VINYL CHLORIDE

This substance was considered by previous IARC Working Groups in June 1974 (IARC, 1974), February 1978 (IARC, 1979) and March 1987 (IARC, 1987). Since that time new data have become available, and these have been incorporated into the monograph and taken into account in the present evaluation.

1. Exposure Data

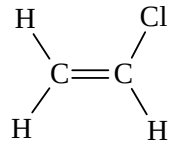
1.1 Chemical and physical data

From IARC (1999), WHO (1999), IPCS-CEC (2000), Lide (2005), ATSDR (2006), Cowfer and Gorensek (2006) and O'Neil (2006), unless otherwise specified

1.1.1 *Nomenclature*

Chem. Abstr. Services Reg. No.: 75-01-4
Chem. Abstr. Name: Chloroethene; chloroethylene; monochloroethylene; VC; VCM; vinyl C monomer
RTECS No.: KU9625000
UN TDG No.: 1086 (stabilized)
EC Index No.: 602-023-00-7
EINECS No.: 200-831-0

1.1.2 *Structural and molecular formulae and relative molecular mass*



C_2H_3C1 Relative molecular mass: 62.5

1.1.3 *Chemical and physical properties of the pure substance*

(a) *Description*: Colourless gas
(b) *Boiling-point:* –13 °C
(c) *Melting-point*: –154 °C
(d) *Relative density*: d_4^{20} 0.9106 (as liquid)
(e) *Relative vapour density*: 2.2 (air = 1)
(f) *Refractive index*: n_D^{20} 1.3700
(g) *Spectroscopy data*: Infrared, nuclear magnetic resonance and mass spectral data have been tabulated (Grasselli & Ritchey, 1975).
(h) *Solubility*: Slightly soluble in water (1.1 g/L at 25 °C); soluble in ethanol; very soluble in ether, carbon tetrachloride and benzene
(i) *Volatility*: Vapour pressure, 2530 mm Hg at 20 °C
(j) *Flash-point*: –78 °C (closed cup)
(k) *Stability*: The substance can, under specific circumstances, form peroxides and initiate explosive polymerization. The substance decomposes on burning to produce toxic and corrosive fumes (hydrogen chloride, phosgene).
(l) *Octanol/water partition coefficient*: log P_{ow}, 0.6
(m) *Auto ignition temperature*: 472 °C
(n) *Explosion limit in air*: 3.6–33%
(o) *Henry's law constant*: 18.8 at 20 °C
(p) *Conversion factor*: $mg/m^3 = 2.6 \times ppm$[1]

1.1.4 *Technical products and impurities*

Vinyl chloride is generally supplied as a compressed liquefied gas.

1.1.5 *Analysis*

Several reviews of methods of sampling and analysis of vinyl chloride in the work-place atmosphere, ambient air, water, water piping, food and cigarette smoke, and of polyvinyl chloride (PVC) are available (Environmental Protection Agency, 1975; Laramy, 1977; Egan *et al*., 1978).

Several methods for the analysis of vinyl chloride in ambient air have been developed. The Environmental Protection Agency method TO-1 analyses volatile organic compounds in ambient air using Tenax® and detection by gas chromatography (GS)–mass spectrometry (MS); method TO-14 analyses volatile organic compounds in ambient air using canister sampling followed by high-resolution GC (Environmental Protection Agency, 1999).

[1] Calculated from: mg/m^3 = (relative molecular mass/24.45) × ppm, assuming normal temperature (25 °C) and pressure (101.3 kPa)

A GC analytical method has been used since 1978 to determine vinyl chloride concentrations in foodstuffs and in vinyl chloride polymers and copolymers that are intended to come into contact with food (Directive 78-142-EEC; European Commission, 1978).

The Department of Labor (1989) of the USA published the Occupational Safety and Health Administration method 75 that detects vinyl chloride in air with a reliable quantitation limit of 0.020 ppm [0.051 mg/m^3]. More recently, Charvet *et al*. (2000) proposed the use of a solid-phase microextraction/GS/MS to analyse vinyl chloride in materials and aqueous samples.

1.2 Production and use

1.2.1 *Production*

The most common method for the production of vinyl chloride monomer (VCM) is by thermal cracking of ethylene dichloride (1,2-dichloroethane). Over 95% of the VCM produced worldwide in 2006 was made by this method. A less common method is by hydrochlorination of acetylene (WHO, 1999; Cowfer & Gorensek, 2006).

In the ethylene-based process, ethylene dichloride is synthesized by the reaction of elemental chlorine with ethylene over a catalyst. The crude ethylene dichloride is washed, dried and purified. Pure, dry ethylene dichloride is thermally cracked to produce VCM and hydrogen chloride. Hydrogen chloride recovered from the cracking of ethylene dichloride is recycled in the process via reaction with oxygen and ethylene over a copper catalyst to make more ethylene dichloride. This process is known as oxychlorination. VCM is purified by distillation, and side-products can be recovered for the manufacture of chlorinated solvents, or combusted or catalytically oxidized usually with recovery of hydrogen chloride (WHO, 1999; Cowfer & Gorensek, 2006).

VCM was initially produced commercially by the acetylene-based process, in which acetylene (usually produced by the reaction of water with calcium carbide) is reacted with hydrogen chloride over a mercury-based catalyst. VCM is again purified by distillation (WHO, 1999; Cowfer & Gorensek, 2006). Acetylene-based plants continue to operate solely in China. In 2001, the chemical corporation Borden stopped production at its acetylene plant in Louisiana, USA (Borruso, 2006).

The ethylene dichloride/VCM/PVC production chain represents the largest single consumer of chlorine (European Commission, 2003).

Vinyl chloride has been produced commercially in the USA for over 70 years (Tariff Commission, 1928). In 1988, the production of vinyl chloride in the USA was 9.1 billion pounds [4.1 million tonnes] and increased to around 13.75 billion pounds [6.2 million tonnes] in 1993 (ACGIH® Worldwide, 2005). In Taiwan, China, production has increased from 12 000 tonnes in 1971 (Luo *et al.*, 1999) to 1.7 million tonnes in 2005 (Borruso, 2006).

In 1999, worldwide production capacity was around 30 million tonnes (SIDS, 2001). Worldwide production capacity of VCM in 2005 was 35 million tonnes (Dow Chemical

Company, 2007). Table 1 gives production levels in various countries and regions (Borruso, 2006).

Table 1. World production capacity for vinyl chloride monomer in 2005

Region/country	Capacity (thousands of tonnes)
North America	
USA/Canada	8 934
Mexico	270
South America	
Brazil	635
Other	410
Western Europe	6 650
Central and eastern Europe	2 195
Africa and the Middle East	1 557
Asia	
Japan	3 050
China	3 443
China, Province of Taiwan	1 710
Korea, Republic of	1 466
Other Asia[a]	2 304
Oceania	0
Total	32 624

From Borruso (2006)

[a] Includes India, Indonesia, Korea (People's Democratic Republic of), Malaysia and Thailand

1.2.2 *Use*

Vinyl chloride is used primarily (> 95%) in the manufacture of PVCs, which comprise about 12% of plastic usage (WHO, 1999). The largest use of PVC resins is in the production of plastic piping. Other important uses are in floor coverings, consumer goods, electrical applications and transport applications. About 1% of PVC capacity is used to produce vinyl chloride/vinyl acetate copolymer. Other minor uses of VCM include the manufacture of chlorinated solvents (primarily 10 000 tonnes per year of 1,1,1-trichloroethane) and ethylene diamine production for the manufacture of resins (WHO, 1999; European Commission, 2003).

Vinyl chloride has been used in the past as a refrigerant, as an extraction solvent for heat-sensitive materials, in the production of chloroacetaldehyde, as an aerosol propellant and in drug and cosmetic products; these uses were banned in the USA by the Environmental Protection Agency in 1974 (ATSDR, 2006).

1.3 Occurrence

1.3.1 *Natural occurrence*

Vinyl chloride is not known to occur naturally.

1.3.2 *Occupational exposure*

According to the 1990–93 CAREX database for 15 countries of the European Union (Kauppinen *et al.*, 2000) and the 1981–83 National Occupational Exposure Survey in the USA (NOES, 1997), approximately 40 000 workers in Europe and 80 000 workers in the USA were potentially exposed to vinyl chloride (see General Remarks).

The major categories of industries that entail exposure to VCM in Europe comprise the manufacture of industrial chemicals (10 400 persons), plastic products (9100 persons) and other chemical products (7600) (Kauppinen *et al*., 2000). In the USA, the major categories of industries were the production of chemicals and allied products (15 400), business services (10 000) and the production of rubber and miscellaneous plastic products (9600) (NOES, 1997).

The Finnish Register of occupational exposure to carcinogens reported that 90 workers were notified as being exposed to vinyl chloride in 2004. This is below 0.01% of the 2.4 million people employed in Finland. Most of the exposed were employed in the chemical industry. The register is based on annual notifications of employers and its completeness is unknown (Saalo *et al.*, 2006).

In Taiwan, China, where production has increased dramatically in recent decades, thousands of workers could be exposed to VCM (Luo *et al.*, 1999).

The main route of occupational exposure is by inhalation, which occurs primarily in vinyl chloride/PVC plants and in PVC processing plants. Few measured exposure data have been reported but estimates from the chemical industry indicate that exposure to VCM amounted to several thousands of milligrams per cubic metre in the 1940s and 1950s, and were several hundreds of milligrams per cubic metre in the 1960s and early 1970s. After its recognition as a carcinogen, occupational exposure standards were set at approximately 13–26 mg/m^3 [5–10 ppm] in most countries in the 1970s (Fleig & Thiess, 1974; WHO, 1999).

A report from the Centers for Disease Control and Prevention (CDC) in the USA concluded that the development and acceptance by the PVC industry of a closed-loop polymerization process in the late 1970s "almost completely eliminated worker exposures" and that "new cases of hepatic angiosarcoma in vinyl chloride polymerization workers have been virtually eliminated" (CDC, 1997; see also Section 1.4). Even after the late 1970s, however, high concentrations were reported and may still be encountered in some countries (see Table 2).

Table 2. Levels of vinyl chloride reported in workplace air samples in vinyl chloride/polyvinyl chloride (PVC) production plants

Reference	Year of study	Country	Workplace	Concentration (mg/m^3)
Filatova & Gronsberg (1957)	NR	Former USSR	PVC producing plant	50–800 (occasionally 87 300)
Anghelescu *et al*. (1969)	1965–67	Romania	PVC production plant	112–554
Baretta *et al*. (1969)	NR	USA	PVC plant	≤ 650 (weekly TWA)
Fleig & Theiss (1974)	1974	Germany	PVC production department	< 65–81
Ott *et al*. (1975)	1950–59	USA	PVC plant	≤ 10 400; 13–2140 (8-h TWA)
	1960–63			≤ 1300; 13–620 (8-h TWA)
Rowe (1975)	1973	USA	Vinyl chloride/PVC plants	≤ 390 (TWA); peaks 2600–10 400
Barnes (1976)	'Early days'	United Kingdom	PVC production plant (full-time autoclave cleaner)	7800
Orusev *et al*. (1976)	1974	Former Yugoslavia	PVC production plant	> 195
German Environmental Office (1978)	1977	Germany	PVC production plant	1.3–91
Hansteen *et al*. (1978)	1974	Norway	PVC plant	65
Haguenoer *et al*. (1979)	1977–78	France	PVC production plant	2.3–7.3 (range of monthly means)
Heger *et al*. (1981)	1979	Germany	PVC production plant	12 (12-h TWA, stationary); 15.5 (12-h TWA, personal)
Bao *et al*. (1988)	1981	China	PVC production plant	9.9–229
Holm *et al*. (1982)	1974–81	Sweden	PVC production plant	0.26–114 (8-h TWA)
	1974–80			0.26–5.7 (6-h TWA)
Coenen (1986); BIA (1996)	1981–84	Germany	24 plants	3% of 33 samples > 5 (90th percentile, < 1) (shift means)
	1989–1992		46 plants	All of 117 samples < 5 (90th percentile < 0.1) (shift means)

Table 2 (contd)

Reference	Year of study	Country	Workplace	Concentration (mg/m^3)
De Jong *et al*. (1988)	1976–77	The Netherlands	PVC plant	2.6–26 (8-h TWA)
Smulevich *et al*. (1988)	Early 1950s	Former USSR	Vinyl chloride/PVC plants	100–800
Studniarek *et al*. (1989)	1974 1975 1976 1977 1978 1979 1981 1982	Poland	Vinyl chloride/PVC plant (several departments)	(30–600)[a] (30–270)[a] (15–60)[a] (6–150)[a] (1–30)[a] (1–15)[a] (0.1–36)[a] (0.1–12)[a]
	1974 1982		(autoclave cleaners)	(990)[a] (9–180)[a]
Fucic *et al*. (1990)	NR	Croatia	Plastics industry	Mean, 13; 5200 (occasional peak)
Hrivnak *et al*. (1990)	NR	Former Czechoslovakia	NR	2–41
Ho *et al.* (1991)	1976 After 1983	Singapore	PVC production plant	2.6–54 (15.3)[a] ≤ 26 (short-term) (3.9)[a]
Pirastu *et al*. (1991)	1950–85	Italy	Vinyl chloride/PVC plants	< 13– ≥ 1300
Dobecki & Romaniwicz (1993)	1986 1987 1988 1989 1990	Poland	Vinyl chloride synthesis mechanic, breathing zone	21.3 66.9 43.7 0.7 0.2
Viinanen (1993)	1981-85 1986–89 1993	Finland	PVC production plant, breathing zone	1.6 (8-h TWA); range, < 0.3–57 1.6 (8-h TWA); range, < 0.3–46 0.3 (8-h TWA); range, < 0.3–26

Table 2 (contd)

Reference	Year of study	Country	Workplace	Concentration (mg/m^3)
Gáliková *et al.* (1994)	1990–93	Russian Federation	Vinyl chloride/PVC plant	
			Whole plant (16 probes)	1–9 (range of annual means)
			Under the reactor	≤ 200 (range of annual means)
			In compressor room	≤ 400 (range of annual means)
Rashad *et al*. (1994)	NR	Egypt	Vinyl chloride/PVC plant	0.05–18 (8-h TWA)
Du *et al*. (1996)	NR	Taiwan, China	5 PVC plants	
			15 different operation units	Range (114 samples), ND (0.13)–1009
			Outside reaction tank[b]	Range (4 samples), 6–1009 (mean, 296; median, 86)
			15 different job titles	Range of TWA (85 samples), ND–3680
			Tank supplier[b]	Range (9 samples), 5.7–3680 (mean, 660; median, 23.7)
Hozo *et al*. (1996, 1997)	1949–87	Croatia	Vinyl chloride/PVC plant	Mean, 543; up to 1300 (peak)
Zhu *et al*. (2005a)	NR	China	PVC plant	Geometric mean, 7.1; range, 0.8–48.4

Updated from WHO (1999)
ND, not detected; NR, not reported; TWA, time-weighted average
[a] Geometric means
[b] Highest mean concentrations of vinyl chloride

(a) Production of vinyl chloride and its derivatives

Measured levels of VCM concentrations in vinyl chloride/PVC production are summarized in Table 2 (WHO, 1999). Only one recent study was found in which levels of exposure to vinyl chloride were reported (Zhu *et al.*, 2005a).

Zhu *et al*. (2005a) reported the exposure to VCM of workers in a plant in China. Ambient air levels of VCM at different worksites in the plant ranged from 0.3 to 17.8 ppm [0.8–48.4 mg/m^3]; the geometric average concentration was 2.6 ppm [7.1 mg/m^3]. In another study in Taiwan, China (Du *et al*., 1996), the highest median concentration was reported for short-term exposure (15–40 min) of a tank cleaner was 70 mg/m^3 [27 ppm].

In former socialist countries in eastern Europe, the stringent regulations for PVC production that were introduced in western Europe and the USA in the 1970s could not be met for socioeconomic reasons, and large plants with old-fashioned technologies continued to function with concentrations of VCM that remained at levels of former standards (Hozo *et al*., 1996).

In vinyl chloride production, workers may be exposed to ethylene dichloride and to catalysts such as iron(III) chloride. In PVC production, concurrent exposure to PVC dust may occur (Casula *et al.*, 1977). The polymerization inhibitor bisphenol-A has been reported to leach from polycarbonate flasks during autoclaving (Krishnan *et al.*, 1993).

(b) PVC processing

Measured levels of VCM in plants where PVC was being processed are considerably lower than those in vinyl chloride and PVC producing plants (Table 3; WHO, 1999). Improvements in PVC production in the 1970s resulted in a much lower content of residual VCM in PVC resin. The lower monomer content led automatically to concentrations in the ambient air of PVC processing factories < 0.1 ppm [0.26 mg/m^3] (Holm *et al*., 1982).

In PVC processing, the polymer may be mixed with antixodants (such as *p*-nonylphenol), stabilizers (such as organic tin compounds), plasticizers (phthalates) and colouring agents (pigments) (reviewed in Summers, 2006) and occupational exposure to these compounds, as well as to PVC dust, may occur (Boraiko & Batt, 2005).

1.3.3 *Environmental occurrence*

(a) Ambient air

Vinyl chloride has been reported in landfill gas and groundwater as a degradation product of chlorinated solvents that were deposited in landfills (WHO, 1999).

In recent years, the industrial release of vinyl chloride into the air in the USA slowly decreased from 734 259 pounds [333 tonnes] in 2001 to 670 992 pounds [305 tonnes] in 2002, 645 804 pounds [293 tonnes] in 2003, 653 837 pounds [297 tonnes] in 2004 and 545 252 pounds [248 tonnes] in 2005 (National Library of Medicine, 2007).

Table 3. Levels of vinyl chloride reported for workplace air samples in polyvinyl chloride (PVC) processing plants

Reference	Country	Workplace	Year	Concentration (mg/m^3)
Bol'shakov (1969)	Russia	PVC processing plant (synthetic leather plant)	Before 1966	< 114
Fleig & Thiess (1974)	Germany	PVC processing department	1974	< 2.6–68
Murdoch & Hammond (1977)	United Kingdom	PVC processing plants (cable factories)	NR	0.4–0.9
Holm *et al*. (1982)	Sweden	PVC processing plant	1974	< 0.26–0.8
Bao *et al*. (1988)	China	PVC processing plant	1981–85	≤ 30
Solionova *et al*. (1992)	Russia	PVC processing plant (rubber footwear plant)	Before 1990	0.007–1.26
Lundberg *et al*. (1993)	Sweden	PVC processing plant		
		Mixing	Before 1975	< 26
			After 1975	<<< 26
		Others	Before 1975	< 13
			After 1975	< 2.6
Nelson *et al*. (1993)	USA	Automotive assembly plant(s)	1970s	0.13–7.8 (2 personal samples)
BIA (1996)	Germany	Polymer extrusion (17 plants)	1989–92	All of 33 samples < 8 (90 percentile, < 0.15) (shift means)

From WHO (1999)
NR, not reported; TWA, time-weighted average

Atmospheric concentrations of VCM in ambient air are low (usually < 3 µg/m^3). A monitoring programme in the 1970s that measured VCM in the air around vinyl chloride and PVC production plants found some relatively high concentrations of vinyl chloride in ambient air. Maximum 24-h average concentrations ranged from 0.32 to 10.6 ppm [0.8–28 mg/m^3]. Levels of VCM were much lower in the vicinity of PVC product manufacturing plants than near vinyl chloride and PVC production plants (Dimmick, 1981).

(b) Accidental releases

In June 1996, 10 of 18 tank wagons filled with vinyl chloride were derailed on the Magdeburg–Halle railway line just outside the Schönebeck station in Germany. One wagon exploded and four others ignited; 28 people received in-patient treatment in a nearby hospital and 268 others were treated as outpatients. Vinyl chloride concentrations of 0.06–8 ppm [0.16–20.8 mg/m^3] were measured in residential areas. Almost 300 urine samples that were taken from rescue workers, residents and a control group were analysed for the vinyl chloride metabolite thiodiacetic acid. The measured values appeared to be in the range of those of unexposed people (Thriene *et al*., 2000).

(c) Residues in PVC resin and products

PVC products contain VCM as a residue from production (WHO, 1999). In a survey from 1976 to 1977, the following articles contained VCM at levels > 0.05 ppm [0.13 mg/m^3]: bathroom tiles, piping, plastic bottles for table oil and kitchen wrapping film. The highest concentrations were found in vinyl music records. The VCM content of toys, kitchen utensils, food wrappings, wallpaper and car interiors was < 0.05 ppm (German Environmental Office, 1978). The introduction of improved manufacturing practices has considerably reduced the residual content of VCM in PVC products (WHO, 1999).

(d) Other occurrences

VCM was identified in mainstream smoke of cigarettes (1.3–16 ng/cigarette) and cigars (14–27 ng/cigar). The measured levels correlated with chloride content of the tobacco (Hoffmann *et al*., 1976; IARC, 2004).

There has been no report of vinyl chloride levels found in food, pharmaceutical or cosmetic products in recent years (WHO, 1999).

1.4 Regulations and guidelines

Historically, the American Conference of Government Industrial Hygienists threshold limit values (ACGIH TLV®) were lowered from a maximum allowed concentration–time-weighted average (MAC–TWA) of 500 ppm in 1946–47 to a TLV–TWA of 200 ppm in 1972. In 1978–79, the carcinogenic classification A1c was added. In 1980, a

TLV–TWA value of 5 ppm was recommended together with the carcinogen classification of A1c, which changed to A1a and then to A1 in 1987. In 1999, a TLV–TWA value of 1 ppm was accepted with the A1 carcinogen classification (ACGIH, 2001).

Many countries, regions or organizations have established exposure guidelines for vinyl chloride in the workplace (Table 4).

The international, national and state regulations and guidelines regarding vinyl chloride in air, water and other media have been summarized by ATSDR (2006).

Since 1978, the European Union has controlled the presence of vinyl chloride in polymers and copolymers that are intended to come into contact with food (78/142/EEC; European Commission, 1978).

Table 4. Exposure guidelines for vinyl chloride in the workplace

Country/region or organization	TWA (ppm)[a]	STEL (ppm)[a]	Carcinogenicity[b]	Notes
Australia	5		1	
Belgium	3		Ca	
Brazil		156 (ceiling)		
Canada				
Alberta	1			
British Columbia	1		1	ALARA
Ontario	1			
Quebec	1	5	A1	Recirculation prohibited
China	10 mg/m^3	25 mg/m^3		STEL based on ultra limit coefficient
China, Hong Kong SAR	5		A1	
Czech Republic	7.5 mg/m^3	15 mg/m^3		
Finland	3			MAC
Germany-MAK			1	
Ireland	3		Ca1	
Japan-JSOH		2.5 (ceiling)	1	
Malaysia	1			Medical surveillance is appropriate
Mexico	5		A1	
Netherlands	7.77 mg/m^3		Ca	
New Zealand	5		A1	
Norway	1		Ca[a]	
Poland	5 mg/m^3	30 mg/m^3	Ca	
South Africa-DOL-RL	7			
Spain	3		Ca1	
Sweden	1	5	Ca	Skin

Table 4 (contd)

Country/region or organization	TWA (ppm)[a]	STEL (ppm)[a]	Carcinogenicity[b]	Notes
United Kingdom	3		R45	
USA				
ACGIH	1		A1	
NIOSH REL			Ca	
OSHA PEL	1	5		STEL is an average not to exceed 15 minutes

From ACGIH® Worldwide (2005)
ACGIH, American Conference of Governmental Industrial Hygienists; ALARA, as low as reasonably achievable; DOL-RL, Department of Labour-recommended limit; JSOH, Japanese Society of Occupational Health; MAC, maximum acceptable concentration; MAK, maximum allowed concentration; NIOSH, National Institute of Occupational Safety and Health; OSHA, Occupational Safety and Health Administration; PEL, permissible exposure limit; REL, recommended exposure limit; STEL, short-term exposure limit; TWA, time-weighted average
[a] Unless otherwise specified
[b] 1, established human carcinogen/substance which causes cancer in humans/carcinogenic to humans; Ca, Carcinogen/substance is carcinogenic; Ca[a], potential cancer-causing agent; A1, confirmed human carcinogen; Ca1, substance known to be carcinogenic to humans; R45, may cause cancer

2. Studies of Cancer in Humans

2.1 Case reports

A case report of three cases of angiosarcoma of the liver in men who had been employed in the manufacture of PVC resins provided the first evidence of an association between vinyl chloride and cancer in humans (Creech & Johnson, 1974). The case report was particularly informative because of the rarity of the tumour. Case reports of hepatocellular carcinoma in workers exposed to vinyl chloride have been published since the mid-1970s in France (Saurin *et al.*, 1997), Germany (Gokel *et al.*, 1976; Koischwitz *et al.*, 1981; Dietz *et al.*, 1985; Lelbach, 1996; Weihrauch *et al.*, 2000), China (Hong Kong SAR) (Evans *et al.*, 1983), Italy (Pirastu *et al.*, 1990), Japan (Makita *et al.*, 1997) and the USA (Bond *et al.*, 1990).

2.2 Methods and main results of epidemiological cohort studies of workers exposed to vinyl chloride

Two epidemiological multicentric investigations of workers who were employed in the vinyl chloride industry have been carried out: one in North America and one in Europe. In addition to reports that related to these cohorts in their entirety, a number of studies reported findings from individual subcohorts. In this section, results for subcohorts are described only when they provide important information that is not available in analyses of the full cohorts. Six cohort studies have also been reported in addition to and separately from the two multicentric investigations.

2.2.1 *North American multicentric study*

The North American multicentric cohort was originally assembled under the sponsorship of the Chemical Manufacturers' Association (now known as the American Chemistry Council). The first published report of this study (Cooper, 1981) included 10 173 workers from 37 plants, whose vital status was updated through to 31 December 1972. Among the 37 plants included in the study, 11 plants with 1214 workers produced only VCM, 18 plants with 6848 workers produced only PVC, three plants with 935 workers produced both VCM and PVC and five plants with 1176 workers produced homopolymers and copolymers. To be eligible for inclusion into the cohort, male employees at the 37 participating plants were required to have been exposed to VCM for at least 1 year before 31 December 1972 and to have been employed in or after 1942. The time at which the employees were included in the study depended on the date at which the plant where they worked began making or using VCM and the earliest date at which personnel records were complete for all employees, whichever was later. A second major follow-up of this cohort was published by Wong *et al.* (1991), at which time vital status had been updated through to 31 December 1989; this update included 10 173 individuals who satisfied the original entry criteria for this study. A third major update included the same eligibility criteria; after minor corrections to study records, 10 109 subjects were included in the analysis and vital status was updated through to 31 December 1995 (Mundt *et al.*, 2000). On the basis of state reference rates, the standardized mortality ratio (SMR) was 0.83 (95% confidence interval [CI], 0.80–0.86) for all causes, 0.96 (95% CI, 0.90–1.03) for all malignant neoplasms and 3.59 (80 deaths; 95% CI, 2.84–4.46) for cancer of the liver and biliary tract. Results for cancer at other sites were given for brain and central nervous system (36 deaths; SMR, 1.42; 95% CI, 1.00–1.97), lung (303 deaths; SMR, 0.82; 95% CI, 0.73–0.92), lymphatic and haematopoeitic tissue (71 observed; SMR, 0.86; 95% CI, 0.67–1.08), lymphosarcoma and reticulosarcoma (International Classification of Diseases (ICD)-9 code 200; 12 deaths; SMR, 1.20; 95% CI, 0.62–2.09) and skin (ICD-9 code 172–173; 12 deaths; SMR, 0.64; 95% CI, 0.33–1.12).

A separate analysis for a plant located in Louisville, KY (USA), that was included in the multicentric cohort was published by Lewis *et al.* (2003). The plant was the site at

which an excess of deaths from angiosarcoma had first been detected in workers exposed to vinyl chloride; it had opened in 1942 and has produced VCM, PVC resin and nitrile rubber copolymers. Among 2200 workers who had been employed for at least 1 year in jobs that entailed exposure to VCM in 1942–72 and who were followed-up during 1942–95, mortality from all causes was below that expected (903 deaths versus 1008.8 expected; SMR, 0.88), while that for all cancers combined was above expectation (264 deaths versus 248.2 expected; SMR, 1.06); mortality from cancer of the liver and biliary tract was also greater than that expected (24 deaths versus six expected; SMR, 4.00).

A subsequent study at this plant compared the exposure histories of cases of liver angiosarcoma and brain cancer with those of 1817 workers who had been exposed for at least 1 year and had been hired before 1967 (Lewis & Rempala, 2003). Exposure variables included history of employment in various PVC and nitrile rubber production buildings, ranked peak exposure to VCM and estimated cumulative exposure to VCM, acrylonitrile (IARC, 1999), 1,3-butadiene (see this volume) and styrene (IARC, 2002). In a nested case–control study, each case was individually matched to controls by year of birth, year of hire and duration of employment. The matched case–control analysis considered ranked exposure to VCM, vinylidene chloride (IARC, 1999), vinyl acetate (IARC, 1995), PVC, acrylonitrile (IARC, 1999), 1,3-butadiene (see this volume) and styrene (IARC, 2002). The occurrence of angiosarcoma was strongly associated with exposure to vinyl chloride but not with exposure to the other chemicals; the risk for brain cancer was highest among workers who had been hired before 1950 but was not associated with exposure to vinyl chloride.

2.2.2 *European multicentric study*

The European multicentric cohort was conducted in four countries (Italy, Norway, Sweden and the United Kingdom). The first report of the study results (Simonato *et al*., 1991) included follow-up of vital status through to 31 December 1986; an update of the study (Ward *et al*., 2001) analysed incidence and mortality through to the latest year for which data were available in each country, which ranged between 1993 and 1997. The study included a total of 19 factories; 11 of these produced VCM/PVC, two produced VCM only, five produced PVC only and one was a PVC processing plant. Male workers who had been employed for at least 1 year in 1942–72 in jobs that entailed exposure to VCM were included. The observation period for the cohort began in 1955, the year for which reference rates were first available. The most recent report provided updated information on vital status for 17 of the 19 factories and on cancer incidence for 13 factories in three countries. In addition, results for most of the national cohorts were published separately (Byren *et al.*, 1976; Fox & Collier, 1977; Molina *et al.*, 1981; Heldaas *et al.*, 1984, 1987; Jones *et al.*, 1988; Hagmar *et al.*, 1990; Pirastu *et al.*, 1990, 1998; Langård *et al.*, 2000).

Of the 12 700 men included in the updated analysis of the full cohort (Ward *et al*., 2001), 9688 (76.3%) were alive (range by country, 66–89%), 2665 (21.0%; range by

country, 10–33%) had died, 63 (0.5%) were lost to follow-up and 284 (2.2%) had emigrated. Overall, the follow-up was 97.3% complete.

Age- and calendar period-specific (men only) national mortality rates were used as the reference for the SMR analysis. These were computed using the WHO mortality database, in which only three-digit ICD codes have been stored consistently since 1955. A search for the best available data for a diagnosis of liver cancer was conducted by reviewing all available documentation. For Sweden and Norway, this included histology on the death certificate, if noted, and morphology coded by the cancer registry. For Italy, where cancer registry data were not available, information was obtained from the death certificate or from medical records. In the United Kingdom, sources of histological diagnosis included the death certificate, cancer registry, medical records and a registry of angiosarcomas developed by the Health and Safety Executive (Baxter, 1981). Records of cases of liver cancer from all of the countries were also matched by indirect identifiers to records of an angiosarcoma registry maintained by the Association of European Plastics Manufacturers (Forman *et al.*, 1985).

Analysis by production process was based on the type of plant. The majority of workers (8032) were employed in mixed VCM/PVC production facilities, followed by PVC production (3047), PVC processing (1353) and VCM production (206). Calendar period-specific job–exposure matrices were provided by industrial hygienists for 13 of the 19 factories, and matrices that provided job- and calendar time-specific estimates of exposure to vinyl chloride in parts per million were created. Each job–exposure matrix was checked and validated as being generally accurate by two other industrial hygienists, one from Sweden and one from the United Kingdom, both of whom had had several years of experience in the vinyl chloride industry.

In general, exposure estimates for the study plants were highest in the earliest years of operation. For example, estimates of exposure to VCM in the highest exposure categories, including reactor operators, were as high as > 500 ppm [> 1300 mg/m^3] in 1950–65 in several of the Italian plants, 2000 ppm [5200 mg/m^3] in 1950–54 in a Norwegian plant, approximately 3000 ppm [7800 mg/m^3] in 1940–44 in one of the Swedish plants and 770 ppm [2000 mg/m^3] in 1944–50 in one of the British plants. Exposure estimates for high-exposure jobs in the 1960s were substantially lower in most plants, and the majority were below 200 ppm [520 mg/m^3]. By the mid-1970s, very few plants had estimated exposures > 5 ppm [> 13 mg/m^3]. Exposure variables in the analysis were autoclave worker (ever/never), duration of employment, and ranked level of exposure and cumulative exposure to VCM in air in ppm–years. Exposures to vinyl chloride in the study plants were estimated to be < 1 ppm [< 2.6 mg/m^3] for all jobs between 1976 and 1988. Most factories had a specific job category for autoclave workers, and the classification of individuals as 'ever autoclave worker' was based on ever having held a job in this category. For these workers, three categories were created: 1, known to have been an autoclave worker; 2, not known to have been an autoclave worker, and from a factory with a specific job code for autoclave worker; and 3, from a factory in which work as an autoclave worker could not be determined.

