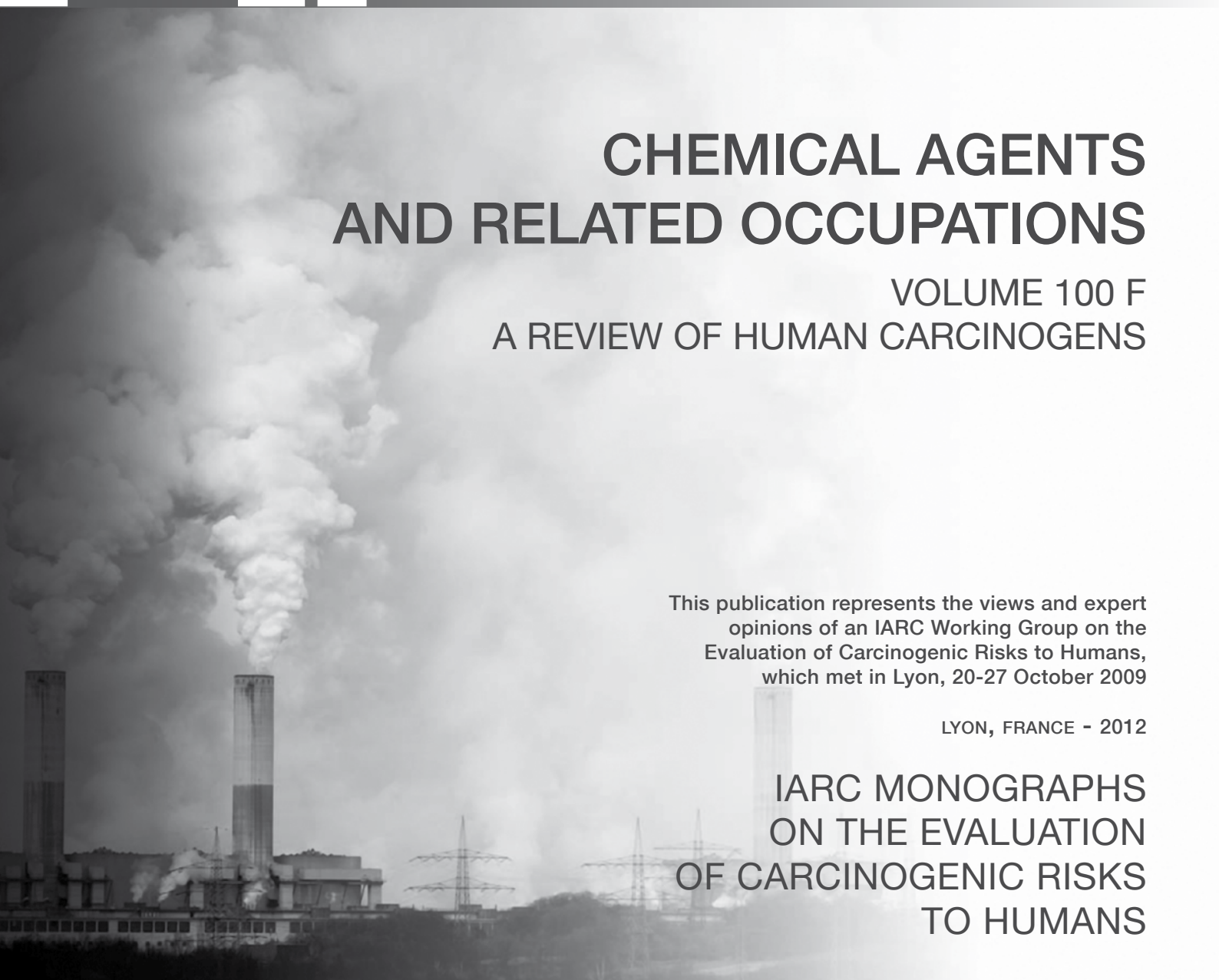
IARC MONOGRAPHS



CHEMICAL AGENTS AND RELATED OCCUPATIONS

VOLUME 100 F
A REVIEW OF HUMAN CARCINOGENS

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 20-27 October 2009

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IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer
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VINYL CHLORIDE

Vinyl chloride was considered by previous IARC Working Groups in 1974, 1978, 1987, and 2007 (IARC, 1974, 1979, 1987, 2008). Since that time new data have become available, which have been incorporated in this *Monograph,* and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agent

From IARC (2008) and Lide (2008)
Chem. Abstr. Serv. Reg. No.: 75-01-4
Chem. Abstr. Serv. Name: Chloroethene

$H_2C{=}CH{-}Cl$

C_2H_3Cl
Relative molecular mass: 62.5
Description: Colourless gas, with a mild, sweet odour
Boiling-point: -13.4 to -13.8 °C
Solubility: Slightly soluble in water (1.1 g/L at 25 °C); soluble in ethanol; very soluble in diethyl ether, carbon tetrachloride and benzene
Conversion factor: 1 ppm = 2.6 mg/m^3

1.2 Uses

Vinyl chloride is used primarily (> 95%) in the manufacture of polyvinyl chloride (PVC), which comprises about 12% of the total use of plastic worldwide (WHO, 1999). The largest use of PVC is in the production of plastic piping. Other important uses are in floor coverings, consumer goods, electrical applications and in the transport sector. About 1% of PVC is used to produce vinyl chloride/vinyl acetate copolymer. Minor uses of vinyl chloride (monomer) include the manufacture of chlorinated solvents (primarily 10000 tonnes per year of 1,1,1-trichloroethane) and the production of ethylene diamine 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 drugs and cosmetic products; these uses were banned in the United States of America (USA) by the Environmental Protection Agency in 1974 (IARC, 2008).

1.3 Human exposure

1.3.1 Occupational exposure

The main route of occupational exposure to vinyl chloride is by inhalation, which occurs primarily in vinyl chloride/PVC plants and in PVC-processing plants. Only few exposure

measurements have been reported, but estimates from the chemical industry indicate that exposure to vinyl chloride monomer (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 human carcinogen (IARC, 1974), occupational exposure standards were set at approximately 13–26 mg/m^3 [5–10 ppm] in most countries in the 1970s (Fleig & Thiess, 1974; NTP, 2005; IARC, 2008).

CAREX (CARcinogen EXposure) is an international information system on occupational exposure to known and suspected carcinogens based on data collected in the European Union (EU) from 1990 to 1993. The CAREX database provides selected exposure data and documented estimates of the number of exposed workers by country, carcinogen, and industry (Kauppinen *et al.*, 2000). Table 1.1 presents the estimated numbers of workers exposed to vinyl chloride in the EU for the top-10 industries (CAREX, 1999).

From the US National Occupational Exposure Survey (1981–83) it was estimated that approximately 81 300 workers (including approximately 28 400 women) were potentially exposed to vinyl chloride (NIOSH, 1990).

A report from the Centers for Disease Control and Prevention (CDC) in the USA concluded that the development and acceptance by the PVC-manufacturing industry of a closed-loop polymerization process in the late 1970s "almost completely eliminated worker exposures" (CDC, 1997). Even after the late 1970s, however, high concentrations may still be encountered and were in fact reported in some countries (IARC, 2008).

(a) Production of vinyl chloride and its derivatives

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).

Measurements of VCM concentrations in indoor air of vinyl chloride/PVC production plants have been summarized in *IARC Monograph* Volume 97 (IARC, 2008). In a study on occupational exposure to vinyl chloride that was not included in the previous *Monograph*, Zhu *et al.* (2005) reported the exposure to VCM of workers in a plant in the People's Republic of China. Concentrations in air 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 mean concentration was 2.6 ppm [7.1 mg/m^3].

(b) PVC processing

Measured concentrations of VCM in PVC-processing plants were considerably lower than those in plants where vinyl chloride and PVC were produced (IARC, 2008). 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 reduced concentrations of vinyl chloride in the workplace air of PVC-processing factories, reaching values of < 0.1 ppm [0.26 mg/m^3] (Holm *et al.*, 1982).

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

(c) Hairdressers and barbers

Infante *et al.* (2009) presented two case reports of hairdressers and barbers who used hairsprays containing vinyl chloride over a period of 4–5 years between 1966 and 1973, and developed angiosarcoma of the liver (ASL). The ranges of exposure were estimated at 129–1234 ppm (peak concentration), and as 70–1037 ppm (average concentration).

Table 1.1 Estimated numbers of workers exposed to vinyl chloride in the European Union (top-10 industries)

Industry, occupational activity	
Manufacture of industrial chemicals	10400
Manufacture of plastic products, not elsewhere classified	9100
Manufacture of other chemical products	7600
Manufacture of fabricated metal products, except machinery and equipment	2900
Manufacture of machinery, except electrical	2400
Services allied to transport	1300
Manufacture of electrical machinery, apparatus, appliances	980
Education services	870
Construction	800
Petroleum refineries	570
TOTAL	39600

From CAREX (1999)

1.3.2 Non-occupational exposure

The general population is potentially exposed to vinyl chloride through inhalation of contaminated air, ingestion of contaminated drinking-water and foods, or dermal contact with consumer products. However, the exposure levels for the majority of the population are very low (NTP, 2005).

