005, 'Doubt is their product', *Scientific American*, (292/6) 96–101.

Miller, H. I. and Conko, G., 2001, 'Genetically modified fear and the international regulation of biotechnology' in: Morris, J. (ed.), *Rethinking Risk and the Precautionary Principle*, Butterworth-Heinemann, 84–104.

Milloy, 2001, *Junk Science Judo*, Cato Institute, Washington, D.C.

Mills, J.L., 1993, 'Spermicides and birth defects' in: Foster, K.R., Bernstein, D.E., Huber, P.W. (eds), *Phantom Risk*, The MIT Press, 87–100.

Moretti, R.H., 1993, *Cost-benefit of poultry irradiation in Brazil*, Proceedings of an International Symposium on Cost-benefit Aspects of Food Irradiation Processing, Jointly Organized by the International Atomic Energy Agency, the Food and Agriculture Organization of the United Nations and the World Health Organization and Held in Aix-En-Provence, 1–5 March 1993. International Atomic Energy Agency, Vienna, 291–300.

Moss, R.H. and Schneider, S.H., 2000, Uncertainties in the IPCC TAR: Recommendations to lead authors for more consistent assessment and reporting, in: Pachauri, R., Taniguchi, T. and Tanaka, K. (eds), *Guidance Papers on Crossing Issues of the Third Assessment Report of the IPCC* (pp. 33–51), Global Industrial and Social Progress Research Institute, Tokyo.

Murch, S.H., Anthony, A., Casson, D.H., Malik, M., Berelowitz, M., Dhillon, A.P., Thomson, M.A., Valentine, A., Davies, S.E. and Walker-Smith, J.A., 2004, 'Retraction of an interpretation', *The Lancet*, (363) 750.

Murray, D. R., 1990, *Biology of Food Irradiation*, John Wiley & Sons Inc., New York.

NACI, 2003, *An Advisory Committee Statement (ACS) Statement on Thimerosal*, Canada Communicable Disease Report 29: ACS-1.

NAPAP, 2011, National Acid Precipitation Assessment Program, noaaresearch (http://ny.cf.er.usgs.gov/napap/about.html) accessed 10 October 2011.

NAPAP, 1996, Biennial Report to Congress: An Integrated Assessment National Science and Technology Council Committee on Environment and Natural Resources, National Acid Precipitation Assessment Program (http://ny.cf.er.usgs.gov/napap/Information/NAPAP%201996%20Assessment.pdf) accessed 10 October 2011.

NAS, 1978, *Saccharin: Technical Assessment of Risks and Benefits*, Report No. 1., National Acadamy Press, Washington, DC.

Nestle, M., 2007, *Food politics: how the food industry influences nutrition, and health — Revised and expanded edition*, University of California Press, Los Angeles.

Neustadt, R.E. and Fineberg, H.V., 1978, *The Swine Flu affair. Decision-Making on a Slippery Disease*, US Department of Health, Education and Welfare, Washington D.C.

NFA, National Food Agency, 1986, *Irradiation of Food* — The Translation of a Report by a Danish Working Group, National Food Agency, Søborg.

Nketsia-Tabiri, J., Alhassan, R., Emi-Reynolds, G. and Sefa-Dedeh, S., 1993, *Potential contributions of food irradiation in post-harvest management in Ghana*, Proceedings of an International Symposium on Cost-Benefit Aspects of Food Irradiation Processing, Jointly Organized by the International Atomic Energy Agency, the Food and Agriculture Organization of the United Nations and the World Health Organization and Held in Aix-En-Provence, 1–5 March 1993, International Atomic Energy Agency, Vienna, 175–189.

NRPB, 2003, *Health effects from radiofrequency electromagnetic fields: Report of an independent Advisory Group on Non-ionising Radiation*, Doc NRPB, 14 (2), 5–177 (http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1254510602951) accessed 10 October 2011.

Ozonoff, D., Boden, L.I., 1987, 'Truth and consequences: Health agency responses to environmental health problems', *Science, Technology and Human Values*, (12) 70–77.

Parker, S.K., Schwartz, B., Todd, J. and Pickering, L.K., 'Thimerosal-Containing Vaccines and Autistic Spectrum Disorder: A Critical Review of Published Original Data', *Pediatrics*. September 2004, (114/3) 793–804.

Piccioni, R., 1987, *Potential Health Hazards of Food Irradiation*, Verbatim Excerpts from Expert Testimony, US Congressional Hearings into Food Irradiation, House Committee on Energy and Commerce Subcommittee on Health and the Environment, June 19 1987 (http://www.ccnr.org/food_irradiation.html) accessed 10 October 2011.

Pierson, M. . and Smoot, L.A., 1982, 'Nitrite, nitrite alternatives, and the control of Clostridium botulinum in cured meats', *Critical Review Food Science and Nutrition*, (17) 141–87.

Politiken, 2001, 'Olivenolie-Fødevaredirektorat overreagerer' (in Danish), *Politiken*, 27 August 2001.

Porter, M. E., 1991, 'America's Green Strategy', *Scientific American*, (168).

Pothisiri, P., Kiatsurayanont, P. and Banditsing, C., 1991, 'The impact of irradiated food on developing countries', in Thorne, S. (ed.): *Food Irradiation*, Elsevier Applied Science, 261–283.

Potter, C., 1998, 'Chronicle of influenza pandemics', in: Nicholson, K.G., Webster, R.G. and Hay, A.J. (eds), *Textbook of Influenza*, Blackwell Science Ltd., Oxford, 252–265.

Public Citizen and Grace, 2002, *Bad Taste*, Public Citizen and Grace, Washington D.C./New York (http://www.citizen.org/documents/BadTaste.pdf) accessed 10 October 2011.

RAJ, 2000, 'Facts versus fictions: the use and abuse of subjectivity in scientific research' in: Morris, J. (ed.), *Rethinking Risk and the Precautionary Principle*, Butterworth–Heinemann, 229–247.

Rampton, S. and Stauber, J., 2001, *Trust us. We're experts!*, Jeremy P. Tarcher/Putnam, Penguin Putnam Inc., New York.

Reid, A., Fanning, T.G., Hultin, J.V. and Taubenberger, J.K., 1999, *Origin and evolution of the 1918 'Spanish' influenza virus hemagglutinin gene*, Proceedings of the National Academy of Sciences, (96) 1 651–1 656.

Reitze Jr., A.W., 1986, 'Federal compensation for vaccination induced injuries', *Boston College Environmental Affairs Law Review*, (13) 169–214.

Roberts, T. and Murrell, K.D., 1993, *Economic Losses Caused by Food-Borne Parasitic Diseases*, Proceedings of an International Symposium on Cost-Benefit Aspects of Food Irradiation Processing, Jointly Organized by the International Atomic Energy Agency, the Food and Agriculture Organization of the United Nations and the World Health Organization and Held in Aix-En-Provence, 1–5 March 1993, International Atomic Energy Agency, Vienna, 51–75.

Ross, G., 2004, 'A needless worry concerning breast milk', *Wall Street Journal*, February 2.

RSC, 1999, *A Review of the Potential Health Risks of Radiofrequency Fields from Wireless Telecommunication Devices*, an Expert Panel Report prepared at the request of the Royal Society of Canada for Health Canada Ottawa, Ontario (http://www.rsc.ca/documents/RFreport-en.pdf) accessed 10 October 2011.

Sanera, M. and Shaw J.S., 1999. *Facts, Not Fear*, Regnery Publishing, Inc., Washington DC.

Sarewitz, D., Kriebel, D., Clapp, R., Crumbley, C., Hoppin, P., Jacobs, M. and Tickner, J., 2010, *The Sustainable Solutions Agenda*, The Consortium for Science, Policy and Outcomes, Arizona State University and Lowell Center for Sustainable Production, University of Massachusetts Lowell (http://www.sustainableproduction.org/downloads/SSABooklet.pdf) accessed 10 October 2011.

SCENIHR, 2009, *Health Effects of Exposure to EMF*, Scientific Committee on Emerging and Newly Identified Health Risks., European Commission Health & Consumer Protection DG (http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_022.pdf) accessed 10 October 2011.

SCF, 1998, *Opinion of the Scientific Committee on Food on the irradiation of eight foodstuffs* (expressed on 17.09.1998), Scientific Committee on Food, European Commission, Brussels (http://ec.europa.eu/food/fs/sc/scf/out15_en.html) accessed on 10 October 2011.

SCF, 2003, *Revision of the Opinion of the Scientific Committee on Food on the irradiation* (expressed on 4 April 2003), Scientific Committee on Food, European Commission, Brussels.

Schoemaker, M.J., Swerdlow, A.J., Ahlbom, A., Auvinen, A., Blaasaas,K.G., Cardis, E., Collatz Christensen. H., Feychting, M., Hepworth, S.J., Johansen, C., Klæboe, L., Lönn, S., McKinney, P.A., Muir,K., Raitanen, J., Salminen, T., Thomsen, J. and Tynes, T., 2005, 'Mobile phone use and risk of acoustic neuroma: Results of the Interphone case-control study in five North European countries', *British Journal of Cancer*, (93/7) 842–848.

Semb, A., 2001, 'Sulphur dioxide: from protection of human lungs to remote lake restoration', in: *Late lessons from early warnings: the precautionary principle 1986–2000*. Environmental issues report No 22, European Environmental Agency.

Shrader-Frechette, K.S., 2003, *Notre Dame philosophical reviews 2003.04.09*.

Shrader-Frechette, K.S., 1993, *Burying Uncertainty*, University of California Press, London.

Shrader-Frechette, K.S., 1991, *Risk and Rationality*, University of California Press Ltd., Berkeley.

Silverstein, A.M., 1978, *Pure Politics and Impure Science: The Swine Flu affair*, The Johns Hopkins University Press, Baltimore and London.

Smeeth, L., Cook, C., Fombonne, E., Heavey, L., Rodrigues, L.C., Smith, P.G. and Hall, A.J., 2004, 'MMR vaccination and pervasive developmental disorders: a case-control study', *The Lancet*, (364) 963–969.

Smith, F.B., 2000, 'Only one side of the risk equation' in: *The Precautionary Principle: Agriculture and Biotechnology*, A Capitol Hill Briefing Sponsored by International Consumers for Civil Society Wednesday, September 27, 2000, 311 Canon House Office Building, Capitol Hill.

Smith Jr., F.L., 1997, 'Caution: Precautionary principle ahead', *Regulation*, (56).

SOU, 1983, *Bestråling av livsmedel? Rapport fråm en expertkommitté* (in Swedish), Statens Offentlige Utredningar 1983, 26.

Sunstein, C.R., 2002, 'The Paralyzing Principle', *Reason*, Winter: 32–37.

Swedish Radiation Protection Authority's Independent Expert Group on Electromagnetic Fields, 2003, *Recent research on mobile telephony and cancer and other selected biological effects: First annual report from SSI's Independent Expert Group on Electromagnetic Fields*, Staten strålingskyddsintitut, Stockholm.

Taylor, B., Miller, E., Farrington, C.P. and Petropoulos, M.C., 1999, 'Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association', *The Lancet*, (353) 2 026–2 029.

Thayer, D.W., 1990, 'Food irradiated: Benefits and concerns', *Journal of Food Quality*, (13) 147–169.

Thorne, S., 1991, *Food Irradiation*, Elsevier Applied Science, 1991, v–viii.

Tickner, J.A. and Gouveia-Vigeant, T., 2005, *The 1991 cholera epidemic in Peru: Lessons learned from a false false-positive*, Risk Analysis.

Todd, E.C.D., 1993, *Social and Economic Impact of Bacterial Food-Borne Diseases and its Reduction by Food Irradiation and other Processes*, Proceedings of an International Symposium on Cost-Benefit Aspects of Food Irradiation Processing, Jointly Organized by the International Atomic Energy Agency, the Food and Agriculture Organization of the United Nations and the World Health Organization and Held in Aix-En-Provence, 1–5 March 1993. International Atomic Energy Agency, Vienna, 19–49.

Tritsch G.L. 2000, 'Food irradiation', *Nutrition,* (16) 698–701.

UK Department of Health, 2003, *Minister notes promising signs of increasing MMR uptake*, Friday 26 September, Reference number: 2003/0356 (http://www.highbeam.com/doc/1G1-108207226.html) accessed 10 October 2011.

UK Department of Health, 2004, *MMR the facts* (http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_105189.pdf) accessed 10 October 2011.

USDA, 1999a, *Food Ingredients and Sources of Radiation Listed or Approved for Use in the Production of Meat and Poultry Products; Final Rule*, US Department of Agriculture, Federal Register 1999; (64) 72 167–72 194.

USDA, 1999b, *USDA Approves Irradiation of Meat to Help Improve Food Safety*, Release No. 0486.99, US Department of Agriculture (http://www.usda.gov/news/releases/1999/12/0486) accessed 10 October 2011.

USDHEW, 1976, 'Rationale for Swine Flu Mass Immunizations in 1976', *Journal of the Medical Association of Georgia Public*, (65) 341–344.

US FDA, 1997, *Irradiation in the Production, Processing and Handling of Food; Final rule*, US Food and Drug Administration, Federal Register 1997; (62) 64 107–64 121.

US FDA, 1986, *Irradiation in the Production, Processing and Handling of Food; Final rule*, US Food and Drug Administration, Federal Register 1986; (51) 13 375–13 399.

US GAO, 2001, Telecommunications Research and Regulatory Efforts on Mobile Phones Health Issues, US General Accounting Office, GAO-01-545, Washington, D.C.

US GAO, 1977, *The Swine Flu Program: An Unprecedented Venture In Preventive Medicine*, United States General Accounting Office, report to the Congress By the Comptroller General of the United States, Department of Health, Education and Welfare, Washington D.C.

Urbain, W.M., 1993, 'Economic Aspects of Food Irradiation', in: *Proceedings of an International Symposium on Cost-Benefit Aspects of Food Irradiation Processing*, Jointly Organized by the International Atomic Energy Agency, the Food and Agriculture Organization of the United Nations and the World Health Organization and Held in Aix-En-Provence, 1–5 March 1993, International Atomic Energy Agency, Vienna, 1–16.

Vijayalaxmi and Rao, K.V., 1976, 'Dominant lethal mutations in rats fed on irradiated wheat', *International Journal of Radiation Biology*, (29) 93–98.

Vijayalaxmi, 1975, 'Cytogenetic studies in rats fed irradiated wheat', *International Journal of Radiation Biology*, (7) 283–285.

Vijayalaxmi, 1978, 'Cytogenetic studies in monkeys fed irradiated wheat', *Toxicology*, (9) 181–184.

Wade, N., 1976, 'Swine flu campaign faulted yet principals would do it again', *Science*, (202) 849, 851–852.

Wakefield, A.J., Murch, S.H., Anthony, A., Linnell, J., Casson, D.M., Malik, M., Berelowitz, M., Dhillon, A.P., Thomson, M.A., Harvey, P., Valentine, A., Davies, S.E. and Walker-Smith, J.A., 1998, 'Ileal lumphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children', *The Lancet*, (351) 637–641.

Walker, S.J., 2004, *Three Mile Island*, University of California Press, Berkeley.

Webb, T., Lang, T. and Tucker, K., 1987, *Food Irradiation Who Want It?*, Thorsons Publishers. Inc., Northamptonshire.

Wecht, C.H., 1979, 'Liability for vaccine-related injuries: Public health considerations and some reflections on the swine flu experience', in: Wecht, C. H., *Legal Medicine Annual: Nineteen Seventy-Eight*, Appleton-Century-Crofts, New York, 227–244.

Whelan, E.M., 1999, *Why Belgium waffles about the safety of coke*, FSNET.

Whelan, E.M., 1993, *Toxic Terror*, 2nd ed. Buffalo, Prometheus Books, New York.

Whelan, E.M., 1985, *Toxic Terror*, Jameson Books, Ottawa/Illinois.

Wildavsky, A., 1995, *But Is It True? A Citizen's Guide to Environmental Health and Safety Issues*, Harvard University Press, Cambridge/London.

Within Worldwide, 2000, 'The Precautionary Principle, Throwing science out with the bath water, a special report prepared in cooperation with Nichols-Dezenhall', *Within Worldwide*, 1–8 February.

WHO, World Health Organization, 2010a, *What are the health risks associated with mobile phones and their base stations?* (http://www.who.int/features/qa/30/en/) accessed 10 October 2011.

WHO, World Health Organization, 2010b, *Electromagnetic fields and public health: mobile telephones and their base stations* (http://www.who.int/mediacentre/factsheets/fs193/en/index.html) accessed on 10 October 2011.

WHO, World Health Organization, 2010c, *Influenza (Seasonal)*.

WHO, World Health Organization, 2004, *Summary of health effects: What happens when you are exposed to electromagnetic fields?* (http://www.who.int/peh-emf/about/WhatisEMF/en/index1.html) accessed 10 October 2011.

WHO, World Health Organization, 2003a, 'Global Advisory Committee on Vaccine Safety 16–17 December 2002 meeting MMR and autism; Oculorespiratory syndrome; Hepatitis B vaccination and leukaemia', *Weekly Epidemiological Record*, (78) 17–24.

WHO, 2003b, *MMR and Autism,* World Health Organization (http://www.who.int/vaccine_safety/topics/mmr/mmr_autism/en/) accessed 10 October 2011.

WHO, 2001, 'Recent Concerns regarding MMR vaccine', World Health Organization, Statement WHO/02 25 January 2001 (http://www.who.int/inf-pr-2001/en/state2001-02.html) accessed 10 October 2009.

WHO, 1999, *High-dose Irradiation: Wholesomeness of Food Irradiated with doses above 10 kGy*, World Health Organization, WHO Technical Report Series 890, Report of a Joint FAO/IAEA/WHO Study Group, World Health Organization, Geneva.

WHO, 1994, *Safety and nutritional adequacy of irradiated food*, World Health Organization, Geneva.

WHO, 1993, 'Report and Recommendations of the Working Group', in: *Proceedings of an International Symposium on Cost-Benefit Aspects of Food Irradiation Processing*, Jointly Organized by the International Atomic Energy Agency, the Food and Agriculture Organization of the United Nations and the World Health Organization and Held in Aix-En-Provence, 1–5 March 1993, International Atomic Energy Agency, Vienna, 477–489.

WHO, 1981, *Wholesomeness of Irradiated Food*, Report of a Joint FAO/IAEA/WHO Expert Committee. WHO Technical Report Series, No. 659, World Health Organization, Geneva.

3 Lead in petrol 'makes the mind give way'

Herbert Needleman and David Gee (1)

This chapter addresses the widespread use of lead in petrol. It focuses on the period 1925–2005, when leaded petrol was first widely marketed in the US and then spread to the rest of the world before being gradually phased out from the 1970s. In Europe, the Aarhus Protocol (UNECE, 1998) initiated the phase-out of leaded petrol in the period 1998–2005.

The neurotoxic effects of lead were recognised as far back as Roman times. And in 1925, at the 'one day trial' of leaded petrol in the US, many experts warned of the likely health impacts of adding lead to petrol. Yet, despite the availability of an equally effective alcohol additive which was assessed by experts to be cleaner, the leaded route to fuel efficiency was chosen in the US and then exported to the rest of the world.

For several decades after the introduction of leaded petrol, virtually no independent research was carried out and the main source of information was industry and industry-sponsored researchers. Not until the 1960s and 1970s did independent scientists from outside this group show, for example, that body burdens of lead arising from human activities were not 'normal', as industry claimed, but were hundreds of times higher than before the industrial revolution and were therefore likely to be harmful.

At its peak in the mid-1970s, leaded petrol released about 200 000 tonnes of lead into the atmosphere annually in both the US and Europe. Following the subsequent phase-out, blood lead levels in children (the most sensitive group exposed) quickly fell, in line with the decrease in air concentrations. The lessons nevertheless remain relevant globally today. Although nearly all countries worldwide had phased out leaded petrol by 2012, lead concentrations in soils and sediments remain high. Meanwhile, electronic wastes containing lead and other contaminants also cause elevated blood lead levels.

Supplementary panel texts focus on the events leading up to the US choice of leaded petrol as the primary fuel source in 1925 and more recent accounts of EU policymaking on lead in petrol and the road to phase-outs in Germany and the United Kingdom.

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(1) Authors would like to thank Gerald Markowitz and David Rosner for their detailed history of the leaded petrol story in *Deceit and denial: the deadly politics of industrial pollution*.

Dr Yandell Henderson, Professor of Physiology at Yale, told the conference that lead was as serious a public health menace as infectious diseases. He foresaw that:

> 'conditions will grow worse so gradually, and the development of lead poisoning will come on so insidiously ... that leaded petrol will be in nearly universal use ... before the public and the government awakens to the situation' (USPHS, 1925).

3.1 Introduction

There were 50–70 years between Henderson's prescient early warning about the long-term, low-level poisoning from leaded petrol, when it was introduced in 1925, and its phase out in the US and then Europe in the 1970s and mid-1980s. This long history is rich in lessons about the science, economics, and politics of identifying and controlling the hazards of toxic substances.

The focus of this chapter is lead in petrol and its damage to children (Box 3.1). However, the even longer histories of lead in pots and paints weave in and out of the leaded petrol saga, both complicating the search for the causes of lead poisoning in children, and creating a ubiquitous stock of lead in people and their environments that persists today in soils, sediments, plants, house dust and old paint. Such exposures affect adults too and recent research emphasises the increasing evidence linking lead with hypertension, heart disease and kidney disease (Navas-Acien et al., 2007; EFSA, 2010).

Most of Europe and North America now has lead free petrol but the lessons from this chapter are relevant for controlling most toxic chemicals. They may also be useful for the millions of people, including children, who are still exposed to leaded petrol or

Box 3.1 Children and lead: health impacts

At high levels of chronic exposure, lead attacks the brain and central nervous system, causing coma, convulsions and even death. Children who survive acute lead poisoning are typically left with grossly obvious mental retardation and behavioural disruption. At lower levels of exposure that cause no obvious symptoms and that were previously considered safe, lead is now known to produce a spectrum of harm involving diminished cognition, shortened attention span, disruptive behaviour, dyslexia, attention deficit disorder, hypertension, renal impairment, immunotoxicity and toxicity to the reproductive organs. For the most part, these effects are permanent and largely untreatable.

The major sources of children's exposure to lead are:

- lead from active industries, such as mining (especially in soils);
- lead-based paints and pigments;
- lead solder in food cans;
- ceramic glazes;
- drinking-water systems with lead solder and lead pipes;
- lead in products, such as herbal and traditional medicines, folk remedies, cosmetics and toys;
- lead released by incineration of lead-containing waste;
- lead in electronic waste (e-waste);
- lead in the food chain, via contaminated soil;
- lead contamination as a legacy of historical contamination from former mining and industrial sites.

Acute lead poisoning still occurs today and is most common among children in low-income countries and marginalised populations or in children living on lead-polluted sites of old lead factories or mines.

Recent research indicates that lead is associated with neurobehavioural damage at concentrations in the blood of 5 µg/dl and even lower. There appears to be no threshold level below which lead causes no injury to the developing human brain (see Box 3.11).

The biology of childhood lead poisoning is similar everywhere and the results of lead studies in one country are largely relevant to children in other countries.

Source: WHO, 2010.

Box 3.2 Ancient lead poisoning

Analysis of the Greenland ice core covering the period from 3 000 to 500 years ago — the Greek, Roman, Medieval and Renaissance eras — shows that from about 500 B.C. to 300 A.D. lead was present at concentrations four times greater than natural values. Greek and Roman lead mining and smelting clearly polluted the northern hemisphere long before the industrial revolution, which initiated the modern era of lead poisoning from about from 1750 onwards. Cumulative lead fallout to the Greenland ice sheet during those eight centuries was as high as 15 % of that caused by use of lead alkyl additives in petrol since the 1930s.

Source: Hong, Candelone et al., 1994.

other sources of lead, such as from old lead works, paint and toys, in many countries of the world.

3.2 Lead toxicity: some early warnings

The neurotoxic properties of lead were first noted during the first century AD by Dioscerides, a physician in Nero's army. In his book *Materia Medica* he observed that 'Lead makes the mind give way'. Exposure came from the leaded glaze on pots and from using lead in winemaking to counteracted the harsh acidity of the grapes (lead plates were dipped into the wine during fermentation and the lead acetate, which is also called 'sugar of lead', sweetened the taste). Centuries later, toddlers who chewed the leaded paint on cradles, beds and verandas found that it tasted like lemon drops.

Lead continued to be used in wine-making and epidemics of lead colic were common in Europe and the Americas. One of the earliest public health laws in the US was passed in 1723 to protect rum drinkers from what was called 'the dry gripes'. The law banned the use of leaden 'worms' (condensing coils) in the distilling process. A penalty of 100 pounds was imposed on law breakers, half being distributed to the poor and half to the person who informed the authorities about the breach of law. This was an early attempt to reward and protect 'whistleblowers' — an issue taken up in Chapter 24.

In early-18th century England, a severe outbreak of colic was reported each autumn in Devon. The disease was strictly limited to particular areas while neighbouring shires escaped. The physician Sir George Baker identified the source of the epidemic as the leaden keys in the millstones used in pressing cider apples. His paper to the Royal College of Physicians showed that Devonshire cider contained lead (Baker, 1768). Rather than receiving praise for his incisive work, Baker was condemned by the clergy, by mill owners and by fellow physicians: cider was Devon's main export.

Baker suffered the fate of many 'early warning' scientists whose inconvenient truths are not welcomed by supporters of the status quo (2).

During his European travels, Benjamin Franklin had also noted how long it took for 'useful truths' about health hazards to be acted on (Box 3.3).

The UK pottery manufacturer, Josiah Wedgewood, also experienced the long delay between 'useful truths' and regulatory actions. He was sufficiently moved by accidents and lead poisoning in his factories, and concerned about the unfair competition that arose from other, less scrupulous, employers, that he asked the British government to extend the recent Factories Act of 1833 from the textiles industries to the potteries industries so that he could share a 'level playing field' with his competitors. Opposition from other pottery manufacturers meant, however, that Wedgewood had to wait some 30 years before legal controls on lead were established in the Potteries Regulations of 1867.

These early warnings about occupational and consumer lead toxicity largely went unheeded. The use of lead for pots, paints, pipes and toys greatly

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(2) Such 'shooting the messenger' is well illustrated by Ibsen's play *An enemy of the people*. The play chronicles the gradual downfall of the town physician who discovers pollution in the river caused by the local leather factory: a discovery that is initially welcomed by the mayor, the media and the public, but then rejected, as the economic implications for local industry begin to emerge. Many public health advocates in similar circumstances to Baker have taken comfort from Ibsen's play, such as Dr Hosokawa of the Chisso Company Japan, which polluted Minimata Bay with mercury. He, like Ibsen's Doctor Stockmann, was told to suppress his early discovery that sewage from Chisso caused the mercury poisoning (see Chapter 5 on the Minamata disaster).

Box 3.3 The 'useful truths' about lead poisoning in French painters, potters and plumbers

In 1818, Benjamin Franklin, while ambassador to France, described the 'dangles' of wrist drop, and the 'dry gripes' of stomach aches in painters, potters and plumbers who were widely known to suffer from lead poisoning. But he also observed two other trades that suffered similarly but seemed not to be obviously exposed to lead: stonecutters and soldiers. Pursuing this puzzle, he found that the stonecutters used lead to set metal rails in stone, and that soldiers found part time employment as painters' assistants. This provided an early example of the value of detailed job and life exposure histories in identifying occupational and environmental hazards.

Franklin concluded: 'this mischievous effect from lead is at least 60 years old; and you will observe with concern how long a useful truth may be known and exist, before it is generally received and practiced on' (Franklin, 1818).

expanded in the 19th and 20th centuries (Hunter, 1975), accompanied by widespread lead poisoning that could sometimes take years to appear:

> 'Lead poisoning develops insidiously' often years after the exposure, deranging the functions and structure of the cells, 'so that life is gradually brought to a close by the intervention of disease of organs, such as the kidney or nervous system' (Oliver, 1911).

This 'insidious' nature of lead poisoning would later be noted by some of the medical experts who assessed the likely risks from lead in petrol when it was introduced in the 1920s. Children were particularly at risk (Box 3.4).

Box 3.4 The early poisoning of children by leaded paint, and current poisoning from paint and battery plants in Asia

Children face increased risk of lead poisoning compared to adults because they can be exposed during pregnancy; they take in more food, drink and air relative to their weight; they have more hands-to-mouth activity; and they are more likely to have nutritional deficiencies that can increase lead absorption (WHO, 2010).

In 1892 an Australian doctor observed the link between the lead-based paints used on porches, verandas, and window frames, and lead poisoning in 10 children who chewed the flakes of paint and swallowed the dust and chips on the floor where they crawled and played (Gibson, 1904).

In 1914 in the US, the first childhood lead poisoning case was reported with a death from lead poisoning in a child who had chewed lead paint from his crib railings (Thomas and Blackfan, 1914).

By 1925 there was much scientific evidence in the US, Europe and elsewhere showing that infants and children were poisoned by lead in the paint that they found in their daily environments. But their eventual protection from this source of lead came via regulations to protect painters, which led to the widespread banning of lead in paint in Europe and Australia between 1909 and the 1930s.

The US, however, only banned leaded paint for interior surfaces in 1971. As a result, government authorities are still dealing with the legacy of lead poisoning in the poorer areas of the US where the housing remediation costs, and associated legal cases over who is to pay remediation, still consume much time and money.

Meanwhile, there is still widespread exposure of children to leaded paint in many regions, particularly, developing countries. A survey of 10 countries in Asia, Africa, South America and eastern Europe found much leaded paint on sale, some with lead levels ranging from 4 000 to nearly 40 000 parts per million (ppm), compared to the US recommended limit of 90 ppm (UNEP/WHO, 2010). Moreover, China has reported many serious childhood lead poisoning incidents in recent years.

3.3 Lead in petrol 1922–1925: the early warnings of hazards to the public

3.3.1 Origins of lead in petrol

Until 1925, the principal source of toxic lead for the public was household paint. This changed dramatically when General Motors, in second place behind Ford Motors in car sales, sought to compete with its new higher performance Cadillac. The new GM engine had a severe engine 'knock' that arose from the premature ignition of the petrol, meaning that GM needed to find an anti-knock additive for the petrol. Their chief chemist, Thomas Midgely, who later invented the CFC chemicals that created the hole in the ozone layer, (see EEA, 2001, Ch. 7 on halocarbons), found an old German patent for tetraethyl lead (TEL) and discovered that it could be used in petrol to control the engine knock.

Alternatives to petroleum-based fuel, such as ethanol, were available. They were likely to be much less profitable, however, especially given the family and financial links between GM, the chemical company, DuPont, and Standard Oil. Pierre Dupont was chair of the GM Board, his brother Irene ran DuPont, both had close links with Standard Oil, and in 1924 the three companies created the Ethyl Corporation of America to produce TEL.

It was made clear at the outset that the word 'lead' was not to be used in the company name or sales literature: the little known term, 'ethyl' was used instead so as not to alarm the public.

This was an early example of the censoring of sensitive words from the discussion of hazards, a practice repeated in the other *Late lessons from early warnings* case studies, for example asbestos (EEA, 2001). For example, the word 'cancer' in the early studies of asbestos workers was initially replaced by the less well known terms, 'tumour' or 'malignancy', at the request of asbestos manufacturers.

3.3.2 Early warnings of risk and 'authoritative assertions' of safety

During World War I, TEL was evaluated for possible use as a battlefield weapon. Mansfield Clark, a professor of chemistry familiar with this work, warned the US Public Health Service (PHS) in 1922 about the 'serious menace to the public health' that would arise from the use of TEL in petrol because 'on busy thoroughfares it is highly probable that the lead oxide dust will remain in the lower stratum.' (Mansfield Clark, 1922)

The Surgeon General of the US Public Health Service, Huge Cummings, responded some months later by writing to Pierre Dupont, Chair of the Board of GM, asking if the public health effects of TEL had been taken into account, 'since lead poisoning in human beings is of the cumulative type resulting frequently from the daily intake of minute quantities.' (Needleman, 1997)

Thomas Midgely replied by saying that GM had given the question 'very serious consideration ... although no actual experimental data has been taken'. However, they were confident that 'the average street will probably be so free from lead that it will be impossible to detect it or its absorption.' (Midgely, 1922)

Midgely's response has parallels in other *Late lessons from early warnings* case studies, including those addressing asbestos, CFCs and BSE in Volume 1 (EEA, 2001). In response to early warnings about public health hazards, interested parties often make 'authoritative assertions' about the absence of risk despite having little or no data to support their claims. 'No evidence of harm' is thereby mischaracterised as 'evidence of no harm'. This approach to early warnings of potential harm is still common (3).

In order to provide some evidence to back up their assertions of safety, GM paid the US government's Bureau of Mines to conduct some animal experiments, but within tight reporting constraints imposed by the Ethyl Corporation. These conditions included the replacement of the word 'lead' by 'ethyl', even in internal correspondence, and the submission of draft reports to the Ethyl Corporation for their 'comments, criticism and approval' before publication. The chief chemist in the Bureau of Mines 'raised his concerns about this censorship but was assured by his director that … it would not be so bad if the word lead were omitted as this term is apt to prejudice somewhat against its use' (Needleman, 1997).

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(3) For example, there are no studies in children of the potential head cancer hazard of using mobile phones: the early suspicions of risk have come from studies in adults only. Yet it is widely asserted that there are no risks to children from the use of mobile phones. In 2007, 2009 and 2011 the EEA issued 'early warnings' about the potential hazard of head cancers from mobile phones, particularly in younger people. See Chapter 21 on mobile phones.

Such contractual gagging had already been condemned as unprofessional by Yandell Henderson, Professor of Physiology at Yale, who had turned down an invitation by GM to study TEL two years earlier. He was now asked by the Bureau of Mines to join their investigation but he declined, saying that it was 'extremely unfortunate' that the work was being funded by GM as there was an 'urgent need for an absolutely unbiased investigation'. He was prepared to investigate the hazards but only 'on the assumption that so terrible a poison as TEL should not be generally introduced until absolute proof was available that no danger to the public would be involved'. Soon after, his long standing contract with the Bureau of Mines was terminated, as well as his contract with Standard Oil: an early example of the harassment of 'early warning' scientists which is repeated in this and other chapters.

Henderson was later to testify against the use of TEL in petrol at its 'one day trial' in 1925 (discussed in Section 3.4.1).

By 1925 industrial production of TEL had been under way for nearly two years but within months it had caused the dramatic deaths of a dozen or so workers and mental illness in many others (Box 3.5).

The news media ran dramatic headlines about the TEL deaths: 'Mad gas claims third victim' and 'Bar Ethyl gas as fifth victim dies' appeared above pictures of workers being taken away in straitjackets.

New York State then banned the sale of leaded petrol. This put pressure on the PHS and the TEL industry to somehow demonstrate that though **workers** may be at risk, partly because of their 'carelessness', or because they 'worked too hard', as the factory management claimed, the **public** would not be at risk from TEL in their car fuel.

Standard Oil had already confidently asserted that no 'perils existed in the use of this gas in automobiles', even though no evidence had been gathered to support that view.

The day after the fifth employee at their TEL plant died, Standard Oil's assertions regarding the safety of TEL received support from the Bureau of Mines, which published a report showing that animal studies indicated no risks to the public from TEL.

On 1 November 1924, *The New York Times* (1924) ran the headline: 'No peril to public after long experiments with motor exhausts'.

However, the Bureau of Mines report was heavily criticised. It was labelled as 'inadequate' by Cecil Drinker, editor of *The Journal of Industrial Hygiene*, David Edsall, Dean of Harvard Medical School, and others, including the Surgeon General (Drinker, 1925). They considered that the number of animals used was too small and the duration of exposure was too short to draw reliable conclusions about safety. These are still features of some current toxicology that can result in underestimation of hazards (see Chapter 26 on science for precautionay decision-making).

Some public health specialists supported the Bureau of Mines and the Ethyl Corporation, but again with confident assertions rather than robust evidence.

For example, Dr Emery Hayhurst of the Ohio Department of Health provided an unsigned

Box 3.5 TEL workers die in the 'house of butterflies'

On Thursday 26 October 1924, Ernest Oelgert, a TEL worker at Standard Oil's Bayway labs in New Jersey, began hallucinating and then became extremely paranoid, running round the plant saying that 'three were coming at me'. By Saturday he had to be forcibly constrained and taken to the nearest mental hospital where he died the next day.

Over the next five days, four other TEL workers from the plant died and another 35 showed severe neurological symptoms of lead poisoning. At the other two TEL workplaces, the DuPont plant at Deepwater, New Jersey, and GM's research lab in Dayton, Ohio, at least six other workers had died.

Despite their declared difficulties in getting the facts out of the companies and the hospitals, *The New York Times* journalists uncovered more than 300 cases of lead poisoning at the Deepwater plant. Workers called that TEL plant 'the house of butterflies' as they frequently had hallucinations about insects during their bouts of lead poisoning.

editorial in *The American Journal of Public Health*, stating that 'observational evidence' and other reports from around the country have 'corroborated the statement of complete safety so far as the public health has been concerned' (Ethyl Gasoline, 1925). Few people knew that, at that time, he was also a paid consultant to the Ethyl Corporation and advisor to the Bureau of Mines (Hayhurst, 1924).

These 'authoritative assurances' failed to quell public and scientific concern. The Surgeon General responded to requests for action from public health experts, who felt that both the public's health and the probity of the PHS were at risk from the TEL issue. He organised a high level conference of all the key actors, stating that leaded petrol 'is a public health question of extreme seriousness … if this product is actually causing slow poisoning and serious effects of a cumulative nature' (New York World, 1925).

The conference took place in Washington on 24 May 1925.

3.4 'Progress' or precaution?

3.4.1 The 'one day trial' of the 'gift of God'

Every major stakeholder was represented at the meeting. Industry opened the debate by making four main points: leaded petrol was essential to the industrial progress of America; all innovation entails risks; the deaths and disabilities caused by TEL in the manufacturing plants were due to the carelessness of the men in not taking precautions; and there was no risk to the public from the different exposure conditions in the streets, compared to the factories.

No 'innovation' other than TEL was discussed at the meeting, despite the declared intention of the Surgeon General to spend two or three days discussing alternatives to TEL. The toxicologist Robert Kehoe spoke first for industry, citing lack of evidence of risks to the public; he was followed by eight other industry representatives who took up the morning session.

The public health representatives used the afternoon to try to shift the burden of proof back to their opponents, arguing that industry needed to show that TEL was safe for the public, rather than public health scientists needing to show that it was dangerous.

Dr Yandell Henderson, Professor of Physiology at Yale, told the conference that lead was as serious a public health menace as infectious diseases. He foresaw that 'conditions will grow worse so gradually, and the development of lead poisoning will come on so insidiously ... that leaded petrol will be in nearly universal use … before the public and the government awakens to the situation' (USPHS, 1925). His claims proved to be prescient.

Dr David Edsall, Dean of Harvard Medical School, also dismissed the view of industry that 'nobody has shown any symptoms of lead poisoning'. He went on to say that: 'I cannot escape feeling that a hazard is perfectly clearly shown … here today, and that it appears to be a hazard of public moment, and that the only way it could be said it is a safe thing to continue with this hazard would be after very careful and prolonged and devoted study.' This did not happen until the 1970s.

Edsall was followed by Dr Touart, who had treated many of the workers. He too emphasised the central issue of the burden and strength of evidence: 'It seems to me that ... this ethyl gas is under suspicion and therefore should be withheld from public consumption until it is conclusively shown that it is not poisonous.'

Haven Emerson, Professor of Public Health at Columbia University, observed that industry's use of deaths as an indicator of hazard was unsound: information about functional and mental disabilities of those that did not die would also be needed.

However, industry was supported by some of the other public health scientists at the meeting. They observed that, while there was solid and direct evidence of industrial benefits from TEL, evidence on health risks to the public was not available. This asymmetry between short-term economic benefits and long-term health hazards is another continuing problem.

Dr Hayhurst of the Ohio Department of Health said that 27 months of public use of leaded petrol 'should have sufficed to bring out some mishaps and poisonings suspected to have been caused by TEL'. It had not, so he was prepared to declare that leaded petrol was safe.

His position was based on two weak assumptions: that existing statistics, collected for other purposes, provided reliable evidence of safety from a new technology; and that a short, two-year-period after first exposure would be enough to uncover any new hazards. These assumptions are still common in debates on current health hazards.

Some public health experts who supported industry at the meeting had earlier expressed their concerns about the health risks, but only in private. Hayhurst, for example, despite being a consultant for the Ethyl Corporation, had written to the PHS a week before the May meeting expressing the concerns that he shared with some of the PHS scientists, such as Dr Thompson, who had declared that 'lead has no business in the human body ... everyone agrees lead is an undesirable hazard and the only way to control it is to stop its use by the general public'.

However, Hayhurst continued his letter by noting that his scientific judgement was influenced by political and economic factors. 'Personally, I can quite agree with Dr Thompson's wholesome point of view but, still, I am afraid human progress cannot go on under such restrictions … if we are to survive among the nations. Dr Thompson's arguments might also be applied to the thousand and one other poisons and hazards which characterise our modern civilisation' (Hayhurst, 1925).

The country's foremost authority on lead, Alice Hamilton, told the May meeting that there was no way to know how to regulate leaded petrol so that it would be safe. 'You may control conditions within a factory ... but how can you control the whole country?' She later spelled out the dangers further, noting that even under the strictest factory conditions the use of lead resulted in poisoning, sooner or later (Hamilton, 1925).

The meeting seemed to be going the way of precaution and public health until Frank Howard, first President of the Ethyl Corporation, concluded the industry view: 'You have only **one** problem', he told the health scientists, 'is this a public health hazard?' Industry, he said, had other problems such as ensuring that automobiles and oil played a key role in the industrial progress of the nation. 'Our continued development of motor fuels is essential in our civilisation'. The development of TEL after a decade of research was an 'apparent gift of God'. What is our duty under these circumstances, he asked, 'should we say no: we will not use a material (that is) a certain means of saving petrol? Because some animals die and some do not die in some experiments, shall we give this thing up entirely?'

In a couple of rhetorical sentences he put the burden of proof back onto the public health scientists to prove that TEL was dangerous. He had also put them on the defensive by making them appear to be reactionaries who were retarding human progress and technological innovation on the unproven grounds that there could be public hazards.

The meeting ended after less than seven hours. The Ethyl Corporation announced that there would be a temporary ban on leaded petrol sales until a 'blue ribbon committee' of top-level scientists set up by the PHS after the meeting had studied the issue.

After the meeting Alice Hamilton thought that the direct involvement of the top scientists and decision-makers from industry and government would produce the right results, especially if there was 'a blaze of publicity turned on their deliberations'.

3.4.2 Blue ribbon committee findings

This perceived victory of objective science over short-term economic and political interests was short lived. The scientific review committee was under great time pressure to produce its report, so a very limited, seven month, study of 252 garage and filling station attendants, chauffeurs and factory workers was conducted. The committee concluded that 'at present there are no good grounds for prohibiting the use of ethyl gasoline [petrol] ... provided that its distribution and use are controlled by proper regulations'. A recommendation from committee member Winslow to continue the search for alternatives was omitted from the final committee report.

The report included clear caveats, however, stating that:

> 'Owing to the incompleteness of the data, it is not possible to say definitely whether exposure to lead dust increases in garages when tetraethyl lead is used. It is very desirable that these investigations be continued ... It remains possible that if the use of leaded petrol becomes widespread, conditions may arise very different from those studied by us which would render its use more of a hazard than would appear to be the case from this investigation. Longer exposure may show that even such slight storage of lead as was observed in these studies may lead eventually in susceptible individuals to recognizable lead poisoning or chronic degenerative disease of obvious character ... The committee feels this investigation must not be allowed to lapse.'

Panel 3.1 A road not taken: the alcohol alternative to lead in 1925

Bill Kovarik

The US Geological Service (USGS) and the US navy performed over 2 000 tests on alcohol and petrol engines in 1907 and 1908 and concluded that: 'In regard to general cleanliness, such as absence of smoke and disagreeable odors, alcohol has many advantages over gasoline or kerosene as a fuel. The exhaust from an alcohol engine is never clouded with a black or grayish smoke.'

USGS continued the comparative tests and later noted that alcohol was 'a more ideal fuel than gasoline' with better efficiency despite the high cost'. Others were also experimenting (see Box 3.6).

GM was also interested in long-term security of fuel supplies, as is apparent in an unpublished du Pont study drafted by a member of the firm's legal staff. According to the study (Wescott, 1936):

> '…An important special motive for this research [into ethyl alcohol] was General Motors' desire to fortify itself against the exhaustion or prohibitive cost of the gasoline supply, which was then believed to be impending in about twenty-five years; the thought being that the high compression motors, which should be that time have been brought into general use if knocking could be overcome, could more advantageously be switched to [ethyl] alcohol.'

The DuPont conclusion is supported by internal memos sent by Midgley. Alcohol was the 'most direct route ... for converting energy from its source, the sun, into a material that is suitable for a fuel…' he said in one internal memo.

To promote alcohol-blended fuels among automotive and chemical engineers in October 1921, Midgley drove a high compression ratio car from Dayton to an October 1921 Society of Automotive Engineers (SAE) meeting in Indianapolis using a 30 % alcohol blend in petrol. 'Alcohol has tremendous advantages and minor disadvantages,' Midgley told fellow SAE members in a discussion. Advantages included 'clean burning and freedom from any carbon deposit... [and] tremendously high compression under which alcohol will operate without knocking... Because of the possible high compression, the available horsepower is much greater with alcohol than with gasoline.'

'From our cellulose waste products on the farm such as straw, corn-stalks, corn cobs and all similar sorts of material we throw away, we can get, by present known methods, enough alcohol to run our automotive equipment in the United States,' he said. The catch was that it would cost two dollars per gallon. However, other alternatives looked even more problematic — oil shale would not work and benzene from coal would only bring in about 20 % of the total fuel need (Midgley, 1921).

Despite their enthusiastic support for alcohol as a 'fuel of the future', Midgley and his boss, Charles Kettering, categorically denied the existence of alternatives to TEL once they had begun to invest in TEL production facilities:

> 'So far as science knows at the present time, tetraethyl lead is the only material available which can bring about these [antiknock] results, which are of vital importance to the continued economic use by the general public of all automotive equipment, and unless a grave and inescapable hazard exists in the manufacture of tetraethyl lead, its abandonment cannot be justified' (*The New York Times*, 7 April 1925).

Information about alternatives could have emerged with more social and scientific force at this critical moment in the history of TEL (⁴). For example, it was widely thought that the May 1925 conference would last several days in order to discuss alternatives to TEL: the Surgeon General had declared his intention to do so at the opening of the May conference (see Section 3.4.1).

A report published but not released by the US Department of Commerce a few days before the May conference showed that alternative antiknock additives (mostly ethyl alcohol blends in petrol) were being

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(⁴) 'Ethyl leaded gasoline crashed through the modest defenses of the American public health system of the 1920s not only through brute force of industry's political influence over government but also due to the disorganized information resources available to public health advocates', particularly regarding the potential for alternatives to TEL (Kovarik, 2003).

Panel 3.1 A road not taken: the alcohol alternative to lead in 1925 (cont.)

used routinely in two dozen other industrial nations. And anyone familiar with the Midgley papers and statements of 1921 and 1922 would see that by 1925 he was contradicting his own published research.

Information about alternatives did not emerge from the 'one day trial' of TEL in 1925, however, except in a few statements by public health scientists and hints in the media. No record of any dissent exists, even though the industry was now flatly contradicting its own previous research and statements on the alcohol alternative.

In 1933 the US Defence Agency and US navy conducted tests on alternative fuels and found that Ethyl leaded petrol and 20 % ethyl alcohol blends in petrol were almost exactly equivalent in terms of brake horsepower and useful compression ratios. This report was never published.

Other potential substitutes for tetraethyl lead known to Kettering and the US automotive industry were based on the I.G. Farben/BASF Fischer-Tropsche and Bergius processes for making synthetic fuels from coal. This was seen as such serious competition to TEL that Standard Oil entered into a 'full marriage' agreement with Farben in which Standard agreed to stay out of the world chemical business and Farben agreed to stay out of the world fuel business — no matter how World War II progressed (Davis, 2007).

The wide variety of alternatives and substitutes known in the 1920s and 1930s were forgotten by the 1960s. Histories of the oil industry omitted any mention of alternatives.

In 1974, when Thomas Reed of MIT began his ground-breaking investigation of alcohol fuel as an alternative to petrol in the wake of the Arab oil embargo, he was unaware of any other similar work before him. It was as if, having found in TEL the one solution to the engine knock problem, no other solution — and no other history — was necessary.

Defeating the alcohol competition to leaded petrol

By the mid-1930s, Ethyl leaded petrol succeeded beyond all expectations. Public health crusaders who found this troubling still spoke out in political forums but competitors were not allowed to criticise leaded petrol in the commercial marketplace. In a restraining order forbidding such criticism, the Federal Trade Commission told competitors to stop criticising Ethyl petrol since it 'is entirely safe to the health of [motorists] and to the public in general when used as a motor fuel, and is not a narcotic in its effect, a poisonous dope, or dangerous to the life or health of a customer, purchaser, user or the general public.' (US FTC 1936)

During the 1930s, the few attempts to promote alcohol petrol were met by fierce and unfair competition from the Ethyl company, which led to an anti-trust case against Ethyl Corporation in 1937. By then Ethyl leaded petrol was used in 70 % or more of American petrol (90 % according to Ethyl's advertising) and in all but one major brand — Sunoco. Dealers who cut prices or who used alcohol or benzene in other fuels were not allowed to wholesale Ethyl's lead additive.

'It seems clear that the Ethyl Gasoline Corporation has exercised its dominant control over the use of Ethyl fluid substantially to restrain competition by regulating the ability of jobbers to buy and sell petrol treated with ethyl fluid and by requiring jobbers and dealers to maintain certain prices and marketing policies', a 1937 Department of Justice memo said. Ethyl lost the suit at the Federal District Court level in 1938 and at the Supreme Court in 1940. The company was ordered to make the product available to any customer who met minimum technical criteria.

Many scientists, businessmen and farmers believed that making fuel from corn and cornstalks would help put people back to work and ease the severe problems of the Depression. This movement for alcohol fuels became part of a broader campaign for industrial uses for farm crops to help fight the Depression. The 'farm chemurgy' movement, as it was called, with alcohol fuel as a controversial centrepiece, had grown into an unprecedented mixture of agronomy, chemistry and prairie populism. Many felt that the time had come to compete directly with the oil industry. 'Try a tankfull — you'll be thankful,' the Agrol brochures said. The blend was sold to initial enthusiasm at 2 000 service stations. Although Agrol sold for the same price as its 'main competitor', leaded petrol, it cost wholesalers and retailers an extra penny to handle it and this cut into their profit. By 1939, the Agrol plant had closed (Hale, 1934; Kovarik, 2003 and 2005).

Box 3.6 Early London buses experiment with alcohol fuels

In 1919 the London General Omnibus Co. also compared petrol with blends of ethyl alcohol and benzene. Mileage was about the same, with petrol slightly ahead. 'In all other respects the [alcohol] fuel compared favourably with petrol, and exhibited the characteristics of other alcohol mixtures in respect of flexibility, absence of knocking and cleanliness' (although it would later emerge that benzene is a dangerous carcinogen.)

The bus experiment also showed that a large-scale switch from petroleum was technically feasible and needed in any case to increase security of fuel Contentsies. 'We are fast squandering the oil that has been stored in the fuel beds, and it seems so far as our present knowledge takes us that it is to the fuels experimented with that we must turn for our salvation,' concluded the omnibus company engineer.

The Committee recognised the limitations of its small, interim and retrospective study and strongly urged the PHS to obtain funds from Congress for long-term prospective studies that could follow the history of leaded petrol and its consequences that were 'not now foreseen'. However, the PHS never undertook such research. For the next 40 years all studies of TEL were conducted and funded by the Ethyl Corporation and GM (Markowitz and Rosner, 2002).

Shortly after the Surgeon General's committee had declared that TEL was safe for general use, in 1926, the Public Health Service recommended that the allowable concentration of TEL be set at 3 cc per gallon. Ethyl quickly agreed to comply, relieving the government of any pressure to introduce the regulations on lead in petrol that had been called for by the expert committee.

For the next 35 years lead toxicity as a public health issue virtually disappeared from sight, while at the peak of TEL production some 250 000 tonnes of lead were released into the air in the United States every year.

3.5 Lead contamination is 'normal and safe'

After the Surgeon General's report of 1926 had given the go ahead to industry, Robert Kehoe, the toxicologist from the University of Cincinnati, who had claimed the safety of TEL at the 1925 meeting, was cultivated by the TEL industry as the dominant authority on lead. C. F. Kettering established a laboratory in Cincinnati with an initial gift of USD 130 000 from Ethyl, E. I. DuPont and General Motors. He had initially asked Kehoe to study the worker deaths at the Ethyl plant in Dayton and now he asked him to direct the Kettering laboratory. Kehoe later also became a corporate officer at GM and a consultant to DuPont.

Data on the health effects of TEL were sparse, and the only source of funding for research came from industry sources. The strong recommendation from the Surgeon General's 1926 report that there should be publicly funded research on TEL was not implemented.

Kehoe's early studies compared lead concentrations in workers in direct contact with TEL with men in the same plant but who had other jobs. He designated this second group as 'unexposed' controls. When he found lead in the excreta of his so-called unexposed group, he concluded that as lead was naturally present in all the workers it could not be very harmful to them. The mere presence of lead in workers, he argued, could not be an indicator of poisoning.

This view had been vigorously attacked by David Edsall, Yandell Henderson and others at the Surgeon General's 1925 meeting. They had argued that, as potentially all workers in the Dayton plant were exposed to TEL fumes, any comparison of workers within the plant would be of little value as exposed controls would mask the full effects of lead.

Kehoe eventually came to see the merit in his critics' assertions: clearly he had chosen the wrong control group. To answer his critics he searched for an unexposed group in a remote farming village outside Mexico City, far removed from industry or urban pollution. There he sampled food, utensils and the excreta of the residents, which he found also contained lead.

This observation of 'natural' lead levels in Mexican farmers became the nucleus of Kehoe's position throughout his career. From this observation he concluded that lead in petrol presented no danger to the public, making the same mistake in argumentation that he had made with the Dayton workers. He assumed that general lead contamination was 'normal' and therefore 'natural' and harmless at those 'low' levels. It was not until the geologist Clair Patterson questioned this view some 30 years later that this argumentation was successfully challenged: 'normal' lead exposures in the 20th century were far from 'natural' (Patterson, 1965).

The Second World War years saw the economics and politics of TEL plumbing new depths. The Ethyl Corporation and Standard Oil had continued to develop their business links with Hitler's Germany which they had begun in the 1930s when Ethyl formed the German company Ethyl Gemeinschaft and Standard Oil linked up with the largest German company, I.G. Farben, one of the main corporate supporters of Hitler. This enabled them to provide the German war machine with the technical ability to improve the fuel efficiency of their tanks, lorries and planes by using leaded petrol (Box 3.7).

Industry control of both the economic and public agenda seemed complete by the 1950s but a new perspective was emerging from well outside the TEL community, which would soon seriously challenge industry's virtual dominance of this intellectual terrain.

Is 'normal' lead contamination really 'harmless'?

In 1965, Kehoe's monopoly on lead data was threatened by a geochemist from outside the public health debates. Clair Patterson was a research associate in geology at the California Institute of Technology. His measurements of the isotopic ratios of certain minerals convinced him that the long-held consensus of geologists that the age of the Earth was 3 billion years old was wildly wrong. Patterson's studies placed the age of the earth at 4.5 billion years, a serious challenge to the orthodox scientific view.

His findings were fiercely rejected by believers in the conventional paradigm but they were eventually confirmed, his sceptics refuted, and the geology textbooks revised.

Patterson uncovered the errors in the conventional geological view by employing extraordinary measures to avoid contamination while collecting and analysing his specimens. As a result his measurements were much more accurate than those of earlier workers.

Many scientists would have treated the contamination of his reagents as a technical annoyance to be overcome and then forgotten. To Patterson it was not a nuisance but a clear indication of lead contamination from human activities, which needed to be further investigated. From the depths of the Pacific Ocean he brought tuna to the surface with extreme care to avoid contamination. He studied pre-iron age mummies that had been buried in sandy soil and he sampled cores from the Greenland ice pack. By slicing the ice cores he was able to date the specimen precisely and show the time course of lead in the atmosphere.

Patterson and his colleagues showed that technological activity had raised modern human body lead burdens to levels that were some 600 times higher than that of our pre-industrial ancestors.

In 1965, in response to an invitation by the editor of the *Archives of Environmental Health*, he submitted a long article entitled 'Contaminated and natural lead

Box 3.7 TEL and 'treason' in Germany

In March 1942, Thurman Arnold, a US Assistant Attorney General, told a Senate Committee investigating war profiteering that without the leaded petrol from Ethyl, the Nazis could not have flown their planes or fuelled their land vehicles so efficiently. The Chairman of the Committee, Harry Truman, called the alliance between some American companies and I.G. Farben 'treason'.

A German memo found after the war supported his view: 'It need not be especially mentioned that without TEL the present methods of warfare would be impossible. The fact that since the beginning of the war we could produce TEL is entirely due to the circumstances that shortly before the war the Americans had provided us with the production plans complete with their know-how. It was moreover the first time that the Americans had decided to give a licence on this process to a foreign country ... and this only on our urgent request to Standard Oil to fulfil our wish' (Davis, 2007).

environments of man'. Kehoe was asked to review the manuscript and to decide whether it should be published. Kehoe argued for the paper's publication so that Patterson could be offered up for demolition. 'I should let the man, with his obvious faults, speak in such a way as to display these faults.'

He went on: 'The inferences as to the natural human body burden of lead are, I think, remarkably naïve. It is an example of how wrong one can be in his biological postulates and conclusions, when he steps into this field, of which he is woefully ignorant, and so lacking in any concept of the depth of his ignorance that he is not even cautious in drawing sweeping conclusions. This bespeaks the brash young man, or perhaps the not so young [Patterson was 43 at the time] passionate supporter of a cause. In either case, hardly the mark of the critical investigator. It must be faced and demolished, and therefore, I welcome its 'public appearance'.' (Kehoe, 1965).

Patterson's *Archives of Environmental Health* paper fundamentally altered the vocabulary of the debate over the health effects of lead. He recognised that because a certain level of lead was commonplace it did not mean it was without harm. He argued that the term 'normal' should be replaced by 'typical'. 'Natural' should be reserved for those concentrations of lead that existed in the body or environment before contamination by human activities.

It also showed that the so-called 'unexposed' subjects in Kehoe's studies of the Dayton plant workers, or his Mexican farmers, were contaminated by lead, and this lack of a truly unexposed part of the study population would dilute or hide risks of exposure. This dilution of risks by background contamination is now a much more common problem for public health, given the widespread exposures of most people to low levels of chemicals and radiations.

The *Archives of Environmental Health* paper released a fusillade of angry responses from orthodox toxicologists. Their fury focused on Patterson for his hubris in stepping outside his field to talk about people instead of rocks, but they also attacked the editor of the *Archives* journal. This is another example of 'shooting the messenger' which pervades this and most other 'Late Lessons' stories, from John Snow and cholera in 1864 (EEA, 2001) to those current scientists who publish warnings of hazards about climate change, genetically modified organisms and electromagnetic fields.

The controversy over Patterson's paper crystallised the opposing views held by him and Kehoe. Those who adhered to Kehoe believed that lead poisoning occurred only at high doses with obvious signs of severe illness. Patterson clearly spelled out the other position: elevated levels of lead found in all humans were associated with sometimes silent disturbances in body chemistry. Perhaps, Patterson argued, everyone was poisoned to some extent.

For the TEL industry, however, much more than professional reputation were at stake. A group from Ethyl Corporation visited Patterson and tried, in his words, to 'buy me out through research support that would yield results favourable to their cause.' He refused to cooperate (Patterson, 1992).

Following the meeting with Ethyl, his longstanding contract with the Public Health Service was not renewed, and his substantial contract with the American Petroleum Institute was terminated. Members of the Board of Trustees at California Institute of Technology visited the chairman of his department asking that he be fired. Patterson responded with a lecture in which he predicted that future scientists would show that Ethyl's activities were poisoning both the environment and people, and that their operations would eventually be shut down.

Publicly vilified and professionally threatened, Patterson would eventually be recognised by the scientific establishment for his extraordinary contributions to science. He would win the Goldschmidt Medal, the equivalent of the Nobel Prize in geochemistry, be elected to the National Academy of Sciences, and have both a mountain peak in Antarctica and a large asteroid named after him. He also provided the main character for a Saul Bellow novel (Box 3.8).

3.6 1966: US Congress asks awkward questions

In 1966, Senator Edward Muskie, Chairman of the Senate Subcommittee on Air and Water Pollution, presided over hearings on the future Clean Air Act of 1970. He gave considerable attention to the status of lead in the air and in petrol. The Surgeon General, William Stewart, one of the first to testify, gave testimony that revealed the government's concern, perhaps for the first time, about the effects of lead at low doses, particularly in children and pregnant women:

> 'Existing evidence suggests that certain groups in the population may be particularly susceptible to lead injury. Children and pregnant women constitute two of the most

Box 3.8 Saul Bellow and 'zones of incomprehension' in scientists

In *The Dean's December*, Saul Bellow described Professor Sam Beech, a character easily recognisable as Clair Patterson, his friend. 'These scientists were diapered babies when they went public with a cause. But Beech somehow inspired respect … He had authoritatively dated the age of the earth, had analysed the rocks brought back from the moon.'

Bellow describes Beech's theories about the relationship between lead and social disorder and the chilly reception they received from the orthodoxy. 'Here science, which itself was designed for deeper realisation, experienced a singular failure. The genius of these evils was their ability to create zones of incomprehension. It was because they were so fully apparent that you couldn't see them' (Bellow, 1982).

> important of such groups. Some studies have suggested an association between lead exposure and the occurrence of mental retardation among children' (Needleman, 2000).

Once again Kehoe was the industry's principal witness. Two years earlier he had said that enough was known about TEL toxicity to allow the amount of TEL to be increased without risk, noting: 'that no other hygienic problem in the field of air pollution has been investigated so intensively, over such a prolonged period of time, and with such positive results'. When Muskie pointed out that the Public Health Service and others disagreed with Kehoe and that many felt that there were unanswered questions and a need for more research, Kehoe responded:

> 'I would simply say that in developing information on this subject, I have had a greater responsibility than any other persons in this country. The evidence at the present time is better than it has been at any time that this is not a present hazard' (Needleman, 1998).

However, Muskie pressed on: 'would it be desirable if a substitute for lead in petrol could be found?' Kehoe replied: 'There is no evidence that this (TEL) has introduced a danger in the field of public health … I may say the work of the Kettering Laboratory … has established that ... lead is an inevitable element in the surface of the earth, in its vegetation, in its animal life, and that there is no way in which man has ever been able to escape the absorption of lead while living on this planet'.

One week later Clair Patterson testified. He began by attacking the belief that natural lead cycling and human activity contributed about the same amount of lead to the environment. About 10 thousand tonnes of lead were naturally recycled each year, he said, while millions of tonnes were emitted due to industrial and transport emissions. Large numbers of people are sickened, he believed, as a result of this unnatural load, and the brain is the most significant target. Patterson attacked the PHS for relying on industry data:

> 'It is not just a mistake for public health agencies to cooperate and collaborate with industries in investigating and deciding whether public health is endangered; it is a direct abrogation and violation of the duties and responsibilities of those public health organisations. In the past, these bodies have acted as though their own activities and those of the lead industries in health matters were science, and they could be considered objectively in that sense. Whether the best interests of public health have been served by having public health agencies work jointly with representatives of the lead alkyl industries in evaluating the hazards of lead alkyl to public health is a question to be asked and answered.'

Industry had traditionally measured the prevalence of lead toxicity by counting deaths, or at least severe damage to the brain. Muskie raised the question of a larger pool of unrecognised toxic illness, an issue that had been first raised at the one day trial of leaded petrol in 1925 (Needleman, 2000): 'Is it conceivable that there is something different in the deleterious effects on health from low-level exposure than from more concentrated exposure leading to classical lead poisoning?'

Patterson replied: 'when you expose an organism to a toxic substance it responds in a continuum, to continuously changing levels of exposure to this toxic substance. There is no abrupt change between a response and no response. Classical poisoning is just one extreme of a whole continuum of responses of an organism, human organism, to this toxic metal.'

Muskie's inquiry marked the government's shift away from complacency about the hazards of lead. His Senate hearings established a new premise: that lead poisoning was not only a disease of workers; it could be an insidious, silent danger to the public. The notion that lead poisoning was an all-or-nothing phenomenon was discredited and replaced by degrees of disease spanning across a biological continuum of 'effects' to 'adverse effects'. The issue still dominates current discussions about chemicals, radiation and other public health hazards, where early 'effects' are often dismissed as having no biological or ecological significance.

3.7 Lead in petrol poisons catalytic converters — so it's got to go

In 1962 GM sold Ethyl and in 1970 GM announced that it would begin installing catalytic converters in its new models in order to comply with the Clean Air Act of 1970. As a result, GM stated, it would be necessary to phase out lead in petrol as it was poisonous for the platinum in the catalytic converter. Apparently, poisoning a technology was more important than poisoning people.

To Ethyl's management this was a betrayal and they resolved to fight the growing environmental movement in the United States. They argued that it was fully justified to speak out for this additive, which had saved billions of dollars for the American economy and helped make the modern automobile possible. To combat lead regulation, it formed a defence team and called it, with unconscious irony, the 'Ethyl Air Conservation Group'. The Group was staffed with Ethyl officials and members of the Hunton and Williams law firm. Lawrence Blanchard, a partner in Hunton and Williams and board member of Ethyl, headed the group.

EPA medical officers continued to push for a separate health standard, fearing that if a substitute for platinum were discovered sometime in the future, lead would return to fuel. In 1973, aware that 200 000 tonnes of lead were emitted from the exhausts of American cars each year, the EPA promulgated a regulation phasing down lead content in all petrol. Its target was to reduce lead in petrol to 0.5 g/gal within five years (Schoenbrod, 1980).

The TEL industry responded by skilfully exploiting the growing national anxiety about fuel supplies caused by the spike in the price of oil, which had reached unprecedented levels by 1973. The EPA estimated that the oil penalty from phasing out lead was 30 000 barrels per day. Industry's calculations were different: on 2 December 1973 a full page advertisement appeared in *The New York Times* showing an oil barrel bearing an American flag pouring oil down a manhole. Its headline proclaimed that removing lead from petrol would have the effect of dumping one million barrels of oil a day.

On 6 December 1973, however, the EPA released the final regulations requiring a phased reduction of lead in petrol to protect health. Ethyl Corporation and DuPont sued in court, arguing that removing lead would cost an enormous amount of money and crude oil resources; that no one had been poisoned by lead in air; and that any effects in humans reported at low doses of lead were not **adverse** health effects. The court agreed with industry, setting aside the regulations as 'arbitrary and capricious'.

On appeal, the earlier judgement was overturned and the EPA regulations upheld. The court stated that 'the regulatory action under this precautionary statute [the Clean Air Act] should precede, and hopefully prevent, the perceived harm.' Furthermore, 'in making his policy judgment by assessing risks the Administrator is not required to limit his consideration to the danger presented by lead additives 'in and of themselves'. He may consider the cumulative impact of lead additives with other sources of human exposure to lead' (Ethyl Corp. v Environmental Protection Agency, 1976).

Ethyl, PPG Industries, DuPont, NALCO Chemical and the National Petroleum Refiners Association then appealed to the Supreme Court, where they lost.

3.8 Public funding to study lead poisoning in children

In 1970, the US Surgeon General had called for early identification of children with 'undue' lead exposure. His statement avoided the loaded term 'poisoning' but indicated that this was probably more lead than a child should have. For the first time since 1925 significant research funds were allocated from Federal sources to study the health impacts of lead on children. The industrial monopoly on scientific data was drawing to an end.

Professor Herb Needleman was one of the public health scientists who used the recently released public funds to research the low-dose effects of lead on children's IQ. His seminal paper on the subject (Needleman et al., 1979) showed that the higher the lead content, the greater the negative impact on IQ. His work shifted another paradigm by focusing not on the **flow** of blood through the body but on the

Box 3.9 Lead in petrol: 'it's all about economics...'

Late one night after a long day's work on the issue of lead in petrol, Herb Needleman and others from the EPA expert committee had dinner at the home of an EPA staffer. After dinner and a liberal amount of red wine, Needleman asked Jacobs from DuPont why, with its wealth of excellent research chemists, it had not developed a safer petrol additive to replace TEL. In Needleman's words:

'Jacobs, who had matched my intake, told me that their economists had modelled the future sales of leaded gasoline and projected that the consumption of gasoline would soon level off, and perhaps decline. Given such a projection, the company would not invest USD 100 million in research and development funds. I learned a valuable lesson that night: the entire debate about scientific studies, about the health risks for children, was merely a shadow play. The real decision had been made by DuPont's economists. Their plan was clear: don't budge on TEL and seek medical and environmental arguments to support the choice' (Needleman, 2000).

stocks of lead in the bones. His innovation was to analyse 'milk' teeth from more than 2 000 infants and to correlate their lead content with their later development in terms of intelligence and behaviour.

He observed that the average IQ of this group of children fell by 5 points, a shift that was dismissed by industry as 'small' and insignificant. This view ignored the effect on very large groups of children who were at both ends of the normal distribution of IQ, i.e. those either severely handicapped or exceptionally gifted, whose numbers would be doubled and halved respectively (Bellinger and Bellinger, 2006) (5).

Industry responded to this dramatic observation with unprecedented opposition, resorting eventually to a character assassination of Needleman.

Needleman later followed up the 1943 Byers discovery of the **chronic** anti-social behaviour of children who had 'recovered' from **acute** lead poisoning, confirming the association between childhood lead poisoning and anti-social adolescent behaviour (Needleman, 1996). Studies have further confirmed the link between lead and anti-social behaviour (WHO, 2010).

3.9 1977–1995: the phase down of lead in petrol

The EPA published its *Air quality criteria for lead* in December 1977, which stated that lead in air and in dust was a significant source of human exposure to lead, and that brain damage could occur in individuals with no acute symptoms of lead poisoning. The Air Office of EPA used the new criteria document to determine a standard for lead concentrations in air.

With the new standard in place and the gradual retirement of old cars that ran on leaded fuel, air lead levels began to fall. In 1977 air concentrations in Philadelphia ranged between 1.3 and 1.6 μg/m^3, whereas by 1980 the concentrations were between 0.3 and 0.4 μg/m^3 (Needleman, 2000). Similar trends were observed in most major cities.

Between 1976 and 1980, the amount of lead consumed in petrol production dropped by 50 % and the blood lead level of the average American dropped by 37 %. Furthermore, in its second volume of the *Air quality criteria for lead* the EPA concluded that, contrary to the claims of the industry, the relationship between petrol production and air lead levels was causal. It noted that between 1975 and 1984 the lead consumed in petrol had decreased 73 %, while the corresponding composite maximum quarterly average of ambient air lead had decreased by 71 % (USEPA, 1986).

In the 1970s the toxic threshold for lead in blood was defined as 60 μg/dl. The reduction of blood lead levels gradually allowed comparisons with children whose background blood lead levels were 1μg/dl or less. As a result, effects of lead on children's IQ have been found at levels below 10 μg/dl, with most of the cognitive impairment seeming to occur at blood lead levels as low as 5 μg/dl (Lanphear et al., 2000).

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(5) Chapter 23 on costs of inaction provides an illustration of this effect in Figure 23.1.

Box 3.10 Lead levels in blood decline

The phasing-out of leaded petrol between 1976 and 1995 was associated with a more than 90 % reduction in the mean blood lead concentration (Annest et al., 1983; CDC, 1997; Jones et al., 2009). The percentage of children in the United States aged between one and five with blood lead levels greater than or equal to 10 µg/dl declined from 77.8 % in the late 1970s to 4.4 % in the early 1990s, and the average lead level of a child in the United States declined to 1.9 µg/dl between 1999 and 2002 (CDC, 2005). At the same time, lead was eliminated from solder used in food cans and new residential paint products (President's Task Force, 2000). An estimated gain of 5–6 points in mean population IQ score was associated with the decline in mean blood lead concentrations, and this gain in IQ has been calculated to yield an annual economic benefit of between USD 100 billion and USD 300 billion in each birth cohort on the US (Grosse et al., 2002).

Similar reports of success in reducing the harm from lead in children level were achieved in Europe and elsewhere as they began to phase out lead in petrol.

In a number of rapidly industrialising countries, too, including China, El Salvador, India, Mexico and Thailand, declines in blood lead levels have followed the removal of lead from petrol (OECD, 1999; Mathee et al., 2006; He et al., 2009). Worldwide, unleaded petrol now accounts for an estimated 99 % of total sales.

Source: WHO, 2010.

Box 3.11 Continuous reductions in the 'safe' level of lead 1960–2010

In the 1960s, an elevated paediatric lead level was defined by the United States Department of Health and Human Services Centers for Disease Control and Prevention (CDC) as a concentration in whole blood of 60 µg/dl.

In the 1970s, the level was reduced to 40 µg/dl, and then to 30 µg/dl. In the 1980s, it was reduced to 25 µg/dl. Most recently, in the early 1990s, the CDC reduced the blood lead level of concern to 10 µg/dl, the level that remains in place today (Surkan et al., 2007).

An international pooled analysis of data from seven cohorts showed an increase in blood lead level from less than 1 µg/dl to 10 µg/dl was associated with a six IQ point decrement, which is considerably greater than the decrement associated with an increase in blood lead level from 10 µg/dl to 20 µg/dl. (Lanphear et al., 2005).

In 2004, 16 % of all children worldwide were estimated to have levels above 10 µg/dl (WHO, 2010).

In 2010 the European Food Standards Agency withdrew its support for a provisional tolerable weekly intake guideline value on the grounds that it was inadequate to protect against IQ loss (EFSA, 2010).

3.10 The pros and cons of leaded petrol

Leaded petrol was finally completely phased out in the US in 1995, seventy years since the 'one day trial' in 1925.

The benefit of taking lead out of petrol exceeded the predictions of even the most convinced lead advocates. Lead levels in children's and adults' blood continued to drop in direct relationship to the reduction in lead in petrol. The average American child's blood lead level in 1976 was 13.7 µg/dl. In 1991 it was 3.2 µg/dl and in 2000 it was 2.0 µg/dl (WHO, 2010).

The health and other costs of lead damaged workers, child bearing women and children to the taxpayer, the Health service and to the economy have been huge and have persisted for decades after the leaded petrol phase out, as contamination persists in soils and dusts (Mielke, 2010). This damage to health has also had large economic consequences as outlined in Box 23.1 in Chapter 23.

Panel 3.2 EU policymaking on lead in petrol — a brief summary

Nigel Haigh (6)

EU policymaking on leaded petrol emerged mainly from the activities of the UK and Germany. In 1971, the UK government received advice from its Chief Medical Officer that air lead levels should not be allowed to increase above current levels. The government responded by deciding on a phased three-stage reduction in petrol's lead content, from 0.84 to 0.4 g/l to be achieved in 1976. This phase down was then delayed and the deadline postponed until required by the subsequent EC directive. In the same year the German government decided to reduce lead levels but chose a faster programme, which was implemented as planned: 0.4 g/l in 1972 and 0.15 g/l in 1976.

In both countries this initial action arose in response to scientific advice, without much public pressure. The more leisurely approach of the UK government was possibly linked to the fact that the largest European plant then manufacturing lead additives for petrol was in the United Kingdom.

In 1971 the UK was not yet a member of the European Communities (EC) and it was Germany's unilateral decision that resulted in the EC Commission establishing two committees in 1971 to study the health and technical aspects of lead pollution from motor vehicles. The memorandum concluded that although there was no immediate danger to public health, it was desirable to prevent an increased lead pollution in air. Increasing car use and cross-border sales of petrol by oil refiners therefore warranted EC-wide limits on lead in petrol.

On 10 November 1975, at the European Parliament, the rapporteur of the Environment Committee said that the proposed second stage reduction of lead to 0.15 g/l for regular grade had met with insurmountable opposition in the Committee because it would have required industry to make substantial investments and increased petrol consumption. Since these objections could not be refuted, the Committee preferred to require the Commission to postpone the introduction of the second stage. The Committee did, however, approve the first stage limit of 0.4 g/l.

All subsequent discussion in the Council — where decisions then had to be taken unanimously — was coloured by the existing German limit of 0.15 g/l. Directive 78/611 therefore had to allow Member States to introduce national limits of 0.15 g/l but its main provision was an upper limit of 0.4 g/l.

This example shows how in favourable circumstances a determined Member State can lead its peers despite considerable opposition and scientific uncertainty. In doing so, Germany ensured that higher environmental standards were achieved more quickly than if the Member States had proceeded at their own pace.

In the United Kingdom in 1981, following the report of a scientific committee on lead and health, chaired by Professor Lawther (Lawther, 1980), and of a government working party on lead in petrol (WOPLIP) (UK Department of Transport, 1979), the government decided to require petrol's lead content to be limited to 0.15 g/l, the lowest level that could be required under the Directive. It did not propose lead-free petrol. This recommendation followed a major battle within government: the health and environment ministries were defeated on the second point by transport, energy and the treasury.

Then there was a dramatic change in policy. In April 1983 the Royal Commission on Environmental Pollution (1983) recommended that the government initiate negotiations with the European Commission and other Member States to secure removal of the lower limit of lead in petrol in Directive 78/611 so that at the earliest practicable date all new cars should be required to run on lead-free petrol. The Government immediately accepted this recommendation.

Between these two decisions in the UK (1981 and 1983) there was an extraordinary public campaign. A new organisation called CLEAR (campaign for lead-free air), supported by a millionaire, provided very effective political lobbying and also publicity for the scientific information. It is possible that the Royal Commission only decided to look at the issue of lead because of the campaign, although that is not the view of its Chairman (Richard Southwood). What can be said with some certainty is that the government only endorsed the Commission's conclusions so quickly (within half an hour of publication) because of the campaign and because of an imminent general election.

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(6) This panel is based on extracts from Haigh (1998).

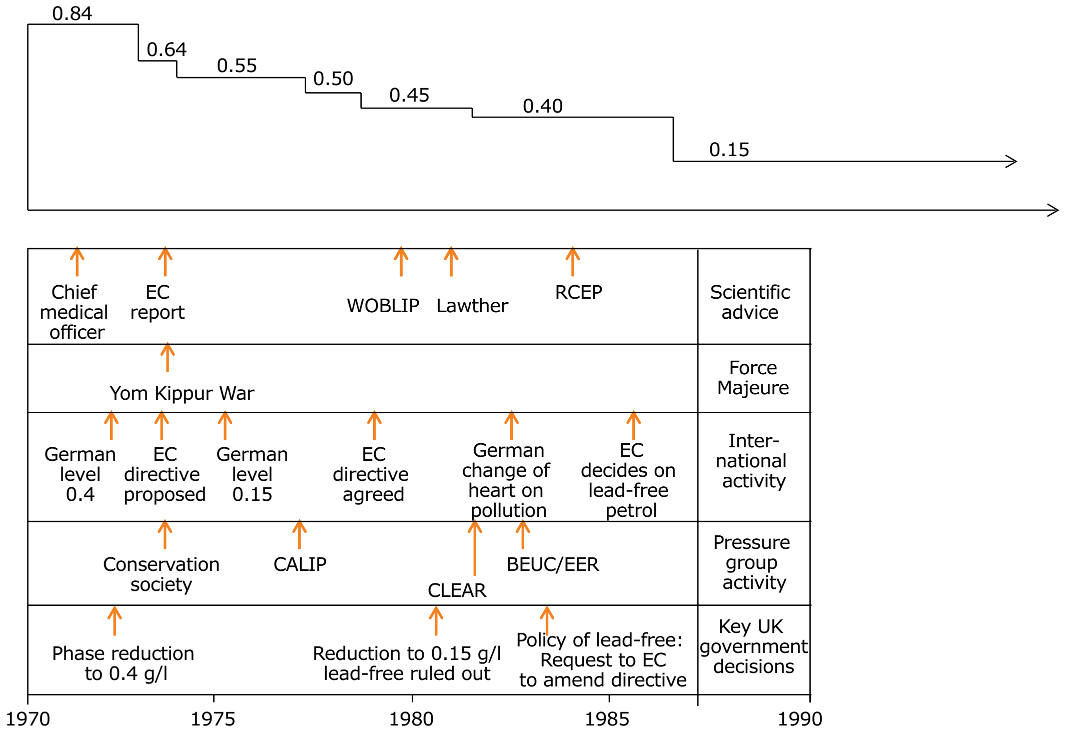
Panel 3.2 EU policymaking on lead in petrol — a brief summary (cont.)

When the first approaches were made to the European Commission in April 1983 the reaction was negative but the coincidence that changed the debate was the concern in Germany about forest die-back, partly caused by air pollution. Germany realised that to achieve its objective of significant NO_x reductions from cars, catalytic converters would be required. Since lead poisons catalytic converters, it would have to be removed. Germany, together with the Netherlands and Denmark, then supported the UK initiative and Directive 85/210 was adopted.

The catalysts for action in the United Kingdom and Germany were similar, but public conscience was excited by two quite different issues: public health and death of forests. It is pure chance that they came together at the same time and if either had been missing it is quite possible that the directive would not have been agreed, or not agreed so quickly. If we are tempted to speculate further, what would have happened if someone had invented a lead tolerant catalytic converter?

Science plays a unique and essential role in informing the public and influencing and guiding public opinion which is a major determinant of policy. But science itself does not always reach the public at a specific point in time when a specific decision is called for. Since we cannot yet claim that there is a European public, but only a collection of national and regional publics, the way the policy debate develops under the pressure of public opinion, more or less informed by science, is very likely to differ between countries. European policymaking is very much about reconciling these differences.

Figure 3.1 **Key events which help to explain reduction in lead levels in petrol in Germany, the United Kingdom and the EU**



Source: Reprinted with permission from Haigh, 1998.

Panel 3.3 Lead in petrol: a reflection on the German experience

Hans von Storch et al. (7)

Environmental matters in the early 1970s featured strongly in German politics (Peters, 1980), and Germany was the first European country to impose restrictions on the lead content in petrol. From 1972, German production and importation of petrol with more than 0.4 g Pb/l was prohibited (down from the usual 0.6 g Pb/l), and from 1976 the stricter limit of 0.15 g Pb/1 was imposed. A preliminary analysis of newspaper coverage found that the health dangers of leaded petrol entered the German press in the 1960s. Comparable British articles at that time focused on urban smog.

Unleaded petrol (0.013 g Pb/1) was introduced in Germany in October 1984. Prohibiting the sale of leaded petrol in Germany was not an option because the European Union did not then allow such trade restrictions among its members. Instead, Germany introduced tax incentives for unleaded petrol in 1984, and in 1985 its availability at all German gas stations became mandatory. Enhanced tax incentives in 1986 made German unleaded petrol cheaper than the leaded variety, and its market share increased steadily.

In 1985, the EU mandated that by October 1989 super unleaded petrol had to be available for sale in all member states, alongside the leaded variety (Council Directive 85/210/EEC). In addition, member states were asked to adopt a 0.15 g Pb/1 limit voluntarily. Unleaded petrol was defined as containing no more than 0.013 g Pb/1. In 1987, Directive 87/416/EEC emphasised the importance of the availability of unleaded petrol for sale in every country. All Member States were then allowed to prohibit national production and sales of leaded 92-octane petrol because of damage to public health and the environment.

According to Löfgren and Hammar (2000), by 1995, unleaded petrol had conquered over 80 % of the market in Germany, Sweden, Finland, Denmark, the Netherlands and Austria, but less than 30 % in France, Greece and Portugal. Higher leaded petrol prices and the widespread adoption of cars using leadaverse catalysts were the two most important factors in reducing the market share of leaded petrol. Löfgren and Hammar also note the importance of effectively informing the public that unleaded petrol can safely be used with non-catalyst cars.

Road lead emissions totalled an estimated 31 000 metric tonnes in 1955 in Europe and this nearly quadrupled to 119 000 in 1975 with increasing car use. While road transport and petrol consumption continued to rise, subsequent petrol lead content regulations nearly halved road lead emissions to 62 000 tonnes in 1985. As unleaded petrol conquered increasingly higher market shares, road lead emissions dropped further to 42 000 tonnes in 1990 and to 19 500 in 1995.

Overall, favourable terms of competition were experienced by producers of cars with high technical standards, who had already gathered experience with catalyst systems on the US market (Hagner, 2000).

Blood levels in Germany with and without the reduction of lead in petrol

In the 1970s, lead in blood (PbB) values were reaching a level that health officials considered potentially harmful for foetuses and small children. To estimate how PbB levels may have developed if regulations of the use of lead in petrol had been implemented differently a model based on lead emissions was applied. In the case of no or delayed regulations, the model estimates that PbB levels well beyond the critical level would have emerged. Thus, the regulation instituted in Germany since the 1970s has reduced health hazards significantly.

The macroeconomic costs of the regulation seem to have been insignificant in spite of concerns that they would be substantial (Hagner, 2000). In fact, the case of leaded petrol demonstrated the limited utility of purportedly objective cost-benefit analyses, as the costs claimed at the time of the regulations turned out to be significantly biased, due to the vested interests that supported the analyses.

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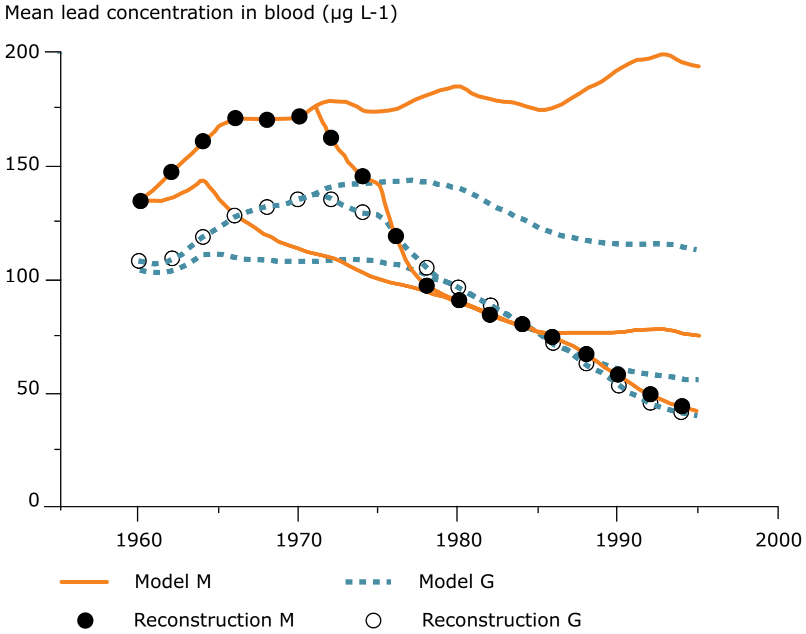
(7) Adapted from von Storch et al. (2003) with permission from authors.

Panel 3.3 Lead in petrol: a reflection on the German experience (cont.)

Figure 3.2 **Scenarios for mean PbB (µg L-1), as derived by the Münster model (M, orange, continuous) and for the Germany model (G, blue, dashed)**



Note: Scenario 1 presents an evolution without regulation (i.e. continuing use of 0.6 g/l lead in petrol in Germany, upper curves).

In scenario 2 no unleaded petrol has been introduced in Germany in 1985 (middle curves).

In scenario 3, the regulation was instituted in Germany already in 1961 (lower curves). The reconstructed lead levels in blood are also given as open (Germany model) and full circles (Münster model).

Source: Helmholtz-Zentrum Geestacht Centre for Material and Coastal Research

The conclusion of a successful regulation in terms of limiting risks for human health should not downplay the consequences of the introduction of tetraethyl lead as an anti-knock additive in petrol, in particular since alternatives were known and available already in the 1920s and 1930s (Kitmann, 2000). Heavy metals such as lead pose a large-scale and long-term environmental problem as reduced emissions have limited influence on accumulations in the soil, which will remain for centuries. The strategy of protecting the environment from persistent substances must be based on continuous assessment and precautionary principles (Johansson et al., 2001).

Panel 3.4 The UK experience — expert risk assessments and public campaigns

Erik Millstone

In the United Kingdom, a committee examined the possible dangers of TEL use and submitted their report to the Minister of Health in 1930 (Departmental Committee on Ethyl Petrol, 1930). The committee received advice from several experts, including Dr Kehoe and US Surgeon General Cummings.

Cummings had moved from initial concern to the enthusiastic promotion of TEL writing dozens of letters touting Ethyl leaded petrol to public health leaders around the world. The fact that Cummings reported to Treasury Secretary Andrew Mellon, whose Gulf Oil Co. had exclusive contracts to distribute Ethyl petrol in the south-eastern US, may have had something to do with his enthusiasm.

The committee concluded that 'the widespread use of Ethyl petrol as a motor fuel for motor vehicles would not, in our opinion, increase the proportion of particulate lead in the atmosphere of our streets to such an extent as to constitute a risk even to the health of that part of the population which is most exposed — namely, police officers on traffic control duty and drivers of motor and other vehicles'.

Given the assurances from this report, TEL readily came into use in the United Kingdom and the rest of Europe.

By the late 1970s there was evidence of high levels of lead exposure in Britain and strengthening evidence of the toxicity of lead, even at low levels of exposure. The UK government responded by establishing a committee of enquiry. The Lawther report (as it came to be known) reported in 1980 that: 'We have not been able to come to clear conclusions concerning the effects of small amounts of lead on the intelligence, behaviour and performance of children' (Lawther, 1980). That statement was highly controversial. It was subsequently repudiated by several members of the committee for having been overly timid and was criticised by other lead experts (Rutter, 1983; Bryce-Smith and Stephens, 1980). Despite downplaying the dangers of lead in petrol, Lawther nevertheless advised the government and industry to reduce emissions of lead into the atmosphere progressively, without explaining why that advice was provided.

The government subsequently tried to represent the report as if it had proved that children's blood lead levels were entirely harmless. And British Petroleum and Associated Octel, which produced leaded petrol, continued to downplay the toxicity of TEL and atmospheric lead pollution, and the British government resisted efforts to reduce the lead concentration in petrol.

In general, scientists adopted a very cautious approach. For example, a report under the auspices of the Medical Research Council concluded that: 'While the observed statistical associations detailed in this review are consistent with the hypothesis that low-level lead exposure has a small negative effect on the performance of children in ability and attainment tests, the limitations of epidemiological studies on drawing causal inferences are such that it is not possible to conclude that exposure to lead at current urban levels is definitely harmful' (MRC Advisory Group on Lead, 1988).

That approach was marginally modified after the Royal Commission on Environmental Pollution pointed out in 1983 that: 'We are not aware of any other toxin which is so widely distributed in human and animal populations and which is also so universally present at levels that exceed even one tenth of that at which clinical signs and symptoms occur' (RCEP, 1983).

The Lawther committee had recommended that if a child was found to have a blood lead level (or PbB) above 35 µg/dl then steps should be taken to ascertain the source of exposure, and to reduce them (Lawther, 1980). By then, however, evidence of adverse effects below that level was available implying a maximum blood lead target significantly below 35 µg/dL (Chishold, 1976; Needleman, 1979). The Lawther report also neglected to recommend the establishment of a screening programme to identify children with elevated blood lead levels. The committee did, however, recommend that 'There should be a programme for the detection of lead in paint coatings accessible to children in areas where a high incidence of old lead paint surfaces may be suspected, such as old inner city residential areas.' That recommendation was sensible but 30 years later has not yet been properly implemented.

Panel 3.4 The UK experience — expert risk assessments and public campaigns (cont.)

When in 1980, the Lawther Committee recommended that, where a child was found to have a PbB level above 35 µg/dL, an investigation should be conducted to identify and reduce their sources of exposure, it was merely reiterating a policy to which the British government and all other EEC Member States had already agreed three years previously. In 1981 the Department of Health went marginally further when it advised that any child with a PbB over 30 µg/dL should be followed up (Quinn and Sherlock, 1990).

In 1982 the UK government shifted its position and set a maximum figure or 'action level' for lead in the blood (PbB) at 25 µg/dL. When it did so, that decision was made by reference to the results of a blood lead survey rather than toxicological considerations. Surveillance work had indicated that the vast majority of the population then had PbB levels below 25 µg/dL, and therefore endorsing that figure as an 'action level' necessitated no further remedial action. This exemplifies the British government's practice of not setting lead targets until they had already been met.

Throughout the 1980s evidence that lead exerted adverse neurotoxic effects on children at ever lower levels of exposure continued to emerge, especially in the US, Greece and Australia. In the UK an influential pressure group, CLEAR, pressed the government to ensure that the use of lead as a petrol additive was ended. The response of the British authorities to those pressures was the classic tactic of establishing yet another investigative committee, this time under the auspices of the Medical Research Council (MRC). The question posed by the UK government to the MRC panel was: 'does the evidence on childhood neurotoxicity **prove** that levels of lead in British children are doing them obvious harm?' Implicitly, it set a particularly high evidential bar: indicative evidence short of proof would be insufficient. It did not ask: in which physiological system(s), and at which lowest level of exposure, are adverse effects detectable? If it had asked a question of that sort, a rather different answer would have been obtained. The government proposed only to act in the face of compelling evidence rather than, for example, the balance of probabilities.

Eventually, the MRC committee produced two reports. The first one sat resolutely on the fence; it just listed several of the important studies, emphasised their methodological limitations and suggested that if lead was having an adverse neurological effect on British children, the effect was a small one (MRC, 1984).

By 1988, several further studies had emerged, and the second report (MRC, 1988) focused on those recent studies. The committee emphasised many of the methodological limitations of the studies but acknowledged that in the intervening four years the evidence had strengthened. It accepted that 'low level lead exposure has a small negative effect on the performance of children in ability and attainment tests', and so concluded that 'it would be prudent to continue to reduce the environmental lead to which children are exposed.' That final remark was an acknowledgement that the levels of lead to which British children were then being exposed were unacceptably high, although it was couched in language designed not to provoke public anxiety.

In 1987 the United Kingdom eventually started to facilitate the increasing use of unleaded petrol after a preferential tax rate on unleaded fuel was introduced. That policy was adopted to facilitate the use of catalytic converters in motor vehicle exhaust systems rather than in response to evidence of lead's neurotoxicity. Curiously, official efforts to monitor childhood blood lead levels in British children then came to an end, so detailed evidence indicating the beneficial effects of phasing out leaded petrol in the UK have been only fragmentarily documented. It remains difficult, moreover, to estimate the proportion of children in the United Kingdom with elevated blood lead levels.

When the preferential tax change was introduced in 1987, the UK was one of the last industrialised countries to embrace unleaded petrol. It has been difficult to establish the extent to which the slow pace of change could be attributed to the fact that one of the world's main producers of lead tetra-ethyl (Associated Octel) was located in the UK. Nonetheless, it is noteworthy that in the summer of 2010 two former senior executives of Octel were convicted of having bribed government officials in Indonesia and Iraq to continue allowing the use of tetra ethyl lead as a fuel additive in those countries (Leigh et al., 2010).

Of course, leaded petrol also brought many benefits. It improved the energy and fuel efficiency of cars and other vehicles, provided thousands of jobs and generated much profit for the lead, oil and car industries of America, Europe and elsewhere. These benefits could, however, have been attained by alternative uses of the economic capital involved. Indeed, a 10-year phase out of leaded petrol at any time since 1925 would have encouraged innovators to develop less hazardous and perhaps more efficient fuel additives and engine designs. Since the early 1900s, such innovations have been widely recognised as a useful defence against high oil prices and insecure oil supplies.

3.11 European reflections on phasing out leaded petrol

Campaigns to take lead out of petrol in other countries went through similar phases and arguments. Panels 3.2, 3.3 and 3.4 provide European reflections on lead in petrol, focusing on the EU, Germany and the United Kingdom.

In Europe the legacy of leaded petrol and other sources of lead, such as old mines and lead shot, that can contaminate the food chain via soils and water still pose a threat to the neurodevelopmental health of some children in Europe (EFSA, 2010), as well as to wildlife (Mateo et al., 2007; Rodriguez-Estival et al., 2012).

Meanwhile, lead in electronic waste is an emerging hazard for children in poor countries in Asia and Africa, where waste from rich countries is dumped (Box 3.12).

3.12 Some late but contemporary lessons

The lessons from the story of leaded petrol are divided into two groups: lessons from the science and lessons from the influence of society on the science. In addition there are some lessons concerning some of the main arguments about the epidemiology that are relevant to many current controversies and which are therefore discussed in Chapter 26 on science for precautionary decision-making.

3.12.1 Some general lessons from the science

1. Much of the early evidence on lead poisoning came from the high exposures of fit, adult, usually male workers. Such findings were widely seen as irrelevant to the much lower exposures of the public to lead in petrol. However, the public can be more vulnerable to low doses of poisons because of sub-groups who are more sensitive to toxicants than workers, such as children, infants, foetuses, the elderly, the sick, pregnant women and the immuno-compromised. In addition, the public are often exposed for up to 24 hours a day and from multiple sources of the same poison via several routes e.g. ingestion and skin absorption from food, water, dust and consumer products, as well as via the inhalation of polluted air. Great care must therefore be taken in assuming that evidence from highly exposed occupational groups, or from low exposures to average populations, is not relevant to sensitive public groups.

2. Much reliance was initially placed on evidence from mortality, or from short-term (acute) poisoning. This can be a poor guide to

Box 3.12 Lead in electronic waste: an emerging hazard

With the global proliferation of computers, cellular telephones and other electronic equipment — as well as rapid cycles of replacement and obsolescence of these instruments — an enormous amount of electronic waste is now generated each year worldwide. Much of this waste — or electronic material near the end of its useful life — is shipped to low-income countries where large numbers of workers in both the formal and informal sectors separate lead, mercury and other metals from the waste for recovery and recycling. In the informal sector, much of the work is performed by children. Elevated lead levels in dust and blood have been reported in the communities and the children performing this work (Xia Huo et al., 2007). In 2004, 16 % of all children worldwide were estimated to have levels above 10 µg/dl (WHO, 2010).

In 2010 the European Food Standards Agency withdrew its support for a provisional tolerable weekly intake guideline value on the grounds that it was inadequate to protect against IQ loss (EFSA, 2010).

long-term (chronic) effects on morbidity such as neurological or reproductive damage.

3. Key assumptions that are critical to outcomes of harm or its absence were confidently asserted rather than demonstrated. For example, the initial assumption from the lead industry, in reply to the US Surgeon General's query about possible health hazards from leaded petrol, was to state that there were none, 'although no actual experimental data has been taken'. This was an early example of assuming that 'no evidence of harm' is the same as 'evidence of no harm' when no relevant research is available to support that assumption. This is a still a common mistake in public health.

4. Another key assumption was that the intake of lead into the body was counteracted by excretion, which was sufficient to achieve a harmless physiological balance, whereby no, or only minimal accumulation of lead in the body would take place. This assumption was not supported by actual evidence of the absence of lead accumulation.

5. Early studies of workers and Mexican farmers did not serve as unexposed control groups as they too were contaminated with lead. When 'unexposed' control groups are also contaminated then true risks will be underestimated.

6. The first study of consumer risks from lead in petrol was too small and short term to detect effects other than acute and gross ones and it was not followed up by the publicly funded longterm monitoring that its authors strongly recommended.

7. Experimental studies in animals documented adverse effects of lead from environmentally relevant concentrations but this evidence was frequently ignored or regarded as irrelevant for humans.

8. Extensive scientific debates, sometimes focusing on diversionary details, or based on the potential for exploiting or even manufacturing scientific doubt helped to maintain the impression that the adverse health effects of environmental lead pollution were unproven. It is often more convenient for a hazardous industry to debate the science than to discuss options for reducing hazards.

9. It was assumed that there was a threshold between biological effects and 'adverse' effects. This is still a dominant assumption in conventional toxicology despite the accumulating evidence that biological effects can be critical steps on the way to adverse effects, as Patterson pointed out in the 1960s. There is usually a biological continuum and not a discrete change. This means that action to avoid significant biological 'effects' will often be needed if we are to prevent, as opposed to merely observe, 'adverse effects'.

3.12.2 The influence of society on science

1. For several decades after the introduction of leaded petrol in the 1920s, virtually no independent research was carried out, and the main source of information was industry and industry-sponsored researchers. It took more independent scientists from outside this group, such as Patterson in the 1960s and Needleman in the 1970s to show, for example, that 'typical' body burdens of lead arising from human activities were not 'normal', as industry claimed, but were hundreds of times higher than before the industrial revolution, and were therefore likely to be harmful, especially to the brains of children.

2. There is a need for sufficient incentives and funds for independent long-term prospective monitoring of potential health hazards when new technologies are introduced.

3. The established and specific technical and economic benefits from leaded petrol, which largely accrued to particular and powerful minorities, were contrasted to the unproven, more general and future health threats to the public. This was an unequal contest, which even influenced many public health specialists, who allowed their appreciation of 'the gift from God', as the car industry described leaded petrol, to override their scientific concerns about health effects.

4. Public health is well served when scientists who discover hazards, especially when funded by the public, play an active role in disseminating both their results and their implications for precautionary or preventive action. Alice Hamilton, Yandell Henderson, Craig Patterson and Herbert Needleman played this role in the US leaded petrol story.

5. Each wave of 'early warning' scientists in the leaded patrol saga, from Yandall Henderson in the 1920s, to Byers in the 1940s, Patterson in the

1960s and Needleman in the 1980s, had either their funding withdrawn, their jobs threatened or their characters assassinated. They share such experiences with other 'early warning' scientists. Such scientists need more support from society via recognition for their work, help with their defence and legal protection against discrimination. This issue is picked up in Chapter 24 on protecting early warners and late victims.

6. The concrete record of decision-making by industries, scientists and governments need to be made publicly available if history is to stand a reasonable chance of being understood and providing relevant lessons for the future. This usually only occurs many years after the relevant events and then only via legal cases for compensation.