In addition to the job–exposure matrix with job- and calendar time-specific estimated exposures to vinyl chloride in parts per million, an index of ranked level of exposure was developed. Classification of subjects in this index was based on the maximum exposure level for any job held by an individual, based on the job- and the calendar time-specific exposure estimates given for that job in the job–exposure matrix. In order to examine the potential association of exposure to PVC dust with lung cancer and non-malignant respiratory disease, stratified analyses were conducted for those workers who had only, ever or never been employed in curing, filtering and packing jobs.

Using national mortality and incidence rates as the reference, mortality from all causes (SMR, 0.85; 95% CI, 0.82–0.88) and from all cancers (SMR, 0.99; 95% CI, 0.93–1.06) was below the reference, as was total cancer incidence (standardized incidence ratio [SIR], 0.85; 95% CI, 0.79–0.91). An increase in the occurrence of primary liver cancer was observed (53 deaths and 29 incident cases; SMR, 2.40; 95% CI, 1.80–3.14; SIR, 3.98; 95% CI, 2.67–5.72). From the best available data on diagnosis, 71 cases of liver cancer were identified and used in the internal analysis for latency, duration of employment, cumulative exposure and employment as autoclave cleaner. On the same basis, 37 cases of angiosarcoma and 10 cases of hepatocellular carcinoma were ascertained for which detailed analyses of latency, duration of exposure, cumulative exposure and ever versus never having worked as an autoclave cleaner were conducted. The results of these internal analyses are presented in Section 2.3. Results for other cancer sites (Ward *et al*., 2001) were: brain cancer — SMR, 0.93 (24 deaths; 95% CI, 0.60–1.39) and SIR, 0.91 (19 cases; 95% CI, 0.55–1.42); lung cancer — SMR, 0.95 (272 deaths; 95% CI, 0.84–1.07) and SIR, 0.80 (154 cases; 95% CI, 0.68–0.94); and lymphatic and haematopoeitic cancer — SMR, 0.94 (62 deaths; 95% CI, 0.72–1.21) [SIR not reported]; no significant excess was reported in any category of leukaemia or lymphoma. A non-significantly elevated SMR was found for malignant melanoma (15 deaths; SMR, 1.60; 95% CI, 0.90–2.65) but the analysis of incidence did not show an excess (18 observed cases; SIR, 1.06; 95% CI, 0.63–1.68) (Ward *et al*., 2001). Results of internal analyses for selected sites are presented in Sections 2.3–2.9.

The European study found evidence of a significant association between exposure to VCM and mortality from liver cirrhosis. The relative risks for cumulative exposures of < 524 (reference), 524–998, 999–3429, 3430–5148 and ≥ 5149 ppm–years were 1.00, 9.38 (eight cases; 95% CI, 3.52–25.0), 4.01 (nine cases; 95% CI, 1.55–10.4), 9.77 (eight cases; 95% CI, 3.66–26.1) and 8.28 (nine cases; 95% CI, 3.15–21.8), respectively.

In a Swedish study of 2031 workers employed for ≥ 3 months in a PVC processing plant during 1961–80 (Hagmar *et al.*, 1990), mortality and cancer incidence in 1961–85 were studied; vital status was established for 95.5% of cohort members. Work activities were classified for estimated exposure to VCM as none, low, moderate or high. The cohort was later included in the European multicentric study. The incidence of all cancers was higher than expected (SIR, 1.16; 95% CI, 0.99–1.36). Two incident cases of cancer of the liver and biliary tract were observed among workers with 10 or more years latency, an incidence that was higher than expected (SIR, 2.44; 95% CI, 0.30–8.80).

A Swedish cohort of 717 workers who had been employed for ≥ 3 months in three PVC processing plants in 1964–74 was followed up for mortality in 1964–86 and for incidence of disease in 1964–84; work activities were classified as having high, intermediate or low potential exposure to VCM and national reference rates were used for comparison. Mortality from all causes was as expected (SMR, 1.0; 95% CI, 0.8–1.2), and no cases of liver cancer were observed (Lundberg *et al.*, 1993).

A prospective follow-up study of French VCM workers was initiated in 1980 (Laplanche *et al*., 1992). The study population included exposed and unexposed workers from 12 plants; 1096 employees, aged 44–55 years, had been exposed to VCM in 1980–81 or earlier and were free of disease at the time of enrolment; the unexposed group included 1093 employees who were individually matched to the exposed group by age, plant and plant physician. Interviews and data collection were conducted by plant physicians. Occupational and medical histories, parental history of cancer, employment status, nationality, tobacco smoking status and alcoholic beverage consumption were recorded. The follow-up period ended in December 1988. During the study period, 20 deaths from cancer were observed among the exposed and 22 among the unexposed. Cancer morbidity was higher among the exposed (38 cases observed) than the unexposed (32 cases observed; relative risk, 1.3; 95% CI, 0.8–2.1).

In an Italian plant in Porto Marghera that was included in the European multicentric study, an internal analysis was completed with mortality follow-up for 1972–95 and employment histories for 1972–85 (Gennaro *et al*., 2003). The relative risks for mortality from all causes and all cancers for autoclave workers versus all other workers were 1.32 (11 deaths; 95% CI, 0.55–3.15) and 1.09 (six deaths; 95% CI, 0.36–3.31), respectively; an increase was also observed for mortality from liver cancer (four deaths; relative risk, 9.57; 95% CI, 1.69–54.1).

In the same plant, mortality and occupational history were updated until 1999 (Pirastu *et al.*, 2003). On the basis of job- and time-specific exposure estimates, cumulative exposure was calculated and classified into six exposure categories (0–735, 735–2379, 2379–5188, 5188–7531 and 7531–9400 ppm–years); employment as an autoclave worker (ever/never) was also considered in the analyses. Data (clinical and pathological) that gave the best diagnosis were used to identify cases of liver angiosarcoma and hepatocellular carcinoma. Regional rates were used as a reference, mortality from primary liver cancer was determined and internal analyses for duration, latency and exposure were completed. A comparison of mortality in the cohort with local reference rates was made for all causes (SMR, 0.75; 90% CI, 0.68–0.83) and all cancers (SMR, 0.94; 90% CI, 0.81–1.09), both of which were lower than expected. For all causes, the analysis by time since leaving employment and adjusted for latency showed that the SMR in the first year after leaving employment was 2.76 (90% CI, 1.94–3.91). Mortality rates for liver angiosarcoma (six cases) increased with latency and cumulative exposure; no cases were associated with duration of employment of < 12 years, latency of < 10 years or cumulative exposure of < 2379 ppm–years. Mortality rates for hepatocellular carcinoma (12 cases) and liver cirrhosis (20 cases) showed a similar pattern.

A cross-sectional study in the same plant examined occupational and non-occupational risk factors for cirrhosis of the liver and hepatocellular carcinoma among 13 individuals who had liver cancer (eight confirmed histologically), 40 individuals who had liver cirrhosis (24 confirmed histologically) and 139 referents who had been examined in a medical surveillance programme in 1999–2002 and were found not to have had any evidence of liver disease or cancer at any site (Mastrangelo *et al*., 2004). Among the 13 cases of hepatocellular carcinoma, 11 also had liver cirrhosis and were included in both groups. [The Working Group noted that it was not clear how the 139 referent subjects with no evidence of liver disease were selected from among the 643 persons examined in the medical surveillance programme.] Exposure to VCM was evaluated using a job–exposure matrix developed by Pirastu *et al*. (1990); history of alcoholic beverage consumption was ascertained from clinical or health surveillance records and chronic infection with hepatitis B (HBV) or hepatitis C virus was examined by serological markers. An association between exposure to VCM and both liver cirrhosis and hepatocellular carcinoma was found with much higher odds ratios among those exposed to multiple risk factors.

2.2.3 *Other studies*

A proportionate mortality study of workers employed in 1964–73 at 55 PVC processing plants in the USA used national mortality rates for comparison; six deaths from primary liver cancer were observed versus an expected 4.19 (Chiazze & Ference, 1981).

Thériault and Allard (1981) compared the mortality of a small cohort of 451 male workers who had been employed for 5 or more years in 1948–72 in a Canadian VCM production and polymerization plant with that of a group of 870 workers who had been employed for ≥ 5 months at a nearby industrial complex that was not involved in the production of VCM or PVC and who were considered to be unexposed, and also with the mortality of the Québec general population in 1971. Occupational histories were obtained by interview either at home or at work with the worker himself or his next of kin. Vital status was ascertained as at the end of 1977. The relative risk for exposed versus unexposed workers for mortality from all causes was 1.48 (95% CI, 0.84–2.61). Eight cases of liver cancer were observed with only 0.14 expected in comparison with the general population; all of these were angiosarcomas. Two deaths from cancer of the ‘bone, skin, connective tissue’ (ICD codes 170–173) were observed compared with 0.38 expected.

Weber *et al*. (1981) reported findings in a historical cohort of 7021 VCM/PVC production workers in Germany. The cohort included German and Austrian men who had been employed from the beginning of VCM/PVC production in all German plants [no details given] to the end of 1974. Vital status and follow-up for cause of death [methods not described] were 93.2% and 92.7% complete, respectively. Mortality rates of the West German male population were used as the reference. To calculate expected numbers for person–years of observation before 1968, rates from 1968 were used. A method described by Tabershaw and Gaffey (1974) was used to take into account unknown causes of

deaths. No information on exposure levels was available. The SMRs for mortality from all causes, all cancers and liver cancer (ICD-8 155) were 0.95 (414 deaths), 1.12 (94 deaths) and 15.23 (12 deaths), respectively. [The Working Group noted that an earlier cohort studied by Frentzel-Beyme *et al.* (1978) appeared to be included in this cohort.]

Smulevich *et al.* (1988) conducted a cohort study at the oldest PVC plants in the former Soviet Union. Overall, 3232 workers (2195 men) were identified as having held jobs that entailed exposure to VCM. Exposure levels were greater than 300 mg/m^3 [115 ppm] for part of the cohort [number unspecified]. Expected deaths were computed in strata of age (15–74 years) from death rates in the same city, based on follow-up for the years 1939–77. The total number of deaths was not in excess in the cohort. The SMR for all cancer was 1.07 (63 deaths). No cases of liver cancer were observed. The proportion of the cohort that was ever exposed to the highest estimated levels of VCM was not reported; however, 40 of 63 cancer deaths occurred in the high-exposure category. A statistically significant excess ($p < 0.05$) was detected for leukaemias and lymphomas (five deaths; SMR, 4.17), while excess mortality from for pancreatic cancer in both sexes (SMR, 1.43) and skin cancer (both melanoma and non-melanoma) in men (SMR, 1.67) were not statistically significant. Histological confirmation of causes of death was available for 60% of the cancer cases. A significant increase in the occurrence of lymphomas and leukaemias (seven deaths; SMR, 6.36) was noted at the highest level of exposure ($p < 0.05$). Although the number of cohort members per exposure level was not reported, 28 cancer deaths occurred in the highest-exposure group, 15 in the intermediate (30–300 mg/m^3 [11.5–115 ppm])-exposure group and one in the lowest (< 30 mg/m^3 [11.5 ppm])-exposure group. [The Working Group noted that few details were provided on the methods used for the computation of expected numbers of deaths.]

Du and Wang (1998) conducted a proportionate morbidity study in Taiwan, China, at five PVC plants that were operational in 1989–95. The 2224 workers who had been exposed to VCM (97% of the total) and who were traced were compared with two other cohorts who were unexposed to VCM—one of optical workers and one of motorcycle manufacturers (work histories were ascertained from records of the Labour Insurance Bureau). Hospital admissions for cancer at several sites were compared with admissions for cardiovascular and cerebrovascular disease as reference conditions and morbidity odds ratios were calculated. An excess of primary liver cancer was noted (morbidity odds ratio, 4.5; 95% CI, 1.5–13.3; or 6.5; 95% CI, 2.3–18.4, depending on the comparison cohort). An excess of deaths from haematopoietic cancer (morbidity odds ratio, 3.4; 95% CI, 1.0–11.8) was seen. Overall, 12 cases of primary liver cancer were observed in the PVC workers, including six hepatocellular carcinomas and six with unknown histology. [The Working Group noted that in a morbidity study, as in a proportionate mortality study, risk estimates may be influenced by differences in the occurrence of the reference diseases as well as those of the disease of interest.]

Wong, O. *et al.* (2002) conducted a retrospective mortality study of a cohort of workers from six vinyl chloride polymerization factories in Taiwan, China. A total of 3293 male workers met the eligibility criteria for the study: they must have been em-

ployed for at least 1 year between 1 January 1950 and 31 December 1992 and have been alive on 1 January 1985. The workers were followed for ascertainment of vital status from 1 January 1985 to 31 December 1997 through a national mortality registry. More than 99% of the study subjects was successfully traced using this method, and the remaining 1% was excluded from the analysis. SMRs were estimated using national rates for men as the reference. Exposure to VCM was estimated to be about 500 ppm [1300 mg/m^3] in the 1960s based on a previous report (Du *et al*., 2001). The SMR for all causes was 0.78 (95% CI, 0.65–0.91) and the number of deaths from for all cancers combined was greater than that expected (SMR, 1.30; 95% CI, 0.99–1.69). A significant excess of mortality from liver cancer was observed in this study (25 cases; SMR, 1.78; 95% CI, 1.15–2.62). None of the deaths from liver cancer appeared to be due to angiosarcoma, although diagnosis of primary liver cancer was only histologically confirmed for five cases.

A study on risk factors for hepatocellular carcinoma was conducted at six PVC polymerization plants in Taiwan, China, an area that has a high prevalence of chronic HBV and hepatitis C virus infection and an associated high incidence of hepatocellular carcinoma (Wong *et al*., 2003a). Among a cohort of 4096 workers, 25 cases of liver cancer were diagnosed in 1985–97. Of the 18 cases of liver cancer for whom medical records were available, all were considered to be hepatocellular carcinomas, although only five were confirmed histopathologically. Four control subjects were selected from among a pool of eligible workers who had known HBV status, no evidence of liver disease and provided information on questionnaires. Indices of exposure to VCM were developed based on job titles. HBV surface antigen (HBsAg)-negative subjects with history of tank cleaning had a 4.0-fold greater risk for liver cancer (95% CI, 0.2–69.1). HBsAg carriers with no history of tank cleaning had a 25.7-fold (95% CI, 2.9–229.4) increased risk, whereas the HBsAg carriers with a history of tank cleaning had the greatest risk (odds ratio, 396.0; 95% CI, 22.6–∞), which suggested an interaction between occupational exposure to VCM and HBV infections for the development of liver cancer.

A meta-analysis of cohort studies of vinyl choride-exposed workers that had been published up to 2002 was conducted (Boffetta *et al*., 2003). The meta-analysis was based on eight independent studies, two multicentric investigations (Mundt *et al*., 2000; Ward *et al*., 2001) and six smaller additional studies (Thériault & Allard, 1981; Weber *et al*., 1981; Smulevich *et al*., 1988; Laplanche *et al*., 1992; Huang, 1996; Wong, O. *et al*., 2002). For a selection of cancer sites, a meta-SMR and 95% CIs were calculated using a random-effects model when the *p*-value for the test for heterogeneity was ≥ 0.01. Six of eight studies reported results for liver cancer, but these were considered to be too heterogeneous to be included in a meta-analysis because, for both liver cancer overall and for liver cancer other than angiosarcoma, the *p* value for heterogeneity was < 0.001. For the two multicentric studies (Mundt *et al*., 2000; Ward *et al*., 2001), the lack of heterogeneity allowed the calculation of meta-SMRs of 2.96 (95% CI, 2.00–4.39) for liver cancer overall (*p* value for heterogeneity = 0.03) and 1.35 (95% CI, 1.04–4.39) for liver cancer other than angiosarcoma (*p* value for heterogeneity = 0.7). [The Working Group noted that the meta-analysis did not evaluate the quality of the studies and that some

heterogeneity between studies may have resulted from variable data quality. Excluding one study in China, other studies reported SMRs that ranged from 1.78 (95% CI, 1.15–2.62) to 57.1 (95% CI, 24.6–113) for liver cancer overall and from 1.27 (95% CI, 0.84–1.83) to 10.1 (95% CI, 4.37–20.0) for liver cancer other than angiosarcoma.]

2.3 Cancer of the liver

2.3.1 *Cohort studies* (Table 5)

(a) North American multicentric study

The most recent update of the multicentric cohort study of men in the North American vinyl chloride industry (Mundt *et al.*, 2000) and reports relative to previous follow-up periods for the same cohort (Tabershaw & Gaffey, 1974; Cooper, 1981; Wong *et al.*, 1991) found, on the basis of state reference rates, an SMR for cancer of the liver and biliary tract of 3.59 (80 deaths; 95% CI, 2.84–4.46). SMRs increased with increasing duration of exposure: 0.83 (95% CI, 0.33–1.71), 2.15 (95% CI, 1.03–3.96), 6.79 (95% CI, 4.83–9.29) and 6.88 (95% CI, 4.40–10.23) for 1–4, 5–9, 10–19 and ≥ 20 years, respectively; and latency: 2.87 (95% CI, 1.31–5.44), 3.23 (95% CI, 2.00–4.93) and 4.34 (95% CI, 3.22–5.72) for 10–19, 20–29 and ≥ 30 years, respectively. In the Cox's proportional hazard model, duration of exposure had the strongest independent and significant effect in comparison with age and year of first exposure; adjusting for age and year of first exposure, and using 1–4 years as the reference, the relative risk values for 5–9, 10–19 and ≥ 20 years of duration were 2.8 (95% CI, 1.0–7.3), 9.0 (95% CI, 4.0–20.7) and 6.0 (95% CI, 2.5–14.4), respectively. For a total of 48 cases of angiosarcoma identified from both death certificates and the World Angiosarcoma Registry, Cox's proportional hazard analysis, adjusting for age and year of first exposure, showed an increase in risk for increasing duration of exposure: using 1–4 years duration as the reference, the relative risks for 5–9, 10–19 and ≥ 20 years of duration were 3.7 (95% CI, 0.9–14.7), 15.9 (95% CI, 4.6–54.8) and 9.7 (95% CI, 2.6–36.4), respectively. [It is not known whether the 32 deaths from liver cancer that were not identified as angiosarcoma were angiosarcoma or hepatocellular carcinoma; however, the number of expected deaths from liver and biliary tract cancer was 22.30.]

In a separate analysis of one plant located in Louisville, KY (USA), that was included in the multicentric cohort (Lewis *et al.*, 2003), mortality from cancer of the liver and biliary tract was higher than that expected on the basis of local rates (24 observed deaths versus six expected; SMR, 4.00). The analysis showed that SMRs for cancer of the liver and biliary tract increased with increasing duration of exposure (durations of 10–19 and ≥ 20 years had SMRs of 10.85 and 3.64, respectively; $p < 0.05$ for both categories) and latency (latencies of 10–19, 20–29 and ≥ 30 years had SMRs of 6.49, 6.94 and 2.55, respectively; $p < 0.05$ for all three categories). In this plant, a total of 28 liver angiosarcomas, 18 from deaths from liver cancer and 10 from other causes of death, were identified.

Table 5. Cohort studies of liver cancer in vinyl chloride monomer (VCM) and polyvinyl chloride (PVC) production workers

Name of study Reference, location	Cohort description	Exposure assessment	Type of cancer (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
North American multicentric study								
Mundt *et al*. (2000), USA	10 109 white male workers (race unknown, 6%) employed ≥ 1 year in jobs that entailed exposure to VCM in 1942–72; mortality follow-up, 1942–95; vital status, 96.8%; cause of death, 99%; 37 plants	JEM	Liver and biliary tract (ICD-9 155–156)	Job exposed to VCM	80	**SMR** (state rates) 3.59 (2.84–4.46) (state rates)		Reference rates: state and USA population; in Cox model, duration of exposure strongest and significant versus age at and year of first exposure
				Duration of exposure (years)				
				1–4	7	0.83 (0.33–1.71)		
				5–9	10	2.15 (1.03–3.96)		
				10–19	39	6.79 (4.83–9.29)		
				≥ 20	24	6.88 (4.40–10.23)		
				Latency (years)				
				10–19	9	2.87 (1.31–5.44)		
				20–29	21	3.23 (2.00–4.93)		
				≥ 30	50	4.34 (3.22–5.72)		
				First exposure (year)				
				≤ 1950	48	4.99 (3.68–6.62)		
				1950–59	32	3.11 (1.97–4.67)		
			48 ASL (33 death certificate, 15 World Angiosar-coma Registry)	*Duration of exposure (years)*		**Hazard ratio**	Age at first exposure, duration of exposure and year of first exposure	
				1–4	3	Reference		
				5–9	6	3.7 (0.9–14.7)		
				10–19	26	15.9 (4.6–54.8)		
				≥ 20	13	9.7 (2.6–36.4)		

Table 5 (contd)

Name of study Reference, location	Cohort description	Exposure assessment	Type of cancer (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
						SMR		
Lewis *et al*. (2003), Lousville, KY, USA	2200 male workers employed ≥ 1 year in jobs that entailed exposure to VCM in 1942–72; mortality follow-up, 1942–95; vital status, 98.5%	JEM	Liver and biliary tract (ICD-9 155–156)	Job exposed to VCM	24	4.00 ($p < 0.05$; 6 exp.)		Reference rates: state of Kentucky
				Duration of exposure (years)				
				1–4	2	0.91 (2.19 exp.)		
				5–9	2	2.20 (0.91 exp.)		
				10–19	14	10.85 ($p < 0.05$; 1.29 exp.)		
				≥ 20	6	3.64 ($p < 0.05$; 1.65 exp.)		
				Latency (years)				
				1–9	0	0 (0.27 exp.)		
				10–19	5	6.49 ($p < 0.05$; 0.77 exp.)		
				20–29	10	6.94 ($p < 0.05$; 1.44 exp.)		
				≥ 30	9	2.55 ($p < 0.05$; 3.53 exp.)		
				First exposure (year)				
				< 1950	12	3.57 ($p < 0.05$; 3.36 exp.)		
				1950–59	10	4.76 ($p < 0.05$; 2.10 exp.)		
				1960–72	2	3.51 (0.57 exp.)		

Table 5 (contd)

Name of study Reference, location	Cohort description	Exposure assessment	Type of cancer (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
European multicentric study								
Ward *et al.* (2001), Italy, Norway, Sweden, United Kingdom	12 700 male workers employed in 19 VCM/PVC plants for ≥ 1 year in 1950–85; mortality follow-up, 1955–97; incidence follow-up, 1955–96	Calendar period JEM for 13/19 factories grouped in 22 broad categories; factory-specific JEM with validated exposure estimates (ppm)	Liver cancer (ICD-9 155)		53	**SMR** 2.40 (1.80–3.14)		Reference rates: national
					29	**SIR** 3.98 (2.67–5.72)		Reference rates: national
				PVC production	10	**SMR** 2.28 (1.09–4.18)		
				VCM and PVC production	41	2.85 (2.05–3.87)		
				Duration (years)				
				1–9	15	1.00		
				10–16	17	2.58 (1.28–5.24)		
				17–20	9	3.48 (1.49–8.15)		
				21–25	18	8.21 (3.98–16.9)		
				≥ 26	12	9.39 (4.17–21.1)		
						Test for linear trend, $p < 0.001$		
				Latency (years)			Age, calendar period	Poisson regression analysis
				0–20	17	1.00		
				21–25	12	2.44 (1.09–5.45)		
				26–30	12	2.99 (1.26–7.09)		
				31–36	17	5.58 (2.34–13.3)		
				≥ 37	12	6.20 (2.30–16.7)		
						Test for linear trend, $p < 0.001$		

Table 5 (contd)

Name of study Reference, location	Cohort description	Exposure assessment	Type of cancer (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Ward *et al*. (2001) (contd)				*Cumulative exposure (ppm–years)*				
				0–734	13	1.00		
				735–2379	12	3.97 (1.81–8.71)		
				2380–5188	15	7.55 (3.57–15.9)		
				5189–7531	13	14.0 (6.43–30.7)		
				≥ 7532	15	28.27 (12.84–62.25)		
						Test for linear trend, $p < 0.001$		
				Autoclave workers				
				Never	22	1.00		
				Ever	38	6.61 (3.90–11.2)		
				Unknown	11	5.43 (2.63–11.2)		
			ASL	*Duration (years)*				
				1–9	7	1.00		
				10–16	8	3.01 (1.06–8.54)		
				17–20	2	2.04 (0.41–10.3)		
				21–25	12	15.7 (5.60–44.0)		
				≥ 26	8	19.67 (6.28–61.59)		
						Trend test, $p < 0.001$		
				Latency (years)			Age, calendar period	Poisson regression analysis
				0–20	10	1.00		
				21–25	6	2.77 (0.89–8.69)		
				26–30	7	4.80 (1.47–15.7)		
				31–36	10	10.38 (3.09–34.9)		
				≥ 37	4	7.99 (1.71–37.3)		
						Trend test, $p < 0.001$		

Table 5 (contd)

Name of study Reference, location	Cohort description	Exposure assessment	Type of cancer (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Ward *et al*. (2001) (contd)				*Cumulative exposure (ppm–years)*				
				0–734	4	1.00		
				735–2379	6	6.56 (1.85–23.3)		
				2380–5188	8	13.6 (4.05–45.5)		
				5189–7531	7	28.0 (8.00–98.2)		
				≥ 7532	12	88.2 (26.4–295)		
						Trend test, $p < 0.001$		
				Autoclave workers				
				Never	4	1.0		
				Ever	26	25.5 (8.86–73.2)		
				Unknown	7	19.3 (5.66–66.2)		
			HCC	*Duration (years)*				
				1–9	1	1.0		
				10–16	3	6.94 (0.71–67.5)		
				17–20	2	12.6 (1.11–143)		
				21–25	1	7.34 (0.44–122)		
				≥ 26	3	35.5 (3.34–377)		
						Trend test, $p = 0.002$		
				Latency (years)			Age, calendar period	Poisson regression analysis
				< 26	2	1.00		
				26–30	1	3.72 (0.29–48.3)		
				31–36	3	15.9 (1.86–135)		
				≥ 37	4	35.7 (3.56–359)		
						Trend test, $p = 0.001$		

Table 5 (contd)

Name of study Reference, location	Cohort description	Exposure assessment	Type of cancer (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Ward *et al*. (2001) (contd)				*Cumulative exposure (ppm–years)*				
				0–734	3	1.0		
				735–2379	2	3.02 (0.50–18.1)		
				2380–5188	1	2.47 (0.26–23.9)		
				5189–7531	1	5.33 (0.54–52.5)		
				≥ 7532	2	20.27 (2.98–138)		
						Trend test, $p = 0.004$		
				Autoclave worker				
				Never	5	1.0		
				Ever	4	2.97 (0.80–11.1)		
				Unknown	1	2.04 (0.24–17.4)		
Gennaro *et al*.. (2003), Porto Marghera, Italy	1658 male workers employed in 1956–85; mortality follow-up, 1973–95	JEM	Liver cancer (ICD-9 155)	Autoclave workers	4	9.57 (1.69–54.1)	Age, calendar time, duration, latency	Internal comparison ; 'job title groups' versus other workers
				PVC baggers	4	3.44 (0.62–18.97)		
				Autoclave + PVC baggers + compound	9	4.08 (0.85–19.57)		
Pirastu *et al*. (2003), Porto Marghera, Italy	1658 male workers employed in 1956–99; mortality follow-up, 1973–99; vital status, 100%; cause of death, 99%	JEMs: job- and time-specific VCM estimates (ppm); ever/never autoclave worker	Primary liver cancer (ICD-9 155.0)		17	**SMR** 2.78 (1.86–4.14)[a]		Reference rates: regional
				Autoclave worker: ever/never		**Relative risk** 4.4 (1.9–10.0)[a]	Age, calendar time, latency	Internal comparison of rates

Table 5 (contd)

Name of study Reference, location	Cohort description	Exposure assessment	Type of cancer (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Pirastu *et al.* (2003) (contd)			ASL	Autoclave worker: ever/never	6	21.1 (3.5–128.7)[a]	Age, calendar time, latency	Best available clinical and pathological data; internal comparison of rates
			HCC	Autoclave worker: ever/never	12	3.5 (1.4–9.2)[a]		
			HCC and ASL	*Cumulative exposure (ppm–years)*		**Rate (× 100 000)**		
				0–735	3	10.0		
				735–2379	1	18.6		
				2379–5188	7	191.7		
				5188–7531	1	62.8		
				7531–9400	0	χ^2 14.52 Trend test, $p < 0.001$		
Other studies								
Thériault & Allard (1981), Québec, Canada	451 male workers exposed to VCM for ≥ 5 years in a polymerization plant, employed in 1948–72; mortality follow-up, 1948–77	JEM	Digestive tract cancer (ICD-7 150–159)		14 (6 deaths from liver cancer)	6.25 (2.69–14.52)		Reference rates: Canadian population in 1971; comparison population: 870 workers not exposed to VCM for ≥ 5 months

Table 5 (contd)

Name of study Reference, location	Cohort description	Exposure assessment	Type of cancer (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Weber *et al*. (1981), Germany	7021 male VCM/PVC production workers from beginning of operation to 1974; mortality follow-up, from beginning of operation to 1974; vital status, > 90%; cause of death, 7–13%	JEM	Malignant tumour of the liver (ICD-8 155)		**12**	**SMR** 15.23		Reference rates: national
				Duration of exposure (months)				
				< 12	0	–		
				13–60	2	8.74		
				61–120	3	15.25		
				≥ 121	7	25.28		
Smulevich *et al*. (1988), former Soviet Union	3232 (2195 men, 1037 women) VCM/PVC production workers employed for ≥ 1 month in VCM-exposed jobs; mortality follow-up, 1939–77	Exposure data in 1953–66 from JEM	Malignant liver neoplasm (ICD-8 155)	Estimated area exposure: low, medium and high	0			City (Gorki) mean death rates in 1959, 1969 and 1975

Table 5 (contd)

Name of study Reference, location	Cohort description	Exposure assessment	Type of cancer (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Laplanche *et al*. (1992), France	1100 VCM-exposed and 1100 unexposed subjects; matched on age, plant, physician, aged 40–55 years, identified in 1980; mortality and morbidity follow-up, 1980–88	JEM	Liver cancer (ICD-9 155)		3 exposed 0 unexposed	NR		Prospective study
Du & Wang (1998), Taiwan, China	2224 workers with occupational exposure to VCM; controls were optical or motor cycle equipment workers.		Liver cancer (ICD-9 155)	VCM versus optical workers VCM versus motor cycle workers		4.5 (1.5–13.3) 6.5 (2.3–18.4)		

Table 5 (contd)

Name of study Reference, location	Cohort description	Exposure assessment	Type of cancer (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Wong, O. et al. (2002); Wong et al. (2003a), Taiwan, China	3293 male workers in 6 PVC polymerization plants exposed to VCM ≥ 1 year in 1950–92; mortality follow-up, 1985–97; vital status, 99%		Malignant neoplasm of the liver (ICD-9 155)		25	**SMR** 1.78 (1.15–2.62)		Reference rates, national; cohort assembled from records of Labour Insurance Bureau
				Duration of exposure (years)				
				< 10	13	2.45 (1.30–4.19)		
				10–19	10	1.76 (0.84–3.24)		
				≥ 20	2	– (3.2 exp.)		
				Latency (years)				
				< 15	8	1.29 (0.56–2.54)		
				15–24	7	1.46 (0.58–3.61)		
				≥ 25	10	3.13 (1.50–5.75)		
				First exposure (year)				
				≤ 1970	11	4.82 (2.41–8.63)		
				1970–79	8	1.92 (0.83–3.79)		
				After 1980	6	0.78 (0.28–1.69)		
				Age at first exposure (years)				
				< 30	10	2.24 (1.07–4.12)		
				30–39	6	1.78 (0.65–3.88)		
				≥ 40	9	1.43 (0.65–2.71)		
						Odds ratio		
			HCC	Tank cleaners		2.9 (1.1–7.3)		

ASL, angiosarcoma of the liver; CI, confidence interval; exp., expected; HCC, hepatocellular carcinoma; ICD, International Classification of Diseases; JEM, job–exposure matrix; SIR, standardized incidence ratio; SMR, standardized mortality ratio

[a] 90% confidence interval

(b) European studies

In the European multicentric cohort study of workers in the vinyl chloride industry, an increase in the incidence of primary liver cancer was observed (53 deaths and 29 incident cases; SMR, 2.40; 95% CI, 1.80–3.14; SIR, 3.98; 95% CI, 2.67–5.72) using national mortality and incidence rates as the reference. On the basis of the best available data for diagnosis, 71 cases of liver cancer were identified and used in the internal analysis for latency, duration of employment, cumulative exposure and employment as an autoclave cleaner. The risk increased with increasing duration and latency of employment with a significant trend (for both latency and duration, $p < 0.001$). For durations of exposure of 10–16, 17–20, 21–25 and ≥ 26 years (1–9 years as the reference), the relative risks for liver cancer were 2.58 (95% CI, 1.28–5.24), 3.48 (95% CI, 1.49–8.15), 8.21 (95% CI, 3.98–16.9) and 9.39 (95% CI, 4.17–21.1), respectively. For latencies of 21–25, 26–30, 31–36 and ≥ 37 years (0–20 years as reference), the relative risks were 2.44 (95% CI, 1.09–5.45), 2.99 (95% CI, 1.26–7.09), 5.58 (95% CI, 2.34–13.3) and 6.20 (95% CI, 2.30–16.7), respectively. The trend was also significant for cumulative exposure ($p < 0.001$); the risk was almost four times that for the reference category (0–734 ppm–years) starting with cumulative exposures of 735–1379 ppm–years (relative risk, 3.97; 95% CI, 1.81–8.71); for 2380–5188, 5189–7531 and ≥ 7532 ppm–years, the relative risks were 7.55 (95% CI, 3.57–15.9), 14.0 (95% CI, 6.43–30.7) and 28.27 (95% CI, 12.84–62.25), respectively. Analysis of the exposure–response trends at low doses (defined as < 1500 ppm–years and thus including 20 cases of liver cancer) yielded a relative risk of 2.0 (95% CI, 1.3–3.0) for one logarithmic unit of cumulative dose. From the best available data for diagnosis, 37 cases of angiosarcoma were ascertained for which a significant increasing trend ($p < 0.001$) was observed for latency, duration of exposure and cumulative exposure; for ever versus never autoclave cleaners, the relative risk was 25.5 (95% CI, 8.86–73.2). Ten cases of hepatocellular carcinoma were also used in the internal analysis. For latency and duration of exposure, the trend in risk was significant ($p = 0.001$ and $p = 0.002$, respectively); the risk was also significant for 7532 ppm–years of cumulative exposure (relative risk, 20.27; 95% CI, 2.98–137.71; $p = 0.004$); for ever versus never having been an autoclave cleaner, the relative risk was 2.97 (95% CI, 0.80–11.1).