(a) Ambient air

Vinyl chloride is released into the environment in emissions and effluents from the plastics industry. Atmospheric concentrations of VCM in ambient air are low (usually < 3 μg/m^3) and ambient air samples in rural and urban areas of the USA typically do not contain detectable levels of vinyl chloride (NTP, 2005). Vinyl chloride has been reported in landfill gas and groundwater, as a degradation product of chlorinated solvents that were deposited in landfills (WHO, 1999).

Populations living near emission sources (e.g. emissions and effluents from the plastics industry) may be exposed to relatively high concentrations of airborne vinyl chloride. Measured concentrations ranged from trace levels to over 2600 μg/m^3, and the average daily intake of vinyl chloride by residents living near such emission sources ranged from trace amounts up to 2100 μg (NTP, 2005). A monitoring programme in the 1970s around VCM- and PVC-production plants found some relatively high concentrations of vinyl chloride in the ambient air. Maximum 24-hour 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 plants where PVC products were manufactured than near VCM- and PVC-production plants (Dimmick, 1981).

(b) Accidental releases

In June 1996, ten of 18 tank wagons filled with vinyl chloride derailed on the Magdeburg-Halle railway line just outside the Schönebeck train station in Germany. Vinyl chloride concentrations of 0.06–8 ppm [0.16–20.8 mg/m^3] were measured in surrounding residential areas. Nearly 300 urine samples were taken from rescue workers, residents and a control group, and analysed for the presence of the vinyl-chloride metabolite thiodiacetic acid. The measured values appeared to be in the range of those of non-exposed people (Thriene *et al.*, 2000).

(c) Residues in PVC resin and products

PVC products may contain VCM as a residue from production and release it in the air. In a German survey (1976–77), the following articles released VCM at levels > 0.05 ppm [0.13 mg/m^3] by off-gassing in the air: bathroom tiles, piping, plastic bottles for table oil, and kitchen wrapping-film. The highest concentrations were observed to come from vinyl music records, with values of 20–50 ppm measured for nine of 14 records sampled, but even higher in some of the others. The VCM concentrations released by toys, kitchen utensils, food wrappings, wall-paper, and car interiors were < 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 sources of exposure

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

Exposure to vinyl chloride in drinking-water is unlikely for the majority of the general population. In a US survey of 945 ground-water supplies and 11202 public water supplies that used surface waters as their primary source, less than 1% of the samples contained detectable levels of vinyl chloride (detection limit, 1 ppb [1 µg/L]). The US Environmental Protection Agency estimated that approximately 0.9% of the US population is exposed to vinyl chloride in drinking-water at concentrations of 1.0 µg/L or higher, and that 0.3% is exposed to concentrations higher than 5 µg/L (NTP, 2005).

2. Cancer in Humans

Vinyl chloride was evaluated in previous *IARC Monographs* (IARC, 1979, 1987, 2008) and was classified in Group 1 based on increased risks for ASL and hepatocellular carcinoma (HCC).

A report of three cases of ASL 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 extreme rarity of this tumour in the general population. The Working Group in 1974 already considered this observation to provide evidence of a causal relationship.

Epidemiological evidence for the carcinogenicity of vinyl chloride in humans derives principally from two large, multicentre 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. In addition to reports that pertained to these cohorts in their entirety, several studies reported findings from individual subcohorts. Results for subcohorts are given in the Tables, but only when they provide important information that is not available in analyses of the full cohorts. Results on six cohort studies have also been reported, in addition to and separate from the two multicentre investigations.

The first published report of the North-American multicentre cohort study (Cooper, 1981) included 10173 workers from 37 plants. 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 one year before 31 December 1972 and to have been employed in or after 1942. A second major update of this cohort was published by Wong *et al.* (1991). A third major follow-up included 10 109 subjects and provided an update of the vital status through to 31 December 1995 (Mundt *et al.*, 2000).

The European cohort study was conducted in four countries (Italy, Norway, Sweden and the United Kingdom). It included workers from 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 one year in 1942–1972 in jobs that entailed exposure to VCM were included (Simonato *et al.*, 1991). 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.

2.1 Angiosarcoma of the liver

In both multicentre cohort studies (Mundt *et al.*, 2000; Ward *et al.*, 2001) a substantial excess of ASL in exposed workers was found (see Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-26-Table2.1.pdf). This tumour is extremely rare in the general population and it is not possible to calculate an SMR or SIR, because age- and calendar time-specific reference rates are not available. In the study from the US, 33 of the 80 deaths from cancer of the liver and biliary tract were identified from the death certificate as due to ASL. A total of 48 deaths due to ASL were identified by combining information from death certificates with that from a registry of ASL-cases that were related to exposure to VCM. This registry is maintained and updated by the Association of Plastics Manufacturers of Europe.

In the European study there were 53 deaths from primary liver cancer and 18 incident cases of liver cancer. This total of 71 cases comprised 37 ASL, 10 HCC, 7 cases of other known histology, and 17 cases of an unspecified type of liver cancer. [The Working Group noted that the authors searched for the best evidence for diagnosis of liver cancers by reviewing all available documentation, including death certificates, cancer-registry records, medical records, and listings of ASL from two registries.]

In both studies, the risk for ASL 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 ASL were also reported in one smaller cohort study (Thériault & Allard, 1981). Two cases of ASL were reported among hairdressers and barbers who had been exposed to vinyl chloride for 4–5-year periods in the late 1960s and early 1970s, when it was used as a propellant in hairspray (Infante *et al.*, 2009).

2.2 Hepatocellular carcinoma

The assessment of vinyl chloride as a cause of HCC is complicated because many studies do not have histological or other definitive clinical information to discriminate HCC from ASL and/or secondary neoplasms (see Table 2.1 online). In the US multicentre study, mortality from cancers of the liver and biliary tract (ICD9-code, 155–156) was increased (SMR 3.6, 95%CI: 2.8–4.5; 80 deaths). Of the 80 deaths, 48 were identified as ASL. The diagnosis of HCC among the remaining deaths was not verified.

In an internal analysis of the European multicentre cohort (Ward *et al.*, 2001) based on 10 verified cases of HCC, the risk increased significantly and substantially with duration of employment and with cumulative exposure to vinyl chloride. The relative risk for workers with the longest duration of employment (> 26 years) was 35 (95%CI: 3.3–377) compared with workers with < 10 years of employment. An analysis of a single Italian plant with extended follow-up – that

was included in the European study – indicated 12 confirmed cases of HCC (Pirastu *et al.*, 2003). The maximal overlap between these two analyses was four cases, since only four HCC from Italy were included in the multicentre cohort. In this subcohort, the incidence of HCC again increased significantly with cumulative exposure to vinyl chloride. There was suggestive evidence that the risk for HCC from vinyl chloride is substantially higher among workers who are infected with hepatitis B virus (Wong *et al.*, 2003), or who report high levels of alcoholic beverage consumption (Mastrangelo *et al.*, 2004).

A meta-analysis of cohort studies of vinyl choride-exposed workers published up to 2002 (Boffetta *et al.*, 2003) was based on eight independent studies, i.e. two multicentric investigations (Mundt *et al.*, 2000; Ward *et al.*, 2001) and six additional, smaller studies (Thériault & Allard, 1981; Weber *et al.*, 1981; Smulevich *et al.*, 1988; Laplanche *et al.*, 1992; Huang, 1996; Wong *et al.*, 2002) (*P*-value for the test for heterogeneity was ≥ 0.01). Six of these eight studies reported results for liver cancer, but these were considered to be too heterogeneous to be included in a meta-analysis because for 'liver cancer overall' and for 'liver cancer other than ASL', the *P*-value for heterogeneity was < 0.001. For the two multicentre studies (Mundt *et al.*, 2000; Ward *et al.*, 2001), the lack of heterogeneity allowed calculation of summary estimates for liver cancer overall (meta-SMR, 2.96; 95%CI: 2.00–4.39; random effects model; *P*-value for heterogeneity = 0.03) and for liver cancer other than ASL (meta-SMR, 1.35; 95%CI: 1.04–4.39; random effects model; *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 quality of the data. Excluding one study from the People's Republic of 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 ASL.]

2.3 Cancer of the lung

Among workers exposed to vinyl chloride, there was no overall evidence of an increased risk for lung cancer (see Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-26-Table2.2.pdf). However, in PVC-packers and -baggers, the risk for lung cancer increased significantly with cumulative exposure to vinyl chloride (Ward *et al.*, 2001). [These workers are known to have had concomitant exposure to PVC-dust; the study did not allow attribution of the association to a specific agent or combination of agents.]