Table 3.1 Early warnings and actions

Year	Event
2nd century BC	First published record of occupational lead poisoning by Nicander.
1695	The count of Württemberg bans lead addition to wine based on Eberhard Gockel's study of lead poisoning in the city of Ulm.
1892	First report of poisoning cases in children from old lead paint.
1920	Leaded paint is banned in Australia and later in Europe.
1921	The octane-boosting property of tetraethyl (TEL) lead is discovered.
1921–1923	Ethanol-based alternative additives are considered by Du Pont and GM but rejected as less profitable than TEL, which goes into production.
1923–1924	Deaths of TEL workers lead to its temporary suspension.
1925	The 'one day trial' of TEL leads to its approval by an expert committee but only under careful monitoring and regulations, which do not take place.
1930–1960s	Kehoe and the TEL industry dominate the research field for next 50–60 years asserting that widespread human lead exposures are 'natural' and therefore safe — and that only acute, clinical effects are serious.
1943	Byers and Lord report chronic brain damage and anti-social behaviour in lead-poisoned children
1965	Patterson reports that current lead exposures are 100 times higher than natural levels and dismisses Kehoes' argument that 'normal' is 'natural'.
1966	Senator Muskie and US Congress start asking questions about leaded petrol and Patterson asserts the likelihood of no safe threshold with a continuum between effects and adverse effects.
1970	US Clean Air Act comes into force. GM announces the phase out of leaded petrol as it poisons the catalytic converters needed to secure the Act's targets for NO_x ,SO_2 and other air pollutants.
1971	UK and Germany begin to reduce permitted levels of lead in petrol.
1973	The US EPA introduces regulations to reduce lead in petrol but is opposed in the courts by industry.
1976	The EPA wins the court case on appeal.
1977	The EPA recognises the existence of subclinical lead poisoning due to environmental lead exposure.
1979	Needleman and colleagues report dose-related mental deficits in children with background lead exposures.
1983	A European Commission study with lead isotopes in northern Italy demonstrates that petrol additives cause substantial human exposures.
1984	Germany introduces low-lead petrol and other countries follow.
1985	A European Commission directive requires Member States to make unleaded petrol available and lowers the limits of lead permissible in petrol.
1995–2000	Virtually all western Europe only uses lead-free petrol.
2013	Nearly all countries worldwide have phased out leaded petrol. Legacy lead persists in water and soils threatening the neurodevelopmental health of some children.

References

Annest, J.L., Pirkle, J.L., Makuc, D., Neese, J.W., Bayse, D.D., Kovar, M.G., 1983, 'Chronological trend in blood lead levels between 1976 and 1980'. *N Engl J Med,* (308/23) 1 373–1 377.

Baker, G., 1768. 'An inquiry concerning the cause of the endemial colic of Devonshire', *Med Trans*.

Bellinger, D., Leviton, A., Waternaux, C., Needleman, H. and Rabinowitz, M., 1987, 'Longitudinal analysis of prenatal and postnatal lead exposure and early cognitive development', *New Engl. J. Med.*, (316) 1 037–1 043.

Bellinger, D.C. and Bellinger, A.M., 2006, 'Childhood lead poisoning: the torturous path from science to policy', *J. Clin. Invest.*, (116) 853–857.

Bellow, S., 1982, *The Dean's December*, Harper & Row, Publishers Inc., USA.

Blackfan, K., 1917, 'Lead poisoning in children with especial reference to lead as a cause of convulsions', *Am. J. Med. Sci.*, (153) 877–887.

Bryce-Smith, D., Stephens, R. and Mathews, J., 1978, 'Mental health effects of lead on children', *Ambio*, (7) 192–203.

Bryce-Smith, D., Stephens, R., 1980, *Lead or health*? Conservation Society Pollution Working Party, London.

Byers, R.L. and Lord E.E., 1943, 'Late effects of lead poisoning on mental development', *Am. J. Dis. Child*, (66) 471–483.

CDC, 1997, Update: blood lead levels — United States, 1991–1994. *Morbidity and Mortality Weekly Report*, (46) 141–145.

CDC, 2005, Blood lead levels — United States, 1999–2002. *Morbidity and Mortality Weekly Report*, (54/20) 513–516.

Chisholm, J.J. Jr, 1976, 'Current status of lead exposure and poisoning in children' (editorial), *Southern Medical Journal*, May 1976, pp 529–531.

Cummings, H.S., 1922, Letter to P. S. DuPont, National Archives Record Group 90, 20 December 1922.

Davis, D., 2007, *The secret history of the war on cancer*, Basic Books, New York.

Departmental Committee on Ethyl Petrol. Final Report, 1930, Ministry of Health. His Majesty's Stationary Office, London.

Drinker, C.K., 1925, Letter to R.R. Sayers, National Archives Record Group 70, 101869, File 725 (12 January, 1925).

EEA, 2001, *Late lessons from early warnings: the precautionary principle 1986–2000*. European Environment Agency, Copenhagen.

EEA, 2011, 'Statement on Mobile Phones and the potential head cancer risk', Hearing on EMF, Council of Europe, Paris, 25 February 2011.

EFSA, 2010, 'Scientific opinion on lead in food', Panel on Contaminants in the food Chain (CONTAM), The European Food Safety Authority, *EFSA Journal*; (8/4) 1 570.

Ethyl Corp. v Environmental Protection Agency, 1976, 541 F.2d I. (http://ftp.resource.org/courts.gov/c/F2/541/541.F2d.1.73-2270.73-2268.73-2205.74-1021.html) accessed on 15 February 2011.

Ethyl Gasoline, 1925, 'Editorial', *American Journal of Public Health*, (15) 239–40.

European Council, 1987, Council Directive 87/416 of 21 July 1987 amending Directive 85/210/EEC on the approximation of the laws of the Member States concerning the lead content of petrol, OJ L225/33.

Franklin, B., 1818, 'Pernicious effects of lead', in: Buzby, B.C., *The Works of Ben Franklin*, Philadelphia.

Gibson, J., 1904, 'A plea for painted railings and painted walls of rooms as the source of lead poisoning among Queensland children', *Aust. Med. Gazette*, (23) 149–153.

Grosse, S.D., Matte, T.D., Schwartz, J. and Jackson, R.J., 2002, 'Economic gains resulting from the reduction in children's exposure to lead in the United States', *Environ. Health Perspect.*, (110) 563–569.

Hagner, C., 2000, 'European regulations to reduce lead emissions from automobiles — did they have an economic impact on the German gasoline and automobile markets?', *Reg. Environ. Change,* (1) 135–151.

Haigh, N., 1998, Challenges and opportunities for IEA: science–policy interactions from a policy perspective', *Environmental Modelling and Assessment*, (3) 135–142.

Hale, W.J., 1934, *The farm chemurgic*, Stratford Company, Boston.

Hamilton, A., 1925, 'What Price Safety, Tetraethyl Lead Reveals a Flaw in Our Defenses', *The Survey Mid-Monthly*, (54) 333–334.

Hayhurst, E., 1924, Letter to Sayers, National Archives Record Group 70, 101869, File 725, September 1924, in which he identifies himself as 'Consultant to Ethyl Gasoline Corporation'.

He, K., Wang, S., Zhang, J., 2009, 'Blood lead levels of children and its trend in China', *Science of the Total Environment*, (407) 3 986–3 993.

Henderson, 1925, Letter to Sayers, National Archives Record Group 70, 101869, File 725, 20 January 1925.

Hong, S.M., Candelone, J.P., Patterson, C.C. and Boutron, C.F., 1994, 'Greenland ice evidence of hemispheric lead pollution 2-millennia ago by greek and roman civilizations', *Science*, (265/5180) 1 841–1 843.

Hunter, D., 1975, *The diseases of occupations*, 5th ed., English Universities Press, London.

Johansson, K., Bergbäck, B. and Tyler, G., 2001, 'Impact of atmospheric long range transport of lead, mercury and cadmium on the Swedish forest environment', *Water Air Soil Pollut. Focus 1*, 279–297.

Jones, R.L., Homa, D.M., Meyer, P.A., Brody, D.J.B., Caldwell, K.L., Pirkle, J.L. and Brown, M.J., 2009, 'Trends in blood lead levels and blood lead testing among US children aged 1 to 5 years', 1988–2004. *Pediatrics*, (123/3) e376–e385.

Kehoe, R., 1965, Letter to K. Boucot, 16 April 1965.

Kitmann, J.L., 2000, 'The secret story of lead', *The Nation*, (270) 11–44.

Kovarik, W., 2003, *Ethyl — The 1920s environmental conflict over leaded gasoline and alternative fuels*, paper to the American Society for Environmental History, Annual Conference, 26–30 March 2003.

Kovarik, W., 2005, 'Ethyl-leaded gasoline: how a classic occupational disease became an international public health disaster', *Int. J. Occup. Environ. Health*, (11) 384–97.

Lanphear, B.P., Dietrich, K., Ausinger, P. and Cox, C., 2000, 'Cognitive deficits associated with blood lead concentrations <10 microg/dL in US children and adolescents', *Public Health Rep*, (115/6) 521–529.

Lanphear, B.P., Hornung, R., Khoury, J., Yolton, K., Baghurst, P., Bellinger, D.C.,Canfield, R.L., Dietrich, K.N., Bornschein, R., Greene, T., Rothenberg, S.J., Needleman, H.L., Schnaas, L., Wasserman, G.,Graziano, J. and Roberts, R., 2005, 'Low-level environmental lead exposure and children's intellectual function: an international pooled analysis', *Environmental Health Perspectives*, (113/7) 894–899.

Lawther, P.J., 1980, *Lead and health: the report of a DHSS working party on lead in the environment*, Department of Health and Social Security, Lead and Health, HMSO.

Leigh, D., Evans, R. and Mahmood, M., 'UK firm Octel bribed Iraqis to keep buying toxic fuel additive', *The Guardian*, 30 June 2010.

Mansfield Clark, W. 1922, Letter to Assistant Surgeon General A.M. Stimson (through Acting Director, Hygenic Laboratory), memorandum, 11 October 1922), National Archives Record Group 90, US Public Health Service.

Markowitz, G. and Rosner, D., 2000, 'Cater to the children: the role of the lead industry in a public health tragedy, 1900–1955', *Am. J. Publ. Health*, (90) 36–46.

Markowitz, G. and Rosner, D., 2002, *Deceit and denial — The Deadly Politics of Industrial Pollution*, University of California Press, Berkeley.

Mathee, A., Röllin, H., von Schirnding, Y., Levin, J. and Naik, I., 2006, 'Reductions in blood lead levels among school children following the introduction of unleaded petrol in South Africa', *Environmental Research*, (100) 319–322.

Mateo,R., Green, A.J., Le Franco, H., Baos, R. and Figuerola, J., 2007, 'Lead poisoning in wild birds from southern spain: a comparative study of wetlands and species affected and trends over time', *Ecotoxicology and Environmental Safety*, (66) 119–126.

Midgley, T.A., 1921, 'Discussion of papers at semi-annual meeting; Alcohol and shale oil', *SAE Journal*, p. 269.

Midgley, T. Jr., 1922, Letter to Cumming, National Archives Record Group 90, 30 December 1922.

Mielke, H.W., Lailaw, M.A.S. and Gonzales, C., 2010, 'Lead legacy from Vehicle Traffic in 8 California Urbanised areas: continuing influence of lead dust on children's health', *Science of Total Environment*, (408) 3 965–3 975.

Ministry of Health, 1930, *Departmental Committee on Ethyl Petrol Final Report*, His Majesty's Stationary Office, London.

MRC, 1984, *The neuropsychological effects of lead in children: a review of recent research 1979–1983*, Medical Research Council, London.

MRC, 1988, *The neuropsychological effects of lead in children: a review of the research, 1984–88*, Medical Research Council, London.

Navas-Acien, A., Guallar, E., Silbergeld, E.K., and Rothenberg, S.J., 2007, 'Lead Exposure and Cardiovascular Disease—A Systematic Review', *Environ Health Perspect.*, (115/3) 472–482.

Needleman, H.L., Gunnoe, C., Leviton, A., Reed, R., Peresie, H., Maher, C. and Barrett, P., 1979, 'Deficits in psychologic and classroom performance of children with elevated dentine lead levels', *New England Journal of Medicine*, 29 March 1979, (300/13) 689–695.

Needleman, H.L., Riess, A., Tobin, M.J., Biesecker, G.E. and Greenhouse J.B., 1996, 'Bone lead levels and delinquent behavior', *JAMA*, (275/5) 363–369.

Needleman, H.L., 1997, 'Clamped in a straitjacket: the insertion of lead into gasoline', *Environ. Res.*, (74) 95–103.

Needleman, H.L., 1998, 'Clair Patterson and Robert Kehoe: two views of lead toxicity', *Environ. Res.*, (78) 79–85.

Needleman, H.L., 2000, 'The removal of lead from gasoline: historical and personal reflections, *Environ. Res.*, (84/1) 20–35.

OECD, 1999, *Phasing lead out of gasoline: an examination of policy approaches in different countries*, Paris, Organisation for Economic Co-operation and Development.

Oliver, T., 1911, 'Lead poisoning and the race', *Eugen. Rev.*, (3/2) 83–93.

Patterson, C., 1992, Letter to H. Needleman , 5 August 1992.

Patterson, C.C., 1965, 'Contaminated and natural lead environments of man', *Arch Environ Health*, (11) 344–360.

Peters, W., 1980, *Umweltpolitik im Kraftfahrzeugverkehr—Eine* ökonomische *Beurteilung ihrer Ziele und Folgen*, Europäische Hochschulschriften Reihe V 280, Frankfurt.

President's Task Force on Environmental Health Risks and Safety Risks to Children, 2000, *Eliminating childhood lead poisoning: a federal strategy targeting lead paint hazards*. Washington, DC, United States Centers for Disease Control and Prevention (http://www.cdc.gov/nceh/lead/about/fedstrategy2000.pdf) accessed 25 November 2009.

Quinn, M.J. and Sherlock, J.C., 1990, 'Correspondence between UK "action levels" for lead in blood and in water', *Food Additives and Contaminants*, (7/3) 390.

RCEP, 1983, *Lead in the environment*, Ninth Report, Royal Commission on Environmental Pollution, HMSO, London.

Rodriguez-Estival, J., Barasona, J.A., Mateo, R., 2012, 'Blood Pb and d-ALD inhibition in cattle and sheep from a Pd polluted mining area', *Environmrental Pollution*, (160) 118–124.

Rosner, D. and Markowitz, G., 1985, 'A "gift of God"?: The public health controversy over leaded gasoline during the 1920s', *Am. J. Publ. Health*, (75) 344–352.

Rosner, D., Markowitz, G. and Lanphear, B.J., 2005, 'Lockhart Gibson and the discovery of the impact of lead pigments on children's health: A review of a century of knowledge', *Public Health Reports*, (120) 120–300.

Rutter, M.L., 1983, 'The relationship between science and policy making: the case of lead', *Clean Air*, (13) 17–32.

Schulte-Rentrop, A., Costa-Cabr al, M., Vink, R., 2005, 'Modelling the overland transport of lead deposited from atmosphere in the Elbe catchment over four decades (1958–1995)', *Water Air Soil Pollut*, (160) 271–291.

Straw, C. A., 1924, Letter to R. R. Sayers, National Archives Record Group, NARG 70,101869, File 725, 22 August, 1924.

Surkan, P.J., Zhang, A., Trachtenberg, F., Daniel, D.B., McKinlay, S. and Bellinger, D.C., 2007, 'Neuropsychological function in children with blood lead levels <10 microg/dL', *Neurotoxicology*, (28) 1 170–1 177.

Thomas, H. M. and Blackfan, K. D., 1914, 'Recurrent Meningitis Due to Lead in a Child of Five Years', *American Journal of Diseases of Children*, Chicago, (8) 377–380.

UK Department of Transport, 1979, *Lead in petrol: an assessment of the feasibility and costs of further actions to limit lead emissions from vehicles.*

UNECE, 1998, *Convention on access to information, public participation in decision-making and access to justice in environmental matters*.

UNEP/WHO, 2010, *Newsletter of the UNEP/WHO Global Alliance to Eliminate Lead in Paints*, no 1.

USEPA, 1977, *Air Quality Criteria for Lead*, EPA 600/8-77-017.

USPHS, 1925, 'Proceedings of a conference to determine whether or not there is a public health question in the manufacture, distribution, or use of tetraethyl lead gasoline', Public Health Bulletin No 158, GPO, Washington.

USPHS, 1926, 'The use of tetraethyl lead gasoline in its relation to public health', *Public Health Bulletin* No 163, GPO, Washington.

USPHS, 1970, *Survey of Lead in the Atmosphere of Three Urban Communities*, Working Group on Lead Contamination, Public Health Service Publication No 999-AP-12.

von Storch, H., Costa-Cabral, M., Hagner, C., Feser, F., Pacyna, J., Pacyna, E. and Kolb, S., 2003, 'Four decades of gasoline lead emissions and control policies in Europe: a retrospective assessment', *Sci. Total Environ.*, (311) 151–76.

Wescott, N.P., 1936, *Origins and early history of the tetraethyl lead business*, Du Pont Corp Report No. D-1013.

WHO, 1977, *Lead (Environmental Health Criteria 3)*, International Programme on Chemical Safety, World Health Organization, Geneva.

WHO, 2010, *Childhood Lead Poisoning*, World Health Organization, Geneva.

Huo, X., Peng, L., Xu, X., Zheng, L., Qiu, B., Qi, Z., Zhang, B., Han, D. and Piao, Z., 2007, Elevated blood lead levels of children in Guiyu, an electronic waste recycling town in China', *Environ Health Perspect*, (15/7) 1 113–1 117.

4 Too much to swallow: PCE contamination of mains water

David Ozonoff

PCE (perchlorethylene, also known as 'perc' or tetrachloroethylene), was used in the production of plastic linings for drinking water distribution pipes in the late 1960s and 1970s. This new and relatively untested type of distribution pipe was used in over 700 miles of New England's water distribution systems. Not until 1976 was it discovered that PCE had been leaching into the water from the pipe lining, causing widespread contamination of water supplies that still today require continuous remediation.

Before the pipes were put into production there was a substantial amount of scientific information available about the potential hazards of PCE. This did not include current concerns about PCE's carcinogenicity, teratogenicity and other health consequences of relatively low-level exposure upper most among today's concerns, but many early warnings suggested the need for caution in introducing PCE-based mains pipe linings.

PCE had been used to treat hookworm and data on side effects were in the literature, while later a variety of occupational users were studied, including aircraft workers, small companies in countries where biological monitoring was required, and dry-cleaning firms. Several environmental studies were also conducted to see if drinking water contaminated with PCE or its close relative, TCE (trichloroethylene), was associated with cancer. Results were mixed and the chemical industry consistently denied that PCE was a human carcinogen.

This case study explores the early (pre 1970) history researching the toxicity of the chemical. It also focuses on the failure of one manufacturer, Johns-Manville Corporation, to recognise the warning signals about using a suspected toxic substance. It examines why a new product was deployed without thought to the public health consequences and why evidence of the potential hazard was ignored.

The science has not been hidden. It has been ineffective in guiding and catalysing action. Whether the problem is a failed duty of care or a lack of clarity about what evidence will trigger action, the contemporary argument over how to interpret the scientific evidence is irresolvable within science itself. There are no overarching criteria from the philosophy of science that can dictate a solution.

This chapter also includes two supplementary texts. A panel that analyses the differences between the conclusions of risk assessments based on the same data, focusing in particular on assessments of PCE and TCE. A further panel describes the opportunities to switch to wet-cleaning technologies to reduce the current use of PCE in dry cleaning.

Institutions, large and small, make decisions every day where a conscious application of foresight could prevent a later hazard. Yet such foresight — based on existing information — is often absent.

The present chapter illustrates this with a case study on the use of a now ubiquitous chlorinated ethylene, PCE (perchlorethylene, also known as 'perc' or tetrachloroethylene), to produce plastic linings for drinking water distribution pipes in the late 1960s and early 1970s. Those years represented a strategic and historical turning point in awareness of the importance of environmental carcinogens and teratogens (substances causing embryo malformations).

Some public water supplies are still today contaminated with PCE and require continuous remediation. The use of PCE to apply plastic lining to water pipes occurred when there was already considerable scientific information about the potential hazards it posed. Admittedly, this understanding did not include current concerns about PCE's carcinogenicity, teratogenicity, and other health consequences of exposure to relatively low levels of PCE via various exposure routes, including water mains, whose public health implications remain unresolved. Nevertheless, certain clear early warnings suggested the need for caution in introducing PCE-lined drinking water pipe linings. And the lessons from this early period remain applicable to the situation today.

4.1 PCE linings in water mains

A new and relatively untested type of distribution pipe, installed in the years 1969–1979, is now known to have caused widespread PCE contamination of water supplies in the US state of Massachusetts (Demond, 1982; MDEE, 1982; Larsen et al., 1983).

Efforts to develop and market the new pipe began in the early 1960s when Providence, Rhode Island, Water Supply Board officials sought to replace cast iron mains in low-flow areas that were troubled with colour and taste problems. The Johns-Manville Corporation, a manufacturer of asbestos cement water mains, experimented with clear plastic linings of various kinds. To apply the lining, the plastic was dissolved in PCE and the resulting slurry used to paint the inside of the pipe. The first trial of plastic-lined pipes in 1966 produced water with a slight chemical taste and odour, whose origin was not revealed by routine water quality tests like pH, alkalinity and hardness. In early 1968 Johns-Manville delivered a pipe with the new type of clear lining to the Providence Water Supply Board for testing. It was immediately apparent that air trapped in the pipe took on a chemical odour of slight to moderate intensity, described as similar to chloroform and strongly resembling a commercial dry-cleaning fluid used at a local cleaning plant. Conventional water tests revealed no taste or odour, although the air in the pipe still had a chloroform-like smell.

Further testing showed that under static conditions the lining material continued to contribute a very slight odour even after substantial volumes of water had run through the pipe. Consequently a Johns-Manville representative visited the Providence Water Supply Board, accompanied by two representatives of the company, and they were shown first hand that the water retained a slight odour of chloroform. At a subsequent visit to inspect water samples at a 277-foot pipe with an eight-inch diameter that had been installed the previous month, neither the company representatives nor the water supply chemist detected a similar odour. Explaining the discrepancy, company representatives argued that the pipe with the odour had been kept covered in brown paper and therefore not 'cured' completely.

There is no indication that the taste and odour incident prompted Johns-Manville to investigate the curing process to evaluate whether PCE remained in the liner and potentially contaminated drinking water. Nor is there any record that tests other than routine water quality measures, which did not indicate the nature or amount of organic contaminants, were ever done on samples from the newly developed lined pipe. Not until 1976, when over 700 miles of this pipe had been installed in New England water distribution systems, was it accidentally discovered that PCE had been leaching from the pipe lining into the water.

4.2 Foreseeable harm?

The use of PCE in water mains is a classic case of deploying a new product without considering the public health consequences. In the ensuing battle over who should pay for the damage, Johns-Manville Corporation argued that it did not and could not have known that PCE was a chemical of public health concern, whose presence in drinking water was certainly inappropriate and probably harmful. Much work after 1970 has revealed potential adverse effects from environmental and occupational exposure to PCE, including various cancers, birth defects and autoimmune disease. But could this have been foreseen? If it was unforeseeable, what factors made it so? Alternatively, if it was foreseeable, what factors prevented adequate foresight?

4.2.1 *An insight from the early history of PCE*

Before examining these questions, the early history of chlorinated hydrocarbons provides at least one lesson involving PCE. Michael Faraday, now best known for his work on electricity but also a great chemist (Williams, 1965) created hexachloroethane, C_2Cl_6, the first chlorinated hydrocarbon to be synthesised. Heating the mixture produced another gas, perchloroethylene, C_2Cl_4 (PCE).

Faraday was attracted to chlorine chemistry because of a philosophical dispute between his mentor, Sir Humphrey Davy, and Antoine Lavoisier, centred on reconciling the mechanical character of Newtonian mechanics with the notion of free will. Davy and Faraday were Kantians and deeply religious, and the philosophical stakes were extremely high. This resulted in intense disputes with other founders of modern chemistry, including Jöns Jacob Berzelius and John Dalton (Sharlin, 1966).

For the purposes of the present study, the key point to note from this early period in PCE's history is the way that non-scientific concerns can distort scientific disputes. Ideology can make it impossible for protagonists to reverse a course of action or alter a position. But other interests, such as money, market share and reputation, can have similar effects.

PCE's infancy was thus characterised by dispute and doubt. Of course, disputes and doubts are normal in science, particularly when the consequences matter. But this has two corollaries. The first is that a scientific finding may become the subject of dispute and doubt (whether real or manufactured to prevent action) because the outcome matters to someone with the means to challenge the finding and delay action. Conversely, the second corollary is that, if nobody cares or nobody with means cares, there will be little pressure to challenge a scientific finding or explore an issue in greater detail. Results of potentially great significance in other contexts may fail to influence the public health landscape.

4.3 PCE and the chlorinated ethylenes

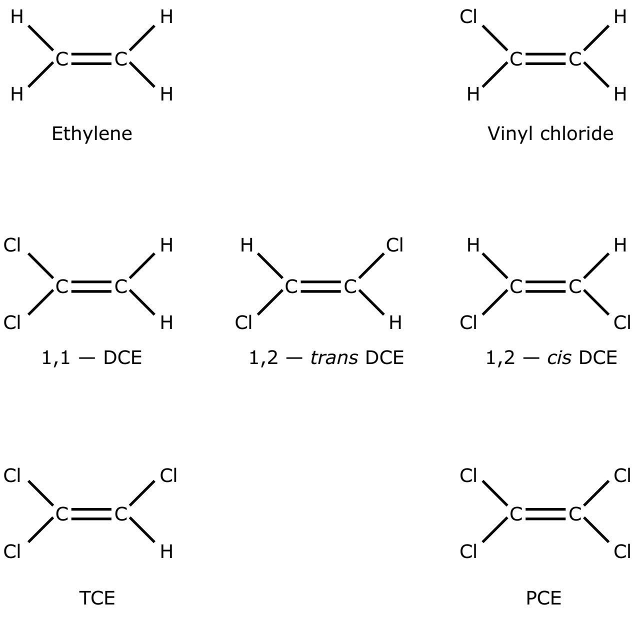
PCE is one of a closely related group of chemicals called chlorinated ethylenes. All the chlorinated ethylenes are built on a common chemical backbone, which consists of two carbon atoms connected by a double-bond. This leaves room or 'slots' for four more atoms, two on each carbon atom. When all slots are occupied by hydrogen atoms, we have the parent hydrocarbon, ethylene. As shown in Figure 4.1, successively replacing each hydrogen atom with a chlorine atom generates vinyl chloride (a known human carcinogen), dichloroethylene (DCE), trichloroethylene (TCE) and tetrachloroethylene (PCE).

All of these chemicals are used by the chemical industry as 'feedstocks' (i.e. the basic ingredients) for plastics or other chemicals. Several are commonly used as solvents for degreasing (i.e. cleaning) metal parts or in the dry-cleaning industry.

The chlorinated ethylenes trichloroethylene (TCE) and perchloroethylene (PCE) were among the highest production volume chlorinated solvents in the twentieth century, used for everything from dry cleaning, metal degreasing and printing to medical applications such as anaesthetics (TCE) or to kill parasitic worms (PCE). These medical and pharmaceutical uses date back almost a century. The familiarity and benefits of these substances should have alerted us to the fact that exposure to these chemicals has biological effects that could also be harmful.

Using PCE to apply plastic resin to the interior of water mains is thus just one of many applications.

Figure 4.1 Chemical structure of chlorinated ethylenes



Ethylene

Vinyl chloride

1,1 — DCE

1,2 — *trans* DCE

1,2 — *cis* DCE

TCE

PCE

But the use of PCE in close connection with drinking water occurred at a time when problems could have been foreseen. The early warnings are outlined briefly below.

4.4 Discovery of PCE's toxic effects

Despite PCE's current importance, for more than a hundred years after its discovery by Faraday it saw no significant commercial use. There was little literature about PCE or knowledge of its toxic effects until the 1920s when it was proposed as a treatment for hookworm — parasites of the small intestine that cause severe anaemia. In the nineteenth and early twentieth centuries, hookworm disease affected the health and vitality of millions of rural poor in the United States and elsewhere, stunting children's growth and robbing communities of productivity. Resulting economic losses were substantial (Rosenau, 1935). In the first decade of the twentieth century the Rockefeller Foundation undertook a massive campaign against hookworm disease in the southern regions of the United States using the relatively toxic medicine, thymol. Because thymol had frequent side effects, there was a continuing search for a better agent. One of the first shown to be effective was carbon tetrachloride (CCl_4), but this was less than ideal, leading to the trial of other similar compounds, including PCE.

The introduction of PCE as an anthelmintic (anti-parasite medication) by Hall and Shillinger in 1925 began a process of toxicological evaluation of PCE that has continued to the present day. As new uses for PCE were found in 1934 (dry cleaning) and 1939 (degreasing metals), further studies were undertaken to investigate the effects of PCE on those exposed to the chemical in these new applications.

This pre-carcinogen literature can conveniently be divided into two phases: in the first, from 1925 until approximately 1940, the main interest was in assessing the side effects of a medicine taken by mouth for hookworm disease. In the second phase, from 1940 to 1970 up to the point where PCE-lined pipes were installed, the effects of inhaling PCE from use as a dry-cleaning fluid or degreasing agent were the principal focus of concern.

4.4.1 *Phase I: 1925–1940 (PCE use in treating hookworm disease)*

When Hall and Shillinger introduced PCE as a treatment for hookworm disease in 1925 they first tested the substance on dogs: 'The question as to the safety of the drug is naturally one of major importance …' (Hall and Shillinger, 1925). Three of the 55 dogs tested died, even though they had received what were believed to be therapeutic doses. None of the dogs that died received the largest doses and as a result Hall and Shillinger became the first of many to comment on potentially significant differences in individual susceptibility.

To test PCE's effects on humans, one of the researchers took a 1 cc (one fifth of a teaspoon) capsule of PCE after breakfast. That night he experienced prompt and complete relaxation of the muscles with slight cerebral discomfort. He had an unusual dream involving levitation, which he believed was due to the effects of the drug.

The dog experiments, self-medication and PCE's chemical structure suggested to Hall and Shillinger that the drug's safety was comparable to carbon tetrachloride (useful in addressing hookworm disease but with known toxicity to the liver), causing lesions similar to those of chloroform. They recommended that PCE be tested under hospital conditions to ascertain its possible value in treating hookworm patients, with due attention to contraindications such as acute or chronic alcoholism, liver disease, infections or other debilitating diseases.

From this modest beginning the use of PCE for hookworm disease gradually increased. Additional studies suggested that PCE, even in relatively small quantities, could have harmful effects on animals and people. But because of its effectiveness as an anthelmintic, PCE's popularity continued to grow and was the subject of several articles (Manson, 1934; AMA Council on Pharmacy and Chemistry, 1936; Wright et al., 1937; Fernando et al., 1939). Thus, while PCE became a commonly used drug, it was not a completely safe one and untoward side effects continued to be reported. These included a paper by Sandground (1941) on two cases of unconsciousness following a normal therapeutic dose. He concluded that:

> 'While for want of a better drug [these cases] should not discourage the use of tetrachlorethylene [PCE], they illustrate the truth of a remark which the late Dr Maurice Hall made to me, to the effect that one cannot assume that any anthelmintic is entirely safe for human use until there are reliable reports on at least a million treatments without any untoward effects.'

The number of other severe side effects from using PCE as a drug is difficult to estimate, although the question was being considered at the time that the PCE-lined pipes were installed (Bwibo, 1969).

Throughout its use over several decades, PCE tended to produce serious detrimental effects on a small percentage of those treated. As with the earlier dog experiments, the effects were not necessarily related to the dosage. The toxicological picture that emerges from this early literature is evidence of pathologic changes in animals at therapeutic doses, together with reported side-effects in humans, some of which were extremely serious or fatal at doses as small as half a teaspoon (2–3 cc). PCE's potentially lethal side-effects were tolerated because hookworm disease was a major public health problem. There remained uncertainties about the degree of absorption of the drug in humans and the individual variation in susceptibility to its effects. But there was a balance to be struck in terms of achieving public health goals — a balance not found in newer uses.

4.4.2 Phase II: 1940–1970 (PCE in degreasing operations and other industrial uses)

The initial information on PCE's adverse effects came from its therapeutic uses and was sufficient to arouse concern. Subsequent modes of PCE exposure were primarily by inhalation and skin absorption rather than ingestion. Investigators soon began to look more closely at inhalation in particular and for the next three decades much of the study of PCE toxicology involved exposure of human volunteers and animals to PCE via the air. Chronic exposure now joined acute effects as a concern. It is significant that the discipline of epidemiology — the systematic evaluation of the incidence, distribution and possible control of diseases and other factors relating to health — was still primitive and did not enter into most decisions.

In a general review of dangerous gases and vapours, Zernik (1933) noted that Lamson et al. (1929) had produced an optimistic assessment of PCE's risks but contrasted a report by Beyer and Gerbis (1932) of stomach and liver disease ending in death after chronic inhalation of a solution containing PCE as the main ingredient. The extent to which other ingredients might have been responsible for this fatal case was not clear but the potential hazard of PCE exposure appeared evident to the authors.

Dr Alice Hamilton, an industrial health pioneer, was among the first to focus on the new uses of PCE. Writing in *The New England Journal of Medicine* in 1936, Hamilton cautioned that data on PCE's effects on animals might be difficult to apply to human exposures. Humans tended to have more liver damage and less kidney damage than animals exposed to the same substances, she observed. Hamilton also emphasised the differences between acute clinical poisonings and chronic industrial exposures, citing lead and benzene as striking examples of the greater damage that can be caused by low, chronic exposures compared to large, acute ones.

In the discussion that followed her paper, a Massachusetts physician bemoaned the fact that manufacturers were marketing products under trade names, with little information for physicians about the effects of the chemicals. On this point, Hamilton (1936) had observed that:

> 'This, in my opinion, is a problem for the general practitioner since the use of these solvents in industry is increasing by leaps and bounds each day. I have seen many individuals, both male and female, who in my opinion were suffering from conditions brought about by prolonged exposure or exposure under definite circumstances to some of these solvents.'

The importance of low-level chronic exposures was emphasised again in a general review of the pathology of exposure to new volatile solvents, published the following year (St George, 1937). St George noted that slow, chronic intoxications were difficult to recognise and he suggested that chemicals could be broken down into other compounds or retained in the body. Outlining the available information on the toxicity of PCE, he described it as a 'relatively new solvent' and listed its symptoms on inhalation as nausea, giddiness and vomiting with mucous membrane irritation, headache and drowsiness. Echoing the Massachusetts physician, St George (1937) made a special point about warnings:

> 'The danger of these solvents should be explained to every worker and they should be instructed in the preventive measures that have been instituted. When these products are marketed for household use under trade names etc., detailed instructions should be stated on each container, and it is especially important to state that the product must only be employed in a room with at least one window wide open.'

One of the first to turn his attention directly to PCE as an industrial poison was Carpenter (1937).

He exposed albino rats and human volunteers to PCE vapours at a variety of concentrations. In the rat experiments no pathology was evident at 70 parts per million (ppm) over a 10-week period, but at the next highest level, 230 ppm, there was evidence of congestion, light granular swelling of the kidneys and minimal changes in the liver. Carpenter also exposed himself and his colleagues to PCE concentrations of 500, 1 000, 2 000 and 5 000 ppm. All of them could smell PCE at 50 ppm in air and this odour threshold was reported by many subsequent studies, citing Carpenter. After some hours of exposure, subjects noticed increased salivation, irritation of the eyes, and tightness in the frontal sinuses. One became slightly nauseated at an exposure of 500 ppm for two hours, while higher levels caused more marked effects of central nervous system depression and mucous membrane irritation. At the highest levels, exposure could only be endured for a few minutes. Carpenter concluded that a safe concentration for continuous daily exposure probably lay somewhere between 100 ppm and 500 ppm, but he stated a more precise statement would require additional human experience with exposures within this range.

In the 1940s, despite much discussion about the hazards of chlorinated solvent use, little original work was done, perhaps because of the war effort and the pressures of industrial production. However, several general reviews (e.g. Lehmann and Flury, 1943; Sappington, 1943) recounted information regarding the use of PCE as a drug and the findings of Carpenter (1937) and Barrett et al. (1939).

Morse and Goldberg (1943) affirmed that:

> 'Nevertheless, both solvents are regarded as toxic. There is only one published medical research with which we are familiar [Carpenter] … This investigation by no means clarified the toxicity of perchlorethylene. It stated that 50 ppm produced a definite odour and concluded that a concentration between 100 to 500 ppm is considered safe for daily exposures not in excess of 40 hours per week. This range of 100 to 500 ppm is in need of extensive study'.

They concluded that complaints of headache, nausea and dizziness were common among degreaser operators even when concentrations were well within the generally accepted toxic limit.

Many writers were alarmed by the lack of hard data and the misperception that PCE was non-toxic based on its therapeutic use. For example, in his 1949 textbook on industrial toxicology Fairhall noted that PCE should not be regarded as harmless; indeed, that under certain conditions it was even more toxic than carbon tetrachloride, which was recognised as a serious industrial hazard. Like other authors before him Fairhall called attention to the phenomenon of varying individual susceptibility.

In 1952 a major manufacturer of PCE for degreasing use, the Dow Chemical Company, began to publish reports on the chemical's toxicity. Rowe et al. (1952) assessed the toxicity of PCE vapour to laboratory animals and its effects on human volunteers, with attention primarily focusing on acute effects. Based on this analysis, Rowe et al. argued that exposure should be limited to an average of 100 ppm and should not exceed 200 ppm. They identified irritation of the eyes and central nervous system depression as the prime toxic effects, and considered serious organic injury to be unlikely.

The following year, however, Coler and Rosmiller (1953) reported the effects of PCE exposure and toxicity at a small pump-manufacturing company where parts covered with grease were cleaned with a solvent that consisted of 99 % PCE. A physician who examined a 35-year-old worker with severe stomach bleeding found that he also suffered from severe cirrhosis of the liver and ruptured oesophageal varicose veins. Two of the patient's co-workers complained of malaise, dizziness, light-headedness, headache and irritation of the nose. All three had been exposed to PCE. Worksite exposure measurements showed levels of 200–400 ppm. Subsequent interviews with other workers revealed similar complaints, including tiredness, and feelings of intoxication and hangovers. A few workers reported passing out after exposure but said that they recovered quickly. One worker reported that his eyes 'did not coordinate'. Staggering, stomach aches and slowed ability to think and remember were among the many complaints. Three of seven workers tested had abnormal liver function. The authors concluded that the liver toxicity of PCE should be investigated more thoroughly rather than disregarded. Thus, contemporary clinical observations contradicted the Dow studies.

Coler and Rossmiller's concern was echoed by Lob (1957) in an article entitled, 'The dangers of perchlorethylene'. Lob noted that a toxic industrial chemical is often considered harmless until experience shows the opposite. He then reviewed the animal literature on PCE, remarking that experience was meagre and that the conditions in which investigations had been conducted were quite varied, meaning that definitive conclusions could not be drawn. He also cited the example of TCE as evidence that the results from animal experimentation could not always be transferred easily to humans.

Lob reviewed clinical experience with PCE, pointing out that it was also scant but identifying ten additional cases of PCE poisoning. One was a fatal case, two more were cases of severe chronic poisoning with damage to the autonomic nervous system, and seven cases were less serious, involving symptoms of fatigue, dizziness, vertigo, headache, nausea and vomiting, anorexia, insomnia, irritability and light cough. The latter symptoms disappeared when the workers were removed from exposure.

Meanwhile, experimental toxicology continued to address PCE (Friberg et al., 1953) but new techniques in animal experimentation were beginning to show inconsistent effects. An investigation attempting to rank chlorinated hydrocarbons according to their liver-damaging potential (Plaa et al., 1958) revealed no correlation between the dose that caused liver damage and the lethal dose in acute exposure experiments.

These concerns spurred further activity in the 1960s on the part of the manufacturer, Dow Chemical Company. In a series of reports, researchers from Dow studied the absorption and excretion of PCE in the body (Stewart et al., 1961a and 1961b; Irish, 1962; Rowe et al., 1963; Stewart et al., 1963; Stewart and Dodd, 1964; Stewart et al., 1965; Stewart and Erley, 1965; Gehring, 1968; Stewart, 1969). Using gas chromatography with infrared spectroscopy or electron capture detection, these researchers discovered that excretion of PCE from the body took an extended time, suggesting that PCE accumulated with chronic exposure. The Dow researchers noted that acute exposure to PCE might, in fact, be a chronic exposure from the body's standpoint because of the slow excretion rate. In studying an accidental over-exposure, they discovered that liver function tests may not become abnormal until two to three weeks after exposure.

The Dow researchers also noted that the mistaken perception that PCE was relatively non-toxic encouraged careless use, which could result in poisoning (Irish, 1962). The Dow reports culminated in a human exposure experiment (Stewart et al., 1970), which found an unexpected prevalence of light-headedness and abnormal neurological results (based on a modified Romberg test) at the lowest exposure levels. The Dow authors could not interpret this unanticipated finding.

Finally, Smyth and his colleagues (1969) added a new and disturbing dimension when they investigated the toxicity of 27 industrial chemicals given to rats in all possible pairs. Using death as the endpoint, they found that most combinations showed no tendency to produce lethal effects in excess of what would be expected from the additive effects of each component separately. Of the nine combinations that did deviate significantly from this pattern, four of them contained PCE, making it the chemical most often associated with causing a net effect greater than the sum of the effects of its separate components. This strongly suggested that PCE could have a potentiating effect on the toxicity of other chemicals (and vice versa).

4.4.3 The view from 1970

The 1960s closed with continued reports of poisoning from PCE at the workplace, usually involving central nervous system depression and concomitant liver damage. There was uncertainty as to the threshold at which such damage first occurred, with some writers considering PCE to be more dangerous than conventionally believed. During that decade there were significant advances in the measurement of PCE and one of its leading manufacturers, Dow Chemical, performed in-house research that was published in the open scientific literature. It was known that individual susceptibility to the effects of PCE varied widely and that the chemical was excreted very slowly from the body, often concentrating there and resulting in a chronic, low-level internal exposure. The suspicion was also raised that PCE could act together with other chemicals to produce a synergistic effect of unknown magnitude.

4.5 Implications for PCE use in water supply infrastructure

What did all the evidence imply for water suppliers contemplating using a product containing PCE?

Leaving aside the acute and chronic effects, there was a potential aesthetic concern. In 1968 the United States Public Health Service Drinking Water Standards stipulated that 'drinking water should contain no impurity which would cause offence to the sense of sight, taste, or smell'. This was done to prevent consumers from seeking alternative but less safe sources of water. Public health experts might have worried that the new pipes could cause a health problem on that basis alone, as a chemical odour was an initial concern.

A review of the medical literature would have added to their unease. It showed that there was considerable individual variation in responses to the chemical, both in the therapeutic environment and in the workplace. Some variation was thought to be inherent and some due to wide variation in the health, diets and exposures of the general population. All these factors were known to affect the potential toxicity. The fact that extremely serious and sometimes fatal side effects were tolerated in mass treatment of a population for a serious disease such as hookworm would probably have been of little relevance to water managers who had no interest in purveying an anthelmintic drug through the water mains.

Experimental work and occupational experience had already shown PCE to be excreted from the body very slowly. Like a bathtub in which the amount flowing from the tap is greater than that draining out, it was plausible that PCE could accumulate from constant daily exposure until it reached the point where it caused toxic effects in some consumers. Using data from Stewart et al. (1965) an elimination rate constant of approximately 25 % (through the lungs) per day can be estimated. Regardless of the level of exposure, after about two weeks (four to five half-lives of 2.5 days each) the level of PCE in the body would have built up to the point where the amount eliminated from the body would be roughly equal to the amount ingested. The final level of PCE would depend on the amount ingested each day.

The maximum level of PCE in water is 100–150 ppm, as determined by its solubility. No measurements of PCE appear to have been made at the time the pipes were installed but assuming a worst case concentration of 125 ppm and the ingestion of 2 litres of water per day implies a constant body burden of approximately 1 gram of PCE. That is close to the dose used to treat hookworm, which had caused serious side effects in some people. For lower exposure, there could plausibly be concern about an 'internal' exposure to levels which would be about four times the daily ingested dose. Concern about such chronic exposures runs through the literature on chlorinated hydrocarbon solvents from Hamilton's 1936 paper onwards.

Public health experts might have been troubled by the emerging literature on the inconsistencies between the animal and human data, as well as inconsistencies in the animal data itself. They might also have been concerned about the possibility that exposures to other chemicals might heighten the toxicity of PCE synergistically.

Public health experts would have been unlikely to view the presence of any PCE in their water favourably unless it was unavoidable. This is not merely a statement based on hindsight. Public health and water managers of that era had been concerned for some time with contamination of groundwater from surface disposal of hazardous wastes like PCE, and the unusual mode of contamination in this case was irrelevant. The environmental historian Craig Colten (1991) has shown that by the early 1950s, 'governmental agencies, professional organisations and industry-trade associations, drawing on three decades of experience, all publicly recognised the hazards posed by the surface disposal of liquid wastes... By the 1940s, it had become apparent that simply protecting a well was insufficient. Public-health officials began to take stronger action to alter industrial waste-disposal practices and thereby prevent the introduction of contaminants into the ground.'

Other historians of waste disposal have come to the same conclusion: the propensity of wastes, including chlorinated solvents, to contaminate groundwater was generally understood in the 1940s–1960s and measures were advocated to prevent it. Put another way, it was understood that contamination of drinking water with chlorinated solvents was a threat to the quality of the water (Amter and Ross, 2001). The fact that in this case the solvent entered the water from the pipe lining rather than land disposal was irrelevant.

4.5.1 *Why did Johns-Manville fail to foresee the potential harm?*

Johns-Manville Corporation (the pipe manufacturer) may only have recognised the potential harm of PCE with the benefit of 'hindsight'. But the question remains as to why the risks were not recognised earlier.

In the best interpretation, it could be argued that Johns-Manville was never aware of the problem of PCE contamination. Yet, while it is possible that no one in this large industrial concern bothered to think about or investigate the medical literature on PCE, it is quite clear they could have done so. At that point they would have had several options, including redesigning the product, alerting water managers to the potential for contamination from an insufficiently 'cured' product, or continuing to act as if it was not a problem. The company did not even consider or worry about the possibility of insufficient curing, and once the problem was detected, it denied that there were any health hazards — a necessary position if it were to avoid paying damages for a faulty product.

What is the lesson here? Although there is abundant evidence that Johns-Manville wilfully disregarded and concealed scientific evidence with respect to its principal asbestos products (Ozonoff, 1988), there is no such evidence in relation to PCE. Assuming that knowledge was not hidden, the proposition that Johns-Manville was merely indifferent to these dangers is a plausible explanation for its action; there are many similar examples involving other companies in this period.

The lack of epidemiological evidence would not have been a reason to delay action. Epidemiology was in its infancy and the requirement that even well accepted findings be reconfirmed with epidemiological studies was not yet the norm. The available evidence mainly circulated in the restricted arena of medical specialist literature and the ignorance of most treating physicians and workers about what materials they were being exposed to further served to keep the problem of solvent toxicity off the agenda. This also prevented workers, their unions and their advocates from entering into the conversation about solvent toxicity. If occupational exposures were not on the table, water contamination was also unlikely to be well recognised in this period.

1970 also marked a turning point in the US from minimal federal engagement in workplace and

Panel 4.1 Differences between risk assessments drawn from the same basic data

Christina Rudén

Trichloroethylene, TCE, a relative of PCE, is widely used as a raw material for chemical synthesis, as a solvent for cleaning metal parts and in dry cleaning. A review of 29 TCE carcinogenicity risk assessments conducted between 1973 and 1997 (Rudén, 2002) explored how differences in the selection, interpretation and weighting of primary data affected their differing conclusions.

Classification of TCE risk in risk assessment reports 1973 and 1997

Conclusions of risk assessments: carcinogenicity, epidemiology, human cancer risk				
	No evidence indicating carcinogenicity: *human risk not plausible*	Plausible evidence of carcinogenicity in animals: *human risk not plausible (animal data not considered relevant for humans)*	Plausible evidence of carcinogenicity in animals: *plausible human risk (based on animal data)*	Plausible evidence of carcinogenicity in animals and in epidemiology: *plausible human risk (based on a combination of animal and epidemiological data)*
Total number of assessments 1973–1997	6	10	9	4
Assessments conducted 1995–1996	1	1	1	3

Note: 'Plausible epidemiological evidence' means that people exposed to TCE have greater prevalence of cancer compared to unexposed people.
'Plausible evidence for carcinogenicity in animals' means that animals exposed to TCE in laboratory experiments have an increased incidence of cancer compared to unexposed animals.

Eight of the 10 evaluations that identified a risk for animals but not for humans were conducted by international organisations or industry. Contrastingly, eight of the nine assessments that concluded a human risk based on animal evidence were conducted by government or academic authors. Rudén (2002) observed that this may reflect more risk-averse assessment policies applied by government agencies and academia, and a tendency for industry to apply less precautionary criteria. These wide variations in conclusions continued even within a narrower period, such as 1995–1996, when the evaluating bodies were working from the same available body of knowledge.

Similarly, as shown in the table below, different risk assessors have reached varying conclusions about PCE.

Panel 4.1 Differences between risk assessments drawn from the same basic data (cont.)

Conclusions on the carcinogenicity of PCE

	ECETOC (1999)	IARC (1995b)	ACGIH (1993)	MAK (1992)
Conclusions on PCE carcinogenicity	Plausible evidence of carcinogenicity in animals: *human risk not plausible*	Plausible evidence of carcinogenicity in animals and in epidemiology: *plausible human risk (based on a combination of animal and epidemiological data)*	Plausible evidence of carcinogenicity in animals: *human risk not plausible (animal data not considered relevant for humans)*	Plausible evidence of carcinogenicity in animals: *plausible human risk (based on animal data)*

One important reason why risk assessors differ in their conclusions concerning the size and even the nature of risk is that scientific knowledge increases over time. As risk assessments are updated to include new data the conclusions may change. This is a time-dependent and natural part of the scientific and regulatory process. However, risk assessors may also select different sets of data to support their risk assessments and may interpret key studies in different ways.

An example of this is the interpretation of PCE epidemiology (Rudén, 2006). PCE epidemiology was considered positive in the risk assessment performed by IARC in 1995 and negative in the ECETOC assessment from 1999. The IARC conclusion on epidemiology is based on findings of elevated relative risk of non-Hodgkin's lymphoma (NHL) in three epidemiological studies: Blair et al. (1990), Spirtas et al. (1991) and Anttila et al. (1995). Contrastingly, ECETOC acknowledged the increased incidence of non-Hodgkin's lymphoma in Spirtas et al. (1991) but assigned little weight to the data since the study was initiated because of a priori concerns about lymphatic cancers. ECETOC described the excess of non-Hodgkin's lymphoma in the Anttila study as not statistically significant. Regarding the Blair study ECETOC stated that it did 'not provide results for NHL as a cause of death'. Furthermore, ECETOC concluded that there was 'no excess of deaths due to lymphosarcoma or reticulosarcoma in the Ruder study (1994) and no excess of deaths due to other lymphatic or hematopoietic cancers'. ECETOC concluded that 'available epidemiological studies were either negative or were not sufficient to provide evidence of a relationship between exposure to [tetra] and cancer in humans'. The varying interpretations in the ECETOC and IARC studies are set out in the table below, which is adapted from Rudén (2006).

Interpretation of four epidemiological studies regarding non-Hodgkin's lymphoma by ECETOC (1999) and IARC (1995b)

	ECETOC 1999	IARC 1995
Anttila et al., 1995	Negative (*)	Positive
Ruder et al., 1994	Negative	Data on non-Hodgkin's lymphoma not reported
Spirtas et al., 1991	Positive (**)	Positive
Blair et al., 1990	Negative	Positive

(*) ECETOC described this study as positive on p. 143 ('Anttila et al. reported an excess of NHL...'), and as negative on p.136 ('Increased risks...but none was significant').

(**) Not considered a key study by ECETOC since it was initiated due to a priori concerns about lymphatic cancers.

Various case studies in the first volume of *Late lessons from early warnings* (EEA, 2001) emphasise that such differences are not uncommon in risk assessments. Indeed, as EEA (2008) indicate, this variance in interpretations is attracting increasing attention from regulators and policymakers.

Evidently, evaluators must communicate better about the approach they use to evaluate the strength of evidence and scientific uncertainties. Different evaluators must also employ clear and consistent terminology. This will help minimise the concerns that arise among risk managers and stakeholders when different experts derive different conclusions from the 'same' body of scientific knowledge, or when conclusions and uncertainties are communicated using unclear or inconsistent terminology.

environmental concerns to a prominent role. With the new attention after 1970 came new concerns about contaminating water.

The scientific information on PCE never figured in the water mains product design. It was ignored or invisible. This suggests that the principal reason that Johns-Manville did not care enough to examine thoroughly the risks of using PCE was that nobody made them care. Industrial firms are not people but they nevertheless have interests and intentions, which are rarely related to public health and environmental concerns. The job of a company is to make money for its owners. For Johns-Manville, PCE water mains represented a means of generating profits, with the actual nature of the product having secondary importance. In order for public health concerns to be brought to the forefront, additional mechanisms are needed, most notably criminal and civil liability, both of which rely on state enforcement of legal rules. Other mechanisms are possible, such as moral pressure and voluntary industry standards, but they must all pass the acid test: are they sufficient to make the company care?

Photo: © istockphoto/Steve Jacobs

Once a problem has risen to the level where it can no longer be ignored (and the ability to ignore a problem depends on contextual factors such as the state of knowledge, power relations, economic considerations and political arrangements), much will depend upon a company's assessment of what is at stake. High stakes mean the deployment of considerable resources — resources more at the disposal of large corporations. In such circumstances, uncertainty favours the side of inaction.

4.6 The view from 2013

The period before 1970 had revealed the outline of acute reactions to PCE, and established concern about chronic and delayed effects. Not long after the Massachusetts pipes were installed, an entirely new dimension of PCE toxicology became apparent, concerning carcinogenicity, teratogenicity and other health effects.

In the early 1970s it was discovered that the first member of the chlorinated ethylene series, vinyl chloride monomer, was a human carcinogen (see Chapter 8 on vinyl chloride). This immediately raised the question as to whether other high-volume chlorinated ethylenes, primarily trichloroethylene (TCE) and PCE, might also be carcinogens. By this time PCE was widely used in the dry-cleaning industry, exposing workers and patrons of dry cleaners, and often producing groundwater contamination from improper disposal of spent solvent from the numerous small firms using it.

Because of this heightened suspicion, both TCE and PCE were tested in animal bioassays for carcinogenicity beginning in the mid-1970s (for PCE see NCI, 1977; Mennear et al., 1986). Both were found to be animal carcinogens, although by this time the methodology and validity of animal bioassays had become a matter of dispute and no finding went unchallenged. Attempts at epidemiological verification of PCE's carcinogenicity were difficult because of the long latency for cancer, lack of exposure information and low statistical power of most studies.

A variety of occupational groups were studied, including aircraft workers, small companies in countries where biological monitoring was required, and dry-cleaning firms. Several environmental studies were also conducted to see if TCE/PCE-contaminated drinking water was associated with cancer. Results were mixed and

Panel 4.2 Wet cleaning technology eliminates PCE use in dry cleaning

Joy Onasch

Massachusetts has designated PCE as a higher hazard substance under the Toxics Use Reduction Act but further policy measures could help phase out the solvent, including by encouraging a shift away from dry cleaning to wet-cleaning technologies. This shift could be further supported by a more comprehensive assistance programme helping convert facilities to professional wet cleaning. As outlined below, the electricity and gas savings involved mean that partnerships with utility companies could help create a programme with additional depth.

Able to dissolve most organic materials, PCE is the most widely used dry-cleaning solvent in the US. The US Environmental Protection Agency estimates that some 85 % of cleaners use PCE as their primary solvent. PCE is also a major contributor to contamination at dry-cleaning facilities, mainly due to past unsafe handling practices. PCE is reported to be the chemical most widely found in groundwater contamination at Superfund sites (TURI, 2007), dry cleaning being one of the main sources.

The concept of wet cleaning in the professional garment care industry has existed for several decades. However, it is only in the last 10 years or so that technology has advanced such that 100 % of garments can be cleaned using the wet-cleaning system. In 1997, Keoleian et al. recommended in the *Journal of Cleaner Production* that larger cleaners could consider operating mixed mode facilities using both dry-cleaning and wet-cleaning equipment.

Today over 150 dedicated wet cleaners operate in California, a state where PCE is being phased out through regulations. California Air Resources Board amendments will over time phase out the use of PCE dry-cleaning machines and related equipment by 1 January 2023. Still, the shift to wet cleaning from solvent-based cleaning has been slow, especially where regulations phasing out solvent use do not exist. Sinsheimer et al. concluded in the *Journal of the Air and Waste Management Association* in 2007 that cleaners they studied in California that switched to professional wet cleaning were able to maintain their level of service and customer base while lowering operating costs. They also found that the cleaners were able to transition to professional wet cleaning without great difficulty and were highly satisfied with the new technology (Sinsheimer et al., 2007).

Onasch (2011) studied a dry cleaning shop in Bellingham, Massachusetts, showing that by becoming a dedicated wet cleaner electricity and natural gas use were reduced by as much as 20 % and even water use was reduced. For this facility, equipment costs were reduced by USD 500 over 12 months, performance costs (claims) were reduced by USD 1 000 over 12 months, operational costs (mainly due to costs of detergents) increased by USD 1 069 over 12 months and costs associated with resource use (calculated using normalised rates) were reduced by USD 2 318 over 12 months. Together, savings totalled USD 2 749 over the 12 months of the study. To replace its solvent machine, the facility spent approximately USD 12 000 (in actual costs, but not factoring in discounts and grant monies received). This implies that the firm would have realised a return on the investment in just under 4.5 years.

With appropriate training and practice the personnel at this facility were able to master difficult garments and even boasted that wet cleaning resulted in 'whiter' whites and brighter colours than had been possible via dry cleaning.

Time spent cleaning garments was difficult to quantify but with proper training and practice total cleaning time could be reduced due to less pre-spotting, the ability to simultaneously wash and dry in separate machines (unlike the all-in-one traditional dry-cleaning machines) and mastery of the finishing equipment. Indirect benefits of improved air quality, reduced liability, elimination of regulatory oversight, and environmentally friendly niche marketing should all also factor into the analysis of the professional wet-cleaning system.

Photo: © istockphoto/Frances Twitty

the chemical industry consistently denied that PCE was a human carcinogen. In each of the individual studies it was possible to find limitations or alternative explanations for positive results (and for negative ones). With each new iteration, new arguments were spun out, sometimes involving epidemiology, later involving sophisticated toxicological arguments as to why PCE could be a carcinogen in rodents but not a carcinogen in humans. In this setting it is not surprising that scientists could look at exactly the same set of data and come to opposing conclusions.

Christina Rudén's panel on inconsistencies between risk assessments of TCE and PCE drawn from the same basic data (Panel 4.1) explores these issues in more detail. Taken as a whole, however, the literature shows a clear and consistent progression towards increasing concern about the carcinogenic effects of PCE. According to Karstadt (1998):

> 'Trichloroethylene and tetrachloroethylene have been reviewed by IARC panels several times: three times (volumes 20, supplement 7, and volume 63) for tetrachloroethylene, four times (volumes 11, 20, supplement 7, and volume 63) for trichloroethylene. Until the consensus meeting that resulted in volume 63 (published 1995) animal evidence for the two chemicals was evaluated as limited and human evidence as inadequate; both evaluations were raised in volume 63, to sufficient in animals and limited in humans. The IARC reviews of those two chemicals clearly show the gradual accretion of human evidence over the years as well as the development of definitive animal data.'

Throughout this period PCE has been on the radar screen of the occupational health and environmental scientific communities, unlike the period before 1970. As a result, fairly strict community drinking water standards have been established, although occupational standards have lagged behind. This inconsistency may partly result from the combination of a weak labour movement and some highly publicised environmental cases involving childhood cancer (e.g. Lagakos et al., 1986).

The problem is no longer invisibility and neglect, but intense scrutiny. The chemical industry has been active and aggressive in countering new information through the strategy of artificially and purposefully creating doubt and uncertainty in the minds of decision-makers. With this chemical now on the cusp of being declared a confirmed human carcinogen in some major national markets, the industry is essentially buying extra time (and creating continuing exposure and disease) by this strategy. Thus 40 years after the hard lesson of the water mains in Massachusetts, a sound precautionary strategy for continued exposure to PCE has still not been initiated.

The means used to avoid or promote action today are different from those of 1970, employing many sophisticated means to create doubt and increase uncertainty about the true value of a regulatory action. The 1970 context was simpler. Evidence was available and not acted on for reasons not complicated by complex regulations, the potential of lawsuits or the activities of environmental or activist organisations. Information about effects and exposure was restricted or non-existent and available primarily to scientists. The industry felt no special need to consult it (although they had contributed to it) and apparently did not. It was of no interest to them.

During both periods the lesson of this small but revealing case study seems clear. Mechanisms are needed to force the production, sharing and publication of information about exposure and effects; normative and legal requirements concerning the duty of care of employers and manufacturers are also required. Alternatives are available, as Joy Onasch's description of wet-cleaning technologies (Panel 4.2) illustrates.

Today, continued argument over how to interpret the scientific evidence is irresolvable within science itself because the same evidence can be interpreted differently and there are no overarching criteria from the philosophy of science that can force a solution.

Whether the problem is a failed duty of care or a lack of clarity about what evidence will trigger action, the history of PCE will continue in the future as it has in the past. The science has not been hidden. It has been ineffective in guiding and catalysing action.

Table 4.1 Early warnings and actions

1860	PCE synthesised
1920s–1960s	PCE used in the treatment of hookworm
1925	First toxicological evaluation of PCE
1925–1940	Clinical and toxicological evaluation of therapeutic use identified a variety of problems and recognised that the responses of different subjects varied
1940–1970	New uses prompt consideration of inhalation dangers; chronic effects studied (central nervous system depression) and new analytical methods brought into play (gas chromatography)
1970–present	Discovery that vinyl chloride is a carcinogen prompts controversy and large literature with competing accounts of PCE's carcinogenicity Environmental and occupational standards were promulgated, generating controversy couched in scientific terms. PCE figures in lawsuits
Today	PCE is regulated in the environmental and occupational environments but controversy continues over where to set standards and whether PCE has caused harm in many legal cases

References

ACGIH, 1993, *Tetrachloroethylene, Documentation of the TLVs*, seventh edition, American Conference of Government Industrial Hygienists.

AMA Council on Pharmacy and Chemistry, 1936, 'Preliminary Report: Report on the Present Status of Tetrachlorethylene', *JAMA*, (107/14) 1 132–1 133.

Amter, S. and Ross, B., 2001, 'Was contamination of souther-n California groundwater by chlorinated solvents foreseen?', *Environmental Forensics,* (2) 179–184.

Anttila, A., Pukkala, E., Sallmén, M., Hernberg, S. and Hemminki, K., 1995, 'Cancer incidence among Finnish workers exposed to halogenated hydrocarbons', *J. Occup. Environ. Med.*, (37) 797–806.

Baader, E.W., 1954, *Gewerbedrankheiten: Klinische Grundlagen der 40 meldepflichtigen Berufskrankheiten*, Urban & Schwarzenberg, Munich, pp. 159–161.

Barrett, H.M., Cunningham, J.G. and Johnston, J.H., 1939, 'A study of the fate inn the organism of some chlorinated hydrocarbons', *J Ind Hyg & Toxicol,* (21) 479–490.

Beyer, A. and Gerbis, H., 1932, 'Jahresberict ubeer die Tatigkeit der preussischen Gewerbemedizinalrate wahrend des Kalenderjahres', *Veroffentlichungen aus dem Gebiete der Medizinialverwaltung*, (39) 1–30.

Blair, A., Stewart, P.A., Tolbert, P.E., Grauman, D., Moran, F.X., Vaught, J., and Rayner, J., 1990, 'Cancer and other causes of death among a cohort of dry cleaners', *Br. J. Ind. Med.*, (47) 162–168.

Bwibo, N.O., 1969, 'Accidental poisoning in children in Uganda', *Br med J*, (4) 601–602.

Carpenter, C.P., 1937, 'The chronic toxicity of tetrachlorethylene', *J Ind Hyg & Toxicol*, (119) 323–336.

Coler, H.R. and Rossmiller, H.R., 1953, 'Tetrachlorethylene exosure in a small industry', *AMA Arch of Indust Hyg & Occ. Med*, (8) 227–233.

Colten, C., 1991, *Geographic Review,* (81) 215–228.

Demond, A.H., 1982, *A source of tetrachloroethylene in the drinking water of New England: an evaluation of the toxicity of tetrachloroethylene and the prediction of its leaching rates from vinyl-lined asbestos-cement pipe* (MS Thesis), Massachusetts Institute of Technology, Cambridge, MA.

ECETOC, 1999, *Tetrachloroethylene*, European Centre for Ecotoxicology and Toxicology of Chemicals, Joint Assessment of Commodity Chemicals, vol. 39.

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

EEA, 2008, *Evaluating and Communicating Scientific Evidence on Environment and Health Issues*, report of the European Environment Agency workshop, Copenhagen, 28–29 May 2008.

Fairhall, L.T., 1949, *Industrial Toxicology*, Williams & Wilkins, Baltimore, p. 442–444.

Fernando, P.B., D'Silva, M. and Stork, G.K.B., 1939, 'Tetrachlorethylene in the treatment of hookworm disease with special reference to toxicity', *Ind J Med Res,* (3) 759–783.

Friberg, L., Kylin, B. and Hystrom, A., 1953, 'Toxicities of trichloroethylene and tetrachlorethylene and Fujiwara's pyridine-alkali reaction', *Acta Pharmacol et Toxicol,* (9) 303–312.

Gehring, P.H., 1968, 'Hepatotoxic potency of various chlorinated hydrocarbon vapours relative to their narcotic and lethal potencies in mice', *Toxicol and Appl Pharmacol*, (13) 287–298.

Hall, M.C. and Shillinger, J.E., 1925, 'Tetrachlorethylene, a new anthelmintic', *Am J Trop Med*, (5) 229–237.

Hamilton, A., 1936, 'Some new and unfamiliar industrial poisons', *NEJM*, (2215) 425–532.

IARC, 1995a, 'Drycleaning, some Chlorinated Solvents and Other Industrial Chemicals', *IARC Monogr Eval Carcinog Risks Hum*, vol. 63.

IARC, 1995b, *Tetrachloroethene*, International Agency For Research On Cancer Monographs, vol. 63.

Irish, D.D., 1962, 'Common chlorinated aliphatic hydrocarbon solvents', *Arch Env Health,* (4) 110–116.

Karstadt, M., 1998, 'Availability of epidemiologic data for chemicals known to cause cancer in animals: an update,' *Am J Ind Med*, (34) 519–525.

Keoleian, G.A., Blackler, C.E., Denbow, R. and Polk, R., 1997, 'Comparative assessment of wet and dry garment cleaning', *Journal of Cleaner Production,* (5/4) 279–289 (and 1998, 6, 23–36).

Lagakos, S.W., Wesson, B. and Zelen, M., 1986, 'An analysis of contaminated well water and health effects in Woburn, Massachusetts', *Journal of American Statistics Association*, (81) 583–596.

Lamson, P.D., Robbins, B.H. and Ward, C.B., 1929, 'The pharmacology and toxicology of tetrachlorethylene', *Am. J. Epidemiol*., (9/2) 430–444.

Larsen, C.D.F., Love, T.O., Reynolds, G., 1983, 'Tetrachloroethylene leached from lined asbestos-cement pipe into drinking water', *J. Am Water Works Assoc*, 75L 184–188.

Lehmann, K.B. and Flury, F., 1943, *Toxicology and hygiene of industrial solvents*, Williams & Wilkins Co., Baltimore, pp. 184–186; 310–325.

Lob, M., 1957, 'Les dangers du perchlorethylene', *Archiv fur Gewerbepatholgie und Gewerbehygiene*, (16) 45–52.

MAK, 1992, *Tetrachloroethylene, Toxikologisch-arbeidsmedizinische Begrundung von MAK-Werten*, Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area.

Manson, D., 1934, 'A comparative record of anthelmintic treatment with tetrachlorethylene and oil of chenopodium', *The Indian Med Gaz,* (69) 500–507.

MDEE, 1982, *Status Report on Tetrachloroethylene Contamination of Public Drinking water Supplies by Vinyl-lined Asbestos Cement Pipe*, Massachusetts Department of Environmental Engineering, Commonwealth of Massachusetts, Boston, MA.

Mennear, J., Maronpot, R., Boorman, G., Eustis, S., Huff, J., Haseman, J., McConnell, E., Ragan, H., Miller, R., 1986, 'Toxicologic and carcinogenic effects of inhaled tetrachloroethylene in rats and mice,' in: Chambers, P., Gehring, P. and Sakai, F., (eds), *New Concepts and Developments in Toxicology,* Elsevier Science Publishers, pp. 201–210.

Morse, K.M. and Goldberg, L., 1943, 'Chlorinated solvent exposures—at degreasing operations', *Ind Med*, (12) 706–713.

NCI, 1977, National Cancer Institute, *Bioassay of Tetrachloroethylene for Possible Carcinogenicity* (CAS No. 127-18-4) Tech. Rept. Ser. 13, Bethesda, MD.

Onasch, J., 2011, 'A feasibility and cost comparison of perchloroethylene dry cleaning to professional wet cleaning: case study of Silver Hanger Cleaners, Bellingham, Massachusetts', *Journal of Cleaner Production*, (19) 477–482.

Ozonoff, D., 1988, 'Failed Warnings: Asbestos Related Disease and Industrial Medicine' in: Bayer, R. (ed.), *The Health and Safety of Workers*, Oxford University Press, New York, pp. 139–218.

Plaa, G.L., Evans, E.A. and Hine, C.H., 1958, 'Relative hepatotoxicity of seven halogenated hydrocarbons', *J Pharmacol & Exp Therap* (123) 224–229.

Rosenau, M., 1935, *Preventive Medicine and Hygiene*, D. Appleton-Century Company.

Rowe, V.K., McCollister, D.D., Spencer, H.C., Adams, E.M. and Irish, D.D., 1952, 'Vapor toxicity of tetrachloroethylene for laboratory animals and human subjects', *AMA Arch of Ind Hyg & Occ Med*, (5) 566–579.

Rowe, V.K., Wujowski, T., Wolf, M.A., Sadek, S.E. and Stewart, R.D., 1963, 'Toxicity of a solvent mixture of 1, 1, 1,-trichlorethane and tetrachloroethylene as determined by experiments on laboratory animals and human subjects', *Am Ind Hyg Assoc J*, (24) 541–554.

Rudén, C., 2002, 'The Use of Mechanistic Data and the Handling of Scientific Uncertainty in Carcinogen Risk Assessments: The Trichloroethylene Example', *Regulatory Toxicology and Pharmacology*, (35) 80–94.

Rudén, C., 2006, 'Science and policy in risk assessments of chlorinated ethenes', *Ann. N.Y. Acad: Sci.*, (1076) 191–206.

Ruder, A.M., Ward, E.M. and Brown, D.P., 1994, 'Cancer mortality in female and male dry-cleaning workers', *J. Occup. Med.*, (36) 867–874.

Sandground, J.H., 1941, 'Coma following medication with tetrachlorethylene', *JAMA*, (117) 440–441.

Sappington, C.O., 1943, *Essentials of Industrial Health*, JB Lippincott, Philadelphia, p. 249.

Sharlin, H.I., 1966, *The Convergent Century: The Unification of Science in the Nineteenth Century*, Abelard-Schuman.

Sinsheimera, P., Grouta, C., Namkoonga, A., Gottlieba, R. and Latif, A., 2007, 'The viability of professional wet cleaning as a pollution prevention alternative to perchloroethylene dry cleaning', *Journal of the Air and Waste Management Association*, (57) 172–178.

Smyth, H.F., Weil, C.S., West, J.S. and Carpenter, C.P., 1969, 'An exploration of joint toxic action: twenty-seven industrial chemicals intubated in rats in all possible pairs', *Toicol and Appl Pharmacol*, (14) 340–347.

Spirtas, R., Stewart, P.A., Lee, J.S., Marano, D.E., Forbes, C.D., Grauman, D.J., Pettigrew, H.M., Blair, A., Hoover, R.N. and Cohen, J.L., 1991, 'Retrospective cohort mortality study of workers at an aircraft maintenance facility I. Epidemiological results', *Br. J. Ind. Med.*, (48) 515–530.

St George, A.V., 1937, 'The pathology of the newer commercial solvents', *Am J Clin Path*, (7) 69–77.

Stewart, R.D. and Dodd, H.C., 1964, 'Absorption of carbon tetrachloride, trichlorethylene, tetrachloroethylene, methylene chloride, and 1,1,1-trichloroethane through the human skin', *Am Ind Hyg Assoc J*, (25) 439–446.

Stewart, R.D., Baretta, E.D., Dodd, H.C. and Torkelson, T.R., 1970, 'Experimental human exposure to tetrachlorethylene', *Arch Environ Health*, (20) 224–229.

Stewart, R.D., Dodd, H.C., Erley, D.S. and Holder, B.B., 1965, 'Diagnosis of solvent poisoning', *JAMA*, (193) 115–118.

Stewart, R.D. and Erley, D.S., 1965, 'Detection of volatile organic compounds and toxic gases in humans by rapid infrared techniques', *Prog Chem Toxicol*, (2) 183–220.

Stewart, R.D., Erley, D.S., Schaffer, A.W. and Gay, H.H., 1961a, 'Accidental vapor exposure to anesthetic concentrations of a solvent containing tetrachlorethylene', *Ind Med Surg*, (30) 327–330.

Stewart, R.D., Gay, H.H., Erley, D.S., Hake, C I. and Schaffer, A.W., 1961b, 'Human exposure to tetrachloroethylene vapor', *Arch Env Health*, (2) 40–46.

Stewart, R.D., Swank, J.D., Roberts C.B. and Dodd, H.C., 1963, 'Detection of halogenated hydrocarbons in the expired air of human beings using the electron capture detector', *Nature*, (198) 696–697.

Stewart, R.D., 1969, 'Acute tetrachloroethylene intoxication', *JAMA*, (208) 1 490–1 492.

TURI, 2007, *Massachusetts Chemical Fact Sheet, Perchloroethylene (PCE)*, Massachusetts Toxics Use Reduction Institute (http://www.turi.org/About/Library/TURI-Publications/Massachusetts_Chemical_Fact_Sheets/Perchloroethylene_PCE_Fact_Sheet/PCE_Details/PCE-Fact-Sheet-pdf) accessed 28 December 2011.

Williams, L.P., 1965, *Michael Faraday*, Da Capo Press.

Wright, W.H., Bozicevich, J. and Gordon, L.S., 1937, 'Studies on oxyuriasis, V. Therapy with single doses of tetrachlorethylene', *JAMA*, (109) 570–573.

Zernik, F., 1933, 'Neuere Erkenntnisse auf dem Begiete der schadlichen Gase und Dampfe', *Ergebnisse der Hygiene Bakeriologie Immunitatsforschung und Experimentellen Therapie*, (14) 139–141, 200–210.

5 Minamata disease: a challenge for democracy and justice

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Minamata disease, which can induce lethal or severely debilitating mental and physical effects, was caused by methylmercury-contaminated effluent released into Minamata Bay by Chisso, Japan's largest chemical manufacturer. It resulted in widespread suffering among those who unknowingly ate the contaminated fish. This chapter documents the story in three phases.

The disease first came to prominence in the 1950s. It was officially identified in 1956 and attributed to factory effluent but the government took no action to stop contamination or prohibit fish consumption. Chisso knew it was discharging methylmercury and could have known that it was the likely active factor but it chose not to collaborate and actively hindered research. The government concurred, prioritising industrial growth over public health. In 1968 Chisso stopped using the process that caused methylmercury pollution and the Japanese government then conceded that methylmercury was the etiologic agent of Minamata disease.

The second part of the story addresses the discovery that methylmercury is transferred across the placenta to affect the development of unborn children, resulting in serious mental and physical problems in later life. Experts missed this at first because of a medical consensus that such transfer across the placenta was impossible.

The third phase focuses on the battle for compensation. Initially, Chisso gave token 'sympathy money' under very limited criteria. In 1971 the Japanese government adopted a more generous approach but after claims and costs soared a more restrictive definition was introduced in 1977, justified by controversial 'expert opinions'. Legal victories for the victims subsequently made the government's position untenable and a political solution was reached in 1995–1996. In 2003, the 'expert opinions' were shown to be flawed and the Supreme Court declared the definition invalid in 2004.

In September 2011 there were 2 273 officially recognised patients. Still, the continuing failure to investigate which areas and communities were affected means that the financial settlement's geographic and temporal scope is still not properly determined. Alongside deep-seated issues with respect to transparency in decision-making and information sharing, this indicates that Japan still faces a fundamental democratic deficit in its handling of manmade disasters.

This chapter is followed by three short updates on the effects of mercury poisoning since Minamata; on attempts to contain it, including the 2009 global agreement to phase mercury out of economic activity; and on the need for better information about contaminant exposures to enable policymakers to make informed choices that balance the benefits of fish consumption against the assumed adverse effects of low-level methylmercury exposures.

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5.1 Introduction

The Minamata disease story is one of blinkered awareness by industry and government, of inaction, refusal to take evidence seriously, insistence on high levels of proof before addressing the problem, and delay, delay, delay.

In 1972 scientists, politicians and the public were shocked by the presence of two Minamata disease patients on the platform at the first global environmental conference, held in Stockholm — the United Nations Conference on the Human Environment (Harada, 2004). They were halting and unsteady, they struggled to speak. They had been poisoned by mercury in their environment.

It took a further thirty-eight years for the first session of an Intergovernmental Negotiating Committee, also held in Stockholm, in June 2010, to start developing a global legally binding instrument on mercury pollution prevention, following the elaboration of a legally binding instrument on mercury at the United Nations Environment Programme (UNEP) Governing Council in February 2009.

At the Intergovernmental Negotiating Committee's opening session, the representative of Japan reported that his government wished to host the conference at which the global mercury agreement would be agreed (UNEP, 2010). He proposed that it be called the 'Minamata Convention', indicating the international community's resolve to ensure that the human health and environmental disaster caused by methylmercury in the Bay of Minamata would never be repeated (UNEP, 2010). He also reported that the Japanese government would contribute all it had learnt about reducing the risk of mercury (METI, 2010).

Despite the Japanese government's apparent determination, many problems remain unresolved in Japan. Key aspects of the disaster are unknown, such as the number of Minamata disease sufferers and exposed residents, and the area and duration

DANDERYDS SJUKHUS

Photo: In 1972 United Nations Conference on the Human Environment in Stockholm focused on the Minamata disease. (From the left) Dr Noboru Ogino, Mr Tsuginori Hamamoto, Dr Masazumi Harada, Ms Fujie Sakamoto (Shinobu's mother), Ms Shinobu Sakamoto, unknown person, and Dr Soubei Togo. Mr Hamamoto and Ms Shinobu Sakamoto are Minamata disease patients.

of exposure. There is not even a consensus on the definition of Minamata disease (Ekino et al., 2007), making it hard to count the number of Minamata disease patients and determine who qualifies for compensation. Indeed, the diagnostic criteria that the Government has consistently used to certify Minamata Disease were judged medically invalid by the Japanese Society of Psychiatry and Neurology (JSPN) in 1998 (JSPN, 1998) and declared invalid by the Supreme Court in 2004 (McCurry, 2006). Nevertheless, the government has not changed the criteria.

The criteria currently being used to diagnose Minamata disease are too strict, meaning that even patients with the related neurological symptoms lack government accreditation. And without government recognition of a Minamata disease diagnosis, a patient will not be properly compensated. Consequently, in September 2011 although 2 273 individuals were officially recognised as Minamata Disease patients (Minamata Disease Museum, 2010), several tens of thousands have neurological symptoms characteristic of methylmercury poisoning but remain formally unrecognised as Minamata disease patients (McCurry, 2006; Watts, 2001; Sankei Shinbun, 2011; Yorifuji et al., 2013).

Given this continuing conflict and suffering, Masazumi Harada (2), has observed that when the government of Japan expressed a desire to share its experience and expertise, and to name the new global convention on mercury phase-out after Minamata, it should not merely report its technical success in controlling mercury pollution. It should also 'report to the world that there still remain unsolved problems in Minamata. Not only cases of success but also cases of failure can be valuable lessons for the world' (Kumamoto Nichinichi Shinbun, 2010b).

In this chapter, the history of Minamata disease is presented chronologically, broadly separating the discussion into three parts: the period before 1968; specific issues associated with congenital Minamata disease; and the period after 1968. The chapter concludes with the lessons that can be drawn from the history of Minamata disease.

5.2 Minamata disease in the period up to 1968

5.2.1 *Early warnings and signs of Minamata disease: from wildlife to children*

> 'Don't think of labourers as humans; treat them as cattle and horses'

This quote is widely attributed to the Chisso factory founder Shitagau Noguchi, suggestive of past attitudes towards workers, residents and the environment in Minamata (Miyazawa, 1996).

Minamata is the south-western part of Kumamoto Prefecture in Japan, facing Shiranui Sea (Map 5.1), 1 000 km from Tokyo. In 1908, the Nihon Carbide factory was established in Minamata. Later that year it merged with Sogi Electric to form Nihon Chisso Hiryo Kabushiki Gaisha (Japan Nitrogenous Fertilisers). The firm initially used carbide to produce ammonia for fertilisers but, having purchased a German patent for producing ammonia without carbide in 1921, it began using carbide and acetylene (derived from carbide) to manufacture a wider range of organic synthetic compounds.

One such compound was acetaldehyde. The factory began producing it in 1932 from acetylene gas, using mercury as a catalyst. The process was developed by Hikoshichi Hashimoto, who later became factory manager and served as Minamata's mayor (3).

It is now understood that the effluent from the acetaldehyde production contained methylmercury and this caused Minamata disease. In fact, Vogt and Nieuwland had already shown in 1921 that organic mercury was synthesised in producing acetaldehyde (Ishihara, 2002). In the 1930s, Zangger (1930) and Koelsch (1937) reported on intoxication due to occupational exposure to organic mercury or methylmercury (short-chain organic mercury) (Ishihara, 2002). A researcher at Chisso factory demonstrated in 1951 that organic mercury is synthesised in the production of acetaldehyde (Arima, 1979) but it is not clear whether the Chisso factory was aware of the toxic effects at that time.

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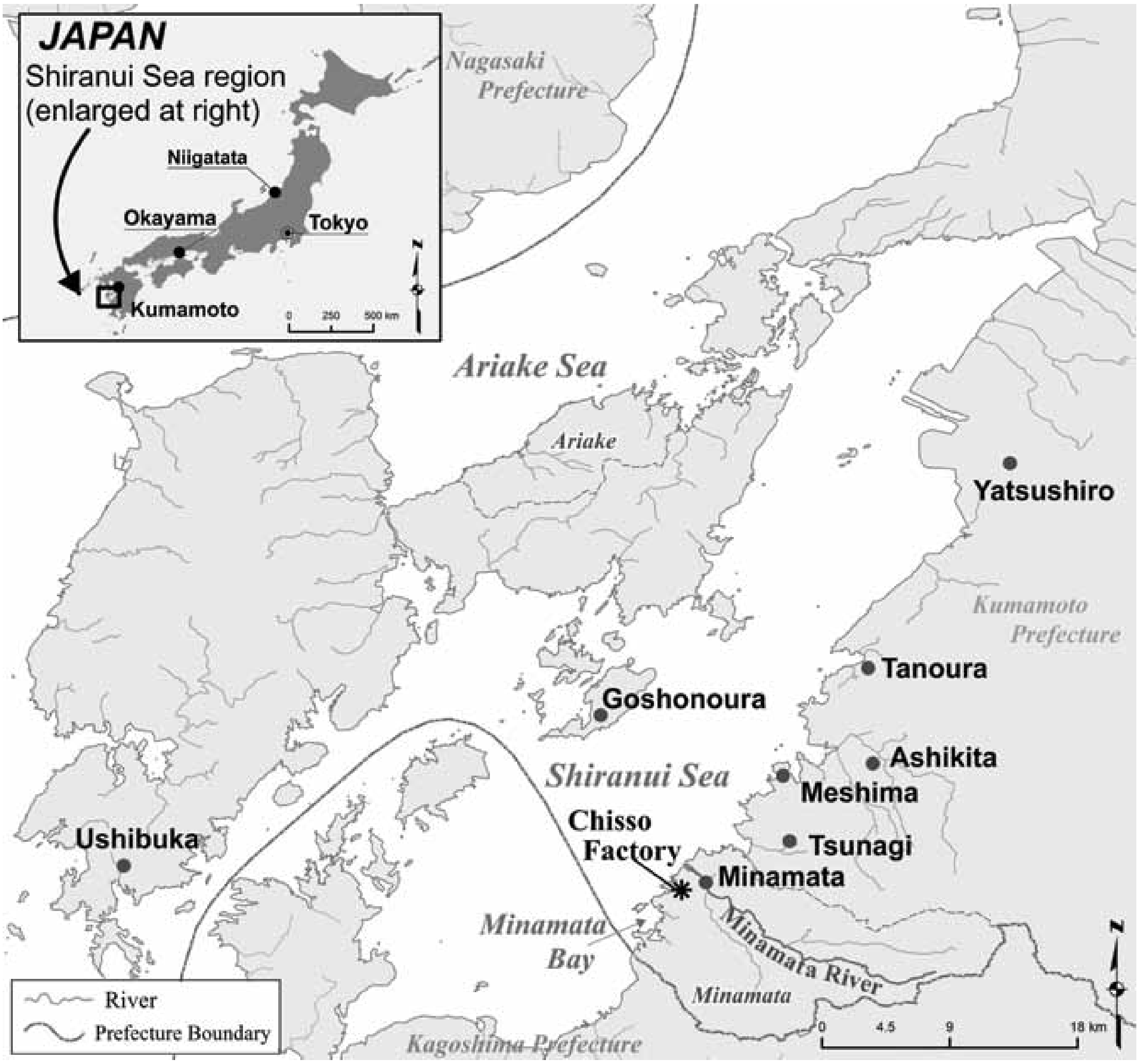
(2) Masazumi Harada, co-author of the present chapter, started researching Minamata disease in 1961 and went to Stockholm with the Minamata patients in 1972.

(3) He seems to have played a similar role as that of Peter Stockmann, the mayor in Ibsen's play 'An enemy of the people', where he opposed taking action on the public health doctor's report on pollution of the town's spa baths and in favour of suppressing the report. The Chisso doctor Hosokawa, whose report on Minamata disease in the Chisso factory cats was also suppressed, drew some comfort from reading 'An enemy of the people.'

Map 5.1 Map of Shiranui Sea region


JAPAN
Shiranui Sea region (enlarged at right)
Niigatata
Okayama
Tokyo
Kumamoto
0 250 500 km
N
Nagasaki Prefecture
Ariake Sea
Ariake
Yatsushiro
Kumamoto Prefecture
Tanoura
Goshonoura
Shiranui Sea
Ashikita
Meshima
Chisso Factory
Tsunagi
Minamata
Ushibuka
Minamata Bay
Minamata River
Minamata
0 4.5 9 18 km
N
River
Prefecture Boundary
Kagoshima Prefecture

Source: Dr. Saori Kashima, Department of Public Health and Health Policy, Hiroshima University Graduate School of Biomedical Sciences, Hiroshima, Japan.

The factory's knowledge of the Zangger study (1930) was considered at the Minamata Disease Trial in 1987 (Hashimoto, 2000) but the findings were inconclusive.

The Chisso factory's acetaldehyde production initially peaked at 9 159 tonnes in 1940, a level not matched after the war until 1955. By 1960, however, it had quintupled to 45 200 tonnes (Figure 5.1), making up 40 % of Japan's total output (Arima, 1979). In 1951, to increase production of acetaldehyde, the factory changed the oxidiser of acetaldehyde production from manganese to iron (Miyazawa, 1996). This production change and related technical improvement are considered to have increased methylmercury waste from the factory (Miyazawa, 1996). Nishimura and Okamoto (2001) estimate a more than eight-fold increase from 1951 to 1959.

In 1952, the factory succeeded in producing octanol from acetaldehyde (Miyazawa, 1996). Japan had previously relied on imports of octanol, an important ingredient in plastics. As a result, the factory increased production of acetaldehyde and by 1959, the factory accounted for 85 % of Japan's octanol output (Hashimoto, 2000). As a consequence the methylmercury waste from the factory also increased.

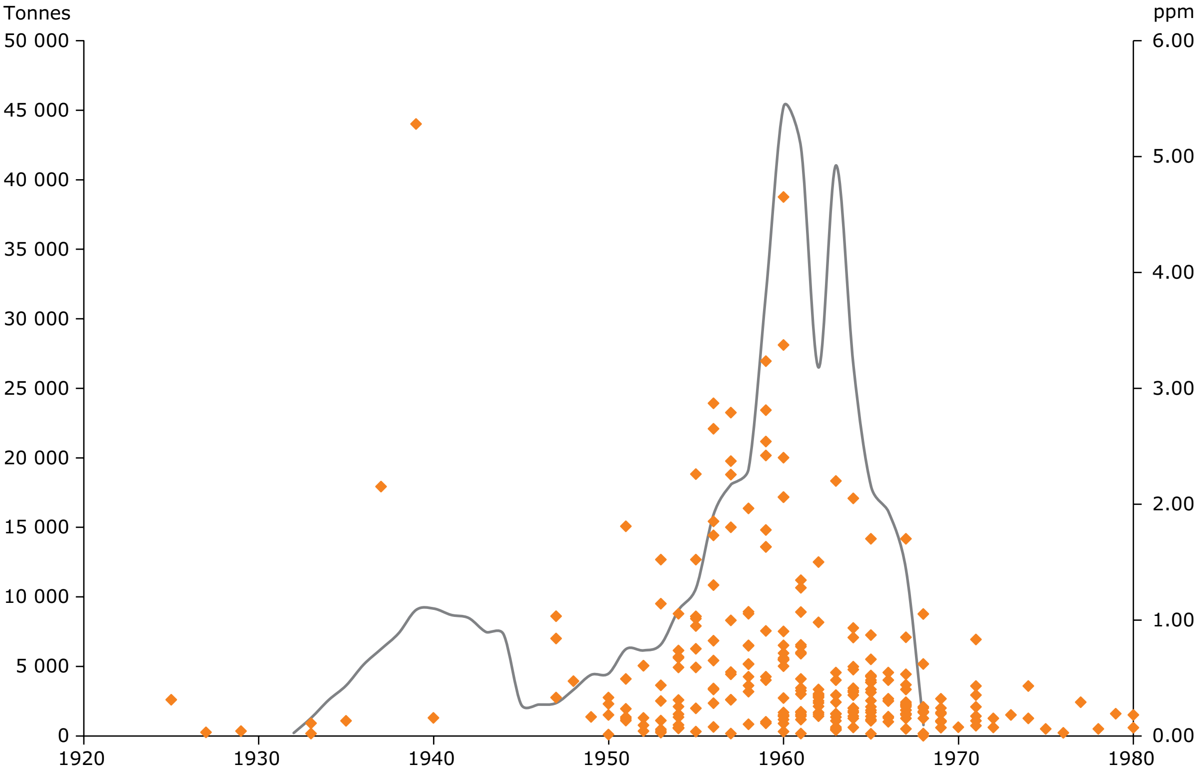
The economic significance of this production was considerable. Japan had recorded a trade deficit since the end of the Second World War (Ministry of Finance, 2011) and plastic products were key Japanese exports at that time helping to reduce its deficit. As the most advanced chemical company during those decades, the Chisso factory clearly had an important economic role.

Minamata city grew with the factory, 'reaching a population of 20 000 in 1921, 30 000 in 1941, 40 000 in 1948, and a peak of 50 000 in 1956' (George, 2001). The factory was a main employer in the city: at least 3 811 of Minamata's 19 819 workers were employed at the factory in 1960 (Ui, 1968). In addition, the factory not only paid half of the local taxes in Minamata but also provided public facilities, such as a factory hospital (Ui, 1968). Hikoshichi Hashimoto, who developed the method to produce acetaldehyde, went on to serve four terms as Minamata's mayor (1950–1958 and 1962–1970) after managing the factory during the Second World War (George, 2001). In these circumstances, Minamata was known as Chisso's 'castle town' (after the capital cities of the feudal lords who controlled much of the lives of its citizens) (Harada, 2004).

The first hints of what was to become Minamata disease may be apparent in reports of the factory's impact on the local fishery (Harada, 2004). Around 1925–1926, the company began to receive requests for compensation from the fishing cooperative. On the condition that no further complaints would ever be lodged, Chisso paid a small amount of 'sympathy money'. The issue of fishery damage arose again in 1943 due to carbide residue from acetylene production and another compensation contract was concluded. And after the war the issue of fishery damage resurfaced in 1949 but compensation negotiations reached no conclusion and the issues faded.

The fishermen knew that it had become more difficult to catch fish; that barnacles did not attach themselves to boats moored near the factory waste outfall; and that fish could not live in water from the outfall. But, the factory would not listen to them, replying that these facts were 'not scientific, not supported by data' (Harada, 2004), although the fishing cooperative

Figure 5.1 Acetaldehyde production at the Chisso factory (line) and methylmercury concentrations in the umbilical cords of residents around the Shiranui Sea (dots)



Source: Reprinted from Science of the Total Environment, vol. 408, 272–276, Yorifuji, T., Kashima, S., Tsuda, T. and Harada, M., 'What has methylmercury in umbilical cords told us? — Minamata disease', Copyright (2009), with permission from Elsevier.

collected and showed detailed data of the fishery damage (described below). In addition, neither the company nor the government assisted in identifying an appropriate scientific protocol for researching the fishermen's significant concerns.

From around 1950, strange phenomena started occurring around Minamata Bay (Harada, 2005). Fishermen witnessed huge numbers of fish rising to the surface and swimming around as though they were crazy. Sea birds that had become unable to fly were seen crouching on the shores of the bay. Oysters and cockles were washed up onto the beach rotting with their shells open, emitting a horrible stench. During this period, according to the data collected by the fishing cooperative, total fish catch of 459 225 kg on average in the period 1950–1953 dropped to 172 305 kg in 1955 and 95 599 kg in 1956 (Harada, 2004).

In 1952, fishermen requested Kumamoto Prefecture to address the situation. The Fisheries Division at Kumamoto Prefecture asked the factory about the discharge treatment and the factory submitted documentation, which reported that mercury was used in the process of producing acetic acid (a substance produced after acetaldehyde) (Chisso factory, 1996). Reiji Miyoshi at the Fisheries Division inspected the factory five months later and reported that the discharge should be analysed (Miyazawa, 1996). However, Kumamoto Prefecture did not conduct a further survey of the fishery damage or the discharge and the fishery damage continued. Moreover, neither Kumamoto Prefecture nor any other group (including the research group at Kumamoto University) ever used the factory documentation indicating mercury use to identify the etiologic agent for Minamata disease or its production mechanism.

Around 1953, local cats, which ate great quantities of fish, began exhibiting strange behaviour: drooling and staggering about, undergoing convulsions or running in circles as though they were mad, or leaping up into the air and charging forward (Harada, 2004). Eventually, fishermen had no more cats. In August, 1954, a local newspaper reported that fishermen in a village (Modo) were annoyed by the increase in mice due to the annihilation of cats (Kumamoto Nichinichi Shinbun, 1954). These strange occurrences were an omen of what would happen next to humans. Watching the 'dancing cats', people began to feel uneasy. Indeed, a few patients with neurological symptoms of unknown origin were detected during this period and a subsequent study revealed that the first patient was traced back to 1942 (Nishigaki and Harada, 1975).

Cats eating great quantities of fish from the polluted Minamata Bay went mad and died after strange dancing and convulsions.

Photo: © istockphoto/Taner Yildirim

On 21 April 1956, a paediatrician at Chisso Hospital, Kaneki Noda, examined a girl aged five years and 11 months. The girl had difficulty in walking and speaking; she appeared to be in a drunken state, unsteady on her feet and slurring her words. She was hospitalised two days later. On the same day, her sister, aged two years and 11 months, developed the same symptoms and she was hospitalised on 29 April. Subsequently, Dr Noda learned of other patients with similar symptoms in the neighbourhood. He officially notified the Minamata Public Health Centre on 1 May 1956 (Harada, 1995 and 2004; Miyazawa, 1996).

Hasuo Ito, the Director of the Public Health Centre, interviewed the children's mother in detail about the disease. He then made a report to the Health Department at Kumamoto Prefecture (Ito, 1996). A newspaper in Kyushu Area, the south-western area of Japan, reported the disease on the 8 May (Miyazawa, 1996). On 28 May, the Minamata Doctors Association, the Public Health Centre, Chisso Hospital, the municipal hospital, and the city government established the Minamata Strange Disease Countermeasures Committee

(Harada, 2004). Subsequently, doctors including Dr Noda and Hajime Hosokawa, the Director of Chisso Hospital, identified numerous new cases. According to the report of Dr Hosokawa, 30 cases including 11 deaths were identified by 29 August (Hosokawa, 1996).

The first official patients lived in a secluded spot at the end of a tiny inlet off Minamata Bay, where five or six families huddled together on the narrow strand. They were so close to the sea that they could have cast a fishing line from the windows at high tide. They were people who lived as one with nature. Because the outbreak of the disease was spontaneous and occurred among neighbours, the doctors at the factory and officials at the Public Health Centre suspected that they were dealing with a contagious disease and moved the patients to an isolation ward. Officials from the Public Health Centre went to the patients' homes and made a show of spraying them with disinfectant.

Transferring the patients to an isolation ward may have indicated an intention on the part of doctors and the city — out of good will or for political reasons — to mitigate the residents' anxiety and to exempt the patients from medical expenses. The patients hated it, however, and it fostered discrimination against them. They were shunned by other community members and experienced years of discrimination (Harada, 2004).

This was the beginning of Minamata disease.

5.2.2 The cause: fish and shellfish contaminated by factory discharge (1956–1957)

In response to the request of the Minamata Strange Disease Countermeasures Committee, Kumamoto University School of Medicine established a research group including various medical departments on 24 August 1956 (MDRG, 1966). In the epidemiological section, Shoji Kitamura and his group conducted both descriptive and analytic epidemiological studies (Kitamura et al., 1957). In the descriptive study, the time sequence of cases was evaluated on a spot map, which indicated that the disease was not contagious. The analytical study revealed a relationship between the family occupation (fishing) and the disease, and a dose-response relationship between eating fish caught in Minamata Bay and the disease. Prof. Kitamura concluded that the disease could be induced by continuous exposure to a common factor, which seemed to be contaminated fish in Minamata Bay.

On 3 November 1956, the Research Group on Minamata Disease reported that the disease was not contagious but rather a food poisoning incident resulting from intake of fish contaminated by a heavy metal in Minamata Bay. It also reported that the factory's effluent was considered the cause of contamination (Kumamoto University, 1956). Furthermore, in the second debrief session on 26 February 1957, the Research Group recommended prohibiting fishing or applying the Food Sanitation Act (Miyazawa, 1996). The Act could be used to take actions against food poisoning, such as prohibiting the sale or distribution of food. An individual disobeying such a prohibition could face criminal punishment.

In November 1956, the Scientific Research Team of the Ministry of Health and Welfare of Japan (MHWJ) started an epidemiological investigation in Minamata (Matsuda et al., 1996). In March 1957, they demonstrated a relationship between the family occupation (fishing) and the disease, consistent with the Kumamoto University Research Group's epidemiological study. Moreover, they showed that families living closer to Minamata harbour, where factory effluent was discharged, were affected more than families living further away. For example, all seven families in the Tsukinoura area included at least one patient, while 33 % (7/24) of families included a patient in the Yudo area. Noting that sea water and mud in Minamata Bay was strongly affected by the factory effluent, the Research Team inferred that fish caught in Minamata Bay were contaminated by the effluent. They concluded that the disease could be induced by contaminated fish in Minamata Bay and that the factory and its effluent should be fully investigated to elucidate the disease's mechanism.

In response to these findings, the local government of Kumamoto Prefecture considered applying the Food Sanitation Act in March 1957 (Kumamoto Prefecture, 1996b) because Shizuoka Prefecture had used the Act to address an episode of shellfish food poisoning in 1950 (Shizuoka Prefecture, 1996). The local government had the authority to decide whether to apply the Act but asked for an opinion from the national government on 16 August (Kumamoto Prefecture, 1996a). On 11 September 1957, Masayoshi Yamaguchi, the Chief of the Public Health Bureau of MHWJ replied to the local government as follows (bold added) (MHWJ, 1996a):

I. 'We recommend that you should continue your policy of warning against the ingestion of fish and shellfish caught in a specified area of Minamata Bay because it may lead to the occurrence of the unknown disease of the central nervous system.'

II. 'There was no clear evidence that **all** fish and **all** shellfish are poisoned in the specified area in Minamata Bay. Therefore, we have decided that it is impossible to apply Provision 4-2 of the Food Sanitation Act to all the fish and shellfish to be caught in that area.'

Japan's Food Sanitation Act provides that a local government's public health centre must investigate food poisoning outbreaks in detail and take measures in response. When a cause (e.g. an institution or food) is identified, the exposed area and residents must be investigated and the sale or distribution of the cause prohibited. In Minamata, despite the risk outlined in paragraph I of the reply, consumption of contaminated fish was not prohibited based on the reasoning in paragraph II. Although the Minamata Public Health Centre, like the Minamata Strange Disease Countermeasures Committee, identified severely affected patients from the start of its work, it did not further investigate the area and the exposed residents epidemiologically. Residents continued to eat contaminated fish without effective information.