In the study of the Porto Marghera plant in Italy (Pirastu *et al.*, 2003), mortality from primary liver cancer was higher than that expected from regional rates (SMR, 2.78; 90% CI, 1.86–4.14). In an internal comparison, death rates for primary liver cancer with latencies of 10–30 years (26.1/100 000) and ≥ 30 years (160.7/100 000) were higher than those for the reference (latency ≤ 10 years). In the internal analysis for employment as an autoclave worker (ever/never), the relative risk was 4.4 (90% CI, 1.9–10.0); a significant increasing trend was seen for increasing cumulative estimated exposure ($p < 0.001$). The analyses of rates for both liver angiosarcoma (six cases) and hepatocellular carcinoma (12 cases) showed that longer latency implied higher rates; employment as an autoclave worker (ever/never) was associated with an increased risk for both angiosarcoma (relative risk, 21.1; 90% CI, 3.5–

128.7) and hepatocellular carcinoma (relative risk, 3.5; 90% CI, 1.4–9.2); for both histotypes, there was a significant increasing trend with increasing estimated exposure ($p < 0.001$).

In the same plant (Porto Marghera), an analysis that used internal reference groups (Gennaro *et al*., 2003) showed that the relative risk for mortality from liver cancer of autoclave workers versus all other workers was 9.57 (four deaths; 95% CI, 1.69–54.1); for two job title groups, 'compound workers' and 'compound + autoclave + PVC bagger workers', the relative risks were 3.44 (four deaths; 95% CI, 0.62–18.97) and 4.08 (nine deaths; 95% CI, 0.85–19.57), respectively.

(c) Other studies

In the Canadian cohort study (Thériault & Allard, 1981), histopathological confirmation was available from medical files at the hospitals for 19 of 20 causes of death from cancer: eight were angiosarcomas of the liver. Two more angiosarcomas of the liver were notified as cirrhosis on the death certificate and were considered as such throughout this study. In comparison with an unexposed cohort, the relative risk for digestive cancers (ICD codes 150–159) was 6.25 (14 observed deaths; 95% CI, 2.69–14.52). [No relative risks for more specific cancer sites were given.]

In the study by Weber *et al*. (1981), the SMRs for liver cancer by duration of exposure for < 12 months, 13–60 months, 61–120 months and > 121 months were 0, 8.74 (two deaths), 15.25 (three deaths) and 25.28 (seven deaths), respectively. [The Working Group noted that an increased mortality from liver cancer was briefly described in a cohort of PVC processing workers. This cohort probably included the data of Frentzel-Beyme *et al*. (1978).]

No deaths from liver cancer were reported in PVC plants in the former Soviet Union (Smulevich *et al*., 1988).

In the French study (Laplanche *et al*., 1992), three angiosarcomas of the liver and three liver cancers were observed among the exposed workers compared with none in the unexposed [no relative risk estimates given].

In a proportionate morbidity study in Taiwan, China (Du & Wang, 1998), an excess of primary liver cancer was noted (morbidity odds ratio, 4.5 or 6.5, depending on the comparison group).

In a retrospective cohort study of mortality in Taiwan, China (Wong, O. *et al*., 2002), the risk for liver cancer decreased with duration of exposure; the authors suggested that this might be attributable to a higher turnover of workers in jobs that entailed high exposures or because workers with illnesses retired early. The excess mortality from liver cancer was most pronounced among workers who began employment before 1970 (SMR, 4.82; 95% CI, 2.41–8.63), when, according to the authors, exposures to VCM were higher, because permissible exposure limits for VCM were not established in Taiwan until 1981. The excess mortality from liver cancer was found to increase with time since first exposure and to reach a peak after more than 25 years (SMR, 3.13; 95% CI, 1.50–5.75). It was also found to be inversely related to age at first exposure; workers who were

under 30 years of age at first exposure demonstrated the highest risk (SMR, 2.24; 95% CI, 1.07–4.12).

A study of risk factors for hepatocellular carcinoma that was conducted in Taiwan, China (Wong *et al*., 2003a), reported an odds ratio of 15.7 (95% CI, 3.6–68.4) for HBsAg status. An odds ratio of 3.6 (95% CI, 1.4–9.2) was estimated for jobs that entailed high exposure to VCM; for tank cleaners specifically, the odds ratio was 2.9 (95% CI, 1.1–7.3). [The Working Group noted that, due to problems in the methodology of this study, the results were not considered to be useful for the evaluation of the potential relationship between exposure to vinyl chloride and hepatocellular carcinoma. These methodological problems included lack of histological confirmation for the majority of cases of hepatocellular carcinoma, the resulting potential that some of the cases were truly angiosarcomas, lack of detail in the methodology for selection of controls and exclusion of individuals with evidence of liver disease from the control group.]

[The Working Group considered that the evidence that exposure to VCM is associated with cirrhosis of the liver supports the likelihood that exposure to vinyl chloride increases the risk for hepatocellular carcinoma, although relative risks for hepatocellular carcinoma are smaller than those associated with angiosarcoma of the liver. Inflammatory and regenerative processes associated with HBV and hepatitis C viral infection and chronic alcoholism are considered to be an important pathway through which the risk for hepatocellular carcinoma is increased by these exposures in the general population.]

(d) Meta-analysis

In meta-analysis of cohort studies of vinyl chloride (Boffetta *et al*., 2003), duration of employment was available in three studies (Weber *et al*., 1981; Mundt *et al*., 2000; Ward *et al*., 2001): in the two multicentric investigations (Mundt *et al*., 2000; Ward *et al*., 2001), an increase in mortality from liver cancer was evident beginning at durations of ≥ 7 years and up to 25 years whereas, in the German study (Weber *et al*., 1981), a sharp increase was found starting from 13–16 years of duration of exposure. Mortality from liver cancer by year of first employment was increased in the two multicentric studies (Mundt *et al*., 2000; Ward *et al*., 2001). [Adjustment for time since first employment would be advisable; the lack of adjustment could be misleading, as a very strong decrease in risk over calendar time was shown, while more recently exposed workers had not completed the latency time necessary for liver cancer to be expressed.]

2.3.2 *Case–control studies* (Table 6)

A case–control analysis of 23 liver angiosarcomas was conducted at the plant in Louisville, KY (USA), and confirmed a strong and significant association with exposure to vinyl chloride and PVC (exposure to vinyl chloride, $p < 0.001$; exposure to PVC, $p = 0.003$); in a case–cohort analysis that used exposure estimated on the basis of a six-point ranking scale of chemicals present in the plant, cases of angiosarcoma had significantly greater exposure to vinyl chloride than the reference cohort (Lewis & Rempala, 2003).

Table 6. Case–control studies of liver cancer in vinyl chloride monomer (VCM) and polyvinyl chloride (PVC) production workers

Reference, location	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Lewis & Rempala (2003), Louisville, KY, USA	ASL	23 men; histologically confirmed	Matched by year of birth and duration of employment		CERM	Logistic regression analysis showed strong, highly significant association with exposure to VC ($p < 0.001$) and PVC ($p = 0.003$)		In Lewis *et al*. (2003), 28 ASL reported
			1817 white men hired before 1967 who had worked at least 1 year		CERM	ASL cases had significantly greater exposure to VC (69.9% > 1000 VC–CERM)		
Wong *et al*. (2003a), Taiwan, China	Liver cancer; HCC	18 men; 5 histologically confirmed; 5 AFP > 1000 µg/L + at least one positive image from angiography, sonography, liver scan and/or CT; 8 from clinical manifestation and imaging studies	68 randomly selected from a pool of eligible workers; matched on age and specific plant employment	Job titles; high VCM-exposure jobs: tank cleaning, unloading PVC, adding catalyst; HBsAg status from medical surveillance records	History of high-exposure job HBsAg-positive versus HBsAg-negative status History of tank cleaning versus no history	2.9 (1.1–7.3) 15.7 (3.6–68.4) 3.6 (1.4–9.2)		Nested case–control; for deceased individuals, validation of exposure by next of kin versus co-workers and industrial hygienist

Table 6 (contd)

Reference, location	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Wong *et al.* (2003a) (contd)					HBsAg-positive status and history of tank cleaning	4.0 (0.2–69.1)	Family history of chronic liver disease	Reference: HBsAg-negative status and no history of tank cleaning
					HBsAg-negative status and history of tank cleaning	396 (22.6–∞)		
					HBsAg-positive status and no history of tank cleaning	25.7 (2.9–229.4)		
					HBsAg-negative status and history of high exposure job	2.9 (0.2–50.0)		
					HBsAg-positive status and history of high exposure job	184.5 (15.0–∞)		
					HBsAg–positive status and no history of high exposure job	26.1 (2.9–235.1)		

Table 6 (contd)

Reference, location	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Mastrangelo *et al.* (2004), Porto Marghera, Italy	HCC	13 men; 8 histologically confirmed; 5 focal hepatic lesions at sonography + AFP > 400 μg/L	139 workers with no clinical or biochemical evidence of chronic liver disease or cancer at any site from medical surveillance in 1999–2002	JEMs, job- and time-specific VCM estimates (ppm); information for cases from company files, from medical surveillance data for controls; alcoholic beverage consumption from hospital/clinical records and surveillance data; serological markers for HBsAg and anti-HCV antibodies	*Cumulative VCM exposure (ppm–years)* < 500 500–2500 > 2500	 Reference 6.32 (0.48–336) 29.3 (3.61–1298)		Nested case–control
					< 2500/alcohol < 60 g/day > 2500/alcohol < 60 g/day < 2500/alcohol > 60 g/day > 2500/alcohol > 60 g/day	Reference 18.8 (1.62–218.0) 42.9 (3.41–540.0) 409 (19.6–8553.0)	Adjusted for age, hepatitis infection	Odds ratio in univariate analysis
					< 2500/HBsAg/HCV-negative > 2500/HBsAg/HCV-negative < 2500/HBsAg/HCV-positive > 2500/HBsAg/HCV-positive	Reference 25.0 (2.77–226.0) 106.9 (4.43–2578.0) 210.3 (7.13–6203.0)	Age, alcoholic beverage consumption	

AFP, α-fetoprotein; ASL, angiosarcoma of the liver; CERM, cumulative exposure rank months; CI, confidence interval; CT, computed tomography; HBsAg, hepatitis B virus surface antigen; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICD, International Classification of Diseases; JEM, job–exposure matrix; VC, vinyl chloride

In the case–control study of cases of liver cancer nested in the cohort in Taiwan, China (Wong *et al.*, 2003a), tobacco smoking, alcoholic beverage consumption and familial history of chronic liver disease were not found to be associated with liver cancer, which may be attributed to the low prevalence of these risk factors in the study population.

A history of employment in a high-exposure job was associated with an increased risk of 2.9 (95% CI, 1.1–7.3). A strong association was observed with HBsAg (odds ratio, 15.7; 95% CI, 3.6–68.4) or a history of tank cleaning (odds ratio, 3.6; 95% CI, 1.4–9.2). Models were also fitted that included both HBsAg and a history of tank cleaning, and a parameter for the potential interaction between the two. Strong evidence for an interaction between HBsAg and a history of tank cleaning was observed in this model; a history of tank cleaning and HBsAg negativity had an odds ratio of 4.0 (95% CI, 0.2–69.1), HBsAg positivity and no history of tank cleaning had an odds ratio of 25.7 (95% CI, 2.9–229.4) and combined HBsAg positivity and a history of tank cleaning had an odds ratio of 396 (95 % CI, 22.6–∞). Similar results were observed when the analysis was based on a history of high exposure to VCM rather than a history of tank cleaning. [The Working Group was concerned that the method used to select controls may have biased the study. The age at which controls were matched to cases was not clear. Of greater concern is that the controls were restricted to individuals who had no history of chronic liver disease. This may have biased the study towards the null since this restriction was not applied to the cases.]

A cross-sectional study of hepatocellular carcinoma in the Porto Marghera (Italy) cohort (Mastrangelo *et al.*, 2004) found an association between exposure to VCM and both liver cirrhosis and hepatocellular carcinoma. The odds ratio for cumulative exposure to VCM of > 2500 ppm × year was 29.3 (95% CI, 3.61–1298). Odds ratios tended to be higher for those subjects who were exposed to multiple risk factors. For example, the odds ratio for exposure to > 2500 ppm × year and consumption of > 60 g per day of alcohol was 409 (95% CI, 19.6–8553). These analyses controlled for age and hepatitis viral infection. Similar patterns were seen in analyses of the relationship between exposure to VCM and HBV/hepatitis C viral infection that controlled for alcoholic beverage consumption. [The Working Group noted that the methodology used to select controls for this analysis, which excluded individuals who had liver cirrhosis, may have resulted in a positive bias in the relative risk estimates.]

2.4 Cancer of the brain and central nervous system

2.4.1 *Cohort studies* (Table 7)

(a) North American multicentric study

An update of the North American multicentric study found an overall SMR for cancer of the brain and central nervous system of 1.42 (36 exposed deaths; 95% CI, 1.00–1.97) (Mundt *et al.*, 2000). There was no apparent trend with increasing duration of exposure (9 observed deaths; hazard ratio, 1.9; 95% CI, 0.8–5.0). The risk for brain cancer was

Table 7. Cohort studies of brain cancer in vinyl chloride monomer (VCM) and polyvinyl chloride (PVC) production workers

Name of study Reference, location	Cohort description	Exposure assessment	Type of cancer (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
North American multicentric study								
Mundt *et al*. (2000), USA	10 109 white male workers employed in 37 plants ≥ 1 year in jobs that entailed exposure to VCM in 1942–72; mortality follow–up, 1942–95; vital status, 96.8%; cause of death, 99%	JEM	Brain and CNS (ICD-9 191–192)	Job exposed to VC	36	**SMR** 1.4 (1.0–2.0)	Age at first exposure, duration of exposure, year of first exposure	Reference rates: state rates and USA population *p* value for likelihood ratio test for equality of survivor functions, controlling for time at risk
				Age at first exposure (years)		**Hazard ratio**		
				< 25	11	1.0		
				25–34	12	0.9 (0.4–2.0)		
				≥ 35	13	2.6 (1.2–5.9) *p* = 0.02		
				Duration of exposure (years)				
				< 5	11	1.0		
				5–9	11	2.0 (0.9–4.7)		
				10–19	5	0.7 (0.2–2.0)		
				≥ 20	9	1.9 (0.8–5.0) *p* = 0.09		

Table 7 (contd)

Name of study Reference, location	Cohort description	Exposure assessment	Type of cancer (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
European multicentric study								
Ward *et al.* (2000, 2001), Italy, Norway, Sweden, United Kingdom	12 700 male workers employed in 19 VCM/PVC plants ≥ 1 year in 1950–85; mortality follow-up, 1955–97; incidence follow-up, 1955–96	Calendar period JEM for 13/19 factories grouped in 22 broad categories; factory-specific JEM with validated exposure estimates (ppm)	Brain and CNS (ICD-9 191–192)			**SMR**		Reference rates: national
				Employed in VC industry (full cohort)	24	0.93 (0.60–1.39)		
						SIR		Reference incidence rates: national
					19	0.91 (0.55–1.42)		
						SMR	Age, calendar period	
				VCM production only	0	0.00 (0.00–5.64)		
				PVC production only	5	0.96 (0.31–2.25)		
				VCM and PVC production	16	0.93 (0.53–1.51)		
				PVC processing	18	1.10 (0.23–3.22)		
				Latency (years)		**Relative risk**	Age, calendar period	Poisson regression analysis
				< 16	9	1.00		
				16–21	4	0.71 (0.19–2.68)		
				22–26	3	0.71 (0.16–3.29)		
				27–34	6	1.37 (0.33–5.63)		
				≥ 35	2	0.77 (0.11–5.47)		
						Test for linear trend, $p = 0.82$		
				Duration (years)				
				1–2	5	1.00		
				3–6	6	1.34 (0.41–4.40)		
				7–11	4	0.95 (0.25–3.57)		
				12–18	4	0.96 (0.25–3.69)		
				≥ 19 years	5	1.59 (0.43–5.91)		
						Test for linear trend, $p = 0.72$		

Table 7 (contd)

Name of study Reference, location	Cohort description	Exposure assessment	Type of cancer (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Ward *et al*. (2000, 2001) (contd)				*Cumulative exposure (ppm–years)*				
				0–34	3	1.00		
				35–99	3	1.37 (0.28–6.82)		
				100–535	10	3.45 (0.94–12.6)		
				536–2811	2	0.75 (0.12–4.50)		
				≥ 2812	3	1.58 (0.31–8.04)		
						Test for linear trend, $p = 0.778$		
				Autoclave worker				
				Never	17	1.00		
				Ever	5	1.08 (0.40–2.92)		
				Unknown	2	1.27 (0.29–5.49)		
Other studies								
Weber *et al*. (1981), Germany	7021 male VCM/PVC production workers from beginning of operation to 1974; mortality follow-up, from beginning of operation to 1974; vital status, > 90%; cause of death, 7–13%	JEM	Brain and CNS (ICD-8 191)	VCM/PVC production and processing	2	**SMR** 1.62 (NR)		Reference rates: national

Table 7 (contd)

Name of study Reference, location	Cohort description	Exposure assessment	Type of cancer (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Smulevich *et al*. (1988), former Soviet Union	3232 VCM/PVC production workers (2195 men, 1037 women) employed for ≥ 1 month in VCM-exposed jobs; mortality follow-up, 1939–77	Exposure data in 1953–66 from JEM	Brain and CNS (ICD-9 191–192)	Estimated area exposure: low, medium and high	4	**SMR** 1.54 (0.41–3.94)		City (Gorki) mean death rates in 1959, 1969 and 1975
Wong, O. *et al*. (2002), Taiwan, China	3293 male workers in 6 PVC polymerization plants exposed to VCM ≥ 1 year in 1950–92; mortality follow-up, 1985–97; vital status 99%	JEM	Brain and CNS (ICD-9 191–192)		2	**SMR** [2.86 (0.57–9.16)]		Reference rates, national; cohort assembled from records of the Labour Insurance Bureau

CI, confidence interval; CNS, central nervous system; ICD, International Classification of Diseases; JEM, job–exposure matrix; NR, not reported; SIR, standardized incidence ratio; SMR, standardized mortality ratio; VC, vinyl chloride

significantly increased with time since first exposure of ≥ 35 years (hazard ratio, 2.6; 95% CI, 1.2–5.9). The highest SMR was found for those first exposed before 1950 (SMR, 1.74; 95% CI, 0.97–2.88). Mortality from brain cancer was also in excess among subjects who had worked in plants that began production before 1946 (22 deaths; SMR, 1.77; 95% CI, 1.11–2.68).

(b) European multicentric study

An update of the European multicentric study found an overall SMR for brain cancer of 0.93 (24 observed deaths; 95% CI, 0.60–1.39); the SIR was 0.91 based on 19 cases (Ward *et al*., 2000, 2001). No trends in the SMRs were observed with respect to time since first employment, duration of employment, cumulative exposure or calendar period of hire. The risk for brain cancer among those who had ever been autoclave workers was similar to that of those who had never been autoclave workers. Poisson regression analyses of deaths from brain cancer found no significant trends with latency, duration of employment or cumulative exposure to vinyl chloride, although the rate ratio was elevated in the middle-dose category of cumulative dose (relative risk, 3.45; 95% CI, 0.94–12.6).

In the incidence analyses, significant excesses were found for the category of 27–35 years since first employment (eight observed deaths; SMR, 2.67; 95% CI, 1.15–5.27) and in the highest category of duration of employment (six observed deaths; SMR, 2.15; 95% CI, 0.79–4.68), but no apparent trend with cumulative exposure was observed (data not shown).

(c) Other studies

An SMR of 1.62 (based on two deaths) was reported in the historical cohort study of VCM/PVC production workers in Germany (Weber *et al*., 1981). The SMRs by duration of exposure of < 12 months, 13–16 months, 61–120 months and > 121 months were 0, 0, 3.50 (one death) and 2.78 (one death), respectively.

An SMR of 1.54 (four observed deaths) was reported in a Russian cohort of more than 3200 VCM/PVC production workers (Smulevich *et al.*, 1988). The SMR was 0.9 for men and 5 for women.

An SMR of 2.86 for brain cancer (based on two deaths) was reported in a cohort in Taiwan, China (Wong, O. *et al*., 2002).

(d) Meta-analysis

In the meta-analysis by Boffetta *et al*. (2003), the meta-SMR for brain cancer calculated from five studies was 1.26 (95% CI, 0.98–1.62). The authors noted that the increase in the meta-SMR was mainly due to the North American multicentric study (Mundt *et al.*, 2000) and that no trend with duration of exposure was found in either of the two large studies (Mundt *et al.*, 2000; Ward *et al.*, 2000).

2.4.2 *Case–control and case–cohort studies*

A case–cohort and matched case–control analysis of brain cancer was conducted at a polymer production plant included in the North American multicentric cohort (Lewis & Rempala, 2003) in which 15 of 36 deaths from brain cancer were identified. The SMR for brain cancer was 2.29 (95% CI, 1.29–3.81) at this facility and 1.12 (95% CI, 0.69–1.71) at all other plants combined (Lewis *et al*., 2003). Sixteen deaths from brain cancer from 1963 to 2000 were included in the case–cohort and case–control studies. The cases of brain cancer were slightly less likely than other cohort members to have worked in any PVC building (18.8% versus 26.5%, respectively), and slightly more likely to have worked in the building that manufactured nitrile rubber copolymers (31.3% versus 25.9%, respectively). In general, estimates of cumulative exposure to materials used in PVC production among cases of brain cancer were lower than those for other cohort members, while exposures to chemicals used in nitrile rubber production were similar. In the matched case–control analysis, no significant associations were observed between status of brain cancer case and any of the materials used in either PVC or nitrile rubber copolymer production.

2.5 Cancer of the lung and respiratory tract

2.5.1 *Lung cancer*

(a) Cohort studies (Table 8)

(i) *North American multicentric study*

In an update of the North American multicentric study (Mundt *et al*., 2000), there was no evidence of any association between employment with exposure to vinyl chloride and mortality from lung cancer overall (303 deaths; SMR, 0.82; 95% CI, 0.73–0.92), nor was there any pattern of association by year of first exposure or year at which production of vinyl chloride began. The authors noted that regional mortality rates for lung cancer, used as the primary referent rates in the analysis, were higher than those in the USA as a whole. The SMR for lung cancer based on national referent rates was 0.96 (95% CI, 0.86–2.07).

(ii) *European multicentric study*

An update of the European multicentric study found an overall SMR for lung cancer of 0.95 (272 cases; 95% CI, 0.84–1.07) and an SIR of 0.80 (154 deaths; 95% CI, 0.68–0.94). No association was observed between mortality from lung cancer and exposure to vinyl chloride, as estimated by ranked level of exposure, latency, duration of employment, cumulative exposure to vinyl chloride and ever/never employment as an autoclave worker (Ward *et al*., 2000, 2001). Non-significant associations were found for time since first employment, production or processing and duration of employment. In Poisson regression

Table 8. Cohort studies of lung cancer in vinyl chloride monomer (VCM) and polyvinyl chloride (PVC) production workers

Name of study Reference, location	Cohort description	Exposure assessment	Type of cancer (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
North American multicentric study								
Mundt *et al*. (2000), USA	10 109 white male workers employed at least ≥ 1 year in jobs that entailed exposure to VCM in 1942–72; mortality follow-up, 1942–95; vital status, 96.8%; cause of death, 99%	JEM	Trachea, bronchus and lung (ICD-9 162)	Job exposed to VC	303	**SMR** (state rates) 0.82 (0.73–0.92) **SMR** (national rates) 0.96 (0.86–2.07)		Reference rates: state rates and USA population
European multicentric study								
Ward *et al*. (2000, 2001), Italy, Norway, Sweden, United Kingdom	12 700 male workers employed in 19 VCM/PVC plants ≥ 1 year in 1950–85; mortality follow-up, 1955–97; incidence follow-up, 1955–96	Calendar period JEM for 13/19 factories grouped in 22 broad categories; factory-specific JEM with validated exposure estimates (ppm)	Trachea, bronchus and lung (ICD-9 162)	Employed in VC industry (full cohort)	272	**SMR** 0.95 (0.84–1.07)		Reference rates: national; incidence rates: national
					154	**SIR** 0.80 (0.68–0.94)		
				VCM production	14	**SMR** 1.47 (0.80–2.47)	Age, calendar period	
				PVC production	56	0.88 (0.67–1.15)		
				VCM and PVC production	184	0.91 (0.79–1.05)		
				PVC processing	18	1.43 (0.85–2.26)		

Table 8 (contd)

Name of study Reference, location	Cohort description	Exposure assessment	Type of cancer (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Ward *et al*. (2000, 2001) (contd)				*Latency (years)*		**Relative risk**	Age, calendar period	Poisson regression analysis
				< 16	57	1.00		
				16–21	55	0.96 (0.65–1.41)		
				22–26	66	1.21 (0.82–1.78)		
				27–34	54	0.73 (0.48–1.11)		
				≥ 35	40	0.76 (0.47–1.25)		
						Test for linear trend, p = 0.119		
				Duration (years)				
				1–2	57	1.00		
				3–6	55	1.12 (0.76–1.64)		
				7–11	66	1.31 (0.91–1.88)		
				12–18	54	0.89 (0.60–1.30)		
				≥ 19 years	40	0.77 (0.52–1.15)		
						Test for linear trend, p = 0.094		
				Cumulative exposure (ppm–years)				
				0–34	52	1.00		
				35–99	52	1.11 (0.75–1.62)		
				100–535	55	0.90 (0.62–1.32)		
				536–2811	46	0.85 (0.57–1.27)		
				≥ 2812	43	0.84 (0.56–1.26)		
						Test for linear trend, p = 0.190		

Table 8 (contd)

Name of study Reference, location	Cohort description	Exposure assessment	Type of cancer (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Ward *et al*. (2000, 2001) (contd)				*Autoclave worker*				
				Never	220	1.00		
				Ever	44	0.84 (0.61–1.16)		
				Unknown	8	0.38 (0.19–0.77)		
				Cumulative exposure (ppm–years)				
				Ever employed as packers and baggers				
				0–34	9	1.12 (0.51–2.13)		
				35–99	9	0.99 (0.45–1.88)		
				100–535	14	1.08 (0.59–1.82)		
				536–2811	9	0.85 (0.39–1.60)		
				≥ 2812	10	1.02 (0.49–1.88)		
				Never employed as packers and baggers				
				0–34	43	0.98 (0.71–1.33)		
				35–99	43	1.09 (0.79–1.46)		
				100–535	41	0.83 (0.60–1.13)		
				536–2811	37	0.86 (0.60–1.18)		
				≥ 2812	33	0.87 (0.60–1.23)		
				Only employed as packers and baggers				
				0–34	5	0.88 (0.28–2.04)		
				35–99	6	1.28 (0.47–2.78)		
				100–535	11	1.63 (0.81–2.92)		
				536–2811	4	1.37 (0.37–3.52)		
				≥ 2812	4	3.12 (0.85–8.00)		
						Test for trend χ^2, $p = 0.009$		

Table 8 (contd)

Name of study Reference, location	Cohort description	Exposure assessment	Type of cancer (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Pirastu *et al.* (2003), Porto Marghera, Italy	1658 male workers employed in 1956–99; mortality follow–up, 1973–99; vital status, 100%; cause of death, 99%	JEMs, job- and time-specific VCM estimates (ppm); ever/never autoclave worker	Lung cancer (ICD-9 162.1–162.9)	Full cohort Only versus never baggers	40 7 7	**SMR** 0.83 (0.64–1.07)[a] 1.73 (0.93–3.21) **SMR** 2.31 (1.15–4.61)[a]	 Not adjusted Latency	Reference rates: regional Internal comparison versus never baggers
Other studies								
Thériault & Allard (1981), Québec, Canada	451 male workers exposed to VCM for ≥ 5 years in a polymerization plant, employed in 1948–72; mortality follow-up, 1948–77	Questionnaire to the worker or next of kin on detailed occupational history	Trachea, bronchus and lung (ICD-9 162)	Exposed to VCM	2	**SMR** 0.34 (0.04–1.25)		Reference rates: Canadian population in 1971; comparison population: 870 workers not exposed to VCM for ≥ 5 months
Smulevich *et al.* (1988), former Soviet Union	3232 VCM/PVC production workers (2195 men, 1037 women) employed for ≥ 1 month in VCM-exposed jobs; mortality follow-up, 1939–77	Exposure data in 1953–66 from JEM	Trachea, bronchus and lung (ICD-9 162)	Estimated area exposure: low, medium and high	17	**SMR** 1.39 (0.81–2.23)		City (Gorki) mean death rates in 1959, 1969 and 1975

Table 8 (contd)

Name of study Reference, location	Cohort description	Exposure assessment	Type of cancer (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Laplanche *et al*. (1992), France	1100 VCM–exposed and 1100 unexposed subjects; matched on age, plant, physician, aged 40–55 years, identified in 1980; mortality and morbidity follow-up, 1980–88	JEM	Trachea, bronchus and lung (ICD-9 162)		6 among exposed; 2 among un-exposed	NR		Prospective study
Wong, O. *et al*. (2002), Taiwan, China	3293 male workers in 6 PVC polymerization plants exposed to VCM ≥ 1 year in 1950–92; mortality follow–up, 1985–97; vital status 99%	JEM	Trachea, bronchus and lung (ICD-9 162)		4	**SMR** 0.59 (0.16-1.52)		Reference rates: national; cohort enumerated from records of the Labour Insurance Bureau

CI, confidence interval; ICD, International Classification of Diseases; JEM, job–exposure matrix; NR, not reported; SIR, standardized incidence ratio; SMR, standardized mortality ratio; VC, vinyl chloride

[a] 90% confidence interval

analyses, non-significant negative trends were observed with increasing cumulative exposure.

A possible association between exposure to PVC dust and lung cancer was suggested by several early studies as well as recent investigations of PVC baggers in a VCM/PVC manufacturing plant in Italy (Pirastu *et al*., 1998; Mastrangelo *et al*., 2003). Therefore, packers and baggers were examined separately in the European multicentric cohort study. No trend in risk was observed with increasing cumulative exposure for those who had ever been employed as packers and baggers, among whom 53 deaths from lung cancer occurred (Ward *et al*., 2000). However, among individuals who only worked as packers and baggers, 30 deaths from lung cancer occurred, and the trend with increasing cumulative exposure was statistically significant.