2.4 Malignant neoplasms of connective and soft tissue

Suggestive evidence was found for malignant neoplasms of connective and soft tissue (ICD9-code, 171). This derived from the multicentre study in the USA (Mundt *et al.*, 2000), in which a nearly threefold statistically significant overall increase in mortality from these neoplasms was observed (SMR 2.7, 95%CI: 1.4–4.7; 12 observed, 4.4 expected). The risk was higher for workers with longer duration of employment (i.e. 10–19 *vs* > 20 years) and for those first employed before 1960. Four of the 12 observed deaths were from angiosarcomas for which the site was unknown. The increased mortality from neoplasms of connective and soft tissue persisted even after exclusion of these four angiosarcomas. [This presumes that the malignant neoplasms of connective and soft tissue were mis-classified deaths from angiosarcoma of the liver.]

The findings mentioned above were not supported by results from the European multicentre study, in which the number of deaths from connective-tissue neoplasms was too small

for an evaluation of exposure–response (Ward *et al.*, 2001): there were six observed deaths from neoplasms of connective and soft tissue (SMR = 1.9, 95%CI: 0.7–4.1), but in a re-evaluation of the diagnoses three of the six deaths coded as tumours of the connective tissue were found to be ASL. [The Working Group noted that, although a statistically significant increase in mortality from neoplasms of connective and soft tissue was found in the US study, the discrepant results with the European study and the difficulties in arriving at a correct diagnosis and coding of the tumour site for this type of neoplasm, complicate an evaluation of these findings.]

2.5 Other cancers

The Working Group did not find strong evidence for associations of exposure to vinyl chloride with cancers of the brain or the lymphatic and haematopoeitic tissues, with melanoma of the skin (see Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-26-Table2.3.pdf, Table 2.4 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-26-Table2.4.pdf, and Table 2.5 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-26-Table2.5.pdf). 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 multicentre study (Ward *et al.*, 2001), and, for several of the sites, the numbers of observed/expected cases were small.

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

2.6 Synthesis

There is compelling evidence that exposure to vinyl chloride is associated with angiosarcoma of the liver, and strong evidence that it is associated with hepatocellular carcinoma. Together with the observation that vinyl chloride increases the risk for liver cirrhosis, which is a known risk factor for hepatocellular carcinoma, the findings from two large multicentre cohort studies provide convincing evidence that vinyl chloride causes hepatocellular carcinoma as well as angiosarcoma of the liver. There is contradictory evidence that exposure to vinyl chloride is associated with malignant neoplasms of connective and soft tissue, and inconsistent or scanty evidence that it is associated with cancers of the lung, brain, lymphohaematopoietic system, and breast, or with melanoma of the skin.

3. Cancer in Experimental Animals

The carcinogenicity of vinyl chloride has been studied intensively and repeatedly in experimental animals, with a wide range of concentrations, spanning orders of magnitude. The many studies consistently showed hepatic and extrahepatic angiosarcomas in mice and rats. Various other malignant neoplasms also occurred at several anatomical sites. However, the reporting of the results 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 in footnotes.

Studies of the carcinogenicity of vinyl chloride in experimental animals after oral administration, inhalation, subcutaneous injection, intraperitoneal injection, and transplacental and perinatal exposure have been reviewed in previous *IARC Monographs* (IARC, 1974, 1979, 1987, 2008). No studies have been published since the most recent evaluation (IARC, 2008). The

following is a summary of the available data (see also Table 3.1).

3.1 Inhalation exposure

Vinyl chloride was tested by inhalation exposure in several studies in mice (Holmberg *et al.*, 1976; Lee *et al.*, 1978; Hong *et al.*, 1981; Maltoni *et al.*, 1981; Drew *et al.*, 1983; Suzuki, 1983), in several studies in rats (Lee *et al.*, 1978; Feron *et al.*, 1979; Feron & Kroes, 1979; Groth *et al.*, 1981; Kurliandskiĭ *et al.*, 1981; Maltoni *et al.*, 1981; Drew *et al.*, 1983), and in two studies in hamsters (Maltoni *et al.*, 1981; Drew *et al.*, 1983). Male and female animals of all three species were included, although some experiments were carried out only in one sex. Vinyl chloride induced hepatic angiosarcomas in three experiments in mice and in eight experiments in rats; a dose–response was observed for hepatic angiosarcomas in both species over a wide range of exposures. Extrahepatic angiosarcomas related to treatment with vinyl chloride were observed in three studies in mice and one study in rats. Vinyl chloride increased the incidence of malignant mammary tumours in seven experiments in mice, in two experiments in one study in rats, and in one study in hamsters. Exposure to vinyl chloride increased the incidence of skin epitheliomas in one study in rats and one study in hamsters, and of skin carcinomas in another study in hamsters. It increased the incidence of Zymbal gland carcinomas in three experiments in rats, with a dose–response pattern in one experiment. In mice, vinyl chloride increased the incidence of benign lung tumours in six experiments, and of lung carcinomas in two experiments. It also increased the incidence of nasal cavity carcinomas in one study in rats, of hepatocellular carcinomas in two experiments in rats, of glandular adenomas in one study in hamsters, and of benign fore-stomach tumours in another study in hamsters.

In one study in rats, combined oral administration of ethanol and inhalation exposure to vinyl chloride increased the incidence of hepatic angiosarcomas compared with exposure to vinyl chloride alone (Radike *et al.*, 1981).

3.2 Oral administration

Vinyl chloride was tested by oral administration in four experiments in male and female rats (Feron *et al.*, 1981; Maltoni *et al.*, 1981; Til *et al.*, 1991). It induced hepatic angiosarcomas in two experiments, lung angiosarcomas in one experiment and hepatocellular adenomas and hepatocellular carcinomas in two experiments.

3.3 Subcutaneous and intraperitoneal injection

When vinyl chloride was tested in rats by subcutaneous injection and by intraperitoneal injection in single studies, no increase in tumour incidence was observed (Maltoni *et al.*, 1981).

3.4 Transplacental administration and perinatal exposure

The transplacental carcinogenicity of vinyl chloride was evaluated in one study in the offspring of rats exposed by inhalation on days 12–18 of pregnancy. A low incidence of tumours was observed in prenatally exposed offspring at several sites including the kidney (nephroblastomas) and the Zymbal gland (carcinomas). However, no angiosarcomas or hepatomas developed in the offspring (Maltoni *et al.*, 1981).

Vinyl chloride was tested by perinatal inhalation exposure in two studies in rats. In one study, rats were exposed transplacentally, as neonates, and during adulthood. Treatment with vinyl chloride induced hepatic angiosarcomas and hepatocellular carcinomas. The rats also showed

Table 3.1 Carcinogenicity studies in experimental animals exposed to vinyl chloride and chloroethylene oxide

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, NMRI (M, F) 26 or 52 wk Holmberg *et al.* (1976)	Inhalation, 0, 50, 500 ppm [0, 130, 1 300 mg/m^3] 6 h/d, 5 d/wk, for 26 wk (0, 500 ppm) or 52 wk, (0, 50 ppm) 12/group/sex	Extrahepatic angiosarcomas: (M) 0/24, 6/12*, 3/12*; (F) 0/24, 8/12*, 5/12* Lung adenomas: (M) 0/24, 9/12*, 12/12*; (F) 0/24, 4/12*, 12/12* Mammary carcinomas: (F) 1/24, 1/12, 4/12	NR, *[$P < 0.05$]	Purity NR The animals exposed to 500 ppm were sacrificed after 26 wk because of poor survival. Control groups were combined.
Mouse, CD-1 (M, F) 52 wk Lee *et al.* (1978)	Inhalation 0, 50, 250, 1000 ppm [0, 130, 650, 2 600 mg/m^3] 6 h/d, 5 d/wk, 52 wk 36/group/sex, 4 animals/group were sacrificed at 1, 2, 3, 6 or 9 mo	Liver angiosarcomas: (M) 0/26, 3/29, 7/29*, 13/33*; (F) 0/36, 0/34, 16/34*, 18/36* Extrahepatic angiosarcomas: (M): 0/26, 5/29*, 2/29, 0/33; (F) 0/36, 1/34, 3/34, 9/36* Lung adenomas: (M) 1/26, 8/29**, 10/29**, 22/23**; (F): 0/36, 4/34, 12/34**, 26/36** Mammary gland tumours (malignant): (F) 0/36, 9/34**, 3/34, 13/36**	*$P < 0.05$ NR, **[$P < 0.05$]	99.8% pure Mammary gland tumours were adenocarcinomas and carcinomas
Mouse, CD-1 (M, F) up to 18 mo Hong *et al.* (1981)	Inhalation 0, 340, 1690, 6760 ppm [0, 130, 650, 2600 mg/m^3] 6 h/d, 5 d/wk for 1, 3 or 6 mo and observed for additional 12 mo 8–28/group/sex	Cumulative incidence Liver haemangiosarcomas: (M) 0/60, 1/40, 8/44*, 6/38*; (F) 1/60, 1/40, 5/40*, 12/38* Bronchioloalveolar tumours: (M) 8/60, 12/40, 29/44*, 27/38*; (F) 8/60, 6/40, 23/40*, 23/38* Mammary gland tumours (malignant): (F) 4/60, 10/40, 13/40*, 6/38*	*$P < 0.05$	Mammary gland tumours were adenocarcinomas and carcinomas; bronchioalveolar tumours were not further described.
Mouse, Swiss (M, F) 81 wk Maltoni *et al.* (1981)	Inhalation 0, 50, 250, 500, 2500, 6000, 10000 ppm [0, 130, 650, 1300, 6500, 15600, 26000 mg/m^3] 4 h/d, 5 d/wk, 30 wk 30/group/sex, 150 controls	Liver angiosarcomas: 0/150, 1/60, 18/60, 14/60, 16/59, 13/60, 10/56 Extrahepatic angiosarcomas: 1/150, 1/60, 3/60, 7/60, 8/59, 1/60, 1/56 Lung tumours: 15/150, 6/60, 41/60, 50/60, 40/59, 47/60, 46/56 Mammary gland carcinomas: 1/150, 12/60, 12/60, 8/60, 8/59, 8/60, 13/56	NR [$P < 0.05$, many exposed group], angiosarcomas (all sites including the liver), lung tumours and mammary gland carcinomas	99.97% pure Data reported for both sexes combined. A low incidence of skin tumours was also reported; lung tumours were not further described.

