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.

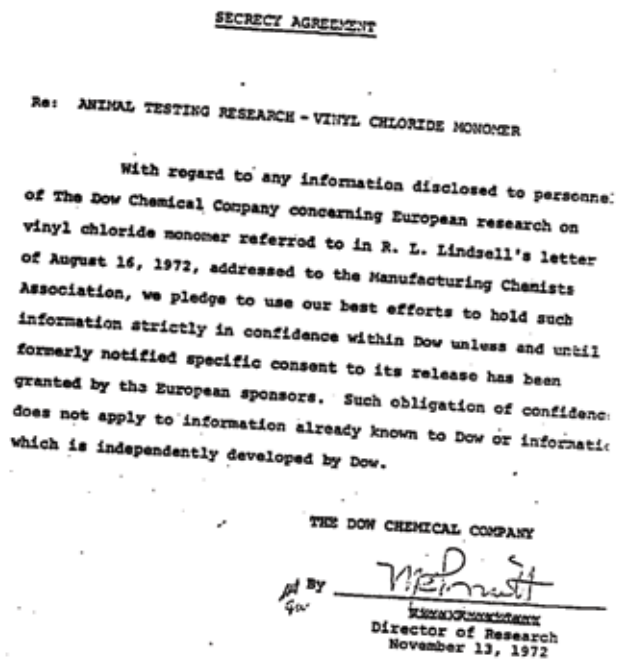
While the companies did not doubt the evidence from these studies, the Secrecy Agreement did not allow them disclose it. Such was the concern about leaks to the public that Mr D. M. Elliott of ICI 'insisted that the work tables be swept clear of paper for note taking before he would discuss anything 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.

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.

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).

([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

([3]) Kehoe also played an important role in the story of lead in petrol, described in the Chapter 3 on lead in petrol.

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).

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.

([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

([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

([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):

([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.

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