

Vinyl chloride monomer

Health-based calculated occupational cancer risk values



Health Council of the Netherlands

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Aan de minister van Sociale Zaken en Werkgelegenheid

Onderwerp : aanbieding advies *Vinylchloride monomeer*

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Geachte minister,

Graag bied ik u hierbij aan het advies over de gevolgen van beroepsmatige blootstelling aan vinylchloride monomeer.

Dit advies maakt deel uit van een uitgebreide reeks, waarin concentratieniveaus in de lucht worden afgeleid die samenhangen met een extra kans op (overlijden aan) kanker van vier per 1.000 en vier per 100.000 door beroepsmatige blootstelling. De conclusies van het genoemde advies zijn opgesteld door de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS) van de Gezondheidsraad en beoordeeld door de Beraadsgroep Volksgezondheid.

In dit advies concludeert de commissie dat vinylchloride monomeer een carcinogene stof is en dat hieraan een stochastisch genotoxisch werkingsmechanisme ten grondslag ligt. Gebaseerd op humane gegevens schat de commissie de extra kans op kanker voor vinylchloride monomeer op:

- 4×10^{-5} bij 40 jaar beroepsmatige blootstelling aan $0,65 \text{ mg/m}^3$
- en 4×10^{-3} bij 40 jaar beroepsmatige blootstelling aan $65,5 \text{ mg/m}^3$.

Ik onderschrijf de aanbevelingen en het advies van de commissie.

Ik heb dit advies vandaag ter kennisname toegezonden aan de minister van VWS en aan de staatssecretaris van IenM.

Met vriendelijke groet,

prof. dr. J.L. Severens,
vicevoorzitter

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Dutch Expert Committee on Occupational Safety (DECOS),
a Committee of the Health Council of the Netherlands

to:

the Minister of Social Affairs and Employment

No. 2017/01, The Hague, February 22, 2017

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Samenvatting

Op verzoek van de minister van Sociale zaken en Werkgelegenheid, schat de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS) van de Gezondheidsraad, de concentraties van een stof in de lucht die overeenkomen met een vooraf vastgesteld extra risico op sterfte aan kanker door beroepsmatige blootstelling gedurende het arbeidzame leven. Het gaat om kankerverwekkende stoffen die door de Gezondheidsraad of de Europese Unie geclassificeerd zijn in categorie 1A of 1B en die kankerverwekkend zijn via een stochastisch genotoxisch mechanisme. Voor de schatting maakt de commissie gebruik van de *Leidraad Berekening risicogetallen voor carcinogene stoffen* van de Gezondheidsraad.¹ In dit advies doet de commissie zo'n schatting voor vinylchloride monomeer (VCM). VCM wordt gebruikt in de productie van polyvinylchloride.

Naar schatting van de commissie is de concentratie van VCM in de lucht, die samenhangt met een extra kans op kanker van

- 4 per 1.000 (4×10^{-3}), bij 40 jaar beroepsmatige blootstelling, gelijk aan 65,5 mg/m³
- 4 per 100.000 (4×10^{-5}), bij 40 jaar beroepsmatige blootstelling, gelijk aan 0,65 mg/m³.

Executive summary

At request of the Minister of Social Affairs and Employment, the Dutch Expert Committee on Occupational Safety (DECOS), a committee of the Health Council of the Netherlands, derives so-called health-based calculated – occupational cancer risk values (HBC-OCRVs) associated with excess mortality levels of 4 per 1,000 and 4 per 100,000 as a result of working life exposure to substances. It concerns carcinogenic substances which are classified by the Health Council or the European Union in category 1A or 1B, and which are considered stochastic genotoxic carcinogens. For the estimation, the committee uses the *Guideline for the calculation of occupational cancer risk values* by the Health Council.² In this report the Committee presents such estimates for vinyl chloride monomer (VCM). VCM is used in the production of polyvinylchloride (plastic).

The Committee estimated that the concentration of VCM in the air, which corresponds to an excess cancer risk of

- 4 per 1,000 (4×10^{-3}), for 40 years of occupational exposure, equals to 65.5 mg/m³
- 4 per 100,000 (4×10^{-5}), for 40 years of occupational exposure, equals to 0.65 mg/m³.