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, CD-1 (F) Lifetime Drew *et al.* (1983)	Inhalation Study 1: 8–9 wk old mice exposed to 0 or 50 ppm [0, 130 mg/m^3] 6 h/d, 5 d/wk, for 6, 12, or 18 mo Initial group size NR	Study 1, incidence for controls and incidences for animals exposed for 6, 12, 18 mo Haemangiosarcomas (all sites): 1/71, 29/67, 30/47, 20/45 Lung carcinomas: 9/71, 18/65, 15/47, 11/45 Mammary gland carcinomas: 2/71, 33/67, 22/47, 22/45	Study 1, $P < 0.01$ (all vinyl chloride-exposed group)	Commercial grade, purity NR
	Study 2: 8 or 14 mo old mice exposed to 0 or 50 ppm 6 h/d, 5 d/wk, for 6 or 12 mo Initial group size NR	Study 2, incidence for controls and incidences for animals exposed for 6 mo (8 mo old at start), 6 mo (14 mo old), 12 mo (8 mo old), 12 mo (14 mo old) Haemangiosarcomas(all sites): 1/71, 11/49**, 5/53, 17/46**, 3/50 Lung carcinomas: 9/71, 13/49*, 7/53, 9/46*, 3/50 Mammary gland carcinomas: 2/71, 13/49**, 2/53, 8/45**, 0/50	Study 2, *$P < 0.05$ **$P < 0.01$	
Mouse, B6C3F1 (F) Lifetime Drew *et al.* (1983)	Inhalation Study 1: 8–9 wk old mice exposed to 0 or 50 ppm [0, 130 mg/m3] 6 h/d, 5 d/wk, for 6 or 12 mo Initial group size NR	Study 1: incidence for controls and incidences for animals exposed for 6, 12 mo Haemangiosarcomas (all sites): 4/69, 46/67**, 69/90** Mammary gland carcinomas: 3/69, 29/67**, 37/90**	*$P < 0.05$ **$P < 0.01$	Commercial grade, purity NR
	Study 2: 8 or 14 mo old mice exposed to 0 or 50 ppm 6 h/d, 5 d/wk, for 6 or 12 mo Initial group size NR	Study 2: incidence for controls and incidence for animals exposed for 6 mo (8 mo old at start), 6 mo (14 mo old), 12 mo (8 mo old), or 12 mo (14 mo old) Haemangiosarcomas (all sites): 4/69, 27/42**, 30/51**, 30/84**, 29/48** Mammary gland carcinomas: 3/69, 13/42**, 4/51*, 9/48**, 4/48**		

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Mouse CD-1 (M) up to 44–45 wk Suzuki (1983)	Inhalation 0, 1, 10, 100, 300, 600 ppm [0, 2.6, 26, 260, 780, 1560 mg/m^3] 6 h/d, 5 d/wk, 4 wk 30/group except 60/control group and 40/600 ppm-treated group	Benign pulmonary tumours: 12 wk after exposure: 0/18, 0/10, 0/9, 0/6, 6/9*, 8/9* 40–41 wk after exposure: 0/17, 1/9, 3/9, 6/9*, 5/7*, 6/7*	NR *[$P < 0.05$]	Purity NR
Rat, CD (M, F) 52 wk Lee *et al.* (1978)	Inhalation 0, 50, 250, 1000 ppm [0, 130, 650, 2600 mg/m^3] 6 h/d, 5 d/wk 36/group/sex, 4 animals/group were sacrificed at 1, 2, 3, 6 and 9 mo	Liver angiosarcomas: (M) 0/35, 0/36, 2/36, 6/34; (F) 0/35, 0/36, 10/34*, 15/36* Extrahepatic angiosarcomas: (M) 0/35, 1/36, 2/36, 4/34; (F) 0/35, 1/36, 3/34, 10/36*	*$P < 0.05$	99.8% pure
Rat, Wistar (M, F) 52 wk Feron & Kroes (1979) Feron *et al.* (1979)	Inhalation 0, 5000 ppm [0, 13000 mg/m^3] 7 h/d, 5 d/wk 62/group/sex, 10 animals/group/sex were sacrificed at 4, 13, 26 or 52 wk	At 52 wk Liver angiosarcomas: (M) 3/9; (F): 6/10* Zymbal gland squamous-cell carcinomas: (M) 3/9; (F): 2/10 Nasal cavity carcinomas: (M) 2/9; (F) 5/10* No tumours observed in controls: (M) 0/10; (F) 0/10	NR *[$P < 0.05$]	99.97% pure Information on survival NR
Rat, Sprague-Dawley (M, F) 43 wk Groth *et al.* (1981)	Inhalation 0, 940 ppm [0, 2465 mg/m^3] 7 h/d, 5 d/wk, 24.5 wk to rats 6, 18, 32, 52 wk of age 110–128/group/sex	Angiosarcomas (mostly in the liver): In rats 6, 18, 32, 52 wk of age at start: (M) 0/37, 0/44, 3/45, 13/55; (F) 2/38, 7/47, 23/49*, 11/54 In controls 32 wk of age at start: (M) 1/86; (F) 0/85	NR *[$P < 0.0001$]	Purity NR Epidemic of pneumonia during the 28th wk prematurely ended the study.
Rat, random bred white (M) 126 wk Kurliandskiĭ *et al.* (1981)	Inhalation 0, 5.4, 9.6, 102, 1420 ppm [0, 14, 25, 266, 3690 mg/m^3] 4.5 h/d, 5 d/wk, 52 wk 50–58/group, 93 controls	Angiosarcomas (all sites): 0% in controls, 9.3–15.7% in the two higher dose-treated group Liver angiosarcomas: 0% in controls, 9.3–11.8% in the two higher dose-treated group	NR	Purity NR