In the cohort of 1658 vinyl chloride workers in Porto Marghera (Pirastu *et al*., 2003), an SMR for lung cancer of 1.73 (seven deaths; 90% CI, 0.93–3.21) was observed among 'only baggers'; the SMR for 'only baggers' versus 'never baggers' adjusted for latency was 2.31 (90% CI, 1.15–4.61; $p = 0.047$).

(iii) *Other studies*

In a Canadian cohort, an SMR of 0.34 (95% CI, 0.04–1.25) was reported for cancer of the lung, trachea or bronchus (Thériault & Allard, 1981).

A study in the former Soviet Union (Smulevich *et al.*, 1988) showed an SMR of 1.39 (17 observed deaths; 95% CI, 0.81–2.23) for lung cancer and a cohort study in France (LaPlanche *et al*., 1992) reported eight observed deaths from lung cancer but did not include risk estimates.

A study in Taiwan, China, reported an SMR of 0.59 (four observed deaths) for lung cancer (Wong, O. *et al*., 2002).

(iv) *Meta-analysis*

The meta-analysis by Boffetta *et al*. (2003) showed a meta-SMR for lung cancer of 0.90 (95% CI, 0.77–1.06) based on five studies.

(b) Case–control studies (Table 9)

In a nested case–control study in Porto Marghera, Italy, risk factors for lung cancer were examined among 38 subjects who had lung cancer and 224 subjects with no history of cancer (Mastrangelo *et al*., 2003). Although no association was observed between estimated cumulative exposure to VCM and lung cancer, the odds ratio for exposure to PVC dust among baggers with known length of exposure was 5.60 (95% CI, 2.03–16.3). When stratified by duration of work as a bagger, the odds ratio was 2.87 (95% CI, 0.84–8.56) among those who were employed for < 3.6 years and 7.15 (95% CI, 2.55–19.3) among those employed for > 3.6 years. Although the quantity of cigarettes smoked per day was associated with lung cancer, this did not appear to confound the association between lung cancer and work as a bagger.

Table 9. Case–control studies of lung cancer in vinyl chloride monomer (VCM) and polyvinyl chloride (PVC) production workers

Reference, location	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure category	No. of cases/controls	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Mastrangelo *et al.* (2003), Italy	Trachea, bronchus and lung (ICD-9 162)	38 histologically confirmed lung cancers	228 with no history of cancer	Facility-specific JEM	*Cumulative exposure to VCM (ppm–years)*			Smoking habits in relation to years of work as a bagger	Italian cohort of 1658 vinyl chloride workers; nested case–control
					≤ 392	16/71	1.00		
					393–1650	13/74	0.78 (0.32–1.87)		
					≥ 1651	9/79	0.51 (0.18–1.31)		
							χ^2 trend $p > 0.01$		
					Circumstances of exposure to PVC dust				
					None	8/87	1.00		
					PVC compounding	8/49	1.78 (0.54–5.78)		
					Baggers (unknown length)	5/55	0.99 (0.24–3.63)		
					Baggers (known length)	17/33	5.60 (2.03–16.3)		
					PVC compounding				
					None	30/175	1.00		
					≤ 8.0 years	4/23	1.10 (0.24–3.28)		
					> 8.0 years	4/26	0.90 (0.21–2.86)		

Table 9 (contd)

Reference, location	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure category	No. of cases/controls	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Mastrangelo *et al.* (2003) (contd)					**Baggers**				Nested case–control
					Duration of job				
					None	21/191	1.00		
					< 3.6 years	6/19	2.87 (0.84–8.56)		
					≥ 3.6 years	11/14	7.51 (2.55–19.3)		
					Calendar year of onset				
					None	21/191	1.00		
					Before 1967	10/19	4.79 (1.73–12.5)		
					Since 1967 onwards	7/14	4.55 (1.38–13.6)		
					Age at onset				
					No	21/191	1.00		
					≤ 33 years	6/20	2.73 (0.80–8.07)		
					> 33 years	11/13	7.70 (2.72–21.1)		
					Length of time elapsed from onset of job to end of follow-up or death				
					None	21/191	1.00		
					20 years	12/29	3.76 (1.51–8.99)		
					≤ 20 years	5/4	11.4 (2.21–60.7)		

Table 9 (contd)

Reference, location	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure category	No. of cases/controls	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Scélo *et al*. (2004), seven European countries	Trachea, bronchus and lung (ICD-9 162)	2861 lung cancers in 1998–2002	3118 (excluded hospital patients admitted for tobacco-related diseases)	For each job held, local experts assessed intensity and frequency of exposure to vinyl chloride, acrylonitrile and styrene	Never Ever *Duration (years)* None 1–6 7–14 > 14 *Cumulative exposure (ppm–years)* None 0.01–1.75 1.76–12.50 > 12.50	2822/3098 2794/3062 18/17 15/18 34/21 2794/3062 25/23 24/16 18/17	1.00 1.05 (0.68–1.62) 1.0 0.74 (0.35–1.56) 0.86 (0.39–1.90) 1.56 (0.81–3.03) Test for linear trend, $p = 0.119$ 1.00 0.90 (0.46–1.75) 0.96 (0.47–1.98) 1.51 (0.65–3.47)	Gender, age, tobacco, acrylonitrile, styrene, plastics pyrolysis products, chromium dust	Population-based

CI, confidence interval; ICD, International Classification of Diseases; JEM, job–exposure matrix

In a case–control study from seven European countries (Scélo *et al.*, 2004) that included 2861 cases of lung cancer and 3118 hospital controls, the odds ratio for ever exposure to vinyl chloride was 1.05 (95% CI, 0.68–1.62). A modest non-significant increase in the risk for lung cancer was found in the highest-exposed subgroup.

2.5.2 *Other cancers of the respiratory tract*

With respect to other cancers of the respiratory tract, neither the European nor the North American multicentric cohort studies found any evidence of an excess incidence of or mortality from laryngeal cancer. Mortality from cancer of the pleura was moderately elevated in the update of the European multicentric cohort (nine deaths; SMR, 1.89; 95% CI, 0.86–3.59) (Ward *et al.*, 2000, 2001). In an update of the North American multicentric study (Mundt *et al.*, 2000), an elevated SMR was found for cancer of other parts of the respiratory tract (six deaths; SMR, 1.80; 95% CI, 0.66–3.92).

2.6 Cancer of the lymphatic and haematopoeitic tissues (Table 10)

2.6.1 *North American multicentric study*

In the update of the North American multicentric study, the SMR for cancer of the lymphatic and haematopoeitic tissues was 0.86 (71 observed deaths; 95% CI, 0.67–1.08). The SMR for lymphosarcoma and reticulosarcoma (defined as ICD-9 code 200) was 1.20 (12 deaths; 95% CI, 0.62–2.09). No excesses were reported for other leukaemias or Hodgkin lymphoma (Mundt *et al.*, 2000).

2.6.2 *European multicentric study*

In an update of the European multicentric cohort study, an SMR of 0.94 (62 deaths; 95% CI, 0.72–1.21) was observed for cancers of lymphatic and haematopoeitic tissue; no significant excess was reported in any category of leukaemia or lymphoma. The overall SMR of 1.19 (26 deaths; 95% CI, 0.78–1.75) for non-Hodgkin lymphoma (Ward *et al.*, 2000, 2001) was much lower than that observed in the original study (seven deaths; SMR, 1.70; 95% CI, 0.69–3.71) (Simonato *et al.*, 1991). The SIR for non-Hodgkin lymphoma (ICD-9 code 200 and 202) in the updated study was 0.78 (20 deaths; 95% CI, 0.48–1.21); SIRs reported for other leukaemias and lymphomas were all below 1.00. Among the four countries, Italy had the highest SMR of 1.86 (95% CI, 0.84–3.54) and much of the excess was in the mixed production plants (SMR, 1.52; 95% CI, 0.96–2.27). No significant trends were observed with time since first employment, duration of employment, cumulative exposure or calendar period of hire. In the Poisson regression analyses, there appeared to be some elevation in rate ratios above the baseline category of cumulative dose, but the trend was not statistically significant (data not shown).

Table 10. Cohort studies of lymphohaematopoietic neoplasms in vinyl chloride monomer (VCM) and polyvinyl chloride (PVC) production workers

Name of study Reference, location	Cohort description	Exposure assessment	Type of cancer (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
North American multicentric study								
Mundt *et al.* (2000), USA	10 109 white male workers from 37 plants (race unknown, 6%) employed at least ≥ 1 year in jobs that entailed exposure to VCM in 1942–72; mortality follow-up, 1942–95; vital status, 96.8%; cause of death, 99%	JEM		Job exposed to VC		**SMR**		Reference rates: state rates
			Lymphohaemato-poeitic (ICD-9 200–208)		71	0.86 (0.67–1.08)		
			Lymphosarcoma or reticulosarcoma (ICD-9 200)		12	1.20 (0.62–2.09)		
			Hodgkin lymphoma (ICD-9 201)		3	0.44 (0.09–1.29)		
			Leukaemia/ aleukaemia (204–208)		31	0.94 (0.64–1.34)		
European multicentric study								
Ward *et al.* (2000, 2001), Italy, Norway, Sweden, United Kingdom	12 700 male workers employed at 19 VCM/PVC plants ≥ 1 year in 1950–85; mortality follow-up, 1955–97; incidence follow-up, 1955–96	Calendar period JEM for 13/19 factories grouped in 22 broad categories; factory-specific JEM with validated exposure estimates (ppm)		Employed in VC industry (full cohort)		**SMR**		Reference rates and incidence rates: national Poisson regression analysis
			Lymphohaemato-poeitic (ICD-9 200–208)		62	0.94 (0.72–1.21)	Age, calendar period	
			Non-Hodgkin lymphoma (ICD-9 200, 202)		26	1.19 (0.78–1.75)		
			Hodgkin lymphoma (ICD-9 201)		7	1.03 (0.41–2.12)		
			Leukaemia (ICD-9 204–208)		22	0.87 (0.54–1.31)		

Table 10 (contd)

Name of study Reference, location	Cohort description	Exposure assessment	Type of cancer (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Other studies								
Thériault & Allard (1981), Québec, Canada	451 male workers exposed to VCM for ≥ 5 years in a polymerization plant, employed in 1948–72; mortality follow-up, 1948–77	Questionnaire to the worker or next of kin on detailed occupational history	Leukaemia (ICD-9 200–209)	Exposed versus unexposed	1	**SMR** 0.60 (NR)		Reference rates: Canadian population in 1971; comparison population: 870 workers not exposed to VCM for ≥ 5 months
Weber *et al*. (1981), Germany	7021 male VCM/PVC production workers from beginning of operation to 1974; mortality follow-up, from beginning of operation to 1974; vital status, > 90%; cause of death, 7–13%	JEM	Lymphatic and haematopoietic (ICD-8 200–209)	Exposed versus unexposed	15	2.14 (1.12–3.53)		Reference rates: national

Table 10 (contd)

Name of study Reference, location	Cohort description	Exposure assessment	Type of cancer (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Smulevich *et al.* (1988), former Soviet Union	3232 VCM/PVC production workers (2195 men, 1037 women) employed for ≥ 1 month in VCM-exposed jobs; mortality follow-up, 1939–77	Exposure data in 1953–66 from JEM	Non-Hodgkin lymphoma and multiple myeloma (ICD-9 200, 202, 203)	Estimated area exposure: low, medium and high	5	**SMR** 4.17 ($p < 0.05$)		City (Gorki) mean death rates in 1959, 1969 and 1975
			Leukaemia (ICD-9 204–207)		5	5.00 ($p < 0.05$)		
Wong, O. *et al.* (2002), Taiwan, China	3293 male workers in 6 PVC polymerization plants exposed to VCM ≥ 1 year in 1950–92; mortality follow-up, 1985–97; vital status, 99%	JEM	Lymphatic and haematopoietic (ICD-9 200–208)		7	**SMR** 2.71 (1.09–5.60)		Reference rates: national; cohort assembled from Bureau of Labour Insurance

CI, confidence interval; ICD, International Classification of Diseases; JEM, job–exposure matrix; NR, not reported; SMR, standardized mortality ratio; VC, vinyl chloride

2.6.3 *Other studies*

Only one death from leukaemia (1.67 expected; SMR, 0.60) was reported in the Canadian study (Thériault & Allard, 1981).

Two independent European studies in Germany (Weber *et al*., 1981) and the former Soviet Union (Smulevich *et al*., 1988) have reported significantly increased mortality from neoplasms of the lymphatic and haematopoeitic system (Germany: SMR, 2.14; 95% CI, 1.12–3.53; former Soviet Union: SMR, 4; $p < 0.05$.

A study in Taiwan, China, reported a significant SMR for neoplasms of the lymphatic and haematopoeitic system (seven deaths; SMR, 2.71; 95% CI, 1.09–5.60) (Wong, O. *et al*., 2002).

2.6.4 *Meta-analysis*

The meta-analysis by Boffetta *et al*. (2003) showed a meta-SMR for neoplasms of the lymphatic and haematopoeitic system of 0.90 (95% CI, 0.75–1.07) based on the two multicentric cohorts. A meta-SMR for all studies was not calculated due to the high degree of heterogeneity between studies.

Non-Hodgkin lymphoma and multiple myeloma (ICD-9 200, 202, 203) were combined in the meta-analysis (Boffetta *et al*., 2003). SMRs for both the European and North American multicentric cohorts were below 1.00. However, an independent study from the former Soviet Union reported a significantly elevated SMR of 4.17 ($p < 0.05$) for this category of neoplasms (Smulevich *et al*., 1988). Due to borderline results for tests of heterogeneity, the multicentric cohorts and three independent studies were combined in the meta-analysis to yield a meta-SMR of 1.23 (95% CI, 0.70–2.19).

2.7 **Malignant melanoma and cancer of the skin** (Table 11)

2.7.1 *North American multicentric cohort study*

In the update of the North American cohort (Mundt *et al*., 2000), no elevation in mortality from skin cancer was observed (12 observed deaths; SMR, 0.64; 95% CI, 0.33–1.12).

2.7.2 *European multicentric cohort study*

An update of the European multicentric study found a non-significantly elevated SMR for malignant melanoma (15 deaths; SMR, 1.60; 95% CI, 0.90–2.65) (Ward *et al*., 2000, 2001). The analysis of incidence did not show an excess of melanoma (18 observed cases; SIR, 1.06; 95% CI, 0.63–1.68). An excess of mortality from melanoma had been previously noted for the Norwegian cohort and was found to be dose-related (Heldaas *et al*., 1984, 1987; Langård *et al*., 2000). In the update of the European multicentric study, the excess in Norway was statistically significant (five deaths; SMR, 6.27; 95% CI, 2.04–14.6) (Ward *et al*., 2001). An excess of mortality from melanoma was also observed in

Table 11. Cohort studies of malignant melanoma or skin cancer in vinyl chloride monomer (VCM) and polyvinyl chloride (PVC) production workers

Name of study Reference, location	Cohort description	Exposure assessment	Type of cancer (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
North American multicentric study								
Mundt *et al.* (2000), USA	10 109 white male workers in 37 plants (race unknown, 6%) employed at least ≥ 1 year in jobs that entailed exposure to VCM in 1942–72; mortality follow-up, 1942–95; vital status, 96.8%; cause of death, 99%	JEM	Skin (ICD-9 172–173)	Job exposed to VC	12	**SMR** 0.64 (0.33–1.12)		Reference rates: state and USA population
European multicentric study								
Ward *et al.* (2000, 2001), Italy, Norway, Sweden, United Kingdom	12 700 male workers employed in 19 VCM/PVC plants ≥ 1 year in 1950–85; mortality follow-up, 1955–97; incidence follow-up, 1955–96	Calendar period JEM for 13/19 factories grouped in 22 broad categories; factory-specific JEM with validated exposure estimates (ppm)	Melanoma (ICD-9 172)	Employed in VC industry (full cohort)	15	**SMR** 1.60 (0.90–2.65)		Reference rates and incidence rates: national
					18	**SIR** 1.06 (0.63–1.68)		
				VCM production	1	**SMR** 5.13 (0.13–28.6)	Age, calendar period	
				PVC production	0	(0.00–2.45)		
				VCM and PVC production	13	2.12 (1.13–3.62)		
				PVC processing	1	0.66 (0.02–3.68)		
				Latency (years)		**Relative risk**	Age, calendar period	Poisson regression analysis
				< 16	4	1.00		
				16–21	3	1.06 (0.20–5.61)		
				22–26	1	0.49 (0.04–5.43)		
				27–34	3	1.78 (0.25–12.8)		
				≥ 35	4	4.41 (0.51–38.4)		
						Test for linear trend, $p = 0.193$		

Table 11 (contd)

Name of study Reference, location	Cohort description	Exposure assessment	Type of cancer (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Ward *et al*. (2000, 2001) (contd)				*Duration (years)*				
				1–2	5	1.00		
				3–6	1	0.22 (0.03–1.85)		
				7–11	1	0.22 (0.03–1.89)		
				12–18	4	0.83 (0.22–3.16)		
				≥ 19	4	1.10 (0.27–4.44)		
						Test for linear trend, $p = 0.665$		
				Cumulative exposure (ppm–years)				
				35–99	3	1.00		
				100–535	4	2.31 (0.51–10.3)		
				536–2811	4	2.57 (0.57–11.5)		
				≥ 2812	3	2.68 (0.53–13.7)		
						Test for linear trend, $p = 0.193$		
Other studies								
Smulevich *et al*. (1988), former Soviet Union	3232 VCM/PVC production workers (2195 men, 1037 women) employed for ≥ 1 month in VCM-exposed jobs; mortality follow-up, 1939–77	Exposure data in 1953–66 from JEM		Estimated area exposure: low, medium and high	1	**SMR** 2.00 ($p > 0.05$)		City (Gorki) mean death rates in 1959, 1969 and 1975

CI, confidence interval; ICD, International Classification of Diseases; JEM, job–exposure matrix; SIR, standardized incidence ratio; SMR, standardized mortality ratio; VC, vinyl chloride

the Italian cohort (four deaths; SMR, 1.96; 95% CI, 0.53–5.01). No association was observed with previous employment as an autoclave cleaner.

2.7.3 *Other cohort studies*

In a study in the former Soviet Union (Smulevich *et al.*, 1988), one case of melanoma skin cancer was reported (SMR, 2.00; $p > 0.05$).

No cases were reported from the other independent studies (Thériault & Allard, 1981; Weber *et al.*, 1981; Laplanche *et al.*, 1992; Wong, O. *et al.*, 2002).

2.7.4 *Meta-analysis*

In the meta-analysis, results for mortality from skin cancer were heterogeneous, with no overall indication of an increased risk (meta-SMR, 1.11; 95% CI, 0.49–2.54) (Boffetta *et al*., 2003).

2.8 Cancer of the breast

Although concern has been raised about a potential association between exposure to vinyl chloride and the risk for breast cancer, human studies to date are not informative on this issue because of the very small numbers of women included. The analyses of both the European and North American cohorts included only men because of the extremely small number of women available for analysis (59 in the European multicentric cohort and 11 in the North American cohort) (Mundt *et al.*, 2000; Ward *et al.*, 2000, 2001). No deaths from breast cancer were observed in the European multicentric cohort (Ward *et al.*, 2000), with only 0.53 expected, and two deaths were observed in the North American cohort, with 1.05 expected (SMR, 1.90; 95% CI, 0.23–6.87) (Mundt *et al.*, 2000).

2.9 Soft-tissue sarcoma

2.9.1 *North American multicentric cohort study*

In the update of the North American multicentric study (Mundt *et al.*, 2000), the SMR for cancer of connective and soft tissue was 2.70 (12 deaths; 95% CI, 1.39–4.72); significant excesses were observed for those employed for 10–19 years (SMR, 4.77; 95% CI, 1.55–11.1) and for those employed for 20 years or more (SMR, 7.25; 95% CI, 1.97–18.6). SMRs were also significantly increased for first exposure before 1950 (SMR, 3.33; CI, 1.08–7.77) and between 1950 and 1959 (SMR, 4.68; 95% CI, 1.88–9.64). Seven of the 12 cancers were specific soft tissue other than angiosarcomas, and four were angiosarcomas with site not specified.

2.9.2 *European multicentric cohort study*

A total of six soft-tissue sarcomas were observed in the European multicentric study (SMR, 1.89; 95% CI, 0.69–4.11) (Ward *et al*., 2000, 2001), all of which occurred in the United Kingdom. Three additional soft-tissue sarcomas were identified from the incidence data (one in the United Kingdom and two in Sweden). However, during the review of the best available data for diagnosis to ascertain cases of liver cancer, it became apparent that three of the six deaths coded as tumours of the connective tissue were actually angiosarcomas of the liver, the primary site of which had been miscoded. A Poisson regression analysis was not conducted for the remaining soft-tissue sarcomas due to the small number of cases involved.

2.9.3 *Other cohort studies*

Two deaths from soft-tissue sarcoma were observed in the Canadian cohort (SMR, 5.26) (Thériault & Allard, 1981).

One case of soft-tissue sarcoma was observed in the cohort from the former Soviet Union (SMR, 1.43; $p > 0.05$) (Smulevich *et al*., 1988)

3. Studies of Cancer in Experimental Animals

Studies of the carcinogenicity of vinyl chloride following oral, inhalation and/or intratracheal administration, subcutaneous and/or intramuscular administration, intraperitoneal administration and perinatal exposure have been reviewed previously (IARC, 1979, 1987). Those that were found to be adequate and/or reported more fully in later publications are included in this section.

The carcinogenicity of vinyl chloride has been studied intensively and repeatedly by inhalation exposure of experimental animals at a range of concentrations that spanned decimal orders of magnitude. The numerous studies were generally mutually reinforced and consistently yielded hepatic and extrahepatic angiosarcomas in mice, rats and hamsters. Various other malignant neoplasms also occurred at several anatomical sites. However, the reporting of this multitude of data has often been incomplete, and the outcomes of many studies are available only from summary tables in the published literature, in which technical details are given only as footnotes.

3.1 Inhalation exposure

3.1.1 *Mouse*

Groups of 12 male and 12 female NMRI mice, 12 weeks of age, were exposed by inhalation to 50 or 500 ppm [130 or 1300 mg/m^3] vinyl chloride [purity unspecified] on

6 h per day for 5 days per week for either 26 (500 ppm) or 52 (50 ppm) weeks. Two groups of 12 male and 12 female control mice were untreated and were observed for either 26 or 52 weeks. The treatment with 500 ppm vinyl chloride was terminated at week 26 because of poor survival. The incidence of treatment-related tumours in males of the two control groups combined, and low- and high-dose groups, respectively, was: extrahepatic angiosarcomas, 0/24, 6/12 and 3/12; and lung tumours, 0/24, 9/12 and 12/12. That in females was: extrahepatic angiosarcomas, 0/24, 8/12 and 5/12; and lung tumours, 0/24, 4/12 and 12/12. Mammary carcinomas were observed in 1/24, 1/12 and 4/12 control, low-dose and high-dose females, respectively [no statistical analysis reported] (Holmberg *et al*., 1976).

Groups of 36 male and 36 female CD-1 mice, 2 months of age, were exposed by inhalation to 0, 50, 250 or 1000 ppm [0, 130, 650 or 2600 mg/m^3] vinyl chloride (99.8% pure) in air for 6 h per day on 5 days per week for 52 weeks. Four animals per group were terminated at 1, 2, 3, 6 or 9 months for laboratory tests and gross and histological examination. The incidence of liver angiosarcomas in control, 50-, 250- and 1000-ppm vinyl chloride-treated mice, respectively, was 0/26, 3/29, 7/29 ($p < 0.05$, Fisher's exact test) and 13/33 ($p < 0.05$) males and 0/36, 0/34, 16/34 ($p < 0.05$) and 18/36 [$p < 0.05$] females; that of extrahepatic angiosarcomas was 0/26, 5/29 ($p < 0.05$), 2/29 and 0/33 males and 0/36, 1/34, 3/34 and 9/36 ($p < 0.05$) females, respectively; and that of lung tumours (adenomas) was 1/26, 8/29, 10/29 and 22/33 males and 0/36, 4/34, 12/34 and 26/36 females, respectively. The incidence of mammary tumours (adenocarcinomas and carcinomas) in female mice was 0/36, 9/34, 3/34 and 13/36, respectively [no statistical analysis reported for lung and mammary tumours] (Lee *et al*., 1978).

Groups of 8–28 male and 8–28 female CD1 mice, 2 months of age, were exposed by whole-body inhalation to 0, 130, 650 or 2600 mg/m^3 [0, 340, 1690 or 6760 ppm] vinyl chloride (99.8% pure) for 6 h per day on 5 days per week for 1, 3 or 6 months and were then removed from exposure chambers and observed for an additional 12 months. The incidence of haemangiosarcoma and lung and mammary gland tumours is presented in Table 12. An increased cumulative incidence of haemangiosarcomas and bronchioloalveolar lung tumours was seen in male and female mice and an increase in the cumulative incidence of mammary gland adenocarcinomas/carcinomas in females (Hong *et al*., 1981).

Groups of 30 male and 30 female Swiss mice [data reported for both sexes combined], 11 weeks of age, were exposed by inhalation to 50, 250, 500, 2500, 6000 or 10 000 ppm [130, 650, 1300, 6500, 15 600 or 26 000 mg/m^3] vinyl chloride (99.97% pure) on 4 h per day on 5 days per week for 30 weeks. Control animals comprised 150 untreated mice [sex distribution not specified; data reported for both sexes combined]. Animals were observed until 81 weeks, when the experiment (experiment BT4) was terminated. Survival rates of the groups were not reported. The incidence of treatment-related tumours in control and 50-, 250-, 500-, 2500-, 6000- and 10 000-ppm vinyl chloride-treated mice, respectively, was: liver angiosarcomas, 0/150, 1/60, 18/60, 14/60, 16/59, 13/60 and 10/56; extrahepatic angiosarcomas, 1/150, 1/60, 3/60, 7/60, 8/59, 1/60

Table 12. Tumour incidence in CD1 mice exposed by inhalation to vinyl chloride for 1–6 months and observed for an additional 12 months

Tumour type	Tumour incidence/no. examined			
	Concentration (ppm) [mg/m^3]			
	0	50 [130]	250 [650]	1000 [2600]
Males				
1 month				
Liver				
Haemangiosarcoma	0/16	1/16	0/16	0/16
Lung				
Bronchioloalveolar tumour	2/16	3/16	10/16	11/16
3 months				
Liver				
Haemangiosarcoma	0/16	0/16	1/16	1/10
Lung				
Bronchioloalveolar tumour	2/16	7/16	11/16	9/10
6 months				
Liver				
Haemangiosarcoma	0/28	0/8	7/12	5/12
Lung				
Bronchioloalveolar tumour	4/28	2/8	8/12	7/12
Cumulative incidence				
Liver				
Haemangiosarcoma[a]	0/60	1/40	8/44[c]	6/38[c]
Lung				
Bronchioloalveolar tumour[b]	8/60	12/40	29/44[c]	27/38[c]
Females				
1 month				
Liver				
Haemangiosarcoma	0/16	0/16	0/16	0/16
Lung				
Bronchioloalveolar tumour	1/16	0/16	9/16	9/16
Mammary gland				
Adenocarcinoma/carcinoma	1/16	4/16	2/16	0/16
3 months				
Liver				
Haemangiosarcoma	0/16	0/16	3/16	4/10
Lung				
Bronchioloalveolar tumour	0/16	5/16	10/16	7/10
Mammary gland				
Adenocarcinoma/carcinoma	0/16	4/16	6/16	2/10

Table 12 (contd)

Tumour type	Tumour incidence/no. examined			
	Concentration (ppm) [mg/m^3]			
	0	50 [130]	250 [650]	1000 [2600]
6 months				
Liver				
Haemangiosarcoma	1/28	1/8	2/8	8/12
Lung				
Bronchioloalveolar tumour	7/28	1/8	4/8	7/12
Mammary gland				
Adenocarcinoma/carcinoma	3/28	2/8	5/8	4/12
Cumulative incidence				
Liver				
Haemangiosarcoma[a]	1/60	1/40	5/40[c]	12/38[c]
Lung				
Bronchioloalveolar tumour[b]	8/60	6/40	23/40[c]	23/38[c]
Mammary gland				
Adenocarcinoma/carcinoma	4/60	10/40[d]	13/40[d]	6/38[d]

From Hong *et al*. (1981)
[a] Significant dose-related incidence (males and females combined); Cochran-Armitage trend test
[b] Significant non-linearity in dose–incidence curve (males and females combined); Cochran-Armitage trend test
[c] Combined incidence in males and females significantly different from controls ($p < 0.05$, Fisher's exact test)
[d] Incidence in females significantly different from controls ($p < 0.05$, Fisher's exact test)

and 1/56; lung tumours, 15/150, 6/60, 41/60, 50/60, 40/59, 47/60 and 46/56; and mammary carcinomas, 1/150, 12/60, 12/60, 8/60, 8/59, 8/60 and 13/56. A low incidence of skin tumours was also reported [no statistical analysis provided] (Maltoni *et al*., 1981).

Groups of female Swiss CD-1 mice [initial numbers not specified], 8–9 weeks of age, were exposed by whole-body inhalation to 0 (control) or 130 mg/m^3 [0 or 50 ppm] vinyl chloride (commercial grade) [purity unspecified] for 6 h per day on 5 days per week for 6, 12 or 18 months. Animals were allowed to complete their lifespan and were necropsied when moribund or dead. There was a significant decrease ($p < 0.01$) in survival of the animals treated for 6, 12 and 18 months compared with controls. Statistically significant increases ($p < 0.01$, life-table analysis) in the incidence of haemangiosarcomas (all sites, mainly peritoneal and skin), mammary gland carcinomas and lung carcinomas were observed in all exposure groups. The incidence of haemangiosarcomas (all sites) was: control, 1/71; exposed for 6 months, 29/67; 12 months, 30/47; and 18 months, 20/45. The incidence of mammary gland carcinomas was 2/71, 33/67, 22/47 and 22/45, respectively; and that of lung carcinomas was 9/71, 18/65, 15/47 and 11/45, respectively. In the same

study, groups of female Swiss CD-1 mice [initial numbers not specified], 8 or 14 months of age, were exposed by whole-body inhalation to 0 (control) or 130 mg/m^3 [0 or 50 ppm] vinyl chloride for 6 h per day on 5 days per week for 6 or 12 months. Animals were allowed to complete their lifespan and were necropsied when found moribund or dead. Among animals exposed for 6 months beginning at 8 and 14 months of age, statistically significant increases (life-table analysis) in the incidence of haemangiosarcomas (all sites) (control, 1/71; 8 months of age, 11/49, $p < 0.01$; and 14 months of age, 5/53), mammary gland carcinomas (control, 2/71; 8 months of age, 13/49, $p < 0.01$; and 14 months of age, 2/53) and lung carcinomas (control, 9/71; 8 months of age, 13/49, $p < 0.05$; and 14 months of age, 7/53) were observed in the animals exposed beginning at 8 months of age only. Among those exposed for 12 months, statistically significant increases in the incidence of haemangiosarcomas (all sites) (control, 1/71; 8 months of age, 17/46, $p < 0.01$; and 14 months of age, 3/50), mammary gland carcinomas (control, 2/71; 8 months of age, 8/45, $p < 0.01$; and 14 months of age, 0/50) and lung carcinomas (control, 9/71; 8 months of age, 9/46, $p < 0.05$; and 14 months of age, 3/50) were observed in the animals exposed beginning at 8 months of age only (Drew *et al.*, 1983).

Groups of female B6C3F$_1$ mice [initial number not specified], 8–9 weeks of age, were exposed by whole-body inhalation to 0 (control) or 130 mg/m^3 [0 or 5.0 ppm] vinyl chloride (commercial grade) [purity unspecified] for 6 h per day on 5 days per week for 6 or 12 months. Animals were allowed to complete their lifespan and were necropsied when found moribund or dead. There was a significant decrease ($p < 0.01$) in survival of the animals treated for 6 or 12 months compared with controls. Statistically significant increases ($p < 0.01$, life-table analysis) in the incidence of haemangiosarcomas (all sites) and mammary gland tumours were observed in all exposure groups. The incidence of haemangiosarcomas (all sites, mainly peritoneal and subcutis) was: control, 4/69; exposed for 6 months, 46/67; and 12 months, 69/90; that of mammary gland carcinomas was 3/69 (control), 29/67 and 37/90, respectively. In the same study, groups of female B6C3F$_1$ mice [initial number not specified], 8 or 14 months of age, were exposed by whole-body inhalation to 0 (control) or 130 mg/m^3 [0 or 50 ppm] vinyl chloride for 6 h per day on 5 days per week for 6 or 12 months. Animals were allowed complete their lifespan and were necropsied when found moribund or dead. There was a significant decrease ($p < 0.01$) in survival of the treated animals compared with controls. Among the animals exposed for 6 and 12 months, statistically significant increases ($p < 0.01$ except $p < 0.05$ where indicated, life-table analysis) were observed in the incidence of haemangiosarcomas (all sites) (control, 4/69; 6-month exposures: 8 months of age, 27/42; and 14 months of age, 30/51; 12-month exposures: 8 months of age, 30/48; and 14 months of age, 29/48) and mammary gland carcinomas (control, 3/69; 6-month exposures: 8 months of age, 13/42; and 14 months of age, 4/51, $p < 0.05$; 12-month exposures: 8 months of age, 9/48; and 14 months of age, 4/48) (Drew *et al*., 1983).