In 1990, the government of Japan asserted that another reason it did not apply the Food Sanitation Act in 1957 was that the etiological agent (methylmercury) had not been identified in 1957 (Environment Agency et al., 1999). While the etiologic agent may not have been clearly identified in 1957, however, the cause/transmission (ingesting fish caught in Minamata Bay) was identified in 1956. Indeed, fish in Minamata Bay were recognised as food causing Minamata disease even in records of food poisoning published by MHWJ in 1956 (Department of Environmental Sanitation, 1957).

It is perhaps surprising that the governments of Shizuoka and Kumamoto Prefectures responded differently to their respective food poisoning episodes, although each had the same strength of evidence that shellfish or fish were contaminated with an unknown etiologic agent. Shizuoka Prefecture decided itself to apply the Food Sanitation Act, while Kumamoto Prefecture asked MHWJ and finally did not apply the Act. Miyazawa (1996) has argued that Kumamoto Prefecture's response reflected the Prefecture's concern about the compensation claims that Chisso factory would have faced if the Act had been invoked.

The early epidemiological studies identified the causes of the health impacts but concentrated solely on severely affected patients and did not investigate the health status of residents in affected areas, as required by the Act. This caused serious problems later. Since the government undertook no effective countermeasure, subsequent research sought to discover the etiologic agent or its mechanism of production in university laboratory settings rather than using epidemiological studies to find moderate cases or investigate health in local settings. During this period, local residents were almost unaware of the finding that the fish and shellfish were contaminated. Although some residents probably knew of the contamination from newspapers and their own experiences, poor fishermen in particular could not stop fishing, as this was their only means of survival.

Whereas affected fishermen lacked political power locally and nationally, Chisso factory was supported by the local government and Ministry of International Trade and Industry of Japan (MITIJ) at that time. Subsequent events clearly indicate that Chisso factory had considerable influence in Japanese industry and society. The Chief of the Department of Environmental Health who recommended not invoking the act in his reply to local government in 1957 had taken measures beyond the law to address a polio outbreak in the 1950s, importing vaccine from Russia. When a lawyer later asked him why he had avoided prohibiting fish consumption in the Minamata disease outbreak in accordance with the Food Sanitation Act despite taking measures beyond the law in the polio outbreak, he replied 'Chisso never existed behind the polio outbreak'.

In the late-1950s, the officers of MITIJ sent weekly demands to the Water Quality Maintenance Section of the Economic Planning Agency of Japan (EPAJ) that wastewater bans should never be implemented. The MITIJ officers urged their counterparts to 'stick it out' and 'offer opposition to the ban', stressing that 'Japanese economic growth would never be realised if such a big industry, Chisso, were stopped. Never stop it!' (Hashimoto, 2000).

5.2.3 *Organic mercury theory (1958–1959)*

With neither the factory nor the Government taking appropriate measures to control the outbreak, exposure continued and spread. Following a research meeting on 15 February 1958, Masayoshi Yamaguchi, Chief of the Public Health Bureau of MHWJ reported to other ministries and local governments on 7 July 1958 that: 'Minamata disease was caused by intake of contaminated fish and shellfish. The discharge from Minamata factory

(Chisso factory) affected Minamata Bay. The same chemical toxicant (which the discharge of which affected the bay) was considered to poison the fish and shellfish' (MHWJ, 1996b).

A local newspaper reported the news, describing it as the first MHWJ statement to mention the factory as a cause (Kumamoto Nichinichi Shinbun, 1958). Yamaguchi, who made the statement, explained later in court that MHWJ had reported to Kumamoto Prefecture because it expected the Prefecture to take control measures based on the Food Sanitation Act (Miyazawa, 1996). However, the Act was not invoked.

Following the MHWJ statement the factory took steps to dilute the discharge containing methylmercury. In September 1958 it changed the drainage route of acetaldehyde production from Minamata Bay to Minamata River (Harada, 1995 and 2004; Miyazawa, 1996), where some effluents (such as phosphoric acid effluent, carbide residue) were already discharged (Nishimura and Okamoto, 2001). Several other factors probably also influenced the factory's decision to act (Miyazawa, 1996): the factory had learned of Kumamoto University's focus on mercury; high mercury concentrations had been detected in shellfish in Minamata Bay; the factory wanted to increase acetaldehyde production; and everyone knew that residents continued to eat fish.

Hajime Hosokawa, Director of Chisso hospital, objected to the plan. He also noted that 'if patients were detected in the area around the Minamata River, it would prove that the discharge was the cause' (Miyazawa, 1996). However, the plan was executed — without the knowledge of local residents. Exposure subsequently spread not only in Minamata Bay but along the entire coast of Shiranui Sea. Fish and cats began to die in other villages (Harada, 1995). And from 1959 onwards, patients with similar neurological symptoms were identified among the residents of other villages around the Shiranui Sea (Kumamoto Nichinichi Shinbun, 1959; Ninomiya et al., 1995; Yorifuji et al., 2008).

Meanwhile, researchers at Kumamoto University's School of Medicine continued their efforts to find the etiologic agent of Minamata Disease and its biological mechanism of action. This was not easy because the Research Group knew nothing about the interior of Chisso factory (Harada, 2005): what was produced, how it was produced, what substances were used and which processes. At that time the Research Group received no assistance from the engineers at Chisso factory or even from the organic chemistry sector of Kumamoto University's School of Engineering.

The Research Group identified various possible etiologic agents — manganese, thallium and selenium — but when fed to cats these substances did not produce effects comparable to organic mercury (Takeuchi et al., 1960). Although mercury was the first etiologic agent considered, Shoji Kitamura of the Research Group has recollected with regret that 'Mercury was taken off the list on the assumption that such an expensive material would never be thrown away in the sea' (Harada, 2004).

Douglas McAlpine, a British neurologist, visited Minamata on 13 and 14 March 1958. He examined 15 Minamata disease patients and made a very valuable observation, noting that symptoms such as constriction of the visual field, impaired hearing and ataxia closely resembled those of methylmercury poisoning reported by Hunter et al. (1940).

McAlpine reported his observations in the journal Lancet in September 1958 (McAlpine and Araki, 1958). In his paper, he pointed out that the disease was caused by eating fish caught in Minamata Bay as well as the toxic action of a chemical compound contained in the effluent from Chisso factory (McAlpine and Araki, 1958). Moreover, he listed methylmercury as one of the metals which could induce Minamata disease. This was the first time that methylmercury was identified as a potential etiologic agent. McAlpine's observations were important but before he could report them to a Japanese Society of Neurology Conference he was stopped by a professor of Kumamoto University on the grounds that too many theories would be confusing (Harada, 2004).

Meanwhile, another researcher, Tadao Takeuchi, also suspected that the etiological agent was organic mercury since he also saw similarities to so-called Hunter-Russell syndrome (Hunter et al., 1940; Hunter and Russell, 1954). Takeuchi et al. (1960) extracted significant levels of mercury (not organic mercury) from patients' organs at autopsy and also succeeded in inducing similar neurological symptoms in cats by feeding them organic mercury.

Shoji Kitamura and his Research Group likewise extracted large quantities of mercury from mud and shellfish in Minamata Bay (Kitamura et al., 1960b), and noted that concentrations decreased as the distance from the factory increased. They extracted mercury from experimentally affected cats at autopsy and ascertained that mercury levels increased in shellfish bred in the bay, demonstrating that mercury was accumulating internally (Kitamura et al., 1960b). On 22 July 1959, researchers finally concluded that the etiological agent was mercury based on the clinical characteristics and animal experiments (Kumamoto Nichinichi Shinbun, 1959; Kumamoto University, 1996).

During this period, researchers at Kumamoto University School of Medicine suspected that the mercury concentrations were a byproduct of vinyl chloride production. This is because when they had asked the factory in 1957, the factory had only mentioned vinyl chloride among organic synthetic compounds that the factory produced, and mercuric chloride was actually used as a catalyst in the production process (Miyazawa, 1996). In addition, they noticed that vinyl chloride output growth paralleled the increase in patients (Takeuchi et al., 1960). Although focusing on the vinyl chloride process, the Kumamoto University Research Group was unable to show how inorganic mercury in the waste from producing vinyl chloride changed to organic mercury.

Leonard Kurland of the National Institute of Health (NIH) in the US visited Minamata in September 1958 and examined patients. In a subsequent article, he supported the Kumamoto University's conclusion that the etiologic agent was organic mercury in *World Neurology* and also focused on vinyl chloride production (Kurland et al., 1960). However, a local newspaper, the *Minamata Times*, published by Masao Shino, a Minamata citizen, already noted on 10 December 1959 that mercuric salt was used as a catalyst in producing acetaldehyde and suspected the relationship between the acetaldehyde production and the disease (Minamata Times, 1996). This information must have been leaked from workers inside the factory.

On 7 October 1959, Hajime Hosokawa, Director of Chisso Hospital, succeeded in inducing Minamata disease in a cat, labelled number 400, which had been given waste water from acetaldehyde production daily for 78 days (Harada, 2004). This important finding, which was not made public, clearly shows that the waste from acetaldehyde production actually contained organic mercury. If the Kumamoto University Research Group had known of this finding it could have made great progress. Instead, when Dr Hosokawa reported the cat number 400 result to the factory, the findings were kept secret and the factory prohibited further studies (Miyazawa, 1996). When allowed to restart experiments in 1960, Hosokawa found that cats given waste water from acetaldehyde production also manifested disease. However, he resigned from the factory in April 1962, without being able to make the results public.

Later in 1962, Jun Ui, a postgraduate engineering student, and Shisei Kuwabara, a photographer, visited a doctor at the Chisso factory (Mishima, 1992) and found a note concerning the results of the experiments on cats. Kuhabara photographed this evidence when the doctor was out of the room. They subsequently showed the photograph to Dr Hosokawa who acknowledged its authenticity. Ui later related these facts along with other details about Minamata disease in the monthly magazine Goka and the information played an important role in the first Minamata disease lawsuit (Tomita, 1965). Despite suffering from lung cancer, Dr Hosokawa testified in the first Minamata disease lawsuit in 1970 from his hospital bed, making two key points (Mishima, 1992): first, cat number 400 had definitely demonstrated symptoms of Minamata disease; second, his recommendation that the factory waste should not be shifted from Minamata Bay to the mouth of the Minamata River had been ignored. He died later that year.

Wastewater containing methylmercury from Chisso factory was led directly into Minamata Bay.

Photo: By Eugene Smith © Aileen M. Smith

Based on the Kumamoto University Research Group's July 1959 report, organic mercury was recognised as the etiological agent by the Minamata Food Poisoning Committee organised by MHWJ on 12 November 1959 (MFPC, 1996). However, there was no mention of the source of the contamination, Chisso factory. Indeed, before the Committee announced that organic mercury was an etiologic agent, the section chief of the MHWJ Environmental Sanitation Department told the Committee's representative not to conclude that the factory was a cause because it was not 'scientifically' proved (Miyazawa, 1996). And after the Committee had reported its opinion to the Minister of Health and Welfare, it was suddenly dissolved. No official reason was ever given.

An inter-ministerial meeting was held on the day before the Minamata Food Poisoning Committee's announcement. There, an MITIJ representative told researchers and other officers that: 'No similar patients have been observed around chemical factories with the same system as Chisso. If the operation by Chisso were causal, we would find such patients around those factories. Furthermore, the mercury used in the Chisso factory as a catalyst is inorganic. The causative agent that you have identified is organic mercury. No means by which inorganic mercury could be converted to organic mercury has been identified. We cannot accept the explanation that waste water from Chisso contains the etiologic agent of Minamata disease' (Hashimoto, 2000).

In September 1959, Chisso factory likewise refuted the organic mercury theory based on the absence of similar disease at other factories; difficulties explaining the abrupt increase in patients since 1954 and uncertainty regarding the organic chemical reaction mechanism (Minamata factory, 1996). This was despite the fact that a factory researcher had already demonstrated that organic mercury was synthesised in the production of acetaldehyde in 1951 (Arima, 1979).

The factory also claimed that it was difficult to trust the Kumamoto University Research Group because it had considered other theories (manganese, thallium or selenium) before identifying organic mercury (Minamata factory, 1996). In line with Chisso's counterargument, Raisaku Kiyoura, a professor at Tokyo Institute of Technology, claimed that mercury concentrations in Minamata Bay were not higher than those in other areas (Harada, 2004). Furthermore, Takeji Ohshima, the Executive Director of the Japanese Association of Chemical Industries, suggested that the cause might be explosives dumped into Minamata Bay by the Japanese military (Harada, 2004).

The debate suggests that Chisso factory intentionally, although inconsistently, used reductionist argumentation to postpone action. On one hand, despite the abundance of evidence that had already existed since 1956, Chisso factory contended that the only way to prove causality between its production processes and the organic mercury concentrations was to demonstrate, via a reductionist approach, the chemical mechanism linking the two. On the other, it criticised the researchers at Kumamoto University for applying a reductionist approach by considering other possible metals first. In addition, the consistency argument (relating to the absence of similar disease in other areas and abrupt increases in patient numbers) was also intentionally used to postpone action.

Recent analysis provides the following explanations for the absence of similar disease near comparable factories. First, the factor's output of acetaldehyde was the highest in Japan at that time, accounting for one third or a quarter of national production (Hashimoto, 2000). Second, methylmercury by-product per unit of acetaldehyde production was higher than at other factories due to technical improvements to increase acetaldehyde production (Hashimoto, 2000; Miyazawa, 1996). Third, the factory's proximity to the sea meant that the chloride ion concentration of industrial water was high, which changed the methylmercury byproduct to volatile methylmercuric chloride (Hashimoto, 2000; Nishimura and Okamoto, 2001). It was then discharged when the acetaldehyde was purified by distillation.

Organic mercury represented the most credible explanation but was resisted by Chisso, the chemical industry and the MITIJ. The MITIJ therefore ordered Chisso to return the drainage outfall of acetaldehyde production to Minamata Bay (from the Minamata River) and to install wastewater treatment equipment within the year (Harada, 2004). The factory therefore established a purifying system for the contaminated water in December 1959 (Arima, 1979; Harada, 2004).

Most residents believed that the discharge of the etiological agent would soon cease. However, the system installed, as should have been known by Chisso at the time of installation, was completely ineffective at removing methylmercury (Irukayama, 1969). It was installed only to give the appearance of action by the company and researchers at Kumamoto University were deceived by being given a fake sample from Chisso factory (Miyazawa, 1996). Unsurprisingly, mercury concentration in fish and shellfish in Minamata Bay failed to decline after the system was installed (Irukayama, 1969). To make matters worse, the effluents also continued to be discharged into Shiranui Sea (Irukayama, 1969). As a result, residents not only in Minamata Bay but also in the other villages around Shiranui Sea continued to be exposed.

5.2.4 *Detecting the organic mercury production process and social recognition of Minamata disease (1960–1963)*

Although researchers were now satisfied that organic mercury was the etiologic agent of Minamata disease, no steps were taken to control the poisoning. Researchers concentrated on identifying organic mercury in organisms or finding the mechanism by which it was produced. On 14 February 1960, Makio Uchida, a professor at Kumamoto University, extracted organic mercury in a shellfish in Minamata Bay (Harada, 2004; Uchida et al., 1960). Subsequently, researchers at Kumamoto University made further important findings: confirming that short-chain organic mercury was toxic, extracting methylmercury sulfide from shellfish, and inducing Minamata disease in cats and mice using the substance (Harada, 2004; Sebe et al., 1961; Uchida et al., 1960).

In February 1960, the Minamata Disease General Investigation Committee was established to replace the dissolved MHWJ committee and research Minamata disease (MDGIC, 1996). Many of the discussions in the Committee centred on possible objections to the organic mercury theory and served only to obscure the theory (George, 2001). Its last meeting was held in March 1961. Finally, in March 1962, Fisheries Agency abandoned research regarding Minamata disease (Arima, 1979). After that, no research activities were conducted by government agencies until 1968.

In April 1960, the Minamata Disease Research Council, known as the 'Tamiya Committee', was established (Miyazawa, 1996). Its chair was Takeo Tamiya, President of the Japanese Medical Association, and all members were from universities in Tokyo. Primarily sponsored by the Chisso factory, the Tamiya Committee attempted to obscure the organic mercury theory. The Committee wished to involve Kumamoto University but Kansuke Sera, Dean of Kumamoto University School of Medicine, refused the request (George, 2001), which was a remarkable and noteworthy act.

Researchers on the supposedly 'authoritative' Tamiya Committee disputed Kumamoto University's organic mercury theory by arguing that other factors were responsible (Harada, 2004). On 13 April 1960, Raisaku Kiyoura published a newspaper article promoting his theory that a group of organic chemicals called amines were responsible (4). He claimed that amines, not mercury, were detected in shellfish that caused Minamata disease in cats. Any detailed examination would have demonstrated the dubious medical validity of that counter-theory but the mass media were enthusiastic (Harada, 2004).

The next year, Kikuji Tokita, a professor of Toho University, proposed that eating rotten fish was the cause and the etiologic agent was again suggested to be amines. However, people in Minamata, despite their poverty, were able to eat as much fresh fish as they wanted. Anyone who visited Minamata and observed the life of its people would understand immediately that his theory was wrong. In his paper, the name of Chisso factory, Takeji Ohshima (who had suggested that dumped munitions were responsible) and Raisaku Kiyoura were listed in the acknowledgments. George (2001) notes the emphasis placed on the 'line of attack-that scientists from the "centre" could be trusted over those from "hick" universities on the periphery'. Importantly, all researchers recognised that fish were a cause.

During this period, researchers at the Department of Internal Medicine at Kumamoto University School of Medicine conducted a large investigation to locate unidentified Minamata disease sufferers and determine whether Minamata disease occurred in a chronic form and, if so, what its diagnostic features were (Tokuomi et al., 1962). They targeted 1 831 residents in affected areas, of whom 1 152 (62.9 %) participated, and used a questionnaire to identify participants who needed further physical examination. The study identified 131 participants with neurological signs similar to Minamata disease (Kumamoto Nichinichi Shinbun, 1962), although only 24 of these had severe symptoms. Finally, the Screening Council for Minamata Disease Patients (described in Section 5.4.2) recognised two of cases as having Minamata disease (Miyazawa, 1996 and 2007).

Although this investigation could be seen as an important step towards fully describing Minamata disease (e.g. the nature, threshold, frequency and severity of symptoms; the scale of poisoning; and the prognosis) in practice the investigation could not go far beyond the boundaries of earlier epidemiological studies. This is probably because researchers at Kumamoto University, keen to protect the organic mercury theory from a steady flow of criticism at that time, focused on the typical and severe cases of organic mercury (Hunter-Russell syndrome) (Miyazawa, 2007), even though this was contrary to the primary object of their investigation. They did not use non-exposed areas as controls to compare prevalence and they did not follow up with the 131 participants identified as having similar symptoms to Minamata disease. Finally, when publishing their findings in March 1962 (Tokuomi et al., 1962), the researchers gave the impression that Minamata disease was no longer a problem, observing that 'Minamata disease seems to have terminated at last.'

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(4) An amine is any derivative of ammonia in which one or more hydrogen atoms are replaced by alkyl or aryl groups.

Meanwhile, in 1960 the Kumamoto Prefecture Institute for Health Research investigated the mercury concentration in hair samples from 1 645 healthy fishermen from around Shiranui Sea (Doi and Matsushima, 1996; Matsushima and Mizoguchi, 1996). It was the first large survey using hair samples. The distribution of a high concentration (0–920 ppm) of mercury among the hair samples indicated that the contamination had spread throughout entire Shiranui Sea. The mercury content in Minamata was the highest (a median of 30 ppm) but the mercury content in Goshonoura (median 21.5 ppm) on the other side of the Shiranui Sea was also about 10 times higher than that of residents in the non-exposed city of Kumamoto (median 2.1 ppm) (Doi and Matsushima, 1996; Matsushima and Mizoguchi, 1996; Ninomiya et al., 2005). Among 199 residents examined in Minamata, 61 residents (30.7 %) had hair mercury concentration greater than 50 ppm, while even in Goshonoura 153 residents (13.2 %) among 1 160 examined had those levels of mercury.

Two other investigations were conducted up to 1962 (Doi et al., 1996). Although the investigators claimed that further follow-up studies were needed because the contamination source was not removed and the mercury concentration in hair samples was high, Kumamoto Prefecture decided to stop the investigation in 1962 (Miyazawa, 1996). Furthermore, the health status of the fishermen who provided hair samples was never followed up and the fishermen were never informed of the mercury concentration results.

After Masachika Kutsuna replaced Kansuke Sera as Dean in April 1961, Kumamoto University School of Medicine adopted a conciliatory attitude to Chisso factory (Miyazawa, 1996). It joined the Tamiya Committee and began to receive research funding from Chisso factory and the Tamiya Committee. Indeed, when Kumamoto University published a volume of their research reports in 1966, Chisso factory was listed in the acknowledgments (MDRG, 1966). From that time, Minamata disease became a sensitive problem in Kumamoto University. When a local news paper reported that Prof. Irukayama extracted methylmercury chloride from the sludge of the factory (Kumamoto Nichinichi Shinbun, 1963), Dean Kutsuna reprimanded him and called Chisso factory to apologise for the news (Miyazawa, 1996). Later on, an instruction was handed down in the School of Medicine: 'you can do experimental research about Minamata disease but do not conduct clinical research.' It was said that clinical research 'is not research but rather work conducted by social activist or Prefecture Government' (Harada, 2004) because if researchers included human beings, they naturally became involved in various social problems surrounding Minamata disease.

Finally in 1962, Katsuro Irukayama, a professor at Kumamoto University School of Medicine succeeded in extracting methylmercury chloride from the sludge of the acetaldehyde production process in the factory (Irukayama et al., 1962). Although it was not disclosed, Chisso factory laboratory also extracted methylmercury chloride from the sludge (Miyazawa, 1996). This showed that methylmercury was a by-product of acetaldehyde production and present in discharges from the factory. However, the Food Sanitation Act was not applied as a result of these findings, nor was the factory regulated in any other manner.

Important scientific findings continued. In addition to the success extracting methylmercury chloride from the sludge of the factory, in 1962 an unusual occurrence of cerebral palsy infants was diagnosed as resulting from methylmercury intoxication during fetal life (Harada, 2004). However, the public's attention began to shift away from Minamata Disease. Chisso factory paid 'mimaikin' ('sympathy money') to patients in 1959 meaning that many, including researchers, believed that the issue was settled. Furthermore, from 1962 to 1963, there was a big dispute at Chisso over workers' pay (Harada, 2004). The issue of Minamata disease began to be forgotten except among sufferers and their families.

5.2.5 *Niigata Minamata disease and proof of the causal relationship (1964–1968)*

Although the source of contamination, the causal food, the etiologic agent and the process creating the methylmercury had all been identied, the government did not regulate fish consumption or factory waste at Chisso. In January 1965, similar methylmercury food poisoning occurred in Niigata, causing 'Niigata Minamata disease' (Niigata Prefecture, 2007; Saito, 2009). The factory responsible (Showa Denko) operated in the same way as Chisso in Minamata, with methylmercury being discharged during acetaldehyde production. Although the damage was less than Minamata, over 1 500 individuals (Niigata Prefecture, 2007) were needlessly affected. Once more, cats started dancing and dying from madness in Niigata as a harbinger to the human consequences that were to follow (Harada, 2004).

From the beginning, MITIJ and Chisso had disputed that the factory was the cause of Minamata disease. A compelling argument, in their eyes, had been the observation that 'No similar patients have been observed around other production plants with the same system as Chisso. If the operation by Chisso was causal, we would find such patients around these other factories' (Hashimoto, 2000). At that time, Chisso was by far the largest producer of acetaldehyde, and Showa Denko was the second most important (Harada, 2004). The appearance of Minamata disease in the vicinity of Showa Denko was a powerful refutation of their argument.

A legal case relating to Niigata Minamata disease went on trial in 1967 and on 26 September 1968 the government of Japan finally agreed that there was the causal relationship between wastewater from Chisso (and Showa Denko) and Minamata disease (MHWJ, 1996c). By then, however, this admission was immaterial as acetaldehyde was no longer necessary and production had stopped by May 1968 (Arima, 1979). Twelve years had passed since the institution and food contaminant had been identified. In total, 488 tonnes of mercury were discharged into the sea from 1932 to 1968 (Miyazawa, 1996).

5.3 Congenital Minamata disease: intrauterine methylmercury poisoning

Minamata disease can be considered a typical example of industrial pollution (Ui, 1968) for several reasons. First is the manner of the outbreak. Minamata disease is a form of food poisoning (and indeed carried through the food chain) as a result of environmental pollution. Second, it is a classic example of how decisions supposedly based on factual judgements were influenced by political, financial, legal and even psychological factors (such as hierarchies within society, within and between scientific disciplines and between different wings of government, and supposed 'loss of face' in admitting error). Corruption also played a role.

However there is another reason why it will long be remembered: the discovery of congenital Minamata disease. Before congenital Minamata disease was proven, it was believed that the womb protected the foetus from poisons. This was the first clear-cut case of chemical poisoning transmitted through the placenta to the foetus. A paragraph from Harada (2005) conveys the normal attitudes towards congenital Minamata disease at that time (1961):

> When conducting a survey in the area of frequent outbreak of Minamata disease, I came upon two brothers on a veranda. Their symptoms were exactly the same; so I assumed that they must both have Minamata disease. However, their mother said, 'The 9 year-old contracted Minamata disease when he was 3 years and 6 months, but the 5 year-old has cerebral palsy.' 'Why?' I asked, to which she responded, 'The younger one has never eaten fish; he was born this way, so it's not Minamata disease.' I was convinced right away. This is because we used to believe at that time that the placenta would not let poisons pass though. Then the mother added, 'That's what doctors say. Both my husband and this older child got Minamata disease. My husband died in 1954. I ate the same fish. At the time the younger boy was inside of me. I think the reason I have few symptoms of the disease is because this child absorbed all the mercury that I ate.' At the time I thought this was just the fancy of an amateur who knew nothing about medical science. But time proved that she was correct. Her words were prophetic in speaking of the suffering of the foetus because after that time we had many experiences of congenital cases.

Many infants born after 1955 showed symptoms resembling those of cerebral palsy in the affected areas (Kitamura et al., 1959 and 1960a). Shoji Kitamura mentioned in 1959, 'It is possible that the substance causing the poisoning was transferred to the infants through the placenta or mother's milk, producing symptoms similar to those of Minamata disease' (Kitamura et al., 1959). Careful clinical and epidemiological studies were conducted (Harada, 1978). All the patients displayed similar symptoms (Harada, 2005) including mental retardation, disturbed coordination, deformities of limbs, poor reflexes, poor nutrition and impaired growth. Most were hyperactive, suffered from muscular spasms and uncontrollable slow writhing, had squints,

One of the symptoms of Minamata disease is deformed limbs.

Photo: By Eugene Smith © Aileen M. Smith

produced excess saliva resulting in drooling, and were subject to sudden mood changes.

Epidemiologically, the patients were coincident with Minamata disease both in timing and location (Harada, 1964). Their mothers consumed a large amount of fish and exhibited mild symptoms of Minamata disease. Furthermore, 13 infants (6.9 %) among 188 infants born during the period 1955–1958 suffered from severe cerebral-palsy-like symptoms in the three most heavily contaminated areas (Harada, 1964). Since the overall incidence of cerebral palsy in Japan was 0.2–0.6 % at that time, this clearly showed that this incidence of cerebral-palsy-like infants (congenital Minamata disease patients) was very high (Harada, 1964).

Despite these clinical and epidemiological features, it took a long time for congenital Minamata disease to be accepted as a fact. Mothers of children seeking assistance with medical costs were told that they would only be helped once some children had died, had been autopsied, and the nature of the illness had been confirmed (Harada, 2004). Finally, two autopsies of infants confirmed methylmercury intoxication during foetal life. Then, in December 1962, 17 patients were officially diagnosed with congenital Minamata disease (Miyazawa, 1996). Later research revealed that the disease existed in a broader region, and 66 cases including 13 deaths were identified by Harada (2005 and 2007). However, no other epidemiological studies to investigate the existence of congenital Minamata disease have ever been conducted.

One reason why it took five to eight years to confirm congenital Minamata disease is that researchers had never previously seen a case of poisoning through the placenta (Harada, 2005). In addition, researchers who became convinced that the disease was being transferred from mother to foetus were told (for example by the Screening Council for Minamata Disease Patients and city officials) that they had no proof (Harada, 2005). Because organic mercury was only recognised as the etiologic agent in 1959, mercury levels in hair or umbilical cord blood were not previously measured at birth. However, in 1968 Masazumi Harada realised that the Japanese tradition of preserving the umbilical cord might make it possible to measure methylmercury concentrations in preserved umbilical cords as an indicator of foetal exposure. He collected umbilical cords among the residents around Shiranui Sea and was able to demonstrate a correlation between acetaldehyde production in Chisso factory and the concentration of methylmercury in umbilical cords (Figure 5.1) (Nishigaki and Harada, 1975; Yorifuji et al., 2009a). This supported the hypothesis that methylmercury affected foetuses in the uterus via the placenta.

A continuing problem relating to intrauterine exposure to methylmercury is the effects of low to moderate exposure (Harada and Tajiri, 2009), i.e. exposure that is below the level that produces the full effects but is nevertheless debilitating. While symptoms of congenital Minamata disease can be similar to cerebral palsy, some individuals exposed to a high umbilical cord mercury level did not show exactly these symptoms — and were therefore disregarded — despite showing other mental disabilities, behavioural anomalies or other cerebral dysfunctions. They were missed because of the failure to implement proactive epidemiological investigation targeting residents exposed to methylmercury via the uterus.

It is well established that methylmercury concentrations in congenital Minamata disease and Minamata disease patients are higher than in healthy individuals. But we now know that methylmercury concentrations in other mentally retarded groups are also higher than in healthy people (Harada et al., 1999). Further investigation of mental retardation cases revealed clumsiness in finger movement and other light motor dysfunctions. The ongoing developments regarding the effects of low to moderate exposure among residents underline the continuing failure to investigate the consequences of Minamata thoroughly. Further follow-up studies are needed targeting congenital Minamata disease patients and more moderate exposure to methylmercury in the uterus. Nothing can reverse the history of exposure but much could and should be done to mitigate and learn from its effects.

5.4 Chaos implementing the Minamata disease accreditation system (1968 to present)

After the Japanese government accepted the causal relationship between Chisso factory and Minamata disease in 1968, attention shifted to the 'accreditation' of the disease in individual patients, in order to determine compensation claims. The payment of compensation can be grouped into four phases. First, Chisso paid 'sympathy money' without accepting responsibility. Second, 1971 witnessed an early application of the precautionary principle, when accreditation criteria were relaxed and applications for compensation soared. Third, the government introduced far harsher accreditation criteria in 1977. Fourth, a period of 'political settlements' took place from 1995/96 until the present, with the government and Chisso factory attempting to settle the conflict by paying lump sums (not as compensation) without changing the strict criteria or recognising affected individuals as official patients.

All of this was done without formally defining Minamata disease and legal cases still continue because the geographic and temporal boundaries for claimants still lack an agreed evidential basis.

5.4.1 Accreditation system

As of 2013, the Minamata disease accreditation system remains based on Japan's Pollution-Related Health Damage Compensation Act. This involves passive assessment based on applications by patients to become accredited (Minamata Disease Museum, 2007; Ministry of Environment, 2006), rather than the active surveillance system based on the Food Sanitation Act, described earlier.

The Judgment Committee for Minamata Disease Accreditation (an advisory body to the Governor of the Prefecture) determines whether 'the applicant is a Minamata disease patient' based on the results of a medical examination (Minamata Disease Museum, 2007; Ministry of Environment, 2006). Committee meetings are held in the cities of Kumamoto and Kagoshima, nearly 70 km from Minamata, and committee members do not directly examine the applicants, regardless of their proximity. The Committee consists largely of neurologists, with a few pathologists, ophthalmologists (eye disorder experts) or otolaryngologists (ear and throat experts). Having considered a case, the Committee makes an assessment by unanimous decision and submits it to the Governor of the Prefecture. If the judgment is positive then the Governor accredits the applicant as an officially recognised Minamata disease patient. Compensation is not available without accreditation, which can take a long time. For example one patient accreditation took 25 years (Miyazawa, 1996), imposing a significant burden on the applicant.

The Environmental Agency of Japan (EAJ), a predecessor of the Ministry of Environment of Japan, determined the official position that patients with a 'probability of 50 % or more' of having the disease are to be accredited as Minamata disease patients (Ministry of Environment, 2006). As such, a quantitative approach is supposed to be applied. In practice, however, the Committee for Accreditation uses a qualitative diagnostic method, based on whether the symptoms match those documented for the 'Hunter-Russell' syndrome.

As described below, the criteria for accreditation have been revised several times since their introduction in 1959 (Yorifuji et al., 2013), with profound implications for those affected by Minamata disease.

5.4.2 History of the accreditation system

Prior to 1969, the initial disease accreditation system, the 'Screening Council for Minamata Disease Patients', was used to identify patients who deserved low 'mimaikin' ('sympathy money') payments from Chisso factory (Harada, 2004; Minamata Disease Museum, 2007). This was not considered compensation, nor was it done based on any law because Chisso factory insisted that it was not proven that it was the cause of Minamata disease (Miyazawa, 2007).

The settlements, in effect decided by Chisso factory, were very small. A death resulted in a lump sum payment of JPY 300 000 (about EUR 2 900 today) while affected adults received JPY 100 000 (about EUR 960) annually and children JPY 30 000 (about EUR 290) annually (Minamata Disease Museum, 2007). The contract provided that 'the patients relinquish their claim to further compensation even if it is decided in the future that Minamata disease is caused by Chisso's effluents' (Harada, 2004). In its judgement at the First Minamata Disease Lawsuit in 1973, the court nullified these agreements as a breach of the common good (Minamata Disease Museum, 2007).

By 1969, eighty-nine Minamata disease patients, excluding those with congenital Minamata disease, had been accredited through this system (Minamata Disease Museum, 2007). At that time, patients suffered not only from the disease itself but also faced discrimination from Minamata citizens in part because accredited patients could obtain compensation money. This climate in Minamata deterred residents from seeking accreditation. Instead, some sought to hide their neurological symptoms (Miyazawa, 2007).

In the 1960s, large-scale incidences of health effects from environmental pollution were identified elsewhere in Japan, for example, methylmercury poisoning in Niigata (Niigata Prefecture, 2007), air pollution in urban areas (Yoshida et al., 1966), cadmium poisoning in Toyama (Osawa et al., 2001), and arsenic poisoning in Miyazaki (Tsuchiya, 1977). This lead to a change in the public mood. The Japanese government was forced to take active measures to prevent further cases, and make better provision for patient support and compensation. In 1969, the Act on Special Measures for Pollution-Related Health Damage Relief (later changed to the Pollution-Related Health Damage Compensation Act) was created. It came into effect the following year (Minamata Disease Museum, 2007). Subsequently, the EAJ was established in July 1971.

As a result of the Act, the Screening Council for Minamata Disease Patients was replaced by the Judgment Committee for Minamata Disease Accreditation (hereafter, 'Committee for Accreditation') at the end of 1969 and this continues to be the responsible body (Minamata Disease Museum, 2007).

On 7 August, 1971, the 'Administrative Vice Director of the EAJ Notice' was published, marking the first real policy change since 1956 (JSPN, 1997). This Notice specified that if it appeared 'clear that a patient had been affected by the consumption of fish and shellfish containing organic mercury, the cause of [his/her neurological signs (characteristic of methylmercury poisoning)] should be presumed to be Minamata disease, even if other causes were conceivable' (George, 2001). The approach reflected the usual thinking with respect to food poisoning and was not dissimilar to the precautionary principle concept, as developed in Europe in the following decade. The Notice listed neurological signs such as constriction of the visual field, ataxia (loss of bodily coordination), hearing loss and paresthesia (a disabling tingling sensation, 'pins and needles', on both sides of the body) and did not require combinations of these neurological signs for Minamata disease to be confirmed.

On 20 March 1973, the Kumamoto District Court ordered Chisso factory to pay compensation to Minamata disease patients engaged in a lawsuit against the company (Minamata Disease Museum, 2007). The patients then signed a compensation agreement with Chisso (Minamata Disease Museum, 2007). This resulted in dramatic increase of the number of accreditation applications.

Meanwhile, in 1971, the Department of Neuropsychiatry at Kumamoto University School of Medicine undertook the first and largest cross-sectional population-based investigation to evaluate the prevalence of neurological signs of Minamata disease among local residents (Tatetsu et al., 1972). Leonard Kurland had first suggested this study to the Japanese Society of Neurology but the proposal was rejected and the Department of Internal Medicine therefore did not cooperate in the study.

In the study, three areas were selected for investigation in Kumamoto Prefecture: Minamata (a high-exposure area), Goshonoura (a medium-exposure area) and Ariake (a low-exposure, reference area). The findings demonstrated the severe effects of methylmercury on residents in Minamata and even in Goshonoura. It provoked debate about the 'Third Minamata disease' (following those experienced in Minamata and Niigata) since even in the reference area there were residents with neurological signs of Minamata disease (Miyazawa, 1996), although the prevalence was not so high.

The analysis was highly plausible because the Ariake and Minamata areas are connected by sea (Map 5.1) and fishermen often went to the Shiranui Sea to catch fish. Unfortunately, the findings were made public before the investigation was complete and created a sensation. People stopped buying fish or shellfish caught in Ariake area, causing Ariake's fishermen to protest against the Prefecture and Kumamoto University. A doctor at Kyushu University diagnosed those with neurological symptoms in Ariake as not having the disease, which caused distrust of Kumamoto University researchers. These pressures meant that the research was terminated after only two thirds of the programme had been completed.

Recent publications in international journals (Yorifuji et al., 2008, 2009b, 2010, 2011 and in press) have shown, however, that even the incomplete findings of the Kumamoto University investigation were valuable and should have been more fully utilised. They fill out the details of Minamata disease: the kinds of symptoms, their frequency and thresholds and the types of residents affected. Unfortunately, this information has never been used for diagnosis or compensation from the 1970s to the present.

The third change in EAJ policy came in 1977 when, following the sensational news of the 'Third Minamata disease', and also a dramatic increase of accreditation applications, the 'precautionary' approach of the 1971 EAJ Notice, based on the notion of food poisoning, was reversed. A new and more rigid set of accreditation criteria for Minamata disease the '1977 Criteria' were established (Minamata Disease Museum, 2007; Ministry of Environment, 2006; Yorifuji et al., 2013) and remain in force today. Subsequently, there was a rise in the number of patients who had methylmercury-related symptoms but were not formally accredited. This is because the 1977 Criteria once more require a combination of neurological signs (Minamata Disease Medical Research Group, 1995, JSPN, 1997). They also provide that in addition to taking into account a person's exposure history, paraesthesia would now be regarded as a necessary but insufficient criterion for accreditation. Unlike the 1971 Criteria, the occurrence of paraesthesia 'alone' would not result in accreditation.

In 1978, it was decided that Kumamoto Prefecture should issue debt to support Chisso factory in paying compensation money (Ministry of Environment, 2006). This meant that the authorities now had a potential conflict of interest between their duty to the patients and their financial situation. It became increasingly apparent that the accreditation system was an important defensive barrier — not only for Chisso but also for the government (Miyazawa, 2007).

The 1977 Criteria became a continuing source of dispute. In August 1985 the Fukuoka High Court decided that the criteria for accreditation should be relaxed again, allowing more people to qualify (Minamata Disease Museum, 2007). In response, in October 1985, the EAJ summoned eight medical specialists to reconsider the 1977 Criteria (Miyazawa, 2007). Their 'expert opinion' stated that the Criteria remained 'valid' and once more asserted that it was not certain that paraesthesia occurred in isolation in Minamata disease and should not, therefore, be used to accredit patients (JSPN, 1997). Only neurologists were present at the meeting, which was both closed and brief (seven hours). The meeting minutes were not published and no medical evidence was given in public to support their conclusion. It seems inconceivable that they would not have been aware of the prominent research of Bakir et al. (1973), which provides evidence that paresthesia can occur in isolation following methylmercury exposure (JSPN, 1999).

By the early 1990s many accreditation applications (including new applicants and those who had reapplied) and lawsuits remained outstanding, in part because the 1977 Criteria were strict. Indeed, of the 944 patients who satisfied the diagnostic criteria and should have been accredited according to the 1977 Criteria, only 205 patients were in fact accredited by 1981 (Miyai, 1997). Even by 1992, only about one third of the qualified applicants had been accredited (316/944) (Miyai, 1999).

The EAJ therefore asked the Japanese Central Council for Environmental Pollution Control, an advisory body to the EAJ Director, to consider the issue in 1991 (Ministry of Environment, 2006). A 14 member Minamata disease working group was set up, comprising nine members with medical backgrounds and five with legal expertise. Based on the working group's advice, the Council stated that its accreditation of Minamata disease was in accordance with the 1985 'expert opinion' and proposed a medical care project to support exposed residents who had signs of the disease but were not accredited as Minamata disease patients.

In 1995–1996, under a condition that there was no liability on government, a reconciliation (the so-called 'first political solution') was reached based on the Central Council's recognition and the medical care project. According to the reconciliation, instead of issuing further Minamata disease accreditation, Chisso would make a lump sum payment to patients with methylmercury-related symptoms living in the exposed areas but these patients must withdraw any legal action or claim against Chisso (McCurry, 2006). In this reconciliation, about 10 000 patients received lump sum payments of JPY 2.6 million (about EUR 25 000 today) as relief money (not compensation) because neither the government nor Chisso admitted liability and they were not formally recognised as 'Minamata disease patients' (Miyazawa, 2007). Accordingly, this situation could be considered as repeating the 'mimaikin' ('sympathy money') payments in 1959. The number of accreditation applicants fell to zero but one legal action continued in Osaka, where some residents born in Minamata had previously moved.

By this time the Japanese Society of Psychiatry and Neurology (JSPN) — an independent academic society consisting mainly of psychiatrists and neurologists — was becoming increasingly involved. In 1998, it examined whether the medical specialists in the EAJ commission in 1975 had used any medical evidence when creating the 1977 Criteria. It concluded that they did not. Moreover, the JSPN judged the 1977 criteria to be medically invalid based on an evaluation of the data gathered in the Kumamoto University study of 1971 (JSPN, 1998). Subsequently, in a 1999 review, JSPN strongly criticised the 1985 'expert opinion', stating that there was no scientific evidence for the 1985 'expert opinion'; that the 'experts' were selected to justify the 1977 Criteria and the position of the EAJ; and that the 'experts' were guilty of pandering to the government's desires (JSPN, 1999).

Throughout the history of Minamata disease, key decisions have been characterised by very little transparency and much secrecy, making it hard to evaluate their reasoning. In 2003, after the first political settlement, JSPN (2003) analysed the minutes of the Central Committee working group's discussions in 1991, which were disclosed under the Access to Government Information Act (5). It concluded that the working group members did not have the medical evidence to support the 1977 criteria; that the 1985 'expert opinion' was not a medical assessment but a government opinion; and that the meeting minutes made it evident that the working group's discussion had been conducted with the sole aim of producing an opinion that complied with the EAJ's view. These facts had, until then, been hidden from the public.

In October 2004, the Japanese Supreme Court decided on the case involving Osaka residents, confirming the liability of the national and Kumamoto Prefecture governments for damage caused by methylmercury poisoning in the Minamata area (McCurry, 2006; Minamata Disease Museum, 2007; Nagashima, 2005). Like the Fukuoka High Court in its 1985 decision, the Japanese Supreme Court also ruled that the 1977 criteria should be relaxed (McCurry, 2006; Nagashima, 2005). Remarkably, the EAJ has still not changed its attitude on the criteria. As a result of the Court's ruling, the number of accreditation applicants began to grow again, exceeding 6 000 by 2008 and 8 000 in 2010) (Minamata Disease Museum, 2010).

In 2009, an Act on Special Measures (the so-called 'second political solution') was passed without changing the strict 1977 criteria. It was determined that Chisso should pay lump sums of JPY 2.1 million (about EUR 20 000) to patients who at least have paresthesia and who had lived in defined affected areas for at least one year during a defined period of time (Kumamoto Prefecture, 2010). Similar to the first reconciliation in 1995–1996, the lump sum money is not compensation but relief money because neither the government nor Chisso admits liability and the patients are not formally recognised as 'Minamata disease patients'.

It is expected that most of the applicants involved in litigation will withdraw their actions. Residents who have never applied for compensation but have neurological symptoms are also able to apply for lump sums. However, the outcome is perplexing. While 2 273 patients were officially recognised as Minamata disease patients in the affected prefectures, there are also at least several tens of thousands of exposed patients with neurological signs characteristic of methylmercury poisoning who have not been formally recognised as Minamata disease patients and not properly compensated.

Despite the enactment of the Act on Special Measures, several lawsuits are still under way because the Act defined the affected area and time period without investigating or defining evidential criteria. It is known that exposed residents with neurological signs characteristic of methylmercury poisoning are observed in areas other than those defined in the Act (Kumamoto Nichinichi Shinbun, 2010a). The approach used in the Act has shortcomings. First, it is inappropriate to define 'areas' based on the notion of food poisoning; instead, exposed persons with relevant symptoms should be counted as patients. Furthermore, the problem will persist because individuals who were exposed in the uterus but were not severely enough affected to be recognised as 'congenital' Minamata disease patients are not covered by the Act.

5.4.3 *Criminal charges*

One criminal case was put forward against Chisso in 1975 although a number of civil trials were raised against the factory. The report by Hunter et al. (1940) was the best known in Japan, although the danger of using organic mercury in the production had been common knowledge long before 7 May 1932, when Chisso began to discharge effluents containing organic mercury into Minamata Bay (Iriguchi 2012). However, the accused stressed that toxicity of methylmercury was not well known before 1956 when the first patient was notified by the Minamata Public Health Center. In 1979, the Kumamoto District Court sentenced the ex-president and the ex-factory-head to two years in prison with three years suspension of sentence. The Japanese Supreme Court accepted the court's ruling as final in 1988.

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(5) The Aarhus Convention and 'right to know' laws have made public access to data and decision-making an issue of critical importance.

5.5 What are the lessons of the Minamata disease story?

5.5.1 Medical, scientific and public health lessons

Respond to the signals of sentinel wildlife

As a result of the pollution route, at Minamata harm to wildlife was observed before human harm. Fish and cats died strangely before the first patients were observed in Minamata and surrounding areas, and the same pattern occurred at Niigata. Subsequently, those who lived and worked close to nature and who ate the local fish were the first to suffer from pollution. The earliest cases identified lived close enough to the sea that they could fish from their windows. They were people who lived at one with nature.

This suggests that, as a general rule, when wildlife impacts are observed we should ensure that we understand the epidemiology, identify the source of the problem and take action to prevent human suffering. Minamata showed that effective action (preventing the discharge of pollution) was possible even before the first patients were notified. Early actions are justified by our responsibility to protect the environment — but they can also avoid subsequent harm to humans.

Prevention is possible and essential

As Hajime Hosokawa (Director of Chisso hospital) pointed out 'prevention is far more important than relief.' (Harada, 2004). It was already known in 1921 that organic mercury was synthesised in the production of acetaldehyde (Ishihara, 2002; Vogt and Nieuwland, 1921). And a researcher at Chisso factory had demonstrated that organic mercury was synthesised in the production of acetaldehyde in 1951 (Arima, 1979). Furthermore, intoxication due to occupational exposure to organic mercury was reported in the 1930s in Europe (Ishihara, 2002; Koelsch, 1937; Zangger, 1930). While these reports were published in Europe, especially in Germany (where Chisso had strong links since the 1920s), this is no excuse for a diligent company to be unaware of such important risks. Prevention was possible before the hideous consequences were first identified in 1956.

Early epidemiological studies are valuable

Early epidemiological studies, 'good enough' for their purpose can play a key role in preventing and minimising future harm. The Kumamoto University research group's early study in 1956 demonstrated that eating fish caught in Minamata Bay was a cause of harm and this conclusion has never changed. Minamata is a classic example of how spurious demands for more precision with respect to the cause of harm resulted in unnecessary delay and continuing exposure ('analysis by paralysis'). It was three years before the etiologic agent was found and six years before the mechanism by which methylmercury was produced was (re)discovered. As an important principle, this shows that prompt countermeasures should be conducted when the cause is identified and should not be postponed until an etiological agent or the biological mechanism of action is identified.

In-depth epidemiological studies are also valuable

While early epidemiological studies should have been heeded, far more could have been done to reduce harm if there had been more early epidemiological effort focusing on the features of the disease (such as the threshold, frequency and severity of symptoms; the scale of poisoning; and the prognosis). The first systematic epidemiological study of the features of the disease was not conducted until 1971. An investigation by the Department of Internal Medicine in 1960 only focused on the severest cases and did not follow up with the participants. Similarly the Kumamoto Prefecture Institute for Health Research's investigation of mercury concentrations in 1 645 healthy fishermen in 1960 was not able to follow up the participants. Follow-up studies would have revealed the developments of neurological symptoms or the dose-response relationship between exposure and symptoms.

Instead, the initial emphasis was placed on clinical manifestation (Hunter-Russell syndrome) and became bogged down in legal dispute about what was and was not Minamata disease. However, after organic mercury or fish was identified as a cause, causal criteria (i.e. cause and disease) should have been used in subsequent epidemiological studies. They should also have been used from the outset to certify patients and determine entitlement to compensation.

Demands for excessive levels of scientific proof can exacerbate harm

The history of Minamata disease provides many examples of spurious obstacles and inappropriate burdens of proof, which prevented speedy and effective action. The demand for high levels of scientific proof (i.e. 'clear evidence' or 'beyond the reasonable doubt') was used as spurious cover, allowing Chisso to delay the search for what turned out to be a simple alternative production technology that avoided methylmercury pollution. Epidemiology demonstrated that poisoning was caused by contaminated fish and the factory discharge in 1956. This was unintentionally confirmed when the drainage route was altered in 1958 causing new victims in the new discharge area. There was a tendency for many stakeholders to accept that high evidential burden was required to justify taking preventative action.

Be wary of deliberately manufactured doubt
Regulators (and others) should be attuned to 'manufacturing of doubt' by those with sufficient means and an incentive to maintain the status quo. At various points, alternative explanations arose for the harm, such as metals, dumped explosives or amines in rotten fish and these were exploited to the full by Chisso and its supporters in government.

Of course, a plurality of viewpoints is essential for scientific analysis. Indeed, during the early stages of the disaster various metals were considered as possible causes but these were dropped when the evidence did not stand up to scrutiny. Ironically, this openness to consider alternative explanations was then used by Chisso to criticise the researchers when they concluded that methymercury was the likely cause.

Several characteristics distinguish those manufacturing doubt, often by proxy, from those promoting genuine open debate. Often they demand high levels of proof for results that demand action from the vested interest but accept low levels of proof (or standards of analysis) for their alternative hypothesis, which may be the object of criticism from scientific peers. They also fail to consider the pros and cons of alternative courses of action judged from the perspective of society as a whole and that of the wider environment.

Look beneath the tip of the iceberg
Throughout the history of Minamata disease, researchers have consistently discovered more subtle effects, at lower exposure concentrations. However neurologists, who occupied a dominant position in the process (6), became fixated on qualitative diagnostic method and a set of symptoms (Hunter-Russell syndrome), which were used to determine the disease's presence. This insistence restricted greater understanding of the disease in all its manifestations.

The legalistic approach to accreditation and compensation compounded the problems, encouraging constant premature attempts to define formally what Minamata disease is and is not. A number of scientists involved in the compensation process ended up having their reputations damaged by defending rigid criteria that became increasingly indefensible as time progressed.

Congenital Minamata disease
The uterus is part of the environment: to pollute the exterior environment is to pollute the uterus and thereby to pollute future life (Harada, 2005). Contrary to previous assumptions, we now know that the biological barrier of the uterus (and also the blood brain barrier) cannot be assumed to prevent the transfer of substances not found in the natural world or high exposure to substances that are naturally of low concentrations. The former are synthetic chemical compounds created by man. The latter are things we dig up from the earth, concentrate, process and use in great quantities.

On a practical note, the Minamata disaster has demonstrated the utility of umbilical cords for assessing pollution and shows that simple methods of preservation of biological tissue are sufficient to capture the disease's history (Miller, 1976).

5.5.2 Social lessons

A narrow focus on economic growth subverts society's wellbeing
The economic and political power of one factory or stakeholder can dominate public health interests in a context that is strongly oriented to promoting economic growth. In this case, the factory was Chisso, which had a great influence in Japanese industry and society in the late 1950s and 1960s. Economic growth was the top priority in Chisso and in Japanese society more broadly.

It is noteworthy that after years of scientific evidence of harm to humans, it was only when the production process was no longer needed that the factory changed its processes and the government altered its stance regarding the harm. In Minamata, acetaldehyde production became unnecessary and stopped on 18 May 1968. Only after this date did the Japanese government officially accept the causal relationship between wastewater from Chisso factory and Minamata disease.

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(6) The excessive dominance of one discipline in a multidisciplinary dispute was noted in *Late lessons from early warnings* Volume 1 (EEA, 2001).

Discrimination perpetuates harm

The Minamata story reveals discrimination in various forms. There was discrimination against the fishermen of South Kyushu, who were poor and situated far from Tokyo, the geographical and political centre of Japan. It is notable that when the discharge from paper manufacturing in Tokyo caused fishery damage in 1958, the Tokyo metropolitan government halted the factory's production (Hashimoto, 2000).

Furthermore, when the disease occurred it was initially considered infectious. Patients were shunned and avoided by other community members and experienced years of discrimination. Fear of this actually prevented patients from coming forward. They also experienced discrimination after they obtained compensation money.

Don't 'shoot the messenger' who brings 'inconvenient truths'

After the Minamata Food Poisoning Committee published its organic mercury theory, the Committee was suddenly dissolved without stated reason. With hindsight, it is evident that their conclusions were not welcome to the authorities. Indeed, researchers at Kumamoto University were criticised as being a 'hick' university by the 'centre' after they proposed the organic mercury theory.

Stakeholders can supress science

Science can be absorbed and suppressed by the stakeholders such as industries and public authorities. Hajime Hosokawa, Director of Chisso hospital, demonstrated that giving a cat wastewater from acetaldehyde production induced Minamata disease. These results were suppressed by the factory. Later, Kumamoto University School of Medicine, which had initially analysed organic mercury as a cause of Minamata disease, joined the (pro-industry, later discredited) Tamiya Committee and began to receive research funds from Chisso factory and the Tamiya Committee. From that time, Minamata disease became a sensitive research issue at Kumamoto University.

Similarly, the Japanese Central Council in 1991 (JSPN, 2003) was not neutral and its discussions were directed towards complying with the EAJ's views. This fact was hidden from the public. Furthermore, JSPN also pointed out that biased distribution of public research funding played an important role in e.g. controlling researchers (JSPN, 2000).

Information must be transparent and broadly communicated

It is important to be transparent with information and to communicate it widely so that events are not repeated elsewhere. With better management of information, Niigata Minamata disease could have been avoided altogether.

While transparency and communications have improved in many advanced industrial economies, the translocation of manufacturing capacity elsewhere means that the consequences of product manufacture may no longer be transparent to consumers in advanced economies. Moreover, there are cases where information is not communicated to the public. Indeed, in Minamata, none of the information generated was publicly communicated to residents during the contamination period.

5.5.3 Inter-disciplinary lessons

Value of lay and local knowledge

Lay and local knowledge should not be ignored. The fishermen knew that fish could not live in water from the outfall from Chisso factory before Minamata disease occurred. Minamata citizens knew that mercuric salt was used to produce acetaldehyde in 1959. Finally, as described in the conversation between Masazumi Harada and the mother of congenital Minamata disease patient, the mother had deduced that neurological signs observed in her son were due to Minamata disease, at a time when this was assumed to be impossible by experts. The value of lay and local knowledge is one of the 'Twelve late lessons' of Volume 1 (EEA, 2001) (7).

Interdisciplinary barriers and the absence of open discussion augment harm

In the Minamata case, a lack of open discussion delayed preventive actions, obscured the features of the disease and postponed its resolution. Researchers at Kumamoto University did not know what was produced at the factory, how it was produced, or what substances were used in which processes. The Research Group did not receive assistance from the engineers at Chisso factory, or from the organic chemistry sector of School of Engineering at Kumamoto University. Even within medicine, epidemiology was considered an inferior discipline and neurologists did not apply epidemiological thinking in certifying patients. Among the universities, it was said that scientists from the 'centre' could be trusted over those from 'hick' universities on the periphery.

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(7) See also the report from EEA workshop on Lay, local traditional knowledge and citizen science, June 2011 (http://lltk.ew.eea.europa.eu/about/lltk-and-citizen-science-meeting-report.pdf).

The Japanese medical community misunderstood or was unfamiliar with the Food Sanitation Act, which must have bolstered the government's position. According to the Food Sanitation Act, doctors who recognise food poisoning must notify the local health centre, which must investigate the problem. No doctors (both clinicians and researchers) notified this outbreak as food poisoning in Kumamoto Prefecture. Instead, they continued to search for the etiologic agents. Had doctors treated and identified this as food poisoning, the government would have had difficulty not applying the Act.

Even the ministry responsible for health policy was unfamiliar with the Act. In 1990, the MHWJ argued that the government did not apply the Act because the etiological agent (methylmercury) had not been identified in 1957. In fact, the Act should have been applied when cause/transmission was identified. The different approach employed in the food poisoning case in Shizuoka in 1950 suggests that not applying the Act in Minamata was a political choice.

Finally, there was little direct discussion between stakeholders. In Japan, even in 2010, policymaking decisions do not involve stakeholders such as patients' organisations. However, EAJ and the exposed patients do share some common perspectives and conclusions regarding Minamata disease. The protracted legal action might have been shortened via direct dialogue between EAJ and the exposed patients. The fact that experts at the university, the health centre and Chisso were not willing to hear and consider the opinions of lay and local people are symptoms of the same problem. Recently, there are some measures toward Minamata's regeneration, such as making Minamata city a model city for the environment, facilitating waste reduction and recycling etc. (Minamata Disease Museum, 2007). In particular, the word 'Moyainaoshi' (the re-establishment of emotional ties or reconciliation) is often used to strengthen interpersonal ties so that citizens can speak up in public about Minamata disease issues. Despite such efforts, there is still little discussion about how to support patients, investigating the exposed patients etc. to solve the real problem of Minamata disease. It can be said that Japan still faces a problem of democracy (George, 2001).

Table 5.1 Early warnings and actions

1908	The Nihon Carbide factory was established in Minamata
1921	Methylmercury synthesised during acetaldehyde production in Germany
1921	The Chisso factory in Minamata Bay bought German patent and began using carbide and acetylene to manufacture a wide range of chemicals
1925–1926	The company began to receive requests for compensation from the fishing cooperative. On the condition that no further complaints would ever be lodged, Chisso paid a small amount of 'sympathy money'
1932	The Chisso factory in Minamata began to produce acetaldehyde from acetylene gas, using mercury as a catalyst
1930–1937	Mercury poisoning in German factories using acetaldehyde
1943	The issue of fishery damage arose again due to carbide residue from acetylene production and another compensation contract was concluded
1949	More fishery damage negotiations failed. Chisso said the catch data were 'not scientific'
1950	Fishermen around Minamata Bay witnessed huge numbers of fish rising to the surface and swimming around as though crazy. Sea birds were unable to fly. Oysters and cockles were washed up onto the beach rotting with their shells open. Barnacles did not attach themselves to boats fishing near factory outlet
1951	Chisso increased production of acetaldehyde and related methylmercury pollution from the factory
1952	Upon request from local fishermen, the Fisheries Division of the Kumamoto Prefecture inspected the factory and Chisso documents about mercury use and discharge. As a result they reported that the discharge should be analysed. Kumamoto Prefecture and Chisso failed to do this and fishery damage continued
1953	Local cats, which ate great quantities of fish, went mad and died after strange dancing and convulsions
1956	1 May: First official notification of strange disease to the Minamata Public Health Centre. 28 May: Minamata Strange Disease Countermeasures Committee was organised by Chisso Hospital, local doctors and Minamata Public Health Centre. 30 cases including 11 deaths were identified. Kumamoto University Research Group reported that the disease was not contagious (as was claimed at first) but rather a food poisoning from eating fish contaminated by a heavy metal in Minamata Bay

Table 5.1 Early warnings and actions (cont.)

1957	Kumamoto University Research Group recommended prohibiting fishing under the Food Sanitation Act. Japanese Ministry of Health and Welfare Research Group from Tokyo confirms local conclusions and recommends full investigation of Chisso effluents. In response to these findings, the local government of Kumamoto Prefecture considered applying the Food Sanitation Act in March 1957, although the Chief of the Public Health Bureau of the Ministry of Health and Welfare of Japan replied to the local government that it is impossible to apply the Food Sanitation Act. Then, the local government abandoned the application
1958	Chisso changed the drainage route of acetaldehyde production from Minamata Bay to Minamata River
1958	UK neurologist Douglas McAlpine examined 15 Minamata disease patients and reported his observations in The Lancet, listing methylmercury as one of the metals which could induce Minamata disease. This was the first time in a scientific paper that methylmercury was identified as possible cause. McAlpine was prevented from presenting his findings to the Japanese Society of Neurology
1959	On 7 October 1959, Chisso Hospital director Hajime Hosokawa fed factory effluent to cats and induced Minamata disease but this was suppressed until a compensation case in 1970
1959	Organic mercury was recognised as the etiological agent by the Minamata Food Poisoning Committee organised by the Ministry of Health and Welfare of Japan on 12 November 1959. However, there was no mention of the source of the contamination, Chisso factory. Indeed, the section chief of the Ministry of Health and Welfare's Environmental Sanitation Department asks for Chisso effluent case to be removed from report as it was not 'scientifically' proven. After the Committee had reported its opinion to the Minister of Health and Welfare, it was suddenly dissolved
1959	In December 1959, Chisso factory established an ineffective purifying system for the contaminated water
1960	Kumamoto Prefecture Institute for Health Research investigated the mercury concentration in hair samples from 1 645 healthy fishermen from around Shiranui Sea. Results indicated that the contamination had spread throughout the entire Shiranui Sea
1962	An unusual occurrence of cerebral palsy infants was officially recognised as congenital Minamata Disease. Professor Katsuro Irukayama succeeded in extracting methylmercury chloride from the sludge of the acetaldehyde production process in the factory but the Fisheries Agency abandoned research on Minamata disease. No research activities were conducted by government agencies until 1968
1965	Methylmercury food poisoning occurred in Niigata, causing 'Niigata Minamata disease'. The factory responsible (Showa Denko) operated in the same way as Chisso in Minamata
1968	In May, Chisso stopped its acetaldehyde production for commercial reasons. In total, 488 tonnes of mercury were discharged into the sea from 1932 to 1968. After that, on 26 September, Japan's government accepts causal link between wastewater from Chisso (and Showa Denko) and Minamata disease
1969–	Government compensation arrangements applied 'chaotically'. Private compensation cases for Minamata victims begin
1971	On 7 August, 1971, the 'Administrative Vice Director of the EAJ Notice' was published, marking the first real policy change since 1956. The Department of Neuropsychiatry at Kumamoto University School of Medicine undertook the first and largest cross-sectional population-based investigation to evaluate the prevalence of neurological signs of Minamata disease among local residents
1972	The United Nations Conference on the Human Environment was held in Stockholm. Two Minamata disease patients attended and created much public awareness
1973	Kumamoto District Court ordered Chisso factory to pay compensation to Minamata disease patients engaged in a lawsuit against the company
1975	From 1968, Masazumi Harada collected umbilical cords (traditionally preserved in Japan) from residents around Shiranui Sea and demonstrated a link between acetaldehyde production in Chisso factory and methylmercury; supporting the hypothesis that methylmercury could affect foetuses
1977	A new and more rigid set of government accreditation criteria for Minamata disease required a combination of neurological signs: the '1977 criteria'. These remain in force today. Subsequently, there was a rise in the number of patients who had methylmercury-related symptoms but were not formally accredited
1978	Kumamoto local government issues debt to help Chisso pay compensation
1995–1996	In the 'first political solution' the government and Chisso factory attempted to settle the conflict by paying lump sums (not as compensation) in 10 000 cases without changing the strict criteria or recognising affected individuals as official patients
2004	The Japanese Supreme Court confirmed the liability of the national and Kumamoto Prefecture governments for damage caused by methylmercury poisoning in the Minamata area. The court also ruled that the 1977 criteria should be relaxed
2009	The Act on Special Measures (the so-called 'second political solution') was passed without changing the strict 1977 criteria. Chisso to pay lump sums to patients, not as compensation but relief money because neither the government nor Chisso admits liability and the patients are not formally recognised as 'Minamata disease patients'
2009–	UNEP initiates a global mercury phase-out and works to develop a global legally binding instrument on mercury, planned for signature in Japan in 2013
2013–	Private law suits still continue

References

Arima, S. (ed.), 1979, *Minamata Disease — researches during 20 years and problems at present* (in Japanese), Seirinsha, Tokyo.

Bakir, F., Damluji, S.F., Amin-Zaki, L., Murtadha, M., Khalidi, A., Al-Rawi, N.Y., Tikriti, S., Dahahir, H. I., Clarkson, T.W., Smith, J.C. and Doherty, R.A., 1973, 'Methylmercury poisoning in Iraq', *Science*, (181) 230–241.

Chisso Factory, 1996, 'Status about treatment of factory discharge' (in Japanese) in: Fukuoka (ed.) *Collection of materials about Minamata Disease Research Group on Minama Disease*, p. 60–64, Ashi publisher.

Clarkson, T.W., Magos, L. and Myers, G.J., 2003, 'The toxicology of mercury — current exposures and clinical manifestations', *N Engl J Med*, (349) 1 731–1 737.

Department of Environmental Sanitation, 1957, *Case file of food poisoning in Japan: 1956* (in Japanese), Ministry of Health and Welfare of Japan, Tokyo, Japan.

Doi, S. and Matsushima, Y., 1996, 'Investigations on mercury content from hair samples regarding Minamata Disease. Report 2' (in Japanese) in: Fukuoka (ed.), *Collection of materials about Minamata Disease Research Group on Minama Disease*, p. 1 508–1 513, Ashi publisher.

Doi, S., Matsushima, Y. and Chiyo, S., 1996, 'Investigations on mercury content from hair samples regarding Minamata Disease. Report 3' (in Japanese) in: Fukuoka (ed.), *Collection of materials about Minamata Disease Research Group on Minama Disease*, p. 1 513–1 519, Ashi publisher.

Ekino, S., Susa, M., Ninomiya, T., Imamura, K. and Kitamura, T., 2007, 'Minamata disease revisited: an update on the acute and chronic manifestations of methyl mercury poisoning', *J Neurol Sci*, (262) 131–144.

Environment Agency, Ministry of Health and Welfare, Ministry of Agriculture and Ministry of International Trade and Industry, 1999, 'Govenment's opinion regarding the Minamata disease suit' (in Japanese) in: Fukuoka (ed.), *The Annals of Minamata Disease Research Group on Mianama Disease*, p. 152–153, Ashi publisher.

George, T.S., 2001, *Minamata: pollution and the struggle for democracy in postwar Japan*, Harvard University Asia Center, Harvard University Press, Cambridge (Mass.).

Grandjean, P. and Landrigan, P.J., 2006, 'Developmental neurotoxicity of industrial chemicals', *Lancet*, (368) 2 167–2 178.

Harada, M., 1964, 'Neuropsychiatric Disturbances Due to Organic Mercury Poisoning During the Prenatal Period', *Seishin Shinkeigaku Zasshi*, (66) 429–468.

Harada, M., 1978, 'Congenital Minamata disease: intrauterine methylmercury poisoning', *Teratology*, (18) 285–288.

Harada, M., 1995, 'Minamata disease: methylmercury poisoning in Japan caused by environmental pollution', *Crit Rev Toxicol*, (25) 1–24.

Harada, M., 2004, *Minamata disease*, Kumamoto Nichinichi Shinbun Culture and Information Centre, Kumamoto, Japan.

Harada, M., 2005, 'The global lessons of Minamata disease: An introduction to Minamata studies', *Advances in Bioethics*, (8) 299–335.

Harada, M., 2007, 'Intrauterine methylmercury poisoning — congenital Minamata disease', *Kor. J. Env. Hlth.*, (33) 175–179.

Harada, M., Akagi, H., Tsuda, T., Kizaki, T. and Ohno, H., 1999, 'Methylmercury level in umbilical cords from patients with congenital Minamata disease', *Sci Total Environ*, (234) 59–62.

Harada, M. and Tajiri, M., 2009, 'An epidemiological and clinical study of infantile and congenital Minamata Disease — A consideration of the effects of methylmercury on fetal and infantile development' (in Japanese), *Shakaikankei Kenkyu*, (14) 1–66.

Hashimoto, M., 2000, *Not to reiterate the tragedy of Minamata disease — lessons from Minamata disease experience* (in Japanese), Chuouhouki publisher, Tokyo.

Hosokawa, H., 1996, 'Report by Hosokawa Hajime' (in Japanese) in: Fukuoka (ed.), *Collection of materials about Minamata Disease Research Group on Minama disease*, p. 795–798, Ashi publisher.

Hunter, D., Bomford, R. and Russell, D.S., 1940, 'Poisoning by methyl mercury compounds', *Qurt J Med*, (9) 193–213.

Hunter, D. and Russell, D.S., 1954, 'Focal cerebellar and cerebellar atrophy in a human subject due to organic mercury compounds', *J Neurol Neurosurg Psychiatry*, (17) 235–41.

Iriguchi, N., 2012, *Minamata Bay, 1932*, Nippon Hyoron Sha, Tokyo.

Irukayama, K., 1969, 'The course of Minamata disease and its problems' (in Japanese), *Koushu eisei*, (33) 70–76.

Irukayama, K., Kondo, T., Kai, F., Fujiki, M. and Tajima, S., 1962, 'Organic mercury compounds in the sladge from the acetaldehyde plant in Minamata' (in Japanese), *Nisshin Igaku*, (49) 536–541.

Ishihara, N., 2002, 'Bibliographical study of Minamata disease', *Nippon Eiseigaku Zasshi*, (56) 649–654.

Ito, 1996, 'About infantile strange disease which happened in Tsukinoura, Minamata' (in Japanese) in: Fukuoka (ed.), *Collection of materials about Minamata Disease Research Group on Minama Disease*, p. 473–474, Ashi publisher.

JSPN, 1997, 'Materials regarding Minamata disease problem' (in Japanese), *Psychiatria et Neurologia Japonica*, (99) 1 142–1 153.

JSPN, 1998, 'An opinion on the criteria on acquired Minamata disease' (in Japanese), *Psychiatria et Neurologia Japonica*, (100) 765–790.

JSPN, 1999, 'An opinion on 'the view of the medical specialists on the criteria of acquired Minamata disease on the 15th October, 1985' (in Japanese), *Psychiatria et Neurologia Japonica*, (101) 539–538.

JSPN, 2000, 'The commitee activity on Minamata disease so far and future consideration' (in Japanese), *Psychiatria et Neurologia Japonica*, (102) 415–423.

JSPN, 2003, 'An opinion about Minamata disease accreditation system and medical specialists' involvement' (in Japanese), *Psychiatria et Neurologia Japonica*, (105) 809–834.

Kitamura, S., Hirano, Y., Noguchi, Y., Kojima, T., Kakita, T. and Kuwaki, H., 1959, 'Results of epidemiological investigation on Minamata disease — part 2' (in Japanese), *Kumamoto Igakkai Zasshi*, (34/3) 1–3.

Kitamura, S., Kakita, T., Kojo, S. and Kojima, T., 1960a, 'Results of epidemiological investigation on Minamata disease —part 3–' (in Japanese), *Kumamoto Igakkai Zasshi*, (35/3) 477–480.

Kitamura, S., Miyata, C., Tomita, M., Date, S., Ueda, K., Misumi, H., Kojima, T., Minanamoto, H., Kurimoto, S., Noguchi, Y. and Nakagawa, R., 1957, 'Results of epidemiological investigation on unknown disease affected central nervous system, which occurred in the Minamata Area' (in Japanese), *Kumamoto Igakkai Zasshi*, (31/1) 1–9.

Kitamura, S., Ueda, K., Niino, J., Ujioka, T., Misumi, H. and Kakita, T., 1960b, 'Analyses of chemical toxicant regarding Minamata Disease — Fifth report —' (in Japanese), *Kumamoto Igakkai Zasshi*, (34/3) 593–601.

Koelsch, F., 1937, 'Gesundheitsschaedigungen durch organische Quecksilberverbindungen' (in German), *Arch fuer Gewerbepath u Gewerbehyg*, (8) 113–116.

Kumamoto Nichinichi Shinbun, 1954, *Annihilation due to cats epilepsy* (in Japanese).

Kumamoto Nichinichi Shinbun, 1958, *The cause of Minamata strange disease is the waste of Shin Nichitsu* (in Japanese).

Kumamoto Nichinichi Shinbun, 1959, *Organic mercury poisoning* (in Japanese).

Kumamoto Nichinichi Shinbun, 1962, *131 participants need careful attention* (in Japanese).

Kumamoto Nichinichi Shinbun, 1963, *Announcement of the cause of Minamata disease* (in Japanese).

Kumamoto Nichinichi Shinbun, 2010a, *Minamata Disease is not over; Part 5 Hidden patients — Statements 50 years later* (in Japanese).

Kumamoto Nichinichi Shinbun, 2010b, *Negotiation about 'Minamata Convention' — listen to Dr. Masazumi Harada* (in Japanese).

Kumamoto Prefecture, 1996a, '(Inquiry) About administrative measures against central nervous disorders in Minamata' (in Japanese) in: Fukuoka (ed.) *Collection of materials about Minamata Disease Research Group on Minama Disease*, p. 499–500, Ashi publisher.

Kumamoto Prefecture, 1996b, 'Liaison conference about strange disease' (in Japanese) in: Fukuoka (ed.) *Collection of materials about Minamata Disease*

Research Group on Minama Disease, p. 481, Ashi publisher.

Kumamoto Prefecture, 2010, 'Leaflet to apply for relief' (in Japanese).

Kumamoto University, 1956, *An interim report about central nervous disorders of unknown origin in Minamata* (in Japanese), Kumamoto University School of Medicine, Kumamoto.

Kumamoto University, 1996, 'Report about the cause of Minamata disease' (in Japanese) in: Fukuoka (ed.) *Collection of materials about Minamata Disease Research Group on Minama Disease*, p. 809, Ashi publisher.

Kurland, L.T., Faro, S.N. and Siedler, H., 1960, 'Minamata disease. The outbreak of a neurologic disorder in Minamata, Japan, and its relationship to the ingestion of seafood contaminated by mercuric compounds', *World Neurol*, (1) 370–395.

Matsuda, S., Kitaoka, M., Ozaki, M. and Arita, S., 1996, 'About strange disease in Minamata, Kumamoto' (in Japanese) in: Fukuoka (ed.) *Collection of materials about Minamata Disease Research Group on Minama Disease*, p. 833–845, Ashi publisher.

Matsushima, Y. and Mizoguchi, S., 1996, 'Investigations on mercury content from hair samples regarding Minamata Disease — Report 1' (in Japanese) in: Fukuoka (ed.) *Collection of materials about Minamata Disease Research Group on Minama Disease*, p. 1 500–1 507, Ashi publisher.

McAlpine, D. and Araki, S., 1958, 'Minamata disease: an unusual neurological disorder caused by contaminated fish', *Lancet*, (2) 629–631.

McCurry, J., 2006, 'Japan remembers Minamata', *Lancet*, (367) 99–100.

MDGIC, 1996, 'Summary of the first meeting of Minamata Disease General Investigation and Research Liaison Council' (in Japanese) in: Fukuoka (ed.) *Collection of materials about Minamata Disease Research Group on Minama Disease*, p. 1 523–1 525, Ashi publisher.

MDRG, 1966, *Minamata disease: studies about methylmercury poisoning* (in Japanese), Minamata Disease Research Group, Kumamoto University School of Medicine, Kumamoto.

METI, 2010, *About the result of the intergovernmental negotiating committee to prepare a global legally binding instrument on mercury on the work of its first session*, Ministry of Economy Trade and Industry of Japan (in Japanese).

MFPC, 1996, 'An interim report about Minamata Disease research' (in Japanese) in: Fukuoka (ed.) *Collection of materials about Minamata Disease Research Group on Minama Disease*, p. 682–689, Ashi publisher.

MHWJ, 1996a, 'About administrative measures against central nervous disorders in Minamata' (in Japanese) in: Fukuoka (ed.), *Collection of materials about Minamata Disease Research Group on Minama Disease*, pp. 670–671, Ashi publisher.

MHWJ, 1996b, 'About research progress and measures about so–called Minamata disease which happened in Minamata city, Kumamoto' (in Japanese), in: Fukuoka (ed.), *Collection of materials about Minamata Disease Research Group on Minama Disease*, p. 675–678, Ashi publisher.

MHWJ, 1996c, 'An opinion regarding Minamata disease and future measures' (in Japanese) in: Fukuoka (ed.) *Collection of materials about Minamata Disease Research Group on Minama Disease*, p. 1 412–1 413, Ashi publisher.

Miller, R., 1976, 'Dried human umbilical cores and study of pollutants', *The Lancet*, (307) 315–316.

Minamata Disease Medical Research Group, 1995, *Medical science of Minamata Disease* (in Japanese), Gyousei, Tokyo.

Minamata Disease Museum, 2007, *Minamata disease — Its history and lessons*, English version.

Minamata Disease Museum, 2010, *Processing status of applications for Minamata disease accreditation* (in Japanese).

Minamata Factory, 1996, 'Reasons why we cannot agree with the organic mercury theory' (in Japanese) in: Fukuoka (ed.) *Collection of materials about Minamata Disease Research Group on Minama Disease*, p. 267–268, Ashi publisher.

Minamata Times, 1996, 'Strange disease dialogue' (in Japanese) in: Fukuoka (ed.) *Collection of materials about Minamata Disease Research Group on Minama Disease*, p. 964, Ashi publisher.

Ministry of Environment, 2006, *White paper on environment* (in Japanese).

Ministry of Finance, 2011, *Trade Statistics of Japan* (in Japanese).

Mishima, A., 1992, *Bitter sea: the human cost of Minamata disease*, Kosei Pub. Co., Tokyo.

Miyal, M., 1997, 'An appraisal on the judgments of the Kumamoto Minamata Disease Certification Commission' (in Japanese), *Nippon Eiseigaku Zasshi*, (51) 711–721.

Miyal, M., 1999, 'An appraisal of the judgments of the Kumamoto Minamata Disease Certification Commission from May 1981 to July 1992 for applicants from December 1975 to April 1981' (in Japanese), *Nippon Eiseigaku Zasshi*, (54) 490–500.

Miyazawa, N., 1996, *Minamata disease incident its 40 years* (in Japanese), Ashi-shobou, Fukuoka, Japan.

Miyazawa, N., 2007, *Minamata disease and accreditation system* (in Japanese), Kumamoto Nichinichi Shinbun Culture and Information Centre, Kumamoto, Japan.

Nagashima, S., 2005, *Minamata disease Kansai lawsuit* (in Japanese), Hougaku seminar, (602) 60–65.

Niigata Prefecture, 2007, *An outline about Niigata Minamata Disease* (in Japanese), Niigata.

Ninomiya, T., Imamura, K., Kuwahata, M., Kindaichi, M., Susa, M. and Ekino, S., 2005, 'Reappraisal of somatosensory disorders in methylmercury poisoning', *Neurotoxicol Teratol*, (27) 643–653.

Ninomiya, T., Ohmori, H., Hashimoto, K., Tsuruta, K. and Ekino, S., 1995, 'Expansion of methylmercury poisoning outside of Minamata: an epidemiological study on chronic methylmercury poisoning outside of Minamata', *Environ Res*, (70) 47–50.

Nishigaki, S. and Harada, M., 1975, 'Methylmercury and selenium in umbilical cords of inhabitants of the Minamata area', *Nature*, (258) 324–325.

Nishimura, H. and Okamoto, T., 2001, *Science of Minamata disease* (in Japanese), Nihon hyoronsha, Tokyo.

Osawa, T., Kobayashi, E., Okubo, Y., Suwazono, Y., Kido, T. and Nogawa, K., 2001, 'A retrospective study on the relation between renal dysfunction and cadmium concentration in rice in individual hamlets in the Jinzu River basin, Toyama Prefecture, Japan', *Environ Res*, (86) 51–59.

Saito, H., 2009, *Niigata Minamata Disease*, Niigata Nippou jigyousha.

Sankei Shinbun, 2011, *Applicants to Minamata Disease Relief: 45,162 in Kumamoto and Kagoshima prefectures* (in Japanese).

Sebe, E., Itsuno, Y., Matsumoto, S. and Akahoshi, M., 1961, 'Research on the organic mercury compound — part 1' (in Japanese), *Kumamoto Igakkai Zasshi*, (35) 1 219–1 225.

Shizuoka Prefecture, 1996, '(Reply) About measures against shellfish poisoning' (in Japanese) in: Fukuoka (ed.) *Collection of materials about Minamata Disease Research Group on Minama Disease*, p. 1 719–1 721, Ashi publisher.

Stern, A.H., 2005, 'A review of the studies of the cardiovascular health effects of methylmercury with consideration of their suitability for risk assessment', *Environ Res*, 98, 133–142.

Takeuchi, T., Kambara, T., Morikawa, N., Matsumoto, H., Shiraishi, Y., Ito, H., Sasaki, M. and Hirata, Y., 1960, 'Observations about the causes of Minamata Disease from the pathological viewpoint' (in Japanese), *Kumamoto Igakkai Zasshi*, (34/3) 521–530.

Tatetsu, S., Kiyota, K., Harada, M. and Miyakawa, T., 1972, *Neuropsychiatric study on Minamata disease — clinical and symptomatological study on Minamata disease* (in Japanese), Epidemiological, clinical and pathological studies after 10 years since Minamata disease, Medical School of Kumamoto University.

Tokuomi, H., Okajima, T., Yamashita, M. and Matsui, S., 1962, 'Epidemiology of Minamata disease' (in Japanese), *Shinkei Shimpo*, 7, 24–37.

Tomita, H., 1965, 'Minamata disease 12' (in Japanese), *Goka*, 7, 346–353.

Tsuchiya, K., 1977, 'Various effects of arsenic in Japan depending on type of exposure', *Environ Health Perspect*, (19) 35–42.

Tsuda, T., Yorifuji, T., Takao, S., Miyai, M. and Babazono, A., 2009, 'Minamata Disease: Catastrophic Poisoning Due to a Failed Public Health Response', *Journal of Public Health Policy*, (30) 54–67.

Uchida, M., Hirakawa, K. and Inoue, T., 1960, 'Experimental development of Minamata disease and its etiologic agent' (in Japanese), *Kumamoto Igakkai Zasshi*, (34/3), 619–630.

Ui, J., 1968, *Politics in pollution — following Minamata disease* (in Japanese), Sanseido, Tokyo, Japan.

UNEP, 2010, *Report of the intergovernmental negotiating committee to prepare a global legally binding instrument on mercury on the work of its first session*, Stockholm.

Vogt, R. and Nieuwland, J., 1921, 'The Role of Mercury Salts in the catalytic transformation of acetylene into acetaldehyde, and anew commercial process for the manufacture of paraaldehyde', *J Am Chm Soc*, (43) 2 071–2 081.

Watts, J., 2001, 'Mercury poisoning victims could increase by 20 000', *Lancet*, (358) 1 349.

Yorifuji, T., Tsuda, T., Takao, S. and Harada, M., 2008, 'Long–term exposure to methylmercury and neurologic signs in Minamata and neighbouring communities', *Epidemiology*, (19) 3–9.

Yorifuji, T., Kashima, S., Tsuda, T. and Harada, M., 2009a, 'What has methylmercury in umbilical cords told us? — Minamata disease', *Sci Total Environ*, (408) 272–276.

Yorifuji, T., Tsuda, T., Takao, S., Suzuki, E. and Harada, M., 2009b, 'Total hair mercury content in hair and neurological signs Historical data from Minamata', *Epidemiology*, (20) 188–193.

Yorifuji, T., Tsuda, T., Kashima, S., Takao, S. and Harada, M., 2010, 'Long-term exposure to methylmercury and its effects on hypertension in Minamata', *Environ Res*, (110) 40–46.

Yorifuji, T., Tsuda, T., Inoue, S., Takao, S. and Harada. M., 2011, 'Long-term exposure to methylmercury and psychiatric symptoms in residents of Minamata, Japan', *Environmental International,* (37) 907–913.

Yorifuji, T., Tsuda, T., Inoue, S., Takao, S., Harada, M. and Kawachi, I., 2013, *Critical Appraisal of the 1977 Diagnostic Criteria for Minamata Disease*, Archives of Environmental and Occupational Health.

Yoshida, K., Oshima, H. and Imai, M., 1966, 'Air pollution and asthma in Yokkaichi', *Arch Environ Health*, (13) 763–768.

Zangger, H., 1930, 'Erfahrungen ueber Quecksilber vergiftungen', *Arch fuer Gewerbepath u Gewerbehyg*, (1) 539–560.

From Minamata to global health risk

Philippe Grandjean (8) (9)

While the Minamata incident was being elucidated, other methylmercury poisonings occurred elsewhere due to extensive use of mercury fungicides and improper labelling. Treated seed grain was mistakenly used for bread-making, and the most serious poisoning incident happened in Iraq during a famine in 1970-1971 (Bakir et al., 1973). A widely cited report on 93 poisoned Iraqi adults reported that facial paraesthesia was the earliest clinical sign of poisoning and showed a clear dose-dependence (Bakir et al., 1973). However, the study was small in comparison with the officially recorded 6 500 hospitalisations, of whom 459 died (Bakir et al., 1973), and the amount of treated grain used (100 000 tonnes) would suggest that many more may have been poisoned. The first author of the science report, Farhan Bakir, was later recognised as Saddam Hussein's personal physician, then in exile along with at least one other Iraqi co-author (Giles, 2003; Hightower, 2009). As no useful dose-response data were available from Minamata, the Iraqi data were used for many years as the main documentation for risk assessment. Given the history of the poisonings, one can assume that methylmercury toxicity was at least not exaggerated (Grandjean et al., 2010).

Attention turned to neurotoxicity during brain development as a result of an experimental study: rats exposed during early development showed adverse effects that were not apparent at first, but later became obvious as deranged behaviour in the mature animals (Spyker et al., 1972). This report clearly supported the Minamata evidence as well as a Swedish report 20 years earlier that described mental retardation in two children exposed to methylmercury from treated grain (Engleson and Herner, 1952).

There was another surprise when Swedish researchers examined the chemical fate of mercury in a simple aquarium: methylmercury was formed from inorganic mercury compounds in the aquarium sediment. None was formed after prior autoclaving of the sediment, suggesting that microorganisms played a role (Jensen and Jernelov, 1967). Although these processes were of little significance in Minamata, where methylmercury was formed in the acetaldehyde plant (Grandjean et al., 2010), methylation of mercury suddenly became a world-wide problem. Widespread use of methylmercury for seed dressing or as a fungicide in paper mills was already known to cause local pollution of waterways and coastal waters. Now it turned out that any release of mercury could be converted into the dangerous methylmercury molecule. Studies in North America verified that bio-accumulation took place, with the highest concentrations at the top of the food chains (Fimreite, 1974). Although the first studies were contradicted and explained away, methylmercury contamination of fish emerged as a worldwide concern. Many rivers and lakes were already so polluted with mercury that fish advisories against eating sports fish were issued, especially in countries like Canada, Sweden and the US Advisories against eating locally caught fish now affect over 16 million lake acres and 1.3 million river miles in the US (US EPA, 2007).

Mercury must always have been a natural component of life on the planet, but pollution has released large amounts to the biosphere. Mercury analyses of preserved hair, teeth, and feathers from Arctic indicator species show that current levels are about ten times those in pre-industrial times (Dietz et al., 2009).

After the discovery that exposures to lead at levels considered to be 'low' could cause damage to brain development (Needleman et al., 1979), researchers suspected that methylmercury might have similar effects and may not be safe at common levels of exposure. Some of the most highly exposed populations were indigenous groups. In Canada, a study of 234 Cree children showed abnormal tendon reflexes with increased mercury concentrations in maternal hair which reflected exposure during pregnancy (McKeown-Eyssen et al., 1983). Soon after, a larger study from New Zealand showed that increased levels of mercury in mothers' hair during pregnancy were associated with delayed brain development of their children (Kjellström et al., 1986; Kjellström et al., 1989). The results were published after peer review by the Swedish Environmental Protection Agency, but were ignored for formal reasons by other regulatory authorities, allegedly because the reports had not appeared in a peer-reviewed scientific journal.

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Two large prospective studies were then initiated in the mid-1980s. The largest consisted of 1 000 children from the Faroe Islands and concluded that low-level methylmercury exposure during prenatal development was associated with deficits in several brain functions at school age; clear deficits were apparent well below a previously proposed safe level of 10 µg/g for mercury concentration in maternal hair (Grandjean et al., 1997). On the other hand, largely non-positive findings were initially reported in children from a similar study in the Seychelles (Myers et al., 2003), and the apparent disagreement was perceived as a controversy and fuelled a debate on uncertainty (Grandjean, 1999), with resonance in trade journals, internet sites, commercial campaigns, and even an editorial in the *Wall Street Journal*. Additional longitudinal data later appeared from Japan, Poland and the US in support of the Faroes conclusions (Jedrychowski et al., 2006; Lederman et al., 2008; Murata et al., 2006; Oken et al., 2008). Although less weighty, several cross-sectional studies also supported the existence of low-level exposure neurotoxicity (Grandjean et al., 2005).

The reasons for the apparent lack of mercury effects in the Seychelles could be that beneficial nutrients in fish might obliterate or dampen the mercury toxicity (Clarkson and Strain, 2003). New research from the Seychelles has recently shown that cognitive development in children was associated neither with maternal fish intake nor with methylmercury exposure, when each of them was considered separately. If maternal fish intake and mercury were included in the statistical analysis at the same time, then fish intake was clearly beneficial, while mercury had negative effects (Strain et al., 2008). Also, in the Faroes, the mercury toxicity became more prominent after adjustment for the beneficial effects of fish intake during pregnancy (Budtz-Jorgensen et al., 2007).

Because of the apparent disagreement between the two major studies and the public health implications of mercury, the US White House in 1998 called for an international workshop with 30 invited experts, who were asked to critically examine the scientific evidence. They emphasised a variety of possible uncertainties. The conclusions stated that 'there are inadequate data … to draw meaningful conclusions at this time' (NIEHS, 1998). Despite the possibility that subclinical toxicity could easily be missed and underestimated, the workshop experts were quite optimistic: 'Measurement error can impact significantly on both the estimated levels of effect and the decision on the level of exposure at which an effect is detected because of the potential for misclassification. However, the data presented in the workshop suggest that the precision of measurements of methylmercury in hair or cord blood is very good.' The experts recommended further research.

At the request of the US Congress, a new expert panel was then convened by the National Research Council (NRC, 2000) to determine whether an exposure limit of 0.1 µg/kg bodyweight per day was appropriate, as proposed by the US Environmental Protection Agency (EPA) on the basis of the data from Iraq. The committee supported the US EPA limit, but recommended that it should be based on the data from the Faroes study (which agreed with the overall evidence including New Zealand and Seychelles).

This recommendation would seem justified and appropriate, but may not be sufficiently protective. First, the exposure limit should address the problem that mercury toxicity may be masked by increased intake of essential nutrients from seafood that promote brain development (Budtz-Jorgensen et al., 2007). If this adjustment is not made, mercury would seem less toxic than it really is. Second, all the calculations have assumed that the mercury exposures are precise, but any imprecision in exposure assessments will result in misclassification and a likely underestimate of the real mercury toxicity. If this factor is taken into account, the exposure limit should be decreased by about 50 % (Grandjean and Budtz-Jorgensen, 2007).

Thus, the first likely cases of developmental methylmercury poisoning were already described in 1952 and subsequently reported from Minamata; replication in laboratory animals was published in 1972; and the first prospective population study of prenatal methylmercury toxicity due to contaminated seafood in humans was published in 1986. However, scientific consensus on prenatal vulnerability was hampered by focusing on scientific details rather than public health implications, and international agreement on the need for protection against prenatal exposures was only reached in 2002, i.e. 50 years after the first medical report that methylmercury can damage brain development.

Environmental methylation of mercury in sediment was discovered accidentally, since systematic studies of mercury's environmental fate were not conducted, and initial studies focused on total mercury concentration, not on the methylmercury compound responsible for brain toxicity. Recognition of contamination of food chains and environmental bioaccumulation of methylmercury was therefore also delayed by several decades.

Following the publication of new data on the adverse effects of low-level exposures to methylmercury,

Important early warnings of methylmercury toxicity

1952	First report on developmental methylmercury neurotoxicity in two infants
1960	Mental retardation in Minamata associated with maternal seafood diet
1955–1972	Poisoning epidemics from use of methylmercury-treated seed grain for baking and cooking
1967	Demonstration of mercury methylation in sediments
1972	Experimental study of delayed effects due to developmental neurotoxicity
1978	Exposure limit based on toxicity in adults
1986	First epidemiology report on adverse effects in children related to maternal fish intake during pregnancy in New Zealand
1997	Confirmation from the Faroe Islands on adverse effects in children from methylmercury in maternal seafood intake during pregnancy
1998	White House workshop of 30 scientists identifies uncertainties in evidence
2000	US National Research Council supports exposure limit based on Faroes data
2004	European Food Safety Authority recommends that exposures be minimised

regulatory agencies requested scientific scrutiny. Expert committees emphasised uncertainties and weaknesses in the available data. Less attention was paid to the question of what could have been known, given the research methods and possibilities, and whether developmental neurotoxicity at low doses could be ruled out. The reports also generally ignored that the imprecision of the measurements most likely resulted in an underestimate of the true effects. Instead, more research was recommended. The insistence on solid evidence promoted by polluters and regulatory agencies therefore agreed with a desire among researchers to expand scientific activities in this area. However, the wish to obtain a more complete proof had the untoward effect of delaying corrective action.

In a commentary on the regulatory delays in dealing with methylmercury poisoning in Minamata, Professor Jun Ui wrote (quoted from D'Itri and D'Itri, 1978): 'It might be a coincidence, but a strange, parallel relationship was observed between the actual symptoms of Minamata Disease and the reactions of these formal organisations. A constriction of the visual field was common among all organizations. Ataxia, a loss of coordination between various parts of the body, was often exhibited in contradictions between the measures taken by various parts of the government. There was also a loss of sensation as the appeal of the victims went unheard and there was little effort to grasp the situation as a whole. Many organisations also reacted with spasmic convulsions when they faced the problem. This was followed by mental retardation and forgetfulness.' It seems that memory loss, narrow-mindedness, and lack of coordination also affected the planning and the interpretation of environmental research on methylmercury in a more general sense.

References

Bakir, F., Damluji, S.F., Amin-Zaki, L., Murtadha, M., Khalidi, A., al-Rawi, N.Y. et al., 1973, 'Methylmercury poisoning in Iraq', *Science,* (181/96) 230–241.

Budtz-Jorgensen, E., Grandjean, P. and Weihe, P., 2007, 'Separation of risks and benefits of seafood intake', *Environ Health Perspect,* (115/3) 323–327.

Clarkson, T.W., Strain, J.J., 2003, 'Nutritional factors may modify the toxic action of methyl mercury in fish-eating populations', *J Nutr,* (133/5/1) 1 539S–1 543S.

Dietz, R., Outridge, P.M., Hobson, K.A., 2009, 'Anthropogenic contributions to mercury levels in present-day Arctic animals--a review', *Sci Total Environ,* (407/24) 6 120–6 131.

D'Itri, P.A., D'Itri, F.M., 1978, 'Mercury contamination: A human tragedy', *Environmental Management,* (2/1) 3–16.

Engleson, G., Herner, T., 1952, 'Alkyl mercury poisoning', *Acta Paediatr,* (41/3) 289–294.

Fimreite, N., 1974, 'Mercury Contamination of Aquatic Birds in Northwestern Ontario', *Journal of Wildlife Management, (*38/1) 120–131.

Giles, J., 2003, 'Iraqis draw up blueprint for revitalized science academy', *Nature,* (426/6966) 484.

Grandjean, P., 1999, 'Mercury risks: controversy or just uncertainty?', *Public Health Rep,* (114/6) 512–515.

Grandjean, P. and Budtz-Jorgensen, E., 2007, 'Total imprecision of exposure biomarkers: implications for calculating exposure limits', *Am J Ind Med,* (50/10) 712–719.

Grandjean, P., Cordier, S., Kjellstrom, T., Weihe, P., Budtz-Jorgensen, E., 2005, 'Health effects and risk assessments' in: Pirrone, N. and Mahaffey, K.R. (eds), *Dynamics of mercury pollution on regional and global scales: atmospheric processes and human exposures around the world*, Springer, Norwell.

Grandjean, P., Satoh, H., Murata, K., Eto, K., 2010, 'Adverse effects of methylmercury: environmental health research implications', *Environ. Health Perspec*t., (118/8) 1 137–1 145.

Grandjean, P., Weihe, P., White, R.F., Debes, F., Araki, S., Yokoyama, K. et al., 1997, 'Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury', *Neurotoxicol Teratol,* (19/6) 417–428.

Hightower, J.M., 2009, *Diagnosis mercury: money, politics, and poison*, Island Press/Shearwater Books, Washington, DC.

Jedrychowski, W., Jankowski, J., Flak, E., Skarupa, A., Mroz, E., Sochacka-Tatara, E., et al., 2006, 'Effects of prenatal exposure to mercury on cognitive and psychomotor function in one-year-old infants: epidemiologic cohort study in Poland', *Ann Epidemiol,* (16/6) 439–447.

Jensen, S. and Jernelov, A., 1967, 'Biosynthesis of methylmercury' (in Swedish), *Nordforsk Biocidinformation,* (10) 4–5.

Kjellström, T., Kennedy, P., Wallis, S. and Mantell, C., 1986, *Physical and Mental Development of Children with Prenatal Exposure to Mercury from Fish. Stage 1: Preliminary tests at age 4*, Report 3080, National Swedish Environmental Protection Board, Solna.

Kjellström, T., Kennedy, P., Wallis, S., Stewart, A., Friberg, L. and Lind, B., 1989, *Physical and Mental Development of Children with Prenatal Exposure to Mercury from Fish. Stage II: Interviews and Psychological Tests at Age 6*, Report 3642, National Swedish Environmental Protection Board, Solna.

Lederman, S.A., Jones, R.L., Caldwell, K.L., Rauh, V., Sheets, S.E., Tang, D., et al., 2008, 'Relation between cord blood mercury levels and early child development in a World Trade Center cohort', *Environ. Health Perspec*t., (116/8) 1 085–1 091.

McKeown-Eyssen, G.E., Ruedy, J., Neims, A., 1983, 'Methyl mercury exposure in northern Quebec. II. Neurologic findings in children', *Am J Epidemiol,* (118/4) 470–479.

Murata, K., Sakamoto, M., Nakai, K., Dakeishi, M., Iwata, T., Liu, X.J. et al., 2006, 'Subclinical effects of prenatal methylmercury exposure on cardiac autonomic function in Japanese children', *Int Arch Occup Environ Health*, (79/5) 379–386.

Myers, G.J., Davidson, P.W., Cox, C., Shamlaye, C.F., Palumbo, D., Cernichiari, E. et al., 2003, 'Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study', *Lancet,* (361/9370) 1 686–1 692.

NRC, 2000, National Research Council (U.S.), Committee on the Toxicological Effects of Methylmercury, *Toxicological effects of methylmercury*, National Academy Press, Washington, DC.

Needleman, H.L., Gunnoe, C., Leviton, A., Reed, R., Peresie, H., Maher, C., et al., 1979, 'Deficits in psychologic and classroom performance of children with elevated dentine lead levels', *N Engl J Med,* (300/13) 689–695.

NIEHS, 1998, National Institute of Environmental Health Sciences, workshop organized by Committee on Environmental and Natural Resources (CENR), Office of Science and Technology Policy (OSTP), The White House, in: *Proceedings of the Scientific Issues Relevant to Assessment of Health Effects from Exposure to Methylmercury*, 18–20 November 1998.

Oken, E., Radesky, J.S., Wright, R.O., Bellinger, D.C., Amarasiriwardena, C.J., Kleinman, K.P. et al., 2008, 'Maternal fish intake during pregnancy, blood mercury levels, and child cognition at age 3 years in a US cohort', *Am J Epidemiol,* (167/10) 1 171–1 181.

Spyker, J.M., Sparber, S.B., Goldberg, A.M., 1972, 'Subtle consequences of methylmercury exposure: behavioral deviations in offspring of treated mothers', *Science,* (177/49) 621–623.

Strain, J.J., Davidson, P.W., Bonham, M.P., Duffy, E.M., Stokes-Riner, A., Thurston, S.W. et al., 2008, 'Associations of maternal long-chain polyunsaturated fatty acids, methyl mercury, and infant development in the Seychelles Child Development Nutrition Study', *Neurotoxicology,* (29/5) 776–782.

US EPA, 2007, United States Environmental Protection Agency, *2005/2006 National Listing of Fish Advisories* (http://www.epa.gov/waterscience/fish/advisories/2006/tech.pdf) accessed 15 November 2009.

Mercury science and policy since Minamata: four insights for policy

Noelle E. Selin

Introduction

The events at Minamata, as well as other serious instances of high-dose exposure, showed the extremely toxic potential of mercury. Furthermore, beginning in the 1960s, widespread environmental contamination by mercury beyond locally-contaminated areas began to be measured by scientists and addressed by policymakers. Mercury emerged through the late 20th century as a substance known to pose risks at locations far from its release, and at low doses (UNEP, 2002). In the 21st century, policies continue to be developed to address the global spread of mercury, and scientists and policymakers are becoming increasingly aware of the complexities of the links between human activities such as energy production and connections between mercury and other environmental and health issues. The case history of mercury beyond Minamata provides four major and partially overlapping insights into the application of scientific knowledge to political efforts to deal with environmental and human health hazards, for both scientists and policymakers.