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Sprague Dawley (M, F) 156 wk Maltoni *et al.* (1981)	Inhalation 0, 50, 250, 500, 2500, 6000, 10000 ppm [130, 650, 1300, 6500, 15600, 26000 mg/m^3] 4 h/d, 5 d/wk, 17 wk 30/group/sex, 190 controls	Liver angiosarcomas: 0/190, 0/58, 0/59, 1/60, 1/60, 1/60, 0/58 Hepatomas: 0/190, 0/58, 0/59, 0/60, 2/60, 1/60, 1/58 Zymbal gland carcinomas: 2/190, 0/58, 1/59, 1/60, 7/60, 9/60, 9/58 Skin epitheliomas: 1/190, 1/58, 0/59, 0/60, 2/60, 5/60, 5/58	NR [$P < 0.05$, some exposed group], Zymbal gland carcinoma, skin epithelioma	99.97% purity Data reported for both sexes combined
Rat, Sprague Dawley (M, F) 154 wk Maltoni *et al.* (1981)	Inhalation 0 (control), 6000 (group I, III, V), 10 000 (group II, IV, VI) ppm [0, 15 600, 26 000 mg/m^3] group I, II: 4 h/d, 5 d/wk, 5 wk; group III, IV: 1 h/d, 4 d/wk, 25 wk; group V, VI: 4 h/d, 1/wk, 25 wk 60/group/sex, 240 controls	controls, I, II, III, IV, V, VI Liver angiosarcomas: 0/227, 1/118, 0/120, 1/119, 3/118, 1/119, 1/120 Extrahepatic angiosarcomas: 0/227, 0/118, 0/120, 0/119, 2/118, 0/119, 1/120 Zymbal gland carcinomas: 0/227, 9/118, 9/120, 9/119, 5/118, 8/119. 9/120 Mammary gland tumours (malignant): 17/227, 13/118, 13/120, 16/119, 11/118, 20/119, 12/120	NR [$P < 0.05$, all exposed group], Zymbal gland carcinoma	99.97% purity Data reported for both sexes combined
Rat, Sprague Dawley (M, F) up to 147 wk Maltoni *et al.* (1981)	Inhalation 0, 1, 5, 10, 25, 50, 50, 100, 150, 200, 250, 500, 2500, 6000, 10000, 30000 ppm [0, 2.6, 13, 26, 65, 130, 130, 260, 390, 520, 650, 1300, 6500, 15600, 26000, 78000 mg/m^3] 4 h/d, 5 d/wk, 52 wk 60–300 M+F/group, 461 controls	Liver angiosarcomas: 0/461, 0/118, 0/119, 1/119, 5/120, 1/60, 14/294, 1/120, 6/119, 12/120, 3/59, 6/60, 13/60, 13/59, 7/60, 18/60 Zymbal gland carcinomas: 4/461, 1/118, 1/119, 2/119, 4/120, 0/60, 9/294, 1/120, 4/119, 4/120, 0/59, 4/60, 2/60, 7/59, 16/60, 35/60	NR [$P < 0.05$, many exposed group] [$P < 0.05$, some exposed group]	99.97% purity Five studies combined to construct a dose–response table. Rats exposed to highest concentration were observed for 68 wk, others for 135–147 wk. There was no dose–response
Rat, Wistar (M) up to 165 wk Maltoni *et al.* (1981)	Inhalation 0, 1, 50, 250, 500, 2500, 6000, 10000 ppm [0, 2.6, 130, 650, 1300, 6500, 15600, 26000 mg/m^3] 4 h/d, 5 d/wk, 52 wk 30–130/group	Liver angiosarcomas: 0/132, 0/99, 0/28, 1/27, 3/28, 3/25, 3/26, 8/27 Extrahepatic angiosarcomas: 1/132, 3/99, 0/28, 1/27, 0/28, 1/25, 1/26, 0/27 Hepatomas: 0/132, 1/99, 0/28, 0/27, 0/28, 1/25, 2/26, 0/27 Zymbal gland carcinomas: 3/132, 2/99, 0/28, 0/27, 0/28, 0/25, 2/26, 2/27	NR [$P < 0.05$, some exposed group], liver angiosarcoma	99.97% purity

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Fischer (F) Lifetime Drew *et al.* (1983)	Inhalation 0, 100 ppm [0, 260 mg/m^3] 6 h/d, 5 d/wk, for 6, 12, 18 or 24 mo 55–112/group	Tumour incidence after 24 mo of exposure: Liver haemangiosarcomas: 1/112, 19/55* Haemangiosarcomas (all sites): 2/112, 24/55* Mammary gland adenocarcinomas: 5/112, 5/55* Hepatocellular carcinomas: 1/112, 9/55*	*$P < 0.01$	Purity NR Rats necropsied when moribund or dead
Rat, Fischer (F) Lifetime Drew *et al.* (1983)	Inhalation 0 (control), 100 ppm [0, 260 mg/m^3] 6 h/d, 5 d/wk for 6 mo (rats 2, 8, 14 or 20 mo old at start) or 12 mo (rats 2, 8 or 14 mo old at start) 51–112/group	Liver haemangiosarcomas: 1/112, 4/76*, 2/52, 0/51, 0/53, 11/55*, 5/54*, 2/49 Haemangiosarcomas (all sites): 2/112, 4/76, 2/53, 0/53, 0/53, 12/56*, 5/55*, 2/50 Mammary gland adenocarcinomas: 5/112, 6/76, 2/53, 3/53, 2/53, 11/56*, 4/55, 0/50 Hepatocellular carcinomas: 1/112, 3/75, 6/52*, 0/51, 1/53, 4/56*, 1/54, 0/49	*$P < 0.01$	Rats necropsied when moribund or dead. Statistically significant increases were also observed for mammary gland fibroadenomas and hepatocellular adenomas.
Rat, Sprague Dawley (M, F) 136 wk Maltoni *et al.* (1981)	Oral (gastric intubation) 0, 3.3, 17, 50 mg/kg bw, 4–5 × / wk, 52 wk 40/group/sex	Liver angiosarcomas: 0/80, 0/80, 10/80*, 17/80* Extrahepatic angiosarcomas: 0/80, 2/80, 0/80, 2/80 Nephroblastomas: 0/80, 0/80, 3/80, 2/80	NR *[$P < 0.05$]	99.97% purity Information on survival NR Data reported for both sexes combined
Rat, Sprague Dawley (M, F) 136 wk Maltoni *et al.* (1981)	Oral (gastric intubation) 0, 0.03, 0.3, 1 mg/kg bw, 4–5 × /wk, 52–59 wk 75/group/sex	Liver angiosarcomas: 0/150, 0/150, 0/148, 3/149. Extrahepatic angiosarcomas: 0/150, 0/150, 0/148, 1/149 Hepatomas: 0/150, 0/150, 1/148, 1/149 Zymbal gland carcinomas: 1/150, 0/150, 0/148, 5/149 Mammary gland tumours (malignant): 7/150, 14/150, 4/148, 12/149	NR, [NS]	99.7% purity Data reported for both sexes combined
Rat, Wistar (M, F) 135 wk (M), 144 wk (F) Feron *et al.* (1981)	Oral (feed) 0, 1, 3, 10% of 4000 ppm vinyl chloride in a PVC powder [resulting in a daily dose of 0, 1.7, 5.0, 14 mg vinyl chloride/kg bw] 4 h/d, 7 d/wk 60–80/group/sex	Liver haemangiosarcomas: (M) 0/55, 0/58, 6/56*, 27/59*; (F) 0/57, 0/58, 2/59, 9/57* Hepatocellular carcinomas: (M) 0/55, 1/58, 2/56, 8/59*; (F) 0/57, 4/58, 19/59*, 29/57* Hepatocellular adenomas: (M) 0/55, 1/58, 7/56*, 23/59*; (F) 2/57, 26/58, 39/59*, 44/57* Lung angiosarcomas: (M) 0/55, 0/58, 4/56*, 19/59*; (F) 0/57, 0/58, 1/59, 5/57*	*$P < 0.05$	99.7% purity

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Wistar (M, F) 149 wk (M), 150 wk (F) Til *et al.* (1991)	Oral (feed) PVC powder in food that resulted in dose of 0, 0.014, 0.13, 1.3 mg vinyl chloride/kg bw 4–6 h/d, 7 d/wk 50–100/group/sex	Hepatocellular carcinomas: (M) 0/99, 0/99, 0/99, 3/49*; (F) 1/98, 0/100, 1/96, 3/49 Hepatocellular adenomas: (M) 0/99, 0/99, 0/99, 1/49; (F) 0/98, 1/100, 1/96, 9/49* Liver haemangiosarcomas: (M) 0/99, 0/99, 0/99, 1/49; (F) 0/98, 0/100, 0/96, 2/49	*$P < 0.05$	99.7% purity
Rat, Sprague-Dawley (M, F) 145 wk Maltoni *et al.* (1981)	Subcutaneous injection Single injection of 0, 4.25 mg in 1 ml olive oil, 35 M/group, 40 F/group	Mammary gland tumours (malignant): 3/75, 1/75. Nephroblastomas: 0/75, 1/75	NR, [NS]	99.97% purity No other tumour types observed Data reported for both sexes combined
Rat, Sprague-Dawley (M, F) 144 wk Maltoni *et al.* (1981)	Intraperitoneal injection 0 (olive oil, once); 4.25 mg/kg bw, once, twice, three, or four times at 2 mo intervals 30/group/sex	Extrahepatic angiosarcomas: 0/55, 0/55, 1/56, 1/53, 0/56 Mammary gland tumours (malignant): 0/55, 2/55, 3/56, 1/53, 1/56	NR, [NS]	99.97% purity No liver angiosarcomas observed Data reported for both sexes combined
Rat, Sprague-Dawley (M, F) 143 wk Maltoni *et al.* (1981)	Transplacental Pregnant females exposed by inhalation to 6000, 10000 ppm [15600, 26000 mg/m^3] on D 12–18 of pregnancy 30–54 dams/group	In offspring Extrahepatic angiomas: 1/32, 0/51 Nephroblastomas: 0/32, 3/51 Zymbal gland carcinomas: 3/32, 5/51 Skin epitheliomas: 1/32, 0/51 Forestomach papillomas and achanthomas: 1/32, 1/51 Mammary gland tumours (malignant): 2/32, 1/51	-	99.97% purity No angiosarcomas (all sites) or hepatomas were observed in offspring. One Zymbal gland tumour at high dose (1/30) was the only tumour observed in dams. Despite the lack of controls, this study provides some evidence of the transplacental carcinogenicity of vinyl chloride. Data reported for both sexes combined.