[The Working Group noted that lung tumours were not observed in B6C3F$_1$ mice exposed to vinyl chloride in the studies of Drew *et al*. (1983), whereas Swiss CD-1 mice,

a strain that is more susceptible to the induction of lung tumours, did develop such tumours in these and other studies.]

Groups of 30, 40 or 60 male CD1 mice, 5–6 weeks of age, were exposed by whole-body inhalation to 0, 2.6, 26, 260, 780 or 1560 mg/m^3 [0, 1, 10, 100, 300 or 600 ppm] vinyl chloride [purity unspecified] for 6 h per day on 5 days per week for 4 weeks and were then observed for an additional 0, 12 or 40–41 weeks. Surviving animals were killed after each observation period. The study focused on lung tumours. After 12 weeks of exposure, the incidence of pulmonary tumours was 0/18, 0/10, 0/9, 0/6, 6/9 and 8/9 for mice treated with 0 (control), 2.6, 26, 260, 780 and 1560 mg/m^3, respectively; after 40–41 weeks of exposure, the incidence was 0/17, 1/9, 3/9, 6/9, 5/7 and 6/7, respectively [no statistical analysis provided] (Suzuki, 1983).

3.1.2 *Rat*

Groups of 36 male and 36 female CD rats, 2 months of age, were exposed by inhalation to 0, 50, 250 or 1000 ppm [0, 130, 650 or 2600 mg/m^3] vinyl chloride (99.8% pure) in air for 6 h per day on 5 days per week for 52 weeks. Four animals per group were terminated at 1, 2, 3, 6 or 9 months for laboratory tests and gross and histological examination. The combined incidence of liver angiosarcomas by increasing level of exposure was 0/35 (control), 0/36, 2/36 and 6/34 in males and 0/35 (control), 0/36, 10/34 ($p < 0.05$, Fisher's exact test) and 15/36 ($p < 0.05$) in females, respectively. Similarly, the incidence of extrahepatic angiosarcomas was 0/35 (control), 1/36, 2/36 and 4/34 in males and 0/35 (control), 1/36, 3/34 and 10/36 ($p < 0.05$) in females, respectively (Lee *et al.*, 1978).

Groups of 62 newly weaned male and female Wistar rats were exposed by whole-body inhalation to 0 or 13 000 mg/m^3 [0 or 5000 ppm] vinyl chloride (≥ 99.97% pure) for 7 h per day on 5 days per week for 52 weeks. Ten animals per dose per sex were killed at 4, 13, 26 and 52 weeks. No information on survival was provided. At 52 weeks, an increase in the incidence of angiosarcomas of the liver (males, 3/9; females, 6/10), Zymbal gland squamous-cell carcinomas (males, 3/9; females, 2/10) and carcinomas of the nasal cavity (males, 2/9; females, 5/10) compared with controls (no tumours) was observed [no statistical evaluation provided] (Feron & Kroes, 1979; Feron *et al.*, 1979).

Groups of 110–128 male and 110–128 female Sprague-Dawley rats, 6, 18, 32 or 52 weeks of age, were exposed in chambers by whole-body inhalation to 0 (controls) or 2465 mg/m^3 [0 or 940 ppm] vinyl chloride [purity unspecified] for 7 h per day on 5 days per week for 24.5 weeks. An epidemic of pneumonia in exposed rats during the 28th week forced premature conclusion of the study and all surviving rats were killed 43 weeks after the beginning of exposure. Rats killed at 3, 6 or 9 months (interim sacrifice group) were evaluated separately from rats that either died, were killed in poor condition or were killed at the conclusion of the study (non-scheduled sacrifice group). Angiosarcomas, mostly primary tumours in the liver, were highly anaplastic and frequently metastasized to the lung. The incidence of angiosarcomas in vinyl chloride-exposed male rats in the non-scheduled sacrifice group was 0/37, 0/44, 3/45 and 13/55 in rats that were exposed

beginning at 6, 18, 32 or 52 weeks of age, respectively. The corresponding incidence of angiosarcomas in exposed females was 2/38, 7/47, 23/49 and 11/54. Only one angiosarcoma occurred in subcutaneous tissues in a control male placed on study at 32 weeks of age (incidence for this control group, 1/86; incidence for all control males, 1/357). The incidence of angiosarcomas in control females was 0/382. Pituitary tumours and mammary tumours occurred in both control and exposed rats at comparable rates. A few rats in the control and exposed groups had Zymbal gland or brain tumours (Groth *et al.*, 1981).

Five groups of 51–93 male random-bred white rats, weighing 160–180 g at the beginning of the experiment, were exposed by whole-body inhalation to 0 (control), 14, 25, 266 or 3690 mg/m^3 [0, 5.4, 9.6, 102 or 1420 ppm] vinyl chloride [purity unspecified] for 4.5 h per day on 5 days per week for 52 weeks and observed until their death, but no longer than 126 weeks. The authors reported the development of angiosarcomas of liver or other sites in rats of the three highest-dose groups (9.3–15.7%). No such tumours were observed in control animals (Kurlyandski *et al.*, 1981).

Groups of 30 male and 30 female Sprague-Dawley rats [data reported for both sexes combined], 12 weeks of age, were exposed by inhalation to 50, 250, 500, 2500, 6000 or 10 000 ppm [130, 650, 1300, 6500, 15 600 or 26 000 mg/m^3] vinyl chloride (99.97% pure) for 4 h per day on 5 days per week for 17 weeks. Control animals comprised 190 untreated rats [data reported for both sexes combined]. Animals were observed until 156 weeks, when the experiment (experiment BT3) was terminated. Survival rates of the groups were not reported. The incidence of tumours was: liver angiosarcomas, 0/190, 0/58, 0/59, 1/60, 1/60, 1/60 and 0/58 in control, 50-, 250-, 500-, 2500-, 6000- and 10 000-ppm vinyl chloride-treated rats, respectively; 'hepatomas', 0/190 (control), 0/58, 0/59, 0/60, 2/60, 1/60 and 1/58, respectively; Zymbal gland carcinomas, 2/190 (control), 0/58, 1/59, 1/60, 7/60, 9/60 and 9/58, respectively; and 'skin epitheliomas', 1/190 (control), 1/58, 0/59, 0/60, 2/60, 5/60 and 5/58, respectively [no statistical analysis reported] (Maltoni *et al*., 1981).

Groups of 60 male and 60 female Sprague-Dawley rats [data reported for both sexes combined], 13 weeks of age, were exposed by inhalation to 6000 or 10 000 ppm [15 600 or 26 000 mg/m^3] vinyl chloride (99.97% pure) for 4 h per day on 5 days per week for 5 weeks (groups I and II), for 1 h per day on 4 days per week for 25 weeks (groups III and IV) or for 4 h per day once a week for 25 weeks (groups V and VI). Control animals comprised two groups of 120 untreated rats [data reported for both sexes combined]. Animals were observed until 154 weeks, when the experiment (experiment BT10) was terminated. Survival rates of the groups were not reported. The incidence of tumours was: liver angiosarcomas, 0/227, 1/118, 0/120, 1/119, 3/118, 1/119 and 1/120 in controls and groups I, II, III, IV, V and VI, respectively; extrahepatic angiosarcomas, 0/227 (control), 0/118, 0/120, 0/119, 2/118, 0/119 and 1/120, respectively; Zymbal gland carcinomas, 0/227 (control), 9/118, 9/120, 9/119, 5/118, 8/119 and 9/120, respectively; and mammary tumours, 17/227 (control), 13/118, 13/120, 16/119, 11/118, 20/119 and 12/120, respectively. The predominant carcinogenic effect was in the Zymbal gland [no statistical analysis reported] (Maltoni *et al*., 1981).

Five experiments (BT1, BT2, BT6, BT9, BT15) performed by Maltoni *et al*. (1981) were combined to construct a dose–response table. Groups of 60–300 male and female Sprague-Dawley rats [data reported for both sexes combined], 13–17 weeks of age, were exposed by inhalation to 1, 5, 10, 25, 50, 100, 150, 200, 250, 500, 2500, 6000, 10 000 or 30 000 ppm [2.6, 13, 26, 65, 130, 260, 390, 520, 650, 1300, 6500, 15 600, 26 000 or 78 000 mg/m^3] vinyl chloride (99.97% pure) for 4 h per day on 5 days per week for 52 weeks. Controls comprised 461 untreated rats from four experiments [data reported for both sexes combined]. Animals were observed until 68 (BT6) or 135–147 (BT1, BT2, BT9, BT15) weeks, when the experiments were terminated. Survival rates of the groups were not reported. Selected tumour incidences are presented in Table 13 [no statistical analysis reported] (Maltoni *et al*., 1981). [The Working Group noted that the clearest dose–response was observed for hepatic angiosarcomas and Zymbal gland carcinomas.]

Groups of 30–40 male (BT7) or 120–130 male [exact numbers not specified] (BT17) Wistar rats, 11–13 weeks of age, were exposed by inhalation to 1, 50, 250, 500, 2500, 6000 or 10 000 ppm [2.6, 130, 650, 1300, 6500, 15 600 or 26 000 mg/m^3] vinyl chloride (99.97% pure) for 4 h per day on 5 days per week for 52 weeks. Control animals comprised 40 (BT7) or 120–130 [exact number not specified] (BT17) untreated rats. Animals were observed until 134 (BT17) or 165 (BT7) weeks, when the experiment was terminated. Survival rates of the groups were not reported. The incidence of selected tumours in order of increasing doses was: liver angiosarcomas, 0/132 (control), 0/99, 0/28, 1/27, 3/28, 3/25, 3/26 and 8/27, respectively; extrahepatic angiosarcomas, 1/132 (control), 3/99, 0/28, 1/27, 0/28, 1/25, 1/26 and 0/27, respectively; 'hepatomas', 0/132 (control), 1/99, 0/28, 0/27, 0/28, 1/25, 2/26 and 0/27, respectively; and Zymbal gland carcinomas, 3/132 (control), 2/99, 0/28, 0/27, 0/28, 0/25, 2/26 and 2/27, respectively [no statistical analysis provided] (Maltoni *et al*., 1981). [The Working Group noted the lack of a dose–response for extrahepatic angiosarcomas, Zymbal gland carcinomas and hepatomas.]

Groups of 55–112 female Fischer 344 rats, 8–9 weeks of age, were exposed by whole-body inhalation to 0 (control) or 260 mg/m^3 [0 or 100 ppm] vinyl chloride (commercial grade) [purity unspecified] for 6 h per day on 5 days per week for 6, 12, 18 or 24 months. Animals were allowed to complete their lifespan and were necropsied when found moribund or dead. There was a significant decrease ($p < 0.01$) in survival of animals exposed for 1 year or more compared with controls. Statistically significant increases ($p < 0.01$, life-table analysis) were observed in the incidence of liver haemangiosarcomas, haemangiosarcomas (all sites), mammary gland fibroadenomas and liver neoplastic nodules [hepatocellular adenomas] in all exposure groups and of mammary gland adenocarcinomas and hepatocellular carcinomas in the groups exposed for 12, 18 and 24 months. Tumour incidence after 24 months of exposure was: haemangiosarcoma of the liver, 1/112 control versus 19/55 exposed; haemangiosarcoma (all sites), 2/112 control versus 24/55 exposed; fibroadenoma of the mammary gland, 24/112 control versus 26/55 exposed; adenocarcinoma of mammary gland, 5/112 control versus 5/55 exposed; liver neoplastic nodules [hepatocellular adenomas], 4/112 control versus 6/55

Table 13. Tumour incidence in a dose–response study of vinyl chloride administered by inhalation to Sprague-Dawley rats for 52 weeks

Exposure (ppm) [mg/m^3]	Experiment	Liver angiosarcomas	Extrahepatic angiosarcomas	Hepatomas	Zymbal gland carcinomas	Mammary tumours	Nephroblastomas[a]	Neuroblastomas[b]
0	BT1, BT2, BT9, BT15	0/461	2/461	0/461	4/461	19/461	0/461	0/461
1 [2.6]	BT15	0/118	0/118	0/118	1/118	15/118	0/118	0/118
5 [13]	BT15	0/119	0/119	0/119	1/119	22/119	0/119	0/119
10 [26]	BT15	1/119	2/119	0/119	2/119	21/119	0/119	0/119
25 [65]	BT15	5/120	0/120	0/120	4/120	17/120	1/120	0/120
50 [130]	BT1	1/60	1/60	0/60	0/60	2/60	1/60	0/60
50 [130]	BT9	14/294	9/294	0/294	9/294	62/294	1/294	0/294
100 [260]	BT2	1/120	0/120	0/120	1/120	4/120	10/120	0/120
150 [390]	BT2	6/119	0/119	0/119	4/119	6/119	11/119	0/119
200 [520]	BT2	12/120	1/120	3/120	4/120	6/120	7/120	0/120
250 [650]	BT1	3/59	2/59	1/59	0/59	2/59	5/59	0/59
500 [1300]	BT1	6/60	1/60	5/60	4/60	1/60	6/60	0/60
2500 [6500]	BT1	13/60	3/60	2/60	2/60	2/60	6/60	4/60
6000 [15 600]	BT1	13/59	3/59	1/59	7/59	0/59	5/59	3/59
10 000 [26 000]	BT1	7/60	3/60	1/60	16/60	3/60	5/60	7/60
30 000 [78 000]	BT6	18/60	1/60	1/60	35/60	2/60	0/60	1/60

From Maltoni *et al.* (1981)

[a] Primary renal tumours were not necessarily embryonal in morphology.

[b] See Working Group comment on this diagnosis in the text that describes the Maltoni and Cotti (1988) study.

exposed; and hepatocellular carcinoma, 1/112 control versus 9/55 exposed. In the same study, groups of 51–112 female Fischer 344 rats, aged 2, 8, 14 or 20 months, were exposed by whole-body inhalation to 0 (control) or 260 mg/m^3 [100 ppm] vinyl chloride for 6 h per day on 5 days per week for 6 or 12 months. Exposures were initiated when the animals were 2, 8, 14 or 20 months of age for the 6-month exposures and 2, 8 or 14 months of age for the 12-month exposures. Animals were allowed to complete their lifespan and were necropsied when found moribund or dead. The incidence of haemangiosarcomas, and mammary gland and liver tumours is presented in Table 14. For the 6-month exposures, increases were observed in the incidence of liver haemangiosarcomas in one exposure group, of mammary gland fibroadenomas and neoplastic liver nodules [hepatocellular adenomas] in the 2- and 8-month-old groups, respectively, and of hepatocellular carcinomas in the 8-month-old group. After the 12-month exposures, increases were observed in the incidence of liver haemangiosarcomas, haemangiosarcomas (all sites) and mammary gland fibroadenomas in the 2- and 8-month-old groups and of mammary gland adenocarcinomas, neoplastic liver nodules [hepatocellular adenomas] and hepatocellular carcinomas in the 2-month-old group (Drew *et al.*, 1983).

Table 14. Incidence of tumours in female Fischer 344 rats exposed to 260 mg/m^3 [100 ppm] vinyl chloride by inhalation

Exposure period (months)	Age at start (months)	Haemangiosarcoma		Mammary gland		Liver neoplastic nodules [hepatocellular adenoma]	Hepatocellular carcinoma
		Liver	All sites	Fibroadenoma	Adenocarcinoma		
0 (control)	–	1/112	2/112	24/112	5/112	4/112	1/112
6	2	4/76[a]	4/76	28/76[a]	6/76	15/75[a]	3/75
6	8	2/52	2/53	23/53[b]	2/53	10/52[a]	6/52[a]
6	14	0/51	0/53	17/53	3/53	2/51	0/51
6	20	0/53	0/53	20/53[b]	2/53	4/53	1/53
12	2	11/55[a]	12/56[a]	28/56[a]	11/56[a]	20/56[a]	4/56[a]
12	8	5/54[a]	5/55[a]	16/55[a]	4/55	4/54	1/54
12	14	2/49	2/50	15/50	0/50	4/49	0/49

Adapted from Drew *et al.* (1983)
[a] Difference from controls, $p < 0.01$ (life-table analysis)
[b] Difference from controls, $p < 0.05$ (life-table analysis)

3.1.3 *Hamster*

Groups of 30 male Golden hamsters, 11 weeks of age, were exposed by inhalation to 50, 250, 500, 2500, 6000 or 10 000 ppm [30, 650, 1300, 6500, 15 600 or 26 000 mg/m^3] vinyl chloride (99.97% pure) for 4 h per day on 5 days per week for 30 weeks. Control animals comprised 60 untreated male hamsters. Animals were observed until 109 weeks, when the experiment (experiment BT8) was terminated. Survival rates of the groups were

not reported. The incidence of treatment-related tumours by increasing dose of exposure was: liver angiosarcomas, 0/60 (control), 0/30, 0/30, 2/30, 0/30, 1/30 and 0/30, respectively; skin epitheliomas, 3/60 (control), 9/30, 3/30, 7/30, 3/30, 1/30 and 7/30, respectively; and forestomach papillomas and acanthomas, 3/60 (control), 3/30, 4/30, 9/30, 17/30, 10/30 and 10/30, respectively. Leukaemia was observed at a similar incidence in control and treated groups (8/60 (control), 6/30, 6/30, 5/30, 9/30, 6/30 and 5/30, respectively), but the authors reported a decrease in the latency period [no statistical analysis provided] (Maltoni *et al.*, 1981).

Groups of female Syrian golden hamsters [initial numbers not specified], 8–9 weeks of age, were exposed by whole-body inhalation to 0 or 520 mg/m^3 [0 or 200 ppm] vinyl chloride (commercial grade) [purity unspecified] or 6 h per day on 5 days per week for 6, 12 or 18 months. Animals were allowed to complete their lifespan and were necropsied when found moribund or dead. There was a significant decrease ($p < 0.01$) in survival of all exposed animals compared with controls. Statistically significant increases (see Table 15) were observed in the incidence of mammary gland carcinomas and stomach adenomas in all exposure groups and of haemangiosarcomas (all sites) in the groups exposed for 6 and 12 months. A significant increase in the incidence of skin carcinomas was also seen in the 12-month exposure group. In the same study, groups of female Syrian golden hamsters, 2, 8, 14 or 20 months of age (Groups I, II, III and IV, respectively) [initial numbers not specified], were exposed by whole-body inhalation to 0 or 520 mg/m^3 [0 or

Table 15. Incidence of tumours in female Syrian golden hamsters exposed to 520 mg/m^3 [200 ppm] vinyl chloride by inhalation

Exposure period (months)	Age at first exposure	Haemangiosarcoma (all sites)[a]	Mammary gland carcinoma	Stomach adenoma	Skin carcinoma
0 (control)	–	0/143	0/143	5/138	0/133
6	8 weeks	13/88[b]	28/87[b]	23/88[b]	2/80
12	8 weeks	4/52[b]	31/52[b]	3/50[c]	9/48[b]
18	8 weeks	2/103	47/102[b]	20/101[b]	3/90
6	8 months	3/53[c]	2/52[c]	15/53[b]	0/49
6	14 months	0/50	0/50	6/49[c]	0/46
6	20 months	0/52	1/52	0/52	0/50
12	2 months	4/52[b]	31/52[b]	3/50[c]	2/80
12	8 months	1/44	6/44[b]	10/44[b]	0/38
12	14 months	0/43	0/42	3/41	0/30

Modified from Drew *et al.* (1983)
[a] These tumours occurred primarily in the skin, spleen and liver.
[b] Difference from controls, $p < 0.01$ (life-table analysis)
[c] Difference from controls, $p < 0.05$ (life-table analysis)

200 ppm] vinyl chloride for 6 h per day on 5 days per week for 6 or 12 months. Exposures were initiated when the animals were 2, 8, 14 or 20 months of age for the 6-month exposures and 2, 8 or 14 months of age for the 12-month exposures. Animals were allowed to complete their lifespan and were necropsied when found moribund or dead. There was a significant decrease ($p < 0.01$) in the survival of animals that were exposed early in life for 12 months compared with controls. In some of the 6-month and 12-month exposure groups (see Table 15), statistically significant increases were observed in the incidence of stomach adenomas, haemangiosarcomas (all sites) and mammary gland carcinomas (Drew *et al.*, 1983).

[The Working Group noted the successful induction of hepatic angiosarcomas in three species (rats, mice and hamsters) exposed to vinyl chloride by inhalation.]

3.2 Oral administration

Rat

Groups of 40 male and 40 female Sprague-Dawley rats [data reported only for both sexes combined], 13 weeks of age, were administered 3.3, 17 or 50 mg/kg bw vinyl chloride (99.97% pure) in olive oil by gastric intubation four or five times a week for 52 weeks. Control rats comprised 40 males and 40 females [data reported for both sexes combined] that were treated with olive oil alone. Animals were observed until 136 weeks, when the experiment (experiment BT11) was terminated. Survival rates of the groups were not reported. The incidence of treatment-related tumours in control and 3.3-, 17- and 50-mg/kg bw vinyl chloride-treated rats, respectively, was: liver angiosarcomas, 0/80, 0/80, 10/80 and 17/80; extrahepatic angiosarcomas, 0/80, 2/80, 0/80 and 2/80; and primary renal tumours (‘nephroblastomas’), 0/80, 0/80, 3/80 and 2/80 [no statistical analysis reported] (Maltoni *et al.*, 1981).

Groups of 75 male and 75 female Sprague-Dawley rats [data reported only for both sexes combined], 10 weeks of age, were administered 0.03, 0.3 or 1 mg/kg bw vinyl chloride (99.97% pure) in olive oil by gastric intubation four or five times a week for 52–59 weeks. Controls comprised 75 males and 75 females [data reported for both sexes combined] that were treated with olive oil alone. Animals were observed until 136 weeks, when the experiment (experiment BT27) was terminated. Survival rates of the groups were not reported. The incidence of several tumours was increased in the treated groups. The incidence in control and 0.03-, 0.3- and 1-mg/kg bw vinyl chloride-treated rats, respectively, was: hepatic angiosarcomas, 0/150, 0/150, 1/148 and 3/149; extrahepatic angiosarcomas, 0/150, 0/150, 0/148 and 1/149; hepatomas [not otherwise specified], 0/150, 0/150, 1/148 and 1/149; Zymbal gland carcinomas, 1/50, 0/150, 0/148, 5/149; and mammary tumours, 7/150, 14/150, 4/148 and 12/149 [no statistical analysis reported] (Maltoni *et al.*, 1981).

Groups of 60–80 male and 60–80 female Wistar rats, 5 weeks of age, were fed diets that contained 0, 1, 3 or 10% of 4000 ppm vinyl chloride (≥ 99.97% pure) in a PVC

powder (vehicle) (which resulted in calculated daily doses of 0, 1.7, 5.0 or 14 mg/kg bw vinyl chloride, respectively) during a 4-h feeding period each day on 7 days per week. Animals were treated for a total of 135 (males) or 144 (females) weeks, after which the experiment was terminated. Survival of males at the end of the study was 14/60 control, 20/60 low-dose, 0/60 intermediate-dose and 0/60 high-dose animals; for females, survival was 19/60 control, 5/60 low-dose, 0/60 intermediate-dose and 0/60 high-dose animals. Neoplastic responses included a significantly increased incidence ($p < 0.05$, χ^2 test) of liver haemangiosarcomas and lung angiosarcomas in high- and mid-dose males and high-dose females, of hepatocellular carcinomas in high-dose males and high- and mid-dose females and of neoplastic liver nodules (hepatocellular adenomas) in high- and mid-dose males and females. The incidence of hepatocellular carcinomas was 0/55 control, 1/58 low-dose, 2/56 mid-dose and 8/59 high-dose males and 0/57 control, 4/58 low-dose, 19/59 mid-dose and 29/57 high-dose females; that of liver haemangiosarcomas was 0/55 control, 0/58 low-dose, 6/56 mid-dose and 27/59 high-dose males and 0/57 control, 0/58 low-dose, 2/59 mid-dose and 9/57 high-dose females; and that of neoplastic nodules (hepatocellular adenomas) was 0/55 control, 1/58 low-dose, 7/56 mid-dose and 23/59 high-dose males and 2/57 control, 26/58 low-dose, 39/54 mid-dose and 44/57 high-dose females (Feron *et al.*, 1981).

As in the previous experiment, groups of 50–100 male and 50–100 female Wistar rats [age unspecified] were fed diets similar to those described in Feron *et al.* (1981) that resulted in calculated daily doses of 0, 0.014, 0.13 and 1.3 mg/kg bw vinyl chloride (≥ 99.97% pure), respectively, during a daily 4–6-h feeding period on 7 days per week. Animals were treated for a total of 149 (males) or 150 (females) weeks, after which the experiment was terminated. Survival of males at the end of the study was 20/100 control, 20/100 low-dose, 18/100 intermediate-dose and 8/50 high-dose animals; for females, survival was 24/100 control, 23/100 low-dose, 26/100 intermediate-dose and 5/50 ($p < 0.05$) high-dose animals. Neoplastic responses included a significantly increased incidence of hepatocellular carcinomas in high-dose males and of liver neoplastic nodules (hepatocellular adenomas) in high-dose females ($p < 0.05$). The incidence of hepatocellular carcinoma was 0/99 control, 0/99 low-dose, 0/99 mid-dose and 3/49 high-dose males and 1/98 control, 0/100 low-dose, 1/96 mid-dose and 3/49 high-dose females; that of neoplastic nodules (hepatocellular adenomas) was 0/99 control, 0/99 low-dose, 0/99 mid-dose and 1/49 high-dose males and 0/98 control, 1/100 low-dose, 1/96 mid-dose and 9/49 high-dose females; and that of liver haemangiosarcomas was 0/99 control, 0/99 low-dose, 0/99 mid-dose and 1/49 high-dose males and 0/98 control, 0/100 low-dose, 0/96 mid-dose and 2/49 high-dose females (Til *et al.*, 1991).

3.3 Subcutaneous injection

Rat

Groups of 35 male and 40 female Sprague-Dawley rats, 21 weeks of age, were administered a single subcutaneous injection of 4.25 mg vinyl chloride (99.97% pure) in 1 mL olive oil. Control animals comprised 35 male and 40 female rats that were treated with olive oil alone (1 mL). Animals were followed until 145 weeks, when the experiment [BT13] was terminated. Survival rates of the groups were not reported. No hepatic or extrahepatic angiosarcomas were observed. Tumour incidence was reported for both sexes combined. Mammary tumours were observed in 1/75 vinyl chloride-treated rats and 3/75 controls. Nephroblastomas were observed in 1/75 treated rats and 0/75 controls. No other tumour types were reported in vinyl chloride-treated animals (Maltoni *et al.*, 1981).

3.4 Intraperitoneal injection

Rat

Groups of 30 male and 30 female Sprague-Dawley rats [data reported for both sexes combined], 17 weeks of age, were administered 4.25 mg vinyl chloride (99.97% pure) in 1 mL olive oil by intraperitoneal injection once, twice, three times or four times at 2-month intervals. Control animals comprised 60 rats that were treated with olive oil alone (1 mL) [number of treatments not reported; data reported for both sexes combined]. Animals were followed until 144 weeks, when the experiment (BT12) was terminated. Survival rates of the groups were not reported. No liver angiosarcomas were observed. Extrahepatic angiosarcomas were observed in 0/55 controls, and 0/55, 1/56, 1/53 and 0/56 rats treated with vinyl chloride once, twice, three times or four times, respectively; mammary tumours were observed in 0/55 controls, and 2/55, 3/56, 1/53, and 1/56 rats treated with vinyl chloride once, twice, three times or four times, respectively [no statistical analysis reported] (Maltoni *et al.*, 1981).

3.5 Transplacental administration

Rat

Groups of 30–54 pregnant female Sprague-Dawley rats, 19 weeks of age, were exposed by inhalation to 6000 or 10 000 ppm [15 600 or 26 000 mg/m^3] vinyl chloride (99.97% pure) for 4 h per day for 7 days, from days 12 to 18 of pregnancy (experiment BT5). Both dams and offspring were observed until the experiment was terminated at 143 weeks, without further exposure to vinyl chloride [the Working Group noted the lack of control groups]. Survival rates of the various groups were not reported. No hepatic or extrahepatic angiosarcomas or hepatomas were observed in either dams or offspring. Tumours appeared at several sites in offspring, including extrahepatic angioma (1/32 low-dose, 0/51 high-dose), kidney tumours (0/32 low-dose, 3/51 high-dose), Zymbal gland

carcinomas (3/32 low-dose, 5/51 high-dose), skin epitheliomas (1/32 low-dose, 0/51 high-dose), forestomach papillomas and achanthomas (1/32 low-dose, 1/51 high-dose) and mammary gland tumours (2/32 low-dose, 1/51 high-dose). No tumours occurred at these sites in low-dose dams. One Zymbal gland carcinoma was seen in a high-dose dam (1/30) (Maltoni *et al.*, 1981). [The Working Group considered that, despite the lack of controls, this study provides some evidence of the transplacental carcinogenicity of vinyl chloride.]

3.6 Perinatal exposure

Rat

Male and female Sprague-Dawley rats (breeders), 21 weeks of age, were exposed by inhalation together with their newborn offspring to 6000 or 10 000 ppm [15 600 or 26 000 mg/m^3] vinyl chloride (99.97% pure) on 4 h per day on 5 days per week for 5 weeks. Offspring [data reported for both sexes combined] included 44 rats in the high-dose and 42 in the low-dose group. All vinyl chloride-treated rats were followed until 124 weeks, when the experiment (experiment BT14) was terminated [the Working Group noted the lack of controls]. Survival rates of the groups were not reported. In rats treated perinatally, the incidence of hepatic angiosarcomas was 17/42 and 15/44 in 6000- and 10 000-ppm vinyl chloride-treated animals, respectively. Other tumours that occurred in low-dose and high-dose groups, respectively, were liver angiomas (1/42, 0/44), extrahepatic angiosarcomas (1/42, 0/44), extrahepatic angiomas (1/42, 3/44), 'hepatomas' (20/42, 20/44), Zymbal gland carcinomas (2/42, 1/44), skin epitheliomas (2/42, 1/44) and mammary tumours (1/42, 0/44). No tumours were reported in breeders at the sites where tumours occurred in offspring (Maltoni *et al.*, 1981).

Male and female Sprague-Dawley rats (breeders), 13 weeks of age, were exposed by inhalation to 0 (controls) or 2500 ppm [6500 mg/m^3] vinyl chloride (99.97% pure) for 4 h per day on 5 days per week for an initial 7-week period during which 54 exposed females and 60 control females became pregnant and delivered young. Exposed dams then continued to receive vinyl chloride by inhalation for 7 h per day on 5 days per week for an additional 69 weeks. Offspring [details of delivery and perinatal husbandry not given] were exposed with their dams pre- and postnatally during the initial 7-week exposure period, and were then either exposed similarly to their dams for 7 h per day on 5 days per week for a further 69 weeks (63 males, 64 females; Group I) or for a shorter 8-week period (60 males, 60 females; Group II). Control offspring were 158 males and 149 females. Hepatocarcinomas occurred in 5/54 exposed female breeders and 0/60 control breeders, in 27/64 male and 38/63 female Group I offspring, in 42/60 male and 43/60 female Group II offspring and in 1/158 control male and 0/149 control female offspring. Angiosarcomas [origin not specified; presumably hepatic] occurred in 27/54 exposed female breeders, in 36/64 male and 46/63 female Group I offspring and 24/60 male and 28/60 female Group II offspring. No angiosarcomas were seen in 60 control breeders or in 158 male and 149 female control offspring. Latencies for both hepatocellular carcinomas

and angiosarcomas averaged approximately 52 weeks in Group I offspring and approximately 80 weeks in Group II offspring. Tumours in the brain described as 'neuroblastomas' were seen in vinyl chloride-exposed rats only: 32/54 female breeders, 31/64 male and 27/63 female Group I offspring and 7/60 male and 11/60 female Group II offspring (Maltoni & Cotti, 1988). [The Working Group noted that these latter neoplasms occurred at a high frequency in vinyl chloride-exposed adult rats which is unprecedented for primary brain tumours in bioassays; that this diagnosis has not been established in other bioassays of vinyl chloride or other chemicals; and that the photomicrographs and the preferential location of the tumours in the anterior frontal lobes support the alternative diagnosis of an origin in the metabolically active olfactory neuroepithelium of the posterior nasal cavity (aesthesioneuroepithelioma).]