These are the need to:

- conduct research into 'blind spots';
- encourage policy-relevant scientific assessments;
- design policies that can be adapted to changing knowledge; and
- acknowledge and manage interactions between different risk issues.

Conduct research into 'blind spots'

A first insight from the mercury case, for the scientific community, is the need to conduct policy-relevant research into 'blind spots,' and be open for that research to challenge the dominant scientific understanding of a problem. (The scientific inertia that can lead to a focus on conventional paradigms is also illustrated in Chapter 26 on science for precautionary decision-making). The conventional wisdom in the 1970s was that mercury was essentially a local problem. The World Health Organization illustrated this view by stating: 'In the global cycle, most of the mercury is derived from natural sources whereas the local cycle is predominantly concerned with man-made release' (WHO and UNEP, 1976). A lawsuit by US swordfish distributors also challenged US Environmental Protection Agency (US EPA) mercury limits for fish, based on the understanding that anthropogenic mercury remained in directly-contaminated areas. The swordfish distributors argued that mercury in fish was naturally-occurring and thus should not be regulated as a contaminated product (US Court of Appeals, 1980). However, there was early evidence that mercury from human activities could be at least as important as natural mercury in remote areas, as reported by the US EPA in 1973: 'Mercury from burning coal is dispersed widely, and may enter the aquatic or terrestrial environment far from the point of discharge. Since mercury discharged in this way is of the same order of magnitude as the total of mercury mined in the world, it appears advisable to try to develop a technology to remove mercury either from the coals or from stack gases' (Klein, 1973). Despite these early warnings, mercury continued to enter the global environment at an increasing rate.

The understanding that mercury was a global problem began to emerge as predominant, at least scientifically, in the 1980s and early 1990s. Scientific research demonstrated clearly that industrial contaminants, including mercury and persistent organic pollutants (POPs), were present at elevated levels in areas far from their sources (Selin, 2010). A review of environmental concentrations of mercury in the Arctic environment in 1997 by the Arctic Monitoring and Assessment Programme (AMAP) noted that circumpolar levels of mercury were increasing in lake and ocean sediments and in the livers and kidneys of marine mammals (AMAP, 1997). While research about the degree of anthropogenic relative to natural contamination was still uncertain, AMAP urged Arctic countries to develop international mechanisms to address mercury contamination. The changed scientific understanding of mercury as a substance that travels long distances and poses risks far from its release points slowly began to shape policies to address mercury internationally.

Scientific understanding of the mercury problem continues to evolve. While international policy is now addressing the widespread spatial scale of mercury as a global problem, scientific research is also illuminating the multiple timescales under which mercury affects humans and the environment (Selin, 2011). Mercury mobilised from fossil sources continues to circulate in the land-atmosphere-ocean system over timescales longer than those considered by policies. It will take an estimated

3 000–10 000 years for mercury so mobilised to return to deep-ocean sediments (Mason and Sheu, 2002; Selin et al., 2008). A corollary to this is that only about one third of mercury currently entering ecosystems comes from direct anthropogenic activity. Another third results from natural sources, and the remainder is legacy mercury, previously emitted from anthropogenic sources, continuing to circulate between the land, ocean and atmosphere. This means that human perturbations to the global mercury cycle are very long-lived, and the Earth system will recover only slowly from historical mercury contamination. On the other hand, some environments may respond very quickly to decreases in mercury input (Harris et al., 2007). One example is the Northeast US, where, coincident with and likely as a result of regional policies to reduce emissions, concentrations of mercury in fish declined from 1999 to 2004 (Hutcheson et al., 2006). Monitoring the continuing impacts of mercury in ecosystems, and potential improvements resulting from policies, will require this evolving scientific understanding of the environmental timescales of mercury to be taken into account.

Encourage policy-relevant scientific assessments

A second insight from the interface with science and policymaking, relevant to both scientists and policymakers, is that scientific information on new risks can influence the policy process through targeted, international scientific assessments. These are widely applied to inform international and global policymaking on environmental issues such as ozone depletion and climate change (Eckley, 2001; Mitchell et al., 2006). In the case of mercury, they provide a mechanism for new scientific understanding to be taken up and addressed. This suggests that scientists should participate actively in international assessment processes.

An example of the influence of scientific assessments on mercury policy occurred in the late 20th century. The process that led to the 1997 AMAP assessment, discussed above, was a critical factor in bringing mercury contamination of remote areas to public attention (Selin and Selin, 2008). Partially influenced by the AMAP work, the Convention on Long-range Transboundary Air Pollution (CLRTAP), a regional agreement among the countries of the United Nations Economic Commission for Europe (including western and eastern European countries, Russia, the United States and Canada), was one of the first international bodies to express interest in addressing mercury. Following their own scientific assessment process (UNECE, 1995), CLRTAP countries negotiated a protocol on heavy metals, which was adopted in 1998 and entered into force in 2003. The protocol requires parties to reduce emissions of three heavy metals (lead and cadmium as well as mercury) below 1990 levels (or, alternately, below the year of their choice between 1985 and 1995), and to apply limit values and best available techniques to control major sources.

Another example of scientific assessments of mercury influencing policy came when, in response to growing global concerns about mercury, a mercury assessment organised by the United Nations Environment Programme (UNEP) concluded that there was 'sufficient evidence of significant global adverse impacts to warrant international action to reduce the risks to human health and/or the environment arising from the release of mercury into the environment' (UNEP, 2002). Despite this strong statement, policy actions following this pronouncement proceeded slowly, as there were strong political interests both in favour of and against a mercury treaty (Selin and Selin, 2006). However, in 2009, partly as a result of a change in the position of the United States (after a change in presidential administration), countries agreed to begin negotiations on a global, legally-binding instrument to address mercury. The process towards a global mercury treaty began in 2009 with the goal of completing negotiations in 2013. This delay shows that even with strong scientific assessments, gaining international consensus, balancing political and stakeholder interests, is a lengthy process, and can be slow to respond to new scientific information and understanding of the problem.

Design policies to adapt to changing knowledge

A third insight, for policymakers, is that policymaking processes and policies should be designed so that specific policies can be revised and adapted to reflect new information and changing scientific understanding. Early policies, focused on local contamination of mercury, did not address its long-range impacts, and new institutional frameworks such as a mercury treaty are thus needed to address mercury as a global problem. As noted above, gaining political agreement for new institutions can delay action for years to decades. As scientific work continues to reveal new information and paradigms change, flexible policies might be able to respond more quickly.

Even today, few policies address the full complexity of mercury in the environment. While there are several forms of mercury emitted from ecosystems

— long-lived forms that transport globally and other forms that cause local impacts — policies generally treat all forms of mercury in the same way. A recent review of the effectiveness of the CLRTAP heavy metals protocol noted that pollution control techniques specified by the protocol primarily address the forms that cause local impacts, raising questions about how effective mercury controls are at addressing the forms that cause global contamination (van der Gon et al., 2005). In addition, there are few links between policies that address emissions and those that address exposure and impacts (Selin, 2011).

Policies for minimising mercury exposure through dietary advice for fish consumers are one area where interventions have been expanded, formalised and revised over time. In 2003, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) revised its provisional tolerable weekly intake (PWTI) of methylmercury from 3.3 μg kg–1 bodyweight per week down to 1.6 μg kg–1 bodyweight per week, specifically to protect against developmental toxicity for childbearing women. Some countries have also set domestic standards. For example, the United Kingdom Food Standards Agency recommends that pregnant women and children under 16 avoid eating shark, marlin and swordfish, and minimise their consumption of tuna to four medium-sized cans or two steaks per week (United Kingdom Food Standards Agency, 2004). In Sweden, pregnant or nursing women are advised to avoid eating fish high in mercury more than two or three times a year (Sweden National Food Agency (Livsmedelsverket), 2011). Some research has shown that the consequence of dietary advice focused on methylmercury has been an overall decrease in fish consumption by pregnant women (Burger and Gochfeld, 2008). There is growing scientific understanding of the benefits of n-3 polyunsaturated fatty acids (n-3 PUFAs), nutrients present in fish and shellfish, on prenatal development (Mahaffey et al., 2011). Some fish, however, such as mackerel or herring, are high in n-3 PUFAs and low in mercury, suggesting that dietary advice could better reflect fish choices to maximise benefit and minimise risk (Mahaffey et al., 2011). However, sensitive populations continue to be exposed to high levels of methylmercury, suggesting the potential for improved risk management (Mahaffey et al., 2009).

Acknowledge and manage interactions between risk issues

As a fourth and final insight, for both scientists and policymakers, the mercury case shows that acknowledging and managing both environmental and societal connections between different risk issues can be critical. From an environmental perspective, in addition to the potential benefits of fish consumption noted above, other pollutants such as PCBs may be present in different kinds of fish, complicating efforts to provide dietary advice (Mahaffey et al., 2011). Climate and other environmental changes can affect the mercury problem by changing environmental pathways of contamination (AMAP, 2011).

Societal issues such as economic development also intersect with the mercury issue. While global emissions of mercury have remained relatively constant since 1990 (Pacyna and Pacyna, 2002; Pacyna et al., 2006; Pacyna et al., 2009), this reflects increases in Asia, resulting from rapid industrialisation and the increasing use of coal, compensating for decreases in North America and Europe. Future Asian economic development, particularly in China, could lead to dramatic increase in mercury emissions from that region (Streets et al., 2009). In addition, increasing gold prices can lead to increased use of mercury in artisanal and small-scale gold mining (Spiegel and Veiga, 2005).

Governance-related connections have additional importance. Actions in the 1980s to reduce air pollution had substantial co-benefits for mercury reductions in Europe and North America, as traditional air pollutant controls can potentially achieve > 90 % emission reductions for mercury (Northeast States for Coordinated Air Use Management, 2010). Information about the long-range transport and low-dose effects of other substances, such as persistent organic pollutants, have also helped to improve the scientific understanding of mercury risks (Selin, 2010). Finding ways to harness and encourage co-benefits, while mitigating shared risks, is a complex and continuing challenge.

Concluding remarks

After decades of science and policy actions, mercury still poses significant challenges to society. A major reason is that conceptions of the mercury problem were initially limited, and scientific and policy understanding has continued to expand and increase in complexity, increasing complexity unfortunately being the rule rather than the exception in addressing environmental risks.

The case of mercury shows that both scientists and policymakers can play an important role in risk management, through the four major insights summarised above. Scientists should encourage early research into 'blind spots' expanding understanding of environmental complexity. Policymakers should support, and scientists should participate in, targeted and international scientific assessments for policy. Policymakers should also be conscious that scientific information can and will change and design policies accordingly. Finally, both scientists and policymakers would benefit from acknowledging the full complexities and links between environmental risks. Understanding and managing multiple, linked environmental and human stressors is a primary challenge for sustainability.

While it is tempting to assume that our current understanding of the mercury problem represents a comprehensive picture of the real world, history suggests that both our understanding of the problem and our strategies to address it probably continue to have blind spots. A substantial area of uncertainty, for example, is the mechanism by which mercury is converted to methylmercury in the ocean. Additional connections with other risks — both environmental and social — are likely to be identified in the future. Drawing lessons from the mercury case, by encouraging expanded research paradigms, supporting scientific assessments, designing dynamic policies, and exploring and taking advantage of cross-issue connections — would help societies to better address risks and surprises in the future.

References

AMAP, 1997, *Arctic Pollution Issues: A State of the Arctic Environment Report*, Arctic Monitoring and Assessment Programme, Oslo.

AMAP, 2011, *Arctic Pollution 2011*, Arctic Monitoring and Assessment Programme, Oslo.

Burger, J., and Gochfeld, M., 2008, 'Knowledge about fish consumption advisories: a risk communication failure within a university population', *The Science of the Total Environment*, 390, 346–354.

Eckley, N., 2001. *Designing Effective Assessments: The Role of Participation, Science and Governance, and Focus. Report from a Workshop Co-organized by the Global Environmental Assessment Project and the European Environment Agency, 1–3 March 2001*. Expert's Corner, Environmental Issue Report No 26. Copenhagen, Denmark, European Environment Agency.

Harris, R.C., Rudd, J.W.M., Amyot, M., Babiarz, C.L., Beaty, K.G., Blanchfield, P.J., Bodaly, R.A., Branfireun, B.A., Gilmour, C.C., Graydon, J.A., Heyes, A., Hintelmann, H., Hurley, J.P., Kelly, C.A., Krabbenhoft, D.P., Lindberg, S.E., Mason, R.P.,Paterson, M.J., Podemski, C.L., Robinson, A., Sandilands, K.A., Southworth, G.R., St. Louis, V.L. and Tate, M.T., 2007, *Whole-ecosystem study shows rapid fish-mercury response to changes in mercury deposition*. Proceedings of the National Academy of Sciences of the United States of America, 104, 16 586–16 591.

Klein, D.H., 1973, *Mercury in the Environment, EPA-660/2-73-008*, U.S. Environmental Protection Agency, Office of Research and Development, Washington, D.C.

Hutcheson, M.S.,Rose, J., Smith, C.M., West, C.R., Pancorbo, O., Sullivan, J. and Eddy, B., 2006, *Massachusetts fish tissue mercury studies: Long-term monitoring results, 1999–2004*, Boston, MA (http://www.mass.gov/dep/toxics/stypes/hgtrend.pdf) accessed 3 March 2012.

Mahaffey, K.R., Clickner, R.P. and Jeffries, R.A., 2009, 'Adult women's blood mercury concentrations vary regionally in the United States: association with patterns of fish consumption (NHANES 1999–2004)', *Environmental Health Perspectives*, 117(1), 47–53.

Mahaffey, K.R., Sunderland, E.M., Chan, H.M., Choi, A.L., Grandjean, P., Mariën, K., Oken, E., Sakamoto, M., Schoeny, R., Weihe, P., Yan, C.H. and Yasutake, A., 2011, 'Balancing the benefits of n-3 polyunsaturated fatty acids and the risks of methylmercury exposure from fish consumption', *Nutrition Reviews*, 69(9), 493–508.

Mason, R.P. and G. . Sheu, 2002, 'Role of the ocean in the global mercury cycle', *Global Biogeochemical Cycles*, 16.

Mitchell, R.B., Clark, W.C., Cash, D.W. and Frank Alcock, eds. 2006, *Global Environmental Assessments: Information, Institutions, and Influence*, MIT Press, Cambridge, MA.

Northeast States for Coordinated Air Use Management, 2010, Technologies for Control and Measurement of Mercury Emissions from Coal-Fired Power Plants in the United States, NESCAUM, Boston (http://www.nescaum.org/documents/hg-control-and-measurement-techs-at-us-pps_201007.pdf) accessed 3 March 2012.

Pacyna, E.G., and Pacyna, J.M., 2002, 'Global Emission of Mercury from Anthropogenic Sources in 1995', *Water, Air, and Soil Pollution*, 137, 149–165.

Pacyna, E.G., Pacyna, J.M., Steenhuisen, F. and Wilson, S., 2006, 'Global anthropogenic mercury emission inventory for 2000', *Atmospheric Environment*, 40, 4 048–4 063.

Pacyna, E.G., Pacyna, J.M., Sundseth, K., Munthe, J., Kindbom, K., Wilson, S., Steenhuisen, F. and Maxson, P., 2009, *Global emission of mercury to the atmosphere from anthropogenic sources in 2005 and projections to 2020*, Atmospheric Environment.

Selin, H., 2010, *Global Governance of Hazardous Chemicals: Challenges of Multilevel Management*, MIT Press, Cambridge, MA.

Selin, H., and Selin, N.E., 2008, 'Indigenous Peoples in International Environmental Cooperation: Arctic Management of Hazardous Substances', Review of European Community and International Environmental Law, 17, 72–83.

Selin, N.E., 2011, 'Science and strategies to reduce mercury risks: a critical review', *Journal of Environmental Monitoring: JEM*, 13(9), 2 389–2 399.

Selin, N.E., and Selin, H., 2006, 'Global Politics of Mercury Pollution: The Need for Multi-Scale Governance', Review of European Community and International Environmental Law, 15, 258–269.

Selin, N.E., Jacob, D.J., Yantosca, R.M., Strode, S., Jaeglé, L. and Sunderland, E.M., 2008, 'Global 3-D land-ocean-atmosphere model for mercury: Present-day versus preindustrial cycles and anthropogenic enrichment factors for deposition', *Global Biogeochemical Cycles*, 22, GB2011.

Spiegel, S.J., and Veiga, M.M., 2005, 'Building Capacity in Small-Scale Mining Communities: Health, Ecosystem Sustainability, and the Global Mercury Project', *EcoHealth*, 2, 361–369.

Streets, D.G., Zhang, Q.and Wu, Y., 2009, 'Projections of Global Mercury Emissions in 2050', *Environmental Science & Technology*, 43, 2 983–2 988.

Sweden National Food Agency (Livsmedelsverket), 2011, Råd om Fisk (http://slv.se/sv/grupp1/Mat-och-naring/Kostrad/Rad-om-fisk/) accessed 7 November 2011.

US Court of Appeals, 1980, United States of America v. Anderson Seafoods, Inc., edited, US Court of Appeals, Fifth Circuit.

UNECE, 1995, *Task Force on Heavy Metals Emissions: State-of-the-Art Report. Second Edition. Executive Body for the Convention on Long-Range Transboundary Air Pollution*, Working Group on Technology. United Nations Economic Commission for Europe, Prague, June 1995.

UNEP, 2002, *Global Mercury Assessment, Inter-Organisation Programme for the Sound Management of Chemicals*, United Nations Environment Programme, Geneva.

United Kingdom Food Standards Agency, 2004, *Mercury in Fish* (http://www.food.gov.uk/multimedia/faq/mercuryfish/) accessed 7 November 2011.

van der Gon, H.A.C.D., van het Bolscher, M., Visschedijk, A.J.H. and Zandveld, P.Y.J., 2005, *Study to the effectiveness of the UNECE Heavy Metals Protocol and costs of possible additional measures*, TNO Built Environment and Geosciences, Apeldoorn, the Netherlands.

WHO and UNEP, 1976, *Environmental Health Criteria I: Mercury, International Programme on Chemical Safety*, World Health Organization and United Nations Environment Programme (http://www.inchem.org/documents/ehc/ehc/ehc001.htm) accessed 3 March 2012.

Mercury in fish — the need for better information about contaminant exposures

Argelia Castaño

There is no doubt about adverse effects of mercury in highly exposed populations, but the question is where to put an acceptable level for the general population? The major source of methyl-mercury is fish and particularly large marine fishes like tuna, sharks and swordfish. Fish and marine products are rich in unsaturated fatty acids which reduce the risk of cardiovascular disease and therefore are beneficial for health. Cardio-vascular disease is related to high consumption of red meat and dairy products and low intake of vegetables and fruits. Public health authorities are therefore recommending a Mediterranean diet with a high proportion of fish, marine products, vegetables and fruit as a way to reduce cardiovascular disease burden.

However, the authorities are facing the dilemma of balancing the benefits of fish consumption with the assumed adverse effects of low level methyl-mercury exposures. Should the policymakers advise against fish consumption because of contaminants or are the negative effects of the contaminant burden still minor compared with the positive effects of a healthier diet? The issue is even more serious for indigenous populations, for example in the Arctic region, which traditionally have a diet based on marine species (seals, whales) which today have high levels of contaminants. Should we recommend these populations to change their diet to a Western life style diet with the accompanying new health problems like obesity and diabetes? The contaminants are there — we have to accept this although we should try to reduce the exposure by all means — but we have to be pragmatic in establishing the safe levels and not exaggerate the risks in the light of the obvious benefits.

Security and confidence are the driving forces for decision-making. For mercury we have a good knowledge base from experimental and epidemiological studies connecting body burdens and adverse effects. What is critical to assess is the exposure. How much mercury are we exposed to in our daily lives and from where is it coming?

The decision-makers need robust information before they can decide on mitigation strategies. The European Commission within the frame of Environment & Health action plan 2004-2010, has funded a project to standardise protocols for human biomonitoring in Europe (10). The protocols and methodologies that were developed are now being tested in a pilot study co-funded by 17 EU Member States with contribution from the EU LIFE+ programme (11). This study, which will be reported by the end of 2012, will provide an insight into mercury levels in children and their mothers in Europe, measured for the first time under strictly standardised and harmonised conditions.

It will then be possible to map human mercury exposure at a European level with real and comparable numbers, even though the sample cannot be considered representative at national levels. For individual Member States this mapping provides an important benchmark which could assist in national mitigation strategies. Information of this kind is essential both for developing a European position for international negotiations concerning the implementation of the Global Mercury Treaty currently being progressed by UNEP and for helping national authorities and consumers to make better-informed choices about healthy diets.

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(10) http://www.eu-hbm.info/cophes.

(11) http://www.eu-hbm.info/democophes.

6 Beryllium's 'public relations problem'

David Michaels (1) and Celeste Monforton (2)

Scores of workers employed in nuclear weapons production have been diagnosed with chronic beryllium disease (CBD), a progressive and irreversible inflammatory lung disease. This chapter presents a history of knowledge and public policy about preventing beryllium-related disease, focusing primarily on the United States beryllium industry's role in shaping US regulatory policy.

Over several decades increasingly compelling evidence accumulated that CBD was associated with beryllium exposure at levels below the existing regulatory standard. The beryllium industry had a strong financial incentive to challenge the data and decided to be proactive in shaping interpretation of scientific literature on beryllium's health effects. It hired public relations and 'product defence' consulting firms to refute evidence that the standard was inadequate. When the scientific evidence became so great that it was no longer credible to deny that workers developed CBD at permitted exposure levels, the beryllium industry responded with a new rationale to delay promulgation of a new, more protective exposure limit.

This case study underscores the importance of considering the hazards from toxic materials throughout the entire product life cycle. While primary producers of beryllium products may be able to control exposures in their own facilities, it is unlikely that many secondary users and recyclers have the expertise, resources and knowledge necessary to prevent beryllium disease in exposed workers and residents in nearby communities.

The primary lessons of this chapter are widely applicable to many environmental health controversies. In particular, it illustrates the practice of 'manufacturing uncertainty' — a strategy used by some polluters and manufacturers of hazardous products to prevent or delay regulation or victim compensation.

This chapter is followed by an analysis of the rationale for corporate behaviour in the regulation of beryllium. It is argued that the availability of occasional and limited opportunities for companies to change course without suffering onerous consequences would encourage them to rethink their position and create an obligation on shareholders to take the responsible course. Although this may be perceived as letting them 'get away with it', the end result may be better public policy and corporate responsibility.

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(1) Although Dr David Michaels currently serves as the Assistant Secretary for the Occupational Safety and Health Administration (OSHA), US Department of Labor, this article was written while he served on the faculty of The George Washington University. It reflects the personal views of the authors, and does not purport to reflect the official views or positions of OSHA or the Department of Labor.

(2) Authors would like to thank David Kriebel for his contributions and Christina Morgan for her assistance in preparing this manuscript.

6.1 Introduction

In a dramatic announcement on a national television news magazine in April 2000, Bill Richardson, the United States Secretary of Energy, acknowledged that his department had collaborated with the beryllium industry to defeat a 1975 attempt by the Occupational Safety and Health Administration (OSHA) to reduce workers' exposure to beryllium. The collaboration had been documented in a powerful newspaper exposé (Roe, 1999). 'Priority one was production of our nuclear weapons', Richardson stated, '[the] last priority was the safety and health of the workers that build these weapons' (ABC, 2000).

The Secretary of Energy's declaration was remarkable; rarely do the most senior officials in government admit deception that resulted in death and disability of its own citizens. Yet, for those in the public health community, Richardson's candid announcement was long overdue. Scores of workers employed in nuclear weapons production have been diagnosed with Chronic Beryllium Disease (CBD), a progressive and irreversible inflammatory lung disease. In the decades leading up to the announcement, increasingly compelling evidence accumulated that CBD was associated with exposure at levels below the standard in place at the time. In response to this evidence, the beryllium industry waged a concerted campaign to delay a safer standard. The industry hired public relations and 'product defence' consulting firms to refute evidence that the old standard was inadequate. Eventually, when the scientific evidence became so great that it was no longer credible to deny that workers developed CBD at levels permitted by an out-dated standard, the beryllium industry responded with a new rationale to delay promulgation of a new, more protective exposure limit.

In the television interview, Secretary Richardson described how the Department of Energy (DOE) had changed course, and was now lowering the level that triggered protection for beryllium-exposed workers in the US nuclear weapons complex from 2.0 $\mu g/m^3$ to 0.2 $\mu g/m^3$ (micrograms of beryllium per cubic meter of air). The Department's new Chronic Beryllium Disease Prevention Program was designed to provide further protection for workers from a substance so hazardous that no safe level of exposure has ever been established.

The DOE standard covers only workers employed in the nuclear weapons complex. Although OSHA has acknowledged the inadequacy of its present workplace beryllium exposure limit, it has not updated its standard, which covers workers in the private sector. Researchers at the National Institute for Occupational Safety and Health (NIOSH) have estimated that there are between 28 000 and 107 000 private-sector workers potentially exposed to beryllium in the US; only 1 500 of these are employed in primary producers of beryllium products (Henneberger et al., 2004).

This case study presents a history of the knowledge and public policy about preventing beryllium-related disease, focusing primarily on the US beryllium industry's role in shaping US regulatory policy. A similar investigation has been performed in the United Kingdom (Watterson, 2005). Although the present study primarily discusses events in the United States, it is worth noting that Brush Wellman, the leading US manufacturer of beryllium products, has operated factories in Europe and that Brush Wellman's actions influenced beryllium safety and health policy throughout the world.

The present study is based on a review of documents and on the personal knowledge of one of the authors (David Michaels), who, as Assistant Secretary of Energy for Environment, Safety and Health, directed the DOE efforts to issue a stronger beryllium standard and develop a programme to provide compensation payments to workers with CBD. Some of the documents cited were obtained from government files and others were provided by attorneys who obtained them via litigation.

6.2 Early warnings and the first beryllium workplace exposure standard

The first significant industrial use of beryllium occurred in the 1930s, in production of fluorescent lamp tubes. Soon after the metal was first introduced, dozens of workers employed at fluorescent lamp factories in Massachusetts developed a form of chemical pneumonitis now known as Acute Beryllium Disease (ABD) (Hardy, 1950). It quickly became apparent that workers could not safely work with beryllium without respiratory protection.

Beryllium's importance grew dramatically with the Manhattan Project, the secret initiative to construct atomic weapons, and the subsequent expansion of the nuclear weapons industry, fuelled by the Cold War. This lightweight metal is a vital component in nuclear weapons. Beryllium slows down the neutrons released when an uranium atom is split in an atomic chain reaction; this facilitates the splitting of more atoms, thereby increasing a weapon's power, or 'yield'. In the early years of US nuclear weapons production many cases of beryllium disease occurred among workers employed at privately operated beryllium production plants and among residents living near these facilities.

To its credit, the DOE's predecessor, the Atomic Energy Commission, acted quickly. Coming soon after the success of the Manhattan Project, the AEC had a group of very capable scientists who had virtually invented the field of radiation protection (Hacker, 1987). The AEC focused its attention on beryllium, funding numerous studies at laboratories and universities throughout the country. Most importantly, AEC environmental health specialists developed a beryllium exposure limit.

In many ways, the AEC had no choice but to tackle the problem directly. Since the weapons complex was now the nation's primary consumer of beryllium products, the AEC tacitly assumed responsibility for researching the health perils that the valuable metal posed. In a 1947 report, *Public Relations Problems in Connection with Occupational Diseases in the Beryllium Industry*, the AEC openly acknowledged problems of both 'obvious moral responsibility' and public relations, the latter exacerbated by the fact that, unlike remote research and bomb-making facilities, some beryllium-processing factories were located in more populous areas. The 1947 report states bluntly,

> 'There is no doubt at all that the amount of publicity and public indignation about beryllium poisoning could reach proportions met with in the cases of silicosis or radium poisoning.' It also notes that the industry was already reporting problems recruiting workers 'because of local prejudice … engendered by actual and rumored experience with beryllium poisoning' (Tumbelson, 1947).

The origin of the AEC beryllium exposure limit is discussed in the autobiography of Merril Eisenbud, an AEC industrial hygienist who went on to be the Environmental Protection Administrator of New York City. Eisenbud describes how he and Willard Machle, a physician who was a consultant to the firm building the Brookhaven Laboratory in Long Island, New York, decided on the number while in the back seat of a taxi on their way to a meeting at the laboratory in 1948. In his autobiography, Dr Eisenbud reports that he and Dr Machle selected 2 μg/m^3 for workplace exposures and 0.01 μg/m^3 for community exposures 'in the absence of an epidemiological basis for establishing a standard' (Eisenbud, 1991). Instead, the scientists used what Herbert Stokinger of the US Public Health Service later described as a 'crude analogy' to protect health (Stokinger, 1966).

The AEC 'tentatively' adopted these exposure limits in 1949 and then reviewed them annually for seven years before permanently accepting them (Stokinger, 1966). The agency applied this exposure limit in its own facilities and incorporated adherence to the exposure limit into its contracts with manufacturers that supplied it beryllium products. OSHA later adopted the 2 μg/m^3 limit when it first issued workplace exposure standards in 1971. While the story of Eisenbud's 'taxicab standard' has been often retold, a recent reviewer of the historical data has suggested that the workplace exposure limit was actually selected on the basis of feasibility not health protection (Egilman et al., 2003).

The 2 μg/m^3 exposure limit was a great step forward. It was very stringent for its time, and its acceptance was probably aided by two factors. The first was that it addressed a severe problem; the human cost of acute beryllium disease was so great that the accompanying 'public relations problems' threatened the AEC's mission. Second, nuclear weapons production was well funded — essentially a 'cost-plus' operation in which the participating companies were assured a healthy profit. For the most part, the weapons plants were run by private employers, with the US government reimbursing their costs, plus an additional percentage awarded as profit. The largest US manufacturer of beryllium products was Brush Wellman, now known as Materion; Brush (as it was often called) was both a vendor to the US government and a contractor, operating a beryllium products production facility for the AEC in Ohio from 1950 to 1956.

The 2 μg/m^3 exposure limit was an immediate success; ABD virtually disappeared and there appeared to be a reduction in new cases of CBD as well. But it was not long before questions arose about the level of beryllium exposure necessary to cause CBD.

6.3 The science and its use

6.3.1 *Evidence of CBD at exposures below the 2 μg/m^3 standard*

With funding from the AEC, Dr Harriet Hardy established the Beryllium Case Registry (BCR) at the Massachusetts General Hospital in 1952. ABD and

CBD case reports were sent to the BCR, to track the disease and to aggregate a sufficient number of cases to conduct epidemiologic analyses (Hardy, 1955; Hall, et al., 1959; Hardy, 1962). As of 1972, the BCR had recorded at least 20 CBD cases among workers who started employment after 1949, the year the AEC exposure limit was adopted (NIOSH, 1972). By 1975, that number had risen to at least 36 (OSHA, 1975), suggesting the disease might be occurring in workers whose exposure was below the 2 μg/m^3 exposure limit. Moreover, CBD had been diagnosed in persons with no workplace exposure to the metal, including individuals who simply laundered the clothes of workers, drove a milk delivery truck with a route near a beryllium plant, or tended cemetery graves near a beryllium factory (NIOSH, 1972).

Although the acute illness was typically seen among workers exposed to very high levels of soluble forms of beryllium, the distribution of the chronic form of beryllium disease did not follow the usual exposure-response model seen for most toxic substances. Instead, CBD was found among workers and community residents without substantial exposure histories. As early as 1951, Sterner and Eisenbud reported that exposure levels were not correlated with CBD severity, and hypothesised an immunological susceptibility (Sterner and Eisenbud, 1951).

Scores of workers exposed to beryllium from manufacturing nuclear weapons developed Cronic Beryllium Disease.

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In 1966, *Beryllium: Its Industrial Hygiene Aspects*, was published under the direction of the American Industrial Hygiene Association for the AEC. Dr Stokinger, the editor of the text, asserted that:

> 'Numerous cases of the chronic disease have occurred from exposures to seemingly **trivial** concentrations of a beryllium compound that at higher levels produced no effect; no dose-response relationship appears to hold' (Stokinger, 1966) (emphasis added).

It was becoming increasingly clear that a simple, linear dose-response relationship (risk increasing in direct proportion to dose) did not apply to this metal, and that it might not be possible to identify a threshold below which no CBD cases would occur.

In these early years, the community cases were evidently viewed as anomalous, or the result of episodes of high exposure. CBD incidence among workers did appear to drop dramatically with the reduced exposure associated with the standard, leading to speculation at the time that the 2 μg/m^3 exposure limit might be overly conservative (Breslin and Harris, 1959; Stokinger, 1966). There thus appeared to be a conundrum: how could there be community cases and occasional case reports of workers with very low exposures, while the standard appeared to be effective in systematic studies of beryllium production workers? With hindsight, we can speculate that the explanation is that CBD is an immune-mediated disease with considerable inter-individual variability in susceptibility, and a dose-response relationship which is probably driven by 'peak' exposures — possibly of very short duration — which standard methods of exposure assessment do not detect.

Throughout the 1970s and 1980s, CBD case reports involving workers whose exposures were below 2 μg/m^3 continued to emerge. In 1974, for example, representatives of NGK, a Japanese beryllium producer that also operated a manufacturing facility in the US, travelled to the US to meet with local beryllium industry executives. The Japanese delegation brought a report of five CBD cases that had occurred among workers exposed below the 2 μg/m^3 standard (Kohara, 1974; Shima, 1974). Similar cases occurred at US plants, including four cases among workers at a single scrap metal reclamation facility who were consistently exposed to beryllium below 2 μg/m^3 (Cullen et al., 1987).

Today, it is understood that CBD is initiated by an immune system response to beryllium exposure; the associated adverse health effects begin well before the disease has pulmonary manifestations that allow diagnosis with a chest x-ray or pulmonary function test (Newman et al., 1996). The first published reports of CBD diagnosed using blood lymphocyte proliferation tests (BeLPT) appeared in 1983 (MMWR, 1983). By the end of the decade the diagnostic techniques had progressed significantly, allowing clinicians to more easily identify individuals with beryllium sensitisation (BeS), an immunologic condition that is a precursor to CBD (Kreiss et al., 1989; Mroz et al., 1991).

Using the BeLPT as a screening tool, researchers have found CBD prevalence rates ranging from 0.1 to 4.4 % among beryllium-exposed workers in the nuclear weapons, ceramics, primary beryllium manufacturing, metal machining, and copper-beryllium alloy industries, with Be(S) prevalence in these groups from 0.9 to 9.9 %. In most of these surveys, workers identified through the BeLPT as beryllium sensitised were given clinical evaluations to determine whether they had CBD. Depending upon the workplace, the CBD rate among workers with BeS ranged from 9 to 100 % (Kreiss et al., 1993a; Kreiss et al., 1993b; Kriess et al., 1996; Stange et al., 1996; Kreiss et al., 1997; Deubner et al., 2001; Henneberger et al., 2001; Newman et al., 2001; Stange et al., 2001; Sackett et al., 2004; Welch et al., 2004; Rosenman et al., 2005; Schuler et al., 2005; Schuler et al., 2008).

These studies diagnosed CBD or BeS among workers, including clerical workers and security guards, who had only experienced bystander exposure to beryllium. Clinical follow-up studies have found that individuals with BeS progress to CBD at a rate of 6 % to 8 % per year, but it is not known if all individuals with BeS will eventually progress to CBD (Newman et al., 2005).

6.3.2 *Evidence of beryllium's capacity to cause cancer*

In addition to its non-malignant effects on the lungs, beryllium has been shown to be a lung carcinogen. By the 1970s, significant toxicological evidence had accumulated on beryllium's carcinogenic effects, leading an NIOSH official to assert in 1977 that 'probably no compounds known to man give so consistent a carcinogenic response in so many animal species as do the compounds of beryllium' (NIOSH, 1977). This indictment of the potential risk of beryllium exposure compelled OSHA to propose a new occupational exposure limit for beryllium of 1 μg/m^3, measured as an eight-hour time-weighted average. NIOSH then recommended lowering the permissible exposure limit further, to 0.5 μg/m^3 (NIOSH, 1977).

Brush Wellman assembled a team of toxicologists, statisticians and physicians to challenge the new regulatory initiative (Michaels, 2008). The stakes were high for Brush: 'If beryllium is determined to be a carcinogen and so labelled and so regulated it would only be a matter of time until its usage would shrink to a point where it would no longer be a viable industry' (Brush Wellman, 1977). Ultimately, intense lobbying by the industry and the US Departments of Defense and Energy and the election of President Ronald Reagan prevented OSHA from finalising a new workplace exposure limit (Roe, 1999). Nonetheless, NIOSH continued to conduct epidemiological studies of cancer risk among beryllium-exposed workers (Steenland and Ward, 1991; Ward et al., 1992). The results of these studies, along with the extensive animal evidence, led the International Agency for Research on Cancer to list beryllium and beryllium compounds as Group 1 agents (i.e. carcinogenic to humans) in 1994 (IARC, 1994) and to reaffirm the designation in 2009 (Straif et al., 2009). Similarly, the US National Toxicology Program designated beryllium in 2002 as a 'known human carcinogen' (NTP, 2002).

6.3.3 *The beryllium industry's public relations efforts*

The increasing evidence of adverse health effects associated with beryllium exposure continued to create a problem for the industry. If government agencies formally designated beryllium as a substance for which there is no safe exposure level or as a carcinogen, the economic consequences for the industry could be significant. The industry's customers would be more likely to look for substitutes for the light-weight metal (Brush Wellman, 1977; Hanes, 1992b).

Beryllium producers decided to be proactive in shaping the interpretation of scientific literature on beryllium's health effects. Aspects of the programme were detailed in a 1987 internal Brush Wellman memo, with the subject line 'Proposed program for filling need for new and accurate beryllium health and safety literature'. The memo by Martin B. Powers, a retired Brush Wellman executive who was a consultant to the company, and Dr Otto P. Preuss, Corporate Medical Director, warned:

> '… the literature on Be published in the last twenty years has been very damaging. The

> literature is constantly being cited, either to our doctors at medical meetings in rebuttal of the Brush experience, or by potential customers as the cause of their unwillingness to use our products. Federal Government regulatory agencies, such as OSHA and EPA [the US Environmental Protection Agency], publish much of this material and then in the absence of good data, cite these erroneous documents to support regulatory activities.'
>
> 'What is needed to combat this situation is a complete, accurate and well written textbook on Be health and safety. It will have to be financed by Brush (or Brush and NGK?) and the bulk of the work done by Marty Powers and Otto Preuss. To be fully acceptable and credible, however, it will have to be published under the auspices of some not-for-profit organisation such as a university or medical group. … In addition to the book, we should have a number of medical papers published in prestigious medical books' (Powers and Preuss, 1987).

Beryllium: Biomedical and Environmental Aspects was published in 1991; two of its editors were Martin Powers and Otto Preuss, along with a respected academic physician (Rossman et al., 1991).

In the face of increasing evidence about the toxic effects of their products, the beryllium industry also turned for assistance to the public relations (PR) firm Hill & Knowlton (Hill & Knowlton, 1986). This firm has gained much notoriety for its now well-known efforts in manufacturing and promoting scientific uncertainty for the tobacco industry (Brandt, 2007; Glantz et al., 1996). In the proposal it sent to Brush describing how it could help, Hill & Knowlton echoed the AEC 'public relations problem' memo of 1947:

> 'Beryllium undoubtedly continues to have a public relations problem. We still see it cited in the media, as well as in our conversations with people who should know better, as a gravely toxic metal that is problematic for workers … We would like to work with Brush Wellman to help change these common erroneous attitudes. We envision a public relations program designed to educate various audiences … to dispel myths and misinformation about the metal' (Marder, 1989a).

Hill & Knowlton proposed to prepare 'an authoritative white paper on beryllium … [which] would serve as the most definitive document available on beryllium.' The PR firm also suggested projects to engage outside scientists in independent reviews of Brush Wellman materials, 'to nurture relations with the Environmental Protection Agency' and 'to challenge all unfair or erroneous treatment in the media to set the record straight' (Marder, 1989a).

Appended to the letter was a document in which Hill & Knowlton boasted of their experience assisting other corporations who faced regulatory difficulties stemming from their production of hazardous products, including asbestos, vinyl chloride, fluorocarbons and dioxin. There was no mention, however, of the firm's work for the cigarette manufacturers. Matthew Swetonic, the staff member proposed to direct the PR effort, had been a key player in Hill & Knowlton's efforts on behalf of a cigarette manufacturer to convince the public that non-smoker exposure to environmental tobacco smoke was harmless (Swetonic, 1987) and to 'create a favorable public climate' to assist in defeating lawsuits filed by smokers with lung cancer (RJR Nabisco, no date). In addition, Swetonic had previously performed public relations work for Johns-Manville, the asbestos producer, and had been the first full-time executive secretary of the Asbestos Information Association (Asbestos Textile Institute, 1973).

Once hired, Hill & Knowlton sought to reassure Brush's customers of the safety of beryllium. The firm drafted a series of letters for Brush to send to their beryllium ceramic customers, downplaying beryllium's hazardous properties (Marder, 1989b; Davis, 1989a; Davis, 1989b).

6.3.4 *Manufacturing uncertainty about beryllium and disease*

By the late 1980s, the continued incidence of new CBD cases raised concerns among health and safety professionals who previously believed the 2 $\mu g/m^3$ 'taxicab standard' was adequate to protect workers from CBD. Dr Eisenbud, who had become a consultant to Brush Wellman, notified the company in 1989 that 'he did not feel that he could defend the 2 microgram standard any longer' (Rozek, 1989).

The rising number of CBD cases also contributed to an increase in litigation. Brush management recognised that a change in the OSHA standard could be used in legal suits brought by sick workers. 'Maintaining the existing [OSHA] standard is fundamental to successfully defending against any product liability litigation', a Brush official asserted in 1989 (Rozek, 1989). This effort was an integral part of Brush's Health, Safety and Environment Strategic Plan in 1991:

> 'Employ legal means to defeat unreasonably restrictive occupational and emission standards and to challenge rulemaking and other regulatory activities that seek to impose unreasonable or unwarranted changes. Resist an attempt to make the existing occupational exposure standard of 2 micrograms/cubic meter, as measured and calculated by Brush, more restrictive. The standard is safe, it is one of the most stringent standards, and it is fundamental to our product liability defense' (Rozek, 1991).

In contrast, the evidence of the standard's inadequacy was clear to the DOE. In 1991, the nuclear weapons agency began the process of lowering the exposure limit to reduce workers' risk of developing CBD. The change was opposed by the beryllium industry, whose position is summarised in this excerpt from a 1992 Brush Wellman letter:

> 'We regret that DOE apparently still intends to abandon the existing standard of over 40 years standing with no evidence, either that the existing standard is unsafe or that the new proposed standard affords any greater degree or [sic] safety. The NIOSH recommendation of 1977, which fortunately no one ever adopted, of 0.5 micrograms, introduced an element of confusion that can only be compounded by DOE's proposed introduction of a third number. A proliferation of numbers as 'standards' can only weaken the acceptance, and therefore, the efficacy of the individual protection afforded. Confusion is never in the best interests of the worker' (Hanes, 1992a).

Progress on a more protective rule was also impeded by opposition from within the DOE. The offices responsible for manufacturing nuclear weapons argued that money spent protecting workers would mean less money for producing arms. The debate continued for several years, leaving the proposed rule in limbo.

Despite the institutional obstacles, US government safety officials continued to advocate a new, more protective standard. The DOE health and safety office sponsored a series of public forums to gather information on beryllium's health effects. At one session, Brush Wellman's Director of Environmental Health and Safety asserted (according to minutes of the meeting): 'Brush Wellman is unaware of any scientific evidence that the standard is not protective. However, we do recognize that there have been sporadic reports of disease at less than 2 μg/m^3. Brush Wellman has studied each of these reports and found them to be scientifically unsound' (DOE, 1997).

This was the industry's primary argument; subsequent studies have demonstrated that the underlying logic to the argument was flawed. At the time, however, it was not difficult to go back into the work history of anyone with CBD and speculate that, at some point, the airborne beryllium level may have exceeded the standard. Even if no evidence for overexposure was found, it was assumed that exposure over the standard had occurred because the worker had developed CBD. Brush did this, and then reasoned that the 2 μg/m^3 must be fully protective since everyone who had CBD must have at some point been exposed to levels above the standard.

Although flawed, this tautological construct served as the basis for Brush's defence of the 2 μg/m^3 exposure limit. Talking points prepared for Brush executives advised:

> 'you may be asked in some fashion whether or not the 2 μg/m^3 standard is still considered by the company to be reliable. Your answer should be as follows:
>
> 1. Experience over several decades has, in our view, demonstrated that levels of airborne beryllium within the OSHA threshold limit value afford a safe workplace.
>
> 2. In most cases involving our employees, we can point to circumstances of exposure (usually accidental), higher than the standard allows. In some cases, we have been unable (for lack of clear history) to identify such circumstances. However, in these cases we also cannot say that there was *not* excessive exposure' (emphasis in original) (Pallum, 1991).

This position, however, could not be maintained indefinitely. As the DOE provided medical screening to more workers, the number of CBD and BeS cases continued to grow, reaching several hundred by the middle of the decade (DOE, 1998). Moreover, the growing literature reporting cases of CBD associated with low levels of exposure undermined the claim that the old standard was safe (Wambach and Tuggle, 2000). Scores of beryllium-exposed workers who had developed CBD filed civil suits against Brush, alleging that the firm failed to disclose information about the material's toxicity. Continued denial of the relationship between low-level exposure and CBD was unlikely to be a successful strategy to oppose either the claims raised by sick workers or the attempts by the DOE and OSHA to strengthen their beryllium exposure standards. Instead, Brush Wellman asserted that not enough was known to prevent CBD from occurring. If true, the industry might avoid liability in CBD litigation.

In 1998, Brush Wellman and NIOSH embarked on a collaborative research initiative, conducting medical surveillance of beryllium-exposed workers and examining the beryllium-CBD relationship. The research partnership has been productive, delivering findings that have substantially contributed to the literature on beryllium disease (NIOSH, 2002).

In December 1998, the DOE officially proposed a rule to protect workers from CBD, including an action level of 0.5 μg/m^3, or 25 % of the OSHA standard, and asked for public comment on the proposal (DOE, 1998). Brush Wellman no longer asserted that the old standard was effective in preventing CBD but instead took the position that not enough was known to prevent CBD from occurring. During a public hearing in February 1999, a Brush representative offered this new rationale for the DOE to delay issuing a new standard. He testified that 'important research is underway which may provide a scientific basis for a revision to the occupational standard for beryllium,' pointing to studies on particle size, particle number and particle surface area (Kolanz, 1999).

For assistance in promoting this new strategy, Brush turned to Exponent, Inc., a US firm that provides scientific and technical support to polluters and manufacturers of dangerous products (Exponent, Inc., 2006). Exponent, Inc. is a leading practitioner of 'product defence', a specialisation that aims to help corporations reduce their regulatory burden and defeat liability claims that arise in the civil justice system (Michaels, 2008). With Exponent's assistance, in September 1999 Brush Wellman convened a conference, co-sponsored by the American Conference of Governmental Industrial Hygienists, to bring 'leading scientists together to present and discuss the current information and new research on the hazards posed by beryllium' (Paustenbach et al., 2001).

At the time of the conference, the DOE was a few months away from issuing its final ruling, and OSHA had recently signalled its intention to revise its outdated 2 μg/m^3 standard (OSHA, 1998). The paper summarising the proceedings, entitled 'Identifying an Appropriate Occupational Exposure Limit (OEL) for Beryllium: Data Gaps and Current Research Initiatives' voiced the same position that DOE officials had heard earlier in the year. Specifically, that more research was needed on the effects on CBD risk of particle size, exposure to beryllium compounds and skin exposure. Although it is not uncommon for a scientific paper to call for additional research, this paper went further, advocating postponement of any changes in the workplace beryllium exposure standard: 'At this time,' the paper concludes, 'it is difficult to identify a single new TLV (threshold limit value) for all forms of beryllium that will protect nearly all workers. It is likely that within three or four years, a series of TLVs might need to be considered… In short, the beryllium OEL could easily be among the most complex yet established' (Paustenbach et al., 2001).

In December 1999, the DOE completed its work, mandating that protection from beryllium exposure in DOE facilities be triggered at 0.2 μg/m^3 rather than the 0.5 μg/m^3 level the agency had proposed some months earlier (DOE, 1999). In its ruling, DOE relied on a common industrial hygiene measure of exposure: full-shift concentration by weight of airborne beryllium.

The government's responsibility is to protect public health using the best available evidence. More research was, and is, needed, but since the relationship of CBD to beryllium particle size, number of particles and surface area was, and remains, poorly understood, the officials responsible for protecting the health of beryllium-exposed workers determined that new policy should not be delayed until this research was completed.

6.3.5 New evidence but no new OSHA standard

Once the DOE prepared to issue its new standard, OSHA, the lead US agency for worker safety and health, recognised an opportunity to update its own beryllium standard. In written comments to the DOE, OSHA's Assistant Secretary acknowledged the inadequacy of the current OSHA standard, writing:

> 'we now believe that our 2 μg/m^3 PEL does not adequately protect beryllium-exposed

> workers from developing chronic beryllium disease, and there are adequate exposure and health effects data to support [the DOE's] rulemaking.'

The letter continues by citing existing data:

> 'Cases of chronic beryllium disease have occurred in machinists where 90 % of the personal exposure samples found levels of beryllium to be below the detection limit of 0.01 µg/m^3 … Viewed from OSHA's regulatory perspective, these DOE study results document risk of sensitization to beryllium of 35–40 per 1 000 workers and risk of chronic beryllium disease to machinists of 94 per 1 000' (Jeffress, 1998).

Despite a commitment to issue a new standard by September 2001 (OSHA, 2000), OSHA did not propose a rule to protect beryllium-exposed workers. When President George W. Bush's Administration took office in 2001, OSHA formally dropped its commitment to strengthen the beryllium standard, asserting it needed more information before deciding how to proceed (OSHA, 2002).

Scientific knowledge on the risks associated with low-level beryllium exposure continues to accumulate, silencing those who had previously defended the adequacy of the current standard. In the few years since DOE issued its standard, US researchers, including several affiliated with Brush Wellman, have published several epidemiologic studies that provide additional evidence that OSHA's standard does not fully prevent CBD (Henneberger et al., 2001; Kelleher, et al., 2001; Schuler et al., 2005; Stange et al., 2001; Rosenman et al., 2005; Madl et al., 2007). Finally, in 2006, a literature review and editorial supported by Brush Wellman acknowledged that the current OSHA standard 'provides insufficient protection for beryllium-exposed workers' (Borak, 2006).

Beryllium exposure continues to be a public health concern at 'downstream' facilities, which use beryllium products but are not involved in primary production, in recycling facilities, and in communities adjacent to beryllium-processing facilities. In 1999, the diagnosis of a sentinel CBD case in a metals recycling plant in Quebec, Canada resulted in the identification of 31 additional cases at three metals plants (Robin, 2005). It also prompted a survey that identified 2 789 workplaces where beryllium was used in that province, including 63 golf club manufacturers and 15 bicycle manufacturers (Tremblay, 2005). There have also been eight new cases of community-acquired CBD recognised between 1999 and 2002 in the US (Maier et al., 2008)

Given the wealth of new research, is it now possible to identify a safe level of beryllium exposure? Unfortunately, it is not. There are many complex questions to answer, and there are relatively few workplaces in which these questions can be easily studied. A committee of the US National Research Council recently concluded that 'it is not possible to estimate a chronic inhalation-exposure level that is likely to prevent BeS and CBD' (National Research Council, 2008). This scepticism is shared throughout the scientific community; in the opinion of three NIOSH scientists, the evidence gathered to date suggests that 'attempts to define a safe air concentration of beryllium for all workers are not likely to be successful' (Kreiss et al., 2007).

This uncertainty does not, however, justify deferring implementation of programmes to reduce exposure. There is ample evidence that interventions designed to reduce beryllium exposure to the lowest achievable levels have successfully decreased BeS and CBD incidence (National Research Council, 2008). Furthermore, in 2009 the American Conference of Governmental Industrial Hygienists issued a Threshold Limit Value recommendation of 0.05 µg/m^3, which is well below both the current OSHA and DOE standards (ACGIH, 2009).

Since at present there is no compelling evidence for a safe level of beryllium exposure, it would be prudent public health policy for manufacturers to substitute a less toxic material for beryllium whenever possible. However, in those products and processes in which there is no adequate substitute for beryllium, such as the production of nuclear weapons, exposure should be reduced to the lowest level technically feasible.

6.4 Lessons for policymakers

The primary lessons of this case study are widely applicable across many environmental health controversies.

The first is that **the absence of evidence is not evidence of absence**. In the decades following the reduction in beryllium exposures in the early 1950s, relatively few new CBD cases were diagnosed. This is likely attributable both to improved working conditions and the limitations of the diagnostic methods available at the time. With the development of the BeLPT, many new cases were diagnosed, no doubt including cases that would not have been previously recognised as CBD.

There were indications before the advent of the BeLPT, however, that the 2.0 μg/m^3 standard was not fully protective. As CBD and BeS were diagnosed in an increasing number of workers with low exposures, this conclusion became more difficult to avoid.

As this evidence accumulated, the beryllium industry had a strong financial incentive to challenge the data, and to oppose regulatory action that would result in a lower exposure limit. It appears this incentive shaped the interpretation given to scientific evidence by scientists employed by the beryllium industry.

This, then, is the second lesson of the case study: **interpretation of scientific data by those with financial incentives for misinterpretation must be discounted**. Scientists employed by the beryllium industry defended the 'taxicab standard' long after it was correctly recognised as inadequate by independent scientists. In particular, work by scientists employed by firms specialising in product defence and litigation support must be seen for what it is: advocacy, rather than science.

This study illustrates the practice of '**manufacturing uncertainty**' — the strategy used by some polluters and manufacturers of hazardous products to prevent or delay regulation or victim compensation (Michaels and Monforton, 2005; Michaels, 2008). The public health paradigm requires that the best available evidence be used to protect the public. By the early 1990s, the accumulated evidence was sufficient for public health officials to justify a more protective workplace beryllium exposure limit. In response, the industry manufactured and magnified uncertainty, producing a series of arguments about why the old standard should not be changed. Extensive research has subsequently confirmed the inadequacy of the OSHA standard; a more protective standard will help prevent CBD and save lives.

Finally, the findings of this case study underscore the importance of **considering the hazards associated with a toxic material throughout the entire life cycle of the product**. While primary producers of beryllium products may be able to control exposures in their own facilities, it is unlikely that many secondary users and recyclers have the expertise, resources and knowledge to prevent beryllium disease in exposed workers and residents in nearby communities. As a result, it would be prudent public health policy to end industrial use of beryllium, except in circumstances where substitution is impossible.

Table 6.1 Early warnings and actions

1930s	First industrial uses of beryllium and first reported cases of beryllium disease
1949	AEC adopted the 2.0 μg/m^3 exposure limit for weapons workers
1952	Establishment of Beryllium Case Registry
1971	OSHA adopted the 2.0 μg/m^3 exposure limit
1975	OSHA proposed a 1.0 μg/m^3 exposure limit but this was never approved
1980s	BeLPT used to diagnose cases of CBD
1989	DOE proposed a 0.5 μg/m^3 exposure limit for DOE weapons and clean-up workers
1999	DOE issued a 0.2 μg/m^3 exposure limit for DOE weapons and clean-up workers
2009	ACGIH recommended a 0.05 μg/m^3 exposure limit
2012	OSHA has yet to propose new workplace beryllium standard

References

ABC, 2000, Transcript of 20/20, *'The Deadly Dust; Thousands of Nuclear Weapons Works Exposed to Beryllium Dust are Sick or Dying'*, 19 April 2000 (available from authors).

ACGIH, 2009, *TLVs® and BEIs®*, American Conference of Governmental Industrial Hygienists.

Asbestos Textile Institute, 1973, *About the speaker: Matthew M. Swetonic. Addendum to meeting minutes for Asbestos Textile Institute general meeting*, Key Bridge Marriott, Arlington, VA, 7 June, 1973 (available from authors).

Borak, J., 2006, 'The beryllium occupational exposure limit: historical origin and current regulatory inadequacy', *J. Occup. Environ. Med.*, (48/2) 109–116.

Brandt, A.M., 2007, *The Cigarette Century*, Basic Books, New York.

Breslin, A.J. and Harris, W.B., 1959, 'Health Protection in beryllium facilities; summary of ten years of experience', *A. M. A. Arch. Ind. Health*, (19/6) 596–648.

Brush Wellman, 1977, *Supplementary Documentation of Brush Wellman Briefing Outline on OSHA*, Bates no. BF 0009665-9677 (available from authors).

Cullen, M.R., Kominsky, J.R., Rossman, M.D., Cherniack, M.G., Rankin, J.A., Balmes, J.R., Kern, J.A., Daniele, R.P., Palmer, L., Naegel, G.P. et al., 1987, 'Chronic Beryllium Disease in a precious metal refinery. Clinical epidemiologic and immunologic evidence for continuing risk from exposure to low level beryllium fume', *Am. Rev. Respir. Dis.*, (135/1) 201–208.

Davis, R.C., 1989a, Memorandum, Subject: 'Defense Logistics Agency Beryllium Oxide Hazmat Program', 12 July 1989.

Davis, R.C., 1989b, Memorandum, Subject: 'DLA Beryllium Oxide HAZMAT Program', August 9, 1989 (http://www.defendingscience.org/upload/Davis_8-9-89.pdf) accessed 8 July 2011.

DOE, 1997, Beryllium Public Forum, Albuquerque, New Mexico, 15 January 1997.

DOE, 1999, 'Chronic Beryllium Disease Prevention Program, Final Rule', *Fed. Regist.*, (64) 68 854.

DOE, 1998, 'Chronic Beryllium Disease Prevention Program', DOE Office of Environment, Safety and Health, *Fed. Regist.*, (63) 66 940.

Deubner, D., Kelsh, M., Shum, M., Maier, L., Kent, M. and Lau, E., 2001, 'Beryllium sensitization, chronic beryllium disease, and exposures at a beryllium mining and extraction facility', *Appl. Occup. Environ. Hyg.*, (16/5) 579–592.

Eisenbud, M., 1991, *An environmental odyssey: people, pollution, and politics in the life of a practical scientist*, University of Washington Press, Seattle, WA.

Egilman, D.S., Bagley, S., Biklen, M., Stern Golub, A., and Rankin Bohme, S., 2003, 'The Beryllium "double standard" standard', *Int. J. Health Serv.*, (33/4) 769–812.

Exponent, Inc., 2006, '10-K Annual Report for Fiscal Year ended December 31, 2006' (http://www.sec.gov/Archives/edgar/data/851520/000119312507049476/d10k.htm#tx48879_9) accessed 8 July 2011.

Glantz, S.A., Slade, J., Bero, L.A., Hanauer, P. and Barnes, D.E., 1996, *The Cigarette Papers*, University of California Press, Berkeley.

Hacker, B.C., 1987, *The dragon's tail: radiation safety in the Manhattan Project, 1942–1946*, University of California Press, Berkeley.

Hall, T.C., Wood, C.H., Stoeckle, J.D. and Tepper, L.B., 1959, 'Case data from the beryllium registry', *AMA Arch. Ind. Health*, (19/2) 100–103.

Hanes, H., 1992a, Vice President, Environmental and Legislative Affairs, Brush Wellman, 1992. Letter to David J Weitzman, Office of Health Physics and Industrial Hygiene, DOE; 10 January 1992 (available from authors).

Hanes, H, 1992b, Memorandum to Rob Rozek. Subject: Environmental and Government Affairs, June 19, 1992 (available from authors).

Hardy, H.L., 1955, 'Beryllium case registry at Massachusetts General Hospital', *Am. Rev. Tuberc*, (72/1) 129–132.

Hardy, H., 1962, 'Beryllium case registry progress report: 1962', *Arch. Environ. Health*, (5) 265–268.

Hardy, H.L., 1950, 'Clinical and epidemiologic aspects', in: Vorwald, A.J. (ed.), *Pneumoconiosis: Beryllium, Bauxite Fumes*, Leroy U. Gardner Memorial Volume: Sixth Saranac Symposium, Paul

B. Hoeber Medical Books Department of Harper & Brothers, New York, pp. 133–151.

Henneberger, P.K., Cumro, D., Deubner, D.D., Kent M.S., McCawley M. and Kreiss K., 2001, 'Beryllium sensitization and disease among long-term and short-term workers in a beryllium ceramics plant', *Int. Arch. Occup. Environ. Health*, (74) 167–176.

Henneberger, P.K., Goe, S.K., Miller, W.E., Doney, B., and Groce, D.W., 2004, 'Industries in the United States with Airborne Beryllium Exposure and Estimates of the Number of Current Workers Potentially Exposed', *J. Occup. Environ. Hyg.*, (1/10) 648–659.

Hill & Knowlton, Inc., 1986, Monthly invoice to Brush Wellman; 17 November 1999 (available from authors).

IARC, 1994, International Agency for Research on Cancer, *Monograph: Beryllium, cadmium, mercury and exposures in the glass manufacturing industry.*

Jeffress, C.N., 1998, Letter to Peter Brush, Acting Assistant Secretary, DOE, 27 August 1998.

Kelleher, P.C,. Martyny, J.W., Mroz, M.M., Maier, L.A., Ruttenber, A.J., Young, D.A. and Newman, L.S., 2001, 'Beryllium particulate exposure and disease relations in a beryllium machining plant', *J. Occup. Environ. Med.*, (43/3) 238–249.

Kohara, T., 1974, Director & General Manager, Personnel Department, NGK Insulators, Inc., Letter to HC Piper. Vice President Brush Wellman, 9 August 1974. Bates 402194–402195 (available from authors).

Kolanz, M., 1999, Director of Environmental Health and Safety, Brush Wellman, Inc., Public testimony at the Department of Energy Public Hearing on proposed Chronic Beryllium Disease Prevention Program, 11 February 1999 (available from authors).

Kreiss, K., Day, G.A. and Schuler, C.R., 2007, 'Beryllium: a modern industrial hazard', *Annu. Rev Public Health*, (28) 259–277.

Kreiss, K., Mroz, M.M., Newman, L.S., Martyny, J. and Zhen, B., 1996, 'Machining risk of beryllium disease and sensitization with median exposures below 2 μg/m^3', *Am. J. Ind. Med.*, (30/1) 16–25.

Kreiss, K., Mroz, M.M., Zhen, B., Martyny, J.W. and Newman, L.S., 1993a, 'Epidemiology of beryllium sensitization and disease in nuclear workers', *Am. Rev. Respir. Dis.*, (148) 985–991.

Kreiss, K., Mroz, M.M., Zhen, B., Wiedemann, H. and Barna, B., 1997, 'Risks of beryllium disease related to work processes at a metal, alloy and oxide production plant', *J. Occup. Environ. Med.*, (54) 605–612.

Kreiss, K., Newman, L.S., Mroz, M.M. and Campbell, P.A., 1989, 'Screening blood test identifies subclinical beryllium disease', *J. Occup. Med.*, (31/7) 603–608.

Kreiss, K., Wasserman, S., Mroz, M.M. and Newman, L.S., 1993b, 'Beryllium disease screening in the ceramics industry: blood test performance and exposure-disease relations', *J. Occup. Med.*, (35) 267–274.

Madl, A.K., Unice, K., Brown, J.L., Kolanz, M.E. and Kent, M.S., 2007, 'Exposure-response analysis for beryllium sensitization and chronic beryllium disease among workers in a beryllium metal machining plant', *J Occup Environ Hyg*, (4/6) 448–466.

Maier, L.A., Martyny, J.W., Liang, J. and Rossman, M., 2008, 'Recent community acquired chronic beryllium disease in residents surrounding a beryllium facility', *Am J Respir Crit Care Med*, (177) 1 012–1 017.

Marder, H., Hill & Knowlton, 1989a, Letter to James E. Gulick, Vice President, Planning and Administration, Brush Wellman Inc., 21 February 1989. RD006548–554.

Marder, H., Hill & Knowlton, 1989b, Memorandum to Bob Rozek, 1 May 1989, MD008133–8144.

Michaels, D., 2008, *Doubt is their Product,* Oxford University Press, New York.

Michaels, D. and Monforton, C., 2005, 'Manufacturing Uncertainty: Contested Science and the Protection of the Public's Health and Environment', *Am. J. Pub. Health*, (95/S1) S39–548.

MMWR, 1983, Morbidity and Mortality Weekly Report, *Beryllium Disease among Workers in a Spacecraft-Manufacturing Plant, California*, (32/32) 419–420, 425.

Mroz, M.M., Kreiss, K., Lezotte, D.C., Campbell, P.A. and Newman, L.S., 1991, 'Reexamination of the blood lymphocyte transformation test in the diagnosis of chronic beryllium disease', *J. Allergy Clin. Immunol.*, (88/1) 54–60.

National Research Council, 2008, *Managing Health Effects of Beryllium Exposure*, The National Academies Press, Washington.

NTP, 2002, *Tenth Report on Carcinogens*, National Toxicology Program.

Newman, L.S., Lloyd, J. and Daniloff, E., 1996, 'The natural history of Beryllium Sensitization and Chronic Beryllium Disease', *Environ. Health Perspect.*, (104/S5) 937–943.

Newman, L.S., Mroz, M.M., Balkissoon, R. and Maier, L.A., 2005, 'Beryllium sensitization progresses to chronic beryllium disease: a longitudinal study of disease risk', *Am. J. Respir. Crit. Care Med.*, (171/1) 54–60.

Newman, L.S., Mroz, M.M., Maier, L.A. , Daniloff, E.M. and Balkissoonm, R., 2001, 'Efficacy of serial medical surveillance for chronic beryllium disease in a beryllium machining plant', *J. Occup. Environ. Med.*, (43/3) 231–237.

NIOSH (National Institute for Occupational Safety and Health), 1972, *Criteria for a Recommended Standard to Beryllium Exposure*, Report No DHEW HSM 72-10268.

NIOSH, 1977, Testimony of Edward J. Baier, Deputy Director. Public hearing on the occupational standard for beryllium, August 19, 1977 (available from authors).

NIOSH, Board of Scientific Counselors, 2002, *Report from the Subcommittee on Beryllium Research*, 2 October 2002.

OSHA, 1975, 'Proposed Occupational Safety and Health Standard for Beryllium'. *Fed. Regist.*, (40/202) 48 815.

OSHA, 1998, Semiannual regulatory agenda, *Fed. Regist.*, (63/80) 22 218.

OSHA, 2000, Semiannual regulatory agenda, *Fed. Regist.*, (65/79) 23 014.

OSHA, 2002, 'Occupational exposure to beryllium: Request for Information', *Fed. Regist.*, (67/228) 70 707–70 712.

Pallum, J.J. and Brush Wellman, 1991, Memorandum, 10 December 1991: 'Meeting Notes—December 6, 1991—BLTT Program', 'Redraft of Exhibit B: 'Efficacy of the 2 microgram per meter Standard', NR001744 (available from authors).

Paustenbach, D.J., Madl, A.K. and Greene, J.F., 2001, 'Identifying an appropriate Occupational Exposure Limit (OEL) for Beryllium: data gaps and current research initiatives', *Appl. Occup. Environ. Hyg.*, (16/5) 527–538.

Powers, M.B. and Preuss, O.P., 1987, 'Memorandum to J.E. Gulick. Proposed Program of Filling Need for New and Accurate Beryllium Health and Safety Literature', 23 January, 1987 (available from authors).

RJR Nabisco (no date), Public relations plan: liability litigation.

Robin, J.P., Noranda Inc./Falconbridge Ltd., 2005, 'Medical surveillance in the recycling industry'. Presentation at the International Beryllium Research Conference, 8 March 2005.

Roe, S., 1999, 'Deadly alliance: weapons over workers', *The Blade*, 12 April 1999.

Rosenman, K., Hertzberg, V., Rice, C. , Reilly, M.J., Aronchick, J., Parker, J.E., Regovich, J. and Rossman, M., 2005, 'Chronic Beryllium Disease and sensitization at a beryllium processing facility', *Environ. Health Perspect.*, (113/10) 1 366–1 372.

Rossman, M.D., Preuss, O.P. and Powers, M.B., 1991, *Beryllium: biomedical and environmental aspects*, Williams and Wilkins, Baltimore.

Rozek, R.H., Vice President, Corporate Development, Brush Wellman, 1989, 'Presentation regarding Governmental and Environmental Affairs activities', 11 September 1989. D101448-87 (available from authors).

Rozek, R.H., Vice President, Corporate Development, Brush Wellman, 1991. 'Brush Wellman, Inc. Health Safety and Environmental Action Plan', Presentation at the Board of Directors Meeting, 25 June 1991. BF 001197-246 (available from authors).

Sackett, H.M., Maier, L.A., Silveira, L.J. Mroz, M.M., Ogden, L.G., Murphy, J.R. and Newman, L.S., 2004, 'Beryllium medical surveillance at a former nuclear weapons facility during cleanup operations', *J. Occup. Environ. Med.*, (46/9) 953–961.

Schuler, C.R., Kent, M.S., Deubner, D.C., Berakis, M.T., McCawley, M., Henneberger, P.K., Rossman, M.D. and Kreiss, K., 2005, 'Process-related risk of beryllium sensitization and disease in a copper-beryllium alloy facility', *Am. J. Ind. Med.*, (47/3) 195–205.

Schuler, C.R., Kitt, M.M., Henneberger, P.K., Deubner, D.C. and Kreiss, K., 2008, 'Cumulative sensitization and disease in a beryllium oxide ceramics worker cohort', *J. Occup. Environ. Med.*, 50 (12) 1 343–1 350.

Shima, S., 1974, Letter to H.S. Van Ordstrand, The Cleveland Clinic Foundation, 16 August 1974, Documents # TW067281 (available from authors).

Stange, A.W., Furman, F.J. and Hilmas, D.E., 1996, 'Rocky Flats beryllium health surveillance', *Environ. Health Perspect.*, (104) Suppl 5, pp. 981–986.

Stange, A.W., Hilmas, D.E., Furman, F.J. and Gatliffe, T.R., 2001, 'Beryllium sensitization and chronic beryllium disease at a former nuclear weapons facility', *App. Occup. Environ. Hyg.*, (16/3) 405–417..

Steenland, K. and Ward, E., 1991, 'Lung cancer incidence among patients with beryllium disease: a cohort mortality study', *J. Natl. Cancer Inst.*, 1991; (83) 1 380–1 385.

Sterner, J.H. and Eisenbud, M., 1951, 'Epidemiology of beryllium intoxication', *Arch. Industr. Hyg. Occup. Med.*, (4) 123–151.

Stokinger, H.E., 1966, 'Recommended hygienic limits of exposure to beryllium', in: Stokinger, H.E. (ed), *Beryllium: its industrial hygiene aspects*, pp. 237–238, Academic Press, New York, NY.

Straif, K., Benbrahim-Tallaa, L., Baan, R., Grosse, Y., Secretan, B., El Ghissassi, F. , Bouvard, V., Guha, N., Freeman, C., Galichet, L. and Cogliano, V., 2009, 'A review of human carcinogens–part C: metals, arsenic, dusts, and fibres', *Lancet Oncol.*, (10/5) 453–454.

Swetonic, M., 1987, Memorandum to P. Allen, RJR Nabisco, 23 July, 1987.

Tremblay, J., 2005, Commission de la santé et de la sécurité du travail (CSST), 'Problematic beryllium: current situation in Québec', Presentation at the International Beryllium Research Conference, 8 March 2005 (http://www.irsst.qc.ca/media/documents/PubIRSST/Be-2005/Session-3/Tremblay.pdf) accessed 8 July 2011.

Tumbelson, R., 1947, US Atomic Energy Commission, Public & Technical Information Service, 'Public Relations Problems in Connection with Occupational Diseases in the Beryllium Industry.' NA-AEC 0112–0136 (available from authors).

Wambach, P.F. and Tuggle, R.M., 2000, 'Development of an eight-hour Occupational Exposure Limit for beryllium', *App. Occup. Environ. Hyg.*, (15/7) 581–587.

Ward, E., Okun, A., Ruder, A., Fingerhut, M. and Steenland, K., 1992, 'A mortality study of workers at seven beryllium processing plants', *Am. J. Ind. Med.*, (22) 885–904.

Watterson, A., 2005, University of Stirling, 'Making sense and 'non-sense' of international research on beryllium toxicity: The history of using, neglecting and 'skewing' research? Presentation at the International Beryllium Research Conference, 9 March 2005 (http://www.irsst.qc.ca/media/documents/divers/Beryllium_ppt/SESSION3/7-Watterson.pdf) accessed 21 July 2011.

Welch, L., Ringen, K., Bingham, E. , Dement, J., Takaro, T., McGowan, W., Chen, A. and Quinn, P., 2004, 'Screening for beryllium disease among construction trade workers at Department of Energy nuclear sites', *Am. J. Ind. Med.*, (46/3) 207–218.

Corporate behaviour in the regulation of beryllium: could there have been a different outcome if the company had room to turn around?

Tee L. Guidotti (3)

The response of commercial organisations to uncertainty with respect to environmental and occupational risks continues to challenge regulators and parties interested in a regulatory intervention in the face of corporate resistance.

Viewed from within the organisation, corporate objectives and protection align with other seemingly valid reasons to oppose change and create a stronger argument from within than may be perceived from the outside. One suspects that most corporate leaders involved in situations like this live in a world of cognitive dissonance and denial rather than cupidity. Few people, other than sociopaths, tolerate the belief that they cause harm and suffering. Rather, most people with strong personalities tend to deny their role in a bad situation and the consequences of their actions, and to believe the denial. Reinforced by group-think, rationalisation, corporate culture, and a technical staff able and willing to provide justification for the denial, such behaviour becomes normative. The challenge is not to condemn the behaviour — that is easy. It is to understand it in order to control it. (Prevention is probably not possible given human nature.)

Beryllium: a case study

Michaels and Monforton (2008 and present volume) have published a comprehensive history of the occupational exposure standard for beryllium in the US and its failure to adequately protect workers. Their work is a valuable contribution to our understanding of the beryllium issue, about which there have been a number of serious misconceptions (Guidotti, 2008).

The only significant manufacturer and supplier of beryllium metal in the US, Brush Wellman, used various arguments to rationalise opposition to the proposed beryllium standard, first asserting that 2 $\mu g/m^3$ was adequate, then playing on uncertainty, challenging the data on which the proposals were grounded, first for beryllium disease and later for carcinogenicity. In this they were initially abetted by the US Department of Energy (DOE), which initially resisted an evidence-based precautionary protective standard, presumably to protect the nuclear industry. There were many allegations of scientific malfeasance and inappropriate political influence. Notwithstanding the fact that both DOE and the American Conference of Governmental Industrial Hygienists, a major voluntary body recommending exposure guidelines, have proposed lower occupational exposure limits, the federal regulator, the Occupational Safety and Health Administration, has still not proposed a new 'permissible exposure limit' for beryllium after at least 35 years of deliberation.

Brush Wellman was, and still is, a highly profitable company that had, and still has, a near monopoly on the product. At the time it had little other business, although it is now more diversified. The company stands accused by Michaels and Monforton of cupidity and arrogance in resisting a protective federal standard in the face of steadily accumulating evidence for the toxicity and carcinogenicity of the metal. Doubtless, the company has a different narrative, but this panel is not about the company's culpability. Seen another way, the story of Brush Wellman, and other companies, is a case study in organisational behaviour and response. However, it may also be read slightly differently to be about pathway dependence and how the initial worldview of a highly organised institution may commit it to a line that ultimately proves disgraceful for itself and tragic for the victims of occupational hazard.

The doctrine of 'shareholder value' and resistance to changing course

Michaels and Monforton assume throughout that the reluctance of Brush to accept new findings regarding Be risk was motivated by the desire to maintain corporate revenues. To set the stage, it is important to realise that, in the US, there appears to be no recognised legal responsibility of corporations other than to shareholders and to obey the law. The concepts of corporate responsibility and of corporate beneficence have been litigated many times and decisions have consistently upheld the interests of shareholders above all other stakeholders (Pérez Carolli, 2007). The most famous example of this is a 1919 Michigan Supreme Court decision that blocked Ford Motor Company from reducing the price of Model T automobiles as a public benefit (and to create a larger consumer class) at the expense of paying dividends to shareholders. Some legal scholars have argued, persuasively, that this ruling has been misunderstood and its significance has been exaggerated (Stout, 2008). However, there have been many other decisions that have had the collective impact of emphasising that although a corporation may act in a beneficent manner, it is not entitled to do so at the expense of shareholder interests, at least not without their permission.

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(3) This text is an adaptation of a critical review prepared for the European Environmental Agency, Copenhagen, as part of *Late lessons from early warnings*.

From the legal point of view, and at least from a lay reading of the legal situation, which is at least what corporate officers would have understood in the 1950s and 1960s, corporations appear to be obliged to optimise value, profits, and shareholder interest, not community or social benefits except insofar as they advance the interests of the corporation and therefore the interests of the shareholders who own it. This reality can be lamented and argued, but it is deeply grounded in American jurisprudence and business culture.

The point to be made before further discussion is not that this concept is, or can be, abusive and antisocial — that it can be is obvious. It is that it was believed and that, notwithstanding waves of management interest in 'corporate responsibility' (most notably in the 1960s), this belief has been assumed in corporate culture and was part of a management philosophy of maximising 'shareholder value' for the last thirty years. Under US law, a corporation cannot be faulted for maximising profits, as long as they are within the law, just as an individual cannot be faulted for trying to minimise the taxes he or she pays, as long as the taxpayer is within the law. Whether Brush Wellman violated the law is outside the scope of this panel and is not directly addressed by Michaels and Monforton (2008).

Likewise, there is also the influence in business circles of the parallel and highly influential argument of Milton Friedman and the Chicago School of economists that the purpose of business is to increase wealth and that social benefit is a question of how that wealth is invested, a decision that the owners of the wealth should make, not the corporation (Friedman, 1970). One answer to Friedman would be that corporations are given a franchise to perform socially useful functions, providing goods and services in exchange for making profit, but this is not the forum to argue this point.

One obvious legal solution is for the interest of stakeholders to be revisited. If the corporation faces catastrophic sanctions if it admits it was wrong, then the interest of the shareholders in a corporation should be for it to capitulate. However, in the real world, fines are too low, sanctions are too weak, and legal actions too likely to settle for the anticipated consequences to force changes in corporate behaviour. The executives of a bad corporation are usually better off seeing the issue through to the end and then, if the consequences are dire, changing management, taking golden parachutes, and leaving the task of refurbishing the image of the company to the next executive team.

Another legal solution should be possible, however. If a corporation has the option of ending a course of action that would lead to consequences so serious that shareholders' interests would be compromised, they would then have a fiduciary and legal responsibility to their shareholders to retreat from an untenable position and accept the need to change course. Opportunities coming at key times in the narrative to change direction without onerous consequences could have made it possible for corporate leaders to drop their resistance to the proposed standard without admitting they were wrong. Creating such opportunities might make it possible for the leaders of such companies to change course on a pragmatic basis on the grounds that they are minimising loss to shareholders and reducing potential punitive damages that the company would have to pay.

Whether this policy would motivate corporate leaders on a destructive track to change course on their own initiative is uncertain, although it is likely that it would if the consequences are high. These are not stupid people, after all. What is certain is that legislation, regulatory policy, or a judicial opinion to this effect would create grounds for shareholders to take legal action against the officers of a corporation and put enormous pressure on them to change their position when it became untenable. Another advantage of such a policy is that it is consistent with conservative business values of responsibility to shareholders and maintaining shareholder value, and therefore hard to argue against.

National security and rationalisation

People tend to believe what is aligned with their own interest and do not recognise these beliefs as rationalisation. It is quite likely that corporate leaders of the day saw reasons other than corporate protection that aligned with their financial interests of profit maximisation. The sequence of events takes on new significance when seen from the perspective of the times.

Initially, the trade-off as seen from the ramparts of the military-industrial complex involved a risk/risk calculation in which the perceived security consequences would have been catastrophic and the potential for harm to workers seemed remote and uncertain. Issues of workers' rights to know, the sustainability of the industry without occupational health controls, and the uncertainty of risk from Be were undoubtedly secondary to security issues **as they were understood at the time**. In hindsight, this was highly unfortunate but at the time it was not unreasonable, given that the world was in a bipolar 'Cold War' between two nuclear powers, the Soviet Union and the US, together with its nuclear-armed allies France and the United Kingdom. Later, the rationale for opposing revision of the standard seems to have been based on a calculus of risk/benefit, in which the perceived risks of inadequate military defence with nuclear weapons was replaced by the perceived benefit to society of Be alloys.

In the context of an industry central to national security, it is not clear that the issue could have played out in any other way, unless there was some means of making a gradual transition to a more protective standard or resolving the uncertainties over the standard test for Be sensitivity (which in combination with a positive chest film or CT scan or biopsy results makes the diagnosis of beryllium disease) at an earlier stage. The 2 μg/m^3 standard is widely recognised as not adequately protective and was shown to be so at the time. However, once it was established, it took on a life of its own and became 'sticky' — that is, difficult to dislodge — until the evidence became overwhelming. This may have been, in part, because the leap to 0.5 μg/m^3 was or appeared to be too great technically and raised fears that the defence industry would be disrupted, leaving the country unacceptably vulnerable. However, reluctance to accept that a change was needed appears to have been driven mostly by uncertainties over the blood test (BeLPT), which was still in development and was perceived as unproven, a perception helped along by its alignment with financial interests.

Toward the end, it is clear that the emerging motivation for delay was perceived risk to the company. Here again there is another, unstated side to the story. It is clear that much of the opposition was self-serving but the company could legitimately have been seen at the time to be what is now called in 'homeland security' terminology a 'critical industry', providing an essential service or product. This dynamic would have, again, conflated the company's interests with the national interest (along the lines of 'what's good for us is good for the nation') and provided a rationale for maintaining the status quo on the grounds (specious but persuasive) that the company needed to stay in business and profitable to meet a national need.

Acceptable risk and accountability in risk assessment

It became apparent as the issue dragged on that no standard was fully protective, because of the stochastic (probabilistic, rather than deterministic) nature of the immune response. When this is true, as it is of many allergens, of fine particulate air pollution, and of lead exposure in children, the problem becomes one of determining 'acceptable risk' based on social criteria. Modern societies usually choose one in a million risk of a serious outcome or death as the acceptable risk, although in practice risks on the order of one in a thousand are the norm in occupational health. In this case, the company management was trying to make this determination alone, without collective input, because they (corporately) believed that they understood the problem best. However, they did not, and they were working in a social vacuum, focused on the company's priorities and beliefs. In a democracy, the question of 'who gets to decide' is answered formally by 'the representative of the people', that is, the government, and informally by who has possession of the data.

In the event, the initial standard of 2 μg/m^3 obviously worked well to reduce pressure to lower the standard. (It has since been reduced, first to 0.5 μg/m^3 in 1998 and then to 0.2 in 1999 but only as an internal standard within the Department of Energy, not through adoption by OSHA.) Although the story (told by Merril Eisenbud, who was involved in its formulation) that the initial 2 μg/m^3 was worked out in a taxicab on the way to the decisive meeting and was revised upward at the last minute, suggests an overly casual approach, in the absence of scientific evidence for a threshold or a 'no-observed adverse effects level' a reasonable consensus based on informed opinion is not a bad substitute for data. It certainly worked to eliminate acute Be disease, which was initially the concern. A standards-setting committee consisting of informed experts is not unlike a Delphi group, making sequential estimates based on feedback from the scientific literature and from their peers. It resembles (imperfectly) the estimation of an a priori probability in Bayesian statistics. Insisting on the inadequacy of a standard which was lacking more rigorous science, when evidence did not exist, is like applying the legal and political standards of today to ancient history. It is also difficult to find experts with practical experience outside the industry or with no interest in the outcome of deliberations, making conflict of interest a given and a matter of degree.

Michaels and Monforton make the blanket statement that 'The interpretation of scientific data by those with financial incentives must be discounted.' However, financial incentives attach to almost everyone who has a professional interest in a particular topic, including those who receive support, to be critical of a position and offer expensive tests. Thus, the essential problems, beyond disclosure, are not the financial incentives but the degree of influence exerted on the investigator, the completeness of reporting, and the validity of the information. The validity question can be further unpacked into issues of honesty and integrity, data quality, methodological issues, bias, handling of uncertainty, correct scientific interpretation of complicated evidence, and whether selection or misclassification bias is introduced due to business or other activities that attach to the position of the party involved. (For example, workers at a particular plant in the Be industry may be different from other workers or workers in other plants, such that a study sponsored by the company may have a bias. But the same may also be true of a study performed by an academic researcher.) Professional and personal incentives, which may be as powerful as financial incentives, attach to everyone involved because once a position is taken publicly it is human nature to be emotionally invested in defending it.

To their credit, Michaels and Monforton use the term 'discounted' rather than 'ignored', but in practice few who advocate tighter regulation may make the distinction. In fact, exclusion of corporately-sponsored research and the 'grey literature' risks losing an immense body of valuable information. Society is already denied significant benefit by obstacles to accessing proprietary information. Current practices within the insurance industry, for example, together with rules against collusion and price-fixing, militate against sharing information that would be highly useful in establishing the health risk of various groups, such as workers covered by workers' compensation (Guidotti, 2000).

Seen in this light, and assuming that accountability is not possible in the adversarial setting of business interests, the issue reduces to one of transparency. Can the data be audited and the analysis reconstructed? Who will ensure the integrity of the auditors? In this regard the experience of the Health Effects Institute (HEI) is pertinent. HEI routinely commissions a reanalysis of data from the most significant studies it supports on air pollution health effects, a process that to date has confirmed the original findings in every case but is considered essential to acceptance of the findings by industry (in this case, the automobile manufacturing industry). This model is not so easily to apply to corporately sponsored research, however, because there is no external mechanism for guaranteeing quality assurance and no contractual obligation to cooperate with an audit or means of ensuring transparency.

Another model that may be applicable is the current drive to require drug companies to register clinical trials, so that those that have negative results or that demonstrate harmful effects cannot be buried. Establishing a data repository is a logical step in this process but there would of course be legitimate issues of business knowledge, anti-trust prohibitions, and proprietary information to navigate. How such an arrangement could be enforced when applied to corporately-sponsored research is not clear but a voluntary approach led by responsible companies would place considerable pressure on those that did not participate.

However, these are technical solutions and partial at best. The deeper issue is one of organisational behaviour and commitment to a wrong decision in the face of diminishing room to manoeuvre.

One could have made the point in 1983 that acceptance of the BeLPT, the blood test for immune sensitivity, would have protected the company through demonstration of due diligence, but at the time a consensus on the validity of the assay had not emerged. (As Michaels and Monforton pointed out, it was impeded by the machinations of a cooperative academic. Even today, the BeLPT has to be positive in two tests before a diagnosis is considered to be confirmed.) Michaels and Monforton make a major case for the idea that 'the absence of evidence is not evidence of absence', however in the case of the BeLPT there was abundant evidence but the performance of the test was disputed. Until the test was validated, it was not unreasonable for non-scientists to be sceptical. The deeper question is who determines when a method is valid: scientists, regulators, or corporate interests? Likewise, who determines when data are sufficient and when evidence is actually absent?

Faced with uncertainty and bolstered by intimations that the test may not be definitive, it was actually a logical (and, from their point of view, probably responsible) decision for the company to delay and to require further information. As time went on, this position may have become untenable scientifically but the stakes were also rising. A late admission that the assay was valid would have been tantamount to admitting that the company had stalled and allowed further cases. In short, the company was pulled along in a situation in which, as uncertainty over the test diminished, the stakes increased, perhaps exponentially, making it increasingly difficult to accept or stop questioning the test and making it paradoxically more attractive to defend their earlier position. Small wonder that, in a classic demonstration of organisational behaviour, the company leadership did not want to admit, and as individuals probably truly did not believe, that they had erred.

Lessons learned

The Brush Wellman experience demonstrates that a significant internal disincentive of companies to accept new findings is fear of liability and reputational damage. Add to this the perceived fiduciary responsibility to shareholders, the shame of admitting that decisions may have harmed workers, and the (probably inflated) costs of installing more stringent controls and it is easy to see how denial and rationalisation would be the mode of behaviour. In the case of Be, these measures were relatively expensive: separation of sensitised workers through Be-free buffer zones and containment and reassignment of sensitised workers.

Seen in that light, and assuming that the Brush Wellman leadership was generally honest in their own terms (on the face of it, a problematical assumption), the company could be viewed as being pulled along by events into an increasingly untenable situation, until their position was completely indefensible. It would be going too far to characterise this as a 'tragedy' for them, in the dramatic sense of a fatal flaw that brings down the protagonist. However, it is apparent that one problem with the narrative is that there was never a moment at which Brush Wellman could change direction without paying what it considered to be an unacceptable penalty. Because of legacy liabilities, the deep investment the company had in believing otherwise, and the slow evolution of the science, the management of the company appears to have been slogging through a tunnel of diminishing dimensions, seeing no exit and no path except what lay ahead. At the beginning, the issue was cost (probably overestimated, as it usually is), loss of market share, and saving face. At the end, it may have been massive financial and legal liability.

Perhaps the key issue is at what point an organisation can change course, when it is allowed to do so, and how it can do so given its internal drivers and culture. The question may need to be recast as how information controlled by the company can be effectively accessed, with protection, so that the leadership has a viable escape route from an impossible situation.

The essential question for reconstructing the company's behavioural and motivational history is, therefore, was there ever a point along the way where it was 'safe' for Brush to change course? Was there an opening that allowed internal forces within the company that might have better understood the issue to break with the management line and to accept the health risks of Be at low levels without what they perceived to be unacceptable consequences (and psychic pain)?

This does happen. Liggett & Myers, the American tobacco company, made a dramatic break with the rest of the industry in 1996 and both settled tobacco-related cases and unilaterally declared that it accepted that smoking is addictive (Borio, 2003). It did so because it saw a window of opportunity to reduce its risk and because it recognised that the industry position had become untenable. (There is no reason to think that they did so because it was right or for the greater good. It was a business decision, pure and simple.)

If one expects corporations, and the attitudes of corporate leadership, to change in response to new information, rather than to fight new information because of fear, denial, or risk of loss, there must be exit or escape opportunities. This may mean unpalatable choices and bright lines where today the picture is murky, such as opportunities to forgive legacy liabilities, legal defences (such as a clear definition of when due diligence has been achieved), and a threshold for sufficient knowledge (a clear standard of when knowledge about risk is sufficient to act, not just first awareness that there may be a problem). Organisations cannot be expected to change their positions unless they are given a 'way out' that may involve forgiving past liability and reducing punitive damages. (This is largely what happened with the DOE contract worker's compensation programme.)

The threat of strong grounds for legal action or board action by dissident shareholders introduces a new counterweight to the equation and is a bigger stick than it might first appear. It is also not necessary to assume that shareholders would force management to choose the path of conciliation out of self-interest to protect their equity, or that a righteous shareholder rebellion would be provoked by outrage over corporate behaviour. After all, most shareholders are apathetic and unengaged in corporate governance. Rather, management would know that if they did not act appropriately, dissident shareholders or hostile suitors could use their failure to act opportunistically for their own purposes, using the argument that they were destroying shareholder value and should be replaced. Also, large shareholders (such as pension funds) are interested in stability and yield and are likely to avoid investing in companies that fail to take opportunities to reduce their risk exposure.

The lessons from the Be case are unpleasant but clear: if corporations are expected to reverse course, there must be room for them to turn around. Pressure builds resistance and ultimately denial and may be counterproductive at times. Perception and judgment align with interests, and people on different sides of an issue see the problem differently. Correcting the system to facilitate resolution may require trade-offs with unpleasant implications. The opening of opportunities for bad corporations to escape legal or financial consequences is not an attractive solution from the moral perspective but may lead to the greatest good for the greatest number.

Another lesson from the Be case is that once a standard is set, it becomes 'sticky'. It develops a constituency and an infrastructure to support it. Changing a standard has to overcome inertia and the accumulated weight of experience and acceptance. A policy of sequential standard-setting based on scientific evidence is inherently flawed. There will always be new scientific information. It is more reasonable to expect that standards will become more stringent and to accept a realistic policy of continuous improvement, anticipating that standards evolve rather than pretending that each standard is definitive. Standards can be as much impediments as instruments of worker protection. A policy of continuing improvement and progression over time in reducing exposures is the natural alternative approach, although perhaps unattainable in the current political context. The problems with such a policy lie in initiating it and sustaining it in an equitable manner.

References

Borio, G., 2003, 'Tobacco timeline: The Twentieth Century 1950–1999: The Battle is Joined' (http://www.tobacco.org/resources/history/Tobacco_History20-2.html) accessed 13 February 2010.

Friedman, M., 1970, 'The social responsibility of business is to increase its profits', *New York Times Magazine*.

Guidotti, T.L., 2008, 'Occupational medicine and the creation of "difficult reputations"', *New Solutions*, (18/3) 288–298.

Guidotti, T.L., 2000, 'Occupational epidemiology [Occupational medicine in the 21st century:]', *Occupational Medicine* (London), (50/2) 141–145.

Michaels, D. and Monforton, C., 2008, 'Beryllium's public relations problem: protecting workers when there is no safe exposure level', *Public Health Reports*, (123/1) 79–88.

Pérez Carrillo, E.F., 2007, 'Corporate governance: shareholders' interests and other stakeholders' interests', *Corporate Ownership & Control*, (4/4) 96–102.

Santo Tomas, L.H., 2009, 'Beryllium sensitivity and chronic beryllium disease', *Current Opinion in Pulmonary Medicine*, *15*(2), pp. 165–169.

Stout, L.A., 2008, 'Why we should stop teaching Dodge v. Ford', *Virginia Law & Business Review*, (3/1) 164–176.

7 Tobacco industry manipulation of research

Lisa A. Bero (¹)

This chapter differs in some ways from the others in Volume 2 of *Late lessons from early warnings*. The history of 'second hand', 'passive' or 'environmental tobacco smoke' (ETS), to which non-smokers are exposed overlaps with the history of active smoking. Those affected include the partners and children of smokers, and the bartenders and other workers who have to work in smoky environments.

The focus in this chapter is on the strategies used by the tobacco industry to deny, downplay, distort and dismiss the growing evidence that, like active smoking, ETS causes lung cancer and other effects in non-smokers. It does not address the history of scientific knowledge about tobacco and how it was used or not used to reduce lung cancer and other harmful effects of tobacco smoke. There is much literature on this (²) and a table at the end of the chapter summarises the main dates in the evolution of knowledge in this area.

The chapter concentrates on the 'argumentation' that was used to accept, or reject, the growing scientific evidence of harm. Who generated and financed the science used to refute data on adverse health effects? What were the motivations? What kind of science and information, tools and assumptions were used to refute data on the adverse health of tobacco?

The release of millions of internal tobacco industry documents due to law suits in the US has given insights into the inner workings of the tobacco industry and revealed their previously hidden involvement in manipulating research. However, this insight is not available for most corporate sectors. The chapter discusses the possibilities of 'full disclosure' of funding sources and special interests in research and risk assessment in order to secure independence and prevent bias towards particular viewpoints.

While smoking bans are now being introduced in more and more countries, other industries are drawing inspiration from tobacco company strategies, seeking to maintain doubt about harm in order to keep hazardous products in the marketplace.

The chapter also includes a summary of the tobacco industry's role in shaping risk assessment in the US and Europe to serve its own interests.

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(²) For example, two contrasting yet complementary histories of cancer in general and smoking in particular are Davies (2007) and Keating (2009).

7.1 Introduction

This chapter describes the strategies that the tobacco industry has used to influence the design, conduct and publication of scientific research on second-hand smoke; and how the tobacco industry used this research in attempts to influence policy. It represents an expansion of an earlier article, 'Tobacco industry manipulation of research' by Bero (2005).

The primary motivation of the tobacco industry has been to generate controversy about the health risks of its products. The industry has used several strategies including:

1. funding and publishing research that supports its position;

2. suppressing and criticising research that does not support its position;

3. changing the standards for scientific research;

4. disseminating interest group data or interpretation of risks via the lay (non-academic) press and directly to policymakers.

The strategies used by the tobacco industry have remained remarkably constant since the early 1950s when the industry focused on refuting data on the harmful effects of active smoking, through to the 1990s, when the industry was more concerned with refuting data on the harmful effects of second-hand smoke. Tobacco industry lawyers and executives, rather than scientists, have controlled the design, conduct and dissemination of this research.

When data on risk appear to be controversial, users of the data should investigate the sources of controversy. This can be done only if interest group involvement in all steps of the risk determination process is transparent and fully disclosed. Since the tobacco industry's efforts to manipulate research are international endeavours and are shared by other corporate interests, individuals around the world should be aware of the strategies that the industry has used to influence data on risk.

Communicating accurate information on risk is essential to risk perception and risk management. Research findings, often from basic science, epidemiology and exposure or engineering research, provide the basis for information on risk. These research findings or 'facts' are, however, subject to interpretation and the social construction of the evidence (Krimsky, 1992). Research evidence has a context. The roles of framing, problem definition and choice of language influence risk communication (Nelkin, 1985). Furthermore, scientific uncertainties allow for a wide range of interpretation of the same data. Since data do not 'speak for themselves' interest groups can play a critical role in generating and communicating the research evidence on risk.

An interest group is an organised group with a specific viewpoint that protects its position (Lowi, 1979). Interest groups are not exclusively business organisations; they can comprise all kinds of organisations that may attempt to influence governments (Walker, 1991; Truman, 1993). Therefore, interest groups can be expected to select and interpret the evidence about a health risk to support their predefined policy position (Jasanoff, 1996). For example, public health interest groups are likely to communicate risks in a way that emphasises harm and, therefore, encourages regulation or mitigation of risk (Wallack et al., 1993). Industry interest groups are likely to communicate risks in a way that minimises harm and reduces the chance that their product is regulated or restricted in any way. Disputes about whether a risk should be regulated or not are sometimes taken to the legal system for resolution (Jasanoff, 1995). Thus, interest groups often have two major goals: to influence policy-making and litigation.

Beginning in the 1970s, the tobacco industry influenced the collection, interpretation and dissemination of data on risks of exposure to second-hand smoke. The analysis below suggests that this was history repeating itself; in the 1950s, the tobacco industry had used similar strategies to manipulate information on the risks of smoking. Moreover, other corporate interest groups appear to use similar tactics (Special Issue, 2005; White et al., 2009).

Many of the strategies available to interest groups — for example sponsoring, publishing and criticising research — are costly. Industry might therefore be expected to dominate examples of such activities because corporate interest groups are more likely to have the resources to launch expensive, coordinated efforts. In contrast, public health groups, which tend to act independently, are less likely to command such resources (Montini and Bero, 2001).

Industry examples may also predominate because some interest group activities have come to light through the documents released during the 'discovery' process in law suits. For example, the asbestos and tobacco industries were required to release large amounts of internal correspondence when they were sued by groups attempting to show that they were harmed by industry products.

7.2 Scientific community knowledge about the hazards of second-hand smoke exposure

Environmental tobacco smoke, or second-hand smoke, is a complex mixture of thousands of gases and fine particles emitted by burning tobacco products and from smoke exhaled by smokers, as well as smoke that escapes while the smoker inhales and some vapour-phase related compounds that diffuse from tobacco products. During the 1970s and 1980s, data on the harmful effects of exposure to second-hand smoke began to be published in the scientific literature. Seminal epidemiological studies in 1981 demonstrated that second-hand smoke exposure was associated with lung cancer (Hirayama, 1981). United States Surgeon General and National Academy of Sciences reports in 1986 concluded that second-hand smoke was a cause of disease (US DHHS, 1986; NRC, 1986).

A landmark European epidemiological study on lung cancer and second-hand smoke was initiated by the International Agency for Research on Cancer (IARC) in 1988 and published in 1998. The publication reported a 16 % increase in lung cancer risk for non-smoking spouses of smokers and a 17 % increase for non-smokers who were exposed in the workplace (IARC, 1998).

In 1992, the US Environmental Protection Agency (EPA) released a risk assessment classifying ETS as a Group A human carcinogen (US EPA, 1992). The tobacco industry criticised the methodology of the US EPA risk assessment for its study selection and statistical analysis. The industry also criticised the epidemiological design of the studies included in the risk assessment, the ways that these studies controlled for bias and confounding, and measured ETS exposure (Bero and Glantz, 1993). The EPA revised the report in response to valid criticisms and the report was approved by the Scientific Advisory Board. The report was improved but the sheer volume of tobacco industry comments that required consideration probably delayed its release. Although the science was valid, the tobacco industry successfully attacked the US EPA risk assessment in court on procedural grounds (Flue-Cured Tobacco Co-op vs. US EPA, 1998) and the tobacco industry had similar procedural objections to the report of Australia's National Health and Medical Research Council, 'The health effects of passive smoking' (NHMRC, 1997).

In 1997 the California EPA published the final report of a risk assessment entitled 'Health Effects of Exposure to Environmental Tobacco Smoke' (Cal-EPA, 1997). The California risk assessment was more comprehensive than the US EPA's assessment because it examined the association of second-hand smoke exposure, lung cancer and respiratory illness, as well as cardiovascular, developmental, reproductive and childhood respiratory effects. The California EPA risk assessment also addressed criticisms brought by the tobacco industry against the US EPA risk assessment. The California risk assessment was the result of a collaborative effort between the Office of Environmental Health Hazard Assessment (OEHHA) and the Air Resources Board (ARB), two of the six constituent organisations of the California EPA. The Scientific Review Panel that endorsed the report concluded that second-hand smoke is 'a toxic air contaminant' that 'has a major impact on public health' (Cal-EPA, 1997).