Scope

1.1 Background

In the Netherlands, occupational exposure limits for genotoxic chemical substances are set using a three-step procedure. In the first step, a scientific evaluation of the data on the toxicity of the substance is made by the Dutch Expert Committee on Occupational Safety (DECOS), a committee of the Health Council of the Netherlands, at request of the Minister of Social Affairs and Employment (Annex A). This evaluation should lead to a health-based recommended exposure limit (HBROEL) for the concentration of the substance in air. Such an exposure limit cannot be derived if the toxic action cannot be evaluated using a threshold model, as is the case for carcinogens acting by a stochastic genotoxic mechanism. In that case, an exposure-response relationship is recommended for use in regulatory standard setting, i.e., the calculation of so-called health-based calculated occupational cancer risk values (HBC-OCRVs). The Committee calculates HBC-OCRVs for compounds, which are classified by the European Union or by the committee as carcinogens in category 1A or 1B.

For the establishment of the HBC-OCRVs, the Committee generally uses a linear extrapolation method, as described in the committee's report *Guideline for the calculation of occupational cancer risk values*.² The linear model is a default method to calculate occupational cancer, unless scientific data would indicate that using this model is not appropriate.

In the next phase of the three-step procedure, the Social and Economic Council advises the Minister of Social Affairs and Employment on the feasibility of using the HBC-OCRVs as regulatory occupational exposure limits. In the final step of the procedure, the Minister sets the official occupational exposure limits.

In the present report, cancer risk values are calculated for vinyl chloride monomer (VCM).

1.2 Committee and procedure

The present document contains the evaluation of the DECOS, hereafter called the Committee. The members of the committee are mentioned in Annex B. A submission letter (in English) to the Minister can be found in Annex C.

In April 2016, the president of the Health Council released a draft of the report for public review. The individuals and organisations that commented on the draft are listed in Annex D. The Committee has taken these comments into account in deciding on the final version of the advisory report.

1.3 Data

The Committee's recommendation has been based on scientific data, which are publicly available. Data were obtained from the online databases Chemical Abstracts, XToxline, and Medline, using vinyl chloride (monomer), chloro-ethylene, carcinogen, cancer, tumour or neoplast and CAS registry number as keywords. The literature was searched for the period between 1986 and 2016. In addition, in preparing the present report, reviews by IARC³, the WHO⁴, US-NTP⁵, and ATSDR⁶ were consulted. The last search was performed in September 2016. Criteria for evaluating the quality of human and animal studies are listed in Annex E and F respectively.

Identity, toxicity profile and classification

2.1 Identity, and physical and chemical properties

VCM is mainly used in the production of polyvinylchloride. The identity and some physicochemical properties of VCM are given below.⁶⁻¹³

Chemical name	: Vinyl chloride
CAS registry number	: 75-01-4
EINECS name	: Chloroethylene
EINECS registry number	: 200-831-0
RTECS number	: -
IUPAC name	: Chloroethene
Synonyms	: 1-chloroethylene; ethylene monochloride; monovinyl chloride; monochloroethene; monochloroethylene; MVCs; Trovidur; VC; VCM; vinyl chloride monomer
Molecular formula	: C_2H_3Cl
Physical description and colour	: Colourless gas (at room temperature), liquid if kept under high pressure or at low temperatures
Structure	: $H_2C=CH-Cl$
Molar mass	: 62,5
Melting point	: -154°C
Boiling point	: -13,3°C
Relative density (air = 1)	: 0.9195 at 15°C/4°C
Solubility in water	: 8,800 mg/L at 25°C
Solubility in organic solvents	: Soluble in alcohol; very soluble in ether

Log P (n-octanol/water)	: 1,620
Vapour pressure	: 2,600 mm at 25°C
Relative vapour density (air = 1)	: 2.15
Flash point (closed cup)	: -159.7°C
Odour threshold	: mild, sweet odour (> 3,000 parts vinyl chloride ppm of air)
Conversion factor (20 °C; 101,3 kPa)	: 1 ppm = 2.6 mg/m ³ ; 1 mg/m ³ = 0.38 ppm
EU classification	: Flam.Gas 1: H220; Carc.1A: H350

2.2 Classification and labelling as a carcinogenic substance

IARC classified VCM as carcinogenic to humans (Group 1) in 1974, 1979, 1987, 2008 and 2012.^{3,8-11}

The European Union has classified VCM in carcinogenicity category 1A (*known to have carcinogenic potential for humans*), as listed under index number # 602-023-00-7 in Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation).¹³

VCM is listed in the Dutch SZW-list of carcinogenic substances.¹⁴

In 1986 a committee of the Health Council of the Netherlands concluded that VCM should be considered a genotoxic carcinogen in humans.¹⁵

2.3 Genotoxicity

Evidence for the genotoxic properties of VCM has been reviewed by IARC (2012)³, ATSDR (2006)⁶, and NTP (2014)⁵. The three agencies concluded that VCM is a mutagen.