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Sprague-Dawley (M, F) 124 wk Maltoni *et al.* (1981)	Perinatal Breeders and newborn offspring exposed together by inhalation to. 6000, 10000 ppm [15600, 26000 mg/m^3] 4 h/d, 5 d/wk, 5 wk 42–44/group (offspring)	In offspring Hepatic angiosarcomas: 17/42, 15/42 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 Mammary gland tumours (malignant): 1/42, 0/44	-	99.97% No concurrent controls No tumours observed in breeders at sites where tumours occurred in offspring Data reported for both sexes combined
Rat, Sprague-Dawley (M, F) Lifetime Maltoni & Cotti (1988)	Perinatal Breeders exposed by inhalation to 0, 2500 ppm [0, 6500 mg/m^3], 4 h/d, 5 d/wk, 7 wk; dams became pregnant and delivered offspring. Dams exposed (7 h/d) for 69 additional wk with group I offspring; group II offspring exposed only for 8 additional wk 54–60 breeders (F)/group, 60–63 offspring/group/sex, 149–158 control offspring/group/sex	Hepatocarcinomas: Breeders (F): 0/60, 5/54 Offspring group I: (M) 27/64; (F) 38/63; group II: (M) 42/60; (F) 43/60; controls: (M) 1/158; (F) 0/149 Liver angiosarcomas: Breeders (F): 0/60, 27/54 Offspring group I: (M) 36/64; (F) 46/63; group II: (M) 24/60; (F) 28/60; controls: (M) 0/158; (F) 0/149 Neuroblastomas (see comments): Breeders (F): 0/60, 32/54 Offspring group I: (M) 31/64; (F) 27/63; group II: (M) 7/60; (F) 11/60; controls: (M) 0/158; (F) 0/149	NR [$P < 0.05$], all exposed group	99.97% purity The photomicrographs and the preferential location of the neuroblastomas in the anterior frontal lobes support the alternative diagnosis of an origin in the metabolically active olfactory neuroepithelium of the posterior nasal cavity (aesthesioneuroepithelioma)
Hamster, Golden (M) 109 wk Maltoni *et al.* (1981)	Inhalation 0, 50, 250, 500, 2500, 6000, 10 000 ppm [0, 130, 650, 1300, 6500, 15600, 26000 mg/m^3] 4 h/d, 5 d/wk, 30 wk 30/group, 60 controls	Liver angiosarcomas: 0/60, 0/30, 0/30, 2/30, 0/30, 1/30, 0/30 Skin epitheliomas: 3/60, 9/30*, 3/30, 7/30*, 3/30, 1/30, 7/30* Forestomach papillomas and acanthomas: 3/60, 3/30, 4/30, 9/30*, 17/30*, 10/30*, 10/30* Leukaemia: 8/60, 6/30, 6/30, 5/30, 9/30, 6/30, 5/30	NR *[$P < 0.05$]	99.97% purity Information on survival NR

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Hamster, Syrian golden (F) Lifetime Drew *et al.* (1983)	Inhalation 200 ppm [520 mg/m^3] 6 h/d, 5 d/wk 0 (untreated control); 6, 12, or 18 mo exposure of hamsters 8 wk old at onset; 6 mo exposure of hamsters 8, 14, or 20 mo old at onset; 12 mo exposure of hamsters 2, 8, 14 mo old at onset Initial group size NR	Haemangiosarcomas (all sites): 0/143, 13/88**, 4/52**, 2/103, 3/53*, 0/50, 0/52, 4/52**, 1/44, 0/43 Mammary gland carcinomas: 0/143, 28/87**, 31/52**, 47/102**, 2/52*, 0/50, 1/52, 31/52**, 6/44**, 0/42 Stomach adenomas: 5/138, 23/88**, 3/50*, 20/101**, 15/53**, 6/49*, 0/52, 3/50*, 10/44**, 3/41 Skin carcinomas: 0/133, 2/80, 9/48**, 3/90, 0/49, 0/46, 0/50, 2/80, 0/38, 0/30	*$P < 0.05$ **$P < 0.01$	Purity NR, commercial grade. Decrease in survival of exposed animals. Hamsters were necropsied when moribund or dead.
Chloroethylene oxide				
Mice, XVIInc./Z (M, F) ~80 wk Zajdela *et al.* (1980)	Subcutaneous 32 injections of 0 (control) or 0.1 mg chloroethylene oxide over 42 wk	Local tumours (mainly fibrosarcomas): 15/28 (M); 12/24 (F); 0/30 (M, controls)	[$P < 0.0001$]	Purity NR
Mice, XVIInc./Z (M) 52–54 wk Zajdela *et al.* (1980)	Skin painting with 1 mg chloroethylene oxide followed by TPA as a promoter 2 wk after initiation (3 × /wk, 42 wk)	Skin papillomas: 18/28 vs 4/28 (TPA controls). Skin carcinomas: 5/28 vs 0/28 (TPA controls)	[$P < 0.001$] $P < 0.02$	Purity NR Chloroethylene oxide tested as an initiator Chloroethylene oxide (1 mg) dissolved in 80 µL benzene

bw, body weight; d, day or days; h, hour or hours; F, female; M, male; h, hour or hours; mo, month or months; NR, not reported; NS, not significant; TPA, 12-*O*-tetradecanoyl phorbol-13-acetate; vs, versus; wk, week or weeks

a high incidence of tumours that were probably of olfactory neuroepithelial origin, but were formerly reported as cerebral neuroblastomas in some studies. Similar results were observed in co-exposed dams (Maltoni & Cotti, 1988). In a second study, rats were exposed to vinyl chloride for five weeks, beginning at birth. Angiosarcomas of the liver and hepatomas occurred at a high incidence in the offspring, but not in the dams that were co-exposed with the offspring (Maltoni *et al.*, 1981).

3.5 Carcinogenicity of metabolites

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 by skin application. It caused a massive increase of fibrosarcomas at the site of injection and increased the incidence of squamous-cell papillomas and carcinomas of the skin at the site of application (Zajdela *et al.*, 1980).

4. Other Relevant Data

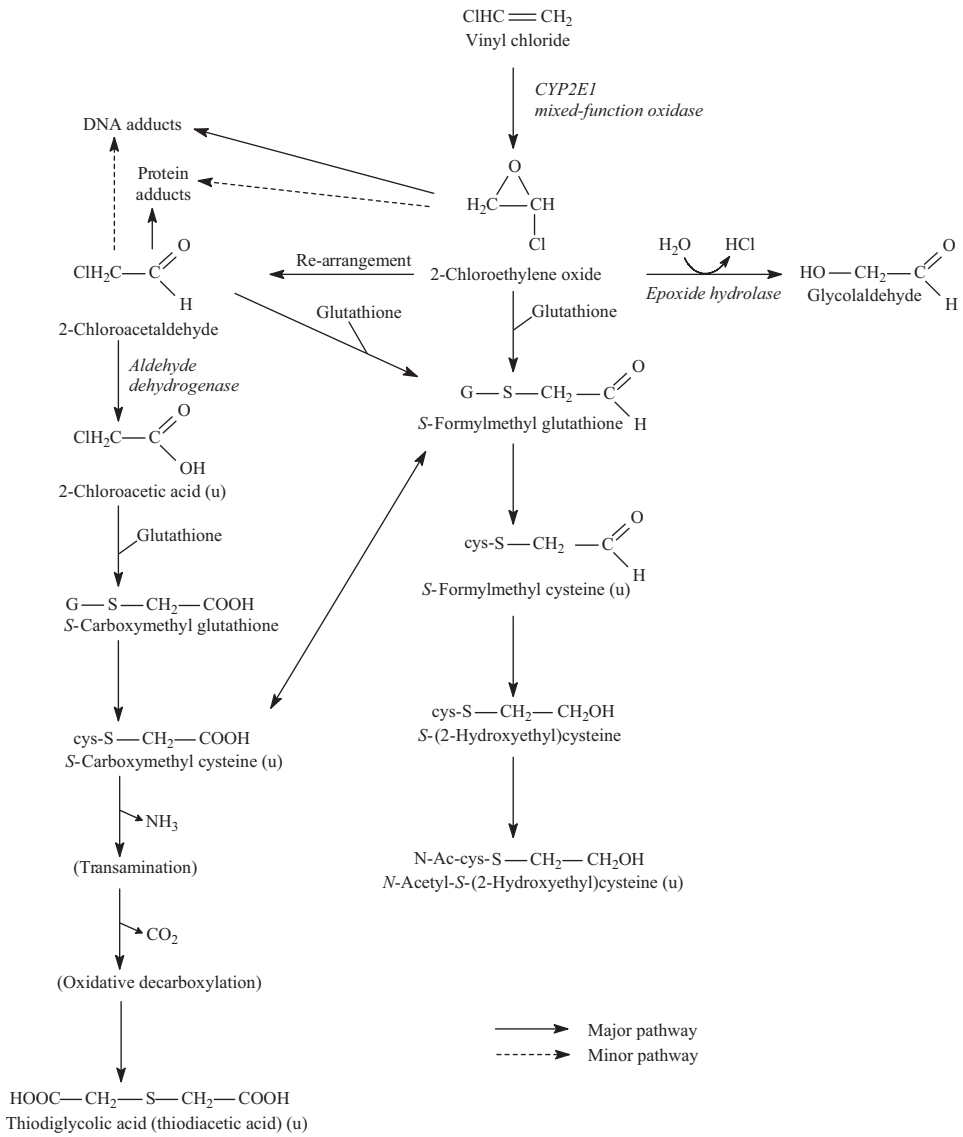
4.1 Kinetics and metabolism – studies in humans