In June 2005 the California Scientific Review Panel approved an updated draft report on Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant (Cal-EPA, 2005). The report concluded that second-hand smoke exposure is causally associated with developmental effects (e.g. inhibited foetal growth, sudden infant death syndrome, pre-term delivery), respiratory effects (e.g. asthma, acute and chronic respiratory symptoms in children, middle ear infections in children), carcinogenic effects (e.g. lung cancer, nasal sinus cancer, breast cancer in younger, premenopausal women) and cardiovascular effects (e.g. heart disease mortality, acute and chronic heart disease, morbidity).

The growing evidence documenting the adverse health effects of second-hand smoke was clearly a threat to the tobacco industry as early as the 1970s. Restrictions on smoking could lead to reduced daily consumption of cigarettes and a decline in sales. The tobacco industry responded with its own science to the independently generated data on tobacco-related adverse health effects.

7.3 Tobacco industry strategies to subvert scientific knowledge

Policymaking is facilitated by consensus (Kingdon, 1984; Mazmanian and Sabatier, 1989; Sabatier, 1991). Scientific research, on the other hand, is characterised by uncertainty. The uncertainty that is familiar to scientists poses problems when decision-making occurs in a public forum. Thus, it is often to the benefit of corporate interest groups to generate controversy about evidence of a product's health risks because such controversy is likely to slow or prevent regulation of that product. Similarly, scientific debate over the data and methods used in risk assessment, for example, can hinder the development of the risk assessment (Stayner, 1999).

The release of previously secret internal tobacco industry documents as a result of the Master Settlement Agreement in 1998 has given the public health community insights into the tobacco industry's motives, strategies, tactics and data (Bero, 2003). These documents show that for decades the industry has been motivated to generate controversy about the health risks of its products. They have also revealed that the industry was concerned about maintaining its credibility as it manipulated research on tobacco (Bero, 2003).

The strategies used by the tobacco industry have remained remarkably constant since the early 1950s. During the 1950s and 1960s, the tobacco industry focused on refuting data on the adverse effects of active smoking. The industry applied the same tools it developed during that period when it subsequently refuted data on the adverse effects of second-hand smoke exposure during the 1970s through the 1990s.

A 1978 report prepared by the Roper Organization for The Tobacco Institute noted that the industry's best strategy for countering public concern about passive smoking was to fund and disseminate scientific research that countered research produced by other sources:

> 'The strategic and long-run antidote to the passive smoking issue is, as we see it, developing and widely publicizing clear-cut, credible, medical evidence that passive smoking is not harmful to the non-smoker's health' (Roper Organization, 1978).

Philip Morris promoted international research related to passive smoking in order to stimulate controversy, as described in the notes of a meeting of the UK [Tobacco] Industry on Environmental Tobacco Smoke, London, 17 February 1988:

> 'In every major international area (USA, Europe, Australia, Far East, South America, Central America and Spain) we are proposing, in key countries, to set up a team of scientists organized by one national coordinating scientist and American lawyers, to review scientific literature or carry out work on ETS **to keep the controversy alive**' (emphasis added) (Boyse, 1988).

The tobacco industry organised teams of scientific consultants all over the world with the main goal of stimulating controversy about the adverse health effects of second-hand smoke (Barnoya and Glantz, 2006; Chapman, 1997; Muggli et al., 2001; Grüning et al., 2006; Assunta et al., 2004).

A variety of studies show that industry sponsorship of research is associated with outcomes that are favourable for the industry (Lexchin et al., 2003; Barnes and Bero, 1998; Barnes and Bero, 1997). One possible explanation for this bias in outcome is that industry-sponsored research is poorly designed or of worse 'methodological quality' than non-industry-sponsored research. However, there is no consistent association between industry sponsorship and methodological quality (Lexchin et al., 2003).

Factors other than study design can affect the outcome of research, including:

- the framing or social construction of the research question;
- the conduct of the study;
- the publication (or not) of the study findings.

The tobacco industry has manipulated these other factors in a variety of ways. First, by using its funding mechanisms to attempt to control the research agenda and types of questions asked about tobacco. Second, the industry's lawyers and executives have been involved in the design and conduct of industry-supported research. Third, the tobacco industry has sponsored publications of its own funded research, and suppressed research not favourable to the industry.

Box 7.1 summarises the range of strategies that the tobacco industry has used for decades to manipulate information on the risks of tobacco. These strategies are described in more detail in the remainder of this section.

7.3.1 Strategy 1: fund research that supports the interest group's position

The first element in the tobacco industry's strategy to influence data on risk has been to sponsor research designed to produce findings that are favourable to the industry.

Funding research can stimulate controversy in multiple ways. First, it can put the research agenda

Box 7.1 Tobacco industry strategies to manipulate data on risk

1. Fund research that supports the interest group position.
2. Hide industry involvement in research.
3. Publish research that supports the interest group position.
4. Suppress research that does not support the interest group position.
5. Criticise research that does not support the interest group position.
6. Change scientific standards.
7. Disseminate interest group data or interpretation of risk in the lay press.
8. Disseminate interest group data or interpretation of risk directly to policymakers.

in the control of the interest group. Second, it can produce data to refute research on risk conducted by others. In addition to stimulating controversy, funding research serves other useful purposes for the tobacco industry. The research can be disseminated directly to policymakers and the lay press. It can provide good public relations for the tobacco industry by establishing it as a philanthropic body that funds scientific research. Similarly, funding research can increase the industry's credibility. One of the criteria that the Philip Morris Worldwide Scientific Affairs Programme considered when deciding whether to fund a research application was whether the research would enhance the credibility of the company (Malone and Bero, 2003).

The US tobacco industry funded research through its trade association, The Tobacco Institute (Bero et al., 1995; Hanauer et al., 1995), internally (e.g. internal company research), externally (e.g. by supporting the research of scientific consultants) and through sponsored research organisations. Tobacco industry lawyers and executives were involved in selecting which research to fund. Most of the research did not undergo any form of independent scientific peer review but was funded on the basis of its potential to protect the interests of the companies.

Lawyer involvement in research

In the mid-1990s, internal tobacco industry documents were circulated by industry whistle-blowers. By 1998, the availability of tobacco industry documents increased exponentially as a result of the settlement of a suit by the State of Minnesota and Blue Cross/Blue Shield against the major tobacco companies. The Master Settlement Agreement between the attorneys general of 46 states and Brown & Williamson/British American Tobacco, Lorillard, Philip Morris, RJ Reynolds, the Council for Tobacco Research and The Tobacco Institute released millions of additional documents to the public. These documents provide an unprecedented look at how tobacco industry lawyers were involved in the design, conduct and dissemination of tobacco industry-sponsored research (Bero, 2003). By involving lawyers in research, the tobacco industry protected their research activities from public discovery and kept their lawyers informed about science relevant to litigation.

The internal tobacco industry documents include descriptions of research that was funded directly by law firms. For example, the law firms of Covington and Burling, and Jacob and Medinger, both of which represent a number of tobacco company clients, funded research on tobacco (Bero et al., 1995). Lawyers selected which projects would be funded. The supported projects included reviews of the scientific literature on topics ranging from addiction to lung retention of particulate matter. The law firms also funded research on factors potential confounding the adverse health effects associated with smoking. For example, projects examined genetic factors associated with lung disease or the influence of stress and low-protein diets on health (Bero et al., 1995). Thus, some of the research funded by law firms served the purpose of deflecting attention away from tobacco as a health hazard and protecting the tobacco companies from litigation.

Other research was funded directly by the tobacco companies but lawyers were involved in selecting and disseminating these projects. For example, tobacco companies funded individuals to serve as consultants to prepare expert testimony for Congressional hearings, attend scientific meetings, review scientific literature or conduct research on the health effects of tobacco or second-hand smoke (Hanauer et al., 1995). At one tobacco company, Brown & Williamson, the legal department controlled the dissemination of internal scientific reports (Hanauer et al., 1995). The lawyers at Brown & Williamson developed methods for screening scientific reports from their affiliated companies in order to ensure that scientific information related to tobacco and health would be protected from discovery by legal privileges. In a memo dated 17 February 1986, J. K. Wells, the Brown & Williamson corporate counsel, outlined one method for protecting industry produced research data:

> 'The only way BAT [British American Tobacco] can avoid having information useful to plaintiff found at B&W is to obtain good legal counsel and cease producing information in Canada, Germany, Brazil and other places that is helpful to plaintiffs' (Wells and Pepples, 1986).

Although tobacco industry public statements claimed that the tobacco companies were funding objective research to gather facts about the health effects of smoking, lawyer involvement in the research served to control the scientific debate on issues related to smoking and health and protect from discovery scientific documents that were potentially damaging to the industry.

Research organisations

The tobacco industry also formed research funding organisations, which gave the appearance that the research they supported was independent of influence from the industry.

The **Council for Tobacco Research** (CTR) was formed by United States tobacco companies in 1954 as the Tobacco Industry Research Committee (TIRC). The industry stated publicly that it was forming the TIRC to fund independent scientific research to determine whether there was a link between smoking and lung cancer. However, internal documents from Brown & Williamson Tobacco Company have shown that the TIRC was actually formed for public relations purposes, to convince the public that the hazards of smoking had not been proven (Glantz et al., 1996).

Research that is sponsored by federal organisations or large foundations is typically peer reviewed by other researchers before funding is approved. Although the Council for Tobacco Research had a Scientific Advisory Board consisting of well respected researchers, not all of the research funded by the CTR was peer reviewed by this board. Beginning in 1966, tobacco industry lawyers became directly responsible for many of the funding decisions of the CTR. Between 1972 and 1991, the CTR awarded at least USD 14 636 918 in special project funding (Bero et al., 1995). Lawyers were not only involved in selecting projects for funding but also in designing the research and disseminating the results (Bero et al., 1995).

The research funded by CTR, although initially useful for public relations, became increasingly important for the tobacco industry's activities in legislative and legal settings. This evolution is described in a memo dated 4 April 1978 from Ernest Pepples, Brown & Williamson's vice president and general counsel, to J. E. Edens, chairman and CEO of Brown & Williamson Tobacco Company:

> 'Originally, CTR was organized as a public relations effort. … The research of CTR also discharged a legal responsibility. … There is another political need for research. Recently it has been suggested that CTR or industry research should enable us to give quick responses to new developments in the propaganda of the avid anti-smoking groups. … Finally, the industry research effort has included special projects designed to find scientists and medical doctors who might serve as industry witnesses in lawsuits or in a legislative forum' (Pepples, 1978).

The Pepples memo gives insight into why lawyers became increasingly involved in the selection of research projects for CTR.

The **Center for Indoor Air Research** (CIAR) was formed by Philip Morris, R. J. Reynolds Tobacco Company and Lorillard Corporation in 1988 (CIAR, 1988). The founding companies were joined by Svenska Tobaks A.B., a Swedish domestic tobacco company in 1994 (CIAR, 1994). The stated mission of CIAR was 'to create a focal point organisation of the highest caliber to sponsor and foster quality, objective research in indoor air issues **including environmental tobacco smoke**, and to effectively communicate research findings to a broad scientific community' (CIAR, 1989). CIAR's mission statement was modified in 1992 to eliminate the words referrring to environmental tobacco smoke (CIAR, 1992a; CIAR, 1992b). The elimination of research on second-hand smoke from the mission statement was followed by a shift in the research agenda of CIAR to one that would prevent it investigating the health effects of second-hand smoke.

Similar to the CTR, CIAR awarded 'peer-reviewed' projects, which were reviewed by a Science Advisory Board, and 'special-reviewed' projects, which reviewed by its Board of Directors consisting of tobacco company executives (Barnes and Bero, 1996). From 1989 to 1993, CIAR awarded USD 11 209 388 for peer-reviewed projects and USD 4 022 723 for special-reviewed projects (Barnes and Bero, 1996). Seventy per cent of the peer-reviewed projects funded by CIAR examined indoor air pollutants other than tobacco smoke. Thus, the industry appeared to be financing peer-reviewed projects through CIAR to enhance its credibility, to provide good publicity and to divert attention away from second-hand smoke as an indoor air pollutant.

In contrast to the peer-reviewed projects, almost two-thirds of CIAR's special-reviewed projects were related to second-hand smoke (Barnes and Bero, 1996). In addition, most special-reviewed projects studied exposure rather than health effects. It is therefore possible that the tobacco industry was funding research through CIAR to develop data it could use to support its frequent claim that persons are not exposed to sufficient levels of passive smoke to cause any serious adverse health effects (Tobacco Institute, 1986).

The tobacco industry may have also been funding special-reviewed research through CIAR to develop scientific data that it could use in legislative and legal settings. Six CIAR-funded investigators have testified at government hearings. All of the statements submitted by them supported the tobacco industry position that second-hand smoke exposure is not harmful to health. Data from two of CIAR's special-reviewed projects were presented at hearings held by the United States Occupational Safety and Health Administration (OSHA) regarding its proposed indoor air quality regulation. Data from a third special-reviewed project was presented at a Congressional hearing related to a proposed ban on smoking on commercial aircrafts. One CIAR-funded study was investigated extensively by the United States Congressional Subcommittee on Health and the Environment after it was cited in testimony before numerous government agencies. The CIAR-funded study had concluded that, with good building ventilation, clean air could be maintained with moderate amounts of smoking (Turner et al., 1992) and was used to support testimony that indoor smoking restrictions are not necessary. However, the Congressional Subcommittee found that data for this study had been altered and fabricated. An earlier CIAR-funded study by the same organisation was also severely compromised because The Tobacco Institute selected the sites where passive smoking levels were measured for the study (Barnes and Bero, 1996).

The Center for Indoor Air Research was disbanded as part of the US Master Settlement Agreement in 1998. However, in 2000, Philip Morris re-created an external research programme called the 'Philip Morris External Research Program' (PMERP) with a structure similar to that of CIAR. Like CIAR, PMERP's grant review panel consisted of a cohort of external peer reviewers, a science advisory board, and an internal, anonymous review and approval committee. Three of the six advisory board members had a previous affiliation with CIAR. The majority of the named reviewers also had previous affiliations with the tobacco industry (Hirschhorn et al., 2001).

Research is an international endeavour
The tobacco industry applied the strategy of covertly funding research on an international scale. In Latin America and Asia, tobacco companies, working through the law firm Covington and Burling, developed a network of physician and scientist consultants to prepare and present data to refute claims about the harms of second-hand smoke (Assunta et al., 2004; Barnoya and Glantz, 2002). In Germany, tobacco companies and the German Association of the Cigarette Industry developed a similar team of consultants and funded research through various foundations and research organisations (Grüning et al., 2006). In many cases, the industry employed the next strategy discussed below: hiding its support for the research.

In summary, funding research serves multiple purposes for the tobacco industry. The research that is directly related to tobacco has been used to refute scientific findings suggesting that the product is harmful and sustain controversy about adverse effects. Tobacco industry-supported research has been used to prepare the industry for litigation or legislative challenges. The industry may also have funded research not directly related to tobacco in order to generate good publicity, enhance industry credibility and to distract from tobacco products as a health problem.

7.3.2 *Strategy 2: hide industry involvement in research*

A defining characteristic of the tobacco industry's response to independent evidence of the harms of second-hand smoke has been attempts to hide its involvement in refuting this evidence. In both of the cases described below, tobacco companies were secretly involved in generating data to suggest that second-hand smoke was not harmful and suppressing data suggesting that it was.

Philip Morris European research programme on second-hand smoke
As early as 1968, executives at Philip Morris began planning a new biological research facility that

would focus on examining the effects, including carcinogenic effects, of second-hand smoke exposure in various animal species. In 1970, Philip Morris purchased a research facility in Germany, Institut für Industrielle und Biologische Forschung GmbH (INBIFO) (Diethhelm et al., 2004). Philip Morris hired Ragnar Rylander, a Swedish university professor, as the coordinator of INBIFO. Rylander communicated INBIFO's research findings to Philip Morris executives in the United States, who would then decide whether to disseminate the research more widely or keep it secret. Research that remained unpublished included studies providing evidence that 'sidestream smoke' (which enters the air from a burning cigarette, cigar or pipe) is more toxic than 'mainstream smoke' (which is inhaled directly) (Diethhelm et al., 2004). Published research included an epidemiological study suggesting an association between lung cancer and green tea, a finding that would be useful to the tobacco industry in distracting from the harms of second-hand smoke (Tewes et al., 1990).

One of the most striking features of the INBIFO programme was that its coordinator, Ragnar Rylander, had long-standing and secret links to the tobacco industry. Thus, he conferred a false sense of credibility to the programme. Professor Rylander's association with the tobacco industry was investigated by an official university committee, the Fact Finding Commission of the University of Geneva. The committee concluded that Rylander was acting as a sponsored agent of the tobacco industry, rather than as an independent researcher when he testified as a scientific expert, organised scientific congresses and directed research at INBIFO (Fact Finding Commission, 2004). An extensive analysis of internal tobacco industry documents found that Rylander took no initiatives 'in the area of [second-hand smoke research] without first consulting extensively with his contacts within the tobacco industry'(Fact Finding Commission, 2004).

Tobacco industry creation and dissemination of a study on second-hand smoke

The tobacco industry's development of the Japanese Spousal Smoking Study provides another example of industry involvement in designing, conducting and disseminating research, and its efforts to hide this involvement.

In 1981, Takeshi Hirayama published an influential study showing an association of second-hand smoke exposure and lung cancer (Hirayama, 1981). The Hirayama study has been voted the most influential paper ever on second-hand smoke (Chapman, 2005) and was the most frequently cited study in regulatory hearings on smoking restrictions (Montini et al., 2002). In these hearings, tobacco industry representatives have argued that the Hirayama study is flawed due to misclassification bias (Bero and Glantz, 1993; Schotland and Bero, 2002). Furthermore, analysis of internal tobacco industry documents by Hong and Bero (2002) has shown how the tobacco industry hid its involvement in creating a study, the Japanese Spousal Smoking Study, to support its arguments about misclassification bias.

The tobacco industry documents reveal that although the Japanese Spousal Smoking Study was undertaken by named Japanese investigators, project management was conducted by Covington and Burling (a tobacco industry law firm), the research was supervised by a tobacco industry scientist and a tobacco industry consultant assisted in reviewing the study design and interpreting the data (Hong and Bero, 2002). The documents show that the tobacco companies that funded the study did not want any of these individuals named as co-authors on any of the resulting scientific publications. Although the tobacco companies considered using the Center for Indoor Air Research (CIAR) as 'a cover' to fund the study, three companies agreed to fund the study directly. Progress reports for the study were prepared on Covington and Burling stationery. When the study was prepared for publication, the tobacco industry consultant was the sole author (Lee, 1995). The publication acknowledged 'financial support from several companies of the tobacco industry' (Lee, 1995). This acknowledgement tells the reader little about who was actually involved in the design, conduct and publication of the study. The hidden roles of the tobacco company lawyers and scientist raise questions about who was accountable for the research (Hong and Bero, 2002).

The analysis of tobacco industry documents (Hong and Bero, 2002) was noticed by Dr E. Yano, one of the Japanese investigators who was originally involved in the Japanese Spousal Smoking study. Dr Yano had been unaware that Dr Lee had published the study. He had retained the original data from the study and has reported that Dr Lee's published analysis excluded data that did not support misclassification bias (Yano, 2005). Dr Yano demonstrated that using the full data from the Japanese Spousal Smoking Study changes the conclusion of Lee's published report. After 10 years, the scientific community was able to obtain data that had been suppressed by the tobacco industry.

7.3.3 *Strategy 3: publish research that supports the interest group position*

Research has little impact unless it can be cited. The tobacco industry has realised that funding research that supports its interests must be followed by the dissemination of such research in scientific literature. The tobacco industry uses several vehicles to publish the findings of its sponsored research, including funding the publication of symposia proceedings, books, journal articles and letters to the editors of medical journals. To suggest that the research it funds meets scientific standards and that there is substantial support for its position, the tobacco industry then cites its industry-funded, non-peer-reviewed publications in scientific and policy arenas.

Symposium proceedings

Scientific meetings or symposia often result in the publication of books or journal articles that summarise the research presented there. The pharmaceutical industry, for example, publishes reports of symposia containing poor quality and unbalanced articles favourable to particular drugs (Bero et al., 1992; Rochon, 1994). The tobacco industry has sponsored numerous symposia on second-hand smoke (Bero et al., 1994) and paid for scientific consultants to organise and attend these meetings (Barnoya and Glantz, 2002, 2006; Muggli et al., 2001).

Between 1965 and 1993, reports on 11 symposia on passive smoking were published. Six were published as special issues of medical journals, while five were published independently as books. None of the symposia was peer reviewed; six were sponsored by the tobacco industry or its affiliates such as the Center for Indoor Air Research, The Tobacco Institute and Fabriques de Tabac Reunies. Two of the six industry-sponsored symposia did not explicitly acknowledge industry sponsorship. The tobacco industry sometimes sponsored conferences through independent organisations so that their sponsorship would be hidden (Bero et al., 1995; Bero et al., 1994).

The symposia on passive smoking were attended by an international group of scientists and held across the world, including Europe, the United States, Canada, Japan and Argentina. One symposium report was published in Spanish. CTR special projects were often used to support scientists to prepare talks for conferences and to send scientists to conferences (Glantz et al., 1996).

On the surface, articles from symposia look like articles from peer-reviewed journals. To test the hypothesis that symposium articles on second-hand smoke differ in content from articles on second-hand smoke appearing in scientific journals, Bero et al. (1994) compared the symposia articles to a random sample of articles on passive smoking from the scientific literature and to two consensus reports on the health effects of passive smoking (US DHHS, 1986; NRC, 1986). Of the symposium articles, 41 % (122/297) were reviews, compared with 10 % (10/100) of journal articles. Symposia articles were significantly more likely than journal articles to agree with the tobacco industry position that tobacco is not harmful (46 % compared to 20 %), less likely to assess the health effects of passive smoking (22 % compared to 49 %), less likely to disclose their source of funding (22 % compared to 60 %), and more likely to be written by tobacco industry-affiliated authors (35 % compared to 6 %). Symposium authors published a lower proportion of peer-reviewed articles than consensus report authors (71 % compared to 81 %) and were more likely to be affiliated with the tobacco industry (50 % compared to 0 %) (Bero et al., 1994).

Symposia proceedings can potentially influence policy because they are often cited as if they are peer-reviewed articles and balanced reviews of the scientific literature, with no disclosure of their industry sponsorship. For example, tobacco industry-sponsored symposia on second-hand smoke have been used to attempt to refute both peer-reviewed journal articles and risk assessments of second-hand smoke (Bero and Glantz, 1993; Schotland and Bero, 2002; Chapman et al., 1990). Symposia articles have also been cited in tobacco industry public relations materials and the press (e.g. Tobacco Institute, 1986); and as the consensus of a gathering 'of leading experts from around the world' who disagree with the published literature on passive smoking (Johnston and Sullum, 1994).

In summary, tobacco industry-sponsored symposia articles on second-hand smoke consist, in large part, of review articles that reach different conclusions about the health effects of passive smoking than peer-reviewed journal articles or consensus reports. Furthermore, symposia are more likely to publish research that discusses issues that distract from tobacco as a health problem. The tobacco industry affiliations of symposia authors suggest that industry control over publication and research funding is likely to influence the presentation of findings.

Quality of tobacco industry-funded symposium publications

When policymakers, judges, lawyers, journalists and scientists are presented with tobacco industry-sponsored symposium articles, they must decide whether to incorporate these publications into their deliberations. Although the lack of balance and peer review suggests that tobacco industry-sponsored literature may lack scientific rigour, the issue of peer review and study quality is a contentious subject. Methodological quality is determined by the presence or absence of study design characteristics aimed at reducing bias, such as blinding, follow-up, controlling for confounding and controlling for selection bias.

Barnes and Bero (1997) assessed the methodological quality of the research presented at symposia. As articles from pharmaceutical industry sponsored symposia have been found to be of poor methodological quality (Rochon, 1994; Cho and Bero, 1996) it was hypothesised that articles from tobacco industry-sponsored symposia would be poorer in methodological quality than peer-reviewed journal articles. Other characteristics of articles were evaluated that might be associated with quality, such as disclosure of the source of research sponsorship and the study's conclusions, topics and design. Original research articles on the health effects of second-hand smoke published in peer-reviewed journals were compared to those published in non-peer-reviewed symposium proceedings from 1980 to 1994.

The study found that peer-reviewed articles were better quality than symposium articles independent of their source of funding, their conclusions on the health effects of second-hand smoke and the type of study design. Peer-reviewed articles received higher scores than symposium articles for most of the criteria evaluated by the quality assessment instrument.

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Quality of tobacco industry-sponsored review articles

Policymakers and clinicians often rely on review articles to provide accurate and up-to-date overviews of a topic of interest (Montini and Bero, 2001). As already noted, a large proportion of symposium articles are reviews of the health effects of second-hand smoke (Bero et al., 1994) and are frequently cited in response to government requests for information (Bero and Glatz, 1993; Montini et al., 2002; Schotland and Bero, 2002). In view of their importance in guiding policy, it is somewhat disconcerting that published review articles often reach markedly different conclusions about the adverse health effects of second-hand smoke.

Barnes and Bero (1998) conducted a study to evaluate the quality of review articles on the health effects of passive smoking and to determine whether the conclusions of review articles are primarily associated with their quality or with other article characteristics. The a priori hypotheses were that review articles concluding that passive smoking is not harmful would tend to be poor in quality, published in non-peer-reviewed symposium proceedings and written by investigators with tobacco industry affiliations. The topic of the review and the year of publication were also reviewed as potential confounding factors.

In the sample of 106 review articles, the only factor associated with concluding that passive smoking is not harmful was whether the author of the review article was affiliated with the tobacco industry (Barnes and Bero, 1998). As shown in Table 7.1, review articles concluding that passive smoking is not harmful were about 90 times more likely to be funded by the tobacco industry than those concluding that second-hand smoke is harmful. Methodological quality, peer-review status, outcomes studied in the reviews, and year of publication were not associated with the conclusions of the articles. Thus, sponsorship of review articles by the tobacco industry appears to influence the conclusions of these articles, independent of methodological quality.

The tobacco industry has argued that independent reviews of second-hand smoke are flawed because studies with statistically significant results are more likely to be published than studies with statistically non-significant results (Dickersin et al., 1992; Shook, Hardy and Bacon, 1993). The industry argues that publication bias — the tendency to publish work with statistically significant results — prevents the identification of all relevant studies for reviews of the health effects of second-hand smoke (e.g. Armitage, 1993). Bero et al. (2004) conducted a preliminary

Table 7.1 Factors associated with review articles concluding that passive smoking is not harmful to health: multiple logistic regression analysis

Factor	Odds ratio (95 % CI)	P value
Quality score	1.5 (< 0.1–67.5)	0.83
Not peer reviewed v. peer reviewed	1.3 (0.3–5.4)	0.70
Tobacco industry sponsored v. not tobacco industry sponsored	88.4 (16.4–476.5)	< 0.001
Outcomes — lung cancer v. other clinical outcomes	1.6 (0.2–10.3)	0.63
Heart disease v. other clinical outcomes	1.6 (0.2–14.7)	0.67
Year of publication	1.1 (0.9–1.3)	0.45

Source: Barnes and Bero, 1998.

study of publication bias showing that statistically non-significant studies are published: approximately 20 % of the published peer-reviewed articles on passive smoking present statistically non-significant findings.

By interviewing investigators studying second-hand smoke and health effects, Misakian and Bero (1998) determined that studies with statistically non-significant results take about two years longer to be published than those with statistically significant results. For studies conducted in humans, only statistical significance was predictive of time to publication, not study design or sample size. Thus, the tobacco industry's argument that statistically non-significant results are not published is invalid.

Since statistically non-significant results are published but take longer to be published than statistically significant results, reviews of research should attempt to include unpublished data and be periodically updated. Reviews conducted by the Cochrane Collaboration, for example, attempt to identify unpublished studies and include them in reviews if they meet quality standards. Cochrane reviews, which are published online, are also regularly updated (Bero and Rennie, 1995).

7.3.4 *Strategy 4: suppress research that does not support the interest group position*

Interest groups are eager to fund and publish research that supports their position and hesitant to publicise research that does not. In some cases, tobacco industry lawyers and editors have edited their externally funded scientific research publications; in other cases they have prevented publication of the research (Hong and Bero, 2002; Muggli et al., 2001; Barnoya and Glantz, 2002). Editing has included attempts to obscure evidence on adverse health effects by using the code word 'zephyr' for 'cancer' in internal memos about health effects research (Glantz et al., 1996; BAT, 1956).

Research conducted internally by tobacco companies or through industry-controlled research organisations is likely to be suppressed if it is unfavourable to the industry. For example, the German tobacco industry-supported research organisation, INBIFO, did not publish its research showing that sidestream smoke is more toxic than mainstream smoke (Grüning et al., 2006).

Tobacco companies have also conducted internal research on the use of chemical additives to reduce, mask or otherwise alter the visibility, odour, irritation or emission of second-hand smoke. Some of these studies showed that the additives increased emissions of toxins such as carbon monoxide or the carcinogenic substances, N'-nitrosoniornicotine and benzo(a) pyrene (Conolly et al., 2000). Virtually none of this research has been published in scientific literature, however, and data on additives is not typically available to public health policymakers.

7.3.5 *Strategy 5: criticise research that does not support the interest group position*

Another strategy that the tobacco industry has used to stimulate controversy about research on risk has been to criticise research that is not favourable to its position. Science is improved by constructive criticism. However, the tobacco industry has misused legitimate means of scientific debate, such as letters to the editor of scientific journals and editorials. The tobacco industry has also used less legitimate methods to criticise research, including attacking the integrity of researchers or obtaining data through lawsuits and reanalysing it using inappropriate techniques (Barnes et al., 1995).

In order to get its views into public commentary on risk assessments (Bero and Glantz, 1993; Schotland and Bero, 2002) or the lay press (Chapman et al., 1990), the tobacco industry has frequently cited letters to the editor as if they were peer-reviewed journal articles. Letter authors affiliated to the tobacco industry often fail to disclose their affiliation. These findings support the suggestions by a number of journal editors that letter writers should disclose potential conflicts of interest and that journals should peer review letters (Rennie, 1993).

As mentioned above, the tobacco industry has maintained large teams of international scientific consultants (Chapman, 1997; Muggli et al., 2001; Barnoya and Glantz, 2002). A major goal of the tobacco industry's scientific consultancy programme was to refute data about the harmful effects of tobacco. Industry consultants were paid to criticise independent research on tobacco and second-hand smoke via participation in scientific conferences; publications such as conference proceedings, journal articles and books; media appearances; testimony at tobacco litigation trials; forming a scientific society on indoor air; and preparing statements for government committees. The industry consultant programmes were international and were used to discredit research conducted by non-industry scientists around the world (Chapman, 1997; Muggli et al., 2001; Barnoya and Glantz, 2002).

7.3.6 Strategy 6: changing scientific standards

As described above, the tobacco industry has devoted enormous resources to attacking and refuting individual scientific studies. In addition, the industry has attempted to manipulate scientific methods and regulatory procedures for its benefit. The tobacco industry has influenced the debate around 'sound science' (Ong and Glantz, 2001), standards for risk assessment (Hirschhorn and Bialous, 2001), international standards for tobacco and tobacco products (Bialous and Yach, 2001) and laws related to data access and quality (Baba et al., 2005).

The tobacco industry has played a major role in developing ventilation standards for indoor air quality and in establishing international standards for tobacco and tobacco products. The International Organization for Standardization (ISO) develops international standards for tobacco and tobacco products, including the measurement of tar and nicotine yield. The tobacco industry, working through the Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA) gathered scientific evidence for ISO and suggested the standards that were adopted (Bialous and Yach, 2001). These standards incorrectly imply that there are health benefits from low-tar and low-nicotine products (Djordjevic et al., 1995). The tobacco industry has also been involved in developing ventilation standards for over 20 years. The industry influenced the development of ventilation standards by the American Society of Heating, Refrigeration, and Air Conditioning Engineers (ASHRAE) by generating data and presenting it to the committee (Bialous and Glantz, 2002). This resulted in a standard that ignores the health effects of second-hand smoke exposure, concentrating instead on a 'comfort' standard.

In the early 1990s, the tobacco industry launched a public relations campaign about 'sound science' and 'good epidemiological practices' (GEP) and used this rhetoric to criticise government reports, particularly on the harms of environmental tobacco smoke. All scientists agree that research should be rigorously conducted. But the 'sound science' and 'GEP' campaigns were public relations efforts controlled by industry executives and lawyers to promote unreasonably high standards of proof about the harm caused by the industry's products. For example, 'sound science' rhetoric argues that epidemiological studies can never establish evidence of harm because they cannot 'prove' causality. This approach ignores the fact that a comprehensive assessment of risk involves considering all the evidence related to a toxin, not just the epidemiology (Ong and Glantz, 2001).

The tobacco industry also developed a campaign to criticise the technique of risk assessment of low doses of a variety of toxins (Hirschhorn and Bialous, 2001). The tobacco industry worked with the chemical, petroleum, plastics and chlorine industries to develop its criticisms of risk assessment. In fact, the first version of GEP was drafted by the Chemical Manufacturers Association. After about ten years, by the late 1990s, the industry's 'sound science' public relations campaign ended. The tobacco industry then turned to advancing the 'sound science' concept through legislation (Baba et al., 2005).

One major goal of the tobacco industry has been to obtain data from independent studies and reanalyse it using 'sound science' criteria to reach different conclusions. Philip Morris, for example, used a three-step strategy to obtain data:

1. asking the researchers for the data directly;

2. litigation;

3. encouraging the enactment of policies that release data (Baba et al., 2005).

The industry's efforts resulted in 'sound science legislation': laws that influenced access to data and standards for data analysis.

In 1998, the United States Congress enacted a data access law as a rider to the Fiscal Year 1999 Omnibus Appropriations Act (US Congress, 1999). The law, for the first time, made all data produced under federally funded research studies available on request through the Freedom of Information Act (FOIA) (Zacaroli, 1998). Two years after the adoption of the data access provision, another amendment was added to the 2001 Omnibus Appropriations Act. The Data Quality Act (2000) requires the Office of Management and Budget to develop government-wide standards for data quality in the form of guidelines. Individual federal agencies must promulgate their own conforming guidelines based on OMB's model and adopt standards that 'ensure and maximise the quality, objectivity, utility and integrity of information disseminated' by federal agencies (OMB Watch, 2002). The standards to be adopted were created by the industry sponsors, not independent researchers.

While the public had an opportunity to comment on implementing the laws, these amendments were initially passed and adopted without a legislative hearing, committee review or debate (Renner, 2002). The scientific, academic research and public health communities voiced concerns during the public comment period about potential problems with confidentiality of medical information, discouragement of research subjects, misinterpretation of incomplete or prematurely released data sets, delay of research, protection of national security information, and administrative and financial burdens (AAAS, 1999). The research community was also concerned that these measures were supported by industry groups seeking to contest environmental and other regulations (Zacaroli, 1998).

Although the tobacco industry intended to hide its involvement in the data access and quality acts, internal industry documents reveal that these policies were driven by tobacco industry efforts to coordinate corporate interests. Tobacco industry strategies to advance sound science legislation included (Baba et al., 2005):

- demonstrating that the public cares about the issue by sponsoring a poll on issues of data access and rules of epidemiological studies that can be made public;
- leveraging allies and groups that have already taken a stand on the issue;
- using scientists and technical conferences to focus on the issue;
- encouraging a small group of members of Congress to take a stand on the issue;
- encouraging the Administration to take a stand for sound science;
- mobilising allied industries (i.e. fishing, utilities, waterworks) to lobby their local representatives;
- helping to organise coalitions for other epidemiological issues coming up soon (e.g. fishing industry, mercury, methyline chloride);
- educating and mobilising the business community on sound science v. junk science and the federal legislative/regulatory process;
- using states to generate action — conducting briefings in states on epidemiological studies and the need for uniform standards and encouraging the passage of state laws;
- developing broad bipartisan support for 'freedom of information' with regards to the data behind regulations and laws;
- leveraging lobbyists to contact key legislative members;
- briefing the media;
- briefing business coalitions on the need for data access;
- using the Congressional Science Committee to influence Congress.

Together, the data access and data quality acts provide a mechanism for challenging the scientific merit of data outside scientific journals and other channels of scientific review (McGarity, 2004; Kaiser, 1997). As scientists, legal experts and environmentalists have pointed out, however, the data access and data quality riders have the potential to block agencies from using emerging science from non-industry sources and to slow the regulatory process (Kaiser, 2003; Hornstein, 2003; Shapiro, 2004). The laws can be used to prevent future policies and to repeal existing policies that do not meet the data quality standards. The laws could shift the scientific standards of data used for policy purposes to favour standards promulgated by industry. Finally, access to data and quality standards are not applied equitably; they only apply to data generated with government funding, not industry funding.

Panel 7.1 Shaping risk assessment in the US and the EU: the role of the tobacco industry

Katherine Smith, Anna Gilmore and Gary Fooks

The interest of Philip Morris in shaping risk assessment was precipitated by the US EPA risk assessment of environmental tobacco smoke (ETS), which resulted in ETS being categorised as a class A human carcinogen (Hirschhorn and Bialous, 2001). Philip Morris challenged the assessment as part of its broader 'sound science' campaign (Ong and Glantz, 2001). This involved lobbying for laws requiring that:

- epidemiological studies meet a particular set of criteria or standards before they can officially inform policy decisions;
- epidemiological data used in publicly funded studies be made available through freedom of information requests.

Although the tobacco industry's campaign was ultimately unsuccessful in overturning the EPA's classification of ETS, it did manage to place 'a cloud over its validity' until 2002 (Muggli et al., 2004), leading to delays in subsequent introduction of protective legislation. Further, Philip Morris had some success in introducing data access laws and shaping the Data Quality Act (2000) (Baba et al., 2005).

Philip Morris believed that a similar campaign might be even more effective in Europe, where officials had not yet taken up the scientific threat of ETS to the same extent. From the mid-1990s onwards, therefore, it focused its campaign more heavily on Europe. Here, informed by what the Chemical Manufacturers Association had termed 'good epidemiological practice' (GEP), Philip Morris concentrated on lobbying for a mandatory set of criteria or standards that epidemiological studies would have to meet before they could be officially considered by policymakers in Europe (Ong and Glantz, 2001). The Philip Morris standards for 'good epidemiological practice' included a requirement for evidence relating to relative risks of less than 2.0 to be disregarded as too weak to warrant policy intervention.

As of late 2000 Ong and Glantz (2001) concluded that, despite the efforts of Philip Morris, 'no European Union resolution on GEP had been produced'. As far as we are aware, this remains the case.

British American Tobacco (BAT) managers studied the Philip Morris campaigns carefully and from 1995 onwards considered lobbying for a mandatory requirement for 'structured risk assessment' in EU policymaking because they believed it could be used to prevent the introduction of public smoking restrictions (Smith et al., 2010; BAT, 1995 and 1996). By this stage, the industry was well aware of the negative health impacts of second-hand smoke and was simultaneously trying to influence the evidence-base on this issue. BAT managers believed that 'a legislated demand for structured risk assessment', governed by strict 'rules for the assessment of epidemiological and animal data' would 'remove the possibility of introducing public smoking restrictions that are based on risk claims' (BAT, 1995).

Our analysis of BAT's internal documents has not yet established precisely what BAT managers meant when they used the term 'structured risk assessment'. All of the documents with titles indicating that they include detailed information on this issue have been redacted (3).

A 1995 BAT document makes it clear that the company's interpretation of 'risk assessment' involved a set of 'rules for the assessment of epidemiologic and animal data', which BAT managers believed would, if applied, make it 'apparent that ETS has not been proven to be a cause of disease in non-smokers' (BAT, 1995).

BAT managers wanted to use risk assessment as a way of limiting officials' discretion. For example, a document discussing the company's efforts to influence risk assessment says: 'The challenge will be to persuade government departments to subordinate policy or judgemental considerations in favour of scientific rigour in risk assessment' (Gretton, undated [circa 1995]).

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(3) See for example BAT (1991 and 1996). The Legacy Tobacco Documents Library website, which hosts these documents, states that the term 'redacted', 'Indicates whether the document contains words or sentences that were erased (redacted) by the tobacco company due to confidentiality issues (i.e. trade secrets, attorney/client privileges) before the document was publicly released' (University of California, 2011).

Panel 7.1 Shaping risk assessment in the US and the EU: the role of the tobacco industry (cont.)

In practice, this constituted a way of undermining the precautionary principle as a basis for policy decisions.

The key innovation of BAT's European campaign was the decision to focus on promoting risk assessment within a framework of 'cost-benefit analysis', a term that BAT used interchangeably with business impact assessment (see Smith et al., 2010). This had the additional effect of embedding economic considerations into the risk assessment process, which would also require interventions to protect the public against particular risks to be justified on the basis of economic costs (BAT, 1996; European Policy Centre, 1997).

BAT initially sought advice on how to shape risk assessment in the EU from the US advisers to Philip Morris, Covington and Burling (Covington and Burling, 1996). They advised BAT that although there was little interest in risk assessment within the European Commission at the time it might be possible to include 'structured risk assessment' in detailed guidance for business impact assessments, which had been flagged as a priority for the European Commission in 1996.

BAT was aware that a campaign for regulatory reform with known links to the tobacco industry was unlikely to succeed (Honour, 1996). It had been advised to work through a 'front group' and to recruit other companies with similar interests, such as other large firms in regulated sectors (MacKenzie-Reid, 1995). Following this advice, BAT approached the European Policy Centre (a prominent Brussels-based think tank with strong links to the Commission) to lobby for regulatory reforms on its behalf (Smith et al., 2010). BAT and the European Policy Centre then jointly set about recruiting other business interests to this campaign (Smith et al., 2010). These companies, which included large corporations from the oil, chemical and pharmaceuticals sectors, established an invitation-only sub-group within the European Policy Centre, known as the Risk Forum (Smith et al., 2010).

These efforts contributed to certain amendments to the Treaty on European Union (EU, 1997), placing a legal duty on the Commission to 'consult widely' and to minimise the potential 'burden' of policy changes on 'economic operators' and others (EU, 1997). BAT interpreted this to mean that business impact assessment and risk assessment were now mandatory within EU policymaking. The company perceived this as 'an important victory' (BAT, undated).

The guidelines for EU officials on how to undertake impact assessment have been revised several times since and now incorporate guidance on undertaking risk assessment (European Commission, 2009).

In 2006–2007, under pressure to open up to civil society organisations and other members of the European Policy Centre (which was under new leadership), the coalition of companies involved in the think tank's Risk Forum left and established a separate organisation called the European Risk Forum. This group describes itself as 'an expert led, not-for-profit think tank' (European Risk Forum, 2008a), despite solely representing corporate interests, virtually all of which are connected to the chemical and tobacco industries. This was confirmed via personal correspondence from the Forum's chair, Dirk Hudig, in February 2010. The European Risk Forum is now actively encouraging the European Commission to adopt a more structured approach to risk assessment and risk management (European Risk Forum, 2008b), although it remains unclear precisely what this involves.

Recent analyses suggest that these corporate efforts have been somewhat successful in redefining policymakers' understandings of and responses to risks, including those that limit use of the precautionary principle in the EU (Löfstedt, 2004) and the United Kingdom (Dodds, 2006). However, as risk assessment continues to be actively debated in Brussels, it is not yet possible to assess the success of the BAT or Philip Morris campaigns.

It is of course legitimate for corporate interests to contribute to discussions on assessing scientific evidence and weighing up risks. However, it is important to ensure that this influence is transparent, is not excessive in comparison to other stakeholders, and does not compromise public welfare.

7.3.7 *Strategy 7: disseminate interest group data or interpretation of risk in the lay press*

While the tobacco industry appears to have recognised the importance of publishing work that supports its position in the scientific literature, the industry also seems aware of the need to get research data directly into the hands of the public and policymakers. How, then, were the public and other stakeholders involved in generating, presenting, understanding, communicating and using science to refute data on the adverse health effects of tobacco?

The important role of the media in communicating risk has been extensively studied (Nelkin, 1985; Raymond, 1985). The tobacco industry has been active in stimulating controversy in lay print media about the health effects of second-hand smoke. In a cross-sectional sample of 180 North American newspaper and 95 magazine articles reporting on second-hand smoke research between 1981 and 1995, Kennedy and Bero (1999) found that 66 % of newspaper articles and 55 % of magazine articles left readers with the impression of continuing controversy about second-hand smoke research. However, the proportion of those articles concluding that the research was controversial remained relatively constant.

Although tobacco industry-sponsored research studies were not widely cited in lay press articles, tobacco industry affiliated individuals were often cited (Kennedy and Bero, 1999; Malone et al., 2001). Among the 180 newspaper articles examined by Kennedy and Bero (1999), 52 % cited tobacco industry officials, whereas 56 % cited government officials and 46 % cited independent scientists. This citation of tobacco industry officials as experts on scientific studies on second-hand smoke could have contributed to the emphasis on controversy.

7.3.8 *Strategy 8: present interest group data or interpretation of risk directly to policymakers*

The last strategy in the tobacco industry's effort to stimulate controversy about data on risk has been to get its funded research directly into the hands of individuals who are likely to influence policy. A series of in-depth case studies have been undertaken, examining the role of research evidence in the development of two risk assessments of second-hand smoke, two state indoor air regulations and two United States federal tobacco regulations (Schotland and Bero, 2002; Roth et al., 2003, Bero et al., 2001; Bryan-Jones and Bero, 2003). Each study addressed the role of the tobacco industry in developing risk assessments and regulations by analysing archival data, including written commentary and hearing transcripts, and interviewing key policymakers.

In the United States, the processes for developing these risk assessments and regulations involves the appropriate government agency reviewing the relevant scientific literature, preparing a draft report, collecting written and oral public commentary, and revising the report based on that public commentary (Jasanoff, 1987 and 1996, Silbergeld, 1993). Public participation in the process is important for shaping the findings of the final risk assessment or regulation, and for public acceptability of the findings (Jasanoff, 1987). Furthermore, public commentary could help prevent the 'capture' of the risk assessment process by interest groups (Wilson, 1989).

Risk assessments of second-hand smoke

As noted earlier in this chapter, the US Environmental Protection Agency (EPA) published a risk assessment of environmental tobacco smoke (ETS) in 1992, which concluded that passive smoking is associated with lung cancer in adults and respiratory disease in children. The risk assessment's development was considerably delayed by the tobacco industry's criticisms of the report (US EPA, 1992). Sixty-four per cent (69/107) of submissions received by the EPA during the public commentary period claimed that the conclusions of the draft were invalid and, of these, 71 % (49/69) were submitted by tobacco industry-affiliated individuals (Bero and Glantz, 1993). The tobacco industry-affiliated reviewers supported their criticisms of the risk assessment by selectively citing non-peer-reviewed literature, especially articles from symposium proceedings (Bero and Glantz, 1993). Thus, tobacco industry-sponsored research that was not published in the peer-reviewed scientific literature was submitted directly to the EPA for review.

Schotland and Bero (2002) examined the development of the California risk assessment, revealing that participation in the public contribution process was not balanced among all interested parties, and was dominated by the tobacco industry. Critics and supporters of the risk assessment used different criteria to evaluate the science, suggesting that they were constructing the evidence to support their predefined positions. Similar to the US EPA risk assessment, the tobacco industry was able to use its funded research to support its arguments against the California risk assessment.

Indoor air regulation

During the 1990s, the Washington and Maryland Occupational Safety and Health Administrations each promulgated regulations restricting smoking in private workplaces. The US Occupational Safety and Health Administration also proposed a workplace smoking restriction but this failed. Internal tobacco industry documents show that one strategy the industry used to defeat the proposed federal regulation was to 'produce data to counter the findings about the adverse health effects of second-hand smoke' (Bryan-Jones and Bero, 2003). Despite the tobacco industry's use of this strategy and others to defeat the Maryland and Washington regulations, the state regulations were passed (Mangurian and Bero, 2000).

The two states' regulatory development processes required a public commentary period. Opposition to the regulation came primarily from the tobacco industry, small businesses, and business organisations and appeared to be coordinated (Bero et al., 2001). Much of the business group opposition was supported by the tobacco industry, although this support was not disclosed in the public commentary (Mangurian and Bero, 2000). Although arguments not related to science were more common than scientific arguments as a whole, arguments about science were used more often by opponents than supporters of the regulations (Bero et al., 2001). As in the other examples cited in this chapter, opponents of regulation, primarily the tobacco industry, cited industry-sponsored symposium proceedings or peer-reviewed journal articles of low methodological quality to support their criticisms of the science on which the regulations were based.

Apparent disagreement among experts during public testimony reinforces uncertainty about the data underpinning risk estimates or regulations. The studies of the Washington and Maryland regulations suggest, however, that the industry-supported experts used different criteria to evaluate the science, different bodies of evidence to support their claims and relied on arguments about specific studies rather than emphasising the body of evidence as a whole. In general, the involvement of tobacco industry lawyers and executives in the design, conduct and dissemination of research has an impact on how controversy can influence public opinion and policy decisions.

Box 7.2 describes how the tobacco industry worked to undermine tobacco control activities at the World Health Organization.

7.4 Lessons learned

The tobacco industry has had a long-standing strategy of funding research and disseminating it through their sponsored, non-peer-reviewed publications. These strategies have remained relatively consistent as the industry has evolved from refuting research on active smoking to refuting research on second-hand smoke. Despite the questionable conduct of much of this research, the tobacco industry has widely disseminated it to lay journalists and policymakers. In addition, the tobacco industry has a record of suppressing and criticising research that is unfavourable to its position. Tobacco industry lawyers and executives, rather than scientists, have been in control of the design, conduct and dissemination of this research, thereby protecting the research from public discovery. Since the tobacco industry's efforts to manipulate research are international endeavours, there is a need for global awareness of the strategies that the industry has used to influence data on risk.

When data on risk appear to be controversial, users of the data should investigate the sources of the controversy. Does the controversy exist only because the findings of interest group-funded research are contrary to data collected by others? Is the controversy supported primarily by evidence published in interest group-supported publications? Is the controversy supported primarily by research publications of low scientific quality? Is the controversy perpetuated in the lay press through citation of interest group-affiliated individuals? Are the data that suggests a controversy presented to policymakers only by the interest group?

Policymakers should apply these questions to all situations in which a company has an interest in creating controversy about the risks of its products. The tobacco industry differs substantially from other industries in the deadly nature of its products when used as directed, and the historical lack of regulation of tobacco products. However, the tobacco industry's methods for influencing the design, conduct and publication of research are similar to those of other corporate interests. For example, studies examining the association of pharmaceutical industry funding and research outcomes suggest that such funding produces studies with outcomes that are favourable to the sponsor (Lexchin et al., 2003; Cho and Bero, 1996; Bekelman et al., 2003). The reasons for this observed association of funding and outcome are not clear (Bero and Rennie, 1996). For example, the funding source does not appear to influence the methodological quality of the published research (Lexchin et al., 2003). Therefore, biased outcomes may

Box 7.2 Tobacco industry strategies to undermine tobacco control activities at the World Health Organization

'Tobacco industry documents reveal that, for many years, tobacco companies have deliberately subverted the efforts of the World Health Organization (WHO) to control tobacco use. The attempted subversion has been elaborate, well financed, sophisticated and usually invisible.

The release of millions of pages of confidential tobacco company documents as a result of lawsuits against the tobacco industry in the United States has exposed the activities of tobacco companies in resisting tobacco control efforts. That tobacco companies resist proposals for tobacco control comes as no surprise. What is now clear is the scale and intensity of their often deceptive strategies and tactics.

The tobacco companies' own documents show that they viewed the WHO, an international public health agency, as one of their foremost enemies. The documents show further that the tobacco companies instigated global strategies to discredit and impede the WHO's ability to carry out its mission. The tobacco companies' campaign against the WHO was rarely directed at the merits of the public health issues raised by tobacco use. Instead, the documents show that tobacco companies sought to divert attention from the public health issues, to reduce budgets for the scientific and policy activities carried out by the WHO, to pit other UN agencies against the WHO, to convince developing countries that the WHO's tobacco control programme was a 'first world' agenda carried out at the expense of the developing world, to distort the results of important scientific studies on tobacco and to discredit the WHO as an institution.

Although these strategies and tactics were frequently devised at the highest levels of tobacco companies, the role of tobacco industry officials in carrying out the strategies was often concealed. In their campaign against the WHO, the documents show that tobacco companies hid behind a variety of ostensibly independent quasi-academic, public policy and business organisations, whose tobacco industry funding was not disclosed. The documents also show that tobacco company strategies to undermine the WHO relied heavily on international and scientific experts with hidden financial ties to the industry. Perhaps most disturbing, the documents show that tobacco companies quietly influenced other UN agencies and representatives of developing countries to resist the WHO's tobacco control initiatives.

That top executives of tobacco companies sat together to design and set in motion elaborate strategies to subvert a public health organisation is unacceptable and must be condemned. The Committee of Experts believes that the tobacco companies' activities slowed and undermined effective tobacco control programmes around the world.

Given the magnitude of the devastation wrought by tobacco use, the Committee of Experts is convinced that, on the basis of the volume of attempted and successful acts of subversion identified in its limited search, it is reasonable to believe that the tobacco companies' subversion of the WHO's tobacco control activities has resulted in significant harm. Although the number of lives damaged or lost as a result of the tobacco companies' subversion of WHO may never be quantified, the importance of condemning the tobacco companies' conduct, and taking appropriate corrective action, is overriding'.

Source: Summary of a report of the WHO Committee of Experts on Tobacco Industry Documents (CETID, 2000).

be the results of how the research questions are asked, how the research is actually conducted and whether the results are published (or not published). Food industry funding for research has also been shown to produce outcomes favourable to the sponsor (Nestle, 2002; Levine et al., 2003).

A report by the Union of Concerned Scientists (2007) has documented how ExxonMobil has used the tactics of the tobacco industry to stimulate controversy about climate science. ExxonMobil has raised doubts about the evidence, hidden involvement behind front groups, sponsored scientific spokespersons to criticise the science and attempted to shift the focus away from existing evidence to the need for 'sound science'.

The public health community must learn more about the internal behaviour of corporations other than the tobacco industry in order to make conclusions about similarities in corporate behaviour. The release of millions of internal tobacco industry documents has given the public health community insights into the inner workings of the tobacco industry and revealed their previously hidden involvement in manipulating research (Bero, 2003). However, this insight is not available for most corporate sectors.

In some of the few other analyses of internal industry documents, Markowitz and Rosner describe how the chemical, asbestos and lead industries manipulated research about the harms of their products (Markowitz and Rosner, 1991, 2000, 2002). Their analysis reveals that these industries used the same tactics as tobacco companies to create controversy about the health effects of tetraethyl lead, asbestos, polyvinyl chloride and other chemicals. A recent issue of the *International Journal of Occupational and Environmental Health* relies heavily on internal company documents that the authors obtained by serving as expert witnesses in litigation (Special Issue, 2005). It describes how a variety of chemical companies and their trade organisations have used the strategies outlined in this article:

1. funding research that supports the interest group's position;
2. hiding industry involvement in research;
3. publishing research that supports the interest group's position;
4. suppressing research that does not support the interest group's position;
5. criticising research that does not support the interest group's position;
6. changing scientific standards;
7. disseminating interest group data or interpretation of risk in the lay press;
8. disseminating interest group data or interpretation of risk directly to policymakers.

The role of the sponsor in designing, conducting and disseminating research can be evaluated only if interest group involvement in all steps of the risk determination process is fully described. Thus, funding sources for all published research should be fully disclosed. Our analyses show, however, that disclosure of funding sources often provides incomplete information about the involvement of the sponsors in the research process. The tobacco industry has a long history of hiding the involvement of its lawyers and executives in the designing, conducting and disseminating research. If internal tobacco industry documents had not been made available to the public, much of what is known about the industry's manipulation of research would have remained undiscovered.

Disclosures should not be limited to describing the roles of the research funders in all stages of the research process. Personal financial ties between investigators and corporate interests (such as consulting fees, stock ownership, honoraria etc.) should also be fully disclosed. Personal financial ties are increasing (Boyd and Bero, 2000) and are associated with favourable research outcomes for the corporate interest, even if the corporate interest is not funding the research (Lexchin et al., 2003). Experts who criticise research describing the harms of a company's product should also fully disclose their financial ties with the company. These complete and accurate disclosures should be found in scientific publications (including research articles, letters to the editor and editorials), citations in the lay press, and testimony in policy or legal settings.

Full disclosure of a sponsor's role in designing, conducting and publishing a study could also improve the peer-review process. Peer reviewers are typically limited by the information available in the article they are reviewing. The peer review process itself should be conducted by individuals with adequate expertise and be independent of industry sponsors.

The findings presented in this chapter also have implications for how experts should be selected to participate in the risk assessment process. As suggested by others, professional competence, diversity of political views, disciplines, opinions and attitudes are important (von Winterfeldt, 1992). However, consideration should also be given to affiliation or interest group bias and how this will affect risk assessment. Encouraging transparency regarding the roles of interest groups in developing and disseminating data on risk will not prevent their involvement in the process. However, such transparency will make it easier to determine which strategies, if any, an interest group has been using to influence the data.

Detailed and accurate financial disclosures of research funding and financial ties are necessary, but not sufficient, for safeguarding the integrity of the research record. One possible benefit of disclosure is that it might discourage scientists from entering into financial relationships that could detract from the perceived integrity of their research. Another possible benefit is that transparency might improve public trust in research (Cho, 1998). Krimsky

(2003), however, has described disclosure as a 'rationalisation for creating more serious conflicts'. He points out that disclosure is a 'public relations' response to dealing with corporate influence on research and not a way of potentially decreasing the effect of the corporate sponsor on research integrity.

Although greater transparency about industry involvement in research could facilitate evaluation of biases in the design, conduct and reporting that might be introduced by such sponsorship, it will not eliminate the biases. Furthermore, if researchers and institutions are concerned that the public views industry-sponsored research as less credible, regardless of any effect on bias, eliminating financial ties may be the best way to deal with the issue. A number of scholars have argued that there should be a total ban on clinical investigators' financial ties to companies that fund their research (Krimsky, 2003; Dana, 2003). These proposed bans eliminate the need for oversight committees to 'manage' the conflict of interest and protect against even the appearance of conflict.

Photo: © istockphoto/Gremlin

Schafer (2003) supports the 'sequestration thesis', which would eliminate direct corporate sponsorship of research and financial ties of investigators. Sequestration could be achieved by forming an independent research institute, funded by companies, to support research. Shamoo and Resnik (2003) have noted, however, that eliminating financial ties and corporate funding may not be realistic today. Some investigators advocate 'self regulation': voluntary compliance with professional society guidelines, or adaptation of the federal conflict of interest policy to clinical trials funded by private sponsors (Boyd et al., 2003).

Support for banning corporate funding of research is most developed among academic institutions that have policies prohibiting researchers from accepting tobacco industry funding for research. For example, some academic institutions, particularly schools of medicine and public health, have developed bans on tobacco industry funding (Herman, 2002). Examples include Harvard University and the University of Sydney. Some funding agencies (e.g. Legacy Foundation) have developed policies that require such bans as a condition for receiving funding (Shield, 2001).

Bans on tobacco industry support for research are warranted in view of the industry's history of deception about its role in designing, conducting and disseminating industry-supported research. They are further justified by the tobacco industry's motives for funding research, which include distracting attention from tobacco's health risks, gaining credibility and using the research for public relations (Cohen, 2003).

Table 7.2 Key dates relating to knowledge of harm from active and second-hand smoke

1604	King James I of England wrote 'A Counterblaste Against Tobacco' expressing his distaste for tobacco, particularly tobacco smoking. This was one of the earliest anti-tobacco publications
1903–1908	In the United Kingdom, the Boer War Recruits Health Report led, in 1908, to restrictions on the sale of tobacco to children under 16 and empowered police to confiscate cigarettes from children smoking in public places
1931	Argentinian oncologist Angel Roffo (1931) produced skin tumours in rabbits with tobacco tar, building on similar work on tars and skin cancer that began with Percival Pott's UK studies of scrotal cancer and chimney sweeps (1775)
1936	US physician Alton Ochsner (1973) sees nine cases of lung cancer in six months after not seeing one in 20 years. Noting that all the patients had begun smoking during World War I, he suggested that smoking was the cause
1938	US statistician Raymond Pearl (1938) uses insurance records to show increased death rates of smokers
1939	Franz Müller (1939) uses 86 cases of lung cancer compared to controls to show that heavy smokers had 16 times the lung cancer deaths than non-smokers: a 'one in a million chance' finding leading to the conclusion that tobacco was the 'single most important cause of the rise in lung cancer'
1930–1941	Schairer and Schöniger (2001) studied 195 lung cancer cases using two control groups (other cancers and no diseases), showing that only three lung cancer cases had not smoked and that a statistical association between tobacco and lung cancer was 'likely'
1942–1944	Seven dissertations were published on tobacco and health effects at the German National Scientific Institute for Research on Tobacco, Jena (Zimmermann et al., 2001)
1946	Percy Stocks (1947), UK chief medical statistician to the General Register Office, noted a 'startling' six-fold increase in male lung cancer between 1930 and 1944
1947	The UK Medical Research Council (MRC) met to discuss action and was attended by Bradford Hill, Alice Stewart, Ernest Kennaway and others. Several possible causes of lung cancer were discussed: tar from roads, urban air pollution, traffic fumes and smoking. These were all probably 'factors which prepare the soil rather than sow the seed' (Tudor Edwards, 1946; Keeting, 2009)
1948	In an MRC study by Doll and Bradford Hill, preliminary results on 156 interviews with patients showed 'definite association' between lung cancer and smoking, although the lack of a link between inhaling and cancer was 'surprising' (Pollock, 1999). This was to provide the eminent statistician, Sir Ronald Fisher, with his denial of the association between smoking and lung cancer for many years
1950	Five papers were published showing the dangers of smoking. Wynder and Graham (1950) (concerning military veterans in the US), Doll and Bradford Hill (1950) (concerning hospital patients in the United Kingdom) concluded that smoking was 'an important factor' in the 'induction/production' of lung cancer. Of 647 cases in the Doll and Bradford Hill study only 0.3 % were non-smokers: a 'one in a million' chance finding. Heavy smokers had 16 times the lung cancer deaths than non-smokers. But this result was 'largely doubted and generally ignored' by the medical establishment (Keating, 2009)
1953	A UK Government Advisory Committee concluded that the 'association was causal' and 'young people should be warned' (Ministry of Health, 1953a, 1953b and 1954)
1954	Preliminary results were released from the study of Doll and Hill (1954) of 40 000 doctors which was to last 50 years. Data on 39 lung cancer cases out of 769 deaths confirmed their earlier findings and now revealed a dose/response effect and an association with heart disease. In the US, Hammond and Horn's (1954) study of 5 000 deaths showed similar results
1954	Publication of scientific studies documenting tobacco's role in cancer and other fatal illnesses together with subsequent media coverage and declining sales was referred to internally by the tobacco industry as the '1954 emergency'. The industry responded with a public relations campaign led by Hill and Knowlton to 'manufacture doubt' about the link between smoking and lung cancer, without actually denying it
1964	A US Surgeon General report, 'Smoking and Health', based on 29 studies, concluded that 'there is a causal relationship between excessive smoking and lung cancer' (US DHEW, 1964)
1970–1980s	The first studies were published showing that second-hand smoking is associated with lung cancer. A US Surgeon General report in 1986 concluded that the link is causal (US DHHS, 1986)
1993–1998	Tobacco industry subverts the WHO International Agency for Research on Cancer (IARC) study and evaluation of second-hand smoking as a human carcinogen

Source: EEA, based on Keating, 2009 and Ong and Glantz, 2000.

References

AAAS, 1999, *American Association for the Advancement of Science and Federal Focus, Inc.*

Armitage, A.K., 1993, 'Environmental tobacco smoke and coronary heart disease', *Journal of Smoking-Related Diseases*, (4/1) 27–36.

Assunta, M., Fields, N., Knight, J. and Chapman, S., 2004, 'Care and feeding: "Our consultants are prepared to do the kind of things they were recruited to do" The Asian ETS Consultants Program', *Tobacco Control*, (13/2) ii 4–12.

Baba, A., Cook, D., McGarity, T. and Bero, L., 2005, 'Legislating "Sound Science": Role of the tobacco industry', *American Journal of Public Health*, S1:S20–S7.

Barnes, D.E. and Bero, L.A., 1997, 'Scientific quality of original research articles on environmental tobacco smoke', *Tobacco Control*, (6/1) 19–26.

Barnes, D. and Bero. L.A., 1998, 'Why review articles on the health effects of passive smoking reach different conclusions', *JAMA*, (279) 1 566–1 570.

Barnes, D. and Bero, L.A., 1996, 'Industry-funded research and conflict of interest: An analysis of research sponsored by the tobacco industry through the Center for Indoor Air Research', *J Health Politics, Policy and Law*, (21) 515–542.

Barnes, D., Hanauer, P., Slade, J., Bero, L. and Glantz, S., 1995, 'Environmental tobacco smoke: The Brown and Williamson documents', *JAMA*, (274) 248–253.

Barnoya, J. and Glantz, S., 2006, 'The tobacco industry's worldwide ETS consultants project: European and Asian components', *Eur J Public Health*, (February 2006) (16/1) 69–77.

Barnoya, J. and Glantz, S., 2002, 'Tobacco industry success in preventing regulation of second-hand smoke in Latin America: the "Latin Project"', *Tob Control*, (11/4) 305–314.

BAT, 1956, *The Zephyr Aspects of PCL*, British American Tobacco, p. 100175775.

BAT, 1991, 'Confidential communication from industry counsel to employee of entity with whom BAT Co shares a common legal interest with copies sent to employee, affiliate employee and joint defense employee containing counsel's advice regarding assessment of EPA Scientific Advisory Board meeting' (http://legacy.library.ucsf.edu/tid/wvd12b00) accessed 9 December 2011.

BAT, 1995, *ETS Pilot Study*, Bates number(s): 700875991–700876043 (http://legacy.library.ucsf.edu/tid/kwj63a99) accessed 15 July 2011.

BAT, 1996, 'Confidential communication from industry counsel to affiliate counsel containing industry counsel's advice and analysis regarding risk assessment' (http://legacy.library.ucsf.edu/tid/hfk42b00) accessed 9 December 2011.

BAT, 1996, *EU Issues*, Bates number(s): 322122073–322122107 (http://bat.library.ucsf.edu//tid/pwt63a99) accessed 15 July 2011.

BAT, undated, *Shaping the Regulatory Environment: Advertising and Public Smoking*, Bates number(s): 322121140–322121143 (http://bat.library.ucsf.edu//tid/xnz82a99) accessed 23 May 2008.

Bekelman, J., Li, Y. and Gross C., 2003, 'Scope and impact of financial conflicts of interest in biomedical research: A systematic review', *JAMA*, (289) 454–465.

Bero, L.A., 2003, 'Implications of the tobacco industry documents for public health and policy', *Annu Rev Public Health*, (24) 267–288.

Bero, L.A., Barnes, D., Hanauer, P., Slade, J. and Glantz, S., 1995, 'Lawyer control of the tobacco industry's external research program: The Brown and Williamson documents', *JAMA*, (274) 241–247.

Bero, L.A., Galbraith, A. and Rennie, D., 1994, 'Sponsored symposia on environmental tobacco smoke', *JAMA*, (271/8) 612–617.

Bero, L.A., Galbraith, A. and Rennie, D., 1992, 'The publication of sponsored symposiums in medical journals', *New Eng J Med*, (327) 1 135–1 140.

Bero, L.A. and Glantz, S.A., 1993, 'Tobacco industry response to a risk assessment of environmental tobacco smoke', *Tobacco Control*, (2) 103–113.

Bero, L.A., Glantz, S.A. and Rennie, D., 1994, Publication bias and public health policy on environmental tobacco smoke', *JAMA*, (272) 133–136.

Bero, L.A., Montini, T., Bryan-Jones, K. and Mangurian C., 2001, 'Science in regulatory policy making: case studies in the development of workplace smoking restrictions', *Tob Control*, (10/4) 329–336.

Bero, L.A. and Rennie, D., 1996, 'Influences on the quality of published drug studies', *Int J Technol Assess Health Care*, (12/2) 209–237.

Bero, L.A., Rennie, D., 1995, 'The Cochrane Collaboration: Preparing, maintaining, and disseminating systematic reviews of the effects of health care', *JAMA*, (274) 1 935–1 938.

Bero, L.A., 2005, 'Tobacco industry manipulation of research', *Public Health Reports*, (120) 200–208.

Bialous, S. and Glantz, S., 2002, 'ASHRAE Standard 62: Tobacco industry's influence over national ventilation standards', *Tobacco Control*, (11) 315–328.

Bialous, S. and Yach, D., 2001, 'Whose standard is it, anyway? How the tobacco industry determines the International Organization for Standardization (ISO) standards for tobacco products', *Tobacco Control*, (10) 96–104.

Boyd, E. and Bero, L., 2000, 'Assessing faculty financial relationships with industry', *JAMA*, (284) 2 209–2 238.

Boyd, E.A., Cho, M.K. and Bero, L.A., 2003, 'Financial conflict-of-interest policies in clinical research: issues for clinical investigators', *Acad Med*, (78/8) 769–774.

Boyse, S., 1988, *Note on a Special Meeting of the UK Industry on Environmental Tobacco Smoke*, British American Tobacco, London, February 17, 1988, p. 1011980–4.

Bryan-Jones, K. and Bero, L.A., 2003, 'Tobacco industry efforts to defeat the occupational safety and health administration indoor air quality rule', *Am J Public Health*, (93/4) 585–592.

Cal-EPA, 2005, California Environmental Protection Agency, *Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant*, California Environmental Protection Agency, Sacramento.

Cal-EPA, 1997, California Environmental Protection Agency, *Health Effects of Exposure to Environmental Tobacco Smoke*, California Environmental Protection Agency, Sacramento.

CETID, 2000, *Tobacco company strategies to undermine tobacco control activities at the World Health Organization*, Report of the Committee of Experts on Tobacco Industry Documents.

Chapman, S., 2005, 'The most important and influential paper ever on second-hand smoke', 2005.

Chapman, S., 1997, 'Tobacco industry memo reveals passive smoking strategy', *Bmj*, (14/7094) 1 569.

Chapman, S., Borland, R., Hill, D., Owen, N. and Woodward, S., 1990, 'Why the tobacco industry fears the passive smoking issue', *Int J Health Services*, (20/3) 417–427.

Cho, M., 1998, 'Fundamental conflict of interest', *The BioMedNet Magazine*, 24.

Cho, M.K., Bero, L.A., 1996, 'The quality of drug studies published in symposium proceedings', *Annals of Internal Medicine*, (124/5) 485–489.

CIAR, 1994, *Board Of Directors Meeting Sheraton Stockholm 940222 & 940223 Agenda, Philip Morris*, p. 2028387250, Center For Indoor Air Research.

CIAR, 1992a, *Research agenda and request for applications*, Center for Indoor Air Research.

CIAR, 1992b, *Request For Proposals, Philip Morris*, p. 2023523350/3369, Center for Indoor Air Research.

CIAR, 1989, *Request For Applications 1989–1990 (890000–900000) Research Agenda, RJ Reynolds*, p. 508146797/6836, Center for Indoor Air Research.

CIAR, 1988, *Lorillard*, p. 87824354/4374, Center For Indoor Air Research.

Cohen, J., 2003, 'Accepting tobacco funding for research: An overview of the issues', *TRDRP Newsletter Burning Issues*, (6/1) 7.

Connolly, G., Wayne, G., Lymperis, D. and Doherty, M., 2000, 'How cigarette additives are used to mask environmental tobacco smoke', *Tobacco Control*, (9) 283–291.

Covington and Burling, 1996, *EC Risk Assessment Proposal*, Bates number(s): 800103063–800103065 (http://bat.library.ucsf.edu//tid/hjt14a99) accessed 15 July 2011.

Dana, J., 2003, 'Harm avoidance and financial conflict of interest', *Journal of Medical Ethic*, (14) (September 12), 1–18.

Davies, D., 2007, *The Secret History of the War on Cance*, Basic Books.

Dickersin, K., Min, Y-I. and Meinert, C.L., 1992, 'Factors influencing publication of research results: follow-up of applications submitted to two institutional review boards', *J Am Med Assoc*, (8267) 374–378.

Diethhelm, P., Rielle, J-C. and McKee, M., 2004, 'The whole truth and nothing but the truth? The research that Philip Morris did not want you to see', *The Lancet,* online version, 11 November 2004.

Djordjevic, M.V., Fan, J., Ferguson, S. and Hoffmann, D., 1995, 'Self-regulation of smoking intensity. Smoke yields of the low-nicotine, low-'tar' cigarettes', *Carcinogenesis*, (16/9) 2 015–2 021.

Dodds, A., 2006, 'The Core Executive's Approach to Regulation: From "Better Regulation" to "Risk-Tolerant Deregulation"', Social Policy & Administration, 40(5) 526–542.

Doll, R. and Bradford Hill, A., 1950, 'Smoking and carcinoma of the lung, preliminary report', *British Medical Journal*, (2) 739–48.

Doll, R. and Bradford Hill, A., 1954, 'The mortality of doctors in relation to their smoking habits — A preliminary report', *British Medical Journal*, (228/i) 1 451–1 455.

European Commission, 2009, *Impact Assessment Guidelines SEC(2009) 92*, Europa, Brussels.

EU, 1997, Treaty of Amsterdam Amending the Treaty on European Union, the Treaties establishing the European Communities and Certain Related Acts. Brussels: Office for Official Publications of the European Communities and Europa.

European Policy Centre, 1997, *Briefing Paper on Risk Assessment,* Bates number(s): 321573155 (http://legacy.library.ucsf.edu/tid/weg63a99) accessed 15 July 2011.

European Risk Forum, 2008a, 'European Risk Forum — ERF' (http://www.euportal2.be/index.php) accessed 15 July 2011.

European Risk Forum, 2008b, *Policy Brief 04: Judicial Review and Risk Management at EU-Level*.

Fact Finding Commission, 2004, *Report of the inquiry into the case concerning Prof. Ragnar Rylander*, University of Geneva, Geneva, September 6, 2004.

Flue-Cured Tobacco Co-op v. US EPA, 1998; 4 F. Supp. 2d 435 (M.D.N.C. 1998).

Glantz, S., Slade, J., Bero, L. and Hanauer, P., 1996, *The Cigarette Papers*, UC Press, Berkeley, CA.

Gretton, K., undated (circa 1995), *Interdepartmental Liaison Group on Risk Assessment: Use of Assessment within Government Departments*, Bates number(s): 800148140–800148145.

Grüning, T., Gilmore, A. and McKee, M., 2006, 'Tobacco industry influence on science and scientists in Germany', *Am J Public Health*, *Am J Public Health*, (96/1) 20–32.

Hammond, E.C. and Horn, D., 1954, 'The relationship between human smoking habits and death rates', *Journal of the American Medical Association*, (155) 1 316–1 328.

Hanauer, P., Slade, J., Barnes, D., Bero, L. and Glantz, S., 1995, 'Lawyer control of internal scientific research to protect against products liability lawsuits: The Brown and Williamson documents', *JAMA*, (274) 234–240.

Herman, R., 2002, *Harvard School of Public Health Faculty Votes Not to Accept Funds from the Tobacco Companies and Subsidiaries*, Harvard School of Public Health, Boston, MA., January 25, 2002.

Hirayama, T., 1981, 'Non-smoking wives of heavy smokers have a higher risk of lung cancer. A study from Japan', *Br Med J*, (282) 183–185.

Hirschhorn, N. and Bialous, S., 2001, 'Second-hand smoke and risk assessment: what was in it for the tobacco industry?', *Tobacco Control, (*10) 375–382.

Hirschhorn, N., Bialous, S.A. and Shatenstein, S., 2001, 'Philip Morris' new scientific initiative: An analysis', *Tobacco Control*, (10) 247–252.

Hong, M.K. and Bero, L.A., 2002, 'How the tobacco industry responded to an influential study of the health effects of second-hand smoke', *BMJ*, (325/7377) 1 413–1 416.

Hornstein, D.T., 2003, 'Accounting for Science: The Independence of Public Research in the New, Subterranean Administrative Law', *Law and Contemporary Problems*, (66/227) 227–246.

Honour, H., 1996, *Risk Assessment*, Bates number(s): 800103062 (http://legacy.library.ucsf.edu/tid/fjt14a99) accessed 15 July 2011.

IARC, 1998, International Agency for Research on Cancer, *Passive Smoking and Lung Cancer in Europe*, IARC, Lyon.

Jasanoff, S.K., 1996, 'Is science socially constructed: And can it still inform public policy?', *Science and Engineering Ethics*, (2/3) 263–276.

Jasanoff, S., 1995, *Science at the Bar: Law, Science, and Technology in America. The Technical Discourse of Government*, Harvard University Press, Cambridge, pp. 69–92.

Jasanoff, S., 1987, 'EPA's Regulation of Daminozide: Unscrambling the Messages of Risk', *Science, Technology and Human Values*, (12/3 & 4) 116–124.

Johnston J, (R. J. Reynolds Tobacco Company) and Sullum, J., (Philip Morris Tobacco Company), 1994, Collection of advertisements, *American Tobacco*, p. 947086708/6724.

Kaiser, J., 2003, 'Economics. Wielding the data-quality cudgel', *Science*, (299/5614) 1 837.

Kaiser, J., 1997, 'Researchers and Lawmakers Clash Over Access to Data', *Science*, (277/5325) 467.

Keating, C., 2009, *Smoking Kills, The Revolutionary Life of Richard Doll*, Signal Books Limited, Oxford.

Kennedy, G. and Bero, L., 1999, 'Print media coverage of research on passive smoking', *Tobacco Control*, (8) 254–260.

Kingdon, J.W., 1984, *Agendas, Alternatives, and public policies*, Little, Brown and Co., Boston.

Krimsky, S., 2003, *Science in the Private Interest*, Rowman & Littlefield Publishers, Inc., Lanham, MD.

Krimsky, S., 1992, 'The role of theory in risk studies', in: Krimsky, S., Golding, D. (eds), *Social Theories of Risk*, Westport, Connecticut London, pp. 3–22.

Lee, P.N.,1995, '"Marriage to a smoker" may not be a valid marker of exposure in studies relating environmental tobacco smoke to risk of lung cancer in Japanese non-smoking women', *Int Arch Occup Environ Health*, (67/5) 287–294.

Levine, J., Gussow, J., Hastings, D. and Eccher, A., 2003, 'Authors' financial relationships with the food and beverage industry and their published positions on the fat substitute Olestra', *Am J Public Health*, (93) 664–669.

Lexchin, J., Bero, L.A., Djulbegovic, B. and Clark, O., 2003, 'Pharmaceutical industry sponsorship and research outcome and quality: Systematic review', *BMJ*, (326/7400) 1 167–1 170.

Löfstedt, R.E., 2004, 'The Swing of the Regulatory Pendulum in Europe: From Precautionary Principle to (Regulatory) Impact Analysis', The Journal of Risk and Uncertainty, (28/3) 237–260.

Lowi, T., 1979, *The End of Liberalism*, Norton, New York.

MacKenzie-Reid, D., 1995, 'Memo from Duncan MacKenzie-Reid to Keith Gretton enclosing paper on risk assessment', Bates number(s): 800147230–800147236 (http://bat.library.ucsf.edu//tid/ctt72a99) accessed 15 July 2011.

Malone, R.E. and Bero, L.A., 2003, 'Chasing the dollar: Why scientists should decline tobacco industry funding', *J Epidemiol Community Health*, (57/8) 546–548.

Malone, R.E., Boyd, E. and Bero, L.A., 2001, 'Science in the news: Journalists' constructions of passive smoking as a social problem', *Social Studies of Science*, (30) 713–735.

Mangurian, C., Bero, L.A., 2000, 'Lessons learned from the tobacco industry's efforts to prevent the passage of a workplace smoking regulation', *Am J Public Health,* (90) 1 926–1 930.

Markowitz, G., Rosner, D., 2002, *Deceit and Denial: The Deadly Politics of Industrial Pollution*, University of California Press, Berkeley, CA.

Markowitz, G and Rosner, D., 2000, '"Cater to the children": the role of the lead industry in a public health tragedy, 1990–1955', *Am J Public Health*, (90/1) 36–46.

Markowitz, G. and Rosner, D., 1991, *Deadly Dust: Silicosis and the Politics of Occupational Disease in Twentieth Century America*, Princeton University Press, Princeton, NJ.

Mazmanian, D. and Sabatier, P., 1989, *Implementation and public policy*, University Press of America; Lanham, MD.

McGarity, T.O., 2004, 'Our Science is Sound Science and Their Science is Junk Science: Science-Based Strategies for Avoiding Accountability and Responsibility for Risk-Producing Products and

Activities', *The University of Kansas Law Review*, (52/4) 897–937.

Michaels, D., 2008, *Doubt is their product: how industry's assault on science threatens your health*, Oxford University Press, New York.

Ministry of Health, 1953a, *Smoking and lung cancer, report of the statistical panel appointed by the CMO*, UK National Archives, London.

Ministry of Health, 1953b, *Minutes of Standing Advisory Committee, 22 December 1953*, UK National Archives, London.

Ministry of Health, 1954, Draft memorandum to cabinet Home Affairs Committee, 26 Jan. 1954, UK National Archives/Ministry of Health papers, MH55/1011.

Misakian, S. and Bero, L., 1998, 'Publication bias and research on passive smoking', *JAMA*, (280/13) 250–253.

Montini, T. and Bero, L.A., 2001, 'Policy makers' perspectives on tobacco control advocates' roles in regulation development', *Tob Control*, (10/3) 218–224.

Montini, T., Mangurian, C. and Bero, L.A., 2002, *Assessing the evidence submitted in the development of a workplace smoking regulation: The case of Maryland*, Public Health Reports, 2002 May–June, (117/3) 291–298.

Muggli, M.E., Forster, J.L., Hurt, R.D. and Repace, J.L., 2001, 'The smoke you don't see: uncovering tobacco industry scientific strategies aimed against environmental tobacco smoke policies', *Am J Public Health*, (91/9) 1 419–1 423.

Muggli, M.E., Hurt, R.D. and Repace, J., 2004, 'The Tobacco Industry's Political Efforts to Derail the EPA Report on ETS', American Journal of Preventative Medicine, (26/2) 167–177.

Müller, F.H., 'Tabakmissbrauch und Lungencarcinom', *Zeitschrift für Krebsforschung*, (49) 78.

Nelkin, D. (ed.), 1985, *The Language of Risk: Conflicting Perspectives on Occupational Health*, Beverly Hills: Sage Publications.

Nestle, M., 2002, *Food Politics*, University of California Press, Berkeley.

NHMRC, 1997, *The health effects of passive smoking*, National Health and Medical Research Council, Canberra.

NRC, 1986, National Research Council, *Environmental tobacco smoke: Measuring exposures and assessing health effects*, National Academy Press, Washington, D.C.

Ochsner, A., 1973, 'Corner of history: My first recognition of the relationship of smoking and lung cancer', *Prev Med*, (2) 611–614, .

OMB Watch, 2002, *Background on Data Quality Guidelines*, (updated 05/28; cited 2004 05/03) (http://www.ombwatch.org/node/645) accessed 15 July 2011.

Ong, E.K. and Glantz, S.A., 2001, 'Constructing "Sound Science" and "Good Epidemiology": tobacco, lawyers, and public relations firms', *Tobacco Control*, (91/11) 1–9.

Oreskes, N. and Conway, E.M., 2010, *Merchants of doubt: how a handful of scientists obscured the truth on issues from tobacco smoke to global warming*, Bloomsbury Press.

Pearl, R., 'Tobacco smoking and longevity', Science, 1938, (87) 216–227.

Pepples, E., 1978, *CTR BUDGET*, Brown & Williamson, p. 680212421/2423.

Pollock, D., 1999, *Denial and delay: the political history of smoking and health, 1951–1964 — scientists, government and industry as seen in the papers at the public record office*, Action on Smoking and Health, London

Raymond, C.A., 1985, 'Risk in the press: Conflicting journalistic ideologies', in: Nelkin, D. (ed.), *The Language of Risk*, Sage Publications, Beverly Hills, p. 87–132.

Rennie, D., 1993, 'Smoke and Letters' (Editorial), *JAMA*, (270) 1 742–1 743.

Renner, R., 2002, 'Little law could block major government decisions', *Environ Sci Technol*, (36/23) 443A.

Rochon, P., 1994, 'Evaluating the quality of articles published in journal supplements compared with the quality of those published in the parent journals', *JAMA*, (272) 108–113.

Roffo, A.H., 1931, 'Durch Tabak beim Kaninchen entwickeltes Carcinom', *Zeitschrift für Krebsforschung*, (33) 312–322.

Roper Organization, 1978, '*A Study Of Public Attitudes Toward Cigarette Smoking And The Tobacco Industry In 1978*, Tobacco Institute, volume 1, May 1978, p. TIMN0210766/0819.

Roth, A.L., Dunsby, J., Bero, L.A., 2003, 'Framing processes in public commentary on US federal tobacco control regulation', *Soc Stud Sci*, (33/1) 7–44.

Sabatier, P.A., 1991, 'Toward better theories of the policy process', *Political Science and Process*, 147–156.

Schafer, A., 2003, 'Biomedical conflicts of interest: a defence of the sequestration thesis', *Journal of Medical Ethics*, September 2003; Online Electronic Version: 1–40.

Schairer, E. and Schöniger, E., 2001, 'Lung cancer and tobacco consumption', *Int. J. Epidemiol*, (30/1) 24–27 (an English translation of an article first published in German in Z Krebsforsch in 1943), (34) 261–269.

Schotland, M.S. and Bero, L.A., 2002, 'Evaluating public commentary and scientific evidence submitted in the development of a risk assessment', *Risk Anal*, (22/1) 131–140.

Shamoo, A.E. and Resnik, D.B., 2003, *Responsible Conduct of Research*, Oxford University Press, New York.

Shapiro, S.A., 2004, 'The Information Quality Act and Environmental Protection: The Perils of Reform by Appropriations Rider', *William and Mary Environmental Law and Policy Review*, winter; (28/2) 339–374.

Shield, M., 2001, 'Policies and positions of other organizations on the funding controversy', *TRDRP Newsletter Burning Issues*, (4/1) 2 p. 4.

Shook Hardy and Bacon, 1993, *Report On Recent Ets And Iaq Developments*, Philip Morris, p. 2046361379/1406.

Smith, K.E., Fooks, G., Collin, J., Weishaar, H., Mandal, S. and Gilmore, A., 2010, 'Working the System' — British American Tobacco's Influence on the European Union Treaty and Its Implications for Policy: An Analysis of Internal Tobacco Industry Documents', *PLoS Medicine*, (7/1) e1000202, doi:10.1371/journal.pmed.1000202.

Silbergeld, E., 1993, 'Risk assessment: the perspective and experience of U.S. environmentalists', *Environmental Health Perspectives*, (101/2) 100–104.

Special Issue, 2005, 'Corporate Corruption of Science', *Int J of Occupational Env Health*, (11/4) 311–455.

Stayner, L., 1999, 'Protecting public health in the face of uncertain risks: the example of diesel exhaust', *American Journal of Public Health*, (89/7) 991–3.

Stocks, P., 1947, 'Regional and local differences in cancer death rates', General Register Office: studies on medical and population subjects, No. 1., HMSO.

Tewes, F., Koo, L., Meisgen, T. and Rylander, R., 1990, 'Lung cancer risk and mutagenicity of tea', *Environ Research*, (52) 23–33.

Tobacco Institute, 1986, *Tobacco smoke and the non-smoker: Scientific integrity at the crossroads*, The Tobacco Institute.

Truman, D., 1993, *The Governmental Process*, 2nd edition, Institute of Governmental Studies Press, Berkeley.

Tudor Edwards, A., 1946, 'Carcinoma of the bronchus', *Thorax*, (1) 1–25, doi:10.1136/thx.1.1.1

Turner, S., Cyr, S. and Gross, A., 1992, 'The measurement of environmental tobacco smoke in 585 office environments', *Environment International*, (18) 19–28.

Union of Concerned Scientists, 2007, *Smoke, Mirrors and Hot Air: How ExxonMobil uses Big Tobacco's Tactics to Manufacture Uncertainty on Climate Science*, Cambridge, MA.

University of California, 2011, 'Legacy Tobacco Documents Library — Field Descriptions' (http://legacy.library.ucsf.edu/help/fields_desc.jsp) accessed 9 December 2011.

US Congress, 1999, *Omnibus Consolidated and Emergency Supplemental Appropriations Act of 1999*, Pub. L. No. 105–277.

US DHEW, 1964, *Report of the Advisory Committee to the Surgeon General of the Public Health Service*, US Department of Health, Education and Welfare.

US DHHS, 1986, United States Department of Health and Human Services, *The health consequences of involuntary smoking: A report of the Surgeon General*, United States Department of Health and Human Services.

US EPA, 1992, United States Environmental Protection Agency, *Respiratory health effects of passive smoking: Lung cancer and other disorders*, Office of Health and Environmental Assessment, Office of Research and Development, Washington D.C., Report No.: U.S. EPA Document No. EPA/600/6–90/006F.

Walker, J.L.J., 1991, *Mobilizing Interest Groups in America*, University of Michigan Press, Ann Arbor.

Wallack, L., Dorfman, L., Jernigan, D. and Themba, M., 1993, *Media Advocacy and Public Health: Power for Prevention*, Sage Publications, Newbury Park, CA.

Wells, J. and Pepples, E., 1986, *Re: BAT Science*. UCSF B&W, p. 1837.01.

White, J., Bandura, A. and Bero, L.A., 2009, 'Moral disengagement in the corporate world', *Accountability in Research*, (16) 41–74.

White, J. and Bero, L.A., 2010, 'Corporate manipulation of research: Strategies are similar across five industries', *Stanford Law & Policy Review*, (21/1) 105–134.

Wilson, J.Q., 1989, *Bureaucracy: What Government Agencies Do and Why They Do It*, 0000Johns Hopkins University Press, Baltimore, MD.

von Winterfeldt, D., 1992, 'Expert knowledge and public values in risk management: the role of decision analysis', in: Krimsky, S. and Golding, D. (eds), *Social Theories of Risk*, Westport Connecticut London, p. 321–342.

Wynder, E.L. and Graham, E.A., 1950, 'Tobacco smoking as a possible etiologic factor in bronchogenic carcinoma', *Journal of the American Medical Association*, (143) 329–336.

Yano, E., 2005, 'Japanese spousal smoking study revisited: How a tobacco industry funded paper reached erroneous conclusions', *Tob Control*, (14) 227–233.

Zacaroli, A., 1998, 'Budget Provision in Spending Law Opens Access to Data Underlying Federally Funded Studies', in: *BNA Daily Environment Report*, editor. Philip Morris, p. 2065231101/1103.

Zimmermann, S., Egger, M. and Hossfeld, Uwe., 2001, 'Commentary: pioneering research into smoking and health in Nazi Germany— The ''Wissenschaftliches Institut zur Erforschung der Tabakgefahren' in Jena''', *Int. J. Epidemiol.*, (30/1) 35–37.

8 Vinyl chloride: a saga of secrecy

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This chapter is about how early warnings in the 1950s and 1960s concerning the short-term harm of vinyl chloride (VC) to the skin and bones of workers, and to the livers of laboratory animals, were initially hidden from other workers and regulators. This was despite some early misgivings by company experts whose advice was initially ignored by their employers. This pattern was repeated when the later, more devastating news of a rare liver cancer in workers was revealed by long-term animal studies and by an attentive and concerned company physician.

Unlike many other histories, however, this story features a very prompt response from the global chemical industry to the publication of the liver cancer evidence, a response that included funding cancer testing and later compliance with a large reduction in the permissible exposure limits. The case also provides early evidence of reproductive effects of vinyl chloride monomer (VCM).

Other features of this story presage the later and common responses of the corporate world to heightened public awareness and pressure from non-governmental organisations (NGOs) and trade unions, including greatly exaggerated estimates of the likely costs of complying with tighter pollution controls; a frequent mismatch between the position of the trade association and that of many, more progressive companies within the association; but also some relatively quick corporate responses to public, NGO and regulatory pressure.

The chapter also features two legal aspects, which, though more common in the US, are also valuable for Europeans. First, the potentially positive role that judicial review of regulatory proposals can play in providing a societal judgement about the behaviour of corporations. This can embrace not just moral judgements but also judgements about the state of the science and what society should do with it.

Second, the role that document discovery in legal compensation cases can play in revealing the real and until then secret activities of corporations. Any proposals to promote justice for victims of environmental and health harms via no fault administrative arrangements need to be accompanied by other measures to extract information about corporate behaviour.

The chapter is followed by a panel analysing the value of animal testing for identifying carcinogens.

(¹) Authors would like to thank Professors David Rosner and Gerald Markowitz for providing original copies of original documents. Many of the documents used to prepare this paper are a part of the collection of the Cesare Maltoni Cancer Research Center in Bentivoglio, Italy. The original industry documents cited by Markowitz and Rosner in their book, *Deceit and Denial*, are available to the public at http://www.deceitanddenial.org.

8.1 A veil of secrecy

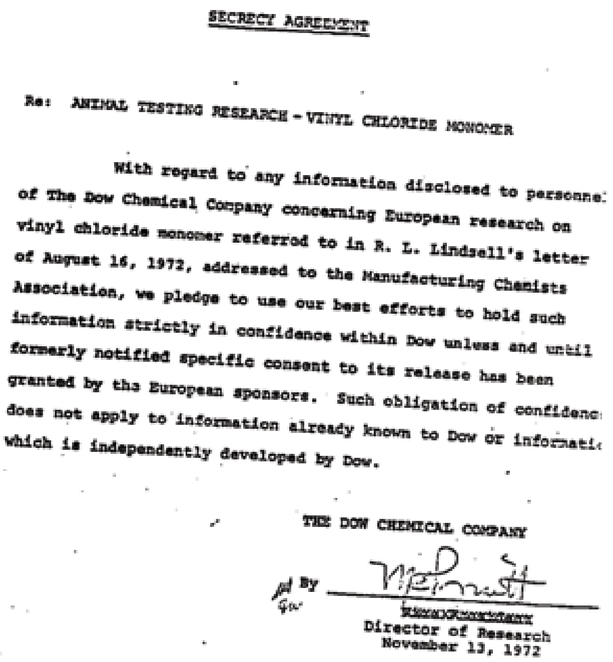
In January 1973 the US National Institute of Occupational Safety and Health (NIOSH) issued an official 'request for information' to the public, including the chemical industry, requiring that all information relevant to the hazards of vinyl chloride be submitted to the government. Compliance was mandatory.

The 'request' put the US chemical industry (both users and manufacturers) in a difficult position. Dow Chemical and other US manufacturers had signed a 'secrecy agreement' (see Figure 8.1) in 1972 with European chemical companies (Markowitz and Rosner, 2002, p. 182–183). The signed agreements, which were collected by Imperial Chemical Industries Ltd (ICI), United Kingdom, obliged signatories to hold in confidence new animal testing research from Italy, which would eventually contribute to more protective workplace standards.

The US and European chemical companies met in Washington DC on 14 November 1972 at the headquarters of the US Manufacturing Chemists Association (MCA), the trade association of industrial chemical manufacturers.

The scientific findings revealed at the meeting came from a medieval castle in Bentivoglio, Bologna, Italy, equipped with a modern scientific laboratory, world-class animal testing facilities and top-notch scientific staff. Seated at microscopes, a scientific team, led by Professor Cesare Maltoni, was the first in the world to see evidence of cancer in the liver and kidneys of laboratory animals that had been exposed to inhalation of a daily concentration of vinyl chloride of 250 ppm — half the level allowed in workplace air at the time.

Figure 8.1 Image of the Secrecy Agreement



SECRECY AGREEMENT

Re: ANIMAL TESTING RESEARCH - VINYL CHLORIDE MONOMER

With regard to any information disclosed to personne of The Dow Chemical Company concerning European research on vinyl chloride monomer referred to in R. L. Lindsell's letter of August 16, 1972, addressed to the Manufacturing Chemists Association, we pledge to use our best efforts to hold such information strictly in confidence within Dow unless and until formerly notified specific consent to its release has been granted by the European sponsors. Such obligation of confidenc does not apply to information already known to Dow or informati which is independently developed by Dow.

THE DOW CHEMICAL COMPANY

By

Director of Research
November 13, 1972

Source: Markowitz and Rosner, 2002.

While the companies did not doubt the evidence from these studies, the Secrecy Agreement did not allow them disclose it. Such was the concern about leaks to the public that Mr D. M. Elliott of ICI 'insisted that the work tables be swept clear of paper for note taking before he would discuss anything regarding the European group's efforts. Such was done' (Markowitz and Rosner, 2002, p. 183).

In fact, Professor Maltoni's work was not the first indication that industry standards were inadequate and risked grievous harm to workers. The MCA had set an upper workplace limit for vinyl chloride concentration of 500 parts per million (ppm) in 1954. And despite a growing body of evidence that it was unsafe, this limit remained unchanged for two decades.

Internal corporate documents reveal that in the 1950s the industry already had animal testing data showing the workplace limit to be excessive. By 1961 company toxicologists were internally recommending a limit no higher than 50 ppm. Only in 1974 did the newly established Occupational Safety and Health Administration (OSHA) issue a new standard of 1 ppm. In the interim, workers were exposed to vinyl chloride concentrations that caused excruciatingly painful bone disease and cancer.

This chapter provides a summary of the early warnings and late responses to the dangers of vinyl chloride.

8.2 1930–1999: rapid growth in PVC output

Industrial output of VC began in the 1930s, mainly to support manufacture of polyvinyl chloride (PVC) products as diverse as shower curtains, food containers, floor coverings, pipes, packaging and wire coating. Since the Second World War, the largest use of VC has been in producing PVC and copolymer resins (HSDB, 2006).

Vinyl chloride is used primarily (> 95 %) in the manufacture of PVC (IARC, 2008). The main uses of

PVC are now in building and construction: window and door profiles, pipes and ducts, flooring and wall coverings, wiring and cable insulation, and stadium roofing. With the addition of 'plasticiser' chemicals to make it more flexible, it is also widely used in medical applications (tubing, bags, containers and other medical equipment, including the tubing in heart-lung bypass machines, catheter tubing, containers for intravenous solutions, blood storage bags, tubing for dialysis); electrical cable insulation; consumer products (inflatable children's toys, sports bags); vehicles (underbody coatings, sealants and floor modules, cable insulation, door panels and arm rests, weather strips and window sealing profiles); and packaging (bottles, toothpaste tubes, food packaging).

Global VC production (which is approximately equal to PVC production (IPCS, 1999)) grew swiftly from 450 tonnes per year in 1933 to 54 000 tonnes during the Second World War. By 1952 production was 145 000 tonnes and in 1971 it stood at around 7 million tonnes (IARC, 1974). Total annual world production in 1985 was about 17 million tonnes and in 1999 it was 26 million tonnes (IPCS, 1999). Global production and consumption of VC in 2010 was approximately 34 million metric tonnes. Global VC consumption is estimated to have increased by 4.6 % in 2010. Demand is expected to average growth of around 4.7 % per year from 2010 to 2015, and 4.2 % from 2015 to 2020 (SRI Consulting, 2011).

In 2005, production in Asia had outgrown that in both Western Europe and North America.

The Asia-Pacific region now accounts for around 54.8 % of the global installed VC capacity. The capacity and production of VC has grown very rapidly in China in the past decade. The export market of China for VC has also grown very rapidly. The country has emerged as the largest producer and exporter of VC in the world. Europe has the second largest VC capacity in the world and North America stands third. The VC capacity in Europe and North America is expected to be almost stagnant in the coming years (GBI Research, 2010).

An increasing number of workers worldwide are exposed to vinyl chloride during either its production, the manufacture of polyvinyl chloride or polyvinyl chloride processing. Since the late 1970s when the closed-loop polymerization process was introduced, the concentrations to which workers are exposed have decreased substantially in North America and Western Europe. Levels before that time had been higher than 38 ppm (100 mg/m^3) (2). In low and medium-resource countries, older technologies have continued to be used and therefore high exposures probably occur. Exposures in polyvinyl chloride processing plants are usually considerably lower than those in vinyl chloride monomer and polyvinyl chloride production; in Western Europe and North America, current exposure levels are generally below 0.4 ppm (1 mg/m^3). Concentrations of vinyl chloride monomer in ambient air are normally below 0.004 ppm (0.01 mg/m^3), but higher concentrations have been measured in the vicinity of vinyl chloride/polyvinyl chloride production plants (IARC, 2008).

Until the mid-1970s, VC gas was also used as a propellant in a wide variety of aerosols including hair spray by Clairol, leading to elevated exposures and eventually cancer in hairdressers (Castleman, 1981; Infante et al., 2009). In 1974 the US Food and Drug Administration (FDA) noted that using such products in small rooms could result in airborne levels far exceeding the workplace limit at the time. The US Environmental Protection Agency (EPA) issued an emergency suspension of its use as a propellant in pesticide sprays in 1974, and the US Consumer Product Safety Commission (CPSC) banned its use in consumer aerosol products in 1978.

In May 1973, citing the 1958 Delaney amendment of the Food and Drug and Cosmetic Act (which prohibited the use of any food additive which was demonstrated to cause cancer in humans or animals), the US FDA suspended approval for using PVC bottles for alcoholic beverages (Food Chem. News, 1973; US FDA, 1973). As a result of PVC food packaging, VC used to be detected in a wide range of foods, including edible oils, vinegars, margarines and bottled water (Page and O'Grady, 1977; Van Lierop, 1979; Benfenati et al., 1991). However, the US government now limits vinyl chloride to no more than 1 ppm in PVC food packaging materials, so it is no longer detected in food (ATSDR, 2006). VC is not known to occur naturally. Unintentional formation of the compound can occur in landfills where VC forms as a degradation product of chlorinated hydrocarbons used as solvents, and may subsequently be emitted as an air pollutant and to groundwater. VC is also found in tobacco smoke (IPCS, 1999).

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(2) 1 ppm = 2.6 mg/m^3.