VCM caused genetic damage in many test systems, including bacteria, yeast, insects, cultured human and other mammalian cells, rodents, and in humans. The genetic damage included mutations and chromosomal aberrations⁶. Tables 1 and 2 in Annex G provide an overview of the in vitro and in vivo evidence of the genotoxicity of VCM.

The Committee concludes, in accordance with the recommendation of the DECOS Subcommittee on the Classification of Carcinogenic Substances (see Annex G), that VCM induces cancer in experimental animals (rodents) and

humans via a mutagenic mode-of-action. VCM is therefore considered a stochastic genotoxic substance.

2.4 Kinetics and metabolism

VCM is readily absorbed through the lungs and has also been shown to be almost completely absorbed from the gastrointestinal tract after oral exposure⁶. Animal studies indicate that the distribution of VCM is rapid and widespread and may be affected by differences in gender, age, and nutritional status⁶. Storage in the body is limited because of rapid metabolism and excretion.

VCM is primarily and rapidly metabolized in the liver with a saturable mechanism. The first step is oxidation, predominantly mediated by the human cytochrome P450 (CYP) isoenzyme 2E1. Since CYP2E1 is present in several tissues at low levels extrahepatic metabolism of systemically available VCM does occur. The primary metabolites of VCM are the highly reactive chloroethylene oxide, and its rearrangement product chloroacetaldehyde. Conjugation of the primary metabolites with glutathione (GSH) eventually leads to the major urinary metabolites *N*-acetyl-S-(2-hydroxyethyl)cysteine and thiodiglycolic acid. Chloroethylene oxide can also be detoxified to glycolaldehyde by microsomal epoxide hydrolase, while chloroacetaldehyde can be converted to chloroacetic acid by aldehyde dehydrogenase 2 (ALDH2) in the urine.^{3,6}

Both primary metabolites of VCM (chloroethylene oxide and chloroacetaldehyde) can bind to proteins, DNA and RNA and form ethenoadducts; chloroethylene oxide is the most reactive with nucleotides. Overall, mechanistic animal and in vitro 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. 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).^{3,6}

In animal studies metabolites of VCM have been found in the liver, kidney, spleen, skin, brain, and placenta. The primary route of excretion of VCM is dose-dependent: while VCM metabolites are excreted primarily in the urine following

oral or inhalation exposure to low doses, at higher doses where metabolic saturation has been exceeded, VCM is exhaled as the parent compound.⁶

2.5 Non-carcinogenic effects

Human data

Several epidemiological studies have associated chronic occupational exposure to VCM with impaired liver function and/or liver damage (including liver cirrhosis).

Ho et al. (1991) reported liver dysfunction in 12 of 271 workers who were reportedly exposed to environmental levels of 1 to 20 ppm VCM.¹⁶ However, this study has been criticised for its weak exposure assessment, small sample size, lack of specificity of the liver tests, and the fact that 8 of the 12 affected workers were current or ex-drinkers.⁶ Du et al. (1995) found that serum levels of gamma-glutamyl transferase (GGT), but not other indicators of liver function, were associated with exposure in a group of 224 VCM workers with time-weighted average exposure ranging from 0.36 to 74 ppm (0.92 to 189 mg/m³).¹⁷ Hepatomegaly, altered liver function as shown by biochemical tests, and Raynaud's phenomenon (RP, cold sensitivity and numbness of fingers) were reported in chemical plant workers exposed to 25 to 250 ppm VCM (64 to 639 mg/m³) at levels much higher than those reported by Ho et al.¹⁸