Pulmonary absorption of vinyl chloride in humans appears to be rapid and the percentage absorbed is independent of the concentration inhaled. Adult male volunteers exposed for six hours to air containing 2.9–23.1 ppm [7.5–60 mg/m^3] vinyl chloride, retained on average approximately 42% of the inhaled amount (Krajewski *et al.*, 1980; cited in ATSDR, 2006). Pulmonary uptake is determined in part by the blood–air partition constant, which is 1.16 for vinyl chloride (Gargas *et al.*, 1989). Even if no data in humans were available, by assuming an identical solubility of vinyl chloride in rodent and human tissues, the tissue–blood partition constants 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.

In the postmitochondrial fractions of liver homogenates of humans and rats, large interindividual variations were noted in the metabolism of vinyl chloride, while the average activity was comparable between rat and human samples (Sabadie *et al.*, 1980). Vinyl chloride is primarily and rapidly metabolized in the liver (see Fig. 4.1), with a saturable mechanism (Reynolds *et al.*, 1975; Ivanetich *et al.*, 1977; Barbin & Bartsch, 1989; Lilly *et al.*, 1998; Bolt, 2005). The first step is oxidation in the liver, predominantly mediated by the human cytochrome P450 (CYP) isoenzyme 2E1 (WHO, 1999). Since CYP2E1 is present in several tissues at low levels – compared with concentrations in the liver – extrahepatic metabolism of systemically available vinyl chloride does occur. Inhibitors of CYP, such as 3-bromophenyl-4(5)-imidazole or 6-nitro-1,2,3-benzothiadiazole, reduce the metabolism of vinyl chloride *in vivo* (Bolt *et al.*, 1976). The primary metabolites of vinyl chloride are the highly reactive chloroethylene oxide, which is formed in a dose-dependent process and has a half-life of 1.6 minutes in aqueous solution at neutral pH (Barbin *et al.*, 1975; Dogliotti, 2006), and its rearrangement product chloroacetaldehyde (Bonse *et al.*, 1975). Both can bind to proteins, DNA and RNA and form etheno-adducts; chloroethylene oxide is the most reactive with nucleotides (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 (Plugge & Safe, 1977). The latter compound has been reported to be the major metabolite in the urine of exposed workers (Cheng *et al.*, 2001) with concentrations in

Fig. 4.1 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

urine that correlated with environmental vinyl chloride concentrations of > 5 ppm (ATSDR, 2006). Chloroethylene oxide can also be detoxified to glycolaldehyde by microsomal epoxide hydrolase (mEH), while chloroacetaldehyde can be converted to chloroacetic acid by aldehyde dehydrogenase 2 (ALDH2) in the urine (Guengerich & Watanabe, 1979; ATSDR, 2006; IARC, 2008). Another route of elimination of vinyl chloride is exhalation of the unmetabolized compound, which occurs at low levels in humans (Müller *et al.*, 1978; Krajewski *et al.*, 1980; Pleil & Lindstrom, 1997). When volunteers were exposed for six hours to air containing 6.8–23.1 ppm [15–60 mg/m^3] vinyl chloride, the mean concentration in exhaled air ranged from 0.21 to 1.11 ppm [0.54–2.84 mg/m^3], representing 3.6 and 4.7%, respectively, of the inhaled amount of vinyl chloride (Krajewski *et al.*, 1980).

4.2 Kinetics and metabolism – studies in animals

Experimental studies on vinyl chloride have been evaluated in previous *IARC Monographs* (IARC, 1979, 1987, 2008). Comprehensive data on the mechanism of vinyl chloride-induced carcinogenicity are available, encompassing toxicokinetics, metabolism, biomarkers, and genotoxicity. Many key events in the pathway of vinyl chloride-induced hepatocarcinogenesis have been established (Bolt, 2005; Dogliotti, 2006; IARC, 2008).

The absorption, distribution, metabolism and elimination of vinyl chloride in rats and mice have been reviewed in *IARC Monograph* Volumes 19 and 97 (IARC, 1979, 2008) and elsewhere (WHO, 1999; ATSDR, 2006); the most relevant data are summarized below.

In animals, pulmonary and gastrointestinal absorption of vinyl chloride occurs readily and rapidly, while dermal absorption is probably not significant. In monkeys exposed (whole body, except the head) to atmospheres containing 7000 and 800 ppm vinyl chloride for, respectively, 2.0 and 2.5 hours, only 0.023–0.031% of the total available amount of vinyl chloride was absorbed via the dermal route (Hefner *et al.*, 1975a), whereas intestinal absorption and uptake in blood was virtually complete in 10 minutes in rats after single oral doses (44–92 mg/kg bw) in aqueous solution (Withey, 1976). Pulmonary absorption in rats amounted to about 40% of inhaled [^{14}C]-labelled vinyl chloride for initial exposure concentrations below 260 mg/m^3 [100 ppm] (Bolt *et al.*, 1976).

The tissue–blood partition constants determine the distribution volume of vinyl chloride, and range from 0.4 (muscle) to 10 (fat) in male rats (Barton *et al.*, 1995). The fat–air partition constant for vinyl chloride, reported by several authors, tends to be higher in females than in males (WHO, 1999). Following inhalation, vinyl chloride is distributed in several tissues such as brain, liver, spleen, kidney, adipose tissue and muscle, with the highest levels found in liver and kidney (Bolt *et al.*, 1976). It has also been detected in fetal blood and amniotic fluid of rats after a 2.5-hour exposure to ~2000–13000 ppm [5200–33800 mg/m^3]), which indicates its capability to cross the placental barrier (Ungváry *et al.*, 1978).

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 (Km) of 7.42 µmol/L (El Ghissassi *et al.*, 1998). Chloroacetic acid was metabolized in rats to two major urinary metabolites, *viz.* *S*-(carboxymethyl) cysteine and thiodiacetic acid (Yllner, 1971). *S*-(carboxymethyl)cysteine, *S*-(2-chloroethyl) cysteine and *N*-acetyl-*S*-vinylcysteine are metabolites of vinyl chloride in rats after oral administration (Watanabe *et al.*, 1976a; Green & Hathway, 1975 and 1977) and *N*-acetyl-*S*-(2-hydroxyethyl)cysteine is a metabolite after inhalation (Watanabe *et al.*, 1976b). Thiodiglycolic

acid was obtained as a common metabolite in rats dosed separately with either chloroacetaldehyde, chloroacetic acid or *S*-(carboxymethyl) cysteine. Therefore, the identification of the same *S*-containing metabolite from vinyl chloride-treated animals lends support to the hypothesis that chloroethylene oxide or chloroacetaldehyde are formed and react with GSH (Green & Hathway, 1977). Following oral administration of [^{14}C]-labelled vinyl chloride to rats, [^{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 inhalation concentrations above 200 ppm [520 mg/m^3] in rhesus monkeys (Buchter *et al.*, 1980) and above 250 ppm [650 mg/m^3] in rats (Bolt *et al.*, 1977; Filser & Bolt, 1979). The plateau of incidence of ASL in carcinogenicity bioassays is also observed in rats at exposures 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; Km, 1 µM) and rhesus monkeys (V_{max}, 50 µmol/h/kg) (based on Buchter *et al.*, 1980; Barton *et al.*, 1995). The latter value (50 µmol/h/kg) was suggested to be a closer approximation to human metabolism than the value of 110 µmol/h/kg estimated for rats by Filser & Bolt (1979) (ATSDR, 2006).

Watanabe *et al.* (1978a) reported that the elimination rate of vinyl chloride was not altered during repeated exposures via inhalation (five days per week during seven weeks) compared with a single inhalation exposure (~13 000 mg/m^3 [5000 ppm]).