Vinyl chloride (VC) is a gaseous chemical intermediate (its boiling point is – 14 °C) used in a number of final products. Even after being polymerised into polyvinyl chloride plastics (PVC), residual unreacted monomers in the plastic can still pose dangers. The VC copolymer 'vinyl chloride-vinyl acetate' is primarily used to produce films and resins, while another copolymer, 'vinylidene chloride-vinyl chloride', is used mainly in food packaging and metal coatings in storage tanks.

8.3 1930–1961: early warnings from animals and humans meet industry indifference

8.3.1 Earliest warnings

The short-term (acute) toxicity of VC was tested by inhalation in animals in the 1930s. It induced drowsiness, loss of coordination and loss of consciousness (i.e. it was a narcotic) at doses ranging from 5 000 to 120 000 ppm depending on the species tested (Patty et al., 1930; Peoples and Leake, 1933; Oster et al., 1947). In rats, congestion of internal organs (particularly the lungs, liver and kidneys) and fluid-filled lungs were observed after inhaling VC at high concentrations (Patty et al., 1930, Mastromatteo et al., 1960; Lester et al., 1963; Prodan et al., 1975). In dogs, severe heartbeat irregularities occurred under narcosis (Oster et al., 1947).

In humans, acute VC intoxication induces giddiness, nausea and headaches. At higher concentrations narcotic effects were also observed (Peoples and Leake, 1933). In a case of accidental poisoning in a PVC plant, VC caused almost immediate death of workers following loss of consciousness (Danzinger, 1960). Accidental spraying of VC caused effects ranging from skin rash to second-degree burns (Harris, 1953).

The first evidence of long-term (chronic) toxicity in workers was reported in the late 1940s by Soviet scientists who expressed concerns about hepatitis-like liver inflammation found in 15 workers (out of 48) exposed to VC (Tribukh et al., 1949). Further studies conducted in PVC factories in the USSR showed cases of vascular disease (angioneuropathy) in workers exposed to VC at levels as low as 5–15 ppm (Filatova and Gronsberg, 1957). Following these observations, technological improvements were made and in 1966 VC levels measured at USSR PVC plants dropped from 40 ppm (100 mg/m^3) to 4–15 ppm (10–40 mg/m^3) (Filatova, 1966).

8.3.2 Ignoring evidence from animal studies

In 1954, the US Manufacturing Chemists Association (CMA) established the workplace threshold limit value (TLV) of 500 ppm, and it remained at that level for two decades despite mounting evidence of its inadequacy. Since the US Occupational Safety and Health Administration (OSHA) would not be established for another 17 years (1971), the TLVs were set by the American Conference of Governmental Industrial Hygienists (ACGIH), which was then as it is now a volunteer organisation with no formal ties to the government. Its members include federal, state, and local government officials, as well as academics and industry consultants (Castleman and Ziem, 1988). Before OSHA, TLVs were often based on inadequate health information, and represented what the industry felt was achievable but not necessarily health protective (Markowitz and Rosner, 2002; Castleman and Ziem, 1988).

A turning point in the history of VC should have occurred by 1961 at the latest. In that year researchers from Dow Chemical published the results of a study on animals (rats, guinea pigs, rabbits and dogs) exposed to VC for seven hours per day at levels ranging from 50 to 200 ppm for six months, and at 500 ppm for 4.5 months. Dow reported liver abnormalities in male and female rats exposed to 500 ppm and an increase in liver weight in rats treated at 100 ppm. Liver enlargement and microscopic degenerative changes at 200 ppm were also observed in rabbits (Torkelson et al., 1961).

In fact, the key conclusions were already known at least two years earlier. Writing to Union Carbide Medical Director Thomas Nale in November 1959, Union Carbide consultant Henry Smyth had remarked that based on an 'off-the-record phone call' from Dow toxicologist V. K. Rowe, it was apparent that vinyl chloride was 'more toxic than has been believed'. 'Even 100 ppm produced organ weight changes and gross pathology', he wrote (Smyth, 1959). According to Smyth, Dow was considering whether this would have 'any bearing on the safety of (food) packaging uses' involving vinyl chloride exposure.

Noting that the 500 ppm TLV was based on a single guinea pig inhalation study from the 1930s, Smyth asked that the information reported remain confidential until published by Dow (Smyth, 1959).

In a letter dated May 1959, V. K. Rowe had likewise indicated to W. E. McCormick at US chemicals firm B. F. Goodrich that the current TLV of 500 ppm would cause 'appreciable injury' to full-time workers and raised particular concerns about the hazards of long-term exposures (Rowe, 1959).

The MCA in effect set the TLV in 1954 at 500 ppm, and it would remain so until it was lowered to 200 ppm in 1971 and finally to 1 ppm in 1974. The first OSHA limits adopted were the 1968 TLVs, so the permissible exposure limit in the US industries remained at 500 ppm until new rulemaking in 1974.

8.3.3 *1963–1971: secrecy over evidence of bone disease in workers*

Evidence of the risks of bone disease from VC exposure was not limited to animal studies. In 1963, Suciu et al. published the results of clinical observations of 168 workers engaged in PVC production, which described for the first time the role of VC in causing acroosteolysis — an extremely rare bone disease characterised by excruciatingly painful bone reabsorption, skin changes (scleroderma-like lesions) and vascular changes associated with Raynaud's syndrome and hepatomegaly and splenomegaly (Suciu et al., 1963).

At around the same time the Belgian chemical company Solvay observed two cases of acroosteolysis among workers in one of its factories in Belgium and informed other VC/PVC manufacturers. The same pathology was observed among workers in another factory of the same company in Romania. Between 1962 and 1965 several cases of acroosteolysis were observed in other Solvay VC/PVC factories (Maltoni, 1974a). However, no reports were made public, or to the independent scientific community, governments or workers.

In 1964 Dr John Creech, a physician who was doing regular medical checks for the US chemical company B. F. Goodrich, followed up a worker's complaint about painfully tender fingers and found four cases of acroosteolysis in workers that all worked in the same area of the VC/PVC plant. For Creech, this seemed to be obvious evidence of a link to their workplace conditions (Markowitz and Rosner, 2002, p. 173; MMWR, 1974). Goodrich asked Robert Kehoe of the Kettering Laboratory to investigate (3). Kehoe concluded that acroosteolysis was an 'entirely new' occupational disease. The medical Director of Goodrich asked a company physician at another Goodrich plant to 'determine as quietly as possible whether similar conditions existed at his plant', adding that 'We do not wish to have this discussed at all and I request you maintain this information in confidence' (Markowitz and Rosner, p. 174; MCA papers, 12 November 1964).

Other chemical companies took the same line. A Monsanto official, following the decision to x-ray exposed workers, said that 'I am sure that Dr Nessel can prepare these people with an adequate story so that no problem will exist' (Markowitz and Rosner, 2002, p. 174, MCA papers, 7 January 1966). The secrecy strategy extended to trying to restrict news of the disease in Europe. On hearing that a doctor from Solvay Chemical was about to publish his finding of workers with the same bone destruction seen in the B. F. Goodrich cases, the corporate vice president of Goodrich attempted to 'discourage or edit' the publication but was ultimately unsuccessful (Markowitz and Rosner, 2002, 174, MCA papers, 7 January 1966).

Although the public, government regulators, and workers were all kept in the dark, the news about acroosteolysis was shared widely among European and American chemical companies who learned at a private meeting of industry medical staff in June 1966 that 1 % of PVC plant workers and 6 % of the workers who cleaned out the vinyl chloride monomer (VCM) vats suffered from acroosteolysis. Goodrich asked companies to 'use discretion in making the problem public' (Markowitz and Rosner, 2002, p. 175, MCA papers, 17 October 1966). The industry was particularly concerned that the media and the public could have concluded that PVC products, especially those used in food packaging, may also be hazardous, which 'would have been very damaging for industry' (Markowitz and Rosner, 2002, p. 175, MCA papers, 24 January 1967).

In 1967 Goodrich researchers prepared a scientific article reporting 31 cases of acroosteolysis among vinyl chloride workers (Markowitz and Rosner, 2002, p. 176. Ref 40). According to later legal testimony from Dr Creech, the first draft of the article that he saw specifically identified VC as the cause of acroosteolysis, but this information was not included in the final version (Markowitz and Rosner, 2002, p. 176, Ref 41).

Two years later, in early 1969, the results from an MCA-funded study of acroosteolysis by the Institute for Industrial Health at the University of Michigan were presented confidentially to the MCA. The report found that acroosteolysis could affect connective tissue and bones beyond the fingers; that the odour of VC could only be detected at 4 000 ppm, not 400 ppm as previously thought, and was therefore an indicator of much more hazardous exposure than had been thought; that it could not be assumed that workers would be safe from disease at the exposure limit of 500 ppm; and that 'sufficient ventilation should be provided to reduce the VC concentration to below 50 ppm' (Markowitz and Rosner, 2002, p. 177, Ref 45). As this recommendation implied that VC was the cause of the disease, the MCA Occupational Health Committee voted seven to three to refuse acceptance of the report as written, and voted unanimously to accept it only when the report stated that 'Inasmuch as the etiologic agent of the disease is unknown, a level of vinyl chloride below 50 ppm should be used as an index of adequate ventilation' (Markowitz and Rosner, 2002, p. 177, Ref 46).

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(3) Kehoe also played an important role in the story of lead in petrol, described in the Chapter 3 on lead in petrol.

This 50 ppm recommendation in Spring of 1969 came after the same recommendation was made by Dow Chemical toxicologists in 1961 based on their own studies showing pathological changes in the livers of rabbits that they had been studying (Torkelson et al., 1961). Upon the recommendation of Robert Scala (Esso) in 1965 the ACGIH proposed lowering the TLV to 50 ppm based on the 1961 animal data of Dow scientists Torkelson and V.K. Rowe (Torkelson et al., 1961; Castleman and Ziem, 1988) But then, in a meeting with the ACGIH TLV Committee Chairman Stokinger in 1966, 50 member companies said 50 ppm was too low. Thus, the proposed change to the TLV was put off, according to an unpublished report of a discussion held at Mellon Institute on 1–2 February 1966 (Castleman and Ziem, 1988).

The ACGIH did not lower the TLV until 1971, and then only to 200 ppm based on unpublished evidence of liver damage in workers (Castleman and Ziem, 1988). Although Dow claims that the company reduced its workplace exposure limit to 50 ppm in 1961, it is known that this limit was exceeded (Castleman and Ziem, 1988).

These recommendations by corporate toxicologists and doctors went unheeded repeatedly, allowing continued excessive exposure of workers to continue. That is because the toxicologists and company doctors do not run the companies; corporate toxicological policy decisions are made by corporate executives as business decisions. Thousands of plants were melting and shaping PVC resins into credit cards, phonograph records and countless other products. No effort was made to limit the amount of residual VC monomer left in those resins. An official evaluation that worker exposures must be limited to 50 ppm could increase costs for the giant firms that made PVC polymer resins and some of the many plastic product manufacturers. Disclosure and recognition of the toxicity of VC could also endanger sensitive markets for PVC food packaging and medical applications. Then, there were aerosol products in which VC was used as a propellant.

The final report on acroosteolysis from the Michigan researchers was ultimately published in 1971 in the *Archives of Environmental Health*. It made no mention of the earlier view that the exposure limit of 500 ppm was not likely to be protective. It omitted reference to the inadequacy of the odour threshold. It said that the cause of acroosteolysis was unknown. Although it recommended further research, this was in fact unlikely; B.F. Goodrich executives explicitly decided not to accept any proposals for additional research into the causes of acroosteolysis. This enabled Goodrich and the rest of the industry to act as if the cause was 'unknown' (Markowitz and Rosner, 2002, p. 177).

8.3.4 1970–1983: recognising VC as a carcinogen

As reported by Maltoni (1974a), recognition of vinyl chloride's carcinogenicity began in the late-1960s. At that time, Solvay Chemical Company asked Prof. P. L. Viola, the company doctor at its VC/PVC factory in Livorno, Italy, to perform a long-term experiment to study acroosteolysis.

It was 1967 when Prof. Viola of the Regina Elena National Cancer Institute in Rome started the experiment exposing rats to 30 000 ppm VC vapours for four hours a day, five days a week, for 12 months. The results were a surprise. As Prof. Viola reported at the 10th International Cancer Congress held in Houston, Texas in May 1970, the study showed that after a period of 10 months, 70 % of rats treated developed malignant tumours of the skin and lungs (Viola, 1970; 1971). Immediately following the May 1970 communication, Prof. Cesare Maltoni, then Director of the Addari Institute of Oncology in Bologna, Italy, contacted Prof. Viola to discuss the findings.

While Prof. Viola was conducting his research, Prof. Maltoni and his group had launched an extensive programme of medical surveillance on workers of several chemical industries. In 1970 Maltoni started to detect a higher rate of abnormal cells in the saliva samples collected from workers exposed to VC in the Italian plastics industry (Maltoni et al., 1974b).

On the basis of Viola's experimental results and Maltoni's surveillance of VC/PVC workers, it became urgently necessary to conduct a large-scale experimental research project to better evaluate the carcinogenic potential of VC. Since Maltoni's institute specialised in occupational cancer prevention and rodent cancer bioassays, the major Italian VC/PVC producer at the time, Montedison, expressed interest in supporting research on the potential carcinogenic effects of VC. Later, other European PVC producers joined Montedison, namely ICI (the United Kingdom), Solvay (Belgium) and Rhône-Prugil (France), giving rise to the European Cooperative Group for the study of biological effects of VC.

In July 1971, Maltoni began a large project of multiple integrated experiments to study the carcinogenicity of VC in a laboratory at the Castle of Bentivoglio in the province of Bologna, Italy. This was partly funded by The Bologna Hospital Administration of which the Institute of Oncology 'F. Addarii' was a part. The project involved administering VC by different routes of exposure, at different doses/concentrations and for different periods to animals of both sexes, of various species (rat, mouse, hamster), strains and ages. The project lasted ten years and encompassed the use of more than 7 000 animals observed until spontaneous death; more than 200 000 histological slides were examined.

The financial resources required at the time amounted to more than USD 2 million which came mainly from public institutions and also from the chemical industry (Maltoni et al., 1981). The main results of the experiments were as follows:

1. VC was carcinogenic in all tested animals (rats, mice, and hamsters), producing tumours in the mammary gland, lung, zymbal gland (a gland not present in humans), skin, angiosarcomas of the liver, and others (Table 8.1);

2. VC was carcinogenic when administered by inhalation, ingestion, prenatal exposure (4) and possibly by intraperitoneal and subcutaneous injection;

3. a correlation existed between concentration, daily dose and length of exposure, and tumour incidence;

4. newborn rats were more susceptible to the carcinogenic effects of VC on the liver;

Table 8.1 Correlation of tumours in rodents to VC exposure

	Rat	Mouse	Hamster
Mammary malignant tumours (mainly carcinomas)	+	+	
Zymbal gland carcinomas	+		
Nephroblastomas	+		
Liver angiosarcomas, angiomas and fibroangiomas	+	+	+
Angiosarcomas, angiomas and fibroangiomas of other sites	+	+	(+)
Hepatomas	+	(+)	
Encephalic neuroblastomas	+		
Forestomach papillomas and acanthomas	+	(+)	+
Lung adenomas	+	+	
Cutaneous epithelial tumours	(+)	(+)	(+)
Melanomas			(+)
Acoustic duct epithelial tumours			+
Lymphomas and leukemias			(+)

Note: + denotes 'clear evidence of carcinogenicity'; (+) denotes 'borderline evidence of carcinogenicity'.

Source: Maltoni et al., 1984.

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(4) Experimental animal studies gave an early indication of foetal toxicity, which is an issue that emerges from several chapters e.g. Chapter 5 on Minamata; Chapter 7 on tobacco and Chapter 10 on BPA in this volume as well as the chapters on DES, radiation and PCBs in vol. 1 (EEA, 2001). This issue is also taken up in Chapter 26 on science for precautionary decision-making.

5. in rats multiple organs were sometimes affected by the carcinogenic effects of VC;

6. later it was shown that VC induced the onset of tumours at concentrations as low as 10 ppm by inhalation and 0.3 mg/kg body weight by ingestion. Although these did not reach statistical significance, they were considered to be biologically relevant (Maltoni et al., 1977).

Maltoni presented his early results to the scientific community at the 2nd International Symposium on Cancer Detection and Prevention, held in Bologna in April 1973. This presentation does not appear to have attracted the attention of government regulators or the general scientific community. Manufacturers aware of Maltoni's findings were still operating under the 'secrecy agreement' and would continue to do so until 1974. In fact, a meeting between NIOSH and the industry representatives from Dow, Ethyl, Union Carbide and the MCA took place on 17 July 1973 but failed to include mention of Maltoni's presentation at the Bologna Conference a few months earlier. Viola's finding of cancers at exposures of 30 000 ppm was mentioned at the NIOSH meeting but not the evidence of cancer at 250 ppm in Maltoni's studies (Markowitz and Rosner, 2002, p. 189, Ref 106). The latter findings were not published until 1974 in the proceeding of the Conference (Maltoni, 1974b).

It was not until 22 January 1974 that B.F. Goodrich alerted the government and the next day issued a public press release announcing it was investigating the deaths of three workers at its VC/PVC plant in Louisville, Kentucky who had died of an otherwise extremely rare cancer called liver angiosarcoma (Markowitz and Rosner, 2002, p. 191, 192). In fact, Dr John Creech, who had identified the rare bone disease acroosteolysis among Goodrich workers ten years earlier had now identified not three but four cases of angiosarcoma deaths from 1968 to 1973; all were among men working in the PVC polymerisation section of the factory (Markowitz and Rosner, 2002, p. 192; MMWR 1974). This time he was sounding an alarm about worker deaths from a cancer so rare that it accounted for just two dozen deaths in the whole country annually — making four deaths among the several hundred plastics workers akin to an epidemic. More damning still, this rare cancer was also showing up in Maltoni's experimental animals at exposures that were half the workplace exposure limit (Creech and Johnson, 1974).

Creech ultimately identified seven cases of liver angiosarcomas in the Goodrich plant between 1964 and 1974, all among 'pot cleaners' who were lowered into polymerisation reactor tanks 10 feet deep, with no more than a six foot opening for fresh air, to chip polymerised residue off the tank insides (Markowitz and Rosner, 2002, p. 192, 193).

8.4 1974: governments swift response

In the US, governmental response was swift. OSHA held a fact-finding hearing on the possible hazards of manufacturing and using VC and PVC in Washington DC on 15 February 1974. Prof. Maltoni was invited to give an oral presentation of his experimental results — the first time that his findings came officially to the attention of the public and government officials. At the end of the hearing, Dr Selikoff of Mount Sinai Medical School in New York stood up and said 'no question, but I rise merely to voice the thanks of the American scientific community for the beautiful piece of work you have done' (Maltoni, 1974c). Shortly thereafter, Creech and the B.F. Goodrich Director of Environmental Health published the medical report of the four deaths from liver angiosarcomas in workers employed in the Louisville plant in 1968, 1971, and two deaths in 1973 (Creech and Johnson, 1974). A footnote by the editor noted that Prof. Maltoni was the first to show the relationship between exposure to VC and angiosarcoma in mammals. Indeed, it is evident that the notification of liver angiosarcoma in workers exposed to VC by B.F. Goodrich to employees, to NIOSH and to the public was influenced by Maltoni's experimental data. The first results of Maltoni's work were published in 1974 (Maltoni, 1974b). Results of the full project were published in 1981 and 1984 (Maltoni et al., 1981 and 1984).

On 5 April 1974 OSHA established that the occupational environment in VC plants should be monitored so that no employee was exposed to VC at a concentration exceeding 50 ppm (127.0 mg/m^3) (Federal Register, 1974). A few months later the OSHA standard was lowered again to a ceiling of 1 ppm, following Maltoni's May 1974 communication at the New York Academy of Sciences that VC was even carcinogenic when administered to rats via inhalation at 50 ppm (Maltoni and Lefemine, 1975). Later, in 1976 Maltoni reported the onset of tumours considered biologically correlated (but not statistically significant) in rats exposed to low dose of VC, namely: liver angiosarcoma and Zymbal gland carcinoma down to 10 ppm by inhalation and 1 mg/kg by ingestion. None of the specifically VC-related tumours were found at doses of 1 ppm (by inhalation) and 0.03 mg/kg by ingestion (Maltoni et al., 1977).

Subsequent VC carcinogenicity bioassays on rodents confirmed the results of Maltoni's project (Keplinger et al., 1975; Lee et al., 1978; Feron and Kroes, 1979). Despite this very strong evidence the US plastics industry lodged an appeal against the OSHA 1 ppm standard. They lost the case in January 1975 and received a scathing condemnation from the judge (see Box 8.1).

Industry responded quickly and easily to the new standard. An analysis in 2000 found that the costs of industry compliance with the 1 ppm standard were only USD 278 million. Industry had earlier estimated that it would cost them up to USD 90 billion and 2 million jobs. As the *New York Times* noted, 'not one of the doomsday predictions (from industry) has proven accurate', noting also that supplies of VC had expanded, prices had not increased and the industry was expanding, not contracting (Rattner, 1975).

This public relations tactic of using an industry trade association to threaten and sue regulators and issue claims no member company would dare make in its own name would become more familiar after 1974 (see Chapter 3 on lead in petrol and the tobacco case studies in Chapter 7).

Industry has generally exaggerated the projected costs of meeting new regulations, see Chapter 23 on understanding and accounting for costs of inaction.

Angiosarcoma of the liver is considered very rare in humans, with only 20–30 cases per year reported in the US (Gehring et al., 1978; ATSDR, 1995). In the years 1975–1978, immediately following Creech and Johnson's first reports of liver angiosarcomas in workers, medical records, pathological material and medical surveillance revealed other liver angiosarcomas in workers exposed to VC, both in the US and in other countries. According to the Liver Angiosarcoma Registry maintained by Imperial Chemical Industries (ICI) in the United Kingdom 103 cases of liver angiosarcoma were reported among workers exposed to VC in various countries in the period 1974–1983 (Stafford, 1983). VC liver cancer deaths have also been reported in Europe and Asia (see Box 8.2 on the IARC Monograph).

Industry responded to these initial cases of liver cancer by commissioning an epidemiological study of the cancer risk in VC-exposed workers. It concluded that 'the overall mortality (of workers in the vinyl industry) was 75 % of what would be expected in a comparable population of US males' and that 'no cause of death showed a statistically significant excess over what would be expected in a comparable US male population' (Tabershaw and Gaffey, 1974; Markowitz and Rosner, 2002, p. 227). However, it did note that, 'cancers of the digestive system (primarily angiosarcomas) respiratory system, brain, and cancers of unknown site, as well as lymphomas, occurred more often than expected in those members of the study population with the greatest estimated exposure' (Tabershaw and Gaffey, 1974; Markowitz and Rosner, 2002, p. 227).

Box 8.1 The judicial critique of industry's lack of action on VCM

In January 1975 Justice Tom Clark, retired from the US Supreme Court, heard the appeal against OSHA for the US Court of Appeals for the 2nd Circuit. Noting the industry policy of delay, feigned ignorance and irresponsibility, he rejected all of the basic arguments of the industry and observed that 'strong warning signals … of long before' had been ignored. Despite years of warnings and research since 1949, including the AOS episode, 'nothing was done' (Markowitz and Rosner, 2002, p. 222–223).

The judge also noted that the ultimate facts regarding the proper standard for protecting workers were 'in dispute' and 'on the frontiers of scientific knowledge' but that 'the factual finger' pointed to the need for a low exposure limit, based on the animal evidence. The OSHA standard came into effect on 1 April 1975.

This favourable ruling for workers and the public, however, was followed by a setback in the US Supreme Court decision of 2 July 1980 in the benzene case which forced OSHA to provide quantitative evidence that there would be a 'significant risk of material health impairment'. OSHA lost its case for a 1 ppm standard for benzene. Dissenting Judge Thurgood Marshall noted that this placed 'the burden of medical uncertainty squarely on the shoulders of the American worker' (Landrigan and Nicholson, 1998). The precautionary principle is designed in part to reverse this burden of proof of harm so that risk makers, not risk takers, have to show, at least beyond reasonable doubt, that chemicals and other stressors are acceptably safe for workers, consumers, and the environment.

The study was criticised by experts at NIOSH for not including some 75 % of workers with the longest exposure (e.g. for over 20 years) where the greatest cancer risk was to be expected. When more of these were found by independent investigator Dr Joseph Wagoner, he calculated that there was a 57 % excess of cancer deaths in the workers (Markowitz and Rosner, 2002, p. 227). Wagoner explained to a Senate Committee that the Tabershaw-Cooper study had diluted the cancer risk by including recently hired workers with only a year or two of exposure. In his study Wagoner only included workers who had been exposed for over 15 years since he knew that 'we were looking for the *latent effects* or the effects of a carcinogen which appear many years after a person was initially employed' (Senate Committee on Commerce, 1974).

Other experts pointed out that comparing workers' death rates with all US males was likely to underestimate the risk as workers were mainly fit whereas all males included the unfit, the unemployed and the disabled. This is called the 'healthy worker effect' which means, in general, that the expected cancer mortality rate for workers with sufficiently long exposure time for cancer latency if there were no occupational cancer risk should be around 75–80 % of the rate expected for all males in the population from which they came (Fox et al., 1982) (see Chapter 26 on science for precautionary decision-making which identifies these and other methodological limitations of much of the health and environmental sciences which try to avoid wrongly labelling an agent as hazardous (a 'false positive') more than trying to avoid wrongly labelling an agent as being safe (a 'false negative')). See also Chapter 2 on the precautionary principle and false alarms.

8.5 1974–present: does VCM cause brain cancer, other cancers and reproductive effects?

Although by the 1970s the industry was no longer able to deny evidence of liver angiosarcoma, Sass et al. (2005) document continued efforts to suppress or play down the evidence of other cancer types, particularly brain cancers.

In an internal memo in 1976, Ethyl Corporation acknowledged risks for liver angiosarcoma, brain, and lung cancers (Sass et al., 2005). A review by the International Agency for Research on Cancer (IARC) in 1979 determined that VC exposure was a known human carcinogen (Group 1) associated with cancers of the liver, brain, lung and haemo-lymphopoietic system, and that there was no exposure level below which an increased risk of cancer would not occur in humans, that is, no threshold or safe level of exposure (IARC, 1979). A second IARC review in 1987 and a third update in 2007 re-confirmed the previous evaluations and updated the scientific references supporting their conclusions (IARC, 1987; 2008). The most recent IARC update additionally noted that animal studies suggest a higher susceptibility to cancer when exposures take place early in life (Grosse et al., 2007; IARC 2008).

A 1991 study of a VC-exposed worker cohort by Wong and co-workers at first reported an, 'excess in cancer of the brain' (Wong et al., 1991). However, at the request of the chemical industry, which had funded this study, two of the authors made a public retraction two years later, saying that, 'We conclude that our finding of an excess of brain cancer among US vinyl chloride workers reported earlier was not likely related to the chemical' (Wong and Whorton, 1993; Sass et al., 2005; Markowitz and Rosner, 2002, p. 229, 230).

In 2010 The Center for Public Integrity's Jim Morris reported on a lawsuit concerning a brain cancer cluster surrounding a chemical plant operated by Rohm and Haas, now a subsidiary of Dow Chemical Co. In their defence, 'Experts for Rohm and Haas argue that the link (with brain cancer) is tenuous at best and concede only that vinyl chloride in high doses can cause a rare liver cancer called angiosarcoma' (Morris, 2010). Morris's report of the proceedings states, however, that the industry-funded study that Rohm and Haas relied on 'failed to include as many as two dozen fatal cases of brain cancer' — which significantly compromised the ability of the study to detect an elevated brain cancer risk (Morris, 2010).

Reports of excessive deaths from liver carcinoma in workers exposed to vinyl chloride have been published since the mid-1970s in the US (Mundt et al., 2000), France (Saurin et al., 1997), Germany (Weihrauch et al., 2000), the European four-country study (the United Kingdom, Sweden, Italy, Norway) (Ward et al., 2001), Taiwan (Wong, 2002); Italy (Pirastu et al., 2003) and Japan (Makita et al., 1997).

Panel 8.1 provides a personal reflection of some events in the United Kingdom following the Goodrich announcement.

Panel 8.1 VCM: a personal perspective of a year in the United Kingdom after the Goodrich announcement of 1974

Charlie Clutterbuck

After the Goodrich announcement about their three workers with liver cancer, some very expensive and comprehensive measures were taken to deal with the VC hazard. In the United Kingdom, the Employment Medical Advisory Service (EMAS), with the help of the Factory Inspectorate and industry initiated many studies (Forman et al., 1985). The PVC manufacturing units were the subject of closest examination. VCM production plants and PVC fabrication processes were also investigated; so too were warehouses storing PVC, transportation services, meat packers using PVC wrappers, drinks contained in PVC bottles, and emissions into the atmosphere.

Later there would be research into the incidence of liver cancer in the vicinity of VCM plants, where some plants were clearly more dangerous than others (Elliot and Kleinschmidt, 1997). Initially monitoring was carried out irregularly, and then accurate to only about 200 ppm. Later this improved to 10, then 1 ppm, then 1 ppb. Within a few years, it was carried out continuously, in such a way that the levels were known to workers immediately. Soon after alarm systems were introduced control engineering concentrated on improved ventilation systems, reducing leakages at valves and finding ways of cleaning the autoclaves where the vinyl chloride is polymerized, using high pressure water systems.

Within the first year, GBP 9 million was spent on re-organising and improving plant design in the United Kingdom. A further GBP 4 million was estimated to have been lost in production. There may have been the same exaggeration of costs beforehand that there was in the US, but it was all less transparent in the United Kingdom. While much of this cost would have been unnecessary if control measures had been built in at the design stage, it must be granted that the industry did undertake expensive control procedures. Why were these extensive measures undertaken? Coal miners and coke oven workers never got that sort of investment, despite their dust diseases and lung cancers.

There are perhaps two main reasons. Angiosarcomas develop so gradually that they are often well established by the time of diagnosis. The combination of aggressive growth, few treatment options, and extreme rarity makes angiosarcoma one of the deadliest cancers. The moral obligation was clear, especially considering the industry's failure to spot it previously. The rarity of the disease also meant that the causal connection with vinyl chloride was undisputed. What if VCM had caused lung cancer? We may not know even today. And it would have been disputed for many years.

The second reason was that the nature of the plastics industry meant that the hazard was controllable. There were six VC fabrication plants, and a similar number of PVC manufacturing plants. The costs of control, though high, were relatively low in such a capital-intensive industry. If the chemical was widely distributed — like VC's close relative, trichloroethylene (trike), which was found in every engineering shop in the country, it would have been much harder to control.

Until the VC cancers, the plastics industry was perceived as 'clean'; a lot cleaner than the mines or the mills around. But just because there was no evidence of harm the lack of evidence did not mean there was no hazard. This worried the toxicologists and epidemiologists who have since been more alert to toxic possibilities.

The reaction of the trade unions was different in the United Kingdom to that in the US. In the US the main union the Oil, Chemical and Atomic Workers Union (OCAW) had already been on strike for improved health and safety so they took up the campaign vigorously. Their role was critical in the setting of the new Threshold Limit Values — the concentrations workers were allowed to be exposed to.

In the US there were transparent court hearings, where the unions went for a 'no detectable level'. The court decided the level should be 1 ppm, with a 15 minute excursion to 15 ppm allowed, and that that was technically feasible. However in the United Kingdom there was a tripartite committee of the TUC, CBI and government which produced a Code of Practice. This is less legally binding, and it recommended working to 25 ppm.

Panel 8.1 VCM: a personal perspective of a year in the United Kingdom after the Goodrich announcement of 1974 (cont.)

Action taken by workers in the United Kingdom was varied. At ICI Runcorn, spasmodic strike action was taken over a period of nine months for 'danger money'. At Vinatex, Chesterfield, concern was centered mainly on the risk of acreosteolysis, as 20 men suffered from this, and in getting compensation for it. This was typical of UK trade unions at that time, where compensation was more important than prevention.

Elsewhere the workers left it to their national unions to deal with. The national TGWU officer told me that 'they were already looking after everything'. This struck me as odd in comparison to the US union reaction. None of the three main UK unions — GMWU, TGWU, and ASTMS then had their own Health and Safety Officers (⁵). The GMWU made the most effort to inform, using the information from the International Chemical Federation. The TUC's Medical Adviser, Dr Robert Murray said: 'What you've got to say to the workers is that the risk is small; that apart from the risks involved when he drives a car and eats too much, and drinks too much, here is another risk which he has got to live with' (*Nature*, 15 February 1974) (⁶).

I contacted the local unions at BP Baglan Bay — and later at ICI Hillhouse. While visiting Baglan Bay, one of the managers said to me 'Actually we are quite pleased about vinyl: it's the only issue that we are in agreement on with the unions'. I knew there must be something wrong with communications, so made sure the unions got all the information coming from the US and the scientific press, both directly and indirectly through programs like TV 'World in Action'. The attitude changed dramatically. The local unions invited me on site. Now I was refused entry by the management. The workers threatened a 24-hour strike — a massive ordeal for a petrochemical plant. But eventually we had to meet outside the plant — and on the TV programme on an 'Open Door' programme. TU reps at ICI Runcorn said that the same thing happened there — that once they were informed by organisations outside their traditional union sources, they could look after their members' interests better.

The petrochemical industry was successful in removing the grosser hazards while keeping the issue confined to the risk of rare cancer. The arguments were not taken up about related chemical — like trichloethylene, nor did the industry accept that other cancers were causally related. The arguments also confined the fears mainly to the fabrication units, less to those handing the finished product PVC. Over the years the consumer lobby has made sure that residual VC in PVC is cleaned out, and there has been replacement of PVC in food wrapping.

Among the lessons learnt for us 'radical' scientists was the role of science in health matters (Clutterbuck, 1986). Good scientific work could be left in academic filing cabinets, having no impact on people's health. We needed to translate that work, without twisting it, to what people would understand. As a result of the VC experience, a group of scientists at the British Society for Social Responsibility in Science set up the magazine *Hazards Bulletin*: it is still alive and well after 35 years but now known simply as 'Hazards'.

(⁵) The 1974 Health & Safety Act made provision for the trade unions to appoint their own safety representatives from amongst the employees and provided for their offsite training by the TUs. This led to ASTMS and GMWU appointing their first National H&S Officers in 1977/1978.

(⁶) Dr Murray had previously played down the risks from the potent occupational carcinogen BCME three times in 1969, 1971 and 1974 when the trade union safety representative, Andrew Tree, sent him the US studies and his own analysis of lung cancer deaths in some young, non-smoking men in his BCME exposed colleagues. It was to be 1982 before the UK BCME workers at Mr Tree's Welsh plant were told of the risks, some eight years after the US OSHA had labelled BCME as a human carcinogen (Doyal et al., 1983).

In summary, VC exposure has been associated with the following, in addition to angiosarcoma of the liver:

- brain cancer (Byren et al., 1976; CMA, 1998; Monson et al., 1975; Weber et al., 1981; Environmental Health Associates, 1986; Wong et al., 1991; Mundt, 2000; Lewis and Rempala, 2003; IARC, 2008);
- hepatocellular carcinoma (Byren et al., 1976; CMA, 1998; Pirastu et al., 1990, 1998; Simonato et al., 1991; IARC, 2008);
- hemolymphoreticular neoplasias (Simonato et al., 1991; Weber et al., 1981);
- lung cancer (Buffler et al., 1979; Monson et al., 1975);
- liver cirrhosis (Ward et al., 2001);
- birth defects near PVC manufacturing plants (Infante, 1975);
- miscarriages among VC-exposed workers' wives (Infante et al., 1976a, b; NIOSH, 1977; ATSDR, 2006).

In 2008 IARC published an updated Monograph on vinyl chloride and related compounds such as vinyl bromide, confirming previous assessments (IARC, 2008) (see Box 8.2).

8.6 Some late lessons from vinyl chloride

1. The most important things that changed between 1959 (when internal company advice to lower exposure limits was ignored) and 1974, was that four deaths from a rare liver cancer from one company were publicised (unlike other earlier warnings); that this evidence was supported by strong animal evidence; and that public awareness and concern about toxic chemicals in the environment ensured that this evidence led to quick and radical regulatory and company action, at least in the US. The creation of new US government regulatory agencies — OSHA and the EPA — at the start of the 1970s, in a climate of union and environmental activism and media interest, helped to create this strong and prompt public health response.
2. It turned out that a simple engineering solution had been available all along to

Box 8.2 Conclusions of 2008 IARC Monograph on VCM and related compounds

VCM causes angiosarcoma and heptacellular cancer and the evidence is sufficient to categorise it as a known (Class 1) human carcinogen.

For other cancers *'the Working Group did not find strong epidemiological evidence for associations of exposure to vinyl chloride with cancers of the brain or lymphatic and haematopoeitic tissue or melanoma. Although the associations found for these cancers in specific studies may reflect true increases in risk, the findings were inconsistent between studies, no clear exposure–response relationships were found in the European multicentric study and, for several of the sites, the numbers of observed and expected cases were small'* (IARC, 2008).

The report also uses chemical 'analogy' when evaluating the cancer evidence on vinyl bromide, a chemical cousin of VC but for which there is very much less evidence available than for VC. 'Analogy' is one of the nine criteria that epidemiologist Bradford Hill set out to help experts and others to move from merely observing an association between an exposure and a health effect, like cancer, to concluding that the association is causal (Bradford Hill, 1965).

'In making the overall evaluation the (IARC) Working Group took into consideration the fact that all available studies showed a consistently parallel response between vinyl bromide and vinyl chloride … For practical purposes, vinyl bromide should be considered to act similarly to the human carcinogen, vinyl chloride'. IARC concluded that vinyl bromide is 'probably' carcinogenic to humans (Group 2A) (IARC, 2008).

This reasoning is based in part on 'analogy', a basis for helping to infer likely causality when evidence is scarce. Experience has shown that similar chemical structures commonly exhibit similar toxic effects. Acting on this knowledge enables us to best utilise the very limited data base in toxic substances control.

lower worker exposures and environmental emissions dramatically. Steam-stripping PVC in polymerisation reactors reduced levels of residual VC in PVC resins by 99 %, dramatically lowering exposures in polymerisation plants and PVC fabrication plants. OSHA moved to reduce its enforceable Permissible Exposure Limit from the 1968 TLV of 500 ppm to 1 ppm in the workplace air. The EPA followed with emission standards that greatly reduced the 4 % loss of VC to the environment during PVC production. The VC/PVC industry was easily able to comply and keep growing to this day. It was finally a regulatory success story and another example of how clear and challenging regulations can stimulate innovation (7) (Ashford and Hall, 2011; 2012).

3. Although it was threatened that a decrease in worker exposure levels to 1 ppm would cause the collapse of the VC/PVC industry, resulting in losses of USD 60 million annually and 2 million jobs (Washington Post, 1974), an important lesson learned was that technological innovation to reduce exposure levels can indeed be accomplished in a short time without catastrophic consequences on production or employment (Sass et al., 2005).

4. Based on information available to major companies using VC in the 1950s, toxic exposures should have been lowered and applications restricted. However, industry resistance to a discretionary increase of production costs, with the possibility of lost markets as well as decreased profits, is rarely if ever overcome merely by corporate conscience (corporate social responsibility is the current term for this concept). To the business executives who decide what will be made and how, the immediate prospects of regulation, liability and market losses to an informed public are much more persuasive and likely to prompt significant change.

5. The story of the carcinogenicity of VC showed without a doubt the validity of long-term bioassays in predicting not only the general carcinogenicity of industrial agents, but even specific target organs and tissues affected. (Maltoni et al., 1984; Soffritti et al., 2002; Huff et al., 2002). See Panel 8.2 on the value of animal tests in identifying carcinogens without waiting for them to appear in humans (8).

6. Although the lowering of the worker exposure level from 500 ppm to 1–3 ppm was undoubtedly a great achievement in 1974, these levels did not continue to be lowered despite experimental evidence which demonstrated even then the risks of exposure at concentrations of 50 ppm and less. The approach to setting exposure levels should be a dynamic one, in which levels are constantly lowered throughout time in light of scientific evidence and technological achievements. This is a lesson that is also found in Chapter 3 on lead in petrol, Chapter 5 on mercury and Chapter 6 on beryllium.

7. The epidemiological evaluation of the carcinogenic effects of VC has certainly underestimated the risk of this compound. From the beginning, attempts were made to reduce the quantification of risk to a few dozen cases of liver angiosarcoma, cases which were discovered often thanks to observations made by workers and clinicians. Beyond liver angiosarcomas however, epidemiological data from the 1970s reported an association between VC and lung cancer, hepatocarcinomas etc. Unfortunately, not enough weight was ever given to these studies, and the 1988 review by Richard Doll, which was widely accepted, concluded that for workers exposed to VC there was no evidence of risk of any other type of tumour than angiosarcoma and a modest risk of lung cancer in workers heavily exposed (Doll, 1988). Doll reported an excess of brain cancers which he dismissed as not statistically significant. However, even in the largest and most well-documented epidemiological study of VC exposure, the average age of the cohort was only 54 years (US EPA, 2000). Given that 80 % of cancer diagnoses are in persons over the age of 55 (ACS, 2005), the absence of a longer time horizon means that not only can we not rely exclusively on epidemiological evidence, but to do so would be a failure of public health, ignoring laboratory evidence

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(7) The link between challenging regulations and the stimulus of innovation was described some years ago (Porter, 1995). It has since been investigated more closely and seems to hold up in many but only specific circumstances (Porter, 2011).

(8) Extensive research efforts are underway to minimise the use of animals whilst retaining, or improving upon, their value in identifying carcinogens.

while we count the bodies until they become statistically significant.

8. Finally, as stated by Cesare Maltoni, 'the history of VC carcinogenicity has brought forth an important lesson: the studies in the field of environmental and occupational carcinogenesis, particularly in industrialized countries, must … represent an important component of the decision-making processes which regulate the developmental trends of society' (Maltoni et al., 1984).

This issue of slow or hostile corporate responses to early warnings is further examined in Chapter 25 'Why did bisiness not react with precaution to early warnings?' Of course there are, and always have been cases of 'progressive business' ([9]).

Table 8.2 Early warnings and actions

1930s–1959	Acute toxicity of VCM demonstrated in animals and workers in USA, Europe and Russia (where limit of 500 ppm ([10]) exposure was established)
1959	Consultant tells Union Carbide that VCM is more toxic than believed and Dow's toxicologist says 500 ppm limit would lead to 'appreciable' harm
1963	Acroosteolysis (AOL) is observed in workers in Belgium and Romania
1964	Dr John Creech followed up a worker's complaint at US chemical company Goodrich about painfully tender fingers and found four cases of AOL clearly linked to workplace exposure to VC
1965	Esso toxicologist recommends to the ACGIH that VC exposure limit should be 50 ppm. ACGIH accepts industry claims that this is too low and costly and the TLV is left at 500 ppm (Castleman and Ziem, 1988)
1966	European and US chemical companies told that 6 % of VC vat workers had AOL. The results were not shared with regulators or workers
1967	Scientific article by Goodrich researchers identifying 31 AOL cases; first draft mentioned VC as the cause but published article did not. Recommended that workplace exposure be reduced to 50 ppm
1968–1970	Prof. Viola demonstrates 70 % of rats with cancer of skin and lungs at high doses of VCM, i.e. 30 000 ppm over 12 months
1970	Prof. Maltoni finds abnormal cells in workers' saliva
1971	Prof. Maltoni begins large-scale, long-term cancer studies in rats, mice and hamsters (from prenatal exposure to natural death) and TLV in US is lowered to 200 ppm based on non-cancerous liver effects in workers
1973	Maltoni released his first results to the scientific community in the context of the 2nd International Symposium on Cancer Detection and Prevention held in Bologna
1974	Four deaths from rare liver disease (angiosarcoma) at PVC plants of Goodrich, USA, reported to the government and in the media. US government orders lowering of exposure limit to 50 ppm and then to 1 ppm after Maltoni's report of liver cancer at 50 ppm in rats
1979	International Agency for Research on Cancer (IARC) confirms VC as Category 1 human carcinogen for liver, brain, lungs and blood-forming system and found no safe exposure level
1982	IARC re-confirms 1979 conclusions

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[9] The Quakers and some others in the early days of the industrial revolution were pioneers in what, for those times, was progressive business. For example, Josiah Wedgewood on noting the passing of the first effective Factories Act to constrain the excesses of capitalism in 1833, wrote to the UK government asking for similar laws to be applied to his pottery industry.

[10] Based on one small guinea pig study sponsored by the Bureau of Mines in 1930s which was assumed to provide sufficient evidence to protect workers at an exposure limit of 500 ppm (Markowitz and Rosner, 2002, p. 172). This represents an example of the 'unsubstantiated authoritative assertion'. See Chapter 3 on lead in petrol for other examples.

Panel 8.2 Value of animal testing for identifying carcinogens

James Huff

> *Results of laboratory animal tests to predict human cancer is effective in identifying potential human carcinogens before human exposure, permitting measures to be taken to prevent that exposure, a foolproof way to prevent human cancer.*
> David Rall, former Director of National Institute of Environmental Health Sciences (NIEHS) and creator of the National Toxicology Programe (NTP) (Rall, 2000).

Certain chemicals, mixtures of chemicals, exposure circumstances, lifestyles and personal or cultural habits, occupations, viruses, living conditions, and physical agents have been causally associated with cancers in humans (CalEPA, 1986; RoC, 2011 and IARC Monographs ([11])). Most, however, are not considered potentially carcinogenic and the proportion of 'agents' eventually identified to cause cancer is projected to be relatively low, likely less than 10–15 %. However this is still a large overall number considering approx. 100 000 chemicals in commerce, with an ever larger number of formulations and myriad of products containing these chemicals. Examples of human carcinogens in different categories are listed, with those covered in this volume and EEA, 2001 in bold:

1) Defined chemicals — **benzene,** butadiene, formaldehyde, **vinyl** bromide/**chloride**/fluoride;
2) Mixtures of chemicals — agent orange (TCDD), **polychlorinated biphenyls (PCBs);**
3) Pharmaceuticals — **diethylstilbestrol (DES),** estrogens, phenacetin;
4) Cancer chemotherapeutics — azathioprine, busulphan, chlornaphazine, MOPP;
5) Lifestyles — alcoholic beverages, sunning/tanning, **tobacco** products;
6) Industrial exposures — acid mists, coke ovens, iron and steel founding, leather and wood dusts, rubber industry;
7) Manufacturing processes — aluminium, auramine, coke production;
8) Occupations — chimney sweeps, hair dresser/barber, painters, wood workers;
9) Biologic agents — Epstein-Barr virus, hepatitis B and C viruses, human papilloma virus;
10) Metals and compounds — arsenic**, beryllium,** cadmium, chromium, nickel;
11) Physical agents — **asbestos, ionizing**/ultraviolet **radiations**, UV tanning devices.

For larger and more detailed listings see CalEPA, 1986; CMCRC, 2012; Soffritti et al., 2002; IARC, 2012; NTP TRs, 2012; RoC, 2011.

Operational definition of a carcinogen

A chemical, substance, mixture, agent, or exposure circumstance will be designated as a carcinogen by inducing tumours as evidenced by one or more of these experimental observations:

1) Increased incidence of organ/tissue tumour type(s) compared to controls;
2) Occurrence of tumours earlier than in controls (reduced latency);
3) Development of tumour types not seen or rarely occurring in controls;
4) Increased multiplicity of organ/tissue tumours in individual animals;
5) Increased incidence of total primary tumours: malignant, benign, and/or combined;
6) Increased ratio of total malignant to total benign tumours.

In this operational perspective tumours may be benign, malignant or an appropriate combination of both types (Huff et al., 1989). In some cases preneoplastic lesions (hyperplasia, metaplasia) may be combined with tumours for evaluation, especially with evidence of progression.

These categories also fit into the overall schema of mammalian, including human, carcinogens, yet for humans less is known about these individually; in fact typically only items 1 and 3 are used to associate human cancers with exposures to a carcinogen, with 2 being less common.

1) Increased incidence of tumour type(s) in exposed population compared to unexposed controls (**benzene, metals**, **tobacco**);
2) Occurrence of tumours earlier than in controls (BCME, lung cancer in young workers; DES, clear cell vaginal cancers in young girls);

([11]) IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 1–100, http://monographs.iarc.fr/ published by International Agency for Research on Cancer (IARC).

Panel 8.2 Value of animal testing for identifying carcinogens (cont.)

3) Development of tumour types not typically seen or occurring only rarely in human controls or populations (**asbestos**, **DES, VCM**).

Current methods to identify carcinogenic potential of chemicals
These rely largely on:

1) Short-term *in vitro* and *in vivo* tests;
2) Mid- and long-term *in vivo* bioassays;
3) Epidemiological investigations;
4) Molecular mechanisms or modes-of-action;
5) Structural-activity-effect-relationships;
6) *In vitro* robotic high-throughput screening (in development);
7) Individual or group scientific interdisciplinary expertise.

> *Primary prevention was … implemented on the basis of the capacity of long-term experimentation in animals to predict similar effects in humans, taking into account biological plausibility but independently of the extent of understanding of the underlying mechanisms.*
> Lorenzo Tomatis, who created IARC Monographs and second Director of IARC (Tomatis, 2006).

Thus, scientific, public health and regulatory communities must continue to utilise all available means and strive to develop newer methods and tools to more easily, quickly, cheaply and reliably identify carcinogens in the human milieu. In particular, there is a need to reduce numbers of animals used in testing for carcinogenic activity and in general to encourage their replacement with other, equally effective, non-animal methods.

This effort continues. However, since adequate human studies are typically absent, are costly and time-consuming or of low power or sensitivity, and alternatives to animals have so far proven unsuccessful, the most useful time-proven method for identifying potential human carcinogens continues to be long-term carcinogenesis experiments (Huff, 1999; Rall, 2000; Tomatis, 2006).

Of approx. 120 recognised human carcinogens (IARC lists 107, RoC 54; with duplications), as well as those probably (61 agents, IARC) or reasonably anticipated (186 agents, Report on Carcinogens (RoC)) to be carcinogenic to humans, all that have been tested adequately are likewise carcinogenic in mammalian cancer bioassays (IARC, 2012; RoC, 2011). Many were identified first in animals and only subsequently in humans (Huff, 1993, 1999). This knowledge, together with similarities in mechanisms of carcinogenesis across species, led to the scientific logic and public health strategy that chemicals shown clearly to be carcinogenic in animals should be considered as being likely and anticipated to present cancer risks to humans; e.g. IARC Monographs Preamble 2012 ([12]); RoC ([13]).

The central aim of hazard identification efforts is cancer prevention, largely by reducing or eliminating exposures to chemicals that cause or are suspected of causing cancer and other diseases (Huff, 2011; Tomatis, 2000).

'Primary prevention has the double ethical privilege of intervening for the purpose of avoiding damage to health for the present and future generations' (Tomatis et al., 1997).

Value and validity of animal bioassays for predicting human cancers
Long-term carcinogenesis bioassays using experimental animals are the most predictive method for identifying likely human carcinogens (Tomatis, 1979; Huff, 1999a; Huff and Melnick, 2006). Since the 1960s, bioassays have proven a mainstay for identifying chemical carcinogens, establishing occupational exposure standards and primary cancer prevention (Tomatis and Huff, 2001). Most importantly, long-term bioassays are both predictive (prospective) and confirmatory (retrospective) for human carcinogens (Fung et al., 1993, 1995). The value and validity of long-term chemical carcinogenesis bioassays centre on the following nine facts (Fung et al., 1993; Huff, 2010; Maltoni, 1976, 1976a; Tomatis, 1979, 2000; Tomatis et al., 1989, 1997, 2001) (list modified from Huff, 2010):

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[12] http://monographs.iarc.fr/ENG/Preamble/index.php.
[13] http://ntp.niehs.nih.gov/?objectid=03C9AF75-E1BF-FF40-DBA9EC0928DF8B15.

Panel 8.2 Value of animal testing for identifying carcinogens (cont.)

1) Rodents and humans are mammals; there are more similarities — physiologically, pharmacologically, biochemically, genomically — than differences; often being quantitative and not qualitative;
2) All known human carcinogens that could be tested experimentally are likewise carcinogenic to animals;
3) Nearly one-third of human carcinogens were first discovered in animal bioassays;
4) One-third would likely be larger but several human carcinogens were discovered in early industrial times (e.g. benzene), predating standard, more frequent bioassays and some human carcinogens are undefined 'exposure circumstances' (e.g. aluminum production, furniture/cabinet making, rubber industry) not readily testable in animals;
5) For those chemicals known as both animal and human carcinogens, there is at least one common cancer-induced tissue/organ site between both mammalian species;
6) Findings from independently conducted bioassays on the same chemicals are consistent, albeit sometimes with additional or different target sites;
7) Bioassays both predict (prospective: 1,3-butadiene; trichloroethylene; TCDD; VCM) or confirm (retrospective: arsenic, benzene) human carcinogenicity;
8) Most chemicals early studied in animals had an a priori suspicion of being carcinogenic, while later randomly selected chemicals identified fewer carcinogens;
9) Less than 10–15 % of all chemicals if evaluated in bioassays would be predicted to be carcinogenic.

No other *in vitro* assay or *in vivo* bioassay or combination of tests, or even epidemiology (Gennaro and Tomatis, 2005; Huff, 2010, 2011; Huff et al., 1991; Rall 1988, 1990, 1994, 2000; Tomatis, 1979, 2000, 2006; Tomatis and Huff, 2001; Tomatis et al., 1989, 1997, 2001), can claim these collective facts and advantages. Of course not all animal (or human) carcinogens are equal, and one must combine the collective experimental findings with experience to best predict human cancer risks from chemicals judged carcinogenic to animals (Fung et al., 1993; Soffritti et al., 1999, 2002).

Despite the predictive success of cancer bioassays using laboratory animals there is vested interest opposition to their use in identifying carcinogens for preventing cancer:

> *Primary prevention of cancer has stumbled from the very beginning because of the interference of powerful economic interests which perceived that any data indicating a possible cancer risk after exposure to industrial chemicals jeopardises their profits, the protection of which being more important than the protection of human health.*
> Tomatis, 2006.

The history of public health is characterised by persistent struggles between short-term economic interests and long-term public, environmental, and occupational health concerns. Intelligent and judicious use of long term animal cancer testing to identify likely human carcinogens has played, and is playing, a critical role in helping public health win the continuing battle on preventing cancers. Meanwhile extensive research efforts are underway to minimise the use of animals whilst retaining, or improving upon, their value in identifying carcinogens.

References

ACS, 2005, *Cancer statistics 2005*, American Cancer Society (http://www.cancer.org).

Ashford, N.A., Hall, R.P., 2011, The importance of regulation-induced innovation for sustainable development, *Sustainability*, (3/1) 270–292.

Ashford, N.A., Hall, R.P., 2012, Regulation-induced innovation for sustainable development, *Admin & Reg L News*, (37/3) 21.

ATSDR, 1995, *Toxicological profile for vinyl chloride — Draft for public comment*, Agency for Toxic Substances and Disease Registry, Public Health Service, US Department of Health and Human Services.

ATSDR, 2006, *Toxicological profile for vinyl chloride, July 2006*, Agency for Toxic Substances and Disease Registry, Public Health Service, US Department of Health and Human Services.

Benfenati, E., Natangelo, M., Davoli, E. and Fanelli, R., 1991, 'Migration of vinyl chloride into PVC-bottled drinking-water assessed by gas chromatography-mass spectrometry', *Food Chem. Toxicol.*, (29) 131–134.

Bradford Hill, A., 1965, 'The environment and disease: association or causation?', *Proceedings of the Royal Society of Medicine*.

Buffler, P.A., Word, S., Eifler, C., Suarez, L. and Kilian, D.J., 1979, 'Mortality experience of workers in a vinyl chloride monomer production plant', *J. Occup. Med*. (21) 195–203.

Byren, D., Engholm, G., Englund, A. and Westerholm, P., 1976, 'Mortality and cancer morbidity in a group of Swedish VCM and PVC workers', *Environ. Health Perspect., (*17) 167–170.

CalEPA, 1986, *Chemicals Known to the State to Cause Cancer or Reproductive Toxicity. Safe Drinking Water and Toxic Enforcement Act of 1986*, Office of Environmental Health Hazard Assessment, Environmental Protection Agency, State of California (http://oehha.ca.gov/prop65/prop65_list/newlist.html) accessed March 2012.

Castleman B.I., 1981, 'Regulations Affecting the Use of Carcinogens', in *Cancer Causing Chemicals* (NI Sax, Ed.) New York: Van Nostrand Reinhold, p. 88.

Castleman, B.I. and Ziem, G.E., 1988, 'Corporate influence on threshold limit values', *Am. J. Ind. Med*., (13/5) 531–559.

Clutterbuck, C., 1986, *Death in the Plastics Industry*. Radical Science Essays Free Association Press London & Humanities Press New Jersey, p. 154–172.

CMA, 1998, *Epidemiological study of men employed in the vinyl chloride industry between 1942 and 1972: I. Re-analysis of mortality through December 31, 1982; and II. Update of Mortality through December 31, 1995, final report*, Chemical Manufacturers Association, Arlington, Virginia.

CMCRC, 2012, Cesare Maltoni Cancer Research Center, Bentivoglio, Italy (http://www.ramazzini.it/ricerca/publications.asp) accessed March 2012.

Cordier, J.M., Fievez, C., Lefevre, M.J. and Sevrin, A., 1966, 'Acro-osteolyse et lésions cutanées associées chez deux ouvriers affectés au nettoyage d'autoclaves', *Cah. Med. Trav.*, (4) 3–39.

Creech, J.L. and Johnson, M.N., 1974, 'Angiosarcoma of liver in the manufacture of polyvinyl chloride', *J. Occup. Med.*, (16) 150–151.

Danzinger, H., 1960, 'Accidental poisoning by vinyl chloride: report of two cases', *Can. Med. Assoc. J.*, (82) 828–830.

Doll, R., 1988, 'Effects of exposure to vinyl chloride', *Scand. J. Work Environ. Health*, (14) 61–78.

Doyal, Epstein, Green, Steward, Williams and Gee, 1983, *Cancer in Britain: the Politics of Prevention*, Pluto Press, p. 71–77.

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

Elliott, P., Kleinschmidt, I., 1997, Angiosarcoma of the liver in Great Britain in proximity to vinyl chloride sites, *Occupational and Environmental Medicine* 1997; (54) 14–18 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1128629/pdf/oenvmed00085-0021.pdf).

Environmental Health Associates, 'Final Report: an Update of an Epidemiological Study of VCM Workers, 1942–1982', October 1986, MCA Papers.

Federal Register, 1974, 'Exposure to vinyl chloride, occupational safety and health standards', 4 October 1974, (39/194, part 2) OSHA, 35890-98.

Feron, V. J. and Kroes, R., 1979, 'One-year time-sequence inhalation toxicity study of vinyl chloride in rats, II Morphological changes in the respiratory tract, ceruminous glands, brain, kidneys, heart, and spleen', *Toxicology*, (13) 131–141.

Filatova, S.V. and Gronsberg, E.S., 1957, 'Sanitary-hygienic conditions of work in the production of polychlorvinylic tar and measure of improvement', *Gigiena Sanit*., (22) 38–42 (in Russian).

Filatova, S.V., 1966, 'Hygienic evaluation of new technological processes in chemical industries', *Gig. Tr. Prof. Zabol*., (10) 3–7 (in Russian).

Food Chem. News, 1973, 'FDA to propose ban on use of PVC for liquor use', *Food Chem. News*, 14 May 1973, 14, pp. 3–4.

Forman, D., Bennett, B., Stafford, J., Doll, R., 1985, Exposure to vinyl chloride and angiosarcoma of the liver: a report of the register of cases, *British Journal of Industrial Medicine*, (42) 750–753 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1007571/pdf/brjindmed00187-0030.pdf).

Fox, J., Gee, D., Jones, D. and Leon, D., 1982, *Cancer and work: making sense of workers' experience with foreword by Sir Richard Doll*, GMB Union.

Fung, V.A., Huff, J., Weisburger, E.K., Hoel, D.G., 1993, 'Predictive strategies for selecting 379 NCI/

NTP chemicals evaluated for carcinogenic potential: scientific and public health impact', *Fundam. Appl. Toxicol*., (20/4) 413–436. Erratum in: *Fundam. Appl. Toxicol*., (21/2) 402.

Fung, V.A., Barrett, J.C., Huff, J., 1995, 'The carcinogenesis bioassay in perspective: application in identifying human cancer hazards', *Environ. Health Perspect*., (103/7–8) 680–683.

GBI Research, 2010, *Ethylene Dichloride (EDC) Global Market Dynamics to 2020 — Poly Vinyl Chloride (PVC) Market Continues to Drive the Global Demand*.

Gehring, P.J., Watanabe, P.G. and Park, C.N., 1978, 'Resolution of dose-response toxicity data for chemicals requiring metabolic activation: example — vinyl chloride', *Toxicol. Appl. Pharmacol*., (44) 581–591.

Gennaro, V., Tomatis, L., 2005, 'Business bias: how epidemiologic studies may underestimate or fail to detect increased risks of cancer and other diseases', *Int. J. Occup. Environ. Health*; (11) 356–359.

Grosse, Y., Baan, R., Straif, K., Secretan, B., El Ghissassi, F., Bouvard, V., Altieri, A. and Cogliano, V., 2007, 'Carcinogenicity of 1,3-butadiene, ethylene oxide, vinyl chloride, vinyl fluoride, and vinyl bromide', *The Lancet*, (8) 679–680.

Harris, D.K., 1953, 'Health problems in the manufacture and use of plastics', *Br. J. Ind. Med*., *(*10) 255–268.

HSDB, 2006, Hazardous Substances Data Bank. (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB).

Huff, J., 1999, 'Value, validity, and historical development of carcinogenesis studies for predicting and confirming carcinogenic risks to humans'. Chapter 2: 21–123. In: Kitchin K.T., (ed). *Carcinogenicity Testing, Predicting, & Interpreting Chemical Effects*, Marcel Dekker, NY.

Huff, J., 1999a, 'Animal and human carcinogens', *Environ. Health Perspect*., (107/7) A341–A342.

Huff, J., 2002, 'Chemicals Studied and Evaluated in Long-Term Carcinogenesis Bioassays by both the Ramazzini Foundation and the National Toxicology Program', *Ann. NY Acad. Sci*., (982) 208–229.

Huff, J., 2010, 'Predicting chemicals causing cancer in animals as human carcinogens', *Occup. Environ. Med*., (67/10) 720.

Huff, J., 2011, 'Primary prevention of cancer', *Science*, (20/332/6032) 916–917.

Huff, J., Eustis, S.L., Haseman, J.K., 1989, 'Occurrence and relevance of chemically induced benign neoplasms in long-term carcinogenicity studies', *Cancer Metastasis Rev*., (8/1) 1–22. Erratum in: *Cancer Metastasis Rev,* (8/3) 281.

Huff, J., Haseman, J., Rall, D., 1991, 'Scientific concepts, value, and significance of chemical carcinogenesis studies', *Annu. Rev. Pharmacol. Toxicol*., (31) 621–652.

Huff, J., Melnick, R.M., 2006, 'What Are the Real Causes of Cancer? An Opinionated Book review of 'Misconceptions about the Causes of Cancer'' (Gold LS, Slone TH, Manley NB, Ames BN), *Int. J. Occup. Environ. Health*, (12/1) 81–86.

IARC, 1974, *Internal Technical Report no 74/005, Report of a working group on vinyl chloride*, 24–25 June 1974, International Agency for Research on Cancer, Lyon.

IARC, 1979, *Monographs on the evaluation of the carcinogenic risks of chemical to humans — Some monomers, plastics and synthetic elastomers, and acrolein*, vol. 19, International Agency for Research on Cancer.

IARC, 1987, *Monographs on the Evaluation of Carcinogenic Risks to Humans, Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42*, Vinyl chloride, Supplement 7 (1987).

IARC, 2008, *Monographs on the Evaluation of Carcinogenic Risks to Humans.* 1,3-Butadiene, Ethylene Oxide and Vinyl Halides (Vinyl Fluoride, Vinyl Chloride and Vinyl Bromide), vol. 97, International Agency for Research on Cancer, Lyon.

IARC, 2012, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 1–100.

Infante, P., 'Oncogenic and Mutagenic risks in Communities with pVC Production Facilities', in Abstracts of papers on VCM presented at the NY Academy of Sciences, Mar 1975, MCA papers.

Infante, P.F., Wagoner, J.K., McMichael, A.J. , Waxweiler, R.J. and Falk, H., 1976a, 'Genetic risks of vinyl chloride', *Lancet*, (3) 734–735.

Infante, P.F., Wagoner, J.K., Waxweiler, R.J. 1976b, 'Carcinogenic, mutagenic, and teratogenic risks associated with vinyl chloride', *Mutat. Res.,* (41) 131–142.

Infante, P.F., Petty, S.E., Groth, D.H., Markowitz, G., Rosner, D., 2009, 'Vinyl chloride propellant in hair spray and angiosarcoma of the liver among hairdressers and barbers: case reports', *Int. J. Occup. Environ. Health,* (15/1) 36–42, Review.

IPCS, 1999, *Environmental health criteria — vinyl chloride*, vol. 215, International Programme on Chemical Safety.

Keplinger, M.L., Goode, J.W., Gordon, D.E. and Calandra, J.C., 1975, 'Interim results of exposure of rats, hamsters, and mice to vinyl chloride', *Ann. NY Acad. Sci.*, (248) 219–224.

Landrigan P.J. and Nicholson W.J., 1998, 'Benzene', in: Rom, W. N. (ed.), *Environmental and Occupational Medicine*, 3rd ed., Lippincott-Raven Philidelphia, 1998, p. 1 112.

Lee, C.C., Bhandari, J.C., Winston, J.M. , House, W.B., Dixon, R.L. and Woods, J.S., 1978, 'Carcinogenicity of vinyl chloride and vinylidene chloride', *J. Toxicol. Environ. Health*, (4) 15–30.

Lester, D., Greenberg, L.A. and Adams, W.R., 1963, 'Effects of single and repeated exposures of humans and rats to vinyl chloride', *Am. Ind. Hyg. Assoc. J.*, (24) 265–275.

Lewis, R., Rempala, G., 2003, 'A case-cohort study of angiosarcoma of the liver and brain cancer at a polymer production plant', *J. Occup. Environ. Med.*, (45) 538–545.

Makita, O., Ono, K., Sakurai, T., Tanigawa, H., Ando, Y., Yamashita, K., Yoshimatsu, M., Takahashi, M, 1997, 'A case of hepatocellular carcinoma related with exposure to vinyl chloridemonomer', *Nippon Shokakibyo Gakkai Zasshi*, (94) 215–219 (in Japanese).

Maltoni, C., 1974a, 'La ricerca sperimentale e i suoi risultati', *Sapere*, (776) 42–45.

Maltoni, C., 1974b, 'Occupational carcinogenesis — Report to the Second International Symposium on Cancer Detection and Prevention, Bologna, 9–12 April 1973', *Adv. Tum. Prev. Detect. Charact.*, (2) 19–26.

Maltoni, C., 1974c, *Testimony at the informal fact-finding bearing on possible hazards of vinyl chloride manufacture and use*, pp. 43–63, Occupational Safety and Health Administration (OSHA).

Maltoni, C., 1976, 'Occupational carcinogenesis. Predictive value of carcinogenesis bioassays', *Ann. NY Acad. Sci.*, (271) 431–443.

Maltoni, C., 1976a, 'Occupational chemical carcinogenesis: new facts, priorities and perspectives', *IARC Sci. Publ.*, (13) 127–149.

Maltoni, C., 1977, 'Vinyl Chloride carcinogenicity: an experimental model for carcinogenesis studies'. In: *Origins of human cancer*, Cold Spring Harbor Laboratory, 119–146.

Maltoni, C. and Lefemine, G., 1975, 'Carcinogenicity bioassays of vinyl chloride, I Research plan and early results', *Environ. Res.*, (7) 387–405.

Maltoni, C., Lefemine, G., Chieco, P. and Carretti, D., 1974, 'La cancerogenesi ambientale e professionale: nuove prospettive alla luce della cancerogenesi da cloruro di vinile', *Ospedali di vita*, (1) 7–76 (in Italian).

Maltoni, C., Lefemine, G., Ciliberti, A., Giuliano, C. and Carretti, D, 1981, 'Carcinogenicity bioassays of vinyl chloride monomer: a model of risk assessment on experimental basis', *Environ. Health Perspect.*, (41) 3–29.

Maltoni, C., Lefemine, G., Cotti, G., Ciliberti, A. and Carretti, D., 1984, 'Experimental research on vinyl chloride carcinogenesis', in: Maltoni, C. and Mehlman, M.A., 1984, *Archives of research on industrial carcinogenesis*, vol. 2, Princeton Scientific Publishers, Princeton.

Markowitz and Rosner, 2002, *Deceit and denial: the deadly politics of industrial pollution*, University of California Press.

Mastrangelo, G., Fedeli, U., Fadda, E., Valentini, F., Agnesi, R., Magarotto, G., Marchì, T., Buda, A., Pinzani, M. and Martines, D., 2004, 'Increased risk of hepatocellular carcinoma and liver cirrhosis in vinyl chloride workers: synergistic effect of occupational exposure with alcohol intake', *Environ. Health Perspect.*, (112) 1 188–1 192.

Mastromatteo, E., Fisher, A.M., Christie, H. and Danziger, H., 1960, 'Acute inhalation toxicity of vinyl chloride to laboratory animals', *Am. Ind. Hyg. Assoc. J.*, (21) 394–398.

McMurry, J.R. and Tarr, J., 1978, 'Vinyl chloride in Texas ambient air', *Proc. Annu. Tech. Meet. Inst. Environ. Sci.*, (24) 149–153.

MMWR, 1974; 'Angiosarcoma of the Liver Among Polyvinyl Chloride Workers — Kentucky', *MMWR*, (23) 49–50 (http://www.cdc.gov/mmwr/preview/mmwrhtml/lmrk103.htm).

Monson, R.R., Peters, J.M. and Johnson, M.N., 1975, 'Proportional mortality among vinyl chloride workers', *Environ. Health Perspect*., (11) 75–77.

Morris J., 2010, *Plastics ingredient vinyl chloride is focus of suit against Rohm and Haas*, The Center for Public Integrity, iWatch News, 15 September 2010.

Mundt, K.A., Dell, L.D., Austin, R.P. , Luippold, R.S., Noess, R. and Bigelow, C., 2000, 'Historical cohort study of 10109 men in the North American vinyl chloride industry, 1942–72: update of cancer mortality to 31 December 1995', *Occup. Environ. Med*., (57) 774–781.

NARA, 1974, Federal Register, (39) 67 (5 April 1974), US Office of the Federal Register, National Archives and Records Administration.

National Research Council, 1977, *Drinking water and health*, vol. 1, National Academy Press, Washington, DC.

Naylor, L.M. and Loehr, R.C., 1982, 'Priority pollutants in municipal sewage sludge', *BioCycle*, (23/4) 18–22.

Neuhoff, S., 1988, 'Safety planning in a city with chemical industry — Cologne', *Brandschutz Deutsch Feuerwehr-Zeitung*, (4) 168–175 (in German).

NIOSH, 1977, *A cross-sectional epidemiologic survey of vinyl chloride workers*. Cincinnati, OH: US Department of Health and Human Services, National Institute for Occupational Safety and Health, Division of Surveillance, Hazard Evaluations, and Field Studies. PB274193.

NTP TR, 2012, Technical Reports on Toxicology and Carcinogenesis Studies of Chemicals, 1–580. Research Triangle Park, NC.

Oppenheimer, B.S., Oppenheimer, E.T., Danishefsky, I., Stout, A.P. and Eirich, F.R., 1955, 'Further studies on polymers as carcinogenic agents in animals', *Cancer Res.*, (15) 333–340.

Oster, R.H., Carr, C.J. and Krantz, J.C., 1947, 'Anesthesia: XXVII, Narcosis with vinyl chloride', *Anesthesiology*, (8) 359–361.

Page, B.D. and O'Grady, R., 1977, 'Gas-solid chromatographic confirmation of vinyl chloride levels in oils and vinegars by using electrolytic conductivity detection', *J. Assoc. Off. Anal. Chem*., (60) 576–578.

Page, G.W., 1981,' Comparison of groundwater and surface water for patterns and levels of contamination by toxic substances', *Environ. Sci. Technol*., (15) 1 475–1 481.

Patty, F.A., Yant, W.P. and Waite, C., 1930, 'Acute response of guinea pigs to vapors of some new commercial organic compounds: v. vinyl chloride', *Public Health Rep.,* (45) 1 963–1 971.

Peoples, A.S. and Leake, C.D., 1933, 'The anesthetic action of vinyl chloride', in: 'Scientific proceedings of the American society for pharmacology and experimental therapeutics: twenty-fourth annual meeting, Cincinnati, OH', *J. Pharmacol. Exp. Ther*., (48) 284.

Pirastu, R., Baccini, M., Biggeri, A. and Comba, P., 2003, 'Epidemiologic study of workers exposed to vinyl chloride in Porto Marghera: mortality update', *Epidemiol. Prev*., (27) 161–172.

Pirastu, R., Bruno, C., De Santis, M. and Comba, P., 1998, 'An epidemiological study of workers exposed to vinyl chloride in the plants of Ferrara, Rosignano and Ravenna', *Epidemiol. Prev*., (22) 226–236.

Pirastu, R., Comba, P., Reggiani, A. , Foa, V., Masina, A. and Maltoni, C., 1990, 'Mortality from liver disease among Italian vinyl chloride monomer/polyvinyl chloride manufacturers', *Am. J. Ind. Med*., (17) 155–161.

Porter, M. and van der Linde, C., 1995, 'Toward a New Conception of the Environment-Competitiveness Relationship', *Journal of Economic Perspectives*, (9/4) 97–118.

Porter, M., 2011, *The Porter Hypothesis After 20 Years: How Can Environmental Regulation Enhance Innovation and Competitiveness?* Eighth Annual Hans Landsberg Memorial Lecture, 19 January, 2011, Resources for the Future, Washington.

Prodan, L., Suciu, I., Pîslaru, V. , Ilea, E. and Pascu, L., 1975, 'Experimental acute toxicity of vinyl chloride (monochloroethene)', *Ann. NY Acad. Sci*., (246) 154–158.

Radike, M.J., Stemmer, K.L. and Bingham, E., 1981, 'Effect of ethanol on vinyl chloride carcinogenesis', *Environ. Health Perspect*., (41) 59–62.

Rall, D.P., 1988, 'Laboratory animal toxicity and carcinogenesis testing. Underlying concepts, advantages and constraints', *Ann. NY Acad. Sci*., (534) 78–83.

Rall, D.P., 1990, 'Carcinogens in our environment', *IARC Sci. Publ.*, (104) 233–239.

Rall, D.P., 1994, 'Shoe-leather epidemiology — the footpads of mice and rats: animal tests in assessment of occupational risks', *Mt. Sinai J. Med.*, (61/6) 504–508.

Rall, D.P., 2000, 'Laboratory animal tests and human cancer', *Drug Metab. Rev.*, May; (32/2) 119–128.

Rattner, S., 'Did Industry cry Wolf?', *New York Times*, 28 December, 1975.

Regnauld, H.V., 1835, 'Composition of a chlorinated hydrocarbon (oils from oil-forming gases)', *Justus Liebig's Ann. Chem.*, (14) 22–38 (in German).

RoC, 2011, *NTP Report on Carcinogens, Twelfth Edition*. National Toxicology Program, Research Triangle Park, NC, 499 pp.

Rowe, V.K., 1959, 'Letter from V. K. Rowe (Dow Chemical) to W. E. McCormick (B. F. Goodrich), 12 May 1959', cited in: Markowitz and Rosner, 2002, *Deceit and denial: the deadly politics of industrial pollution*, University of California Press.

Salkinoja-Salonen, M., Uotila, J., Jokela, J., Laine, M. and Saski, E., 1995, 'Organic halogens in the environment: studies of environmental biodegradability and human exposure', *Environ. Health Perspect.*, (103) 63–69.

Sass, J.B., Castleman, B., Wallinga, D., 2005, 'Vinyl chloride: a case study of data suppression and misrepresentation', in: *Environ. Health Perspect.*, (113/7) 809–812.

Saurin, J.C., Tanière, P., Mion, F., Jacob, P., Partensky, C., Paliard, P., Berger, F., 1997, 'Primary hepatocellular carcinoma in workers exposed to vinyl chloride: a report of two cases', *Cancer*, (79/9) 1 671–1 677.

Selikoff, I.J. and Seidman, H., 1991, 'Asbestos-associated deaths among insulation workers in the United States and Canada, 1967–1987', in: *The third wave of asbestos disease: exposure to asbestos in place, Annals of the New York Academy of Sciences*, vol. 643.

Senate Committee on Commerce, 1974, 'Hearing on dangers of vinyl chloride', Senate Commitee on Commerce, Subcommittee on the Environment, 93rd Congress, 2nd session, 21 August 1974, Serial NO., 93–110, 42.

Simonato, L., L'Abbe, K.A., Andersen, A., Belli, S., Comba, P., Engholm, G., Ferro, G., Hagmar, L., Langård, S., Lundberg, I. et al., 1991, 'A collaborative study of cancer incidence and mortality among vinyl chloride workers', *Scand. J. Work Environ. Health*, (17) 159–169.

Smyth, H.F. Jr, 1959, 'Letter from H. F. Smyth Jr to T.W. Nale 'attn: Weidlein', 24 November 1959', *MCA Papers*.

Soffritti, M., Belpoggi, F., Minardi, F., Bua, L., Maltoni, C., 1999, 'Mega-experiments to identify and assess diffuse carcinogenic risks', *Ann. NY Acad. Sci.*, (895) 34–55.

Soffritti, M., Belpoggi, F., Minardi, F., and Maltoni, C., 2002, 'Ramazzini Foundation Cancer Program. History and Major Project, Life-span Carcinogenicity Bioassay Design, Chemicals Studied and Results', *Ann. NY Acad. Sci.*, (982) 26–45.

SRI Consulting, 2011, *World Petrochemical Report on PVC*.

Stafford, J., 1983, *Liver angiosarcoma case registry*, ICI.

Suciu, I., Drejman, I. and Valeskai, M., 1963, 'Investigation of the diseases caused by vinyl chloride', *Internal Medicine*, (15) 967–977 (in Romanian).

Tabershaw, I.R. and Gaffey W.R., 1974, 'Epidemiologival study of workers in the manufacture of Vinyl Chloride and IOts Polymers', *JOM*, 509–518.

Tomatis, L., 1979, 'The predictive value of rodent carcinogenicity tests in the evaluation of human risks', *Ann. Rev. Pharmacol. Toxicol.*, (19) 511–530.

Tomatis L., 2006, 'Role of experimental and epidemiological evidence of carcinogenicity in the primary prevention of cancer', *Ann. Ist. Super. Sanita*, (42/2) 113–117.

Tomatis, L., 2000, 'The identification of human carcinogens and primary prevention of cancer', *Mutat. Res*, (462/2–3) 407–421.

Tomatis, L, Aitio, A, Wilbourn, J, Shuker, L., 1989, 'Human carcinogens so far identified', *Jpn. J. Cancer Res.*, (80/9) 795–807.

Tomatis, L., Huff, J., 2001, 'Evolution of cancer etiology and primary prevention', *Environ Health Perspect*, (109/10) A458–A460.

Tomatis, L., Huff, J., Hertz-Picciotto, I., Sandler, D.P., Bucher, J., Boffetta, P., Axelson, O., Blair, A., Taylor, J., Stayner, L., Barrett, J.C., 1997, 'Avoided and avoidable risks of cancer', *Carcinogenesis*, (18/1) 97–105.

Tomatis, L., Melnick, R.L., Haseman, J., Barrett, J.C., Huff, J., 2001, 'Alleged misconceptions' distort perceptions of environmental cancer risks', *FASEB J.*, (15/1) 195–203.

Torkelson, M.S, Oyen, F. and Rowe, V.K., 1961, 'The toxicity of vinyl chloride as determined by repeated exposure of laboratory animals', *Am. Ind. Hyg. Assoc. J.*, (22) 354–361.

Tribukh, S.L., Tikhomirova, N.P., Levin, S.V. and Kozlov, L.A., 1949, 'Working conditions and measures for their sanitation in the production and utilization of vinyl chloride plastics', *Gigiena Sanit.*, *(*10) 38–45.

US EPA, 1975, *Scientific and technical assessment report on vinyl chloride and polyvinyl chloride*, Environmental Protection Agency, EPA 600/6-75-004.

US EPA, 2000, *Toxicological review of vinyl chloride in support of summary information on the Integrated Risk Information System (IRIS)*, Environmental Protection Agency, EPA 635R-00/004.

US FDA, 1973, *Prior-sanctioned polyvinylchloride resin*, Federal Drug Administration, Fed. Regist. 51, 4 173–4 188.

US NLM, 2006, 'Hazardous Substances Data Bank', United States National Library of Medicine (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB) accessed 25 January 2012.

US Tariff Commission, 1927, 'Census of dyes and of other synthetic organic chemicals', *1928 Tariff Information Series* no 37, 139.

Van Lierop, J.B.H., 1979, *Determination of potentially carcinogenic compounds in food: trace analysis of vinilchloride, vinilydenechloride, acrylonitrile, epichlorohydrin and diethylpyrocarbonate*, University of Utrecht.

Viola, P.L., 1970, 'Carcinogenic effects of vinyl chloride', *Proc. X Int. Cancer Congr.*, *(*291: abstr.).

Viola, P.L., Bigotti, A. and Caputo, A., 1971, 'Oncogenic response of rat skin, lungs, and bones to vinyl chloride', *Cancer Res.*, (31) 516–522.

Wagner, M. 2003, *The Porter Hypothesis Revisited. A Literature Review of Theoretical Model and Empirical Test*, Centre for Sustainability Management.

Ward, E., Boffetta, P., Andersen, A., Colin, D., Comba, P., Deddens, J.A., De Santis, M., Engholm, G., Hagmar, L., Langard, S., Lundberg, I., McElvenny, D., Pirastu, R., Sali, D. and Simonato, L., 2001, 'Update of the follow-up of mortality and cancer incidence among European workers employed in the vinyl chloride industry', *Epidemiology*, *(*12) 710–718.

Washington Post, 1974, 'Chemical hazard kept quiet', *The Washington Post*, 20 May 1974.

Weber, H., Reinl, W. and Greiser, E., 1981, 'German investigations on morbidity and mortality of workers exposed to vinyl chloride', *Environ. Health Perspect.*, (41) 95–99.

Weihrauch, M., Lehnert, G., Köckerling, F., Wittekind, C., Tannapfel, A., 2000, 'p53 mutation pattern in hepatocellular carcinoma in workers exposed to vinyl chloride', *Cancer*, (1/88/5) 1 030–1 036.

Wong, O., Whorton, M.D., Foliart, D.E. and Ragland, D., 1991, 'An industry-wide epidemiologic study of vinyl chloride workers, 1942–1982', *Am. J. Ind. Med.*, (20) 317–334.

Wong, O., Whorton, M.D., 1993, Diagnostic bias in occupational epidemiologic studies: an example based on the vinyl chloride literature, *Am. J. Ind. Med.*, (24) 251–245.

R-H., Wong, R-H., Chen, P-C., Du, C-L., Wang, J-D., Cheng, T-J., 2002, 'An increased standardised mortality ratio for liver cancer among polyvinyl chloride workers in Taiwan', *Occup. Environ. Med.*, (59) 405–409, doi:10.1136/oem.59.6.405.

Zhao, M.Y., Ying, C.J., Shao, N. , Yang, Y., Yang, C.F., Shi, L., Liu, W.Q., 1994, 'The study of health effects of vinyl chloride air pollution on population', *Biomed. Environ. Sci.*, (7) 36–43.

9 The pesticide DBCP and male infertility

Eula Bingham and Celeste Monforton

Dibromochloropropane (DBCP) is a pesticide used against nematodes (roundworms or threadworms) that damage pineapples, bananas and other tropical fruits. It was introduced into US agriculture in 1955 and approved for use as a fumigant in 1964. By 1961 laboratory experiments had shown that it made the testicles of rodents shrink and significantly reduced the quantity and quality of sperm. Nonetheless, the compound was widely marketed and became a commercial success.

In 1977, workers at a production plant became worried that they were unable to father children. An emergency study by a US government agency discovered that in many cases the workers were suffering from deficient or absent sperm. While controls were improved at US facilities, the product continued to be marketed and sprayed in Latin America, the Philippines, some African countries, and elsewhere.

By the 1990s, tens of thousands of plantation workers in these countries had allegedly suffered adverse reproductive effects from DBCP use. The story continues today with contentious legal claims for compensation, contamination of drinking water and industry attempts to prevent a Swedish documentary on the issue from being screened.

This chapter looks at the knowledge available about the hazards and the actions taken, or not taken, to avert them. The DBCP story is significant as it is the first clear example of reproductive damage to workers who manufactured and used a synthetic chemical. This is one of many examples supporting the growing concerns about increasing rates of reproductive and developmental disease, and about the endocrine disrupting chemicals that seem to be playing a role in these disorders.

Protecting production workers, users, consumers and the environment from chemicals that may damage reproduction demands closer integration of scientific disciplines, as well as government action. The lessons of DBCP may help in ensuring timely protection from harm, based on precautionary approaches to scientific evidence.

> 'If anyone wants to use a male birth control drug, I think we have identified one, but it is not very pleasant to use.'
>
> — Dr Charles Hine, Shell Contractor, c. 1960, quoted in Goldsmith (1997).

9.1 The discovery 1977: 'our union members are sterile'

In July 1977, one of the authors of this chapter (Eula Bingham, then US Assistant Secretary of Labor for Occupational Safety and Health) was contacted by Tony Mazzocchi, Vice President of the Oil, Chemical, and Atomic Workers International Union (OCAW) in the United States. He wrote:

> 'In a chemical factory in California during a lunch hour, several workers confided to each other that they were worried about not having children. One worker had a child, but had been trying for another for almost two years and two other young workers had no children and were concerned that there was something wrong. Their wives had been examined and now they thought it might be that they themselves had a problem. When the concerns were passed to other workers, the union arranged for the seven of them to have sperm counts performed. The sperm counts were either zero, or so low, that they showed the men sterile and the union was contacting the US National Institute of Occupational Safety and Health (NIOSH) to perform a Health Hazard Evaluation'.

The chemical responsible for causing sterility in the workers at the California chemical plant was 1,2-Dibromo-3-Chloropropane (DBCP). The compound was first produced in the United States in 1955 and used as a soil fumigant to control nematode worms in the soil. DBCP products carried trade names such as Fumazone, Nemagon, Nemaset, and Nematox (US EPA, 1979; OSHA, 1977a and 1977b; Misko et al., 1993; Clark and Snedeker, 2005; NIOSH, 1977) and were primarily used to protect crops, such as pineapple, bananas, sugar cane and other produce, mostly in the tropics. As a soil fumigant, DBCP was applied at a rate of 10–125 kg/ha, either injected directly into the soil or added to irrigation water.

The three main US manufacturers were Dow Chemical Company, Shell Chemical Company and Occidental Chemical Company, but DBCP was also produced in Europe (by International Chemical Company in the United Kingdom) and in Japan. At its peak an estimated 14.7 million kg of DBCP were used annually prior to its suspension in 1977. Most production was used in the US, Latin America, the Philippines and some African countries.

9.2 Early warnings: 1961–1975

The earliest research on DBCP toxicity was carried out by two chemical companies producing the compound for use as a nematocide. By 1958, both Shell and Dow had obtained toxicological data from experiments on rats showing that DBCP was absorbed through the skin and by inhalation and affected the liver, lung, kidney and testes.

Charles Hine, working then under contract for Shell, reported a variety of adverse effects in laboratory animals, depending on the dose of DBCP vapour administered. At an exposure to 5 ppm (5 parts of the chemical in one million parts of air), the testes in male rats shrank, at 10 ppm most of the male rats had testes half the normal size and at 20 ppm all the male rats were sterile. An internal memorandum prepared by Shell noted: 'We understand that Dow Chemical Company have similar data and are very upset by the effects noted on the testes' (Lykken, 1958).

At that time, scientists working for these companies were clearly worried about the results. John Goldsmith, epidemiologist, later wrote: 'I recall a conversation with the late Dr Charles Hine from the University of California at San Francisco about 1960 at a party, when he said, "If anyone wants to use a male birth control drug, I think we have identified one, but it is not very pleasant to use"' (Goldsmith, 1997).

In 1961, the industry toxicologists published their data from experimental studies (NIOSH, 1977), supporting the initial observations (see Box 9.1). These studies revealed that DBCP had two outstanding toxic effects: an antispermatogenic effect in males and damage to kidneys in both sexes of the rat.

9.3 Pesticide registration and inadequate 'hazard control' 1961–1977

The years 1958–1961 were a critical period for decisions on hazard protection and for the use and marketing of DBCP in the United States and globally. Charles Hine, working as an expert consultant for Dow and Shell, supported a request for the US Food and Drug Administration (USFDA) to register DBCP as an approved pesticide. His report called for workplace concentrations to be less than 1 ppm and impermeable protective clothing to be used if skin contact was likely.

In a series of discussions between the USFDA, Shell and Dow, the regulator noted that at the lowest exposure level studied, 5 ppm, there were adverse effects after repeated exposures and that the current safety precautions therefore appeared inadequate. However, the Shell representative considered the Hine recommendations to be impractical.

By 1961, Torkelson, Hine and colleagues (Torkelson et al., 1961) recommended that occupational exposure to DBCP should be limited by keeping the airborne concentration below 1 ppm, and stressed that suitable analytical methods rather than sensory perception should be depended upon for control. These authors had interviewed men who had been briefly exposed to 1.7 ppm of DBCP and they described a definite, not unpleasant odour (NIOSH, 1978).

In 1961 the US Food and Drug Administration approved and registered DBCP as a pesticide and recommended the exposure limit of 1 ppm. Thereafter the US Department of Agriculture (USDA) was asked to approve the product labelling, which simply stated: 'Do not breathe vapours, use only in a well-ventilated area and avoid prolonged breathing'. As such, the warning label included no reference to testicular damage.

The USDA initially expressed reservations regarding the warnings on the label but Shell argued that at 5 ppm no adverse effects had been reported and that the odour threshold of 1.7 ppm therefore provided an adequate 'warning' of excessive exposure (Thrupp, 1991). USDA accepted these reassurances even though no studies had been performed to indicate that this approach was safe. Virtually no attempts were made to determine if the measures adopted were indeed safe for manufacturing workers or pesticide sprayers. Neither group was subjected to medical surveillance.

In fact, the 'odour threshold' for DBCP exposure was too high to ensure reliable protection against the toxicity reported in the animal studies. DBCP fumes are only a mild irritant and unlikely to be reported as potentially harmful. Workers could therefore be exposed to dangerous amounts of the chemical without being aware of it.

The labelling and workplace exposure precautions were therefore inadequate from the 1950s until 1977, failing to provide accurate information about the potential health effects of DBCP or to ensure safe working conditions, in the light of the animal evidence. The toxicological data available in 1961 on the potential adverse health effects of DBCP was sufficient to have required specific health warnings, personal protective equipment and medical surveillance. None was provided.

Box 9.1 Animal toxicity data for DBCP: 1958–1975

Torkelson et al. (1961) evaluated the effects of exposing rats to DBCP by inhalation for seven hours a day, five days a week for 10 weeks. The lowest concentration, 5 ppm (parts per million), produced an 18.6 % decrease in the mean weight of the testes, which was not statistically significant. Exposure to 10 ppm resulted in a statistically significant decrease (49 %) in the mean weight of the testes and a significant increase in the weight of the kidney (31.7 %).

In another study reported by Torkelson et al. (1961) male and female rats were exposed to 12 ppm DBCP for seven hours a day, five days a week for 10 weeks. Degenerative changes occurred in the tissue where sperm are formed, reducing the number of sperm cells and increasing the proportion of abnormal sperm cells. Significant increases in the weights of the kidneys occurred in both sexes and there were changes in the kidneys of the males. Changes in the livers of both sexes were also noted.

Exposing guinea pigs and rabbits to 12 ppm DBCP vapour inhalation resulted in statistically significant decreases in the mean weights of the testes in both species (Torkelson et al., 1961).

Toxicological studies by European laboratories also reported around 50 % reductions in the weight of testes and in sperm counts and motility (Rakhmatulayve, 1971; Reznik and Sprinchan, 1975). In female rats, the reproductive cycle was disrupted.

9.4 Actions to reduce exposure in DBCP manufacturing: 1977 and 1978

The National Institute for Safety and Health (NIOSH) was created in 1970. Responding to the suspicions of the DBCP manufacturing workers and a request by their trade union, OCAW, for government help, NIOSH (1977) conducted a health hazard evaluation at the Occidental Chemical Company's Lathrop plant. It reported airborne DBCP concentrations of 0.29–0.43 ppm, measured as an eight-hour time-weighted average. Of 13 workers in the production area, nine had no sperm (azoospermia) and another four workers had very reduced sperm counts (oligospermia). The researchers conducting the evaluation for NIOSH found a 'clear increase in the prevalence of oligospermia with increasing exposure' to DBCP (Whorton et al., 1977). These exposure levels were far below those used in the toxicological studies and also below the recommended 'safe' levels for workers of 1 ppm.

With this alarming information, the President of OCAW formally petitioned the US Occupational Safety and Health Administration (OSHA) on 23 August 1977 to take action to limit worker DBCP exposure to 1 part per billion (1 ppb) parts of air and to conduct medical testing to identify cases of sterility and cancer among exposed workers. This call for action was met with a flurry of activity at the federal government level. OSHA issued an Emergency Temporary Standard (ETS) on 9 September 1977 and proposed a permanent standard in November. Public hearings were held in December 1977 and a final standard was published in the Federal Register on 11 March 1978.

The results of the medical examinations of the OCAW workers provided compelling evidence for OSHA action, but the Administration also evaluated all other available information on DBCP as part of the rulemaking process. This included, for example, data from the Dow Chemical facility in Magnolia, Arkansas, where DBCP was manufactured. Air sampling results revealed concentrations of 0.04 ppm to 0.4 ppm of DBCP calculated as an 8-hour time-weighted average. Furthermore, medical tests revealed that 50 % of the 106 workers examined there had either oligospermia or azoospermia.

These data suggested that exposures below 1 ppm were associated with adverse reproductive effects. However, because DBCP is also absorbed through the skin, dermal exposures may have contributed an unknown but potentially significant amount to the workers' total dose of DBCP.

Based on the evidence of the serious adverse reproductive health effects in animals and humans, and its carcinogenicity in animals (see below), OSHA issued a final standard to limit workers' DBCP exposure to 1 ppb (based on an 8-hour time-weighted average), and to 10 ppb over any 15-minute period. OSHA also required employers to provide initial and annual medical examination for DBCP-exposed workers, respiratory protection and training, among other provisions.

The new rules took effect in April 1978 and were not effectively challenged by any interested party. The US National Peach Council did, however, attempt to delay the regulation with a direct plea to OSHA, expressed in a letter to Eula Bingham, co-author of this chapter. The Council argued that:

> 'While involuntary sterility caused by a manufactured chemical may be bad, it is not necessarily so. After all, there are many people who are now paying to have themselves sterilized to assure they will no longer be able to become parents. How many of the workers who have become sterile were of an age that they would have been likely to have children anyway? How many were past the age when they would want to have children? These, too, are important questions.
>
> 'If possible sterility is the main problem, couldn't workers who were old enough that they no longer wanted to have children accept such positions voluntarily? They could know the situation and it wouldn't matter. Or could workers be advised of the situation and some might volunteer for such work posts as an alternative to planned surgery for a vasectomy or tubal ligation, or as a means of getting around religious bans on birth control when they want no more children. We do believe in safety in the work place, Dr Bingham, but there can be good as well as bad sides to a situation' (US National Peach Council, 1977).

This argument found little favour with OSHA.

Meanwhile studies on exposed production workers were conducted in Israel. In a series of publications researchers discovered DBCP-induced sterility in the six workers at a DBCP-production facility that had been exposed for two to ten years (Potashnik et al., 1978). The workers also had an elevated serum concentration for one sex hormone (follicular stimulating hormone, FSH, which increases with testicular damage) and damage to the testicular tissue responsible for producing sperm cells.

In a related study, 18 of 23 workers (78 %) involved in DBCP production had abnormal sperm counts, including 12 workers with azoospermia. After several years without exposure to DBCP, some of the workers' testicular function improved but the men exposed for more than 120 hours experienced no improvement (Potashnik, 1984). Similarly, 17 years after being exposed to DBCP the extent of recovery from sperm damage was mixed (Potashnik and Porath, 1995).

9.5 DBCP and cancer?

In 1975, as part of a programme to test pesticides for carcinogenicity, the National Cancer Institute reported that DBCP was carcinogenic in rats and mice. Industry representatives criticised the study at an OSHA hearing in 1977 because of the high doses used. Subsequently, a rodent study of both sexes using much lower doses by Dow Chemical at the Hazleton Laboratory in 1977 resulted in carcinomas of the stomach, liver and renal tubules at the highest dose and a statistically non-significant increase in carcinomas at the two lower doses.

Today, animal experiments using high exposure levels are still employed to evaluate the safety of many chemicals. Industry and other interested parties often assert that such experiments are irrelevant to human exposures, which are usually much lower. There are, however, good reasons to doubt these claims. The small number of animals used in experiments (e.g. usually 20 per exposure group) mean that the doses have to be high in order to reveal any possible hazard that thousands of workers (or many more consumers) face at much lower exposure levels. As a result, high doses have been shown, in very many cases, to be reliable predictors of the hazards humans face at much lower doses.

Since 1992, the US Environmental Protection Agency (EPA) has classified DBCP as a 'probable human carcinogen' ([1]). The International Agency for Research on Cancer (IARC) assessed the evidence as sufficient in experimental animals to classify DBCP as a 2B ('possible') carcinogen (IARC, 1999).

9.6 DBCP risks: from manufacturing to pesticide spraying

While OSHA was attempting to protect workers manufacturing DBCP, the US EPA took steps to protect the health of workers using the pesticide. In September 1977, US EPA administrator Douglas M. Costle announced that under the authority granted by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) he was suspending distribution of DBCP. Costle noted that he had this special authority 'in situations where the use of that pesticide appears likely to pose an unreasonable risk to man during the period necessary to conduct and complete a more lengthy administrative proceeding.'

The US EPA examined the scientific evidence and, even though early studies of DBCP sprayers in California and Israel had produced mixed results (Glass et al., 1979; Karraazi et al., 1980), determined that the risk of harm was sufficient to take emergency temporary action to protect workers spraying the pesticide. The US EPA prohibition on using DBCP became permanent in November 1979 and applied to all crops, except for pineapples grown in Hawaii. In 1985 the US also prohibited use of DBCP on pineapples.

9.7 DBCP exports from 1969 to the 1980s: spreading sterility?

DBCP was developed for use against nematodes that attack pineapple plants, so it was not surprising that it was also effective on another tropical fruit: bananas. In the mid-1960s, the Standard Fruit Company began testing DBCP on its banana plantations in Central America; by 1969, DBCP was in full-scale use in Costa Rica and Honduras. The pesticide containers were boldly marked with the brand names Fumazon and Nemagon but, like containers in the United States, provided no warnings to workers about the risk of sterility. Moreover, the labels on the pesticides exported were in English. Even if they had been written in Spanish, there is no guarantee that pesticide sprayers could have read them, since many were illiterate.

The US EPA regulatory ban on using DBCP pesticide in the US did not ban Shell and Dow from manufacturing it and the Standard Fruit Company

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([1]) http://www.epa.gov/ttn/atw/hlthef/dibromo-.html.

Box 9.2 The Swedish film documentary, the Dole lawsuit and freedom of speech

Maria Albin

'Bananas!', a 2009 documentary by independent Swedish filmmaker Fredrik Gertten, addresses the attempts of 12 banana plantation workers in Nicaragua to sue Dole Food Company (previously named Standard Fruit) for DBCP-induced sterility. The film closely follows the workers and the controversial personal injury Californian lawyer, Juan Dominguez, who took on their claims.

In July 2009 Dole sued Gertten and the film's producer Margarete Jangard, claiming defamation and seeking a permanent injunction against them screening 'Bananas' in public, displaying the film website or giving interviews promoting the film 'in which any portion of the accusations made against Dole in the documentary film Bananas are republished'.

The lawsuit followed other steps by Dole to obstruct the film's release. Dole sought to have the film withdrawn from the Los Angeles film festival where it was due to be shown in June 2009 (it was moved to a 'special case study screening' to avoid possible legal action). Dole also sent a letter to the Swedish ambassador Jonas Hafström in Washington, asking him to take 'appropriate steps to limit its damaging impact, including urging the filmmakers, WG Film AB and Mr Gertten to act responsibly and halt dissemination of this film in the United States of America and Europe.

The media's response to Dole's efforts was robust. Filmmakers launched a petition for free speech during the Los Angeles film festival. The CEO of the German Documentary Film Association wrote a letter demanding that Dole cease its 'attacks on the freedom of information as well as stop your company's inhuman practices in Latin America which the film "Bananas" criticizes.' The International Federation of Journalists likewise condemned the use of the law to evade media scrutiny and public accountability as an unforgiveable violation of free speech.

Gertten and Jangard regarded Dole's lawsuit as a strategic lawsuit against public participation (SLAPP) — a deliberate attempt by a wealthy party to silence its critics by outspending them in launching a legal action. Accordingly, the filmmakers filed an anti-SLAPP motion and a cross-complaint.

Swedish reaction was strong and media coverage was extensive. The film was shown in Sweden's parliament, causing an exchange of letters between the executive vice-president of Dole and the two MPs responsible for the screening, Mats Johansson of the Conservative Party and Luciano Astudillo of the Social Democrats. Their unusually frank letter reflects Swedish public opinion at that stage:

'It seems clear to us that you are misled by your PR-firm on how to influence Swedish opinion, with a poor understanding of our tradition of free speech during more than two hundred years. As the saying goes: all business is local. We strongly recommend a change of bureau and tactics, if you are at all interested in the Swedish market. But first and most we urge you — in the name of free speech — to withdraw your lawsuit against Mr Gertten.'