3.7 Carcinogenicity of metabolites

Mouse

Local tumours (mainly fibrosarcomas) were observed in 15/28 male, 12/24 female and 0/30 control male XVIInc/Z mice, 8–10 weeks of age, following 32 subcutaneous injections of 0 (controls) or 0.1 mg chloroethylene oxide [purity unspecified] over 42 weeks (the experiment was terminated 36.5 weeks post-exposure). Chloroethylene oxide increased the incidence of skin papillomas and carcinomas in male XVIInc/Z mice in a classical initiation–promotion experiment (chloroethylene oxide was used as an initiator and 12-*O*-tetradecanoylphorbol-13-acetate [TPA] as a promoter) (skin papilloma, 18/28 versus 4/28 TPA controls; skin carcinoma, 5/28 versus 0/28 TPA controls), whereas chloroacetaldehyde [purity unspecified]did not produce such tumours under comparable conditions (Zajdela *et al.*, 1980).

Chloroacetaldehyde (≥ 95% pure with no identifiable impurities) slightly increased the incidence of hepatocellular tumours (10/26 versus 3/20 controls [not significant]) in male $B6C3F_1$ mice when administered orally in the drinking-water at a mean daily ingested dose of 17 mg/kg bw per day for 104 weeks (Daniel *et al.*, 1992).

3.8 Co-exposure with modifying agents

Rat

Groups of 80 male Sprague-Dawley rats [age not specified] were used in a 2 × 2 factorial design and were exposed by whole-body inhalation to 1500 mg/m^3 [577 ppm] vinyl chloride (99.9% pure) for 4 h per day on 5 days per week for 12 months and were then held for an additional 18 months. Animals were kept until spontaneous death or were killed at the end of the 18-month post-exposure observation period. Additional groups were exposed to vinyl chloride and ingested 5% ethanol in water (v/v), were exposed to filtered air and ethanol or were exposed to filtered air alone. Ingestion of 5% ethanol was begun 4 weeks before inhalation of vinyl chloride and continued for life or until ter-

mination of the study 30 months after the first vinyl chloride exposure. No information on survival was provided. The incidence of hepatocellular carcinomas was: 1/80 control, 8/80 ethanol-treated, 35/80 vinyl chloride-treated and 48/80 vinyl chloride plus ethanol-treated rats; that of liver angiosarcomas was: 0/80 control, 0/80 ethanol-treated, 18/80 vinyl chloride-treated and 40/80 vinyl chloride plus ethanol-treated rats; that of pituitary tumours was: 8/80 control, 26/80 ethanol-treated, 19/80 vinyl chloride-treated and 12/80 vinyl chloride plus ethanol-treated; and that of lymphosarcomas was 2/80 control, 4/80 ethanol-treated, 6/80 vinyl chloride-treated and 11/80 vinyl chloride plus ethanol-treated rats. The authors stated that these results indicate that ethanol potentiates the carcinogenicity of vinyl chloride (Radike *et al.*, 1981). [The Working Group noted that isocaloric and isonutrient intakes were not controlled in either the treated or control groups.]

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism and excretion

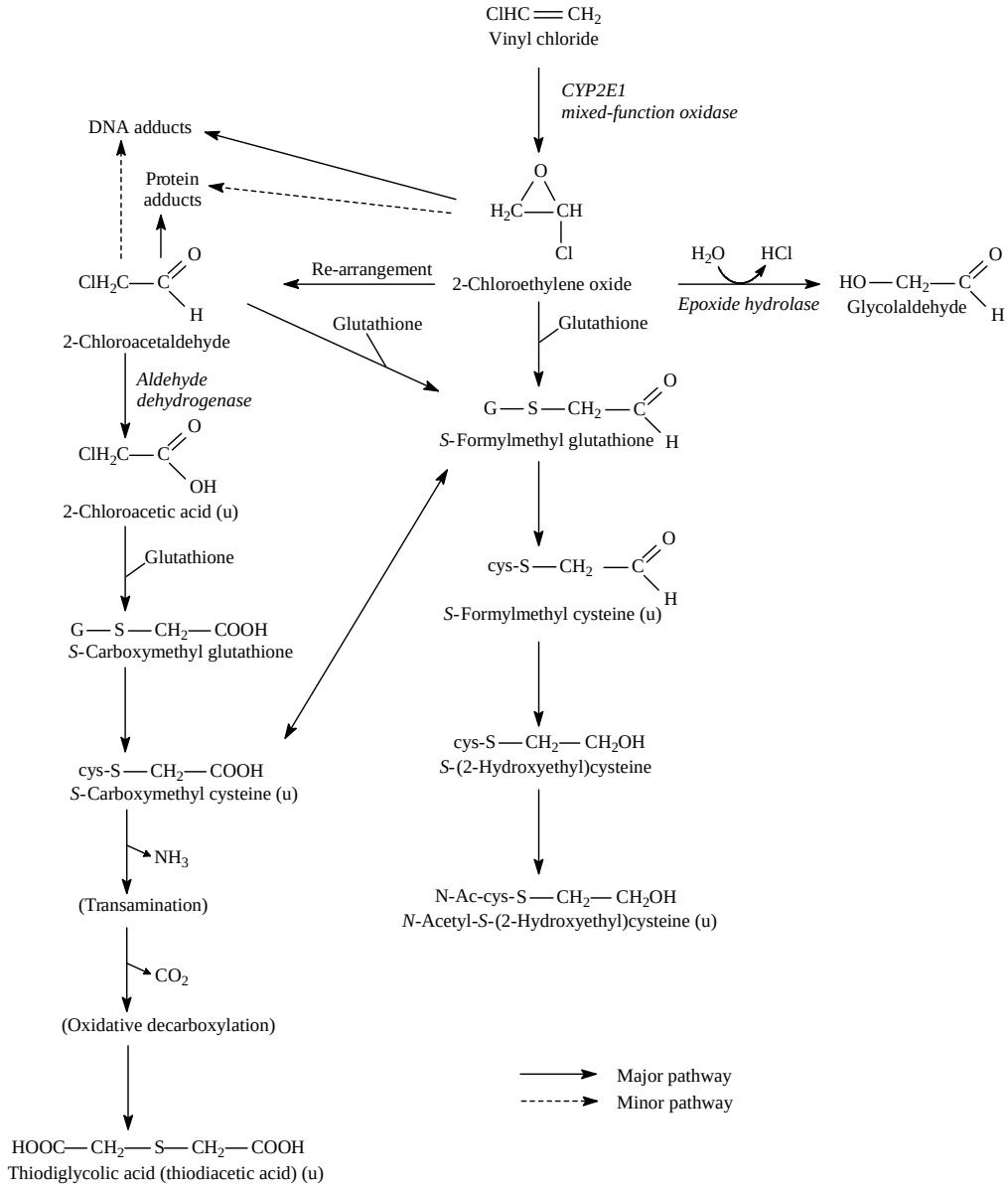
4.1.1 *Humans*

No data on absorption, distribution, metabolism or elimination of vinyl chloride in humans were presented in the previous review (IARC, 1979). Since that time, a number of studies have contributed to the understanding of the inhalation pharmacokinetics of vinyl chloride in humans.

Pulmonary absorption of vinyl chloride in humans appeared to be rapid and the percentage absorbed was independent of the concentration inhaled. Krajewski *et al.* (1980; cited in ATSDR, 2006) reported that adult male volunteers exposed for 6 h to 2.9, 5.8, 11.6 or 23.1 ppm [7.5, 15, 30 or 60 mg/m^3] by gas mask retained on average approximately 42% of inhaled vinyl chloride. Pulmonary uptake is determined in part by the blood:air partition coefficient, which is 1.16 for vinyl chloride (Gargas *et al.*, 1989). No data were available on human tissue:blood partition coefficients or tissue concentrations of vinyl chloride in exposed humans. However, calculations based on the assumption of an identical solubility of vinyl chloride in rodent and human tissues indicate that the tissue:blood partition coefficients of vinyl chloride would be twofold greater in humans (Clewell *et al.*, 2001), as a consequence of the twofold lower blood:air partition coefficient of vinyl chloride in humans compared with rats and mice.

Vinyl chloride is primarily and rapidly metabolized in the liver, and this metabolism is saturable (Bolt, 2005). The proposed metabolic pathways for vinyl chloride are presented in Figure 1. The first step in the metabolism of vinyl chloride is oxidation, which is predominantly mediated by human cytochrome P450 (CYP) 2E1, to form the highly reactive chloroethylene oxide, which can spontaneously rearrange to chloroacetaldehyde (Barbin *et al.*, 1975). Both metabolites can bind with proteins, DNA and RNA and form etheno-adducts; chloroethylene oxide is the most reactive with nucleotides

Figure 1. Proposed metabolic pathways for vinyl chloride



From Barbin *et al*. (1975); Plugge & Safe (1977); Green & Hathway (1977); Guengerich & Watanabe (1979); Guengerich *et al*. (1979); Bolt *et al*. (1980); adapted from ATSDR (2006)
CYP, cytochrome P450; (u), excreted in urine

(Guengerich *et al.*, 1979). Conjugation of chloroethylene oxide and chloroacetaldehyde with glutathione (GSH) eventually leads to the major urinary metabolites *N*-acetyl-*S*-(2-hydroxyethyl)cysteine and thiodiglycolic acid. Chloroethylene oxide and chloroacetaldehyde can also be detoxified to glycolaldehyde by microsomal epoxide hydrolase (mEH) and to the urinary metabolite chloroacetic acid by aldehyde dehydrogenase 2 (ALDH2), respectively (Guengerich & Watanabe, 1979; ASTDR, 2006).

A number of in-vitro studies that used purified human CYP2E1 and liver microsomes confirmed that vinyl chloride is activated mainly by CYP2E1 (reviewed in WHO, 1999). In hepatic postmitochondrial fractions, Sabadie *et al*. (1980) found significant interindividual variability in the metabolism of vinyl chloride, although the average activity in human samples was comparable with that in rat samples.

The main routes of elimination of vinyl chloride and its metabolites are exhalation and urinary excretion, respectively. Accordingly, thiodiglycolic acid has been reported to be the major metabolite of vinyl chloride detected in the urine of exposed workers (Cheng *et al*., 2001). Urinary levels of thiodiglycolic acid were correlated with levels of vinyl chloride in the air at concentrations of > 5 ppm (ATSDR, 2006). In contrast, exhalation of unmetabolized vinyl chloride has been reported to occur in humans at low levels (Müller *et al*., 1978; Krajewski *et al*., 1980; Pleil & Lindstrom, 1997). For example, the mean concentration in expired air of humans exposed for 6 h to air that contained 6.8–23.1 ppm [15–60 mg/m^3] vinyl chloride ranged from 0.21 to 1.11 ppm [0.54–2.84 mg/m^3], which represented 3.6 and 4.73% of the inhaled amounts, respectively (Krajewski *et al*,. 1980).

4.1.2 *Experimental systems*

The absorption, distribution, metabolism and elimination of vinyl chloride in rats and mice have been reviewed (IARC, 1979; WHO, 1999; ATSDR, 2006). The following section summarizes the salient features of the studies reviewed in IARC (1979) as well as significant new information on the metabolism and pharmacokinetics of vinyl chloride in animals.

Animal data have demonstrated that pulmonary and gastrointestinal absorption of vinyl chloride occurs readily and rapidly. On the contrary, dermal absorption of airborne vinyl chloride is probably not significant. In monkeys, Hefner *et al*. (1975a) reported that only 0.023–0.031% of the total available vinyl chloride was absorbed by the dermal route, whereas absorption in rats was virtually complete following single oral doses (44–92 mg/kg bw) of vinyl chloride in aqueous solution (Withey, 1976). When rats were exposed to initial concentrations of < 260 mg/m^3 [100 ppm], about 40% of inhaled [^{14}C]vinyl chloride was absorbed by the lung (Bolt *et al*., 1976).

The tissue:blood partition coefficients (which determine the volume of distribution) of vinyl chloride range from 0.4 (muscle) to 10 (fat) in male rats (Barton *et al*., 1995). The fat:air partition coefficient for vinyl chloride, reported by several authors, tended to be higher in female than in male rats (WHO, 1999). Bolt *et al*. (1976) reported that, following inhalation exposure to [^{14}C]vinyl chloride, several tissues (brain, liver, spleen,

kidney, adipose tissue and muscle) contained radioactivity, and that the highest levels were found in liver and kidney. Ungvary *et al*. (1978) reported that vinyl chloride was present in fetal blood and amniotic fluid following exposure of pregnant rats on gestation day 18 to ~2000–13 000 ppm [5500–33 000 mg/m^3] (2.5-h exposures), which indicates that vinyl chloride crossed the placental barrier.

Osterman-Golkar *et al*. (1977) reported the alkylation of cysteine and histidine of haemoglobin and small amounts of alkylated histidine in proteins from the testis mice exposed to [^{14}C]vinyl chloride.

The metabolism of vinyl chloride to chloroethylene oxide, the probable carcinogenic metabolite, appears to be a saturable, dose-dependent process that occurs in the liver predominantly through the CYP system (Reynolds *et al*., 1975; Ivanetich *et al*., 1977; Barbin & Bartsch, 1989; Lilly *et al*., 1998; Bolt, 2005). CYP2E1 appears to account for all metabolic activity in rat liver microsomes, with a maximum velocity (V_{max}) of 4674 pmol/mg protein/min and a Michaelis-Menten constant (K_m) of 7.42 µmol/L (El Ghissassi *et al*., 1998). Since CYP2E1 has been demonstrated to be present in several other tissues at low levels (compared with the liver), it is reasonable to anticipate that extrahepatic metabolism of systemically available vinyl chloride occurs

Inhibitors of CYP, such as 3-bromophenyl-4(5)-imidazole or 6-nitro-1,2,3-benzothiadiazole, reduced the metabolism of vinyl chloride *in vivo* (Bolt *et al*., 1976). Chloroethylene oxide, which has a half-life of 1.6 min in aqueous solution at neutral pH (Barbin *et al*., 1975), rearranges to chloroacetaldehyde (Bonse *et al*., 1975), conjugates with GSH and can be hydrolysed by EH to glycolaldehyde (WHO, 1999). Chloroacetaldehyde combines directly or enzymatically via glutathione-*S*-transferase (GST) with GSH to form *S*-formylmethyl glutathione, which is excreted as *N*-acety1-*S*-(2-hydroxyethyl)cysteine (Green & Hathway, 1977) (Figure 1). Chloroacetaldehyde can be oxidized to chloroacetic acid, which is either excreted as such or bound to GSH to form *S*-carboxymethyl glutathione, which, upon further enzymic degradation, is excreted as thiodiglycolic acid (thiodiacetic acid) (Plugge & Safe, 1977).

Chloroacetic acid was metabolized in rats to two major urinary metabolites, *S*-carboxymethyl cysteine and thiodiacetic acid (Yllner, 1971). *N*-Acetyl-*S*-(2-hydroxyethyl)cysteine (a major metabolite) (Watanabe *et al*., 1976a,b; Green & Hathway, 1977), *S*-(carboxymethyl)cysteine and *N*-acetyl-*S*-vinyl cysteine have been shown to be metabolites of vinyl chloride in rats after oral administration (Green & Hathway, 1977) and *N*-acetyl-*S*-(2-hydroxyethyl)cysteine after inhalation (Watanabe *et al*., 1976b); *S*-(2-chloroethyl)cysteine was also identified after oral administration of vinyl chloride to rats (Green & Hathway, 1975). As thiodiglycolic acid was obtained as a common metabolite in rats dosed separately with chloroacetaldehyde, chloroacetic acid or *S*-(carboxymethyl)cysteine, the identification of the same *S*-containing metabolite from vinyl chloride-treated animals gives further support to the hypothesis that chloroethylene oxide or chloroacetaldehyde are formed and react with GSH (Green & Hathway, 1977).

Following oral administration of [^{14}C]vinyl chloride, [^{14}C]carbon dioxide (Green & Hathway, 1975; Watanabe *et al*., 1976a), ^{14}C-labelled urea and glutamic acid were identified as minor metabolites (Green & Hathway, 1975).

Saturation of the metabolism of vinyl chloride (Gehring *et al*., 1978; Filser & Bolt, 1979) appears to occur at an inhalation concentration of above 200 ppm [518.6 mg/m^3] in rhesus monkeys (Buchter *et al*., 1980) and 250 ppm [648 mg/m^3] in rats (Bolt *et al*., 1977; Filser & Bolt, 1979). The plateau of incidence of hepatic angiosarcoma in rat carcinogenicity bioassays is also observed at above 250 ppm (reviewed in Bolt, 2005).

ATSDR (2006) summarized the kinetic constants obtained *in vivo* in male Sprague-Dawley rats (V_{max}, 58 µmol/h/kg; K_m, 1 µM) and rhesus monkeys (V_{max}, 50 µmol/h/kg) (based on Buchter *et al*., 1980; Barton *et al*., 1995). The V_{max} of 50 µmol/h/kg in rhesus monkeys was suggested to be a closer approximation of metabolism in humans than the value of 110 µmol/h/kg estimated for rats by Filser and Bolt (1979) (ATSDR, 2006). Although vinyl chloride has not been associated with the induction of CYP, several authors reported the destruction of CYP protein following exposures to vinyl chloride (WHO, 1999). However, Watanabe *et al*. (1978a) reported that the rate of elimination of vinyl chloride was not altered during repeated exposures (5 days per week for 7 weeks) compared with single inhalation exposure (~13 000 mg/m^3 [5000 ppm]).

Urinary excretion of polar metabolites is the predominant process of elimination at low concentrations of exposure, and very small amounts are expired in air as unchanged vinyl chloride (Hefner *et al*., 1975b). Following exposure of male rats by inhalation to 26 mg/m^3 [10 ppm] [^{14}C]vinyl chloride for 6 h, urinary ^{14}C activity and expired vinyl chloride comprised 68 and 2%, respectively, of the recovered radioactivity; after exposure to 2600 mg/m^3 [1000 ppm] [^{14}C]vinyl chloride, the proportion of radioactivity in the urine was lower and that expired as vinyl chloride was higher, and represented 56 and 12%, respectively (Watanabe *et al*., 1976b). Following a single oral administration of 0.05, 1 or 100 mg/kg bw [^{14}C]vinyl chloride to male rats, excretion in the urine was 68, 59 and 11%, respectively; [^{14}C]carbon dioxide in expired air accounted for 9, 13 and 3%, respectively; pulmonary elimination of unchanged vinyl chloride represented only 1–3% of the lower dose and 67% of the higher dose (Watanabe *et al*., 1976a). These data are consistent with the fact that, once metabolic saturation is attained, the elimination of vinyl chloride occurs via other routes, mainly exhalation of the parent chemical. The route of elimination also depends upon the route of administration; urinary excretion is favoured following oral or intraperitoneal administration, which indicates a first-pass effect due to metabolism in the liver (reviewed in Clewell *et al*., 2001).

Several investigators have observed the binding of non-volatile metabolites of [^{14}C]vinyl chloride to liver macromolecules, both *in vitro* and in rats exposed by inhalation (Kappus *et al*. 1976; Watanabe *et al*., 1978a,b; Guengerich & Watanabe, 1979; Guengerich *et al*., 1979; Bolt *et al*., 1980; Guengerich *et al*., 1981; Barton *et al*., 1995). Jedrychowski *et al*. (1984) reported a decrease in non-protein sulfhydryl concentration in rats exposed to high concentrations of vinyl chloride, and Kappus *et al*. (1975) and Laib and Bolt (1977) reported binding of vinyl chloride to RNA *in vitro* and *in vivo*. In single-

exposure experiments at various concentrations, the extent of macromolecular binding increased proportionately to the amount of vinyl chloride metabolized and disproportionately to the exposure concentration (Watanabe *et al*., 1978b).

4.1.3 *Toxicokinetic models*

The data on absorption, distribution, metabolism and excretion of vinyl chloride have been analysed with the use of empirical and physiologically based compartmental models (Gehring *et al*., 1978; Chen & Blancato, 1989; Clewell *et al*., 1995; Reitz *et al*., 1996; Clewell *et al*., 2001). These models indicate that vinyl chloride is rapidly absorbed by the inhalation and oral routes and is distributed to all tissues; the adipose tissues show the greatest affinity. The physiologically based pharmacokinetic models developed by Chen and Blancato (1989), Clewell *et al*. (1995, 2001) and Reitz *et al*. (1996) permit the prediction of the pharmacokinetics, GSH depletion and the amount of vinyl chloride metabolized in animals and/or humans exposed to various concentrations by different routes and schedules. However, these models do not currently permit the simulation of the time course of the formation and persistence of DNA adducts in target tissues.

4.2 Genetic and related effects

Since the last review of vinyl chloride (IARC, 1979), a large amount of data on vinyl chloride has been produced and reviewed (WHO, 1999). Only the more recent data that are relevant to the comprehension of vinyl chloride-induced carcinogenicity are reported in this section.

4.2.1 *Humans*

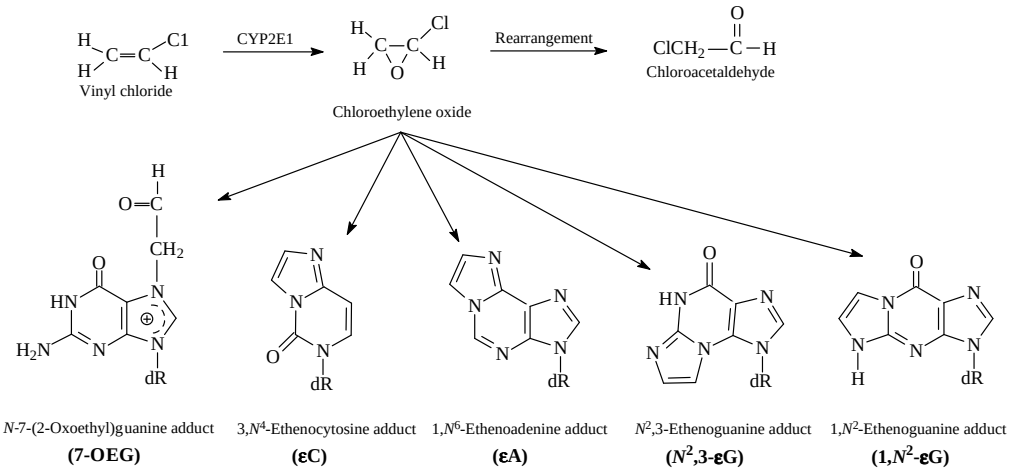
(a) DNA adducts

In vitro, both chloroethylene oxide, the biologically reactive intermediate of vinyl chloride that is formed in the liver, and its rearrangement product, chloroacetaldehyde, can form etheno adducts with nucleic acid bases. Chloroethylene oxide has, however, greater reactivity and it was shown *in vitro* to be the main entity that gives rise to etheno adducts (Guengerich, 1992). The reaction of 2-chloroethylene oxide with nucleic acid bases yields the *N*-7-(2-oxoethyl)guanine adduct (7-OEG) and four etheno adducts—1,N^6-ethenoadenine (εA), 3,N^4-ethenocytosine (εC), N^2,3-ethenoguanine (N^2,3-εG) and 1,N^2-ethenoguanine (1,N^2-εG) (Figure 2) (Ciroussel *et al.*, 1990; Guengerich, 1992). Another adduct, formed by chloroethylene oxide, 5,6,7,9-tetrahydro-7-hydroxy-9-oxoimidazo[1,2-*a*]purine (HO-ethanoG), has also been identified *in vitro* (Müller *et al*., 1996).

Data on the occurrence and persistence of DNA adducts in tissues of humans exposed to vinyl chloride are lacking. Only one study that used immunoaffinity purification of the etheno adducts and subsequent ^{32}P-postlabelling reported levels of 14.1 εA and 8.1 εC per

10^9 parent bases in non-neoplastic liver tissue of a vinyl chloride-exposed patient with hepatocellular carcinoma (Nair *et al*., 1995). These adducts can also result from lipid peroxidation (El Ghissassi *et al*., 1995) and their level can be quite high (in the range of $\leq$ 0.5–40 εA and εC per 10^9 parent bases in liver DNA samples from patients with unknown exposure) (Bartsch & Nair, 2000a,b).

Figure 2. Reactive metabolites and main nucleic acid adducts of vinyl chloride identified *in vitro* and *in vivo*



Adapted from Ciroussel *et al.* (1990)
CYP, cytochrome P450

(b) Mutations and other related effects

(i) *Mutated p21^{ras} and p53 proteins in the blood of vinyl chloride-exposed workers*

Mutated p21^{ras} and p53 proteins in the blood of vinyl chloride-exposed workers may reflect the mutagenic effects of vinyl chloride. A G→A transition at the second base of codon 13 of the Ki-*ras* gene was found in four liver angiosarcomas that were associated with occupational exposure to vinyl chloride (Marion *et al*., 1991). The resulting Asp13p21^{ras} protein was also detected in the serum of these four patients by immunohistochemistry using a monoclonal antibody specific for the Asp13p21^{ras} protein (De Vivo *et al*., 1994). The presence of the mutant RAS protein in the blood correlates with the mutated *ras* gene in the tumour (Table 16).

Several studies showed a high concentration of the Asp13p21^{ras} mutant protein in the sera of workers who had been heavily exposed to vinyl chloride whereas all unexposed controls showed negative results. In addition, these studies found a significant dose–

Table 16. Ki-*ras* and *p53* Gene analysis of vinyl chloride-related liver angiosarcoma (ASL) and detection of mutated p21^{ras} and p53 proteins and anti-p53 antibodies in the serum from the same patients

	Ki-*ras* 2 Gene			*p53* Gene		
	Tissue		Serum	Tissue	Serum	
	DNA $GGC_{13}\rightarrow GAC_{13}$	Asp13p21^{ras}	Asp13p21^{ras}	DNA	Mutant p53 protein	Anti-p53 antibodies
ASL1	+	+	+	ATC→TTC	+	–[a]
ASL2	+	+	+	AGG→TGG	+	++
ASL3	+	+	+	–	–	–
ASL4	+	+	+	–	–	–
ASL5[b]	–	–	–	CAT→CTT	±	+
ASL6	–	–	–	NR	–	++

From Marion (1998)
NR, not reported; +, positive; –, negative; ±, equivocal; ++, strongly positive
[a] Patient with abnormal immunological response
[b] Fibroblastic cell line established from a liver angiosarcoma

response relationship between exposure to vinyl chloride and the detection of Asp13p21^{ras} mutant protein in the sera of exposed workers (Tables 17 and 18).

Mutated p53 proteins and/or anti-p53 antibodies were also found in the blood of vinyl chloride-exposed patients. In a pilot study, Trivers *et al*. (1995) analysed 148 serum samples from 92 vinyl chloride-exposed workers from factories in France and industrial plants in Kentucky, USA. Serum anti-p53 antibodies were found in five of 15 workers who had liver angiosarcoma (33%), two of whom had confirmed mutated *p53* gene (Hollstein *et al*., 1994), and in four (5%) of 77 workers with no clinical evidence of cancer. Two of 26 workers who had clinical symptoms of vinyl chloride toxicity had antibodies that were detectable by enzyme immunoassays. No antibodies were detected in the two workers who had hepatocellular carcinoma or in seven of eight workers who had liver angiomas. In two liver angiosarcoma patients, anti-p53 antibodies were detected 4 months and 11 years, respectively, before the diagnosis of cancer and one patient had anti-p53 antibodies before and after surgery. Anti-p53 antibodies were thought to be the result of earlier antigenic presentation to the immune system, through accumulation of the mutated protein.

The main purpose of these studies was to determine whether the expression of serum biomarkers was indeed related to exposure to vinyl chloride. The finding of a significant dose–response relationship strongly supports this hypothesis and confirms that *RAS* gene mutations are involved in the onset of liver angiosarcoma induced by vinyl chloride and that mutant p21^{ras} plays a key role in the development of vinyl chloride-induced liver

Table 17. Dose–response relationship between the detection of Asp13p21^{ras} protein in blood and exposure to vinyl chloride (VC)

References	Cohort description	Exposure assessment	Exposure categories	No. of Asp13p21-positive	Odds ratio (95% CI) (adjusted)	Adjustment for potential confounders
De Vivo *et al*. (1994)	60 male workers heavily exposed to VC (at least 1 year before 1974 or 5 years of total exposure); average exposure, 19.5 years with an average of 12.2 years before 1974; 5 ASL, 1 HCC, 9 liver angiomas, 45 subjects with no liver lesion	Estimates of VC based on years worked with VC: total years worked and years worked before 1974	*Years of total exposure* 0 (n = 28) < 10 (n = 10) 10–19 (n = 22) 20–29 (n = 20) ≥ 30 (n = 8)	 0 4 11 13 6	 1.0 37 56 104 168 χ^2 for linear trend = 24.986; $p < 10^{-5}$	None
Li *et al*. (1998a)	225 men randomly selected among the job categories involving exposure to VC; average exposure level, 3735 ppm–years (range, 4–46 702 ppm–years); 42.2% with a history of having smoked cigarettes, 25.3% with regular daily alcoholic beverage consumption	VC exposure levels were attributed to each subject on the basis of the job, using estimated values assigned to the various jobs[a]	0 (n = 111) ≤ 500 ppm–years (n = 54) 501–2500 ppm–years (n = 62) 2501–5000 ppm–years (n = 51) > 5000 ppm–years (n = 58)	4 13 19 18 26	 10.18 (2.94–35.25) 13.61 (4.26–43.46) 15.43 (4.83–49.28) 21.55 (6.99–66.44) $p < 0.0001$	Age, smoking, alcoholic beverage consumption
Luo *et al*. (1998)	117 randomly selected workers including 7 with liver tumours (angiomas); average exposure, 2734.9 ± 4299.9 ppm–months (range, 5.4–34 521 ppm–months)	Estimated accumulated ppm–months	No exposure (n = 18) > 1000 ppm–months (n = 69) ≤ 1000 ppm–months (n = 48)	0 10 4	1.0 2.65 (0.42–16.8) 1.64 (0.17–15.8) χ^2 for linear trend = 3.92; p = 0.048	Age, alcoholic beverage consumption, smoking, hepatitis C and HBV infection

ASL, liver angiosarcoma; CI, confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma

[a] Estimates of VC exposure in ppm–years were based on years of a given job category weighted by the presumed level of exposure as defined by the exposure matrix of Heldaas *et al*. (1984)

Table 18. Prevalence of Asp13p21^{ras} mutant protein in blood samples of vinyl chloride-exposed workers

Reference	Mean exposure to vinyl chloride	No. of subjects tested	Asp13p21-positive (%)
De Vivo *et al*. (1994)	19.5 years, 12.2 years before 1974	60, including 5 ASL and 1 HCC	56.6 (0 in controls)
Li *et al*. (1998a)	2735 ppm–years (range, 4–46 702 ppm–years)	225	33.8 (3.7 in controls)
Luo *et al*. (1998)	2734.9 ppm–months (range, 5.4–34 521 ppm–months)	117	12 (0 in controls)

ASL, liver angiosarcoma; HCC, hepatocellular carcinoma

angiosarcoma (Table 17). A similar relationship was found between the presence of mutated p53 in blood and exposure to vinyl chloride (Tables 19 and 20).

Anti-p53 antibodies have also been tested as a possible biomarker of exposure to vinyl chloride. The occurrence of anti-p53 antibodies in the blood of vinyl chloride-exposed workers seems to be related to the level of exposure with a threshold [~1000 ppm–years]. Below this threshold, this effect is not detected (Table 21).

When two markers, Asp13p21^{ras} and mutated p53, were tested against exposure to vinyl chloride, each biomarker alone demonstrated a highly statistically significant trend with exposure ($p < 0.0001$). Similarly, a highly statistically significant increase was observed in the serum concentration of one or both of the biomarkers with increasing exposure (Table 22).

(ii) *Cytogenetic studies of vinyl chloride-exposed workers*

Studies on the genotoxicity of vinyl chloride, including studies of chromosomal aberrations, micronucleus formation and sister chromatid exchange, have recently been reviewed (WHO, 1999). There was a clear relationship between the incidence of chromosomal aberrations and exposure concentration, although exposure concentration and duration of exposure were only estimated. Lesser or no effects were seen when the exposure was reduced to levels < 5 ppm [< 13 mg/m^3].

The frequency of sister chromatid exchange increased with the level of exposure to vinyl chloride, and sister chromatid exchange was generally not detected in the blood of workers exposed to levels < 5 ppm [< 13 mg/m^3]. A recent study conducted to investigate the genotoxicity of vinyl chloride at low levels confirmed the absence of sister chromatid exchange in the blood of workers exposed to vinyl chloride levels of approximately 1 ppm [2.59 mg/m^3] (Cheng *et al*., 2000).