Neurological effects – including dizziness, drowsiness and fatigue, headache, euphoria and irritability, nervousness and sleep disturbances, nausea, visual and hearing disturbances, and loss of consciousness – have been observed following exposure via inhalation. Signs of pyramidal and cerebellar disturbances have also been observed. Dizziness has been reported by volunteers acutely exposed to 20,800 mg/m³, while nausea and subsequent headache resulted from exposures of 52,000 mg/m³. Peripheral neurological effects have been reported, including paraesthesia, tingling or warmth in the extremities, numbness or pain in the fingers, and depressed reflexes. Human studies into reproductive and developmental effects from VCM exposure resulted in equivocal results. Studies examining parental employment and/or residential proximity to VCM facilities and birth defects reported links to foetal loss and defects of the central nervous system, alimentary tract, genitalia, and incidence of club foot. Other studies found no such association or suggested that inappropriate or inadequate study designs and statistical methodology were employed.^{4,6,18}

Animal studies

In animal studies, the lowest observed adverse non-cancer effects in the liver included liver cell polymorphisms and development of hepatic cysts resulting from chronic oral exposures of 2 mg/kg bw/day; centrilobular hypertrophy and fatty liver changes resulted from intermediate-duration inhalation exposures of 26 and 130 mg/m³, respectively. A variety of effects in animals from single inhalation exposure include ataxia, decreased coordination, twitching, tremors, and unconsciousness. Repeated exposure resulted in damaged nerve tissue, including degeneration of brain tissue and fibrosis of peripheral nerve endings. In animals, a few studies have identified reproductive and developmental effects. Decreased testicular weight, reduced male fertility, and spermatogenic epithelial necrosis resulted from intermediate-duration inhalation exposures of 260-1,300 mg/m³, but were not observed in rats exposed to up to 2,860 mg/m³. Gestational exposures of 6,500 mg/m³ resulted in ureter dilation in rat offspring, while delayed ossification was observed following 1,300 mg/m³ exposures in mice. This exposure also resulted in 17% maternal mortality. No delayed ossification was found for mice exposed at 130 mg/m³.⁶

2.6 Existing occupational exposure limits

A summary of occupational exposure limits for VCM in various countries is given in Table 1.

In 2002 the scientific committee on occupational exposure limits (SCOEL) of the European Commission evaluated risk assessments for VCM including those conducted by WHO and US EPA.²¹ SCOEL concluded that a linear high dose - low dose extrapolation of tumour risk was the most appropriate approach for VCM and observed that even though different approaches were used, including those based on human epidemiological data and those based on extrapolation from animal data by means of PBPK modelling, resulting risk estimates were essentially consistent. SCOEL concluded that continuous exposure for working life to 1 ppm VCM would be associated with a cancer risk for hepatic angiosarcoma of about 3×10^{-4} .²¹

Table 1 Occupational exposure limits.

Country (Organization)	OEL (ppm)	OEL (mg/m ³)	TWA	Type of exposure limit ^a
The Netherlands ¹⁹	-	7.77	8h	OEL
European Union ²⁰	-	7.77	8h	OEL
Germany ⁴	7	18.2	8h (person)	MAK
Germany ⁴	3	8	Annual (working area)	MAK
Denmark ²⁰	1	3	8h	OEL
Finland ²⁰	3	7.7	8h	OEL
France ¹⁹	1	2.59	8h	OEL
United Kingdom ²⁰	3	7.8	8h	OEL
Norway ²⁰	1	3	8h	OEL
Sweden ²⁰	1	2.5	8h	OEL
Switzerland ²⁰	2	5.2	8h	OEL
Spain ²⁰	3	7.8	8h	OEL
USA (ACGIH) ⁴	1	2.6	8h	TLV
USA (NIOSH) ⁴	0	-	-	TLV
USA (OSHA) ⁴	5	12.8	15 min	PEL
USA (OSHA) ⁴	1	2.6	8h	PEL

^a MAK, maximum acceptable concentration; OEL, occupational exposure limit; OES, occupational exposure standard; PEL, permissible exposure limit; TLV, threshold limit value.

Carcinogenicity studies

3.1 Human studies

The Committee finds the current data available on malignancies other than liver cancer (especially angiosarcoma of the liver (ASL)) inconsistent (see Annex E). The Committee will focus on the key cohorts for exposure-response analysis and will not specifically discuss malignancies that are less consistently linked to VCM exposure, as these do not influence the carcinogenic classification of VCM nor do these provide a basis for a quantitative risk analysis. Details of all the studies included in the report are summarized in the Tables 4 en 5 in Annex E.

Case reports

The first evidence for an association between exposure to VCM and cancer in humans comes from case studies of individuals diagnosed with ASL working in VCM producing or processing plants.²² These studies are listed below in Table 2. The high incidence of ASL in these plants was remarkable considering the low background rate of ASL in the background population (0.0014 cases ASL/100,000, or about 25-30 cases per year in the entire US population).²³

Table 2 Case studies.