MPs signed a cross-party petition urging Dole to withdraw their legal action in the name of free speech, and they were joined in these demands by the CEOs of leading food chains. The action was sufficient to make Dole withdraw its legal action in October 2009. It stated that it made its decision in view of the free speech concerns being expressed in Sweden, although it continued to believe in the merits of its case. The filmmakers withdrew their counter-claim but demanded that their legal fees be reimbursed. However, the threat that Dole would reinstitute the action hampered the distribution of the film.

In 2010, a Los Angeles court decided in favour of the filmmakers, stating that the lawsuit had been what is commonly known as a SLAPP, awarding them almost USD 200 000 in fees and costs and enabling Bananas! to be released in the US.

Having made a film about Dole being sued, Gertten has now made a new film about being sued by Dole. 'Big boys gone bananas!' premiered in October 2011 at the International Documentary Film Festival in Amsterdam.

Sources: http://www.bananasthemovie.com/wp-content/uploads/resources/slapp_ruling_nov17_10.pdf;
http://www.bananasthemovie.com/wp-content/uploads/resources/bananas_defamation_complaint_july8_09.pdf;
http://www.iidh.ed.cr/comunidades/ombudsnet/docs/doctrina/doc_ccpdh_resoluciones/resolucion%20nicaragua%20final.htm;
http://www.bananasthemovie.com/wp-content/uploads/resources/letter_dole-hafstrom_june5_09.pdf;
http://www.ifj.org/en/articles/ifj-condemns-attempts-by-embattled-food-company-to-censor-free-speech-in-us.

and other growers continued to use it. When Dow informed Standard Fruit that it was halting shipments of DBCP, Standard Fruit threatened Dow with a claim of breach of contract. To settle the matter, Standard Fruit Company agreed to indemnify Dow for any injuries resulting from exposure to DBCP and implement 'applicable work standards in respect of protective clothing, training etc.' as outlined in the OSHA standard.

Shipping records and billing invoices made available through litigation on behalf of DBCP-injured workers reveal that Shell Chemical also sold the pesticide to growers in the Ivory Coast from 1977 to 1980. Another US manufacturer, Amvac Chemical Corporation, sold DBCP in 1979 to companies in the Philippines, Honduras and Nicaragua. DBCP was still used in Central American banana plantations until at least 1985 (New York Times, 2003).

In the Philippines, workers employed by subcontractors of Standard Fruit used DBCP until about 1986. According to reports collected by lawyers, some of these workers became sterile and reported that they had not been informed about the risk of using the chemical and had not been given appropriate personal protective equipment. In Costa Rica too, there was inadequate protection of DPCP sprayers (Thrupp, 1991).

Similarly, medical evaluations of 28 Panamanian banana workers in August 1993 diagnosed 25 with damaged sperm (Navaro, 1993).

9.8 Banana workers bring compensation cases: 1990–2010

In the early 1990s, more than 16 000 banana plantation workers from Central America and the Philippines filed a class action lawsuit in Texas against US fruit and chemical companies, demanding compensation for permanent sterility linked to DBCP. A 1992 settlement in Costa Rica provided USD 20 million for 1 000 workers.
In another lawsuit involving 26 000 workers employed in Latin America and elsewhere, the total settlement in 1997 of USD 41 million provided an average compensation of USD 1 500 to each

Photo: © istockphoto/Francisco Orellana worker. In 2002, a national tribunal in Nicaragua sentenced the American multinational companies to pay USD 489 million in damages and interest to 450 workers affected by Nemagon. In a lawsuit, filed on behalf of 13 Nicaraguan banana plantation workers, Amvac Chemical agreed in April 2007 to a total compensation of USD 300 000 to the now-sterile workers.

These settlements came 20 years after each of these firms knew about the potential reproductive health risks to DBCP pesticide spray workers, which had stopped their use in the US. Nevertheless, the firms marketed and sold DBCP abroad without ensuring that worker health would be adequately protected. Tens of thousands of banana workers still have suits pending in courts in the US and elsewhere but many of the relevant facts are still unclear and contested by the growers.

9.9 Environmental pollution of soils and water by DBCP

DBCP is a persistent and mobile chemical and has been found in the soil, and in ground and surface water in areas where it has been used. Torkelson et al. (1961) noted that 'its relatively low vapour pressure and high density assures a long residence in the soil', depending on the method of application.

Although DBCP has been banned for use in agriculture for more than 20 years it persists in the environment and in water supplies. Underground aquifers in the Sacramento Valley of California are contaminated with DBCP and, depending on the temperature and pH, the chemical can persist for over a century (Peoples et al., 1980; Burlington et al., 1982; California Environmental Protection Agency, 1999). It was the most frequently detected contaminant in California wells in the early 1990s (Bartkowiak et al., 1995).

The 2010 update of the California Well Inventory Database reported DBCP detections in 254 of 1 312 wells sampled. Concentrations of DBCP found ranged from 0.01–1.7 ppb compared to the US EPA and Californian maximum contaminant level of 0.2 ppb. Between 1986 and 2009 DBCP concentrations declined in about half of the wells sampled from 49 % above the maximum concentration level (MCL) of 0.2 ppb to 25 % being above the MCL.

The US-based interest group Environmental Working Group (EWG) analysed 20 million tap water quality tests performed by water utilities between 2004 and 2009 (EWG, 2009). Their investigations identified 191 water systems in 18 states with DBCP levels in drinking water above health guidelines set by federal and state health agencies. Of these, 48 water utilities had DBCP levels above the US EPA's legally enforceable maximum contaminant level of 0.2 ppb. The World Health Organization's guideline value for drinking water quality is 1 ppb (WHO, 2003).

More than 20 years after DBCP was banned, levels continue to exceed health limits in the tap water of over 4 million Californians.

EWG also noted that 'in 38 communities, the levels of DBCP in tap water are above the so-called 'negligible' risk for carcinogens. In 31 communities, the levels ranged from 20–200 times the amount associated with a 'negligible' risk. A particular concern raised was in the case of infants drinking formula prepared with the tap water.'

9.10 Some late lessons

Lessons for science

1. DBCP exposures below the lowest dose tested in animal studies were mistakenly assumed to be safe.
2. While adverse effects on crude testicular morphology and sperm counts were documented, further studies were not carried out to determine the exposure levels that could have provided more subtle indicators of early stage infertility.
3. The early toxicity studies were carried out before modern protocols became available, but continued application of DBCP in developing countries did not lead to the use of updated protocols to assess the toxicity in further detail.
4. Evidence of harm in animals was not seen by many scientists as relevant to humans.
5. Human reproduction may be sensitive to subtle derangements of physiological processes, thereby causing sub-fertility or infertility in the absence of obvious pathology.
6. No attention was paid to the possible effects on sons of exposed women.
7. Routine medical records and health statistics can be of limited use in regard to adverse effects on reproduction.

8. Skin exposure can contribute significant doses of DBCP: air monitoring alone, as with other skin penetrating chemicals, therefore underestimated total doses received.

9. Independent expert assessments e.g. by the US governmental body, NIOSH, were needed to identify harm and to better protect employees.

Communication and use of research evidence

1. The original evidence for DBCP effects on human male sterility came from the lay and local knowledge of the workers and their wives.

2. It was confidentially asserted that DBCP was safe to use without there being any studies of workers or relevant animal studies to confirm this assumption: an example of the '**authoritative assertion but without evidence**' which appears in other chapters.

3. The toxicity information was translated only into very general warnings on labels: no translations were provided for products exported.

4. The animal toxicological findings did not lead to any surveillance studies of men exposed to DBCP at the production plants until after evidence was observed by the workers.

5. No action was taken to avoid the earlier biological 'effects' in animals until they had become 'adverse effects' in people.

6. The application of DBCP was considered essential by growers, including multinational companies, and they considered the toxicity concerns were too small to be significant.

7. The early scientific warnings were not widely reported but confined to specialist scientific journals or internal company communications.

8. Knowledge from the manufacturing risks did not get taken up by the companies responsible for user risks.

9. National standards to control the risks of DBCP were not transferred into international standards to protect workers from globalised exposures to hazardous chemicals.

10. Early warnings about the persistence of DBCP in soils and water did not get acted upon until many years later.

Compensation for victims

1. Much information about the responses of DPCP producers and user companies only emerged via legal procedures in the compensation cases.

2. Compensation cases in the law courts can be difficult, expensive and very time consuming to pursue (see Chapter 24 on protecting early warners and late victims).

9.11 Conclusion

There is now widespread concern about male infertility, and related reproductive problems, such as testicular cancer and developmental defects, in wildlife, workers and consumers (e.g. WHO, in press; EEA, 2012; BCPT, 2008).

The lessons of DBCP are very relevant to these concerns and to the current exposures of many workers and consumers to the endocrine disrupting substances (EDSs) which seem to be playing a role in the reproductive ill health of both humans and wildlife (see also Chapter 13 on ethinyl oestradiol in the aquatic environment and Chapter 10 on BPA).

Protecting production workers, users, consumers, and the environment from chemicals that may damage reproduction needs the closer integration of scientific disciplines, and government actions if the timely protection from harm, using precautionary approaches to the evidence from science, is to be achieved. The lessons of DBCP may help in this.

Table 9.1 Key early warnings about and recognition of DBCP toxicity

1956	Manufacturing of DBCP began
1958	Two independent rodent studies document testicular toxicity
1961	DBCP is registered as an approved pesticide in the US
1961	Animal studies show effects on testes and sperm
1961	Medical examination of workers at a DBCP production plant takes place but testicular function is not examined
1961	Data on persistence and water solubility are published
1969	Use of DBCP at banana plantation in Costa Rica occurs without appropriate warning labels or safety precautions
1975	DBCP is found to be carcinogenic in two species of rodents, both male and female
1977	Episodes of reduced sperm counts occur in US manufacturing workers
1977	US authorities investigate DBCP toxicity, issue new guidelines, enforce new exposure limits and remove approval, except for special pineapple protection in Hawaii
1977–?	DBCP continues to be exported for use outside the US
1990s	Court cases are brought against employers and producers to compensate for adverse health effects in plantation workers in Latin America and the Philippines
1999	State of California decides to regulate DBCP contamination of drinking water
1990s–2010	Compensation cases for DBCP users in South America are won and lost
2007–today	DBCP remains a contaminant of drinking water in 38 cities in California and elsewhere

References

Albin, M. and Giwercman, A., 2009, 'Evidence of toxic effect of a chemical on reproduction ignored' *Lakartidningen*, (106/37) 2 296–2 297 (in Swedish).

Bartkowiak, D., Newhart, K., Pepple, M., Troiano, J. and Weaver, D., 1995, Sampling for Pesticide Residues in California Well Water, 1995 update of the Well Inventory Data Base, Report No EH95-06 (http://www.cdpr.ca.gov/docs/empm/pubs/ehapreps/e9506.htm) accessed 12 April 2011.

BCPT, 2008, 'PPTOX Prenatal Programming and Toxicity', *Basic & Clinical Pharmacology & Toxicology*, (102/2).

Beasley Allen Law Firm, 2007, 'Pesticide company settles sterility lawsuit', 24 April 2007.

Burlington, N.E., Lee, L.A. and Rosenblatt, D.H., 1982, 'Kinetics and products of hydrolosis of 1,2-dibromo-3-chloropropane', *Environ Sci Technol*., (16) 627–632.

California Environmental Protection Agency, 1999, *Public health goal for 1,2-Dibromo-3-chloropropane (DBCP) in drinking water* (http://www.oehha.ca.gov/water/phg/pdf/dbcp_f.pdf) accessed 12 April 2011.

Clark and Snedeker, 2005, 'Critical evaluation of the cancer risk of dibromochloropropane (DBCP)', *J. Environ. Sci. Health C. Environ. Carcinog. Ecotoxicol. Rev.*, (23/2) 215–260.

EEA, 2012, *The impacts of endocrine disrupters on wildlife, people and their environments*, EEA Technical report No 2/2012, European Environment Agency.

EWG, 2009, 'National Drinking Water Database', Environmental Working Group, December 2009 (http://www.ewg.org/tap-water/home) accessed 5 January 2012.

Glass, R.I., Lyness, R.N., Mengle, D.C., Powel, K.E. and Kahn, E., 1979, 'Sperm count depression in pesticide applicators exposed to dibromochloropropane', *Am. J. Epidemiol.*, (109) 346–351.

Goldsmith, J.R., 1997, 'Dibromochloropropane: Epidemiological Findings and Current Questions', *Annals New York Academy of Sciences*, (26/837) 300–306.

Goldsmith, J.R., Potashnik, G., Israeli, R., 1984, 'Reproductive outcomes in families of DBCP exposed men', *Arch. Environ. Health,* (39) 85–89.

International Agency for Research on Cancer (IARC), 1999, 'Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide', *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, (71) 470–500.

Kharrazi, M., Potashnik, G. and Goldsmith, J. R., 1980, 'Reproductive effects of dibromochloropropane', *Isr. J. Med. Sci.*, (16) 403–406.

Kloos, H., 1996, '1,2 Dibromo-3-chloropropane (DBCP) and ethylene dibromide (EDB) in well water in the Fresno/Clovis metropolitan area, California', *Arch. Environ. Health*, (51/4) 291–299.

Lykken, L., 1958, 'Letter to M.R. Zavon, Kettering Laboratory, University of Cincinnati, June 4, 1958', in: Misko, F., Siegel, C.S. et al., 1993, *DBCP: The Legacy*, Dallas, Texas.

Miller, T.C., 2007, 'Pesticide company settles sterility suit for $300,000', *Los Angeles Times*, 16 April 2007.

Misko F., Siegel, C.S. et al., 1993, *DBCP: The Legacy*, Dallas, Texas.

Navaro, C., 'Laboratorio Clinico Navarro, Changuinola, Panama, Agosto de 1993', in: Misko, F., Siegel, C. S. et al., 1993, *DBCP: The Legacy*, Dallas, Texas.

New York Times, 2003, 'Banana Workers Get Day in Court', 18 January 2003.

NIOSH, 1977, *Health Hazard Evaluation: Occidental Chemical Company, Lathrop, California*, United States National Institute of Occupational Safety and Health, August–October 1977.

NIOSH, 1978, *A Recommended Standard for Occupational Exposure to DBCP*, US Department of Health, Education and Welfare.

OSHA, 1977a, *Proposed Standard on Occupational Exposure to 1,2-Dibromo-3-Chloropropane*, Occupational Safety and Health Administration, 42 Federal Register 57267, 1 November 1977.

OSHA, 1977b, *Emergency Temporary Standard on Occupational Exposure to 1,2-Dibromo-3-Chloropropane*, Occupational Safety and Health Administration, 42 Federal Register 45536, 9 September 1977.

OSHA, 1978, *Final Rule on Occupational Exposure to 1,2-Dibromo-3-Chloropropane*, Occupational Safety and Health Administration, 43 Federal Register 11514, 17 March 1978.

Peoples, S.A., Maddy, K.T., Cusick, W., Jackson, T., Cooper, C. and Frederickson, A.S., 1980, 'A study of samples of well water collected from selected areas in California to determine the presence of DBCP and certain other pesticide residues', *Bull. Environ. Contam. Toxicol.*, (24) 611–618.

Potashnik, G., Ben-Aderet, N., Israeli, R., Yanai-Inbar, I. and Sober. I., 1978, 'Suppressive effects of 1,2-dibromo-3-chloropropane on human spermatogenesis', *Fertility and Sterility*, (30) 444–447.

Potashnik, G., Yanai-Inbar, I., Sacks, M.I. and Israeli, R., 1979, 'Effect of dibromochloropropane on human testicular function', *Israel Journal of Medical Sciences*, (15) 438–442.

Potashnik, G., Goldsmith, J.R. and Insler, V., 1984, 'Dibromochloropropane-induced reduction of the sex-ratio in man', *Andrologia,* (16) 213–218.

Potashnik, G., and Porath, A., 1995, 'Dibromochloropropane (DBCP): A 17-year reassessment of testicular function and reproductive performance', *J. Occup. Environ. Med., (*37) 1 287–1 292.

Rakhmatulayve, 1971, 'Hygienic features of nematocide nemagon in relation to water pollution protection', *Hyg. Sanit.*, (36) 334–348.

Reed, N.R., Olson, H.E., Marty, M., Beltran, L.M., McKone, T., Bogen, K.T., Tablante, N.L. and Hsieh, D.P.H., 1987, *Health risk assessment of 1,2-Dibromo-Chloropropane (DBCP) in California drinking water*, University of California Davis, Department of Environmental Toxicology.

Reznik, I.B. and Sprinchan, G.K., 1975, 'Experimental data on gonadotoxic action of nemagon' (in Russian) *Gig Sanit,* (6) 101–102.

Thrupp, L.A., 1991, 'Sterilization of workers form pesticide exposure: The causes and consequences of DBCP-induced damage in Costa Rica and beyond', *International Journal of Health Services*, (21/4) 731–757.

Torkelson, T.R., Sadek, S.E., Rowe, V.K., Kodama, J.K., Anderson, H.H., Loquvam, G.S. and Hine, C.H., 1961, 'Toxicologic investigations of 1,2-dibromo-3-chloropropane', *Toxicol. Appl. Pharmacol.*, (3) 545–559.

US EPA, 1979, *Dibromochloropropane: Suspension order and notice of intent to cancel*, United States Environmental Protection Agency, Federal Register 65135, 9 November 1979.

US National Peach Council, 1977, Personal communication to Eula Bingham, September 1977.

WHO, 2003, WHO Guidelines for Drinking-Water Quality, undated, Water Sanitation and Health (WSH).

WHO, in press, *Global assessment of the State-of-the-Science of Endocrine Disruptors*, World Health Organization.

Whorton, D., Kraus, R.M., Marshall, S. and Milby, T.H., 1977, 'Infertility in male pesticide workers', Lancet, (2/8051) 1 259-1 261.

WSJ, 1997, 'Filipino workers receive compensation from banana pesticide settlement fund', Wall Street Journal, 12 December 1997.

10 Bisphenol A: contested science, divergent safety evaluations

Andreas Gies and Ana M. Soto (1)

Bisphenol A (BPA) is currently one of the world's best-selling chemicals and primarily used to make polycarbonate plastics. It is widely used in common products such as baby bottles, household electronics, medical devices and coatings on food containers. BPA is known to mimic the female hormone oestrogen and has been found to leach from the materials where it is used.

Studies have suggested that even exposure to low doses of BPA may cause endocrine disrupting effects. As with other hormones, it appears that an organism is most sensitive during development but that effects are often not observed until much later in the lifecycle. This means that at the time when the effects become detectable, the chemical exposure has vanished. This makes it extremely difficult to link exposure to effects in humans.

This chapter maps some of the findings in studies of rodents and humans. It also discusses the challenges of evaluating scientific findings in a field where industry-sponsored studies and independent scientific research seem to deviate strongly. The authors offer suggestions for ways to uncouple financial interests from scientific research and testing.

A widely used and dispersed industrial chemical like Bisphenol A is a controversial example of an endocrine disrupting substance that has implications for policymakers. Different approaches to risk assessment for BPA by US and European authorities are presented. It throws light on the ways in which similar evidence is evaluated differently in different risk assessments and presents challenges for applying the precautionary principle.

The intense discussion and scientific work on BPA have slowly contributed to a process of improving test strategies. While traditional toxicology has relied on a monotonic increasing dose-response relationship as evidence that the effect is caused by the test agent, studies on BPA and other endocrine disruptor chemicals (EDCs) have demonstrated the limitations of this approach and adjustments have been made in some cases.

It has also been widely accepted that effects cannot be predicted by simply thinking of BPA as a weak oestrogen and extrapolating from what is observed for more potent endogenous oestrogens. This lesson is particularly evident in the intense pharmaceutical interest in selective oestrogen response modifiers (SERMs).

The chapter is followed by a panel analysing the value of animal testing for identifying carcinogens.

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(1) This paper is based on the scientific opinions of the authors and does not necessarily reflect the opinions or policies of the institutions they are working for.

10.1 The first known endocrine disruptor: early warnings

Bisphenol A (BPA) is one of the industrial chemicals often referred to as 'emerging environmental substances'. This categorisation is in fact somewhat euphemistic. BPA was probably the first synthetic substance known to mimic the natural female sex hormone oestrogen. As early as 1934, Dodds and Lawson (1936, 1938) were searching for synthetic chemicals that could replace expensive natural oestrogen in pharmacological applications. They identified BPA as a weak functional oestrogen, utilising rat test systems that are still in use today. It failed to make a career as a medicine. Later, other substances like Diethylstilbestrol (DES) were discovered by the same team of British scientists (Dodds et al., 1938). The synthetic oestrogen DES was much more potent than BPA and was subsequently used as a pharmaceutical that showed severe side effects (Meyers, 1983).

Not suitable as a pharmaceutical, BPA was marketed as an industrial chemical. In 1957 BPA was polymerised with phosgene, resulting in what is known today as polycarbonate. That started the plastics revolution that has changed the lives of people around the world. At that time everyone thought that plastics, particularly polycarbonate, were significant advances that would improve our lives.

10.2 A growing problem

BPA is currently one of the world's best selling chemicals, with a total annual production of 3.8 million tonnes in 2006 (Association of Plastics Manufacturers, Polycarbonate/BPA group, 2007). In 2005 and 2006, about 1.15 million tonnes were consumed within the European Union (European Commission, 2008). These figures reflect an increase in consumption of 69 % over a seven year period, an annual increase of 7 to 8 %. Most BPA is used to produce plastics, mainly polycarbonate (66 %) and epoxy resins (33 %) (Association of Plastics Manufacturers, Polycarbonate/BPA group 2007). Many other uses have been identified, such as an ingredient in thermal paper. This is why BPA is regularly found in recycled paper (Terasaki et al., 2007; Vinggaard et al. 2000), which is frequently used to produce food containers (Ozaki et al., 2006; Lopez-Espinoza et al., 2007).

It should be noted that the European Risk Assessment Document was not able to identify the purpose of use of more than 7 000 tonnes of the BPA that is consumed annually within the European Union (European Commission, 2008). Commercial BPA contains up to 16 different phenolic impurities that show structural features of oestrogenic chemicals but have never been toxicologically characterised. These 'minor impurities' represent another 10 000 tonnes annually (Terasaki et al., 2004).

Leaching from plastics

Two out of three tonnes of BPA produced are used to manufacture polycarbonates. This clear hard plastic material is increasingly used where transparent and low-weight synthetic materials are wanted; DVDs, modern car roofs and headlight covers, baby bottles and plastic dishes for use in microwave ovens are all made of polycarbonate. These plastic materials can easily be identified by the recycling code 07 in a triangle or the letters PC. Though BPA is a covalently-bound building block of polycarbonates, the monomer is subsequently released over time from the plastic material (Krishnan et al., 1993; Tan and Mustafa, 2003). Leaching of BPA is increased by the age of the material, alkaline conditions and heating. All polycarbonate items are probably a source of BPA. This gives rise to the concern that a growing stock of material has been built up in our homes and in the environment that is a potential continuous source of BPA exposure.

Polycarbonates are probably the main but not the only source of BPA. It also leaches from dental sealants (Joskow et al., 2006), inner coatings of cans and microwave containers (Brotons et al.,1994; Mariscal-Arcas et al., 2009), and in relatively high concentration from medical devices used in intensive care units (Calafat et al., 2009). Thus BPA is found in many matrices including house dust (Butte et al., 2001), indoor air, hand wipes, solid food, liquid food (Wilson et al., 2007) and drinking water (Shao et al., 2008). The European Union Directive 90/128/EEC includes BPA in the list of chemicals with a specific migration limit in food, set at 3 mg/kg (European Commission, 1990). BPA has been found in canned food at concentrations up to 380 μg/kg (Goodson et al., 2002), but only up to 4.5 μg/kg in canned drinks (Cao et al., 2009).

It is not surprising that BPA is one of those ubiquitous chemicals that are a real nightmare for analytical chemists. The substance can leach easily from plastic laboratory equipment and thus contaminate samples that are to be analysed. As with softeners such as phthalates, great care has to be taken to avoid such contamination.

10.3 Identifying the risk was an accident, not the result of a regulatory process

In 1991, a conference taking place in Wingspread Racine, Wisconsin used the phrase 'endocrine disruptor' for the first time (Markey et al., 2002). In 1992 the first scientific paper using this was published by Bason and Colborn (1992). It described indicators of hormonal de-regulation in wildlife and humans and suspected mainly pesticides as the cause of these emerging effects. BPA was added to the list of potential endocrine disruptors one year later. It was by accident that the risks associated with it were re-discovered. In 1993 a team of endocrinologists at Stanford University found an unknown oestrogenic substance that contaminated their assays. Finally they identified BPA leaching from their polycarbonate cell culture dishes when they were autoclaved (Krishnan et al., 1993). It may be surprising that neither any governmental nor any industry programme for risk identification or risk assessment identified BPA as a problematic hormonally-active substance although such programmes had been run in Europe since 1982 with considerable financial and intellectual input from governments and industry. Although several European chemical companies had a history of hormone research over decades, they did not play a role in identifying and assessing environmental chemicals with hormone-disrupting properties. Industry missed a chance to care for their products responsibly.

In 1995 a number of workshops took place in Denmark, the United Kingdom, Germany and the United States to discuss the upcoming issue of hormonally-active environmental chemicals. One year later the book by Colborn, Dumanowski and Myers (1996) 'Our stolen future', with a foreword by former US Vice-President Al Gore, put this issue on the global political agenda. Meanwhile, in the second half of the 1990s, BPA became the most prominent example of an endocrine disruptor in the scientific and public debate.

10.4 Bisphenol beyond Paracelsus

In the past 100 years almost no toxicological textbook failed to quote Philippus Aureolus Theophrastus Bombast von Hohenheim, better known by his nickname Paracelsus:

> 'Alle Ding sind Gift und nichts ist ohn Gift; alein die Dosis macht das ein Ding kein Gift ist' (Paracelsus, 1539)
>
> (All things are poison and nothing is without poison, only the dose permits something not to be poisonous).

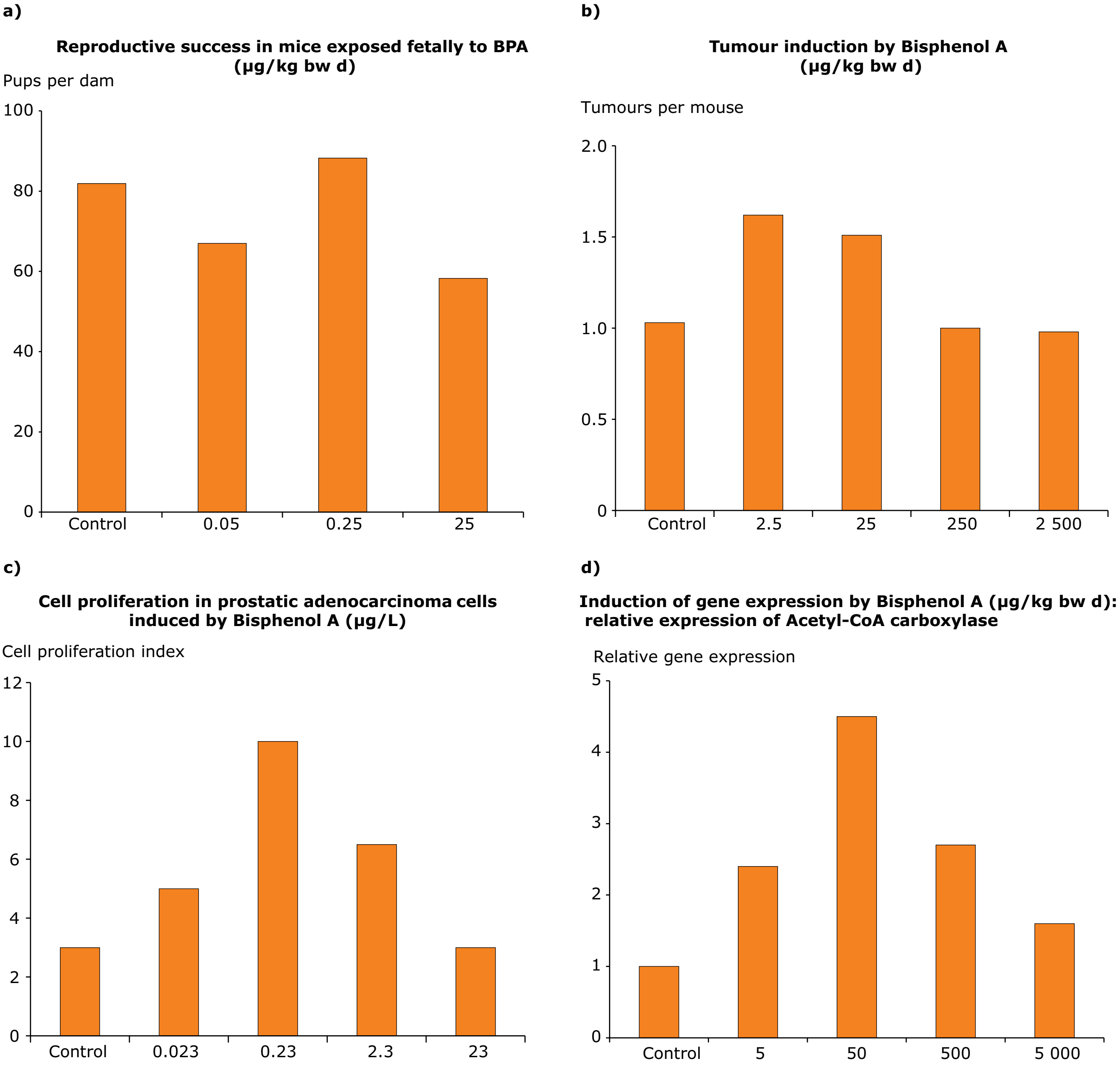
Probably all students of toxicology were taught by their professors that sugar and salt and even water can be a poison if the dose is high enough. BPA challenged our belief that high doses produce more serious effects than low ones. Instead, BPA, like natural hormones, frequently produces dose-response curves that are non-linear. In such experiments very low doses or concentrations show a small effect, intermediate doses cause the most serious effects while high concentrations again show no or only moderate effects. These dose-response curves resemble an upside-down 'U' and are therefore called inverted u-shaped dose-response curves (Sonnenschein et al., 1989). Such dose-response curves occur when tumours are induced in transgenic mice (Jenkins et al., 2011), in snail test systems with regard to clutch size (Schulte-Oehlmann et al., 2001), serum estradiol levels in rats (Akingbemi et al., 2004), calcium influx in rat pituitary cells (Watson et al., 2007), effects on pupal weight and sex ratio in the housefly (Izumi et al., 2008), and reproductive performance in female mice (Cabaton et al., 2011) when these animals are exposed to BPA (Figure 10.1).

Several mechanisms have been hypothesised to try to explain this phenomenon. The global assessment of state-of-the-science of endocrine disruptors published on behalf of the International Programme for Chemical Safety (IPCS) of the WHO (Damstra et al., 2002) pointed out that no common dose-response mechanism can be expected when endocrine disruptors are under study. These chemicals often mimic naturally-occurring hormones or antagonise them. So they interfere with a naturally-activated system that may be stimulated by low doses and inhibited by over-dosing because receptor-mediated responses saturate (Welshons et al., 2003). Several different mechanisms involving activation of different genes may be involved in the expression of one visible effect. An endocrine-disrupting mechanism resulting in a u-shaped dose response curve may be the result of two or more effects with different dose-response characteristics each, as demonstrated in experiments using cell line models. These non-monotonic effects have been shown experimentally in many *in vivo* and *in vitro* systems (Vandenberg et al, 2012). Although the Endocrine Society, the largest professional organisation of endocrinologists, points out in a recent statement that non-traditional dose-response relations are very common in the action of hormones (Diamanti-Kandarakis et al., 2009), the existence and plausibility of such effects are still disputed by some scientists and members of regulatory bodies (Sharpe, 2010).

Deviations from monotonic dose-response curves for hormone action are very frequent. Neither do they seem to be rare in toxicology. In 2001, Calabrese and Baldwin analysed 668 dose-response curves that were published in toxicological or eco-toxicological papers in three major journals from 1962–1998: 37 % of the curves were non-monotonic and exhibited a u-shaped form.

This kind of curve is much more than a curiosity. What toxicology did in past centuries was to extrapolate from high doses with frequent and serious effects to low doses where only small effects were expected. A prerequisite for doing this is that the curve is monotonic. The central paradigm of

Figure 10.1 Examples of non-monotonic dose-response curves for BPA



Note: In the test systems shown, small doses show small effects, intermediate doses cause the most pronounced effects while high doses cause no change or even a decrease in effect.

Schematic graphs adopted from the papers, for data and details see the original references.

Source: a) Data from Cabaton et al., 2010; b) Data from Jenkins et al., 2011; c) Data from Wetherill et al., 2002; d) Data from Marmugi et al., 2011 toxicological assessment was: if a high dose of a chemical does not cause harm, then a low dose will not either. Obviously this does not hold true at least for physiological responses to endocrine disruptors. After 500 years it has become clear that Paracelsus's paradigms do not contribute to the protection of human health and environment if they are applied to risk assessments in a naive way.

1997 Colerangle and Roy reported that a low dose of BPA induced a proliferative effect in breast tissue and that BPA was much more potent than expected from its oestrogen-receptor binding profile. Science reacted immediately and since then hundreds of papers on low-dose effects have been published (see Table 10.1). These further demonstrate that the organism is most sensitive during development, that effects are often not observed until later in the lifecycle, and that conventional toxicology testing could be insensitive to BPA if it fails to include in-utero dosing and later life follow-up of appropriate endpoints. The papers also support the observation of non-monotonic dose-response curves for BPA and other hormones, reflecting feedback mechanisms, receptor saturation, and multiple mechanisms of action (Vandenberg et al., 2012). Within the scientific community, there is far-reaching agreement on these concepts and findings. However BPA industry organisations continue to claim that these findings are invalid as 'no study purporting to show low-dose effects has been replicated in a second lab, despite repeated efforts to do so' (Polycarbonate/BPA Global Group, 2012).

10.5 The time makes the poison

The proper development of an organism is an extremely complex process, dependent on external and internal cues and hormonal regulation. Not only the chemical characteristic and the internal dose are important but also the exact timing of the stimulus (Neubert, 1997). For BPA, so far, it has been shown that irreversible developmental effects are caused during the foetal, neonatal or juvenile period in test animals (Palanza et al., 2008) and that the effects observed may be different if the organism is exposed during early or later life-stages (Richter et al., 2007).

Assessing the effects of endocrine disruptors is extraordinary difficult because the time of exposure is not necessarily the time when the effects can be detected. Perinatal exposure to BPA has been shown to affect females: it alters ovarian cyclicity and induces early cessation of oestrus cycles, impairs reproduction, interferes with sexual differentiation of the brain, alters behaviour, alters mammary gland development and induces mammary gland neoplasia (Soto and Sonnenschein, 2010). It has also been shown that BPA can interfere with normal spermatogenesis, reducing sperm numbers later in life in rodents and when the mothers of the pups are dosed during pregnancy and lactation (vom Saal et al., 1998; Okada et al., 2008a). If this also happens in humans, the effects of exposure of the foetus or the newborn may only be seen more than a decade later when the boys reach puberty and sperm becomes available for characterisation. This temporal disconnection between exposure and effect is even larger when the effect observed is breast cancer, because the age of prevalence for this disease is 50–60. For example, prenatal exposure to synthetic oestrogens like DES (Hoover et al., 2011) increase the incidence of breast cancer at 40 years of age or older. At the time when the effects become detectable the chemical exposure has vanished. This makes it extremely difficult to apply epidemiological methods to link exposure to effects in humans. For a realistic risk assessment it is also crucial to characterise the exposure to BPA at the appropriate life stage. Young children have the highest rate of daily ingestion of this chemical (European Commission, 2008) and the internal concentrations of free and toxicologically-active BPA may be much higher than in adults because of their different metabolic capacity (Edginton and Ritter, 2009).

These examples illustrate that dose is only one of the factors that make a poison. Equally important are the time of exposure and the time when effects become visible. For a long time BPA has been erroneously viewed as only a weak oestrogen (Völkel et al., 2005; Goodman et al., 2009). Indeed, *in vitro* studies indicated that BPA competes with estradiol to bind the oestrogen receptors alpha and beta. In these tests relative binding affinities were at least a thousand-fold lower than that of estradiol (Kuiper et al., 1998). Recent results from *in vivo* and *in vitro* studies indicate that BPA can act via a number of different additional cellular target systems, including binding to a non-classical membrane-bound oestrogen receptor (ncmER) (Nadal et al., 2000, 2004; Alonso-Magdalena et al., 2005), an orphan nuclear receptor called oestrogen-related receptor gamma ERR-γ (Okada et al.. 2008b), a seven-transmembrane oestrogen receptor called GPR30 (Thomas and Dong, 2006), and the aryl hydrocarbon receptor (AhR) (Kruger et al., 2008).

In vitro studies also show that BPA can act as an androgen receptor antagonist. BPA can also interact with thyroid hormone receptors (TRs) (Moriyama et al., 2002; Zoeller et al., 2005). These multiple modes of action have recently been reviewed in a number of papers (NTP, 2008; Chapin et al., 2008; Wetherill et al., 2007). In some of these systems BPA can exhibit equal or even stronger potency than the naturally occurring hormones (Wozniak et al., 2005; Watson et al., 2007).

For a long time influential scientists claimed that low-dose findings were neither credible nor plausible because, from the relative binding strength of oestrogen and bisphenol, considerably lower effects of BPA would have been expected (Greim, 2004). Today we know that their expectations were based on inappropriate assumptions. Recent experiments showing that low-dose effects of BPA are abolished in null mutants of nuclear oestrogen receptors provide irrefutable evidence in this regard (Soriano et al., 2012).

Nowadays there is widespread agreement that BPA is an endocrine-active chemical with multiple modes of action. A recent paper from US Environmental Protection Agency (EPA)'s high throughput testing group, ToxCast, showed that BPA was active in a wide variety of mechanistic assays — one of the most active chemicals tested (Judson et al., 2010) — and a literature review from a US National Toxicology Program (NTP) draft report on obesity provides an excellent review of BPA's multiple modes of action (NIEHS/NTP, 2011).

10.6 Concern or no concern: that is the question

When BPA was polymerised to make polycarbonate, neither the data on non-monotonic dose responses nor the deleterious effects of foetal exposure to DES were known or commonly recognised in science. In addition, since BPA seemed to be a weak oestrogen with activity 1 000–10 000 fold less than estradiol, and since it was assumed that the BPA monomer would not be released from the polycarbonate plastic (Biles et al., 1997), there was no real concern about human exposure and thus toxicity.

The complexity of the exposure assessment, the toxicological profile of BPA, and probably the high economic importance of this substance may have contributed to the fact that risk assessments for this substance differ more markedly than for any other chemical. A number of scientific and regulatory bodies and committees have published risk assessments for BPA. The identified acceptable doses for humans differ by many orders of magnitude.

10.7 BPA reviews and risk assessments

BPA is regulated as a food contaminant and thus falls under the jurisdiction of the Food and Drug Administration (FDA) in the US and the European Food Safety Authority (EFSA) in the EU. Both agencies have provided risk assessments over the past decade, all based on toxicity tests in experimental animals. These regulatory agencies have essentially used Good Laboratory Practice (GLP) guideline studies as the only source of data on the toxicity of BPA (see Box 10.1 for GLP and Good Scientific Practice).

Let's take a look at the GLP guideline studies that have been done to assess BPA toxicity and

Box 10.1 Good Science and Good Laboratory Practice

Science is a self-regulating system. To ensure high quality standards, scientists have developed rules for themselves on how to perform scientific work. These have been laid down by international organisations like WHO (2006) or national scientific societies like DFG (1998) in Germany in comprehensive guidance documents. A peer-review system is the core instrument for safeguarding these rules. As a prerequisite for publication, results and scientific papers are reviewed by peer scientists. In prestigious journals more than three out of four papers are not accepted for publication. This system is a very rigorous form of quality control.

For regulatory purposes, particularly for the testing of chemicals and pharmaceuticals, not all results and procedures need to be published and peer-reviewed. As a reaction to low quality and fraud, a different system of quality control has been established. The system of Good Laboratory Practice (GLP) (OECD, 1998) has been tailor-made for commercial research laboratories, and regulatory agencies worldwide require that this system is applied for tests conducted to fulfil regulatory requirements. GLP regulates how to conduct protocols and report tests. GLP can give technical advice but cannot judge whether a test is appropriate to solve a problem or whether, for example, the relevant outcomes have been studied. GLP does not indicate that good science has been performed or that the scientific results are adequate and sufficient to protect human health and the environment (for comprehensive discussion, see also Myers et al., 2009).

that have been pivotal in the FDA and EFSA risk assessment. There are two multigenerational reproduction studies in rats (Tyl et al., 2002) and one multigenerational mouse study (Tyl et al., 2008) that were regulatory guideline studies done according to GLP. These studies all showed only non-specific toxicity (number of live pups per litter) and they were used to identify a Lowest Observed Adverse Effect Level (LOAEL) of 50 mg/kg body weight per day (bw d) and a No Observed Adverse Effect Level (NOAEL) of 5 mg/kg bw d. At least in the rat study there were significant effects below this level (Heinze and Chahoud, 2003). These effects were regarded as not relevant by the authors. The studies have been criticised because they use traditional toxicological endpoints that cannot detect subtle developmental changes and effects caused by hormones (Myers et al., 2009). Recently a large independent trans-generational study (Ryan et al., 2010) also could not find effects at low doses on behaviour, puberty and fertility of female rats.

On the other hand there are many *in vivo* studies describing developmental effects in rodents at very low doses (Table 10.1). The effects under study were reproductive organ morphology, neurodevelopment and behaviour, male reproductive health, and immunology. At least 46 peer-reviewed published studies report effects at oral doses of 50 µg/kg bw d or less (see Table 10.1) (for review, see Gies, 2007). This dose has been regarded as a safe Acceptable Daily Intake (ADI) in the recent European assessment of the European Food Safety Agency (EFSA, 2010).

Recently a working group of the French health agency ANSES (2011) carefully re-examined all animal studies with low doses of BPA, assessed their quality and compared their results. The panel concluded that animal experiments show effects that could be confirmed on male sperm production, induction of ovarian cysts, endometriosis, and advanced puberty in females. Behavioural effects have been confirmed for maternal behaviour and sexual dimorphic behaviour such as anxiety. Effects on lipogenesis, immune behaviour and breast development were also regarded as confirmed.

An important aspect of dose-response assessment is that it is still not clear what is a no-effect level for BPA's most sensitive end-points. Further research is needed to continue refining methods to reliably assess sensitive endpoints and to conduct the studies with a sophisticated approach to connecting internal free BPA dose with effects. As these studies are pursued, we may find that effects of BPA occur in the low or sub- pg/ml range, the same range as estimates of current human exposure. It is clear that most sensitive endpoints include effects on mammary gland development (Rudel et al., 2011b) and neuro-behavioural endpoints that are not commonly assessed in toxicity studies, even those recently adopted for testing endocrine-active chemicals.

The different assessment documents weight this evidence differently. The main areas of controversy are:

- Do any of the non-GLP peer-reviewed papers that show effects of BPA at low doses contain sufficiently reliable information to be considered in the risk assessment? Putting this question the other way: is the study sponsored by The Society of the Plastics Industry, Inc. (Tyl et al., 2002) and the study of Ryan et al. (2010) so reliable that nearly all other studies can be dismissed?
- Are there any relevant concentrations of free BPA in the body that can cause biological effects or is this substance so readily metabolised that it cannot harm humans?

The assessment of the European Food Safety Agency (EFSA) 2010 and the Risk assessment report of the European Union (European Commission, 2008) state that none of the low dose studies has the quality to provide data for the risk assessment. All these studies have been dismissed. The reasons given were:

- only one or two doses tested;
- low number of animals;
- inadequate statistical processing of the data;
- results not consistent with other studies.

The application of these criteria was used to exclude or ignore significant peer-reviewed scientific results. The fact that they were peerreviewed and published in reputable scientific journals indicates that the members of the scientific community that reviewed all these many papers do not agree with the criteria chosen by EFSA.

10.8 EFSA and EU risk assessments

EFSA identified the study of Tyl et al. (2002) as pivotal. With an assessment factor of 100 applied to the No Observed Adverse Effect Level (NOAEL) an Acceptable Daily Intake (ADI) of 50 µg/kg bw d was derived. It should be noted that the assessment of the EFSA and other regulatory bodies is based on arbitrarily selected data from this study. The original data from this study showing a significant increase in anogenital distance (AGD) in males but not in females were not taken forward to the risk assessment (Heinze and Chahoud, 2003). Although AGD is not a validated endpoint for regulatory studies, it is an important marker of sexual development in rodents and humans. Changes in AGD show that sexual development has been disturbed (Swan et al., 2005; Longnecker et al., 2007). An increase in AGD is considered a surrogate for virilisation, while a decrease indicates de-masculinisation. In humans, a lower AGD has been shown to be a predictor of poor semen quality in later life (Mendiola et al., 2011). Similar changes of AGD due to low doses of BPA have been found in independent studies in rodents by Gupta (2000) and Somm (2009). In a recent paper, Tyl (2009) the principal author stated that no low-dose effects have been found in this study. This is not in line with the data presented.

EU Risk Assessment Report (RAR)

In contrast to the majority of EU Member States, some Nordic Countries regarded four neuro-behavioural studies as valid for risk assessment (Negishi et al., 2004; Carr et al., 2003; Ryan and Vandenberg, 2006; Adriani et al., 2005). In a footnote to the assessment document they proposed to take these as pivotal studies. The lowest effective concentration in these studies was described by Adriani as 40 μg/kg bw d. With a factor of three for extrapolation from LOAEL to NOAEL and an extrapolation factor of 100 this would result in an ADI of 0.13 μg/kg bw d. This ADI would be lower by a factor of 380 than that of EU RAR.

The National Toxicology Program (NTP) of the United States of America (NTP, 2008). The NTP assessment concluded that BPA was clearly toxic at high doses over 5 mg/kg bw d. In contrast to the EU RAR, NTP does include the results of the low-dose studies in their assessments. Although it states that low-dose effects are difficult to interpret in many cases, NTP concludes that these results should not be dismissed. The low-dose studies provide limited evidence that human health may be affected and there is some evidence that human health may be at risk at current exposure levels. NTP does not indicate a 'pivotal' study but in their risk characterisation they base their estimates on developmental effects reported from mice studies at a dose of 2.4 μg/kg bw d. NTP did not calculate a Tolerable Daily Intake (TDI) in its assessment. If one applies routine methods to derive an Acceptable Daily Intake (ADI), with a factor of 3 for extrapolation from LOAEL to NOAEL and an extrapolation factor of 100, this would result in an ADI of 0.008 μg/kg bw d. This ADI would be a factor of 6 250 lower than that derived by the EFSA.

Environment Canada and Health Canada (2008). The 2008 Canadian assessment states that 'collectively these (low dose) studies provide evidence that exposure to BPA during gestation and early postnatal life may be affecting neural development and some aspects of behaviour in rodents, the overall weight of evidence was considered limited from the perspective of rigour'. Nevertheless, taking a precautionary approach, the Canadian authorities decided to characterise BPA as a substance that may constitute a risk to humans. So the precautionary risk assessment is based on low-dose neuro-developmental studies. It is not stated which of the studies are taken as decisive. In 2010 the Canadian government listed BPA as a toxic substance.

The Chapel Hill Consensus statement (vom Saal et al., 2007) is not a risk assessment in the classical sense. Thirty-eight scientists, including most of the leading scientists working on BPA, expressed confidence that low doses of BPA disrupt development in many animal models. Their key message is that action is warranted when internal exposure of humans reaches or exceeds the levels that cause serious effects in experimental animals in low dose studies. This consensus statement clearly points to the developing gap between scientific knowledge about BPA and the published opinions of regulatory committees.

The US Food and Drug Administration (FDA, 2008, 2010). In 2008 the FDA issued its risk assessment of BPA which stated that the 'no observable adverse effect' level of 5mg/kg bw d was an adequate margin of safety. The scientific committee of the FDA established a subcommittee in 2008 to review this assessment. The subcommittee harshly criticised the FDA assessment. In particular, it did not agree that the large number of non-GLP studies should be excluded from the safety assessment.

It stated that the weight of the evidence provided scientific support for use of a point of departure substantially (i.e. at least one order of magnitude) lower than the 5 mg/kg bw d level selected in the draft FDA assessment.

In summary the Subcommittee concluded: 'Coupling together the available qualitative and quantitative information (including application of uncertainty factors) provides a sufficient scientific basis to conclude that the Margins of Safety defined by FDA as 'adequate' are, in fact, inadequate.' The Scientific committee of the FDA later adopted this opinion of its subcommittee. Such an explicit statement fundamentally criticising the work of an agency by its scientific advisors is unprecedented.

The report of its scientific advisory committee resulted in the FDA changing its position. On 10 January 2010, the FDA stated that they now 'have some concern about the potential effects of BPA on the brain, behaviour and prostate gland in foetuses, infants and younger children' (FDA, 2010). Thus, for the first time, while it did not change its actual risk assessment of the acceptable daily intake level, it did acknowledge the existence and possible importance of investigator-initiated studies. At that time there were more than 800 investigator-initiated studies published on BPA toxicity.

European Food Safety Authority 2010 BPA Risk Assessment (EFSA, 2010). In 2010 EFSA released an updated risk assessment of BPA. They basically reiterated what they stated in 2006, that BPA was safe to human health and noted that there had been no new compelling non-GLP studies published on BPA. At that time there were more than 800 investigator-initiated studies that were not included in the BPA risk assessment, each one discarded for not meeting specific guidelines.

Thus at that time, the FDA and EFSA still relied exclusively on a handful of GLP multi-generational studies done in contract laboratories that assessed only reproduction, body and organ weights, clinical chemistry and organ histopathology using H&E staining. The same endpoints had been used for the past 50 years: before endocrine disruptors were known, before the developmental basis of disease and gene expression and epigenetics were known, and before low-dose and non-monotonic dose responses were known.

It is remarkable that the FDA and EFSA used guideline studies to indicate that BPA is safe while ignoring over 800 peer-reviewed studies that showed toxicity of BPA at exposure levels below the level of human exposure.

Certainly there are data gaps, but the practice of regulatory agencies of disregarding, or worse, declaring unfit every peer-reviewed study that does not follow the guideline study design cannot be defensible. The scientific literature needs to be assessed on the basis of the strength of the individual studies and the overall strength of the evidence of all the studies in order to show the same or similar effects across doses and times and species.

The German Federal Environment Agency (UBA) (2010). The view of the German Federal Environment Agency (UBA) is that there are sufficient grounds for concern. Numerous studies present, on the whole, a consistent picture, so that, despite uncertainties and gaps in knowledge concerning risk assessment and levels of exposure, there is need for action. The UBA is therefore in favour of precautionary action and restrictions on the use of certain products that contain BPA.

The French Agency for Food, Environmental and Occupational Health and Safety, ANSES (2011). Based on an analysis of all the available scientific literature, an ANSES scientific expert group found 'that there were proven effects in animals (effects on reproduction, effects on the mammary gland, effects on metabolism, the brain and behaviour) and other suspected effects in humans (effects on reproduction, the metabolism of sugars and fats, and cardiovascular diseases). These effects were demonstrated at doses that were significantly lower than the reference doses used for regulatory purposes, especially during certain periods of life characterised by susceptibility to the effects of BPA (pregnancy, pre- and post-natal periods)' (ANSES 2011). This assessment questions parts of EFSA's current assessments.

A joint ANSES and EFSA paper has recently been prepared (EFSA and ANSES 2011). This paper shows that differing assessments persist, partly because they evaluated evidence at different stages of the risk assessment and partly because they use different study quality criteria (2).

10.9 Bisphenol A in human bodies

There is little controversy about the external exposure of humans to BPA. The EU Risk Assessment Report

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(2) ANSES and EFSA agree that they have covered different stages of the risk assessment process: ANSES a hazard identification and EFSA a hazard characterisation (2010) and a full risk assessment (2006) from dietary exposure to BPA (2006). This represents one of the reasons for the divergences between their respective work in 2011 and 2010. They recognise that their selection of critical effects is not based on the same study evaluation criteria e.g. routes of exposure (EFSA and ANSES, 2011).

(European Commission, 2008) used two exposure models to estimate human daily intake. One of these was for regional exposure and one for local exposure near a BPA production plant. Total human exposure was calculated by the regional model to be 1.49 µg/kg bw d, and by the local model to be 43 µg/kg bw d. Estimates of daily BPA intake in adults fell within the range 0.008–1.5 µg/kg bw d. Worst-case scenarios for young children estimated up to 11–13 µg/kg bw d. These data, calculated from exposure scenarios, are well in accordance with daily intake figures recalculated from concentrations in urine. Daily intakes estimated from the Centers for Disease Control and Prevention National Health and Nutrition Examination Survey (CDC NHANES) bio-monitoring data range from 0.15–0.22 µg/kg bw d for adults aged 20–60+ years at the 95th percentile (this means that 95 % of the people had concentrations at or below this value) (LaKind and Naiman, 2011). In German children aged 3 to 14, the 95th percentile of the daily intake recalculated from urine concentrations was 0.37 µg/kg bw d and the maximum value among 599 children was 7 µg/kg bw d (Becker et al., 2009). These intakes were similar to those found in children aged 6 to 11 in the US (Calafat et al., 2008). Bottle-fed infants have two times higher urine BPA levels than breast-fed infants (Völkel et al., 2011). Children in neonatal intensive care units have median urinary BPA concentrations about ten times higher than in children aged 6–11 (Calafat et al., 2008; 2009) and 20 participants eating food with limited packaging for three days showed a 66 % reduction in urinary BPA (Rudel et al., 2011a). In studies that report both conjugated and free BPA in urine, > 90 % is conjugated, including in neonates (Calafat et al., 2009). This indicates that there are particularly highly exposed risk groups in vulnerable life phases that have not yet been recognised in current risk assessments. A recent analysis of NHANES data showed that BPA levels did not decline rapidly with fasting time as expected. This suggests significant levels of exposure not related to food, or accumulation in body tissues. The recent finding of transdermal exposure points to additional sources of exposure, and thus to a higher than expected total BPA exposure (Stahlhut et al., 2009)

Major differences exist concerning internal exposure. Only free bisphenol is believed to be biologically active while its conjugated metabolites are probably inactive; however, it should be considered that conjugated metabolites that may be found in the blood can be de-conjugated in peripheral tissues and thus become re-activated. Human bio-monitoring studies from Germany and the US (Schönfelder et al., 2002a; Padnmanabhan et al., 2008) found 4–6 ng/ml free bisphenol in the blood of mothers. These results are almost identical although the studies used totally different techniques. However pharmacokinetic studies (Doerge et al. 2011a), together with data from bio-monitoring studies and model calculations, resulted in estimates of free BPA levels in human blood between 0.1 and 10 pg/ml (Fisher et al., 2011), around three orders of magnitude lower than the above-mentioned directly measured ones.

No free BPA above the detection limit of 2 ng/ml was found in the blood of nine volunteers dosed intentionally with 5 mg/person (Völkel et al., 2002). This study is still the basis of the risk assessment of the EFSA suggesting that no relevant internal concentrations of free BPA can be found in humans. In summary, the EU Risk Assessment report states: 'Considering the evidence as a whole, EFSA concluded that the validity of the reported high blood levels of BPA in unintentionally exposed human subjects is questionable.' Again EFSA ignores consistent results from peer-reviewed scientific work.

New pharmacokinetic studies (Prins et al., 2011; Doerge et al., 2010, 2011; Taylor et al., 2011) show that caveats in this field are legion. Of particular relevance, the Taylor et al study shows that BPA pharmacokinetics is similar in primates and rodents and thus that rodents are suitable models. Moreover routes of exposure, such as dermal exposure (Stahlhut et al., 2009; Liao and Kannan, 2011a, b) and excretion, such as sweat (Genuis et al., 2012), have recently been recognised but have not yet been quantified and thus are additional sources of uncertainty.

Risk assessment is only a protocol used by the regulatory community, not science per se. Uncertainty has to be taken into account and has to be quantified. The plethora of peer-reviewed research showing low-dose effects indicates that applied test protocols and regulatory procedures are not suitable for assessing endocrine disruptors.

A recent review extensively discusses the relevance of measurements of free and conjugated BPA in human blood (Ginsberg and Rice, 2009). Many peripheral organs, including the placenta, show high activity of glucuronidases and sulphatases that are able to cleave conjugated BPA to its free and metabolic active form. Finding the conjugated form in the blood does not predict that the substance is biologically inactive in the tissue. The assumption of EFSA that rapid conjugation protects humans from adverse effects is far from being precautionary.

In contrast the National Toxicology Program (NTP) recognises the possibility that the published values of free BPA may, in some cases, not accurately represent the 'true' concentrations of free BPA in the blood or body fluids of humans or laboratory animals. However, because of the similarity between values reported with different analytical methods, the NTP accepts the published values as sufficiently reliable for use in this evaluation.

10.10 Spheres of influence

In the case of BPA, a large body of scientific literature obviously indicates deleterious effects in rodents at low doses. The effective doses in these studies overlap the doses of current human intake. Most of the European, American and Asian authorities declare BPA to be safe. Industries rely on these risk assessments. Massive pressure from consumers and politicians has forced many companies, for example the major American baby bottle manufacturers and a European aluminium drinking bottle manufacturer, to withdraw their BPA-releasing products from the market. Without doubt, this has had considerable negative effects on the image of the companies, the reputation of their brands and on the earnings of these branches. For many people the question arises whether BPA-producing industries had previously influenced the assessment processes. Such industrial influences on scientists and authorities have been well documented for the risk assessment of tobacco smoke and second-hand smoking in particular (Grüning et al., 2006).

At least one consulting company that had been active for the tobacco industry, the Weinberg Group, has been successfully hired by the BPA industry to influence the European assessment, in particular the classification and labelling (C&L) which is a key instrument for the risk management of chemicals. In its internet presentation the Weinberg Group itself proudly admits:

'In Europe, THE WEINBERG GROUP and its associates have had a five-year long history of working on the polycarbonates/BPA issue… It also includes identification of opponent's likely arguments, and formation of responses to counter these arguments. THE WEINBERG GROUP contributed its academic and regulatory network to the advocacy effort. This approach proved very effective, as ultimately the C&L working group did not follow the recommendation of the Rapporteur Member State to classify BPA as a Category 2 reproductive toxicant, agreeing instead on the more benign Category 3 classification .We have a long-term relationship with this client, and will continue to support this industry as it faces persistent NGO attacks on its products' (The Weinberg Group, 2005).

Classification as a category 2 reproductive toxicant would have required labelling this substance with a skull and bones sign as toxic. Moreover under the new chemical legislation of the European Community, every use of BPA would have required a formal authorisation.

Science is vulnerable. It is based on the independence of scientists and of science itself. In the committee of the European Food Agency AFC — (Panel on additives, flavourings, processing aids and materials in contact with food) nine of the 21 members stated, in the conflict of interest statements they supplied to the agency, that they had worked for at least one company or association under the influence of the industry or for industry itself or had strong links with associations like Greenfacts or ILSI Europe that are dependent on financial support or industries including BPA producers. One member received financial benefits from industry for writing a review (Dekant and Völkel, 2008) on BPA for a scientific journal.

Meanwhile the European Food Safety Authority made considerable efforts to strengthen transparency and scientific independence, as 'the value of its scientific advice is directly linked to the level of trust held in it by the public and therefore seeks to guarantee independence in all aspects of its governance and scientific activities (EFSA, 2012). New rules for independence policy have been launched by EFSA recently.

Without doubt, working for the chemical industry and its organisations or other NGOs is a job like any other. Whether it is wise to give people who are directly or indirectly paid by industry the task of controlling industry may be questioned.

Various scientific papers have investigated whether the outcomes of scientific studies are dependent of the source of funding. In most cases, a significant association has been found (Lesser et al., 2007; Moses et al., 2005; Blumenthal, 2003). An association of funding and outcome can also been detected for studies on BPA (Table 10.2).

Since EFSA reassessed BPA in Europe in 2006 and increased the tolerable daily intake by a factor of five, scientific evidence has accumulated that shows low dose toxicity and doubts have occurred whether EFSA's decision was unbiased:

- At least ten additional peer-reviewed papers were published showing effects in rodent offspring at oral doses lower than the Tolerable Daily Intake set by the EFSA (see Table 10.1). BPA has been shown to influence body weight and metabolism (Somm, 2009; Rubin et al., 2001) and may be one of the factors contributing to the increasing rates of obesity in humans.
- Numerous other *in vivo* and *in vitro* studies indicate that BPA may not be safe at doses we are currently exposed to.
- Bio-monitoring studies showed that some European and American children are exposed to doses that can produce adverse effects in rodents (for review, see Betts, 2010).
- Vulnerable and highly exposed subgroups, like children in intensive care units, that are not sufficiently covered by current exposure assessments, have been identified (Calafat et al., 2009).
- New sources of BPA have been identified like pacifiers and warm-water tubes (Shelby, 2008).
- Epidemiological studies show that higher exposure of mothers to BPA is associated with increased aggressiveness of daughters when they are two years old (Braun et al., 2009). Like other cross-sectional studies, these associations are not a proof of causation but should be regarded as additional warning signs.
- Free BPA concentrations are associated with oocyte quality (Fujimoto et al., 2011) and embryo quality indicators (Bloom et al., 2011) during human *in vitro* fertilisation.
- BPA levels in the blood of workers are negatively associated with male sexual function (Li et al., 2010).
- Higher BPA exposure is associated with obesity in the general population in the US (Carwile et al., 2011).
- BPA exposure in workers is negatively correlated with the birth weight of their offspring (Miao et al., 2011).
- Gestational BPA exposure affected behavioural and emotional regulation at three years of age, especially among girls (Braun et al., 2011).
- EFSA's assumption that internal doses of free BPA are lower in humans than in rodents at comparable doses is unproven (Gies et al., 2009).
- The European Union has banned baby bottles containing BPA. This ban became effective in 2011 (EU, 2011).

10.11 Lessons to be learned

The 'late lesson' with respect to BPA is the 'same old story' of putting a chemical into widespread use without understanding its health implications, and then trying to resolve public health questions while facing the intense pressure of serious economic consequences. The competing urgency of public health and economic stakes puts the scientific process under enormous pressure. In this perspective the story of BPA resembles those of asbestos, polychlorinated Biphenyls (PCB) and Diethylstilboestrol (DES).

Best science and transparency

In Europe it is timely to dare to start again with the risk assessment of BPA. This assessment must be transparent and conducted by the scientists authoring the papers with high scientific impact in this field. Stakeholder conferences may serve as a forum to make the interests and influence of industry and other NGOs transparent.

Precaution

Until final decisions are made, precautionary measures should be taken to lower human exposures to well below those that cause adverse effects in rodents and behavioural changes in humans in epidemiological studies. This would mean terminating those uses of BPA involving close contact with humans via food or the environment.

Towards more independent science

The new European chemicals legislation REACH (**R**egistration, **E**valuation, **A**uthorisation and Restriction of **Ch**emical substances) relies on the activities of the industry for most risk assessments and toxicity test data. The case of BPA clearly

Table 10.1 Summary of mammalian studies on BPA with effect levels at or below 50 μ/kg bw d, oral administration

Dose (μg/kg bw d)	**Organism, age at dosing**	**Effect**	**Reference**
0.2	Rat, 2-generation study	Anogenital distance in F 1 males, 2 μg/kg in F1 females and 20 μg/kg in F2 females	Ema et al., 2001
0.2	Rat, male adult	Superoxide dismutase, catalase, glutathione reductase and glutathione peroxidase activity in liver ↓, H_2O_2, lipid peroxides ↑	Bindhumol et al., 2003
0.2	Rat, male adult	Prostate size ↑, Testis, epididymis size ↓ H2O2, lipid peroxides ↑	Chitra et al., 2003
0.6	Mouse, pregnancy	Effects on mammary gland development	Ayyanan et al., 2011
1	Rat, 3-generation study	Paired ovary weight in F2 generation ↓, uterine weight in F0 ↓, anogenital distance in female F2 ↓ (Effects were not regarded as relevant by the authors)	Tyl et al., 2002
1.2	Rat, 3-generation study	Litter size ↓, sperm number and motility ↓, post implantation loss ↑	Salian et al., 2009
2	Mouse, pregnancy	Testis and epididymal weights ↑ in offspring	Ashby et al., 1999
2	Mouse, gestation day 11–17, offspring	Aggression ↑, testis weight ↓ in offspring	Kawai et al., 2003
2	Mouse, gestation day 11–17, offspring	Prostate weight ↑, epididymis weight ↓	vom Saal et al., 1998
2	Gerbil, females, 3 weeks after pairing	Changed maternal behaviour	Razzoli et al., 2005
2	Mouse, prenatally, early postnatally	Anxious behaviour ↑ in offspring	Ryan et al., 2006
2	Rat, 3-generation study	Spermatogenesis, sperm quality	Peknicova et al., 2002
2.4	Mouse, gestation day 11–17	Vaginal opening, first oestrus in offspring	Howdeshell et al., 1999
2.4	Rat, male, Postnatal day 21–35	LH, Testosterone and oestrogen levels ↓	Akingbemi et al., 2004
2.5	Mouse, 5 wk	Immune, IFN-gamma and IgG2a ↓	Sawai et al., 2003
2.5	Mouse, pregnancy and lactation	Brain, kidney liver and testes weight ↓, oxidative stress markers ↑ in offspring	Kabuto et al., 2004
2.5	Transgenic mice	Tumour development ↑	Jenkins et al., 2011
5	Mouse, adult male	Testis and seminal vesicle weights ↓	Al-Hiyasat et al., 2002
10	Mouse, gestation day 14–18	Maternal behaviour in offspring	Palanza et al., 2002
10	Mouse, gestation day 14–18	Number and size of dorsolateral prostate ducts in offspring ↑	Timms et al., 2005
10	Mouse, gestation day 11–18	Long-term alteration in neurobehavioral functions in females	Laviola et al., 2005
10	Mouse, gestation day 11–day 8 post partum	Decreased sex differences in behaviour	Gioiosa et al., 2007
10	Rat	Increased prostate hyperplasia	Wu et al., 2011
10	Rat, neonatal	Increased oestrogen-induced prostate intraepithelial neoplasia	Prins et al., 2011
15	Rat, last week of pregnancy	Male behaviour in 6-9 week old offspring altered	Fujimoto et al., 2006
20	Mouse	Chromosomal aberrations, aneuploidy ↑	Hunt et al., 2003
20	Rat, 13 wk	Spermatogenesis ↓	Sakaue et al., 2001
20	Rat, pregnancy	Vaginal morphology in offspring	Schönfelder et al., 2002b
25	Mouse, gestation day 8–23	Structural and histological changes of prostate in offspring	Ramos et al., 2001
25	Mouse, female adult	Number of embryo resorptions ↑, uterine weights ↑	Al-Hiyasat et al., 2004
25	Rat, lactating	DMBA induced carcinogenicity in breast tissue of offspring	Jenkins et al., 2009
25	Mouse, pregnancy	DMBA induced carcinogenicity in breast tissue of offspring	Weber Lozada and Keri, 2011
30	Rats during pregnancy and lactation	Less pronounced sexual behaviour in male offspring, reversed sex differences in brain development	Kubo et al., 2003

Table 10.1 Summary of mammalian studies on BPA with effect levels at or below 50 µ/kg bw d, oral administration (cont)

Dose (µg/kg bw d)	Organism, age at dosing	Effect	Reference
30	Mouse	Immune responses ↑	Yoshino et al., 2003
40	Rat, gestation day 14–postnatal day 6	Sex associated behavioural changes in offspring ↑	Dessí-Fulgheri et al., 2002
40	Rat, pregnancy and lactation	Aggression behaviour in offspring	Farabollini et al., 2002
40	Rat, pregnancy and lactation	Pain sensitivity (hyperalgesia) in offspring	Aloisi et al., 2002
40	Rat, pregnancy and lactation	Changes in spontaneous and amphetamine induced behaviour in offspring	Adriani et al., 2003
40	Rat, pregnancy and lactation	Decrease of playful interactions in offspring	Porrini et al., 2005
40	Rat, pregnancy and lactation	Changes in maternal behaviour in adult females	Della Seta et al., 2005
40	Rat, male PND 23–30	Brain estrogen receptor number altered, testosterone ↓	Ceccarelli et al., 2007
40	Rat, pregnancy and lactation	Spatial recognition memory impaired in offspring, changes in female exploration behaviour	Poimenova et al., 2010
40	Rat, pregnancy and lactation	Impairment of memory, sexual behaviour and locomotor activity in offspring	Goncalves et al., 2010
40	Mouse, day 32–87	Elimination of sex differences in non-reproductive behaviour	Xu et al., 2011
45	Mouse, gestation and weaning	Memory impairment associated with reduction of acetylcholine production in the hippocampus in the male offspring	Miyagawa et al., 2007
45	Mouse, gestation and weaning	↑ Morphine-induced hyperlocomotion and rewarding effect in offspring	Narita et al., 2006
50	Mouse, gestation day 16–18	Anogenital distance and prostate size ↑, epididymal weight ↓ in offspring	Gupta, 2000
50	Rat, gestation and lactation	Deficits in male sexual behaviour in adulthood	Jones et al., 2010
50	Rat, gestation and lactation	Body weight ↑, impaired glucose tolerance, serum insulin ↓	Wei et al., 2011

Note: This table is not comprehensive. Many other studies with other application routes show similar effects. These studies should also not be dismissed for risk assessment purposes as it has been shown that other routes of exposure result in similar internal exposures in the animals.

Source: Taylor et al., 2008, modified from Gies, 2007.

Table 10.2 Outcome of studies on BPA and source of funding

Source of funding	Harm	No harm
Government	94 (90.4)	10 (9.6)
Chemical corporations	0 (0)	11 (100)

Note: Number of studies and percentage in brackets.

Source: Data from Hughes and vom Saal 2005, including studies published until 2004.

shows that the results of industry-sponsored studies and independent scientific studies deviate strongly. Independent science and regulatory toxicology seem to speak different languages. Numerous papers from different laboratories indicate risks at low doses, BPA industry-sponsored studies need doses orders of magnitude higher to produce any effects and if effects are detected they are not taken forward to the risk assessment.

Independent science is interested in finding the effects of a substance and publishing these findings. Independent laboratories usually specialise in a biological system and often have decades of experience in this field. Contracting laboratories have to cover a broad range of endpoints with different chemicals. Thus academic laboratories may be better qualified for testing for subtle changes such as those in early development and behaviour. Also, contract laboratories are per se not economically independent from the producers of a chemical. This has to be considered when weighing the evidence produced by academic research and by contract laboratories.

Independence of scientific advisors to regulatory agencies has been a controversial issue within the scientific community. These problems are obviously not restricted to the case of BPA. A number of measures have been proposed to strengthen scientific independence within the risk assessment process (Holland et al., 2012).

Uncoupling of financial interests and scientific and regulatory research and testing seems to be necessary. Chemical regulation should be based on science and the basis of science is independence. This independence of researchers can be achieved if laboratories are not contracted directly by industry. Research laboratories could be paid by a fund that is financed by the industry, over which industry has no control and which is managed by governments.

The case of BPA shows that results of independent science are of great value and should have an adequate weight within the decision-making process. Without doubt, standard testing by contract laboratories has its value in risk assessment procedures and regulations but their results must not outweigh those from independent academic laboratories. However, there is a need to update the standard testing procedures to incorporate the new knowledge acquired through independent research.

Strengthening the independence of scientific advisors is necessary and timely. Close cooperation with industry or industry-dominated bodies like the International Life Science Institute (ILSI) may be regarded as incompatible with the degree of independence required for advisory bodies.

Transparent and reliable documentation of possible conflicts of interest has not yet been achieved in all cases.

Performing or reviewing risk assessments for public agencies is time-consuming. Experts have to be paid adequately for doing this work. This would allow attracting the best qualified and independent scientists. Both testing and assessment can be financed by charging industry a fee. The employers of these qualified members of the scientific community (universities, research institutions) should be required by government agencies to decrease the workload of these scientists so that they can perform this important service to society.

10.12 Lessons learned

The intense discussion and scientific work on BPA have slowly contributed to a process of improving test strategies. While traditional toxicology has relied on a monotonic increasing dose-response relationship as evidence that the effect is caused by the test agent, studies on BPA and other endocrine disruptor chemicals (EDCs) have demonstrated the limitations of this approach and adjustments have been made in some cases. For example, the US NTP Expert Panel report on BPA (NTP-CERHR, 2007) and the report of the French ANSES 2011 included both single dose and multiple dose studies in their compilations of studies that are useful for evaluating the risks of BPA (Arnich et al., 2011). It has also been widely accepted that effects cannot be predicted by simply thinking of BPA as a weak oestrogen and extrapolating from what is observed for more potent endogenous oestrogens, and this lesson is widely evident in the intense pharmaceutical interest in selective oestrogen response modifiers (SERMs), although some investigators persist in referring to BPA simply as a weak oestrogen.

Under its testing guideline programmme, OECD is currently modifying its guidelines and incorporating many new endpoints that are sensitive to hormonal perturbation, such as timing of vaginal opening, and anogenital distance.

References

Adriani, W., Seta, D.D., Dessi-Fulgheri, F., Farabollini, F. and Laviola, G., 2003, 'Altered profiles of spontaneous novelty seeking, impulsive behavior, and response to D-amphetamine in rats perinatally exposed to bisphenol A', *Environ. Health Perspect*., (111) 395–401, Erratum 2005 in *Environ Health Perspect,* (113) A368.

Akingbemi, B.T., Soitas, C.M., Koulova, A.I., Kleinfelter, G.R. and Hardy, M.P., 2004, 'Inhibition of testicular steroidogenesis by the xenooestrogen bisphenol A is associated with reduced pituitary luteinizing hormone secretion and decreased steroidogenic enzyme gene expression in rat Leydig Cells', *Endocrinology,* (145) 592–603.

Al-Hiyasat, A.S., Darmani, H. and Elbetieha, A.M., 2002, 'Effects of bisphenol A on adult male mouse fertility.', *Eur. J. Oral Sci,* (110) 163–167.

Al-Hiyasat, A.S., Darmani, H. and Elbetieha, A.M., 2004, 'Leached components from dental composites and their effects on fertility of female mice', *Eur J Oral Sci,* (112) 267–272.

Aloisi, A.M., Della Seta, D., Rendo, C., Ceccarelli, I., Scaramuzzino, A. and Farabollini, F., 2002, 'Exposure to the oestrogenic pollutant bisphenol A affects pain behaviour induced by subcutaneous formalin injection in male and female rats', *Brain Res, (*937) 1–7.

Alonso-Magdalena, P., Laribi, O., Ropero, A.B., Fuentes, E., Ripoll, C., Soria, B. and Nadal, A., 2005, 'Low doses of bisphenol A and diethylstilbestrol impair Ca2+ signals in pancreatic alpha-cells through a nonclassical membrane oestrogen receptor within intact islets of Langerhans', *Environ. Health Perspect*., (113) 969–977.

ANSES, 2011, Agence Nationale de Sécurité Sanitaire Alimentation, Environment, Travail (ANSES). 'Effets sanitaires du bisphénol A' (http://www.anses.fr/Documents/CHIM-Ra-BisphenolA.pdf) accessed 30 November 2011.

Arnich, N., Canivenc-Lavier, M.C., Kolf-Clauw, M., Coffigny, H., Cravedi J.P., Grob, K., Macherey, A.C., Masset, D., Maximilien, R., Narbonne, J.F., Nesslany, F., Stadler, J. and Tulliez, J., 2011, 'Conclusions of the French Food Safety Agency on the toxicity of bisphenol A'. *Int J Hyg Environ Health*; (214) 271–275.

Ashby, J., Tinwell, H. and Hasemann, J., 1999, 'Lack of effects for low dose levels of bisphenol A and diethylstilbestrol on the prostate gland of CF-1 mice exposed in utero', *Regul Toxicol Pharmacol*, (30) 156–166.

Association of Plastics Manufacturers, Polycarbonate/BPA group, 2007, 'Applications of Bisphenol A'.

Ayyanan, A., Laribi, O., Schuepbach-Mallepell, S., Schrick, C., Gutierrez, M., Tanos, T., Lefebvre, G., Rougemont., J. Yalcin-Ozuysal, O. and Brisken, C., 2011, 'Perinatal exposure to bisphenol a increases adult mammary gland progesterone response and cell number'. *Mol Endocrinol,* (25) 1 915–1 923.

Bason, C.W. and Colborn, T., 1992, 'US application and distribution of pesticides and industrial chemicals capable of disrupting endocrine and immune systems', *Advances in Modern Environmental Toxicology,* (21) 335–345.

Becker, K., Seiwert, M., Pick-Fuß, H., Conrad, A., Schulz, C., Wittassek, M., Goen, T. and Kolossa-Gehring, M., 2009, 'GerES IV: Phthalate metabolites and bisphenol A in urine of German children', *Int. J. Hyg. Env. Health,* (212) 685–692.

Betts, K.S., 2010, 'Body of Proof: Bio-monitoring Data Reveal Widespread Bisphenol A Exposures', *Environ Health Perspect,* (118) a353.

Biles, J.A., McNeal, T.P., Begley, T.H. and Hollifield, H.C., 1997, 'Determination of Bisphenol-A in Reusable Polycarbonate Food-Contact Plastics and Migration to Food-Simulating Liquids' *Journal of Agricultural and Food Chemistry*, (45) 3 541–3 544.

Bindhumol, V., Chitra, K.C. and Mathur, P.P., 2003, 'Bisphenol A induces reactive oxygen species generation in the liver of male rats' *Toxicol,* (188) 117–124.

Bloom, M.S., vom Saal, F.S., Kim, D., Taylor, J.A., Lamb, J.D. and Fujimoto, V. Y., 2011, 'Serum unconjugated bisphenol A concentrations in men may influence embryo quality indicators during in vitro fertilization', *Environ Toxicol Pharmacol,* (32) 319–323.

Blumenthal, D., 2003, 'Academic-industrial relationships in the life sciences', *N Engl J Med,* (349) 2 452–2 459.

Braun, J., Yolton, K., Dietrich, K.N., Hornung, R.W., Ye, X., Calafat, A. and Lanphear, R.W., 2009, 'Prenatal Bisphenol A Exposure and Early

Childhood Behavior', *Environ Health Perspect.*, (117) 1 945–1 952.

Braun, J.M., Kalkbrenner, A.E., Calafat, A.M., Yolton, K., Ye, X. Dietrich, K.N. and Lanphear B.P., 2011, 'Impact of early-life bisphenol a exposure on behavior and executive function in children', *Pediatrics,* (128) 873–882.

Brotons J.A., Olea-Serrano M.F., Villalobos M. and Olea N., 1994, 'Xenooestrogens released from lacquer coating in food cans', *Environ Health Perspect,* (103) 608–612.

Butte, W., Hoffmann, W., Hostrup, O., Schmidt, A. and Walker, G., 2001, Endocrine disrupting chemicals in house dust: Results of a representative monitoring', *Gefahrstoffe Reinhaltung der Luft,* (61) 19–23.

Cabaton, N.J., Wadia, P.R., Rubin, B.S., Zalko, D., Schaeberle, C.M., Askenase, M.H., Gadbois, J.L., Tharp, A.P., Whitt, G.S., Sonnenschein, C. and Soto, A.M. 2011, 'Perinatal exposure to environmentally relevant levels of Bisphenol-A decreases fertility and fecundity in CD-1 mice', *Environ Health Perspect,* (119) 547–552.

Calabrese, E.J. and Baldwin, L.A., 2001, 'The Frequency of U-Shaped Dose Responses in the Toxicological Literature', *Toxicol Sci,* (62) 330–338.

Calafat, A.M., Ye, X., Wong, L.Y., Reidy, J.A. and Needham, L.L., 2008, 'Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003-2004', *Environmental Health Perspect,* (116) 39–44.

Calafat, A.M., Weuve, J., Ye, X., Jia, L.T., Hu, H., Ringer, S., Huttner, K. and Hauser, R., 2009, 'Exposure to Bisphenol A and other Phenols in Neonatal Intensive Care Unit Premature Infants', *Environ Health Perspect,* (117) 639–644.

Cao, X.L., Corriveau, J. and Popovic, S., 2009, 'Levels of Bisphenol A in Canned Soft Drink Products in Canadian Markets', *Agric Food Chem,* (57) 1 307–1 311.

Carr, R., Bertasi, F., Betancourt, A., Bowers, S., Gandy, B.S., Ryan, P. and Willard, S., 2003, 'Effect of neonatal rat bisphenol a exposure on performance in the Morris water maze', *J Toxicol Environ Health A,* (66) 2 077–2 088.

Carwile, J.L. and Michels, K.B., 2011, 'Urinary bisphenol A levels and obesity: NHANES 2003-2006', *Environm Res,* (111) 825–830.

Ceccarelli, I., Della Seta, D., Fiorenzani, P., Farabollini, F. and Aloisi, A. M., 2007, 'Oestrogenic chemicals at puberty change ERalpha in the hypothalamus of male and female rats', *Neurotoxicol Teratol,* (29) 108–115.

Chapin, R.E., Adams, J., Boekelheide, K., Gray, L.E., Jr., Hayward, S.W., Lees, P.S., McIntyre, B.S., Portier, K.M., Schnorr, T.M., Selevan, S.G., Vandenbergh, J.G. and Woskie, S.R., 2008, 'NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Bisphenol A', *Birth Defects Res B Dev Reprod Toxicol,* (83) 157–395.

Chitra, K.C., Latchoumycandane, C. and Mathur, P.P., 2003, 'Induction of oxidative stress by bisphenol A in the epididymal sperm of rats', *Toxicology,* (185) 119–127.

Colborn, T., Dumanowski, D. and Myers, J.P., 1996, 'Our Stolen Future', *Penguin Books. New York.*

Colerangle, J.B. and Roy, D., 1997, 'Profound effects of the weak environmental oestrogen-like chemical bisphenol A on the growth of the mammary gland of Noble rats. *J. Steroid Biochem Mol. Biol.*, (60) 153–160.

Damstra, T., Barlow, S., Bergman, A., Kavlock, R., and Van der Kraak, G., 2002, Global Assessment of the State-of-the-Science of Endocrine Disruptors', *WHO publication World Health Organization, Geneva, Switzerland.*

Dessì-Fulgheri, F., Porrini, S. and Farabollini, F., 2002, 'Effects of perinatal exposure to bisphenol A on play behavior of male and male juvenile rats', *Environ Health Perspect,* (110) Suppl 3, 403–407.

Dekant, W. and Völkel, W., 2008, Human exposure to bisphenol A by bio-monitoring: Methods, results and assessment of environmental exposures', *Toxicol Appl Pharmacol,* (228) 114–134.

Della Seta, D., Minder, I., Dessi-Fulgheri, F. and Farabolini, F., 2005, 'Bisphenol-A exposure during pregnancy and lactation affects maternal behavior in rats', *Brain Res Bull,* (65) 255–260.

DFG, 1998, Deutsche Forschungsgemeinschaft: Proposals for Safeguarding Good Scientific Practice.

Diamanti-Kandarakis, E. Bourguignon, J.P., Giudice, L.C., Hauser, R., Prins, G.S., Soto, A.M., Zoeller, R.T. and Gore, A.C., 2009, 'Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement', *Endocrine Reviews,* (30) 293–342.

Dodds, E.C. and Lawson, W., 1936, 'Synthetic oestrogenic agents without the phenanthrene nucleus', *Nature,* (137) 996.

Dodds, E.C. and Lawson, W., 1938, ' Molecular structure in relation to ooestrogenic activity. Compounds without a phenanthrene nucleus', *Proceedings of the Royal Society,* (125) 222–232.

Dodds, E.C, Goldberg, L., Lawson, W. and Robinson, R., 1938, 'Oestrogenic activity of certain synthetic compounds', *Nature,* (141/3562) 247–248.

Doerge, D.R., Twaddle, N.C., Woodling, K.A., and Fisher, J. W., 2010, Pharmacokinetics of bisphenol A in neonatal and adult rhesus monkeys, *Toxicol. Appl. Pharmacol.,* (248) 1–11.

Doerge, D.R., Twaddle, N.C.,Vanlandingham, M., Brown, R.C. and Fisher, J.W., 2011a, 'Distribution of bisphenol A into tissues of adult, neonatal, and fetal Sprague–Dawley rats'. *Toxicol. Appl. Pharmacol.*, (247) 158–165.

Doerge, D.R., Twaddle, N.C., Vanlandingham, M. and Fisher, J.W., 2011b, 'Pharmacokinetics of Bisphenol A in neonatal and adult CD-1 mice: Inter-species comparisons with Sprague-Dawley rats and rhesus monkeys', *Toxicology Letters*, (207) 298–305.

Edginton, A.N. and Ritter, L., 2009, 'Predicting plasma concentrations of bisphenol A in young children (<two years) following typical feeding schedules using a physiologically-based toxicokinetic model', *Environ Health Perspect,* (117) 645–652.

EFSA, 2010, 'Scientific Opinion on Bisphenol A: evaluation of a study investigating its neurodevelopmental toxicity, review of recent scientific literature on its toxicity and advice on the Danish risk assessment of Bisphenol A', *EFSA Journal*, (8) 1 829–1 945.

EFSA, 2012, 'EFSA publishes Implementing Rules for Independency Policy, press release, 5 March 2012 (http://www.efsa.europa.eu/en/press/news/120305.htm) accessed 12 April 2012.

EFSA and ANSES, 2011, 'Agreed joint report of EFSA and ANSES according to Article 30 of the Regulation (EC) No 178/2002 on Bisphenol A (BPA), Parma, 30 November 2011'.

Ema, M., Fujii, S., Furukawa, M., Kiguchi, M., Ikka, T. and Harazono, A., 2001. 'Rat two-generation reproductive toxicity study of bisphenol A', *Reprod. Toxicol.,* (15) 505–523.

Environment Canada, 2008, Government of Canada: 'Environment Canada draft screening assessment and risk management documents', April 2008 (http://www.gazette.gc.ca/rp-pr/p2/2010/2010-10-13/html/sor-dors194-eng.html) accessed at 17 December 2011.

Environment Canada and Health Canada, 2008, 'Screening Assessment for the Challenge Phenol, 4,4' -(1-methylethylidene)bis- (Bisphenol A). Chemical Abstracts Service Registry Number 80-05-7.

EU, 2000, 'Communication from the commission on the precautionary principle COM (2000) 1'. Commission of the European Communities, Brussels.

EU, 2011, Commission Directive 2011/8/EU of 28 January 2011 amending Directive 2002/72/EC as regards the restriction of use of Bisphenol A in plastic infant feeding bottles.

European Commission, 1990, 'Commission Directive 90/128/EEC of 23 February 1990 relating to plastics materials and articles intended to come into contact with foodstuffs', Official Journal of the European Communities Vol. L75/10.

European Commission, 2008. Updated European Risk Assessment Report 4,4'-Isopropylidenediphenol (Bisphenol-A), Brussels.

European Parliament, 2009. 'Written Question by Hiltrud Breyer (Verts/ALE) Subject: Conflict of interests at EFSA concerning bisphenol A. E-2861/09', 22 April 2009.

Farabollini, F., Porrini, S., Della Seta, D., Bianchi, F. and Dessi-Fulgheri, F., 2002, 'Effects of perinatal exposure to bisphenol A on sociosexual behavior of female and male rats', *Environ Health Perspect,* (110) Suppl. 3, 409–414.

Fisher, J.W., Twaddle,N.C., Vanlandingham,M. and Doerge, D.R., 2011, 'Pharmacokinetic modeling: Prediction and evaluation of route dependent dosimetry of bisphenol A in monkeys with extrapolation to humans', *Toxicol. Appl. Pharmacol.,* (257) 122–136.

FDA, 2008, (U.S. Food and Drug Administration), Draft Assessment of Bisphenol A for Use in Food Contact Applications, 14 August 2008.

FDA, 2010, (U.S. Food and Drug Administration), 'Update on Bisphenol A (BPA) for Use in Food: January 2010'.

FDA Science Board Subcommittee on Bisphenol A, 2008, Scientific Peer-Review of the Draft Assessment of Bisphenol A for Use in Food Contact Applications, 31 October 2008.

Fujimoto, T., Kubo, K. and Aou, S., 2006, 'Prenatal exposure to bisphenol A impairs sexual differentiation of exploratory behavior and increases depression-like behavior in rats', *Brain Res,* (1068) 49–55.

Fujimoto,V.Y., Dongsul, Kim B.S.b., vom Saal, F.S., Lamb, J.D. and Bloom, M.S., 2011, 'Serum unconjugated bisphenol A concentrations in women may adversely influence oocyte quality during in vitro fertilization', *Fertil Steril,* (95) 1 816–1 819.

Genuis, S.J., Beesoon, S., Birkholz, D. and Lobo, R.A., 2012, 'Human Excretion of Bisphenol A: Blood, Urine, and Sweat (BUS) Study,'*J. Environ Public Health*, (2012), Article ID 185731, doi:10.1155/2012/185731.

German Federal Environment Agency, 2010, 'Bisphenol A: An industrial chemical with adverse effects' (http://www.umweltdaten.de/publikationen/fpdf-l/3992.pdf) accessed 30 November 2011.

Gies, A., 2007, 'Problems in assessing low dose effects of endocrine disrupters'. In: P. Nicolopoulou-Stamati et al. (eds.)', *Reproductive Health and the Environment, Springer. Dordrecht,* The Netherlands, pp. 283–296.

Gies, A., Heinzow, B., Dieter, H.H. and Heindel, J., 2009. ‚Bisphenol A workshop of the German Federal Environment Agency — 30–31 March, 2009 work group report: public health issues of bisphenol a', *Int J Hyg Environ Health,* (212) 693–696.

Gioiosa, L., Fissore, E., Ghirardelli, G., Parmigiani, S. and Palanza, P., 2007, 'Developmental exposure to low-dose oestrogenic endocrine disruptors alters sex differences in exploration and emotional responses in mice', *Horm Behav,* (52) 307–316.

Ginsberg, G. and Rice, D. C., 2009, 'Does rapid metabolism ensure negligible risk from bisphenol A?', *Environ Health Perspect,* (117) 1 639–1 643.

Goncalves, C.R., Cunha, R.W., Barros, D.M. and Martinez, P.E., 2010, 'Effects of prenatal and postnatal exposure to a low dose of bisphenol A on behavior and memory in rats', *Environ Toxicol Pharmacol,* (30) 195–201.

Goodman, J.E., Witorsch, W.J., McConnell, E.E. and Sipes, G., 2009, 'Weight-of-Evidence Evaluation of Reproductive and Developmental Effects of Low Doses of Bisphenol A', *Crit Rev Toxicol,* (39) 1–75.

Goodson, A., Summerfield, W. and Cooper, I., 2002, 'Survey of bisphenol A and bisphenol F in canned foods', *Food Addit Contam,* (19) 796–802.

Greim, H.A., 2004, 'The Endocrine and Reproductive System: Adverse Effects of Hormonally Active Substances?', *Pediatrics,* (113) 1 070–1 075.

Gupta, C., 2000, 'Reproductive malformation of the male offspring following maternal exposure to oestrogenic chemicals', *Proc Soc Exp Biol Med,* (224) 61–68.

Grüning, T., Gilmore, A. B. and McKee, M., 2006, 'Tobacco industry influence on science and scientists in Germany', *Am J Public Health,* (96) 20–32.

Heinze, J. E. and Chahoud, I., 2003, 'Adverse health effects of Bisphenol A in early life (multiple letters) [3]', *Environ Health Perspect,* (111) A382–A383.

Holland, N., Robinson, C. and Harbinson, R., 2012, 'Conflicts on the menu' Corporate Europe Observatory (ed.) Brussels (http://www.corporateeurope.org/sites/default/files/publications/Conflicts_%20on_the_menu_final_0.pdf) accessed 23 February 2012.

Hoover, R.N., Hyer, M., Pfeiffer, R. M., Adam, E., Bond, B., Cheville, A.L., Colton, T., Hartge, P., Hatch, E.E., Herbst, A.L., Karlan, B. Y., Kaufman, R., Noller, K.L., Palmer, J.R., Robboy, S.J., Saal, R.C., Strohsnitter, W., Titus-Ernstoff, L. and Troisi, R., 2011, 'Adverse health outcomes in women exposed in utero to diethylstilbestrol', *N Engl J Med.*, (365) 1 304–1 314.

Howdeshell, K.L., Hotchkiss, A.K., Thayer, K.A., Vandenbergh, J.G. and vom Saal, F.S., 1999, 'Exposure to bisphenol A advances puberty', *Nature,* (401/6755) 763–764.

Hunt, P.A., Koehler, K.E., Susiarjo, M., Hodges, C. A., Ilagan, A., Voigt, R.C., Thomas, S., Thomas, B.F. and Hassold, T.J., 2003, 'Bisphenol A exposure causes meiotic aneuploidy in the female mouse', *Curr Biol.*, (13) 546–553.

Izumi, N., Yanagibori, R., Shigeno, S. and Sajiki, J., 2008, 'Effects of bisphenol on the development, growth, and sex ratio of the housefly Musca domestica', *Environ Toxicol Chem*., (27) 1 343–1 353.

Jenkins, S., Raghuraman, N., Eltoum, I., Carpenter, M., Russo, J. and Lamartiniere, C. A., 2009, 'Oral Exposure to Bisphenol A Increases Dimethylbenzanthracene-Induced Mammary Cancer in Rats', *Environ Health Perspect,* (117) 910–915.

Jenkins, S., Wang, J., Eltoum, I., Desmond, R. and Lamartiniere C.A., 2011, 'Chronic Oral Exposure to Bisphenol A Results in a Nonmonotonic Dose Response in Mammary Carcinogenesis and Metastasis in MMTV-erbB2 Mice'. *Environ Health Perspect,* (119/11), 1 604–1 609.

Jones, B.A., Shimell, J.J. and Watson, N.V., 2011, 'Pre- and postnatal Bisphenol A treatment results in persistent deficits in the sexual behavior of male rats, but not female rats, in adulthood', *Horm Behav.,* (59) 246–251.

Joskow, R., Barr, D.B., Barr, J. R., Calafat, A.M., Needham, L.L. and Rubin, C., 2006, 'Exposure to bisphenol A from bis-glycidyl dimethacrylate-based dental sealants', *J Am Dent Assoc.,* (137) 353–362.

Judson, R.S., Houck K.A., Kavlock R.J., Knudsen T.B., Martin M.T., Mortensen H.M., Reif D.M., Rotroff D.M., Shah I., Richard A.M. and Dix DJ., 2010, 'In vitro screening of environmental chemicals for targeted testing prioritization: the ToxCast project'. *Environ Health Perspect,* (118) 425–432.

Kabuto, H., Amakawa, M. T. and Shishibori, T., 2004, 'Exposure to bisphenol A during embryonic/fetal life and infancy increases oxidative injury and causes underdevelopment of the brain and testis in mice', *Life Sci,* (74) 2 931–2 940.

Kawai, K., Nozaki, T., Nishikata, H., Aou, S., Takii, M. and Kubo, C., 2003, 'Aggressive Behaviour and Serum Testosterone Concentration during the Maturation Process of Male Mice: The Effects of Fetal Exposure to Bisphenol A', *Environ Health Perspect,* (111) 175–178.

Krishnan, A.V., Stathis, P., Permuth, S.F., Tokes, L. and Feldman, D., 1993, 'Bisphenol-A: An oestrogenic substance is released from polycarbonate flasks during autoclaving', *Endocrinology,* (132/6) 2 279–2 286.

Kruger, T., Long, M. and Bonefeld-Jorgensen, E.C., 2008, 'Plastic components affect the activation of the aryl hydrocarbon and the androgen receptor', *Toxicology,* (246) 112–123.

Kubo, K., Arai, O., Omura, M., Watanabe, R., Ogata, R. and Aou, S., 2003, 'Low dose effects of bisphenol A on sexual differentiation of the brain and behavior in rats', *Neurosci Res,* (45) 345–356.

Kuiper, G.G.J.M., Lemmen, J.G., Carlsson, B., Corton, J.C., Safe, S.H., Van Der Saag, P.T., Van Der Burg, B. and Gustafsson, J.-Å., 1998, 'Interaction of oestrogenic chemicals and phytooestrogens with oestrogen receptor β', *Endocrinology,* (139) 4 252–4 263.

LaKind, J.S. and Naiman, D.Q., 2011, 'Bisphenol A daily intakes in the United States: Estimates from the 2003–2004 NHANES urinary bisphenol A data', *J Expos Sci Environ Epidemiol,* (18) 608–618.

LaKind, J.S. and Naiman, D.Q., 2011, 'Daily intake of bisphenol A and potential sources of exposure: 2005–2006 National Health and Nutrition Examination Survey', *J Expos Sci Environ Epidemiol,* (21) 272–279.

Laviola, G., Gioiosa, L., Adriani, W. and Palanza, P., 2005, 'D-amphetamine-related reinforcing effects are reduced in mice exposed prenatally to oestrogenic endocrine disruptors', *Brain Res Bull,* (65) 235–240.

Lesser, L.I., Ebbeling, C.B., Goozner, M., Wypij, D. and Ludwig, D.S., 2007, 'Relationship between Funding Source and Conclusion among Nutrition-Related Scientific Articles', *PLoS Med,* (4/1) e5. doi:10.1371/journal.pmed.0040005.

Li, D.K., Zhou, Z., Miao, M., He, Y., Qing, D., Wu, T., Wang, J., Weng, X., Ferber, J., Herrinton, L. J., Zhu, Q., Gao, E., Yuan, W., 2010, 'Relationship between urine bisphenol-A level and declining male sexual function', *J Androl,* (31) 500–506.

Liao, C. and Kannan, K., 2011a, 'High levels of bisphenol A in paper currencies from several countries, and implications for dermal exposure'. *Environmental Science & Technology,* (45) 6 761–6 768.

Liao, C. and Kannan, K. 2011b, 'Widespread Occurrence of Bisphenol A in Paper and Paper Products: Implications for Human Exposure' *Environmental Science & Technology,* (45) 9 372–9 379.

Longnecker, M.P., Gladen, B.C., Cupul-Uicab, L.A., Romano-Riquer, S.P., Weber, J.-P., Chapin, R.E., 2007, 'In utero exposure to the antiandrogen 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE) in relation to anogenital distance in male newborns from Chiapas, Mexico', *Am J Epidemiol,* (165) 1 015–1 022.

Lopez-Espinosa, M.J., Granada, A., Araque, P., Molina-Molina, J.M., Puertollano, M. C., Rivas, A., Fernàndez, M., Cerrillo, I., Olea-Serrano, M.F., Lòpez, C. and Olea, N., 2007, 'Oestrogenicity of paper and cardboard extracts used as food containers', *Food Addit Contam,* (24) 95–102.

Markey, C.M., Rubin, B.S., Soto, A.M. and Sonnenschein, C., 2002, 'Endocrine disruptors: from Wingspread to environmental developmental biology', *J Steroid Biochem Mol Biol,* (83) 235–244.

Mariscal-Arcas, M., Rivas, A., Granada, A., Monteagudo, C., Murcia, M.A. and Olea-Serrano, F., 2009, 'Dietary exposure assessment of pregnant women to bisphenol-A from cans and microwave containers in Southern Spain', *Food Chem Toxicol,* (47) 506–510.

Marmugi, A., Ducheix, S., Lasserre, F., Polizzi, A., Paris, A., Priymenko, N., Bertrand-Michel, J., Pineau, T., Guillou, H., Martin, P.G. and Mselli-Lakhal, L. 2011, 'Low doses of bisphenol A induce gene expression related to lipid synthesis and trigger triglyceride accumulation in adult mouse liver', *Hepatology,* doi:10.1002/hep.24685.

Mendiola, J., Stahlhut, R.W., Jørgensen, N., Liu, F. and Swan, S.H., 2011, 'Shorter anogenital distance predicts poorer semen quality in young men in Rochester, New York', *Environ Health Perspect,* (119) 958–963.

Meyers, R., 1983, *D.E.S., the bitter pill*, Seaview/Putnam, New York.

Miao, M., Yuan, W., Zhu, G., He, X. and Li, D.-K., 2011, 'In utero exposure to bisphenol A and its effect on birth weight of offspring', *Reprod Toxicol,* (32) 64–68.

Miyagawa, K., Narita, M., Narita, M., Akama, H. and Suzuki,T. 2007. 'Memory impairment associated with a dysfunction of the hippocampal cholinergic system induced by prenatal and neonatal exposures to bisphenol-A'. *Neurosci Lett,* (418) 236–241.

Moriyama, K., Tagami, T., Akamizu, T., Usui, T., Saijo, M., Kanamoto, N., Hataya, Y., Shimatsu, A., Kuzuya, H. and Nakao, K., 2002. 'Thyroid hormone action is disrupted by bisphenol A as an antagonist', *J Clin Endocrinol Metab,* (87) 5 185–5 190.

Moses, H., Dorsey, E.R., Matheson, D.H. and Their, S.O., 2005, 'Financial anatomy of biomedical research', *JAMA,* (294) 1 333–1 342.

Myers, J.P., vom Saal, F.S., Akingbemi, B.T., Arizono, K., Belcher, S., Colborn, T., Chahoud, I., Crain, D.A., Farabollini, F., Guillette, L.J. Jr, Hassold, T., Ho, S.M., Hunt, P.A., Iguchi, T., Jobling, S., Kanno, J., Laufer, H., Marcus, M., McLachlan, J.A., Nadal, A., Oehlmann, J., Olea, N., Palanza, P., Parmigiani, S., Rubin, B. S., Schoenfelder, G., Sonnenschein, C., Soto, A.M., Talsness, C.E., Taylor, J.A., Vandenberg, L.N., Vandenbergh, J.G., Vogel, S., Watson, C.S., Welshons, W.V. and Zoeller, R.T., 2009, 'Why public health agencies cannot depend on good laboratory practices as a criterion for selecting data: the case of bisphenol A', *Environ Health Perspect,* (117) 309–315.