DNA single-strand breaks measured in the alkaline comet assay were thought to occur by transformation of apurinic sites that resulted from repair of vinyl chloride–etheno

Table 19. Dose–response relationship between detection of mutant p53 protein in blood and occupational exposure to vinyl chloride (VC)

Reference, location	Cohort description	Exposure assessment	Exposure categories	No of mutant p53-positive	Odds ratio (95% CI) (adjusted)	Adjustment for potential confounders
Smith *et al*. (1998), France	225 men randomly selected among job categories that involved exposure to VC; average VC exposure level, 3735 ppm–years (range, 4–46 702 ppm–years)	VC exposure levels were attributed to each subject on the basis of the job, using estimated values assigned to the various jobs[a]	0 (n = 111) ≤ 500 ppm–years (n = 54) 501–2500 ppm–years (n = 62) 2501–5000 ppm–years (n = 51) > 5000 ppm–years (n = 58)	9 16 21 24 30	1 4.16 (1.63–10.64) 5.76 (2.39–13.85) 10.24 (4.20–24.95) 13.26 (5.52–31.88) $p < 0.0001$	Age, smoking status, alcoholic beverage consumption

CI, confidence interval

[a] Estimates of VC exposure in ppm–years were based on years of a given job category weighted by the presumed level of exposure as defined by the exposure matrix of Heldaas *et al*. (1984)

Table 20. Prevalence of mutant p53 and anti-p53 antibody-positive blood samples in vinyl chloride-exposed workers

Reference	Mean cumulative exposure to vinyl chloride	No of subjects tested	Mutant p53-positive (%)	Anti-p53 antibody-positive (%)
Smith *et al*. (1998)	3735 ppm–years (range, 4–46 702 ppm–years)	225	40.4 (8 in controls)	–
Luo *et al*. (1999)	1341 ± 3148 ppm–months (range, 0–34 521 ppm–months)	251	11 (2.8 in controls)	3.6 (2.3 in controls)
Mocci & Nettuno (2006)	484 ppm–years (range, 4–2823 ppm–years)	151	2 (0 in controls)	3.3 (0 in controls)

adducts through base-excision repair by glycosylase. The level of DNA single-strand breaks was found to be significantly higher in workers exposed to levels of vinyl chloride > 5 ppm [13 mg/m^3] than in workers exposed to levels < 5 ppm (Lei *et al*., 2004).

(iii) *Mutations at the hypoxanthine guanine phosphoribosyl transferase (HPRT) locus*

With the *HPRT* lymphocyte clonal assay, it is possible to determine the mutation frequency of the *HPRT* gene and to characterize its mutant spectra. Mutagenesis induced in the lymphocytes of PVC production workers was measured by selecting resistant mutant T cells in a medium that contained 6-thioguanine. Exposed workers and controls had similar mutation frequencies. However, great differences occurred in the spectrum of mutants. In particular, the percentage of large deletions in the exposed group was much higher (21%) than in unexposed controls (11%) (Hüttner & Holzapfel, 1996). The mutant frequency of *HPRT* in T lymphocytes of 29 individuals accidentally exposed to levels of vinyl chloride between 1 and 8 ppm [2.6–20.7 mg/m^3] was measured after the accident and in a follow-up study 2 years later. A statistically significantly higher cloning efficiency was observed in the exposed population after the accident (68.1 versus 50.7% in the controls; $p = 0.007$, Mann-Whitney test). However, no significant difference in the mutant frequency could be found between the exposed population and controls ($3.28 \pm 1.84 \times 10^{-6}$ versus $3.01 \pm 2.38 \times 10^{-6}$) (Becker *et al*., 2001).

4.2.2 *Experimental systems*

(a) DNA adducts

Studies on the formation of DNA adducts in animals have recently been reviewed (WHO, 1999). New data are summarized in Table 23.

Table 21. Dose–response relationship between detection of mutant p53 protein and anti-p53 antibody in blood and occupational exposure to vinyl chloride (VC)

Reference, location	Cohort description	Exposure assessment	Exposure categories	No of mutant p53-positive	Odds ratio (95% CI) (adjusted)	No. of total p53 responses (mutant or antibody)	Odds ratio (95% CI) (adjusted)	Adjustment for potential confounders	Comments
Luo *et al.* (1999), Taiwan, China	251 workers including 7 with liver tumours (assumed to be angiomas); average cumulative exposure, 1341 ± 3148 ppm–months (range, 0–34 521 ppm–months)	Estimated accumulated ppm–months	0 (n = 36)	1	1	2	1	Age, smoking, alcoholic beverage consumption	Significant dose–response relationship between plasma total p53 protein overexpression and cumulative VC exposure concentration
			Low exposure ≤ 480 ppm–months (n = 156)	14	1.6 (0.21–12.54) χ^2 for linear trend = 1.37; p = 0.24	19	1.49 (0.24–9.2) χ^2 for linear trend = 0.95; p = 0.33		
			High exposure > 480 ppm-months (n = 95)	11	3.5 (0.54–22.5)	14	2.5 (0.5–12.14)		
Mocci & Nettuno (2006), Italy	151 male workers; mean cumulative exposure, 484 ± 725 ppm–years (range, 4–2823 ppm–years)	VC exposure levels before 1983 were attributed to each subject on the basis of the job, using estimated values assigned to the various jobs	0 (n = 136)	0		0		Age, smoking, alcoholic beverage consumption	Trend for increasing serum positivity for p53 antibodies with increasing level of VC exposure; logistic regression using mutant p53 antigen or p53 antibodies adjusted for smoking, alcoholic beverage consumption and age shows cumulative VC exposure as only significant predictor (p = 0.03 and 0.005)
			1–100 ppm–years (n = 86)	0		0			
			101–1000 ppm–years (n = 35)	0		1	1		
			1001–2000 ppm–years (n = 18)	1		1	2		
			> 2000 ppm–years (n = 12)	2		3	11.33 χ^2 for linear trend = 5.6; p = 0.02		

CI, confidence interval

Table 22. Dose–response relationship between detection of Asp13p21^{ras} protein and/or mutated p53 protein in blood of vinyl chloride (VC)-exposed workers

Reference, location	Cohort description	Exposure assessment	Exposure categories	One marker positive	Both markers positive	Odds ratio (95% CI) (adjusted)	Adjustment for potential confounders	Comments
Li *et al*. (1998b), France	172 exposed men randomly selected among job categories that involved VC exposure employed since 1950; average VC exposure level, 4107 ppm–years (range, 4–46 702 ppm–years)	VC exposure levels were attributed to each subject on the basis of the job, using estimated values assigned to the various jobs[a]	0 (n = 43)	5	0	1	Age, smoking, alcoholic beverage consumption	Each biomarker alone demonstrated a highly statistically significant trend with exposure ($p < 0.0001$). Similarly, highly statistically significant increasing likelihood of seropositivity for one or both of the biomarkers with increasing exposure
			≤ 500 ppm–years (n = 42)	21	1	11.1 (3.3–37.5)		
			501–2500 ppm–years (n = 45)	21	4	12.8 (4.1–40.2)		
			2501–5000 ppm–years (n = 31)	19	6	29.9 (9.0–99.1)		
			> 5000 ppm–years (n = 54)	22	17	31.2 (10.4–94.2) $p < 0.0001$		
Luo *et al*. (2003), Taiwan, China	251 workers (7 with liver tumours assumed to be angiomas); average cumulative exposure, 112 ± 262 ppm–years (range, 0–2877 ppm–years)	Estimated accumulated ppm–months	0 (n = 44)	2	0	1		Significant linear trend between exposure concentration and one oncoprotein over-expression
			0–10 ppm–years (n = 71)	12	1	2.18 (0.09–54.8)		
			10–40 ppm-years (n = 77)	13	1	2.01 (0.08–50.5)		
			> 40 ppm–years (n = 95)	29	0	–		

CI, confidence interval

[a] Estimates of VC exposure in ppm–years were based on years of a given job category weighted by the presumed level of exposure as defined by the exposure matrix of Heldaas *et al*. (1984)

Table 23. Formation of DNA adducts in rats exposed to vinyl chloride (VC)

Strain, sex, age	Treatment	Organs investigated	Alkylated bases/10^8 unmodified bases in DNA		Comments	Reference
			Background levels	After vinyl chloride exposure		
Sprague-Dawley, male, 6 weeks	1300 mg/m^3 [500 ppm], 4 h/d, 5 d/wk for 8 wks	Liver, lung, kidney, circulating lymphocytes, brain, spleen testis	**εA**: mean value from 0.043 in the liver to 35 in brain **εC**: mean value from 0.062 in the liver to 20.4 in brain	**εA**: 4.1 ± 1.5 in liver, lung, lymphocytes and testis; no increase in kidney and spleen **εC**: 7.8 ± 1.2 in liver, kidney, lymphocytes and spleen No significant increase in brain for either etheno adduct	Levels of VC-induced and endogenous adducts were not higher in the liver, the major target organ of VC, than in other tissues	Barbin (1999)
Sprague-Dawley, female, 10 days	600 ppm [139 mg/m^3], 4 h/d, 5 d	Liver	NR	**εA**: (immunohistochemical levels) 1.5 times higher in VC-exposed rats than in controls	After VC exposure, staining for εA was higher in both parenchymal cells and non-parenchymal cells. Significantly elevated adduct levels persisted in the liver of VC-exposed rats 14 days after cessation of exposure	Yang *et al*. (2000)
Fischer 344	0, 10, 100, 1100 ppm [0, 26, 259, 2858 mg/m^3], 6 h/d, 5 d/wk, 1 or 4 wks	Liver	***N*^{2},3-εG**: 9 ± 0.4	***N*^{2},3-εG**: 10 ppm VC, 5 d: 20 ± 5.0 10 ppm VC, 20 d: 53 ± 1.1 100 ppm VC, 5 d: 68 ± 9 100 ppm VC, 20 d: 228 ± 18	After 10 ppm VC exposure, respectively 2.2- and 5.9-fold increase in *N*^{2},3-εG compared with the amount of endogenous *N*^{2},3-εG	Swenberg *et al*. (2000)
Sprague-Dawley, male, 11 weeks	0 and 1100 ppm [2858 mg/m^3], 6 h/d, 5 d/wk, 1 or 4 wks	Liver	NR	***N*^{2},3-εG**: 20 d, 80.6 ± 2.58 **1,*N*^{2}-εG**: below the detection limit of 15 fmol		Morinello *et al*. (2001)

Table 23 (contd)

Strain, sex, age	Treatment	Organs investigated	Alkylated bases/10^8 unmodified bases in DNA		Comments	Reference
			Background levels	After vinyl chloride exposure		
Adult study Sprague-Dawley, male, 11 weeks *Weanling study* 40 pups weaned at day 25	Whole-body inhalation: 0 and 1100 ppm [2852 mg/m^3], 6 h/d, 5 d/wk, 1 or 4 wks	Liver, brain	*Adult study* **N^2,3-εG**: ~ 5 in liver and brain *Weanling study* **N^2,3-εG**: ~ 1.5 in liver and brain	*Adult study* **N^2,3-εG**: 110 ± 20 in liver after 20 d exposure *Weanling study* **N^2,3-εG**: 97 ± 5.0 in liver after 5 d exposure; 4.4 ± 1.1 in brain after 5 d exposure	*Adult study* No increase after 5 d exposure in liver; no increase observed in brain *Weanling study* Levels of N^2,3-εG in wealings after 5 d exposure similar to those in adults exposed for 4 wks; small but statistically significant increase of N^2,3-εG in brain	Morinello *et al.* (2002a)
Adult study Sprague-Dawley, male, 11 weeks *Weanling study* 40 pups weaned at day 25	Whole-body inhalation: 0, 10, 100, 1100 ppm [0, 26, 259, 2852 mg/m^3], 6 h/d, 5 d/wk, 1 or 4 wks	Liver, hepatocytes (HEP) and non-parenchymal cells (NPC)	*Adult study* **N^2,3-εG**: ~ 5 in HEP; ~ 9 in NPC *Weanling study* **N^2,3-εG**: ~1.6 in HEP; ~ 4.9 in NPC	*Adult study* **N^2,3-εG**: ~35 in HEP and NPC after 5 d exposure to 100 ppm; 110 ± 1 and 71 ± 1.1 in HEP and NPC, respectively, after 20 d exposure to 100 ppm *Weanling study* **N^2,3-εG**: 90 ± 0.7 and 43 ± 0.5 in HEP and NPC, respectively, after 5 d exposure to 100 ppm	Linear increase from 0 to 100 ppm and plateau between 100 and 1100 ppm In contrast to adults, difference in adducts concentration detected between the HEP and NPC populations from the weanlings	Morinello *et al.* (2002b)

d, day; **εA**: 1,N^6-ethenoadenine; **εC**: 3,N^4-ethenocytosine; **N^2,3-εG**: N^2,3-ethenoguanine; **1,N^2-εG**: 1,N^2-ethenoguanine; NR, not reported; wk, week

The DNA adducts εA and εC have been found in various organs in rats after inhalation exposure to vinyl chloride. 7-OEG was shown to be the major DNA adduct formed *in vivo* and was found in greater amounts in young animals (Swenberg *et al*., 2000). However, 7-OEG has a short half-life of about 62 h while etheno adducts were more persistent. For example, N^2,3-εG has a half-life of about 30 days (Fedtke *et al*., 1990). Of the etheno adducts, N^2,3-εG was present in greatest amounts in tissues of exposed animals (10–100-fold greater than other etheno adducts).

After exposure of rats to 500 ppm [1300 mg/m^3] vinyl chloride for 8 weeks, the level of εA was increased significantly above background in the liver, lung, lymphocytes and testis. The level of εC was also increased significantly in the liver, kidney, lymphocytes and spleen. No significant increase was found in brain for either ethano adducts (Guichard *et al*., 1996; Barbin, 1999). When adult rats were exposed to 1100 ppm [2858 mg/m^3] vinyl chloride for 1 or 4 weeks, there was a significant increase in the level of N^2,3-εG in hepatocytes, but not in the brain. In contrast to adults, there was a small, statistically significant increase in N^2,3-εG in the brain of weanling animals exposed for 5 days. In addition, in weanlings, the concentration of N^2,3-εG in hepatocytes was significantly greater than that measured in non-parenchymal cells after exposures to 10 and 100 ppm [26 and 259 mg/m^3] vinyl chloride (Morinello *et al*., 2002a). These differential responses between weanlings and adults may contribute to the particular susceptibility of young rats to vinyl chloride-induced neuroblastomas and hepatocarcinomas (Maltoni & Cotti, 1988).

In adult rats, N^2,3-εG was clearly induced in both hepatocytes and non-parenchymal cells after exposure to vinyl chloride for 1 or 4 weeks, with a linear increase at exposure concentrations from 0 to 100 ppm [259 mg/m^3] and a plateau at levels of 100–1100 ppm [259–2852 mg/m^3]. There was no significant difference in N^2,3-εG adduct levels, nor in the rate of repair between hepatocytes and non-parenchymal cells (Morinello *et al*., 2002b), which confirms the earlier observation of Yang *et al*. (2000) (see also Table 23).

(b) Mutations and other related effects (see Table 24)

Genotoxicity studies on vinyl chloride *in vitro* and *in vivo* have recently been reviewed (WHO, 1999). The genotoxicity of vinyl chloride has been clearly demonstrated in several in-vitro systems. Vinyl chloride vapour induced reverse mutation in various strains of *Salmonella typhymurium.* In aqueous or alcoholic solutions, vinyl chloride induced mutations in *Escherichia coli, Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*. It was also mutagenic in the recessive lethal test in *Drosophila melanogaster*, but not in the dominant lethal test in mice. It induced DNA strand breaks, sister chromatid exchange, micronucleus formation and chromosomal aberrations in rodents. *In vitro,* a higher mutagenic response was obtained in the presence of an exogenous metabolic activation system from rat liver.

Table 24. Genetic and related effects of vinyl chloride

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Salmonella typhimurium TA100, TA1535, reverse mutation	+	+	200 000 ppm/48 h	McCann *et al*. (1975)
Salmonella typhimurium TA100, TA1535, reverse mutation	+	+	1000 ppm	Shimada *et al.* (1985)
Salmonella typhimurium TA1530, TA1535, G-46, reverse mutation	+	+	2000 ppm/48 h	Bartsch *et al*. (1975)
Salmonella typhimurium TA1530, reverse mutation	+	+	2–20% in air	de Meester *et al*. (1980)
Salmonella typhimurium TA1535, reverse mutation	+	+	110 000 ppm	Rannug *et al*. (1974)
Salmonella typhimurium TA1536, TA1537, TA1538, reverse mutation	–	–	200 000 ppm	Rannug *et al*. (1974)
Salmonella typhimurium TA1538, G-46, reverse mutation	(+)	(+)	200 000 ppm	Bartsch *et al*. (1975)
Salmonella typhimurium TA1537, TA1538, TA98, reverse mutation	–	–	100 000 ppm	Shimada *et al.* (1985)
Escherichia coli K12, gene mutation	+		10.6 mM (medium)	Greim *et al*. (1975)
Schizosaccharomyces pombe P1, SP.198, gene mutation	+	+	16–48 mM (medium)	Loprieno *et al.* (1976)
Drosophila melanogaster male Berlin K, sex-linked recessive lethal mutation	+		850 ppm/2 d or 30 ppm/17 d	Verburgt & Vogel (1977)
Drosophila melanogaster male Karnäs, sex-linked recessive lethal mutation	+		10 000 ppm/3 h	Magnusson & Ramel (1978)
Drosophila melanogaster male Berlin K, dominant lethal test	–		30 000 ppm/2 d	Verburgt & Vogel (1977)
Drosophila melanogaster male Berlin K, aneuploidy (sex chromosome loss)	–		30 000 ppm/2 d	Verburgt & Vogel (1977)
Drosophila melanogaster male Berlin K, aneuploidy (sex chromosome loss)	+		48 500 ppm	Ballering *et al*. (1996)
Host-mediated assay, forward mutation, *Schizosaccharomyces pombe* SP.198 in Swiss mice	+		74 mg/kg bw po	Loprieno *et al.* (1976)
Host-mediated assay, gene conversion, *Saccharomyces cerevisiae* in male Wistar rats	+		10 000 ppm/24 h	Eckardt *et al*. (1981)
DNA single-strand breaks, female NMR mice *in vivo*	+		500 ppm, 6 h/d × 5	Walles & Holmberg (1984)
Mouse spot test, pregnant female C57BL mice	–		4600 ppm/5 h	Peter & Ungvá ry (1980)
Sister chromatid exchange, male and female Chinese hamsters in vivo	+		12 500 ppm/6 h	Basler & Röhrborn (1980)
Micronucleus formation, male CBA mice *in vivo*	+		50 000 ppm/4 h	Jenssen & Ramel (1980)
Micronucleus formation, male and female C57BL/6J mouse bone-marrow cells *in vivo*	+		50 000 ppm/6 h	Richardson *et al*. (1983)

Table 24 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Chromosomal aberrations, male and female Chinese hamster bone-marrow cells *in vivo*	+		25 000 ppm/24 h	Basler & Röhrborn (1980)
Chromosomal aberrations, male Wistar rat bone-marrow cells *in vivo*	+		1500 ppm, 6 h/d × 5	Anderson & Richardson (1981)
Dominant lethal test, male CD-1 mice *in vivo*	–		30 000 ppm, 6 h/d × 5	Anderson *et al.* (1976, 1977)
Dominant lethal test, male CD-1 mice *in vivo*	–		10 000 ppm, 4 h/d × 5	Himeno *et al*. (1983)
Dominant lethal test, male CD-1 mice *in vivo*	–		5000 ppm, 4 h/d, 5 d/wk × 10	Himeno *et al*. (1983)
Dominant lethal test, male CD rats *in vivo*	–		1000 ppm, 6 h/d × 5	Short *et al.* (1977)

[a] +, positive; (+), weak positive; –, negative
[b] LED, lowest effective dose; HID, highest ineffective dose; d, day; po, orally; wk, week

4.2.3 *Mutagenic or promutagenic properties of DNA adducts formed by vinyl chloride metabolites*

The major DNA adduct 7-OEG lacks miscoding properties (Barbin *et al*., 1985). In contrast, promutagenic properties have been shown for the etheno and related exocyclic DNA adducts, εA, εC, N^2,3-εG, and HO-ethanoG that involve mainly base-pair substitution mutations (WHO, 1999; see Table 25)

Various assays have been designed to explore the mutagenic properties of DNA adducts, which have been incorporated into oligonucleotides or into site-specific vectors and used in experiments of misincorporation. Vector plasmids have also been treated with 2-chloroethyleneoxide or 2-chloroacetaldehyde and propagated in *E. coli* or mammalian cells. The more significant and recent studies are listed in Table 25. The mechanism by which adducts cause mutations still remains unclear. At least two vinyl chloride-induced DNA adducts, HO-ethanoG and 1, N^2-εG have been shown to block replication with many different polymerases, thereby causing base misincorporation (Langouët *et al.*, 1997, 1998; Guengerich *et al*., 1999). The misincorporation events appear to be clearly dependent on the individual mechanisms of DNA polymerases (Choi *et al.*, 2006). Mutation frequencies induced by etheno adducts may also depend on the system used since εA was shown to be highly miscoding in COS7 simian kidney cells, in contrast to the findings in *E. coli* (Pandaya & Moriya, 1996). [Clearly, the patterns of base substitution vary among the different systems used and cannot be extrapolated easily to predict mutations in human tumour tissue.]

4.2.4 *Alterations in oncogenes and suppressor-genes in tumours*

(a) RAS genes

Carcinogens are believed to alter genes that are involved in cell proliferation and differentiation. The *RAS* genes, Ha-*ras*, Ki-*ras* and N-*ras*, are members of a family of genes that code for closely homologous proteins that are termed $p21^{ras}$ and function as signal-switch molecules in the cell. *RAS* genes activated by point mutations are found in a wide variety of human cancers. In a study of mutations of *RAS* oncogenes at codons 12, 13 and 61 in angiosarcomas of the liver of vinyl chloride-exposed workers, five of six tumours were found to contain a G→A transition at the second base of codon 13 (GGC→GAC) of the Ki-*ras*-2 gene (Marion *et al*., 1991). This mutation leads to substitution of glycine by aspartic acid at amino acid residue 13 in the encoded $p21^{ras}$ protein. In another series, eight of 15 tumours contained a mutated Ki-*ras* gene, either at codon 12 or at codon 13. In five cases, the mutation led to substitution of glycine by aspartic acid. Two mutations were also found in non-neoplastic tissue (Weihrauch *et al*., 2002a).

In studies of hepatocellular carcinomas of vinyl chloride-exposed workers, three tumours were found to contain mutations at codon 12 in the first exon of the Ki-*ras*-2 gene due to a G→A transition in two tumours (GGT→GAT) and to a G→T transversion

Table 25. Miscoding specificities of etheno bases

Method	Etheno base tested	Incorporation opposite the lesion	Mutation	Comments	Reference
Incorporation of etheno bases into oligodeoxynucleotides and used as templates with the Klenow fragment of *Escherichia coli* DNA polymerase I	εC	A, T	CG→TA CG→AT	εC facilitates translesional synthesis	Zhang *et al.* (1995)
Incorporation of etheno bases into oligodeoxynucleotides and used as templates with various polymerases	1,N^2-εG HO-ethanoG	A, G A, G	GC→AT (2%) GC→TA (0.74%) GC→AT (0.71%) GC→TA (0.71%)	Both adducts strongly blocked replication with all polymerases tested.	Langouët *et al*. (1997, 1998)
Incorporation of 1,N^2-εG into oligodeoxynucleotides and used as templates with translesion human DNA polymerases	1,N^2-εG	G		Incorporation events are determined by the individual mechanisms of DNA polymerases.	Choi *et al*. (2006)
Incorporation of 1,N^2-εG at a single site in a pCNheIA vector integrated in the chromosomes, CHO cells	1,N^2-εG	G	Various mutations mainly GC→AT		Akasaka & Guengerich (1999)
Incorporation of HO-ethanoG in the single-stranded vector pMS2, COS7 simian kidney cell line	HO-ethanoG		GC→TA (11 mutations) GC→CG (2 mutations) GC→AT (1 mutation)		Fernandes *et al*. (2005)
Single-stranded vector pMS2 containing a single εA residue; propagated in 5 strains of *E. coli* and in COS7 simian kidney cell line	εA	G > T > C	AT→GC (63%) AT→TA (6%) AT→CG (1%)	εA highly miscoding in COS cells (frequency of mutations 70%) in contrast to results for *E. coli*	Pandya & Moriya (1996)
supF Gene in vector plasmid pMY189 treated with CAA, human fibroblast W138-VA13 cells	εC and N^2,3-εG as possible adducts		GC→AT (53.8%) GC→TA (29.5%) GC→CG (6.4%)	71% of mutations were single base mutations	Matsuda *et al*. (1995)

εA, 1,N^6-ethenoadenine; εC, 3,N^4-ethenocytosine; N^2,3-εG, N^2,3-ethenoguanine; 1,N^2-εG, 1,N^2-ethenoguanine; CAA, chloroacetaldehyde; CHO, Chinese hamster ovary; HO-ethanoG, 5,6,7,9,-tetrahydro-7-hydroxy-9-oxoimidazo[1,2-*a*]purine

in one tumour (GGT→TGT). In addition, one tumour contained a mutation due to a G→T transversion at the second base of codon 12 (GGT→GTT) in neoplastic tissue and a G→A transition at the second base of codon 12 in non-neoplastic tissue (GGT→GAT). One tumour contained a mutation at the first base of codon 13 (G→T transversion, GGC→TGC) in neoplastic tissue and a G→A transition at the second base of codon 13 in non-neoplastic tissue (GGC→GAC). In one case, the wild-type Ki-*ras*-2 gene was detected in neoplastic tissue while a codon 13 mutation was found in non-neoplastic cirrhotic tissue (GGC→CAT) (Weinrauch *et al*., 2001a). In the same study, 20 hepatocellular carcinomas from a control group and associated with hepatitis B or C virus infection or alcoholic beverage consumption were also analysed. Ki-*ras*-2 mutations were found in three cases, two of which were attributed to HBV infection (GGT→GTT and GGC→GAC) and one to hepatitis C virus infection (GGT→TGT) (Weihrauch *et al*., 2001a,b).

No mutations were found in the Ki-*ras* gene in vinyl chloride-induced liver angiosarcoma or hepatocellular carcinoma in rats. One mutation was found at codon 13 of N-*ras* in a liver angiosarcoma (G→A, GGC→GAC). However, mutations that involved the second base of codon 61 of the Ha-*ras* gene and were due to A→T transversions (CAA→CTA) were found in five of eight hepatocellular carcinomas (Froment *et al*., 1994; Boivin-Angèle *et al*., 2000a) (Table 26).

(b) p53

The *p53* gene is a tumour-suppressor gene at the crossroads of many cellular pathways that involve cell cycle control, DNA repair, DNA replication, apoptosis and senescence. The majority of cancer-related mutations in *p53* cluster in several regions of the gene that determine the protein structure and that have been highly conserved through evolution. These regions occur in the sequence-specific DNA-binding core domain of the protein between amino acid residues 102 and 292. The mutations found in malignancies could result in substitution of amino acid residues in these regions that are critical for p53 function (Cho *et al*., 1994; Brandt-Rauf *et al*., 1996).

A comparison of the mutation spectra in the *p53* gene in vinyl chloride-associated liver tumours in humans and rats is detailed in Table 27.

Five liver tumours (four liver angiosarcomas and one hepatocellular carcinoma) from workers who were heavily exposed to vinyl chloride were investigated for mutations in the *p53* gene in exons 5 to 8. Two A→T missense mutations were found in a highly conserved domain: one at codon 249 (AGG→TGG, *Arg* to *Trp*) and one at codon 255 (ATC→TTC, *Ile* to *Phe*) each in the tumour but not in the normal cells of two of the liver angiosarcoma patients, of whom both were smokers (Hollstein *et al*., 1994). A third mutation, also due to an A→T transversion, was found at codon 179 (CAT→CTT, *His* to *Leu*) in a fibroblastic cell line established from a liver angiosarcoma from a vinyl chloride-exposed patient (Boivin-Angèle *et al*., 2000b). Such mutations are uncommon in human cancers (2.7% of a total of 5085 cancers; Hollstein *et al*., 1996). Futhermore, *p53* gene mutations are uncommon in sporadic (non-vinyl chloride-induced) liver angiosarcomas

Table 26. Comparison of the mutation spectra in *ras* proto-oncogenes in vinyl chloride-associated liver tumours in humans and rats

Tumour origin	Gene involved	Codon	No. of mutations/ no. of tumours	No. of base-pair changes/codon change	Reference
Human ASL	Ki-*ras*-2	13	5/6	5 G→A/GGC→GAC	Marion *et al*. (1991)
Human ASL	Ki-*ras*-2	12	5/8	3/5 G→A/GGT→GAT 2/5 G→T/GGT→GTT, GGT→TGT	Weihrauch *et al*. (2002a)
		13	3/8	2/3 G→A/GGC→GAC, GGC→CAT 1/3 G→T/GGC→TGC	
		12		1/2 G→T/GGT→TGT (non-neoplastic tissue) 1/2 G→A/GGT→GAT (non-neoplastic tissue)	
Human HCC	Ki-*ras*-2	12	4/12	2 G→A/GGT→GAT G→T/GGT→TGT G→T/GGT→GTT (with GGT→GAT in the non-neoplastic tissue)	Weihrauch *et al*. (2001a)
		13	1/12	G→T/GGC→TGC (with GGC→GAC in the non-neoplastic tissue) G→A/GGC→CAT non-neoplastic tissue	
Rat ASL	Ki-*ras*-2 N-*ras* A	12, 13, and 61	0/11	None	Froment *et al*. (1994); Boivin-Angèle *et al*. (2000a)
		13 36	2/11	G→A/GGC→GAC A→T/ATA→CTA	
Rat HCC	Ha-*ras*	61	5/8	5 A→T/CAA→CTA	Froment *et al*. (1994); Boivin-Angèle *et al*. (2000a)

ASL, liver angiosarcoma; HCC, hepatocellular carcinoma

Table 27. Comparison of the mutation spectra in the *p53* gene in vinyl chloride-associated liver tumours in humans and rats

Tumour origin	No. of mutations/no. of tumours	Codon (exon)	No. of base-pair changes/ codon change	References
Human ASL	2/4		2 A→T/	Hollstein *et al.* (1994)
		249 (7)	AGG→TGG	
		255 (7)	ATC→TTC	
Human ASL	6/17	131 (5)	1 A→T/AAC→ATC	Weihrauch *et al.* (2002b)
		248 (7)	1 G→A/CGG→CAG	
		282 (8)	1 C→T/CGG→TGG	
		342 (10)	1 C→T/CGA→TGA	
		200 (6)	del-2	
		216 (6)	del-3	
Human fibroblastic cell line from an ASL	1/1	179 (5)	1 A→T/CAT→CTT	Boivin-Angèle e*t al.* (2000b)
Human HCC	11/18	130 (5)	1 T→G/CTC→CGC	Weihrauch *et al.* (2000)
		175 (5)	1 C→A/CAC→AAC	
		282 (8)	1 C→T/CGG→TGG	
		179 (5)	1 A→T/CAT→CTT	
		193 (6)	1 A→C/CAT→CCT	
		246 (7)	1 A→G/ATG→GTG	
			3 G→A/	
		245 (7)	GGC→GAC	
		248 (7)	CGG→CAG	
		273 (8)	CGT→CAT	
		226 (6)	1 G→C/GGC→GCC	
		236 (7)	del(-3)	
Rat ASL	11/25		4 A→T/	Barbin *et al.* (1997)
		160 (5)	ATC→TTC	
		235 (7)	ATG→TTG	
		253 (7)	ATC→TTC	
		253 (7)	ATC→TTC	
		235 (7)	1 A→C/ATG→CTG	
			2 A→G/	
		203 (6)	TAT→TGT	
		203 (6)	TAT→TGT	
			2 G→A/	
		152 (5)	GGT→AGT	
		246 (7)	CGC→CAC	
		147 (5)	1 C→T/TCC→TCT	
		235 (7)	1 T→G/ATG→AGG	
		177–181 (5)	del(-12)	
Rat HCC	1/8	283 (8)	1 A→T/GAG→GTG	Barbin *et al.* (1997)

ASL, liver angiosarcoma; HCC, hepatocellular carcinoma

(2/21 cases, 9%; Soini *et al*., 1995), which supports the evidence that links exposure to vinyl chloride with liver angiosarcoma that contains *p53* mutations due to A→T transversions.

In another series, six mutations were found in 17 vinyl chloride-induced liver angiosarcomas (four point mutations and two deletions); only one mutation was due to an A→T transversion (codon 131, AAC→ATC) (Weihrauch *et al*., 2002b).

Eighteen hepatocellular carcinomas from vinyl chloride-exposed workers were analysed for mutations in the *p53* gene in exons 5–9. In this series, 11 of 18 hepatocellular carcinomas exhibited a *p53* gene mutation, with five transversions and five transitions. Five of the 11 mutations (codons 175, 245, 248, 273 and 282) affected CpG dinucleotides, three of which (codons 175, 248, 273) were also found in hepatocellular carcinomas induced by alcoholic beverage consumption and viral or autoimmune cirrhosis, which led the authors to conclude that the *p53* mutations in their series might be due to spontaneous processes such as deamination of 5-methylcytosine (Weihrauch *et al*., 2000). In studies of both liver angiosarcoma and hepatocellular carcinoma, no *p53* mutations were found in the surrounding non-neoplastic tissue.