Number of angiosarcoma cases	Population/ cohort	Reference
13 (+2)	Four vinyl chloride plants (20,000 workers), USA	23,24
10	Shawinigan (Canada) population: All ten cases were traced to be workers that had been employed at the same vinyl chloride polymerization plant	25
173	Worldwide database for workers exposed to vinyl chloride	26,27
7	253 deaths that occurred in seven plants manufacturing vinyl chloride monomers and/ or polyvinylchloride and one plant extruding polyvinylchloride in Italy	28

Cohort and case-control studies

The main epidemiological evidence for the carcinogenicity of VCM comes from two large multicentre cohort studies from Europe and North America.

The first report on the European multicentre cohort study was published by Simonato et al.²⁹ Collaborators from four countries (Italy, Norway, Sweden and the United Kingdom) participated in the cohort study and contributed a total of 14,351 subjects to the combined database. Both existing studies and newly collected cohorts were enrolled from 19 factories in total.^{14,21,23,25,30,35} The pooled analysis revealed no significant excess of total cancer mortality. Mortality of cancer of the liver and hepatic bile ducts and cancer of an unspecified site were significantly in excess. In a subset of four Nordic factories (for which incidence data were available), total cancer incidence was again not in excess, but the incidence of cancer of liver and intrahepatic bile ducts was significantly in excess. Cancer incidence for several other cancer categories was in excess, though not significantly. A positive relation was observed between duration of employment or cumulative exposure to VCM and liver cancer mortality. Among the 24 liver cancer deaths, 16 were confirmed histopathologically to be angiosarcomas, and one was reported as a primary liver cancer without further specification. For the remaining 7 a specific histopathological diagnosis was not available. Based on the risks observed in this study, the maximum incidence for angiosarcoma of the liver (for individuals with ≥ 25 years since first exposure and a cumulative exposure of $\geq 10,000$ ppm (26,000 mg/m³)-years), was calculated to be 280/100,000.

The most recent publication on the European multicentre cohort study is from Ward et al.³⁰ In this study the follow-up period was extended with 10 years compared to the Simonato report. A total of 71 deaths from liver cancer (primary liver cancer, including 37 angiosarcomas, 10 hepatocellular carcinomas (HCC), and 24 liver cancers of other and unknown histology) were observed. A strong positive trend for time since first employment, duration of employment, and cumulative exposure was found with relative risks for all liver cancers, angiosarcoma, and hepatocellular carcinoma. The highest relative risks were observed for angiosarcoma of the liver. As the incidence of angiosarcoma of the liver with unknown etiology in the general population was estimated to be about 0.1 per million population per year, the workers in the study population experienced a 200-fold higher risk of angiosarcoma than the general population (based on 4 cases among approximately 200,000 person-years). No other type of cancer was found in excess. Pirastu et al. and Mastrangelo et al. report a significant exposure response relationship between cumulative exposure to VCM and HCC ($p < 0.001$ in both studies) based on an Italian cohort that was included in the Ward et al. analysis, but for which more follow-up time was accrued.^{31,32}

A number of publications have reported on the North American multicentre cohort.³³⁻³⁷ In the most recent and complete publication on this cohort by Mundt et al. 895 cancer deaths were reported. While total cancer mortality was not elevated, mortality from cancers of the liver and biliary tract was significantly increased. Modest excesses of brain cancer and cancer of connective and soft tissue were also observed. Hazard rates from proportional hazard analyses supported associations with age at first exposure, duration of exposure, and year of first exposure for cancers of the liver and soft tissues, but not the brain. Hazard rates for 'all known angiosarcomas' ($n=48$) were associated with duration of exposure, though not with age at first exposure and year of first exposure.

Results from the European and North American multicentre studies were combined with six independent studies of cancer among VCM workers (from (Former USSR, France, Canada, Germany, China, Taiwan) in a meta-analysis by Boffetta et al.³⁸ Together these studies include 43,810 VCM/PVC workers with variable follow-up ranging between 1940 and 1997. Most of the smaller cohorts included in the analysis were published individually and are summarized in Annex E.^{15,23-29,31-71} With SMR values ranging from 1.63 to 57.1, all six studies for which these ratios could be obtained suggested an increased risk of liver cancer, though these results were deemed too heterogeneous to be included in a meta-analysis. A significantly increased meta-SMR was also reported for liver

cancers other than ASL (based on the 2 multicentre studies) and for soft-tissue sarcomas, however, these results may have been influenced by the underdiagnosis of true ASL. A meta-analysis for ASL was not conducted as relevant SMRs were difficult to estimate due to the extreme rarity of the disease in the general population.