Nadal, A., Ropero, A. B., Laribi, O., Maillet, M., Fuentes, E. and Soria, B., 2000, 'Nongenomic actions of oestrogens and xenooestrogens by binding at a plasma membrane receptor unrelated to oestrogen receptor alpha and oestrogen receptor beta', *Proc Natl Acad Sci U S A,* (97) 11 603–11 608.

Nadal, A., Ropero, A.B., Fuentes, E., Soria, B. and Ripoll, C., 2004, 'Oestrogen and xenooestrogen actions on endocrine pancreas: from ion channel modulation to activation of nuclear function', *Steroids,* (69) 531–536.

Narita, M., Miyagawa, K., Mizuo, K., Yoshida, T. and Suzuki, T., 2006, ' Prenatal and neonatal exposure to low-dose of bisphenol-A enhance the morphine-induced hyperlocomotion and rewarding effect', *Neurosci. Lett*., (402) 249–252.

Negishi, T., Kawasaki, K., Suzaki, S., Maeda, H., Ishii, Y., Kyuwa, S., Kuroda, Y. and Yoshikawa, Y., 2004, 'Behavioral alterations in response to fear-provoking stimuli and tranylcypromine induced by perinatal exposure to bisphenol A and nonylphenol in male rats'. *Environ Health Perspect,* (112) 1 159–1 164.

Neubert, D., 1997, 'Vulnerability of the endocrine system to xenobiotic influence', *Regul Toxicol Pharmacol,* (26) 9–29.

NIEHS/NTP, 2011, Workshop on Role of Environmental Chemicals in the Development of Diabetes and Obesity held 11–l3 January 2011. Appendix C: BPA Mechanisms of Action and other Biochemical/Molecular Interactions (Updated 27 December 2010).

NTP-CERHR, 2007, NTP-CERHR expert panel report on the reproductive and developmental toxicity of bisphenol A.

NTP, 2008, National Toxicology Programme, 'The NTP-CERHR Monograph on Bisphenol A', *NIH Publication,* No. 08-5994.

OECD, 1998, 'OECD principles on Good Laboratory Practice', OECD series on principles on Good Laboratory Practice and compliance monitoring, Number 1, Paris.

Okada, A. and Kai, O., 2008a, 'Effects of estradiol-17β and bisphenol A administered chronically to mice throughout pregnancy and lactation on the male pups' reproductive system', *Asian J Androl,* (10) 271–276.

Okada, H., Tokunaga, T., Liu, X., Takayanagi, S., Matsushima, A. and Shimohigashi, Y., 2008 b, 'Direct evidence revealing structural elements essential for the high binding ability of bisphenol A to human oestrogen-related receptor-gamma', *Environ Health Perspect,* (116) 3 238.

Ozaki, A., Kawasaki, C., Kawamura, Y. and Tanamoto, K., 2006, 'Migration of bisphenol A and benzophenones from paper and paperboard products used in contact with food', *Shokuhin Eiseigaku Zasshi, Journal of the Food Hygienic Society of Japan,* (47) 99–104.

Padmanabhan, V., Siefert, K., Ransom, S., Johnson, T., Pinkerton, J., Anderson, L., Tao, L. and Kannan, K., 2008. 'Maternal bisphenol-A levels at delivery: A looming problem?', *J Perinatol,* (28) 258–263.

Palanza, P., Gioiosa, L., vom Saal, F.S. and Parmigiani, S., 2008, 'Effects of developmental exposure to bisphenol A on brain and behavior in mice', *Environ Res,* (108) 150–157.

Palanza, P.L., Howdeshell, K.L., Parmigiani, S. and vom Saal, F.S., 2002, 'Exposure to a low dose of bisphenol A during fetal life or in adulthood alters maternal behavior in mice', *Environ Health Perspect,* (110/3) 415–422.

Paracelsus, T., 1539, 'Septem defensiones', manuscript.

Peknicova, J., Kyselova, V., Buckiova, D. and Boubelik, M., 2002, 'Effect of an endocrine disruptor on mammalian fertility. Application of monoclonal antibodies against sperm proteins as markers for testing sperm damage', *Am J Reprod Immunol,* (47) 311–318.

Poimenova, A,. Markaki, E., Rahiotis, C. and Kitraki, E., 2010, 'Corticosterone-regulated actions in the rat brain are affected by perinatal exposure to low dose of bisphenol A', *Neuroscience,* (167) 741–749.

Polycarbonate/BPA Global Group, 2012, *Bisphenol A — a consumer health and safety information* (http://www.bisphenol-a.org/sixty-minutes.html) accessed 23 February 2012.

Porrini, S., Belloni, V., Della Seta, D., Farabolini, F., Gianelli, G., Dessì-Fulgheri, F., 2005, 'Early exposure to a low dose of bisphenol A affects sicio-sexual behaviour of juvenile female rats', *Bain Res Bull,* (65) 261–266.

Prins, G.S., Ye, S.-H., Birch, L., Shuk-mei Ho, S.–M. and Kannan, K., 2011, 'Serum bisphenol A pharmacokinetics and prostate neoplastic responses following oral and subcutaneous exposures in neonatal Sprague-Dawley rats', *Reprod Toxicol,* (31) 1–9.

Ramos, J.G., Varayoud, J., Sonnenschein, C., Soto, A. M., Muñoz de Toro, M. and Luque, E. H., 2001, 'Prenatal Exposure to Low Doses of Bisphenol A Alters the Periductal Stroma and Glandular Cell Function in the Rat Ventral Prostate', *Biol Reprod,* (65) 1 271–1 277.

Razzoli, M., Valsecchi, P. and Palanza, P., 2005, 'Chronic exposure to low doses bisphenol A interferes with pair-bonding and exploration in female Mongolian gerbils', *Brain Res Bull,* (65) 249–254.

Richter, C.A., Birnbaum, L.S., Farabollini, F., Newbold, R.R., Rubin, B.S., Talsness, C.E., Vandenbergh, J.G., Walser-Kuntz, D.R. and vom Saal, F.S., 2007, 'In vivo effects of bisphenol A in laboratory rodent studies', *ReprodToxicol,* (24) 199–224.

Rubin, B.S., Murray, M.K., Damassa. D.A., King, J.C. and Soto,A.M., 2001. ' Perinatal exposure to bisphenol A affects body weight, patterns of estrous cyclicity, and plasma LH levels', *Environ Health Perspect,* (109) 675–680.

Rudel, R.A., Gray, J.M., Engel, C.L., Rawsthorne, T.W., Dodson, R.E., Ackerman, J.M., Rizzo, J., Nudelman, J.L. and Green Brody, J., 2011a,' Food packaging and bisphenol A and bis(2-ethylhexyl) phthalate exposure: findings from a dietary intervention', *Environ. Health Perspect.,* (119) 914–920.

Rudel, R.A., Fenton, S.E., Ackerman, J. M., Euling, S.Y. and, Makris, S.L., 2011b, 'Environmental exposures and mammary gland development: State of the Science, Public Health Implications, and Research Recommendations', *Environm. Health Perspect.,* (119), doi:10.1289/ehp.1002864.

Ryan, B.C. and Vandenbergh, J.G., 2006, 'Developmental exposure to environmental oestrogens alters anxiety and spatial memory in female mice', *Horm. Behav.,* (50) 85–93.

Ryan, B.C., Hotchkiss, A.K., Crofton, K.M. and Gray, L.E. Jr., 2010. 'In utero and lactational exposure to bisphenol a, in contrast to ethinyl estradiol, does not alter sexually dimorphic behavior, puberty, fertility, and anatomy of female le rats', *Toxicol. Sci.*, (114) 133–148.

Sakaue, M., Ohsako, S., Ishimura, R., Kurosawa, S., Kurohmaru, M., Hayashi, Y., Aoki, J., Yonemoto, J. and Tohyama, C., 2001, 'Bisphenol-A Affects Spermatogenesis in the Adult Rat Even at a Low Dose', *J Occup Health,* (43) 185–190.

Salian, S., Doshi, T. and Vanage, G., 2009, 'Perinatal exposure of rats to Bisphenol A affects the fertility of male offspring', *Life Sci,* (85) 742–752.

Sawai, C., Anderson, K. and Walser-Kuntz, D., 2003, 'Effect of bisphenol A on murine immune function: modulation of interferon-gamma, IgG2a, and disease symptoms in NZB X NZW F1 mice', *Environ Health Perspect,* (111) 1 883–1 887.

Schönfelder, G., Wittfoht, W., Hopp, H., Talsness, C.E., Paul, M. and Chahoud, I., 2002a, 'Parent bisphenol a accumulation in the human maternal-fetal-placental unit', *Environ Health Perspect,* (110) A703–A707.

Schönfelder, G., Flick, B., Mayr, E., Talsness, C., Paul, M. and Chahoud, I., 2002b. 'In utero exposure to low doses of bisphenol A lead to long-term deleterious effects in the vagina', *Neoplasia,* (4) 98–102.

Schulte-Oehlmann, U., Tillmann, M., Casey, D., Duft, M., Markert, B. and Oehlmann, J., 2001, 'Östrogenartige Wirkung von Bisphenol A auf Vorderkienmenschnecken (Mollusca: Gastropoda: Prosobranchia)', *UWSF- Z Umweltchem Ökotox,* (13) 319–333.

Shao, X.L., Ma, J. and Wen, G., 2008, 'Investigation of endocrine disrupting chemicals in a drinking water work located in Songhua river basin', *Huanjing Kexue/Environmental Science,* (29) 2 723–2 728.

Sharpe, R.M., 2010, 'Is it time to end concerns over the oestrogenic effects of bisphenol A?', *Toxicol Sci,* (114) 1–4.

Shelby, M.D. 2008, 'NTP-CERHR monograph on the potential human reproductive and developmental effects of bisphenol A', *NTP CERHR MON.*, (22) v, vii–ix, 1–64.

Somm, E., 2009, 'Perinatal exposure to bisphenol A alters early adipogenesis in the rat. *Environ Health Perspect,* (117) 1 549–1 555.

Sonnenschein, C., Olea, N., Pasanen, M.E. and Soto A.M. 1989, 'Negative controls of cell proliferation: human prostate cancer cells and androgens', *Cancer Res,* (49) 3 474–3 481.

Soriano, S., Alonso-Magdalena, P., García-Arévalo, M., Novials, A., Muhammed, .S.J, Salehi, A., Gustafsson, J.A., Quesada, I. and Nadal, A., 2012, 'Rapid Insulinotropic Action of Low Doses of Bisphenol-A on Mouse and Human Islets of Langerhans: Role of Oestrogen Receptor β', *PLoS One,* (7/2) e31109, Epub 8 February 2012, PubMed PMID: 22347437; PubMed Central PMCID: PMC32756110.

Soto, A.M. and Sonnenschein, C., 2010, 'Environmental causes of cancer: endocrine disruptors as carcinogens', *Nat Rev Endocrinol*, (6) 363–370.

Stahlhut R.W., Welshons W.V. and Swan S.H., 2009, 'Bisphenol A data in NHANES suggest longer than expected half-life, substantial nonfood exposure, or both', *Environ Health Perspect.,* (117) 784–789.

Swan, S.H., Main, K.M., Liu, F., Stewart, S.L., Kruse, R.L. and Calafat, A.M., 2005, 'Decrease in anogenital distance among male infants with prenatal phthalate exposure', *Environ Health Perspect,* (113) 105–106.

Tan, B.L.L. and Mustafa, A.M., 2003, 'Leaching of bisphenol A from new and old babies' bottles, and new babies' feeding teats', *Asia Pac J Public Health,* (15) 118–123.

Taylor, J.A., Welshons, W.V. and Vom Saal, F.S., 2008, 'No effect of route of exposure (oral; subcutaneous injection) on plasma bisphenol A throughout 24h after administration in neonatal female mice', *Reprod Toxicol,* (25) 169–176.

Taylor, J.A., vom Saal, F.S., Welshons, W.V., Drury, B., Rottinghaus, G.,Hunt, P.A. and Vandevoort, C.A. 2011, 'Similarity of bisphenol A pharmacokinetics in rhesus monkeys and mice: Relevance for human exposure', *Environ Health Perspect,* (119) 422–430.

Teeguarden, J.G., Calafat, A.M., Ye, X., Doerge, D.R., Churchwell, M.I., Gunawan, R. and Graham, M.K., 2011, 'Twenty-four hour human urine and serum profiles of bisphenol a during high-dietary exposure', *Toxicol. Sci.,* (123) 48–57.

Terasaki, M., Nomachi, M., Edmonds, J.S. and Morita, M., 2004, 'Impurities in industrial grade 4,4'-isopropylidene diphenol (bisphenol A): possible implications for oestrogenic activity', *Chemosphere,* (55) 927–931.

Terasaki, M., Shiraishi, F., Fukazawa, H. and Makino, M., 2007, 'Occurrence and oestrogenicity of phenolics in paper-recycling process water: Pollutants originating from thermal paper in waste paper', *Environ Toxicol Chem,* (26) 2 356–2 366.

The Weinberg Group, 2005, *Case studies: European Advocacy* (http://www.weinberggroup.com/) accessed 9 August 2005.

Thomas, P. and Dong, J., 2006, 'Binding and activation of the seven-transmembrane oestrogen receptor GPR30 by environmental oestrogens: a potential novel mechanism of endocrine disruption', *J Steroid Biochem Mol Biol,* (102) 175–179.

Timms, B.G., Howdeshell, K.L., Barton, L., Bradley, S. and Richter, C.A., 2005, 'Oestrogenic chemicals in plastic and oral contraceptives disrupt development of the fetal mouse prostate and urethra', *PNAS,* (102) 7 014–7–019.

Tyl, R., 2009, 'Basic Exploratory Research Versus Guideline-Compliant Studies Used for Hazard Evaluation and Risk Assessment: Bisphenol A as a Case Study', *Environ Health Perspect,* (117) 1 644–16 51.

Tyl, R.W., Myers, C.B., Marr, M.C., Thomas, B.F., Keimowitz, A.R., Brine, D.R., Veselica, M.M., Fail, P.A., Chang, T.Y., Seely, J.C., Joiner, R.L., Butala, J.H., Dimond, S.S., Cagen, S.Z., Shiotsuka, R.N., Stropp, G.D. and Waechter, J.M., 2002, 'Three-generation reproductive toxicity study of dietary bisphenol A in CD Sprague-Dawley rats', *Toxicol Sci,* (68) 121–146.

Tyl, R.W., Myers, C.B., Marr, M.C., Sloan, C.S., Castillo, N.P., Veselica, M.M., Seely, J.C., Dimond, S.S., Van Miller, J.P., Shiotsuka, R.N., Beyer, D., Hentges, S.G., Waechter, J.M., 2008, 'Two-generation reproductive toxicity study of dietary bisphenol A in CD-1 (swiss) mice', *Toxicol Sci,* (104) 362–384.

Vandenberg, L.N., Colborn, T., Hayes, T.B., Heindel, J.J., Jacobs, D.R. Jr, Lee, D.H., Shioda, T., Soto, A.M., Vom Saa, F.S., Welshons, W.V., Zoeller, R.T. and Myers, J.P., 2012, 'Hormones and Endocrine-Disrupting Chemicals: Low-Dose Effects and Nonmonotonic Dose Responses', *Endocr Rev.*, 14 March. PubMed PMID: 22419778.

Vinggaard, A.M., Körner, W., Lund, K.H., Bolz, U. and Petersen, J.H., 2000, 'Identification and quantification of oestrogenic compounds in recycled and virgin paper for household use as determined by an in vitro yeast oestrogen screen and chemical analysis', *Chem Res Toxicol,* Vol. 13 (12), 1 214–1 222.

Völkel, W., Colnot, T., Csanady, G.A., Filser, J.G. and Dekant, W., 2002, 'Metabolism and kinetics of bisphenol A in humans at low doses following oral administration', *Chem Res Toxicol,* (15) 1 281–1 287.

Völkel, W.V., Bittner, N. and Dekant, W., 2005, 'Quantitation of bisphenol A and bisphenol A glucuronide in biological samples by high performance liquid chromatography-tandem mass spectrometry', *Drug Metab Dispos,* (33) 1 748–1 757.

Völkel, W., Kiranoglu, M. and Fromme, H., 2011, 'Determination of free and total bisphenol A in urine of infants', *Environm. Res.,* (111) 143–148.

vom Saal, F.S., Cooke, P.S., Buchanan, D.L., Palanza, P., Thayer, K.A., Nagel, S.C., Parmigiani, S. and Welshons, W.V., 1998, 'A physiologically based approach to the study of bisphenol A and other oestrogenic chemicals on the size of reproductive organs, daily sperm production, and behavior', *Toxicol Ind Health,* (14) 239–260.

vom Saal, F.S. and Hughes, C., 2005, 'An extensive new literature concerning low-dose effects of bisphenol A shows the need for a new risk assessment', *Environ Health Perspect,* (113) 926–933.

vom Saal, F.S., Akingbemi, B.T., Belcher, S.M., Birnbaum, L.S., Crain, D.A., Eriksen, M., Farabollini, F., Guillette, L.J. Jr, Hauser, R., Heindel, J. J., Ho, S.M., Hunt, P.A., Iguchi, T., Jobling, S., Kanno, J., Keri, R.A., Knudsen, K.E., Laufer, H., LeBlanc, G.A., Marcus, M., McLachlan, J.A., Myers, J.P., Nadal, A., Newbold, R.R., Olea, N., Prins, G.S., Richter, C.A., Rubin, B. S., Sonnenschein, C., Soto, A.M., Talsness, C.E., Vandenbergh, J.G., Vandenberg, L.N., Walser-Kuntz, D.R., Watson, C.S., Welshons, W.V., Wetherill, Y. and Zoeller, R. T., 2007, 'Chapel Hill bisphenol A expert panel consensus statement: integration of mechanisms, effects in animals and potential to impact human health at current levels of exposure', *Reprod Toxicol,* (24) 131–138.

Watson, C.S., Bulayeva, N.N., Wozniak, A.L. and Alyea R.A., 2007, 'Xenoestrogens are potent activators of nongenomic estrogenic responses', *Steroids,* (72) 124–134.

Weber Lozada, K. and Keri, R.A., 2011, 'Bisphenol A increases mammary cancer risk in two distinct mouse models of breast cancer', *Biol Reprod,* (85) 490–497.

Wei, J., Lin, Y., Li, Y., Ying, C., Chen, J., Song, L., Zhou, Z., Lv, Z., Xia, W., Chen, X. and Xu, S. 2011, 'Perinatal exposure to bisphenol A at reference dose predisposes offspring to metabolic syndrome in adult rats on a high-fat diet', *Endocrinology,* (152) 3 301–3 303.

Welshons, W.V., Thayer, K.A., Judy, B.M., Taylor, J.A., Curran, E.M. and vom Saal, F.S., 2003, 'Large effects from small exposures. I. Mechanisms for endocrine-disrupting chemicals with oestrogenic activity', *Environ Health Perspect,* (111) 994–1 006.

Wetherill, Y.B., Petre C.E., Monk, K.R., Puga, A. and Knudsen, K.E., 2002, 'The xenoestrogen bisphenol A induces inappropriate androgen receptor activation and mitogenesis in prostatic adenocarcinoma cells', *Mol Cancer Ther,* (1) 515–524.

Wetherill, Y.B., Akingbemi, B.T., Kanno, J., McLachlan, J.A., Nadal, A., Sonnenschein, C., Watson, C.S., Zoeller, R.T. and Belcher, S.M., 2007, '*In vitro* molecular mechanisms of bisphenol A action', *Reprod Toxicol,* (24) 178–198.

WHO, 2006, 'IARC code of Good Scientific Practice', World Health Organization.

Wilson, N.K., Chuang, J.C., Morgan, M.K., Lordo, R.A. and Sheldon, L.S., 2007, 'An observational study of the potential exposures of preschool children to pentachlorophenol, bisphenol-A, and nonylphenol at home and daycare', *EnvironRes,* (103) 9–20.

Wozniak, A.L., Bulayeva, N.N. and Watson, C.S., 2005, 'Xenooestrogens at picomolar to nanomolar concentrations trigger membrane oestrogen receptor-alpha-mediated Ca2+ fluxes and prolactin release in GH3/B6 pituitary tumor cells', *Environ Health Perspect,* (113) 431–439.

Wu, J.-H., Jiang, X.-R., Liu, G.-M., Liu, X.-Y., He, G.-L. and Sun, Z.-Y., 2011, 'Oral exposure to low-dose bisphenol A aggravates testosterone-induced benign hyperplasia prostate in rats'.*Toxicol Ind Health*, doi:10.1177/0748233711399310.

Xu, X., Tian D., Hong X., Chen,L.and Xie,L., 2011, 'Sex-specific influence of exposure to bisphenol-A between adolescence and young adulthood on mouse behavior', *Neuropharmacol,* (61) 565–573.

Xu, X.H., Zhang, J., Wang, Y.M., Ye, Y.P.and Luo, Q,Q, 2010, 'Perinatal exposure to bisphenol-A impairs learning-memory by concomitant down-regulation of N-methyl-d-aspartate receptors of hippocampus in male offspring mice', *Horm Behav,* (58) 326–333.

Yoshino, S., Yamaki, K., Yanagisawa, R., Takano, H., Hayashi, H. and Mori, Y., 2003, 'Effects of bisphenol A on antigen-specific antibody production, proliferative responses of lymphoid cells, and TH1 and TH2 immune responses in mice', *Br J Pharmacol,* (138) 1 271–1 276.

Zoeller, R.T., Bansal, R. and Parris, C., 2005, 'Bisphenol-A, an environmental contaminant that acts as a thyroid hormone receptor antagonist in vitro, increases serum thyroxine, and alters RC3/neurogranin expression in the developing rat brain', *Endocrinology,* (146) 607–612.

11 DDT: fifty years since *Silent Spring*

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'There was a strange stillness. The birds for example — where had they gone? Many people spoke about them, puzzled and disturbed. The feeding stations in the backyards were deserted. The few birds seen anywhere were moribund: they trembled violently and could not fly. It was a spring without voices ... only silence lay over the fields and woods and marsh.'

The book *Silent Spring* by Rachel Carson is mainly about the impacts of chemicals (in particular in particular dichlorodiphenyltrichlorethane also known as DDT) on the environment and human health. Indeed, the close association between humans and birds remains very apt. Representing the only two warm-blooded groups of life on Earth, mammals and birds share the same environments and threats.

Carson's claim that she lived in 'an era dominated by industry, in which the right to make a dollar at whatever cost is seldom challenged' still resonates strongly with the problems that societies face all over the world. One chapter heading, 'The obligation to endure', derived from the French biologist and philosopher Jean Rostand's famous observation that, 'the obligation to endure gives us the right to know'. United States President John F. Kennedy responded to the challenge posed by Carson by investigating DDT, leading to its complete ban in the US. The ban was followed by a range of institutions and regulations concerned with environmental issues in the US and elsewhere, driven by public demand for knowledge and protection.

DDT was the primary tool used in the first global malaria eradication programme during the 1950s and 1960s. The insecticide is sprayed on the inner walls and ceilings of houses. Malaria has been successfully eliminated from many regions but remains endemic in large parts of the world. DDT remains one of the 12 insecticides — and the only organochlorine compound — currently recommended by the World Health Organization (WHO), and under the Stockholm Convention on Persistent Organic Pollutants, countries may continue to use DDT. Global annual use of DDT for disease vector control is estimated at more than 5 000 tonnes.

It is clear that the social conscience awakened by Rachel Carson 50 years ago gave momentum to a groundswell of actions and interventions that are slowly but steadily making inroads at myriad levels. Chapter 17 of her book, 'The other road' reminds the reader of the opportunities that should have been seized much earlier. With more than 10 % of bird species worldwide now threatened in one way or another, it is clear that we missed early warnings or failed to act on them. Will we continue to miss signposts to 'other roads'? Are our obligations to endure met by our rights to know? As Carson said 50 years ago: 'The choice, after all, is ours to make.'

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11.1 Introduction

> 'There was a strange stillness. The birds for example — where had they gone? Many people spoke about them, puzzled and disturbed. The feeding stations in the backyards were deserted. The few birds seen anywhere were moribund: they trembled violently and could not fly. It was a spring without voices. ....only silence lay over the fields and woods and marsh.'

This narrative by Rachel Carson in *Silent Spring* (1962) (2) of an imagined town and surroundings, representing thousands such all over America, frames the context of one of the 20th century's most powerful books on humans and the environment. Fifty years on, with an enduring and strengthening message, Rachel Carson's *Silent Spring* is an unmistakeable icon for early environmental awareness and current concern.

Silent Spring is mainly about the impacts of chemicals — with an emphasis on dichlorodiphenyltrichloroethane (DDT) — on the environment and human health. Its impact is as strong now as then. Indeed, the close association between humans and birds remains very apt; representing the only two warm-blooded groups of life on earth — mammals and birds — we share the very same environments and threats. Carson's realisation of humankind-in-nature, arguably as important as humankind-in-cosmos, contributed significantly to modern and enduring environmental and even social movements, resulting in regulations and restrictions on activities and practices that now exceed chemicals alone. In her second chapter, *The obligation to endure*, Carson points a finger which then, and indeed still now, resonates strongly with problems that societies face all over the world, 'it is also an era dominated by industry, in which the right to make a dollar at whatever cost is seldom challenged'. Carson took her chapter heading and context from the French biologist and philosopher Jean Rostand's famous thought, 'the obligation to endure gives us the right to know'. United States President John F. Kennedy responded to the challenge posed by Carson by investigating DDT, eventually leading to its complete ban in the United States. Despite many counter-claims and arguments from various sources, the ban on DDT and other chemicals resulted in the return of the bird chorus to affected areas. The ban was followed by a range of institutions and regulations concerned with environmental issues in the United States and elsewhere, driven by a public demand for knowledge and protection.

The right to know and the willingness to endure, so crucial to advancing civilisation and freedom, poses interesting and challenging issues that continue to face humanity on many economic, political, social, and environmental fronts. Indeed, DDT remains part of the conundrum of 'enduring yet knowing', a situation described in more detail below.

11.2 History

The DDT molecule was first synthesized in 1873 (Zeidler, 1874), a time when organic chemistry was still a young discipline, and the synthesis was performed to study what happens when different reagents are mixed under specific conditions with no notion of what the product could be used for. It was not until 1939 that Paul Müller showed the insecticidal property of DDT (Nobelprize.org, 2012a). The first DDT formulations marketed in the United States against a variety of insect pests drew the attention of the military; means to combat insect-borne diseases in the theatres of World War II were in great demand. The key event to popularise DDT was an outbreak of typhus in Naples, Italy, in October 1943. By January 1944, and after treating 1 300 000 people over a three week period with DDT, the epidemic was brought under control (Nobelprize.org, 2012b). Based on work by De Meillon (1936), indoor residual spraying (IRS) with DDT to interrupt malaria transmission was introduced in South Africa in 1946, achieving complete coverage of malaria areas by 1958 (Sharp and le Sueur, 1996).

Paul Müller was awarded the Nobel Prize for Medicine or Physiology in 1948, but already in the prize presentation speech, problems with flies developing resistance to DDT were mentioned. However, resistance development was not viewed in any environmental light but rather as an opportunity to develop new chemical pesticides to solve the problem (Nobelprize.org, 2012b). There was no mention in the prize presentation speech of potential environmental concerns, rather, the persistence of DDT, today considered as one of the main environmental concerns, was viewed as positive for the practical use of the insecticide (Nobelprize.org, 2012b), and the early recommendations on how to use DDT were, to modern eyes, staggeringly indiscriminate, with much dusting of both individuals and food without any precaution (West and Campbell, 1946). However, some restrictions on indiscriminate use came already in 1948, the same year as the Nobel Prize, when use of DDT inside dairies was prohibited (American Journal of Public Health, 1949). In Sweden, cases in the 1950s were reported of flies dying after contact with dairy products with very high DDT content (Löfroth, 1971).

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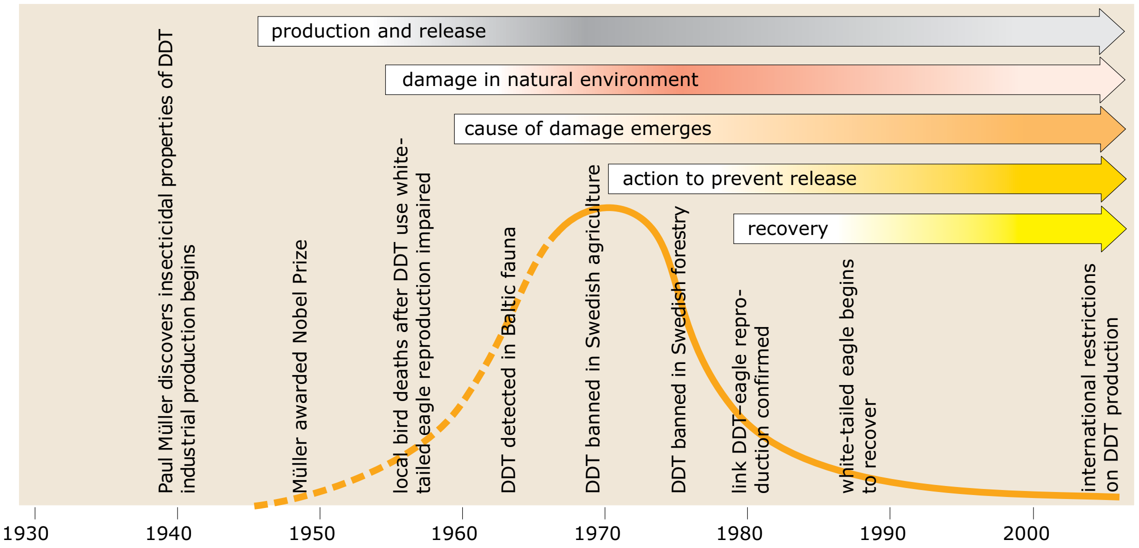
(2) All quotations are taken from the 1972 reprint of *Silent Spring* by Hamish Hamilton, London.

Arguably, the publication of *Silent Spring* (Carson, 1962) triggered the development of environmental chemistry as an academic discipline. Technical developments in analytical chemistry during the 1950s were prerequisites for development of the discipline, and, indeed, for the writing of the book, as these instrument developments were necessary to identify DDT and other organochlorine pesticides as potential environmental problems. However, it was *Silent Spring* that made the potential environmental problems everyone's concern and pressured resource allocation into environmental chemistry. In Sweden, for example, the government gave special funding to Stockholm University to set up a laboratory for the analysis of DDT in the environment (Bernes, 1998). These activities started in 1964, less than a year after the book was published in Swedish, and led, inter alia, to the identification of polychlorinated biphenyls (PCB) as environmental contaminants in 1966 (Jensen, 1966). It is difficult to envisage this development had it not been for the impact of *Silent Spring*.

That DDT was the first organic environmental pollutant that came under scrutiny was probably not only due to it being the first organochlorine pesticide to gain wide use. Another reason was probably that the negative effects first reported were on birds as many people were (and are) interested in birds, particularly large birds, and declines in the populations of birds of prey were observed in many places of the world and tied to eggshell thinning after bioaccumulation of DDT (Bernes, 1998; Bernes and Lundgren 2009). In addition, DDT was a pesticide deliberately released into the environment, which is why its presence in the environment was no great surprise. In comparison, PCB was put into production earlier than DDT, but as it was used in industry and not actively released into the environment, its presence in the environment was much of a surprise. In addition, there was no great incentive among the public to observe the negative effects of PCB as these were most severe in fish-eating mammals such as seals (Bernes, 1998; Bernes and Lundgren, 2009). The only people to regularly observe seals were fishermen, who mainly regarded them as a pest that competed for the fish. Thus, looking at the time-line for DDT and PCB (Figure 11.1), DDT was identified as a

Figure 11.1 The development of DDT concentrations in the Baltic Sea in relation to historical events, the development of environmental awareness and legal measures restricting their use



Note: The dashed portion of the line is estimated from museum material (seals), while the solid lines are based on data on Guillemot eggs analysed in the Swedish National Environmental Programme. Most uses of DDT were banned in Sweden around 1970.

Source: Bernes and Lundgren, 2009.

possible environmental problem much sooner after it was taken into use than PCB. In addition, although DDT and PCB were banned at about the same time in Sweden, the decline of DDT concentrations was more rapid as there were many remaining diffuse sources of PCB contamination, but for DDT the only use was as an insecticide (Bernes, 1998; Bernes and Lundgren, 2009).

Based on the increasing amount of data on environmental effects, restrictions on the use of DDT were put in place in different countries from the early 1970s, but the use and misuse of DDT continued. In Bangladesh, for example, fish intended for human consumption was until recently dried in DDT to avoid fly infestation in the market (Amin, 2003), even though DDT was banned in Bangladesh. With the Stockholm Convention on Persistent Organic Pollutants (Stockholm Convention, 2004), which came into force in 2004, new means to assist developing countries to reduce problems with DDT and other persistent organic pollutants (POPs) have come into place. However, the convention recognises the need to use DDT for malaria vector control until other practical and economically viable methods have been developed.

11.3 Current uses

11.3.1 DDT and malaria control

DDT was the primary tool used in the first global malaria eradication programme during the 1950s and 1960s. The insecticide was used to spray the walls and ceilings of houses and animal sheds with coverage of entire populations. Early mathematical modelling had convincingly shown that indoor residual spraying with insecticides, such as DDT, to kill adult mosquitoes had a major impact on malaria transmission (MacDonald, 1956). The insecticides prevented the female mosquitoes from surviving long enough to become infective, since it takes around 12 days for malaria parasites to migrate to the mosquito's salivary glands and, hence, only mature female mosquitoes can infect humans. Malaria has been successfully eliminated from many regions, but remains endemic in large parts of the world (Mendis et al., 2009).

The development of insect resistance to DDT, reported as early as 1951 (with even earlier indications in 1948 house flies in Sweden), became an obstacle in the eradication of malaria, and was one of the reasons behind the abandonment of the global malaria eradication campaign in 1969 (Najera et al., 2011). Amidst concerns about the safety of DDT during the 1970s, the insecticide was banned for use in agriculture in many countries. Nevertheless, DDT remained effective in a number of countries and continues to be used for malaria control today (van den Berg et al., 2012).

The negotiations that led to the inclusion of DDT as one of the initial twelve chemicals restricted under the Stockholm Convention sparked a debate about the continued need for DDT to control malaria (Curtis and Lines, 2000). An important series of developments took place over the same period. After South Africa had banned the use of DDT for malaria control in 1996, the highly effective malaria vector *Anopheles funestus* was able to reinvade the country because it had developed resistance to the pyrethroids that were being used, but not to DDT (Hargreaves et al., 2000). This situation, which was unique to South Africa, resulted in serious outbreaks of malaria, forcing the government to revert to DDT, after which the number of malaria cases declined. When simultaneously a global ban on DDT use was being proposed, fierce debates emerged over the benefits and adverse effects of DDT (The Lancet, 2000). In the final negotiations that led to the Stockholm Convention, an exception was made for DDT with an acceptable purpose for use in disease vector control. Thus, under the Stockholm Convention, countries may continue to use DDT, in the quantity needed, provided that the guidelines and recommendations of the World Health Organization (WHO) and the Stockholm Convention are met, and until locally appropriate and cost-effective alternatives become available for a sustainable transition from DDT.

DDT is one of the 12 insecticides, and the only organochlorine compound, currently recommended by the WHO for use in indoor residual spraying for disease vector control (WHO, 2006). Other recommended compounds are organophosphates, carbamates and pyrethroids. DDT has the longest residual efficacy, reportedly from 6–12 months, when sprayed on the walls and ceilings of traditional housing and, hence, one or two applications per year suffice to provide continuous protection to populations at risk. In the past few years, however, increased monitoring has shown that resistance of malaria vectors to DDT, and to other available insecticides, is now widespread in sub-Saharan Africa and India (WHO, 2011a).

11.3.2 Trends in production and use

Currently, DDT is produced only in India, from where it is exported as a pure (also called 'technical') or as a commercially formulated product to other, mostly African, countries (UNEP, 2010). China has recently stopped production of DDT but South Africa formulates DDT using technical product from India, and exports the formulated product to several other African countries. DDT can be produced at low cost, which is relevant because it has been recommended for use at a dosage that is on average 60 times higher than that for pyrethroid insecticides. As a consequence of these differences in application rates, 71 % of the global annual amount of insecticides used for vector control is DDT, even though pyrethroids are much more widely used in terms of surface area covered (van den Berg et al., 2012). DDT is used mostly for malaria control, but 19 % of the global share is sprayed to control leishmaniasis transmission by sandflies.

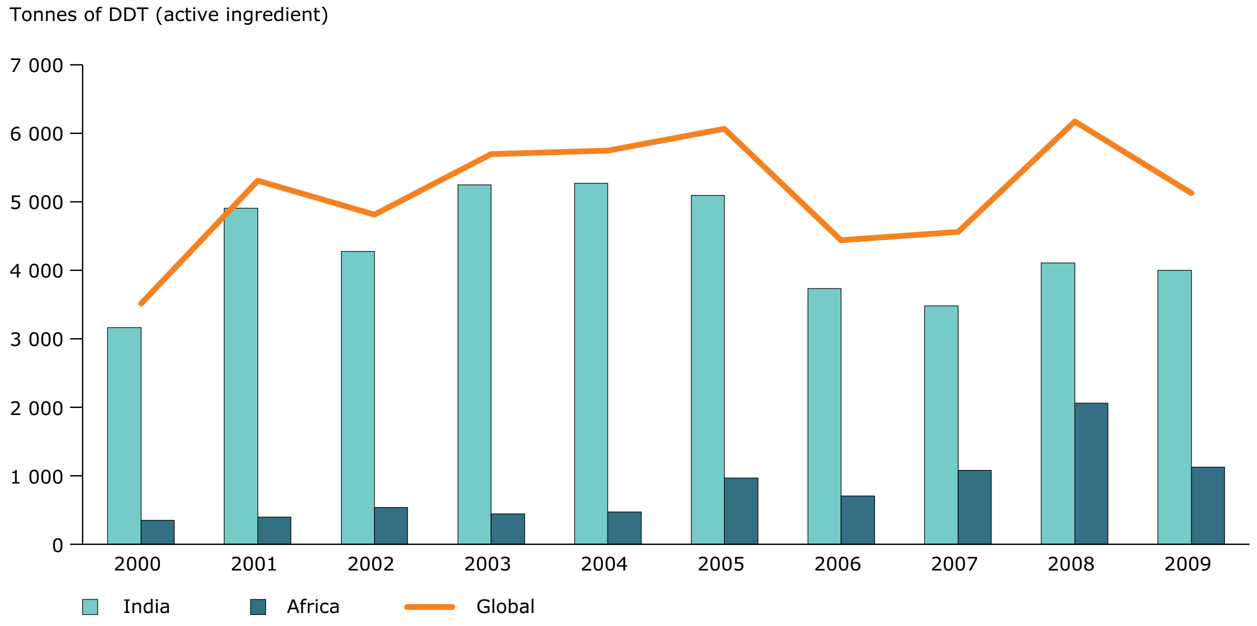
Global annual use of DDT for disease vector control is estimated at more than 5 000 tonnes of active ingredient. The amount has fluctuated during the past decade but has not declined substantially since the Stockholm Convention was enacted (van den Berg et al., 2012). India has the lion's share, with 82 % of global use. African countries also significantly increased their DDT use until 2008 (Figure 11.2) because of countries either scaling-up indoor residual spraying programmes using DDT or re-introducing its use. Only four African countries reported using DDT in 2000, compared to nine in 2008: Eritrea, Ethiopia, Mauritius, Mozambique, Namibia, South Africa, Swaziland, Uganda and Zimbabwe (WHO, 2011b). More recently, however, Ethiopia, Mozambique, and Uganda have reportedly stopped using DDT because of either policy change away from DDT or the development of insecticide resistance. It remains to be seen whether the decline in DDT use in Africa in 2009 is part of a new trend.

In DDT-using countries, it is of utmost importance that DDT is used for its acceptable purpose only. However, a recent global survey in countries at risk of vector-borne diseases revealed critical deficiencies in the capacity for regulatory control and management of pesticides, which include DDT, thus increasing the risks of adverse effects on human health and the environment (Matthews et al., 2011; van den Berg et al., 2011). For example, there are clear indications that DDT has been illegally traded on local markets for use in agriculture and termite control and there is also information to suggest that DDT is, or has been, widely used in agriculture in the Democratic People's Republic of Korea (van den Berg, 2009).

11.4 Current human health concerns

Carson (1962) devoted Chapter 12 of *Silent Spring* to a summary of the environmental health

Figure 11.2 Trends in the global use of DDT



Source: van den Berg et al., 2012.

effects associated with DDT, as then known. Very perceptively, Carson said, 'even research men suffer from the handicap of inadequate methods of detecting the beginnings of injury. The lack of sufficiently delicate methods to detect injury before symptoms appear is one of the great unsolved problems in medicine'. Since then, research men and women have added much to the arsenal of tools available, and a short summary of some follows.

The Agency for Toxic Substances and Disease Registry (ATSDR) report on DDT (2002) discussed in detail the acute exposure effects on the nervous system, the effects of chronic exposure to small amounts of DDT being almost limited to changes in liver enzymes. However, in the environment DDT is transformed to DDE which is even more persistent, leading to concerns that elevated concentrations of *p,p*'-DDE in human breast milk shortened the period of lactation and increased the chances of a pre-term delivery (see Box 11.1 for terminology on DDT and its related compounds). The International Agency for Research on Cancer (IARC) classified DDT as possibly carcinogenic to humans. Two recent publications extensively reviewed the human health consequences of DDT exposure (Eskenazi et al., 2009) and the human health aspects of IRS associated with DDT use (WHO, 2011). When the transplacental transfer of DDT and the exposure of the new-born child through breast milk became clear, there were concerns that DDT or its metabolites might affect, in particular, the reproductive and nervous systems. Moreover, some of these health effects may not become evident immediately but only long after exposure. Carson said, 'when one is concerned with the mysterious and wonderful functioning of the human body, cause and effect are seldom simple and easily demonstrated relationships. They may be widely separated in space and time'.

11.4.1 Breast cancer

The human female breast seems particularly vulnerable to environmentally-induced carcinogenesis during several critical periods such as *in utero* and before puberty (Eskenazi et al., 2009). Evidence that adult DDT exposure is associated with breast cancer was equivocal until Cohn et al. (2007) reported DDT levels in archived serum samples collected between 1959 and 1967, peak years of DDT use, from pregnant women participating in the Child Health and Development Studies (CHDS). Considering women ≤ 14 years old in 1945 when DDT was introduced, subjects with levels in the highest tertile were five times more likely to develop breast cancer than those in the lowest tertile. Moreover, in women exposed after the age of 14, there were no associations between the risk of breast cancer and *p,p*'-DDT levels. Therefore, exposure to *p,p*'-DDT during the pre-pubertal and pubertal periods is the critical exposure events to risk the development of breast cancer later in life.

11.4.2 Endometrial cancer

Sturgeon et al. (1998) reported on possible associations between endometrial cancer (cancer that starts in the lining of the uterus) and DDT serum levels, but the findings were inconclusive (Sturgeon et al., 1998). However, Hardell et al. (2004) found weak but significant associations with serum DDE levels and the topic needs further investigation.

Box 11.1. DDT-compounds

When DDT is produced the technical mixture, 'technical DDT', mainly consists of two compounds, approximately 80% *p,p'*-DDT (1,1,1-trichloro-2,2-*bis*(4-chlorophenyl) ethane), the insecticidal component, and 15% *o,p'*-DDT (1,1,1-trichloro-2-(2-chlorophenyl)-2-(4-chlorophenyl) ethane). The major degradation products in the environment of *p,p'*-DDT are *p,p'*-DDE (1,1-dichloro-2,2-*bis*(4-chlorophenyl) ethene) and *p,p'*-DDD (1,1-dichloro-2,2-*bis*(4-chlorophenyl) ethane). The major degradation products of *o,p'*-DDT are *o,p'*-DDE (1,1-dichloro-2-(2-chlorophenyl)-2-(4-chlorophenyl) ethene) and *o,p'*-DDD (1,1-dichloro-2-(2-chlorophenyl)-2-(4-chlorophenyl) ethane).

In environmental samples the concentrations of all these compounds are often added to a total DDT (ΣDDT) concentration. Generally, the *p,p'*-isomers are more persistent than the *o,p'*-isomers, and *p,p'*-DDE is the most persistent of all these compounds. Therefore, high DDT/DDE or DDT/ΣDDT ratios indicate a recent release of DDT while low ratios are typical of old releases of DDT or that DDT has undergone long-range transport.

11.4.3 Male reproductive effects

There is increasing evidence suggesting that DDT and metabolites have harmful effects on the quality of human semen and sperm function, particularly in young adult healthy men from an endemic malarial area with very high DDT and DDE levels (Aneck-Hahn et al., 2007). Sperm DNA integrity in this population was also adversely affected (De Jager et al., 2009).

Bornman et al. (2010) determined the association of external urogenital birth defects (UGBD) in newborn boys from DDT-sprayed and non-sprayed villages in a malarial area. Between 1995 and 2003, mothers living in villages sprayed with DDT had a 33 % greater chance of having a baby with a UGBD than mothers whose homes were not sprayed. A stay-at-home mother significantly increased the risk of having a baby boy with a UGBD to 41 %. Further studies are necessary to determine possible causal relationships with DDT and any possible genetic or epigenetic predispositions.

11.4.4 Testicular germ cell tumours

Concentrating on a selection of recent studies, McGlynn et al. (2008) found some evidence of an association between DDE and testicular germ cell tumours. There was a positive, but not statistically significant, association between DDE and testicular cancer. However, similar associations were also found for other chemicals such as chlordane, PCB, and some insecticides (Purdue et al., 2009). Therefore, the implications of DDE associated with testicular germ cell tumours need further studies. Cohn et al. (2010) examined maternal serum levels of DDT-related compounds in relation to sons' risk of testicular cancer 30 years later. Mothers of testicular cancer cases had lower levels of *p,p'*- DDT, *o,p'*-DDT and *p,p'*-and DDE, but a higher DDT/DDE ratio, than their matched controls. However, the possible role of DDT in the development of testicular cancer is still not clear (Hardell et al., 2006).

11.4.5 Diabetes

Various studies reported findings suggesting that body burdens of DDT and/or DDE may be associated with the prevalence of diabetes (1980 Morgan et al., 1980; Rylander et al., 2005; Rignell-Hydbom et al., 2007). However, a variety of other persistent environmental chemicals are also associated with diabetes prevalence and the WHO (2011d) concluded that the evidence is inconclusive. Nevertheless, the findings of Turyk et al. (2009) of an association between DDE exposure and diabetes incidence warrants further research to define the specific contributions of DDT and DDE.

Ukropec et al. (2010), in a cross-sectional study from Eastern Slovakia, investigated possible links between environmental pollution and pre-diabetes/diabetes (Type 2 diabetes). The prevalence of pre-diabetes and diabetes increased in a dose-dependent manner, with individuals with highest DDT levels showing striking increases in prevalence of pre-diabetes. PCBs showed comparable associations, but increased levels of hexachlorobenzene (HCB) and β-hexachlorocyclohexane β-HCH seemed not to be associated with increased prevalence of diabetes. The synergistic interaction of industrial and agricultural pollutants in increasing prevalence of pre-diabetes or diabetes is likely. For Type 1 diabetes, Rignell-Hydbom et al. (2010) found no evidence that in utero exposure to DDT could predispose the development of the disease.

11.4.6 Pregnancy

Women exposed to DDT had shorter menstrual cycles (Onyang et al., 2005) and both DDT and DDE reduced progesterone and estrogens (Windham et al., 2005; Perry et al., 2006). Other studies, however, found no relationship between menstrual abnormalities or cycle length and DDE or DDT exposure (Yu et al., 2000; Chen et al., 2005). There is limited evidence that DDT/DDE can increase the risk of miscarriage and the risk of preterm delivery. In the U.S. Collaborative Perinatal Project, high DDE concentrations were associated with an increased risk of foetal loss in previous pregnancies (Longnecker et al., 2005). Each 1 ng/g increase in serum DDE was associated with a 1.13 increased odds of miscarriage (Korrick et al., 2001). Venners et al. (2005) studied Chinese textile workers with comparable DDE concentrations and reported a similar increased odds of 1.17 for each 10 ng/g serum increase in total DDT. Together the two cohort studies (Longnecker et al., 2005; Venners et al., 2005) indicated an association between increasing DDT and DDE levels and foetal loss. In the Longnecker et al. (2001) study, the odds of preterm delivery were 3.1 times higher in women with serum DDE ≥ 60 µg/L than in those with DDE < 15 µg/L during pregnancy. Inconsistent results on the possible association between DDT/DDE levels and gestational age were reported in other studies.

Taken together, the positive dose-response relationships for these endocrine-regulated end-points raise concern for effects of exposure to DDT on female reproductive health. It should be noted that the 'high' DDE serum may be substantially lower than in populations where indoor residual spraying is still occurring, emphasising the need for research in the context of IRS (WHO, 2011d). In some studies the onset of menopause was associated with DDT/DDE studies (Cooper et al., 2002; Akkina et al., 2004; Eskenazi et al., 2005), but in the Agricultural Health Study DDT exposure was associated with slightly older age at menopause (Farr et al., 2006).

11.4.7 Breast milk

DDT may shorten (Gladen and Rogan, 1995; Kostyniak et al., 1999; Rogan et al., 1987; Rogan and Gladen, 1985), prolong (Weldon et al., 2006), or have no effect (Cupul-Uicab et al., 2008) on the duration of lactation, due to the endocrine disruptive properties of DDT isomers (Wetterauer et al., 2012). It is not clear whether DDT or DDE exposure per se is linked to the duration of lactation. However, a recent study from an area where DDT is sprayed as IRS for malaria control showed no differences in lengths of lactation between three DDT sprayed villages and a reference village where no DDT has ever been applied (Bouwman et al., 1012).

Infant exposure to DDT is directly related to intake through breast milk and milk levels are linked to IRS spraying for malarial vector control. Bouwman et al. (1990b) analysed breast milk from mothers visiting baby clinics, in one regularly IRS controlled area and in a control area, ten years after DDT use in agriculture was banned in South Africa. Parity, maternal age, infant age, and percentage of milk fat between the two groups were similar. DDT was detected in all samples analysed, while DDE levels were significantly lower in the non-exposed group. It should be noted that in South Africa, as in many parts of Africa, extended periods of breastfeeding (up to two years) seems the norm in rural communities (Bouwman et al., 2006). Since there is no maximum residue level (MRL) for breast milk (FAO, 2005), comparing it to bovine milk MRLs found that, based on the volume of 800 mL of breast milk consumed by a 5-kg infant, the MRL for total DDT (ΣDDT) in cow's milk is notably exceeded (Bouwman et al., 2006).

First-born infants receive much higher levels of DDT in breast milk than their siblings (Bouwman et al., 2006; Gyalpo et al., 2012; Harris et al., 2001), but recently it became clear that there are also differences in pollutant levels and effects on male and female infants (Gascon et al., 2011; Grimalt et al., 2010; Jackson et al., 2010; Jusko et al., 2006; Ribas-Fitó et al., 2006). Therefore, infant gender may somehow affect levels of pollutants in breast milk by a mechanism that is not immediately clear. One gender being exposed to higher levels than the other would add to concern about possible effects of DDT on development as result of endocrine-disruptive properties of DDT chemicals, a situation already suspected in South Africa (Bornman et al., 2010). A recent study has shown indications of gender involvement (Bouwman et al., 2012).

11.4.8 Neurodevelopment

The main mode of action of DDT as an insecticide is disruption of the nervous system. In other animal studies, DDT is a neurodevelopmental toxicant (ATSDR 2002). In mice, particular exposure to DDT during sensitive periods such as prenatal (Craig and Ogilvie, 1974) and neonatal periods (Eriksson and Nordberg, 1986; Eriksson et al., 1990; Johansson et al., 1996) affected development of the nervous system and caused behavioural and neurochemical changes into adulthood (Eskenazi et al., 2009). Eskenazi et al. (2006) was the first study to show that prenatal exposure to DDT, and not only to DDE, was linked to neurodevelopmental delays during early childhood. Ribas-Fito et al. (2006) assessed neurocognitive development relative to DDT levels in cord serum of 475 children. At age 4, the level of DDT at birth was inversely associated with verbal, memory, quantitative and perceptual performance skills, and the associations were stronger among girls. Torres-Sanchez et al. (2007) found that the critical window of exposure to DDE *in utero* may be the first trimester of the pregnancy, and that psychomotor development in particular is targeted by the compound. The authors also suggested that residues of DDT metabolites may present a risk of developmental delay for years after termination of DDT use.

Sagiv et al. (2008) demonstrated an association between low-level DDE exposures and poor attention in early infancy. In a follow-up study, they found that prenatal organochlorine DDE was associated with attention deficit hyperactivity disorder (ADHD) behaviour in childhood (Sagiv et al., 2010).

11.4.9 Immune effects

Cooper et al. (2004) demonstrated that DDE modulates immune responses in humans with evidence of potential immunosuppression and immune-mediated health effects such as infectious diseases and autoimmune diseases. Higher levels of prenatal DDE were associated with an increased incidence of otitis media in a study of Inuit infants (Dewailly et al., 2000). Workers directly exposed to DDT and lindane for 12–30 years, compared to a control population of individuals, had a higher prevalence of infectious diseases and of upper respiratory tract infections such as tonsillitis, bronchitis, and pharyngitis (Hermanowicz et al., 1982).

11.4.10 Recent health assessments of DDT

Two recent assessments of DDT and human health indicated issues that need attention. Eskenazi et al. (2009) found after reviewing 494 recent studies: 'The recent literature shows a growing body of evidence that exposure to DDT and its breakdown product DDE may be associated with adverse health outcomes such as breast cancer, diabetes, decreased semen quality, spontaneous abortion, and impaired neurodevelopment in children'. Focusing on DDT used in IRS, Bouwman et al. (2011) found that: 'The evidence of adverse human health effects due to DDT is mounting. However, under certain circumstances, malaria control using DDT cannot yet be halted. Therefore, the continued use of DDT poses a paradox recognized by a centrist-DDT position. At the very least, it is now time to invoke precaution. Precautionary actions could include use and exposure reduction.' They concluded that 'There are situations where DDT will provide the best achievable health benefit, but maintaining that DDT is safe ignores the cumulative indications of many studies. In such situations, addressing the paradox from a centrist-DDT position and invoking precaution will help design choices for healthier lives.' This was however, challenged by others (Tren and Roberts, 2011).

11.4.11 Carson on human health

The following quotations from Carson (1962) on the relationship between humankind and chemicals illustrate the concerns that are still with us today, but care should be taken not to interpret them out of context.

'Their [chemicals including pesticides] presence casts a shadow that is no less ominous because it is formless and obscure, no less frightening because it is simply impossible to predict the effects of lifetime exposure to chemical and physical agents that are not part of the biological experience.'

'The whole problem of pesticide poisoning is enormously complicated by the fact that a human being, unlike a laboratory animal living under rigidly controlled conditions, is never exposed to one chemical alone.'

'Some of the defects and malformations in tomorrow's children, grimly anticipated by the [US] Office of Vital Statistics, will most certainly be caused by these chemicals that permeate our outer and inner worlds.'

'The most determined effort should be made to eliminate those carcinogens that now contaminate our food, our water supplies, and our atmosphere, because these provide the most dangerous type of contact — minute exposures, repeated over and over throughout the years.'

11.5 Current human exposure

11.5.1 DDT used for indoor residual spraying

Following the essentially global ban on DDT use in agriculture, the only remaining repeated exposure of people to DDT is via IRS. It is otherwise assumed that illegal use is irregular and decreasing as stocks are dwindling. With between 2–3 grams of DDT applied per square metre on indoor walls, rafters, and outside under eaves, an average house may receive between 64–128 g/year, applied prior to the malaria transmission season. As DDT is long-lasting, the residual effect interrupts malaria transmission from an infected to an unaffected person by killing the female mosquito vector that rests indoors. It also acts as a contact irritant or spatial repellent (Grieco et al., 2007).

Arguably, the millions of people living in dwellings treated by DDT to protect them from malaria could be the largest non-occupationally exposed community in the world. The exposure is non-intentional, but inevitable (Bouwman et al., 2011). A closer look at how people are exposed in a domestic environment may indicate options for reduction in exposure and amounts applied. Such an exercise would be generic for any chemical used in similar ways. Again, despite the decades of DDT used as IRS, very little has been published on this subject.

11.5.2 DDT in air

DDT in ambient air is decreasing worldwide as its production and use has decreased dramatically with the ban on its use in agriculture (Schenker et al., 2008). Background levels in air for the general population are therefore low, with a concomitant reduction in risk. However, DDT, applied repeatedly on various indoor and associated surfaces of dwellings as IRS, remains continuously available. Because DDT has to interrupt transmission by the vectors, it must remain bio-available for six months or longer. Sereda et al. (2009) proposed a process of continuous indoor sublimation, revolatilsation, and re-deposition of DDT, effectively redistributing the DDT throughout the treated dwelling. Transport via air, airborne dust, as well as regular sweeping and removal of house dust to the outside results in DDT pollution of the outdoor environment. Applied DDT therefore, does not remain stationary. For spatial repellence of mosquitoes to remain effective for months also implies that DDT remains in the indoor air for substantial periods. Van Dyk et al. (2010) presented evidence that DDT remains detectable in indoor air for at least 84 days after application. DDT in indoor air, and probably at lower concentrations in outdoor air near the homesteads, therefore remains chronically available for inhalation by all homestead residents. Recently, Ritter et al. (2011) modelled air and human intake in an IRS situation and found inhalation exposure to DDT as an important route of uptake. A particular concern are individuals who remain close to home for long periods, such as infants, children, the elderly, pregnant mothers, and those with domestic responsibilities.

11.5.3 DDT in food and water

Van Dyk et al. (2010) reported on levels of DDT in various environmental matrixes, food, and human serum from a DDT-sprayed village in South Africa. High levels of DDT were found, especially in food items such as chickens and outdoor soil, but less so in vegetables and water. The patterns of DDT, DDD, and DDE (breakdown products of DDT; DDD is dichlorodiphenyldichloroethane) were also such that it seems far more likely that DDT in humans was derived from home-produced animal foods and outdoor soil rather than from air, indoor dust, and water. Elsewhere it was also found that DDT in fish was less likely to contribute towards DDT burdens in humans under IRS conditions (Barnhoorn et al., 2009; Bouwman et al., 1990a). DDT uptake by humans living in dwellings treated by IRS with DDT is therefore mainly through DDT entering the food chain in the immediate environs of the sprayed dwellings themselves. This differs from the situation where DDT is used on crops as insecticide, and the human route of uptake is mainly via treated crops, dairy products, or contaminated fish. A situation can be envisaged where both types of exposures occur, but large commercial agriculture was and is rarely found in malaria areas. It seems that people living in DDT-treated dwellings have a greater DDT burden than those exposed otherwise (Eskenazi et al., 2009). Gyalpo et al. (2012) using models based on data showed that primiparous mothers have greater DDT concentrations than multiparous mothers, which causes higher DDT exposure of first-born children. The DDT in the body mainly was found to be mainly from diet, likely derived from the immediate environment of the homestead (van Dyk et al., 2012).

The results presented in the previous paragraph point towards options for exposure reduction to all chemicals used in IRS, not only DDT. For such options to be investigated, the dynamics of the IRS chemicals, inhabitants, and vector mosquitoes need to be better understood. The procedures involving IRS have remained static since their introduction in the early 1940s. In the meanwhile, much more knowledge has become available about environmental chemistry, health impacts, and vector behaviour. It is clear that, where possible, all measures should be taken to reduce the exposures of the inhabitants to IRS chemicals as far as possible. A Total Homestead Environment (THE) approach has been proposed whereby these interactions are studied with the aim of identifying opportunities of exposure reduction (Bouwman et al., 2011; Bouwman and Kylin, 2009; Sereda et al., 2009).

11.5.4 Legacy issues

Except for use in disease vector control, any other current use of DDT is illegal (Section 1.3.2). Although global production of DDT may gradually be declining, legacy sources remain a problem. With vast amounts of DDT having been manufactured in industrial countries, it comes as no surprise that wastes and emissions resulted in large pollution problems near factories that are now closed down. On the Pine River in Michigan, United States, for instance, even though a Superfund site, DDT is still found in the environment, and health concerns persist (Eskenazi et al., 2009). A no-consumption of fish advisory is still in effect, and clean-up of nearby residential properties is scheduled for 2012, among a whole range of other protective and mitigating measures (EPA, 2012c). Likewise, previous mitigation of sediments at the DDT formulation site of United Heckathorn Co. in Richmond Harbor, California, which went bankrupt in 1966, seems not to have been as effective as anticipated and high levels of DDT in sediments and water persist (EPA, 2012b). An advisory against fish consumption (initially due to mercury but now for multiple pollutants) has been in effect since 1972. A search of the EPA Superfund site (EPA, 2012a) reveals 213 sites under United States jurisdiction that list DDT in one way or another at various stages of intervention.

Other legacy issues remain. DDT can undergo long-range transport via, air, water, and biota, contaminating areas where it has not been used or released (Bailey et al., 2000; Beyer et al., 2000; Iwata et al., 1993; O'Toole et al., 2006). Residues in glaciers are now being released as a result of climate change (Bettinetti et al., 2008; Geisz et al., 2008).

11.5.5 Effects of mixtures of chemicals

Legacy situations relating to DDT and malaria control hardly ever concern DDT only. With many commercial chemicals available, DDT now occurs together with many other pollutants in all manner of media and biota. Carson, after deliberating on combinations of pesticides in a common salad bowl said: 'Residues well within legally permissible limits may interact.', then said: 'What of other chemicals in the normal human environment? What in particular of drugs?' Later she brought in other chemicals: 'Added to these are the wide variety of synthetic oestrogens to which we are increasingly exposed — those in cosmetics, drugs, food, and occupational exposures. The combined effect is a matter that warrants the most serious concern.' Now, 50 years later, the issue of mixture effects, referred to in the Stockholm Convention as 'toxicant interactions', pharmaceuticals and personal care products (PPCPs) is a major area of research.

Scientific advances are finding ever more effects associated with chemicals in more and more biological systems; some effects such as endocrine disruption was barely understood at the time of Rachel Carson. This is evident from her statement: 'The ultimate answer is to use less toxic chemicals so that the public hazard from their misuse is greatly reduced. Such chemicals already exist. … the pyrethrins, rotenone, ryania, and other derived from plant substances.' We now know that even pyrethroids have health concerns (Bouwman and Kylin, 2009) and may interact with DDT (Eriksson et al., 1993). Even if DDT is not the major component of the cocktail of pollutants in many areas, it poses a legacy that cannot be ignored. Now that DDT is universally distributed in the biosphere, its interactions with other pollutants cannot be ignored, and will occupy science for many years to come, long after the final batch of DDT has been produced.

11.6 Future directions

11.6.1 Malaria, DDT, and the Stockholm Convention

Carson devoted relatively little space to DDT and malaria, but highlights the problem of development of resistance to DDT: 'Malaria programmes are threatened by resistance among mosquitoes.', and describes a number of instances around the world, including behavioural resistance. 'Apparently the adult mosquitoes had become sufficiently tolerant of DDT to escape from sprayed buildings.' The reverse of this situation, of pyrethroid-resistant mosquitoes re-invading South Africa when DDT was withdrawn, puts this issue into a new context. DDT had to be re-introduced to return to pre-1996 levels of morbidity and mortality. DDT resistance in South Africa and many other African countries was absent, not detected, or not strong enough to result in a breakdown of control. Whether behavioural resistance to DDT — where mosquitoes leave treated houses or fail to enter — effectively interrupts transmission is still not adequately resolved.

As described in Sections 11.2 and 11.3.1 above, DDT is one of the chemicals restricted by the Parties to the Stockholm Convention. The text of the convention is provided in Box 11.2. The provisions in the Convention regarding DDT can be seen as balancing the need for the continued use of DDT for malaria control where alternatives are not yet effective or proven, with an (undated) eventual aim of banning it. However, the experience in South Africa with pyrethroids (Maharaj et al., 2005) failing as an alternative to DDT in IRS has probably increased the threshold of expectation of proof of sustainability, especially regarding the requirements of viable alternatives listed in paragraph 5 (b) of the Stockholm Convention (see Box 11.2). No Party would want to revert to DDT if the alternatives are not as effective or better, measured by increased morbidity and mortality. The Stockholm Convention is driving various activities that can be followed on their website (www.pops.int).

11.6.2 Integrated vector management

The urgency of developing and establishing suitable alternatives to DDT for disease vector control is now widely recognised. Indeed the need for alternatives

Box 11.2 DDT in the Stockholm Convention, Annex B. Restriction, Part II

1. The production and use of DDT shall be eliminated except for Parties that have notified the Secretariat of their intention to produce and/or use it. A DDT Register is hereby established and shall be available to the public. The Secretariat shall maintain the DDT Register.
2. Each Party that produces and/or uses DDT shall restrict such production and/or use for disease vector control in accordance with the World Health Organization recommendations and guidelines on the use of DDT and when locally safe, effective and affordable alternatives are not available to the Party in question.
3. In the event that a Party not listed in the DDT Register determines that it requires DDT for disease vector control, it shall notify the Secretariat as soon as possible in order to have its name added forthwith to the DDT Register. It shall at the same time notify the World Health Organization.
4. Every three years, each Party that uses DDT shall provide to the Secretariat and the World Health Organization information on the amount used, the conditions of such use and its relevance to that Party's disease management strategy, in a format to be decided by the Conference of the Parties in consultation with the World Health Organization.
5. With the goal of reducing and ultimately eliminating the use of DDT, the Conference of the Parties shall encourage:
   (a) Each Party using DDT to develop and implement an action plan as part of the implementation plan specified in Article 7. That action plan shall include:
      (i) Development of regulatory and other mechanisms to ensure that DDT use is restricted to disease vector control;
      (ii) Implementation of suitable alternative products, methods and strategies, including resistance management strategies to ensure the continuing effectiveness of these alternatives;
      (iii) Measures to strengthen health care and to reduce the incidence of the disease.
   (b) The Parties, within their capabilities, to promote research and development of safe alternative chemical and non-chemical products, methods and strategies for Parties using DDT, relevant to the conditions of those countries and with the goal of decreasing the human and economic burden of disease. Factors to be promoted when considering alternatives or combinations of alternatives shall include the human health risks and environmental implications of such alternatives. Viable alternatives to DDT shall pose less risk to human health and the environment, be suitable for disease control based on conditions in the Parties in question and be supported with monitoring data.
6. Commencing at its first meeting, and at least every three years thereafter, the Conference of the Parties shall, in consultation with the World Health Organization, evaluate the continued need for DDT for disease vector control on the basis of available scientific, technical, environmental and economic information, including:
   (a) The production and use of DDT and the conditions set out in paragraph 2;
   (b) The availability, suitability and implementation of the alternatives to DDT; and
   (c) Progress in strengthening the capacity of countries to transfer safely to reliance on such alternatives.
7. A Party may, at any time, withdraw its name from the DDT Registry upon written notification to the Secretariat. The withdrawal shall take effect on the date specified in the notification.

to DDT has been one of the drivers that led the WHO to develop a global strategic framework on integrated vector management (IVM) (WHO, 2004). IVM is a strategy for the optimal use of vector control methods, procedures and resources aiming to improve the efficacy, cost-effectiveness, ecological soundness and sustainability of vector control (WHO, 2012). Development of alternative insecticides is one way to address the problem of insecticide resistance, and it is probable that improved formulations of existing insecticide molecules will be available soon although new insecticide molecules will take considerably longer to come to the market (Hemingway et al., 2006). However, evolutionary selection for resistance will continue against any new modes of action unless the selection pressure on vector populations is substantially reduced (Read et al., 2009).

It is therefore critical that the choice of vector control methods should be carefully based on the evidence of their effect on transmission reduction and their appropriateness in the local context. Combinations of methods, including house screening, environmental management, repellents, trapping, and biological control, with insecticide-treated bed nets or indoor residual spraying, may provide superior control while reducing reliance on single modes of action (Takken and Knols, 2009). For example, the use of IRS or insecticidal bed nets could usefully be complemented by larval source management or repellents, particularly where part of the vector population bites outdoors (Fillinger et al., 2009; Hill et al., 2007).

In its implementation, vector control should not be combined only with disease control programmes. Integrated vector management would benefit substantially from integration within the health sector, collaboration between sectors and active participation of communities (WHO 2012; Chanda et al., 2008; Beier et al., 2008).

11.6.3 Malaria, DDT, and the World Health Organization

The WHO has a major commitment to combating malaria using prompt treatment of cases, and vector control by insecticide-treated bed nets and IRS, implemented within an integrated vector management strategy. The summary of the latest WHO position statement on DDT (WHO, 2011c) is provided in Box 11.3, confirming that DDT is still required for malaria control. The WHO also introduced a global strategic framework for integrated vector management, expanded on in the previous section.

Recent unease with safety issues about DDT also prompted the WHO to reassess the potential health impact of DDT used for IRS (WHO, 2011d). The Consensus statement concluded: 'For households where IRS is undertaken, there was a wide range of DDT and DDE serum levels between studies. Generally, these levels are below potential levels of concern for populations. Considering the ranges of exposures in treated households that are summarised in Table 11.1, in some areas, the exposures in treated residences have been higher than potential levels of concern. Efforts are needed to implement best practices to protect residents in treated households from exposures arising from IRS. Of particular concern would be women of childbearing age who live in DDT IRS-treated dwellings and transfer of DDT and DDE to the fetus in pregnancy and to the infant via lactation.' The WHO has a number of initiatives and programmes relating to malaria control and IRS, which can be followed on their website (http://www.who.int/malaria/en/).

11.6.4 Likely future developments

It is clear that there is a roadmap for the exit of DDT. There remains the need to find, further refine, convincingly demonstrate sustainability, and implement alternatives. Although there is a roadmap, there is no timetable. The pieces need to be found and fitted within the budgetary constraints and competing agendas. Given the current climate regarding research and development budgets and interfacing political agendas, the final demise of DDT still seems some way off. However, DDT has taught us a lot. It is probably the most widely known quintessential environmental pollutant. It will remain a model molecule and benchmark against which many others will be compared. It has shown the good and bad side of what can be done by chemicals. One thing is for certain — DDT will remain a source of contention for some time to come. It will probably remain in inert environmental media for decades to come, but there may come a time when it will only be found in books, such as *Silent Spring*, to be read in gardens with birds.

11.7 The legacy of Rachel Carson

It is clear that the social conscience awakened by Rachel Carson 50 years ago gave momentum to a groundswell of actions and interventions that is

Box 11.3 Global Malaria Programme: The use of DDT in malaria vector control. WHO position statement, 2011

DDT is still needed and used for disease vector control simply because there is no alternative of both equivalent efficacy and operational feasibility, especially for high-transmission areas. The reduction and ultimate elimination of the use of DDT for public health must be supported technically and financially. It is essential that adequate resources and technical support are rapidly allocated to countries so that they can adopt appropriate measures for sound management of pesticides in general and of DDT in particular. There is also an urgent need to develop alternative products and methods, not only to reduce reliance on DDT and to achieve its ultimate elimination, but also to sustain effective malaria vector control (WHO, 2011e).

slowly but steadily making inroads at a myriad of levels addressing human and environmental concerns about chemicals. Reading *Silent Spring*, one is struck by how modern and current many of the issues that she raised are, although some are now described by other terminology. Resistance development, genetic damage, genetic modification, cancer, effects of mixtures, the need for more and improved biomarkers, sterile male techniques, push-pull biological control, ethical choices, and the need for concerted action at all levels, are just some of these. Although not yet aware of endocrine disruption as a mode of action of pesticides, effects such as cancer involving reproductive hormones was one of the issues she addressed. Not only did she attack the indiscriminate use of pesticides, she also proposed forms of integrated pest/vector management and biological control in chapter 17 that seem so modern and obvious today, but conceptually are more than 50 years old. Long-range transport of chemicals through air was also not well understood at the time of *Silent Spring*.

The heading of Chapter 17 — The Other Road — elicits a strong feeling that we have not taken the road that we should have taken much earlier on, an opportunity that was missed, an option not taken that will resonate for decades to come. Carson opined in her last sentence of *Silent Spring*: 'The concepts and practices of applied entomology for the most part date from the Stone Age of science. It is our alarming misfortune that so primitive a science has armed itself with the most modern and terrible weapons, and that in turning them against the insects it has also turned them against the earth.' Applied entomology has long since incorporated pest control measures other than chemicals and one can but ponder how much this was due to *Silent Spring*?

With more than 10 % of bird species worldwide now threatened in one way or another, and some already gone since *Silent Spring*, the silence that Carson called upon to illustrate the impact of chemicals has now also crossed into other realms of environmental impact. Radiation (also addressed by Carson), climate change, habitat destruction, economic mismanagement of the environment, human population expansion, and more — all of them have Other Roads, and we missed the obvious early signposts or failed to act upon them. Will there be more signposts to Other Roads that we will miss? Two final thoughts on this. Paraphrasing Jean Rostand; are our obligations to endure met by our rights to know? As Carson said 50 years ago: '*The choice, after all, is ours to make*.'

Table 11.1 Early warnings and actions

1873	The DDT molecule was first synthesised
1939	Paul Müller showed the insecticidal property of DDT
1943-44	Typhus broke out in Naples, Italy in October 1943. By January 1944, and after treating 1 300 000 persons over a three week period with DDT, the epidemic was brought under control
1946	Indoor residual spraying (IRS) with DDT to interrupt malaria transmission was introduced in South Africa
1948	Paul Müller was awarded the Nobel Prize for Medicine or Physiology. Already in the prize presentation speech problems with flies developing resistance against DDT was mentioned
1948	Use of DDT inside dairies in the US was prohibited
1950s-60s	DDT was the primary tool used in the first global malaria eradication programme. The insecticide was used to spray the walls and ceilings of houses and animal sheds with coverage of entire populations
1951	First reports of the development of insecticide resistance to DDT. This became an obstacle in the eradication of malaria, and was one of the reasons behind the abandonment of the global malaria eradication campaign
1958	Complete coverage of malaria areas in South Africa via indoor residual spraying with DDT achieved
1962	The novel *Silent Spring* was published, drawing attention to the impacts of chemicals on the environment and human health. Special emphasis was given to DDT
1964	Stockholm University, Sweden, set up a laboratory for the analysis of DDT in the environment. These activities led, inter alia, to the identification of polychlorinated biphenyls (PCB) as environmental contaminants
1970s	Based on the increasing amount of data on environmental effects, restrictions on the use of DDT were set in place in different countries, but still, the use and miss-use of DDT continued. Amidst concerns about the safety of DDT, the insecticide was banned for use in agriculture in many countries
1996	South Africa discontinued the use of DDT for malaria control and introduced pyrethroids on a large scale
2000	South Africa re-introduced DDT after failure of pyrethroids in many areas. Pyrthroids are used where viable
2004	The Stockholm Convention on Persistent Organic Pollutants came into force eliminating the production and use of DDT except for disease vector control where safe, effective and affordable alternatives are not available
2010	DDT is now only produced in India, from where it is exported to other, mostly African, countries. China has recently stopped its production of DDT. South Africa formulates DDT with the technical product from India, and exports the formulated product to several other African countries.

References

Akkina, J., Reif, J., Keefe. T. and Bachand. A., 2004, 'Age at natural menopause and exposure to organochlorine pesticides in Hispanic women', *J. Toxicol. Environ. Health A*, (67) 1 407–1 422.

American Journal of Public Health, 1949, Possible hazards from the use of DDT, 39 ed., pp. 925–927.

Amin, N. 2003, *Chemically processed fish injurious to health*, The Independent, City edition, Dhaka, Bangladesh, 13 January 2003.

Aneck-Hahn, N.H., Schulenburg, G.W., Bornman, M.S., Farias, P., De Jager, C., 2007, 'Impaired semen quality associated with environmental DDT exposure in young men living in a malaria area in the Limpopo Province, South Africa', *J. Androl.,* (28) 423–434.

ATSDR, 2002, *Toxicological Profile for DDT, DDE, DDD*, Agency for Toxic Substances and Disease Registry, Department of Health and Human Services, Public Health Service.

Bailey, R., Barrie, L.A., Halsall, C.J., Fellin, P. and Muir, D.C.G., 2000, 'Atmospheric organochlorine pesticides in the western Canadian Arctic: Evidence of transpacific transport', *J. Geophysical Research-Atmospheres,* (105) 11 805–11 811.

Barnhoorn, I.E.J., Bornman, M.S., van Rensburg, C.J. and Bouwman, H., 2009, 'DDT residues in water, sediment, domestic and indigenous biota from a currently DDT-sprayed area', *Chemosphere,* (77) 1 236–1 241.

Beier, J.C., Keating, J., Githure, J.I., Macdonald, M.B., Impoinvil, D.E. and Novak RJ., 2008, 'Integrated vector management for malaria control', *Malar J,* 7 (Suppl. 1): S4.

Bernes, C., 1998, Persistent organic pollutants. 'A Swedish view of an international problem', *Monitor,* Vol. 16, Swedish Environmental Protection Agency, Stockholm.

Bernes, C. and Lundgren, L., 2009, 'Use and misuse of nature's resources, An environmental history of Sweden', *Monitor,* Vol. 21, Swedish Environmental Protections Agency, Stockholm.

Bettinetti, R., Quadroni, S., Galassi, S., Bacchetta, R., Bonardi, L. and Vailati, G., 2008, 'Is meltwater from Alpine glaciers a secondary DDT source for lakes?', *Chemosphere,* (73) 1 027–1 031.

Beyer, A., Mackay, D., Matthies, M., Wania, F. and Webster, E., 2000, 'Assessing long-range transport potential of persistent organic pollutants', *Environ. Sci. & Tech.,* (34) 699–703.

Bornman, R., De Jager, C., Worku, Z., Farias, P. and Reif, S., 2010, 'DDT and urogenital malformations in newborn boys in a malarial area', *Brit. J. Urol. Int.,* (106) 405–410.

Bouwman, H., Coetzee, A. and Schutte C.H.J, 1990a, 'Environmental and health implications of DDT-contaminated fish from the Pongolo Flood Plain', *Afr. J. Zool.,* (104) 275–286.

Bouwman, H., Cooppan, R.M., Reinecke, A.J. and Becker, P.J., 1990b, 'Levels of DDT and metabolites in breast milk from Kwa-Zulu mothers after DDT application for malaria control', *Bull. WHO,* (88) 761–768.

Bouwman, H. and Kylin, H., 2009, Malaria control insecticide residues in breast milk: The need to consider infant health risks, *Environ. Health Perspect*., (117) 1 477–1 480.

Bouwman, H., Kylin, H., Sereda, B., Bornman, R., 2012, 'High levels of DDT in breast milk: Intake, risk, lactation duration, and involvement of gender', *Environ. Poll*., (170) 63–70.

Bouwman, H., Sereda, B.L. and Meinhardt, H.R., 2006, 'Simultaneous presence of DDT and pyrethroid residues in human breast milk from a malaria endemic area in South Africa', *Environ. Poll.,* (144) 902–917.

Bouwman, H., van den Berg, H. and Kylin, H., 2011, 'DDT and Malaria Prevention: Addressing the Paradox', *Environ. Health Perspect.,* (119) 744–747.

Carson, R., 1962, *Silent Spring,* Houghton Mifflin, Boston.

Chanda, E., Masaninga, F., Coleman, M., Sikaala, C., Katebe, C., MacDonald, M., Baboo, K.S., Govere, J. and Manga, L., 2008, 'Integrated vector management: the Zambian experience', *Mal. J.,* (7) 164.

Chen, A., Zhang, J., Zhou, L., Gao, E-S., Chen, L., Rogan, W.J. and Wolff, M.S., 2005, 'DDT serum concentration and menstruation among young Chinese women', *Environ. Res*., (99) 397–402.

Cohn, B.A., Cirillo, P.M., Christianson, R.E., 2010, 'Prenatal DDT Exposure and Testicular Cancer:

A Nested Case-Control Study', *Arch. Environ. Occup. Health*, (65) 127–134.

Cohn, B.A., Wolff, M.S., Cirillo, P.M. and Sholtz, R.I., 2007, 'DDT and breast cancer in young women: new data on the significance of age at exposure', *Environ. Health Perspect.*, (115) 1 406–1 414.

Cooper, G.S., Martin, S.A., Longnecker, M.P., Sandler, D.P. and Germolec, D.R., 2004, 'Associations between plasma DDE levels and immunologic measures in African-American farmers in North Carolina', *Environ. Health Perspect.*, (112) 1 080–1 084.

Craig, G. and Ogilvie, D., 1974, 'Alteration of T-maze performance in mice exposed to DDT during pregnancy and lactation', *Environ. Physiol Biochem.*, (4) 189–199.

Cupul-Uicab, L.A., Gladen, B.C., Hernandez-Avila, M., Weber, J.P., Longnecker, M.P., 2008, 'DDE, a degradation product of DDT, and duration of lactation in a highly exposed area of Mexico', *Environ. Health Perspect*, (116) 179–183.

Curtis, C.F. and Lines, J.D., 2000, 'Should DDT be banned by international treaty?', *Parasit. Today*, (16) 119–121.

de Jager, C., Farias, P., Barraza-Villarreal, A., Avila, M.H., Ayotte, P., Dewailly, E., Dombrowski, C., Rousseau, F., Sanchez, V.D., Bailey, J.L., 2006, 'Reduced seminal parameters associated with environmental DDT exposure and p,p'-DDE concentrations in men in Chiapas, Mexico: A cross-sectional study', *J. Androl*, (27) 16–27.

de Meillon, B., 1936, 'The control of malaria in South Africa by measures directed against the adult mosquitoes in habitations', *Bull. Health Org. League Nations*, (5) 134–137.

Dewailly, E., Ayotte, P., Bruneau, S., Gingras, S., Belles-Isles, M. and Roy, R., 2000,' Susceptibility to infections and immune status in Inuit infants exposed to organochlorines', *Environ. Health Perspect.*, (108) 205–211.

EPA, 2012a, Search Superfund Site Information (http://cumulis.epa.gov/supercpad/cursites/srchsites.cfm) accessed March 2012.

EPA, 2012b, United Heckathorn Co. (California) (http://yosemite.epa.gov/r9/sfund/r9sfdocw.nsf/vwsoalphabetic/United+Heckathorn+Co.?OpenDocument) accessed March 2012.

EPA, 2012c, Velsicol Chemical Corp (Michigan) (http://www.epa.gov/R5Super/npl/michigan/MID000722439.html) accessed March 2012.

Eriksson, P., Archer, T. and Fredriksson, A., 1990, 'Altered behaviour in adult mice exposed to a single low dose of DDT and its fatty acid conjugate as neonates', *Brain Res.*, (514) 141–142.

Eriksson, P., Johansson, U., Ahlbom, J. and Fredriksson A., 1993, 'Neonatal exposure to DDT induces increased susceptibility to pyrethroid (bioallethrin) exposure at adult age — changes in cholinergic muscarinic receptor and behavioural changes', *Toxicology*, (29) 21–30.

Eriksson, P. and Nordberg, A., 1986, 'The effects of DDT, DDOH-palmitic acid, and chlorinated paraffin on muscarinic receptors and the sodium-dependent choline uptake in the central nervous system of immature mice', *Toxicol. Appl. Pharmacol.*, (85) 121–127.

Eskenazi, B., Chevrier, J., Rosas, L.G., Anderson, H.A., Bornman, M.S., Bouwman, H., Chen, A., Cohn, B.A., de Jager, C., Henshel, D.S., Leipzig, F., Leipzig, J.S., Lorenz, E.C., Snedeker, S.M. and Stapleton, D., 2009, 'The Pine River Statement: Human health consequences of DDT use', *Environ. Health Perspect.*, (117) 1 359–1 367.

Eskenazi, B., Marks, A.R., Bradman, A., Fenster, L., Johnson, C., Barr, D.B. and Jewell, N.P., 2006, 'In utero exposure to dichlorophenyltrichloroethane (DDT) and dichlorodiphenyldichloroethylene (DDE) and neurodevelopment among young Mexican American children', *Pediatrics*, (118) 233–241.

FAO, 2005' Codex Alimentarius (www.codexalimentarius.net) accessed January 2006.

Fillinger, U., Ndenga, B., Githeko, A and, Lindsay, S.W., 2009, 'Integrated malaria vector control with microbial larvicides and insecticide-treated nets in western Kenya: a controlled trial', *Bull World Health Organ*, (87) 655–665.

Gascon, M., Vrijheid, M., Martinez, D., Forns, J., Grimalt, J.O., Torrent, M. and Sunyer, J., 2011, 'Effects of pre and postnatal exposure to low levels of polybromodiphenyl ethers on neurodevelopment and thyroid hormone levels at 4 years of age', *Environ. Int*, (37) 605–611.

Geisz, H.N., Dickhut, R.M., Cochran, M.A., Fraser, W.R. and Ducklow, H.W., 2008, 'Melting glaciers:

A probable source of DDT to the Antarctic marine ecosystem', *Environ. Sci. Technol.*, (42) 3 958–3 962.

Gladen, B.C. and Rogan, W.J., 1995, 'DDE and shortened duration of lactation in a northern Mexican town', *Am. J. Pub. Health,* (85) 504–508.

Grieco, J.P., Achee, N.L., Chareonviriyaphap, T., Suwonkerd, W., Chauhan, K., Sardelis, M.R. and Roberts, D., 2007, 'A new classification system for the actions of IRS chemicals traditionally used for malaria control', *PloS ONE,* (2) e716

Grimalt, J.O., Carrizo, D., Gari, M., Font-Ribera, L., Ribas-Fito, N., Torrent, M. and Sunyer, J., 2010, 'An evaluation of the sexual differences in the accumulation of organochlorine compounds in children at birth and at the age of 4 years', *Environ. Res,*. 110, pp. 244–250.

Gyalpo, T., Fritsche, L., Bouwman, H., Bornman, R., Scheringer, M., Hungerbühler, K., 2012, 'Estimation of human body concentrations of DDT from indoor residual spraying for malaria control', *Environ. Poll.,* (169) 235–241.

Hardell, L., Bavel, B., Lindstrom, G., Eriksson, M. and Carlberg, M., 2006, 'In utero exposure to persistent organic pollutants in relation to testicular cancer risk', *Int. J. Androl.,* (29) 228–234.

Hardell, L., van Bavel, B., Lindstrom, G., Bjornforth, H., Orgum, P., Carlberg, M., Sorensen, C.S. and Graflund, M., 2004, 'Adipose tissue concentrations of p,p'-DDE and the risk for endometrial cancer', *Gynecologic Oncol.,* (95) 706–711.

Hargreaves, K., Koekemoer, L.L., Brooke, B., Hunt, R.H., Mthembu, J. and Coetzee, M., 2000, '*Anopheles funestus* resistant to pyrethroid insecticides in South Africa', *Med. Vet. Entomol.,* (14) 181–189.

Harris, C.A., Woolridge, M.W. and Hay, A.W.M., 2001, 'Factors affecting the transfer of organochlorine pesticide residues to breastmilk', *Chemosphere,* (43) 243–256.

Hemingway, J., Beaty, B.J., Rowland, M., Scott, T.W. and Sharp, B.L., 2006, 'The Innovative Vector Control Consortium: improved control of mosquito-borne diseases', *Trends Parasitol.,* (22) 308–312.

Hill, N., Lenglet, A., Arnez, A.M. and Carneiro, I., 2007, 'Plant based insect repellent and insecticide treated bed nets to protect against malaria in areas of early evening biting vectors: double blind randomised placebo controlled clinical trial in the Bolivian Amazon', *Brit. Med. J.,* (335) 1 023.

IARC, 1991, DDT and associated compounds. In: *Occupational exposures in insecticide application, and some pesticides*, International Agency for Research on Cancer, (53) 179–249.

Iwata, H., Tanabe, S., Sakal, N. and Tatsukawa, R., 1993, 'Distribution of persistent organochlorines in the oceanic air and surface seawater and the role of ocean on their global transport and fate', *Environ. Sci. & Technol.,* (27) 1 080–1 098.

Jackson, L.W., Lynch, C.D., Kostyniak, P.J., McGuinness, B.M. and Louis, G.M.B., 2010, 'Prenatal and postnatal exposure to polychlorinated biphenyls and child size at 24 months of age', *Reprod. Toxicol.,* (29) 25–31.

Jensen, S., 1966, 'Report of a new chemical hazard', *New Scientist*, (32) 612.

Jusko, T.A., Koepsell, T.D., Baker, R.J., Greenfield, T.A., Willman, E.J., Charles, M.J., Teplin, S.W., Checkoway, H. and Hertz-Picciotto, I., 2006, 'Maternal DDT exposure in relation to fetal growth and 5-year growth', *Epidemiology,* (6) 692–700.

Korrick, S.A., Chen, C., Damokosh, A.I., Ni, J., Liu, X., Cho, S.I., Altshul, L., Ryan, L. And Xu, X., 2001, 'Association of DDT with spontaneous abortion: a case–control study', *Ann Epidemiol,* (11) 491–496.

Kostyniak, P.J., Stinson, C., Greizerstein, H.B., Vena, J., Buck, G. and Mendola, P., 1999, 'Relation of Lake Ontario fish consumption, lifetime lactation, and parity to breast milk polychrlobiphenyl and pesticide concentrations', *Environ. Res. A,* (80) S166–S174.

Löfroth, G., 1971, 'Introduction to the Swedish edition of Graham Jr. F', *Since Silent Spring*, Tidens förlag, Stockholm.

Longnecker, M.P., Klebanoff, M.A., Dunson, D.B., Guo, X., Chen, Z., Zhou, H. and Brock, J.W., 2005, 'Maternal serum level of the DDT metabolite DDE in relation to fetal loss in previous pregnancies', *Environ. Res*., (97) 127–133.

Longnecker, M.P., Klebanoff, M.A., Zhou, H and Brock, J.W., 2001, 'Association between maternal serum concentration of the DDT metabolite DDE and preterm and small-for-gestational-age babies at birth', *Lancet,* (358) 110–114.

MacDonald, G., 1956, 'Epidemiological basis of malaria control', *Bull.WHO*, (15) 613–626.

Maharaj, R., Mthembu, D.J. and Sharp, B.L., 2005, 'Impact of DDT re-introduction on malaria transmission in KwaZulu-Natal', *S. Afr. Med. J.*, (95) 871–874.

Matthews, G., Zaim, M., Yadav, R.S., Soares, A., Hii, J., Ameneshewa, B., Mnzava, A., Dash, A.P., Ejov, M., Tan, S.H. and van den Berg, H., 2011, 'Status of legislation and regulatory control of public health pesticides in countries endemic with or at risk of major vector-borne diseases', *Environ. Health. Perspect.*, (119) 1 517–1 522.

McGlynn, K.A., Quraishi, S.M., Graubard, B.I., Weber, J-P., Rubertone, M.V. and Erickson, R.L., 2008, 'Persistent organochlorine pesticides and risk of testicular germ cell tumors', *J. Natl. Cancer Inst.*, (100) 663–671.

Mendis, K., Rietveld, A., Warsame, M., Bosman, A., Greenwood, B. and Wernsdorfer, W.H., 2009, 'From malaria control to eradication: The WHO perspective', *Trop. Med. Int. Health*, (14/7) 802–809.

Morgan, D.P., Lin, L.I. and Saikaly, H.H., 1980, 'Morbidity and mortality in workers occupationally exposed to pesticides', *Arch. Environ. Contam. Toxicol.*, (9) 349–382.

Najera, J.A., Gonzalez-Silva, M. and Alonso, P.L., 2011, 'Some lessons for the future from the global malaria eradication programme (1955–1969)', *PloS Med.*, (8) e1000412.

Nobelprize.org., 2012a, *Paul Müller — Biography*. (http://www.nobelprize.org/nobel_prizes/medicine/laureates/1948/muller-bio.html) accessed March 2012.

Nobelprize.org., 2012b, *Award ceremony speech for Paul Müller* (http://www.nobelprize.org/nobel_prizes/medicine/laureates/1948/press.html) accessed March 2012.

O'Toole, S., Metcalfe, C., Craine, I. and Gross, M., 2006, 'Release of persistent organic contaminants from carcasses of Lake Ontario Chinook salmon (*Oncorhynchus tshawytscha*)', *Environ. Poll.*, (140) 102–113.

Ouyang, F., Perry, M.J., Venners, S.A., Chen, C., Wang, B., Yang, F., Fang, Z., Zang, T., Wang, L., Xu, X., Wang, X., 2005, 'Serum DDT, age at menarche, and abnormal menstrual cycle length', *Occup. Environ. Med.*, (62) 878–884.

Perry, M.J., Ouyang, F., Korrick, S.A., Venners, S.A., Chen, C., Xu, X., Lasley, B.L. and Wang, X., 2006, 'A prospective study of serum DDT and progesterone and estrogen levels across the menstrual cycle in nulliparous women of reproductive age', *Am. J. Epidemiol.*, (164) 1 056–1 064.

Read, A.F., Lynch, P.A. and Thomas, M.B., 2009, 'How to make evolution-proof insecticides for malaria control', *PLoS Boil*, (7) e1000058.

Ribas-Fito, N., Torrent, M., Carrizo, D., Munoz-Ortiz, L., Julvez, J., Grimalt, J.O. and Sunyer, J., 2006, 'In utero exposure to background concentrations of DDT and cognitive functioning among preschoolers', *Am. J. Epidemiol.*, (164) 955–962.

Rignell-Hydbom, A., Rylander, L. and Hagmar, L., 2007, 'Exposure to persistent organochlorine pollutants and type 2 diabetes mellitus', *Hum. Exp. Toxicol.*, (26) 447–452.

Rignell-Hydbom, A., Elfving, M., Ivarsson, S.A., Lindh, C., Jonsson, B.A., Olofsson, P. and Rylander L., 2010, 'A nested case-control study of intrauterine exposure to persistent organochlorine pollutants in relation to risk of type 1 diabetes', *PLoS ONE*, (5) e11281.

Rogan, W.J. and Gladen, B.C., 1985, 'Study of human lactation for effects of environmental contaminants: The North Carolina Breast Milk and Formula Project and some other ideas', *Environ. Health Perspect*., (60) 215–221.

Rogan, W.J., Gladen, B.C., McKinney, J.D., Carreras, N., Hardy, P., Thullen, J., Tingelstad, J. and Tully, M., 1987, 'Polychlorinated biphenyls (PCBs) and dichlorodiphenyl dichloroethene (DDE) in human milk: Effects on growth, morbidity, and duration of lactation', *Am. J. Pub. Health*, (77) 1 294–1 297.

Rylander, L., Rignell-Hydbom, A. and Hagmar, L., 2005, 'A cross-sectional study of the association between persistent organochlorine pollutants and diabetes', *Environ. Health*, (4) 28.

Sagiv, S.K., Nugent, J.K., Brazelton, T.B., Choi, A.L., Tolbert, P.E., Altshul, L.M. and , Korrick, S.A., 2008, 'Prenatal organochlorine exposure and measures of behavior in infancy using the Neonatal Behavioral Assessment Scale (NBAS)', *Environ. Health Perspect*, (116) 666–673.

Sagiv, S.K., Thurston, S.W., Bellinger, D.C., Tolbert, P.E., Altshul, L.M., Korrick, S.A., 2010, 'Prenatal organochlorine exposure and behaviors associated with attention deficit hyperactivity disorder in school-aged children', *Am. J. Epid*., (171) 593–601.

Sereda, B., Bouwman, H. and Kylin, H., 2009, 'Comparing water, bovine milk, and indoor residual spraying as possible sources of DDT and pyrethroid residues in breast milk', *J. Toxicol. Environ. Health A,* (72) 842–851.

Sharp, B.L. and le Sueur, D., 1996, 'Malaria in South Africa — The past, the present and selected implications for the future', *S. Afr. Med. J,* (86) 83–89.

Stockholm convention, 2004, *Stockholm Convention on Persistent Organic Pollutants,* United Nations Environment Programme (http://chm.pops.int/Convention/ConventionText/tabid/2232/Default.aspx) accessed 12 June 2012.

Sturgeon, S.R., Brock, J.W., Potischman, N., Needham, L.L., Rothman, N., Brinton, L.A., Hoover, R.N., 1998, 'Serum concentrations of organochlorine compounds and endometrial cancer risk', *Cancer Causes Contr*., (9) 417–424.

Takken, W. and Knols, B.G.J., 2009, 'Malaria vector control: current and future strategies', *Trends Parasit.,* (25) 101–104.

The Lancet, 2000, 'Correspondence: The DDT question', *The Lancet*, (356) 1 189–1 190.

Tren, R. and Roberts, D., 2011, 'DDT paradox', *Environ. Health Perspect.,* (119) A423–A424.

TTorres-Sanchez, L., Rothenberg, S.J., Schnaas, L., Cebrian, M.E., Osorio, E., Del Carmen Hernandez, M., García-Hernández, R.M., Del Rio-Garcia, C., Wolff, M.S. and López-Carrillo, L., 2007, 'In utero p,p'-DDE exposure and infant neurodevelopment: a perinatal cohort in Mexico', *Environ. Health Perspect.,* (115) 435–439.

Turyk, M., Anderson, H., Knobeloch, L., Imm, P. and Persky, V., 2009, 'Organochlorine exposure and incidence of diabetes in a cohort of Great Lakes sport fish consumers', *Environ. Health Perspect.,* (117) 1 076–1 082.

Ukropec, j., Radikova, Z., Huckova, M., Koska, J., Kocan, A., Sebokova, E., Drobna, B., Trnovec, T., Susienkova, K., Labudova, V., Gasperikova, D., Langer, P. and Klimes, I., 2010, 'High prevalence of prediabetes and diabetes in a population exposed to high levels of an organochlorine cocktail', *Diabetologia,* (53) 899–906.

UNEP, 2010, *Report of the Expert Group on the assessment of the production and use of DDT and its alternatives for disease vector control.* Third meeting Geneva, 10–12 November 2010, UNEP/POPS/DDT-EG.3/3, United Nations Environment Programme, Geneva.

van den Berg, H., Hii, J., Soares, A., Mnzava, A., Ameneshewa, B., Dash, A.P., Ejov, M., Tan, S.H., Matthews, G., Yadav, R.S. and Zaim, M., 2011, 'Status of pesticide management in the practice of vector control: a global survey in countries at risk of malaria or other major vector-borne diseases', *Malar. J.,* (10) 125.

van den Berg, H., Zaim, M., Yadav, R.S., Soares, A., Ameneshewa, B., Mnzava, A., Hii, J., Dash, A.P. and Ejov, M., 2012, 'Global trends in the use of insecticides to control vector-borne diseases', *Environ. Health Perspect.,* (120) 577–582.

van den Berg, H., 2009, 'Global status of DDT and its alternatives for use in vector control to prevent disease', *Environ. Health Perspect*., (117) 1 656–1 663.

van Dyk, J.C., Bouwman, H., Barnhoorn I.E.J., Bornman, M.S., 2010, 'DDT contamination from indoor residual spraying for malaria control', *Sci. Tot. Environ*., (408) 2 745–2 752.

Venners, S.A., Korrick, S., Xu, X., Chen, C., Guang, W., Huang, A., Altshul, L., Perry, M., Fu, L. and Wang, X., 2005, 'Preconception serum DDT and pregnancy loss: a prospective study using a biomarker of pregnancy', *Am. J. Epidemiol*., (162) 709–716.

Weldon, R.H., Webster, M., Harley, K., Bradman, A., Fenster, L., Barr, D.B., Jewell, N.P., Holland, N. and Eskenazi, B., 2006, 'Exposure to persistent organic pollutants and duration of lactation in Mexican-American mothers', *Epidemiology,* (17) S193.

West, T.F. and Campbell, G.A., 1946, *DDT — the synthetic insecticide*, Chapman & Hall, London.

Wetterauer, B., Ricking, M., Otte, J., Hallale, A., Rastall, A., Erdinger, L., Schwarzbauer, J., Braunbeck, T. and Hollert, H., 2012, 'Toxicity, dioxin-like activities, and endocrine effects of DDT metabolites — DDA, DDMU, DDMS, and DDCN', *Environ. Sci. Poll. Res*., (19) 403–415.

WHO, 2004, *Global strategic framework for Integrated Vector Management*, WHO document WHO/CDS/CPE/PVC/2004.10, World Health Organization, Geneva.

WHO, 2006, *Pesticides and their application for the control of vectors and pests of public health importance*, WHO/CDS/NTD/WHOPES/ GCDPP/2006.1, Geneva: World Health Organization.

WHO, 2011a, *The technical basis for coordinated action against insecticide resistance: preserving the effectiveness of modern malaria vector control: meeting report*. Geneva: World Health Organization.

WHO, 2011b. *Global use of insecticides for vector-borne disease control: a 10-year assessment, 2000–2009*, WHO/ HTM/NTD/VEM/WHOPES/2011, Geneva: World Health Organization.

WHO, 2011c, *DDT in indoor residual spraying: Human health aspects*, Environmental Health Criteria 241, World Health Organization, Geneva, pp. 1–309.

WHO, 2011d., *Environmental Health Criteria 241, DDT in Indoor Residual Spraying: Human Health Aspects*, World Health Organization, Geneva.

WHO, 2011e, *The use of DDT in malaria vector control*, WHO position statement, Global Malaria Programme, World Health Organization, Geneva.

WHO, 2012, *Handbook for integrated vector management*, WHO/HTM/NTD/VEM/2012.3, World Health Organization, Geneva.

Zeidler, O., 1874, Verbindungen von Chloral mit Brom- und Chlorbenzol. *Berichte der Duetschen Chemischen Gesellschaft zu Berlin*, (7) pp. 1 180–1 181.