Mutations in the *p53* gene were also found in 11 of 25 (44%) liver angiosarcomas induced by vinyl chloride in Sprague-Dawley rats and in one of eight hepatocellular carcinomas (Barbin *et al*., 1997). Five mutations involved an A→T transversion as seen in human vinyl chloride-induced liver angiosarcoma. The A→T transversion in the first base of codon 253 in two rat liver angiosarcomas was equivalent to the transversion observed in codon 255 in one human liver angiosarcoma associated with exposure to vinyl chloride (Hollstein *et al*., 1994) (Table 27).

4.3 Mechanisms of carcinogenesis

Many key events in the pathway of vinyl chloride-induced hepatocarcinogenesis have been established. These include (*a*) metabolic activation (to chloroethylene oxide), (*b*) DNA binding of the reactive metabolites (characteristic exocyclic etheno-adducts, (*c*) promutagenicity of these adducts that lead to G→A and A→T transitions and (*d*) effects of such mutations on proto-oncogenes/tumour-suppressor genes at the gene and gene product levels, with tumorigenesis as the final outcome (Bolt, 2005).

Vinyl chloride has been demonstrated to be a genotoxic carcinogen in animal and human studies (Block, 1974; Creech & Johnson, 1974; Lee & Harry, 1974; Maltoni *et al*., 1974, 1981). It is absorbed rapidly after inhalation and oral exposure (Bolt, 1978), and is metabolized (activated) mainly by CYP2E1 to 2-chloroethylene oxide which spontaneously rearranges to 2-chloroacetaldehyde. 2-Chloroethylene oxide and 2-chloroacetaldehyde can be transported intercellularly from parenchymal cells to non-parenchymal cells in the liver (Kuchenmeister *et al*., 1996). The primary detoxification reaction of the two reactive metabolites is conjugation with GSH catalysed by GST; the conjugation products are then excreted in urine (reviewed in WHO, 1999).

Both 2-chloroethylene oxide and 2-chloroacetaldehyde can form DNA adducts. Five DNA adducts are formed by 2-chloroethylene oxide or 2-chloroacetaldehyde (Cheng *et al*., 1991; Basu *et al*., 1993). These include the major adduct, 7-OEG, and four cyclic etheno adducts (1,N^2-εG, εC, εA and N^2,3-εG). These etheno adducts generate mainly base-pair substitution mutations and specific mutations in cancer-related genes (i.e. *RAS* oncogenes, *p53* tumour-suppressor genes). The major reaction product of 2-chloroethylene oxide is 7-OEG, but 2-chloroacetaldehyde does not form this adduct. 7-OEG does not exhibit promutagenic properties whereas εA, εC, N^2,3-εG and 1,N^2-εG do. εA, εC and N^2,3-εG have demonstrated miscoding potential *in vitro* and *in vivo* (Singer *et al*., 1987; Cheng *et al*., 1991; Mroczkowska & Kusmierek, 1991; Singer *et al*., 1991; Basu *et al*., 1993) and others have shown that εA causes A→G transitions and A→T transversions, εC causes C→A transversions and C→T transitions and εG causes G→A transitions (reviewed in Bolt, 2005; see Table 25). These changes were consistent with the mutations of *p53* and *RAS* genes observed in tumours from vinyl chloride-exposed humans and rats (Tables 26 and 27).

Etheno adducts appear to have long persistence and are repaired by glycolases (Gros *et al*., 2004). In addition to the DNA adducts produced by vinyl chloride, a physiological background of endogenously produced etheno adducts is possibly the product of oxidative stress and lipid peroxidation (Bartsch & Nair, 2000a,b; De Bont & van Larebeke, 2004; Bolt, 2005).

The induction of extrahepatic tumours by vinyl chloride has been established experimentally, but the mechanism for this extrahepatic tumour formation, e.g. in the brain or lung, is not well elucidated (Bolt, 2005).

While the data overall suggest that etheno adducts are probably involved in the initiation of hepatocarcinogenesis by vinyl chloride, some factors have yet to be explained. These include observed tissue and cell specificity and variability in various biomarkers such as mutant p53 protein and anti-p53 antibodies in vinyl chloride-exposed workers with tumours (Trivers *et al*., 1995; Brand-Rauf *et al*., 1996). One source for this variability might be explained by differences in genetic polymorphisms of genes that encode for enzymes involved in vinyl chloride metabolism and for proteins involved in DNA repair (Li *et al*., 2003a).

4.4 Susceptibility

4.4.1 *Genetic polymorphisms and enzyme induction*

The enzymes that are involved in vinyl chloride activation and detoxification, i.e. CYP2E1, ALDH2, GST and mEH (Figure 1), are known to have polymorphic variants with altered activity. Polymorphisms of each of these enzymes may modulate the metabolism of vinyl chloride, the levels of 2-chloroethylene oxide and 2-chloroacetaldehyde and hence the frequency and nature of vinyl chloride-induced mutations.

For example, individuals who have high-activity variants of CYP2E1 and/or low-activity variants of ALDH2 or GST enzymes may have elevated levels of chloroethylene oxide and chloroacetaldehyde and increased DNA damage.

Among the many CYP2E1 polymorphisms described, *c1* and *c2* alleles have been identified in the 5-regulatory region of the gene. According to in-vitro studies that investigated gene transcription and enzyme activity, workers who have at least one *c2* allele may have higher CYP2E1 activity than the homozygous *c1c1*, although this was not clearly confirmed *in vivo*. The frequency of the rare *c2* allele is 24–30% for Asian populations, 2–3% for Caucasians, 0.3–7% for African-Americans, 15% for Mexican Americans and 18% for Chinese (Province of Taiwan) (Danko & Chaschin, 2005). The levels of CYP2E1 vary in human populations and have been shown in addition to be induced by repetitive alcoholic beverage consumption and exposure to other agents (Lieber & DeCarli, 1970; Roberts *et al*., 1995; Mastrangelo *et al.*, 2004).

GSTs are encoded by a supergene family that is divided, on the basis of the chromosomal location and sequence homology, into four classes; Alpha, Mu, Pi and Theta (Lo & Li-Osman, 2007). Approximately half of the Caucasian population has no GSTM1-1 enzyme because of a homozygous deletion of the *GSTM1* gene. The other half is either heterozygous or homozygously normal. The frequency of the *GSTM1* null-null genotype is similar in Asians but lower in African-Americans (~ 27%) (Parl, 2005).

Genotypic differences are also frequent for the *GSTT1* gene. The $GSTT1^{-/-}$ genotype is more common in Asians, at frequencies that range from 47 to 64%, whereas this homozygous null genotype is found only in 20% of Caucasians (Parl, 2005).

There is a structural polymorphism at amino acid position 487 of the *ALDH2* gene. A substitution of lysine for glutamic acid results from a transition of G (allele 1) to A (allele 2). The *ALDH2* alleles that encode the active and inactive subunits are termed *ALDH2*1* and *ALDH2*2*, respectively (Farres *et al.*, 1994). The dominant-negative mutant allele, *ALDH2*2*, is extremely rare in Caucasians, but is widely present in Mongoloids (28–45%; Goedde *et al.*, 1992).

Polymorphisms in genes that encode for the proteins that are involved in DNA-repair processes, such as XRCC1 (X-ray cross-complementing group 1) and XPD (xeroderma pigmentosum group D), may also modulate the occurrence of vinyl chloride-induced mutations. The XRCC1 protein is responsible for the repair of DNA lesions that are caused by alkylating agents. Etheno adducts produced by vinyl chloride are normally removed by the base-excision repair pathway which contains several proteins that are coordinated by XRCC1. Three polymorphisms have been identified at codon 194 (*Arg* to *Trp*), 280 (*Arg* to *His*) and 399 at codon 10 (*Arg* to *Gln*, termed *Gln* phenotype) for XRCC1 (Lindahl & Wood, 1999; Goode *et al.*, 2002).

The XPD protein is an adenosine triphosphate-dependent 5'-3' helicase involved in nucleotide excision repair. Several polymorphisms have also been described for the *XPD* gene (Lindahl & Wood, 1999; Goode *et al.*, 2002).

Few studies have investigated vinyl chloride-induced alterations at the chromosome level (sister chromatid exchange) and at the gene level (*RAS* and *p53* point mutations) in

vinyl chloride-exposed workers with various polymorphisms. In a study from Taiwan, China, *CYP2E1c1c2/c2c2*, *ALDH2 1-2/2-2* and *XRCC1 Gln-Gln* polymorphisms appeared to be weak susceptibility factors for the frequency of sister chromatid exchange in relation to exposure to vinyl chloride, but not *GSTT1* or *GSTM1* genes (Table 28). *CYP2E1 c2c2* was also associated with a higher risk for p53 protein overexpression in the plasma of vinyl chloride-exposed workers (adjusted odds ratio, 9.8; 95% CI, 1.2–81.6), and this increased risk was also associated with *GSTT1* non-null (odds ratio, 2.4; 95% CI, 0.8–7.6) or *ALDH2* 1-2/2-2 (odds ratio, 1.6; 95% CI, 0.5–4.6), particularly in the low-exposure group (≤ 40 ppm–years) (Wong, R.H. *et al*., 2002). These authors suggested that frequency of sister chromatid exchange reflects recent exposure to vinyl chloride, while *p53* gene mutations reflect cumulative exposure to vinyl chloride. However, *CYP2E1 c1/c2* genotype compared with the wild-type *c1/c1* genotype appeared to contribute only slightly to the occurrence of mutant $p21^{ras}$ or p53 proteins in French vinyl chloride-exposed workers (Li *et al.*, 2003b).

In contrast, a joint effect of the *XRCC1* codon 399 polymorphism and cumulative exposure to vinyl chloride on the occurrence of the p53 biomarker was observed (Li *et al.*, 2003a). While *GSTM1, GSTT1* and *GSTP1* polymorphisms were not found to be associated with an increased occurrence of mutant p53, a significant trend for the prevalence of p53 biomarkers was observed when the combined effects of *GSTM1, GSTT1* and *XRCC1* were analysed. The *GSTM1* and *GSTT1* null genotypes appeared to modify the effect of *XRCC1* codon 399 genotype on p53 biomarker status, possibly in a synergistic fashion (Table 29) (Li *et al*., 2005a). All *XRCC1* codon 194, 280 and 399 polymorphisms also had an effect on the occurrence of the p53 biomarker (Table 30), but not on that of the $p21^{ras}$ biomarker in the blood of vinyl chloride-exposed workers (Li *et al.*, 2006). In contrast, the *mEH* genotype has no effect on $p21^{ras}$ or p53 biomarkers of vinyl chloride-induced mutagenic damage and may not be involved as a major detoxification enzyme in the metabolism of vinyl chloride in humans (Li *et al.*, 2005b). A follow-up of these studies has recently reported the analysis of a cohort of 597 French vinyl chloride-exposed workers. The presence of biomarkers for mutant $p21^{ras}$ and mutant *p53* was found to be highly significantly associated with cumulative exposure to vinyl chloride (p for trend < 0.0001). The *CYP2E1* variant *c2* allele was significantly associated with the presence of either or both mutant biomarkers even after controlling for potential confounders including cumulative exposure to vinyl chloride (odds ratio, 2.3; 95% CI, 1.2–4.1), and the effects of the *c2* allele and vinyl chloride exposure were approximately additive. *GSTT1* null status was found to have an increased but not significant association with the presence of either or both biomarkers after controlling for confounders (odds ratio, 1.3; 95% CI, 0.8–2.0) (Schindler *et al*., 2007).

The effects of polymorphisms of the DNA repair gene *XPD* on DNA damage in lymphocytes were studied in vinyl chloride-exposed workers in China using the comet assay. The study compared workers with ≥ 5 damaged cells per 100 cells studied with workers with no DNA damage who were matched for age, gender, cumulative exposure to VCM and worksite. Three *XPD* polymorphisms were investigated: *Ile199Met, Asp312Asn*

Table 28. Association between frequency of sister chromatid exchange and different polymorphisms (multiple regression model for frequencies of sister chromatid exchange per cell)

Reference	Cohort description	Exposure assessment	Exposure categories	One marker positive	Regression coefficient/SE	*p* value
Wong *et al*. (1998)	44 men with 4–36 years' exposure to VC, from 3 PVC plants; study based on predetermined VC exposure levels and smoking status; mean age, 45.1 ± 1.4 years; current smokers, 55.6%	A TWA exposure to VC assigned to each category of job based on monitored air levels of VC	High VC exposure group > 1 ppm (*n* = 28) Low VC exposure < 1 ppm (*n* = 16)	Smoking status, yes versus no VC exposure, high versus low *CYP2E1 c1c2/c2c2* versus *c1c1* *ALDH2 1-2/2-2* versus *1-1* *GSTM1* non-null versus null *GSTT1* non-null versus null	0.85/0.31 0.64/0.34 0.50/0.33 0.63/0.31 –0.41/0.31 0.27/0.30	< 0.01 0.06 0.14 0.05 0.19 0.38
Wong *et al*. (2003b)	61 men, 29 controls	A TWA exposure to VC assigned to each category of job based on monitored air levels of VC	Controls (*n* = 29) High VC exposure > 1 ppm (*n* = 32) Low VC exposure < 1 ppm (*n* = 29)	Smoking status, yes versus no Alcohol drinking, yes versus no High VC exposure versus controls Low VC exposure versus controls *XRCC1* exon 10: *Gln-Gln* versus *Arg-Arg/Arg-Gln* *CYP2E1 c2c2* versus *c1c1/c1c2* *ALDH2 1-2/2-2* versus *1-1* *GSTT1* null versus non null	0.56/0.26 –0.21/0.33 1.00/0.46 0.60/0.42 1.09/0.49 1.54/0.72 0.44/0.25 0.12/0.25	0.03 0.52 0.03 0.16 0.03 0.04 0.08 0.63

ALDH2, aldehyde dehydrogenase 2; CYP, cytochrome P450; GST, glutathione-*S*-transferase; PVC, polyvinyl chloride; SE, standard error; TWA, time-weighted average ; VC, vinyl chloride; XRCC1, X-ray cross-complementing group 1

Table 29. Association between *XRCC1/GSTM1/GSTT1* polymorphisms and mutant p53 in vinyl chloride (VC) workers

Reference	Cohort description	Exposure assessment	*XRCC1* codon 399/*GSTM1* or *GSTT1* genotypes	Exposure categories (in ppm–years)	No. positive mutant p53 biomarker (%)	Adjusted odds ratio (95% CI)[a]
Li *et al*. (2003a)	211 VC-exposed workers; average age, 56 years (range, 35–74 years); current smokers, 39%; current drinkers, 20%	Average cumulative exposure, 5871 ppm–years (range, 6–46 702 ppm–years); VC exposure levels were attributed to each subject on the basis of the job, using estimated values assigned to the various jobs[b]	*Arg-Arg*	≤ 1000 (*n* = 24)	6 (25)	1.00
				1001–4000 (*n* = 31)	12 (39)	2.19 (0.65–7.40)
				> 4000 (*n* = 31)	11 (35)	1.96 (0.56–6.80)
			Arg-Gln	≤ 1000 (*n* = 26)	10 (38)	1.90 (0.55–6.52)
				1001–4000 (*n* = 25)	9 (36)	1.89 (0.53–6.69)
				> 4000 (*n* = 39)	23 (59)	5.43 (1.57–18.83)
			Gln-Gln	≤ 1000 (*n* = 11)	5 (45)	2.50 (0.54–11.51)
				1001–4000 (*n* = 14)	10 (71)	8.84 (1.87–41.70)
				> 4000 (*n* = 10)	8 (80)	12.17 (1.88–78.67)
						p for trend = 0.0004
Li *et al*. (2005a)	Same cohort as Li *et al*. (2003a)	Same as Li *et al*. (2003a)	*Arg-Arg*/both wild types (*n* = 31)	NR	8 (26)	1
			Arg-Arg/either null (*n* = 47)		18 (38)	1.8 (0.7–5.0)
			Arg-Arg/ both null (*n* = 8)		3 (38)	1.8 (0.3–9.3)
			Arg-Gln+*Gln-Gln*/both wild types (*n* = 50)		25 (50)	2.9 (1.1–7.8)
			Arg-Gln+*Gln-Gln*/either null (*n* = 68)		35 (51)	3.2 (1.2–8.3)
			Arg-Gln+*Gln-Gln*/both null (*n* = 7)		5 (71)	8.4 (1.3–54.0)
						p for trend = 0.00037

CI, confidence interval; GST, glutathione-*S*-transferase; NR, not reported; XRCC1, X-ray cross-complementing group 1

[a] Adjusted for age, smoking, alcoholic beverage consumption and cumulative VC exposure

[b] Estimates of VC exposure in ppm–years based on years of a given job category weighted by the presumed ppm level of exposure as defined by the exposure matrix of Heldaas *et al*. (1984)

Table 30. Association between *XRCC1* codons 194, 280 and 399 polymorphisms and mutant p53 in vinyl chloride (VC) workers

Reference	Cohort description	Exposure assessment	*XRCC1* codons 194, 28 and 399	Mutant p53 biomarker		Adjusted odds ratio (95% CI)[a]
				+	–	
Li *et al*. (2006)	211 VC-exposed workers; average age, 56 years (range, 35–74 years); current smokers, 39%; current drinkers, 20%	Average cumulative exposure, 5871 ppm–years (range, 6–46 702 ppm–years); VC exposure levels were attributed to each subject on the basis of the job, using estimated values assigned to the various jobs[b]	All wild type One variant allele Two variant alleles	21 (34%) 41 (43%) 32 (60%)	41 (66%) 55 (57%) 21 (40%)	1 1.5 (0.8–3.0) 3.1 (1.4–6.7) *p* for trend = 0.005

CI, confidence interval; XRCC1, X-ray cross-complementing group 1

[a] Adjusted for age, smoking, alcoholic beverage consumption and cumulative exposure to VC

[b] Estimates of VC exposure in ppm–years based on years of a given job category weighted by the presumed ppm level of exposure as defined by the exposure matrix of Heldaas *et al*. (1984)

and *Lys751Gln*. Using univariate analysis, it was shown that only the *XPD751 Lys/Gln* and *Gln/Gln* genotypes were significantly associated with DNA damage (odds ratio, 2.21; 95% CI, 1.01–5.13; $p < 0.05$). After adjusting for the effects of smoking, alcoholic beverage consumption, liver damage and polymophisms of the DNA repair gene, and using the group with low exposure to vinyl chloride and the *XPD312 Asp/Asp* genotype as a reference, it was found that workers with high exposure and the *XPD312 Asp*/*Asn* and *Asn*/*Asn* genotypes had a significantly reduced risk for DNA damage (odds ratio, 0.33; 95% CI, 0.11–0.95) (Zhu *et al*., 2005b).

These results suggest possible interactions between polymorphisms in the metabolic pathway of vinyl chloride and/or in the DNA repair processes and exposure to vinyl chloride that could contribute to the variable susceptibility to the mutagenic effects of vinyl chloride in exposed populations and might shed some light on the mechanism of tumour formation in humans.

4.4.2 *Age*

After results were published to indicate that hepatocytes of young, postnatal rats are much more susceptible than those of adult rats to the carcinogenic effect of vinyl chloride (Maltoni *et al.*, 1981; see Section 3), several investigations began to characterize the potentially susceptible period and the underlying mechanisms.

Laib *et al.* (1985a) investigated the age-dependence of the induction of preneoplastic enzyme-altered hepatic foci. Male and female Wistar rats were exposed to 2000 ppm [5186 mg/m^3] vinyl chloride either transplacentally or immediately (1 day) after birth for a period of 5, 11, 17, 47 or 83 days, or from age 7 days or 21 days until death. Adenosine triphosphatase-deficient foci were increased compared with control rats after newborn exposures of 11 days or more, although foci area did not further increase after 17 days. Transplacental exposure and exposures before day 5 did not increase adenosine triphosphatase-deficient foci.

In accompanying studies, Laib *et al*. (1985b) also investigated the effects of a range of lower concentrations administered early in life. Wistar rats were exposed to 10, 40, 70, 150, 500 or 2000 ppm [26, 104, 182, 389, 1300 or 5186 mg/m^3] vinyl chloride for 10 weeks beginning at 1 day of age, and Wistar and Sprague–Dawley rats were exposed to 2.5, 5, 10, 20, 40 or 80 ppm [6.5, 13, 26, 52, 104 or 208 mg/m^3] vinyl chloride for 3 weeks beginning at 3 days of age. In each case, a linear relationship was observed between the concentration of vinyl chloride and the percentage of foci area induced, with no obvious threshold for the induction of preneoplastic foci.

Ciroussel *et al.* (1990) measured the levels of εA and εC adducts in DNA from several target organs. Rats were exposed to 500 ppm [1300 mg/m^3] vinyl chloride for 2 weeks beginning at 7 days or 13 weeks of age. Both εA and εC adducts were detected in the liver, lungs and brain (but not kidneys) of rats that were 7 days old when first exposed. In rats that were 13 weeks old when first exposed, only liver DNA was analysed and levels of each adduct were one-sixth of those observed in the younger rats.

Fedtke *et al.* (1990) investigated the formation and persistence of the DNA adducts 7-OEG and N^2,3-εG. Lactating Sprague–Dawley rats and their 10-day-old offspring were exposed to 600 ppm [1560 mg/m^3] vinyl chloride for 4 h per day for 5 days. In the neonatal rats, concentrations of both DNA adducts were highest in the liver, followed by kidney and lung. No adducts were found in the brain or spleen. DNA adducts were detected only in the liver and lung of the dams. Concentrations of DNA adducts in the liver and lung were fourfold higher in the neonatal rats than in the dams.

Morinello *et al.* (2002a) studied the exposure–response relationship of N^2,3-εG adducts over a range of dose levels. Adult Sprague-Dawley rats were exposed to 0, 10, 100 or 1100 ppm [0, 26, 260 or 2852 mg/m^3] vinyl chloride for 1 or 4 weeks, and weanlings were similarly exposed for 5 days. The exposure–response relationship was linear from 0 to 100 ppm, then did not increase further. Compared with adult rats, two- to threefold higher concentrations of *N*2,3-εG adduct were measured in hepatocytes in the weanlings.

5. Summary of Data Reported

5.1 Exposure data

Vinyl chloride is a gas that is produced predominantly by breaking down ethylene dichloride into smaller molecules. Production of vinyl chloride by the initial acetylene-based process is still carried out in China. More than 95% of vinyl chloride is used for the production of polyvinyl chloride resin, which in turn is mainly used to produce plastic piping and other plastic items. Vinyl chloride is also used in the manufacture of chlorinated solvents. Production of vinyl chloride monomer is increasing. In 2005, production in Asia had outgrown that in both western Europe and North America. An increasing number of workers worldwide are exposed to vinyl chloride monomer 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 100 mg/m^3. 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/polyvinyl chloride production; in western Europe and North America, current exposure levels are generally below 1 mg/m^3. Concentrations of vinyl chloride monomer in ambient air are normally below 0.01 mg/m^3, but higher concentrations have been measured in the vicinity of vinyl chloride/polyvinyl chloride production plants.

5.2 Cancer in humans

Epidemiological evidence for the carcinogenicity of vinyl chloride in humans derives principally from two large, multicentric cohort studies, one of which was carried out in the USA and the other in Europe. These investigations focused on plants that manufactured vinyl chloride monomer, polyvinyl chloride or polyvinyl chloride products. Additional information is provided by several smaller cohort studies.

Both of the multicentric cohort studies found a substantial increase in the relative risk for angiosarcoma of the liver, a tumour that is extremely rare in the general population, in exposed workers. In both studies, the risk for liver angiosarcoma increased strongly with duration of exposure to vinyl chloride. In the European study, there was also a clear trend of higher risk with increasing cumulative exposure. Multiple cases of liver angiosarcoma were also reported in two smaller cohort studies. Overall, these findings constitute compelling evidence that vinyl chloride causes angiosarcoma of the liver.

Assessment of whether vinyl chloride also causes hepatocellular carcinoma is complicated because many studies do not have histological or other definitive clinical information to discriminate hepatocellular carcinoma from angiosarcoma of the liver and/or secondary neoplasms. However, in an internal analysis of the European multicentric cohort, the risk for hepatocellular carcinoma increased significantly and substantially with cumulative exposure to vinyl chloride, based on nine confirmed cases. Another analysis of a single Italian plant with extended follow-up that was included in the European multicentric study included 12 confirmed hepatocellular carcinomas. The maximal overlap between these two analyses was four cases, since only four hepatocellular carcinomas from Italy were included in the multicentric cohort. In this subcohort, the incidence of hepatocellular carcinoma again increased significantly with cumulative exposure to vinyl chloride. Together with the observation that vinyl chloride increases the risk for liver cirrhosis, which is a known risk factor for hepatocellular carcinoma, these findings provide convincing evidence that vinyl chloride causes hepatocellular carcinoma as well as angiosarcoma of the liver.

There was suggestive evidence that the risk for hepatocellular carcinoma from vinyl chloride is substantially higher among workers who are infected with hepatitis virus or report high levels of alcoholic beverage consumption.

Among vinyl chloride workers overall, there was no evidence of an increased risk for lung cancer. However, in polyvinyl chloride packers and baggers, the risk for lung cancer increased significantly with cumulative exposure to vinyl chloride. These workers are known to have had concomitant exposure to polyvinyl chloride dust, and the study did not allow attribution of the association to a specific agent or combination of agents.

Among the other cancer sites, suggestive evidence was found for malignant neoplasms of connective and soft tissue. This derived from the multicentric study in North America, in which a nearly threefold statistically significant overall increase in incidence was observed that persisted after the exclusion of four angiosarcomas for which the site was unknown. The risk was higher for workers with longer duration of employment

(i.e. 10–19 and ≥ 20 years). These findings were not supported by the European multicentric study, in which too few cases of connective tissue neoplasms were observed for an evaluation of exposure–response.

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. No conclusion could be reached for breast cancer since the studies included too few women.

5.3 Cancer in experimental animals

The carcinogenicity of vinyl chloride has been studied intensively and repeatedly in experimental animals. The numerous studies are generally mutually reinforced. This wealth of data has generally been incompletely reported, however, and the outcomes of many experiments in the published studies are available only from summary tables, in which technical details are given only as footnotes.

Vinyl chloride was tested by inhalation exposure in seven studies in mice, in nine studies in rats and in two studies in hamsters. Male and female animals were treated in all three species, although some experiments were carried out only in one sex. Vinyl chloride induced hepatic angiosarcomas in three studies in mice and in eight studies in rats; a positive dose–response was observed for hepatic angiosarcomas in mice and rats over a wide range of exposures. It induced angiosarcomas (all sites) in four studies in mice, in three studies in rats and in one study in hamsters. Extrahepatic angiosarcomas related to treatment with vinyl chloride were observed in three studies in mice and two studies in rats. Vinyl chloride increased the incidence of mammary tumours in six studies in mice, in three studies in rats and in one study in hamsters. Exposure to vinyl chloride increased the incidence of skin tumours in one study in rats and in two studies in hamsters, and increased the incidence of Zymbal gland carcinomas in four studies in rats, with a dose–response pattern in one experiment. Vinyl chloride increased the incidence of lung tumours in six studies in mice, induced renal tumours and tumours of the nasal cavity in one study in rats, increased the incidence of hepatocellular carcinomas in two studies in rats and increased the incidence of glandular stomach tumours in one study in hamsters.

In one study in rats, combined oral administration of ethanol and inhalation exposure to vinyl chloride caused more liver tumours (including angiosarcomas and hepatocellular carcinomas) than exposure to vinyl chloride alone.

Vinyl chloride was tested by oral administration in four studies in male and female rats. It induced hepatic angiosarcomas in all studies, extrahepatic angiosarcomas in one study and hepatocellular carcinomas in two studies. When vinyl chloride was tested by subcutaneous injection and by intraperitoneal injection in single studies in rats, no hepatic angiosarcomas were induced.

The transplacental carcinogenicity of vinyl chloride was evaluated in one study in the offspring of rats exposed by inhalation during pregnancy. A low but significant incidence of tumours was observed in exposed offspring at sites that included the kidney, Zymbal gland and several others. However, no angiosarcomas or liver-cell tumours developed in the offspring.

Vinyl chloride was tested by perinatal inhalation exposure in two studies in rats. In one study, rats were exposed transplacentally, neonatally and during adulthood. Treatment with vinyl chloride induced hepatic angiosarcomas and hepatocellular carcinomas. Rats also demonstrated high incidences of tumours that were probably of olfactory neuroepithelial origin, but which were formerly reported as cerebral neuroblastomas in some studies. In a second study, rats were exposed to vinyl chloride for 5 weeks only beginning at birth. Hepatic angiosarcomas and 'hepatomas' occurred at a high incidence in the offspring, but not in the dams that were co-exposed with the offspring.

Chloroethylene oxide, a chemically reactive metabolite of vinyl chloride, was tested for carcinogenicity in a single study in mice by subcutaneous injection and in an initiation–promotion protocol on the skin. It caused fibrosarcomas at the site of subcutaneous injection and increased the incidence of squamous-cell papillomas and carcinomas of the skin at the site of application.

5.4 Mechanistic and other relevant data

Pulmonary absorption of vinyl chloride in humans appears to be rapid, and the percentage that is absorbed (about 40%) is independent of the concentration inhaled. Vinyl chloride is oxidized to highly reactive chloroethylene oxide, which rearranges to chloroacetaldehyde. The initial oxidation is predominantly mediated by cytochrome P450 2E1, an enzyme that is induced by ethanol among other agents. In rats, the metabolism of vinyl chloride is saturable at an inhalation concentration of 250 ppm [~650 mg/m^3], at which the incidence of hepatic angiosarcoma in these animals has been reported to plateau. The rate of vinyl chloride metabolism in humans is approximately 50 µmol/h/kg. The rate of elimination of vinyl chloride does not appear to be altered during repeated compared with single inhalation exposures.

Following metabolic activation of vinyl chloride in rats, the two metabolites, chloroethylene oxide and chloroacetaldehyde, react with nucleic acid bases to form adducts. These include the major adduct *N*7-(2-oxoethyl)guanine, four etheno adducts and 5,6,7,9-tetrahydro-7-hydroxy-9-oxoimidazol[1,2-*a*]purine, as identified *in vitro* and in rats *in vivo*. In rats exposed to vinyl chloride, increased levels of etheno adducts have been found in different organs, such as the liver, lung and kidney, and in lymphocytes but not in the brain. Young animals are particularly prone to the formation and persistence of vinyl chloride-induced adducts. In rats, adducts have been found equally in non-parenchymal liver cells and in hepatocytes. In humans, etheno adducts are formed by lipid peroxidation; there is, however, a paucity of data on the occurrence of such adducts in vinyl

chloride-exposed humans. The mechanism that leads to base misincorporation following adduct formation is still unclear.

Vinyl chloride is mutagenic, usually in the presence of metabolic activation, in various assays with bacteria, yeast or mammalian cells and is clastogenic in in-vivo and in-vitro systems. It induces unscheduled DNA synthesis and increases the frequency of sister chromatid exchange in rat and human cells. Exposure to vinyl chloride has been associated with an increase in the frequency of chromosomal aberrations, micronucleus formation and sister chromatid exchange in humans.

Ki-*ras* gene mutations are associated with vinyl chloride-induced angiosarcoma in humans but not in rats. In half of the cases, Ki-*ras* mutations lead to the incorporation of aspartate instead of glycine. Ki-*ras* mutations were also found to a lesser extend in vinyl-chloride induced hepatocellular carcinomas. A specific Ha-*ras* gene mutation (CAA61CTA) was found vinyl chloride-induced hepatocarcinomas in rats. A mutated *p53* gene was found in approximately half of the angiosarcomas in humans and rats that resulted from exposure to vinyl chloride. The *p53* mutations in both species are often due to A→T transversions.

The presence of mutated $p21^{ras}$ and p53 proteins in the blood of a high proportion of workers exposed to vinyl chloride and the positive correlation between the occurrence of the mutated proteins and cumulative exposure to vinyl chloride suggest that the mutation is an early event.

In humans, genetic polymorphisms in genes that encode the enzymes involved in the metabolism of vinyl chloride (*CYP2E1*, *GSTT1*, *GSTM1*, *ALDH2*) and in DNA repair (*XRCC1*) modulate the DNA damage induced by vinyl chloride.

6. Evaluation and Rationale

6.1 Carcinogenicity in humans

There is *sufficient evidence* in humans for the carcinogenicity of vinyl chloride. Vinyl chloride causes angiosarcomas of the liver and hepatocellular carcinomas.

6.2 Carcinogenicity in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of vinyl chloride.

There is *sufficient evidence* in experimental animals for the carcinogenicity of chloroethylene oxide.

6.3 Overall evaluation

Vinyl chloride is *carcinogenic to humans (Group 1).*

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