Urinary excretion of polar metabolites of vinyl chloride is the predominant route of elimination at low concentrations, and only very small amounts are expired in the air unchanged (Hefner *et al.*, 1975b). Once metabolic saturation is attained, vinyl chloride is eliminated via other routes, mainly exhalation of the parent chemical. Following exposure of male rats to 26 mg/m^3 [10 ppm] [^{14}C]-labelled vinyl chloride by inhalation during six hours, urinary [^{14}C] radioactivity and expired vinyl chloride (measured as [^{14}C]-labelled carbon dioxide) were recovered in amounts of 68% and 2%, respectively; after exposure to a 100-fold higher concentration, the proportion of radioactivity in the urine decreased to 56% and the amount expired increased to 12% (Watanabe *et al.*, 1976b). Moreover, the same authors showed that after single oral doses of 0.05, 1 or 100 mg/kg bw [^{14}C]-labelled vinyl chloride, urinary excretion of radioactivity was 68, 59 and 11%, respectively; expired [^{14}C]-labelled carbon dioxide accounted for 9, 13 and 3%, respectively; pulmonary elimination of [^{14}C]-labelled vinyl chloride represented only 1–3% of the lower dose and 67% of the higher dose (Watanabe *et al.*, 1976a). The route of elimination may depend upon the route of administration, since urinary excretion is favoured after oral or intra-peritoneal administration, which indicates a first-pass effect due to metabolism in the liver (Clewell *et al.*, 2001).

4.3 Reaction with cellular macromolecules

Vinyl chloride is a genotoxic carcinogen in animals and humans (Block, 1974; Creech & Johnson, 1974; Lee & Harry, 1974; Maltoni *et al.*, 1974, 1981). It is mutagenic, usually in the presence of metabolic activation, in various assays with bacteria, yeast or mammalian cells; it is also clastogenic *in vivo* and *in vitro*. Vinyl chloride induces unscheduled DNA synthesis, increases the frequency of sister chromatid exchange in rat and human cells, and increases the frequency of chromosomal aberrations and micronucleus formation in mice, rats, and hamsters *in vivo* (IARC, 2008).

Osterman-Golkar *et al.* (1976) reported the alkylation of haemoglobin – at cysteine and

histidine – and small amounts of alkylated histidine in proteins from the testis of mice exposed to [^{14}C]-labelled vinyl chloride. Binding of non-volatile metabolites of [^{14}C]-labelled vinyl chloride to liver macromolecules has been observed, 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). A decrease in non-protein sulfhydryl concentration was seen in rats after exposure to high concentrations of vinyl chloride (Jedrychowski *et al.* (1984). Kappus *et al.* (1975) and Laib & Bolt (1977) reported binding of vinyl chloride to RNA in an in-vitro incubation with rat-liver microsomes, and to liver RNA of rats exposed *in vivo*. Watanabe *et al.* (1978b) reported macromolecular binding proportional to the amount of vinyl chloride metabolized, but not proportional to the exposure concentration.

Chloroethylene oxide and chloroacetaldehyde can form etheno adducts with nucleic acid bases *in vitro* (Guengerich, 1992). Chloroethylene oxide yields the *N*7-(2-oxoethyl)guanine adduct (7-OEG), 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) (Ciroussel *et al.*, 1990; Guengerich, 1992), and 5,6,7,9-tetrahydro-7-hydroxy-9-oxoimidazo[1,2-*a*]purine (HO-ethanoG) (Müller *et al.*, 1996). In rats, the DNA adducts εA and εC have been found in various organs after exposure to vinyl chloride by inhalation. 7-OEG was 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 hours, while the etheno adducts are more persistent. For example, N^2,3-εG (which is 10–100-fold more abundant than other etheno adducts in exposed animals) has a half-life of about 30 days (Fedtke *et al.*, 1990). After exposure of rats to 500 ppm [1300 mg/m^3] vinyl chloride for eight weeks, the εA level was significantly increased above background in liver, lung, lymphocytes and testis, while the amount of εC was increased in liver, kidney, lymphocytes and spleen, but not in brain (Guichard *et al.*, 1996; Barbin, 1999). When adult rats were exposed to 1100 ppm [2860 mg/m^3] vinyl chloride for one or four weeks, there was a significant increase in the level of N^2,3-εG in hepatocytes and non-parenchymal cells, but not in the brain, with a linear increase at exposure concentrations from 0 to 100 ppm [260 mg/m^3] and a plateau at 100–1100 ppm [260–2860 mg/m^3]. In weanling animals there was a small, statistically significant increase in N^2,3-εG in the brain after five days of exposure and the amount 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 260 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 HCC (Maltoni & Cotti, 1988). 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). Data on the occurrence and persistence of vinyl chloride-DNA adducts in humans are still lacking. Nair *et al.* (1995) used immunoaffinity purification of the etheno adducts and subsequent [^{32}P]-postlabelling, and reported values 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 HCC. These adducts may also result from lipid peroxidation (El Ghissassi *et al.*, 1995) and their level can be quite high in patients with unknown exposure (up to 0.5–40 εA and εC per 10^9 parent bases in liver-DNA samples) (Bartsch & Nair, 2000a, b).

Barbin *et al.* (1985) reported that the 7-OEG–DNA adduct lacks miscoding or promutagenic properties. In contrast, etheno adducts and related exocyclic DNA adducts (e.g. εA, εC,

N^2,3–εG, and HO-ethanoG) may be involved in base-pair substitution and other specific mutations in cancer-related genes (i.e. *RAS* oncogenes, *TP53* tumour-suppressor gene) (WHO, 1999). The DNA lesions 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 & Kuśmierek, 1991; Singer *et al.*, 1991; Basu *et al.*, 1993). The adduct εA causes A→G transitions and A→T transversions, εC causes C→A transversions and C→T transitions and εG causes G→A transitions (Bolt, 2005). The same mutation types are observed in *TP53* and *RAS* genes in vinyl chloride-induced tumours. Mutations in K_i-*RAS* are associated with vinyl chloride-induced angiosarcomas in humans but not in rats, and to a lesser extent with vinyl chloride-induced HCC (CAA61CTA Ha-*Ras* mutation) in rats (IARC, 2008). In half of the cases, these mutations led to the incorporation of aspartate instead of glycine. *TP53* mutations associated with exposure to vinyl chloride (frequently A→T transversions) are found in approximately half of the angiosarcomas in both humans and rats. The presence of mutated p21ras 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 (IARC, 2008).

Various assays have been designed to explore the mutagenic properties of DNA adducts introduced into oligonucleotides or into site-specific vectors. Vector plasmids have also been treated with 2-chloroethyleneoxide or 2-chloroacetaldehyde and propagated in *E. coli* or mammalian cells. The mechanism by which adducts cause mutations still remains unclear, as misincorporation events depend on the individual mechanisms of DNA polymerases (Choi *et al.*, 2006). HO-ethanoG and 1,N^2-εG block the replication process with many different polymerases, thereby causing base misincorporation (Langouët *et al.*, 1997, 1998; Guengerich *et al.*, 1999).

The induction of extrahepatic tumours (e.g. in the brain or lung) by vinyl chloride has been established experimentally, but the mechanism is not well elucidated (Bolt, 2005). Overall, data suggest that etheno adducts are probably involved in the initiation of hepatocarcinogenesis, but the effects of the observed tissue- and cell-specificity and the variability in various biomarkers such as mutant p53 and anti-p53 antibodies are not completely clear (Trivers *et al.*, 1995; Brandt-Rauf *et al.*, 1996). One source for this variability may be explained by differences in polymorphisms in genes (i.e. *CYP2E1*, *GSTT1*, *GSTM1*, *ALDH2*) that encode metabolising enzymes or DNA-repair proteins (i.e. the *XRCC1* gene) (Li *et al.*, 2003a).

4.4 Synthesis

Numerous studies on the toxicokinetics, metabolism, genotoxicity, and molecular biology of vinyl chloride provide strong evidence that the carcinogenicity of this chamical involves a genotoxic mechanism of action, mediated by reactive metabolites. The extensive information on the mechanism underlying vinyl chloride-induced carcinogenicity has established many key events in the pathway of vinyl chloride-induced liver carcinogenesis. These key events include metabolic activation to reactive metabolites, binding of the metabolites to DNA, promutagenic action of these adducts leading to G→A and A→T transitions, and the effects of such mutations on the functioning of proto-oncogenes and tumour-suppressor genes at the gene and protein levels, with tumourigenesis as the final outcome. Many of these key events identified in experimental animals have also been demonstrated in humans.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of vinyl chloride. Vinyl chloride causes angiosarcoma of the liver, and hepatocellular carcinoma.

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.

There is strong evidence that the carcinogenicity of vinyl chloride operates by a genotoxic mechanism that involves metabolic activation to reactive metabolites, binding of the metabolites to DNA, promutagenic action of these adducts leading to mutations in proto-oncogenes and tumour-suppressor genes. Many of these key events identified in experimental animals have also been demonstrated in humans.

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

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