

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 haematopoietic 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 [$\sim 650 \text{ mg/m}^3$], 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 $50 \text{ } \mu\text{mol/h/kg}$. 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 extent 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 (*XRCCI*) modulate the DNA damage induced by vinyl chloride.