Several studies were published in addition to the cohorts that were included in the Boffetta meta-analysis. Many studies suffered from limited statistical power (especially for ASL). The details of these studies can be found in Annex E. We highlight the most relevant analysis here. An analysis by Beaumont and Breslow from 1981 included nine (partially overlapping) early studies conducted in the VCM industry.²⁶⁻³³ The combined data revealed a significant risk for liver and brain cancer, whereas no significantly increased risk for lung cancer was found.

Exposure levels in occupational studies

The highest occupational exposure levels to VCM have generally been incurred at VCM/PVC plants and in PVC-processing plants. Only few exposure measurements 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. Occupational exposure standards were set at approximately 13-26 mg/m³ [5-10 ppm] in most countries in the 1970s.³

Conclusions of the human studies

The epidemiological literature indicates a strong association between exposure to VCM and liver cancer incidence and mortality. The elevated risk for liver cancer appears to be primarily driven by ASL and HCC. Studying the exposure-response relationship between exposure to VCM and ASL is difficult because this form of liver cancer is extremely rare. Studying the association between exposure to VCM and liver cancer excluding ASL is also difficult because of the risk of misdiagnosis of true ASL. Several other forms of cancer are reported to be associated with exposure to ASL in individual studies, but these associations are not consistent across studies.

3.2 Animal experiments

The carcinogenicity of VCM has been studied extensively in mice, rats, and hamsters. These studies have been reviewed in depth by IARC (1974, 1979, 1987, 2008, 2012), ATSDR (2006), and NTP (2014).^{3,5,6,8-11} The 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.³ Results from all studies are summarized in Annex F of this report. While studies have assessed the effects of exposure via inhalation, skin, and ingestion, exposure via inhalation is likely the most relevant exposure route for humans. Three relevant inhalation studies are described below.

Hong et al.⁷² reported on an experiment in which rats and mice were exposed to 0, 130, 650 or 2,600 mg/m³ VCM via inhalation for 6 hours/day, 5 days/ week during 1, 3 or 6 months and describe the development and incidence of neoplastic changes and other effects during a 12 month post-exposure follow-up period. Unscheduled mortality increased in both species in a dose-related way, and occurred at earlier time points at higher concentrations. There was no significant sex-related difference in the number of unscheduled deaths (or sacrifices). In mice, cumulative incidence of hepatic haemangiosarcomas during recovery period was increased at higher VCM concentration. The tumour was mostly multiple in site distribution and varied greatly in size. Overall, the incidence of this tumour rose as the concentration and duration of VCM exposure increased. Also the incidence of bronchioloalveolar tumours was greater in mice exposed to increasing levels of VCM and for longer exposure periods. In female mice mammary gland adenocarcinoma/carcinoma was observed. Metastatic adenocarcinomas originating from the mammary gland were also seen in lungs of mice exposed to VCM, but not in lungs of control mice.

Drew et al.⁷³ observed induced haemangiosarcomas and mammary gland carcinomas in two strains of mice and lung carcinomas in Swiss mice after six months of exposure to 130 mg/m³ VCM. Longer exposure had no significant effect on tumour incidence. Incidence was higher when exposure started earlier in life. In rats, mainly haemangiosarcomas of the liver, mammary neoplasms and hepatocellular carcinomas were found after 6 months of exposure. The incidence of haemangiosarcomas was a function of the duration of the exposure. If the

exposure took place early in life, a higher incidence of haemangiosarcomas was noted. In hamsters, haemangiosarcomas, mammary gland carcinomas, stomach adenomas, and skin carcinomas were produced by exposure to 520 mg/m³ VCM. The highest incidence was seen in animals exposed early in life.

A large series of experiments was performed by Maltoni et al. using rats (Sprague-Dawley and Wistar), mice, and hamsters.⁷⁴⁻⁷⁶ In one group of studies, Maltoni et al. exposed Sprague-Dawley rats to VCM for 52 weeks at concentrations ranging from 1 to 30,000 ppm. Animals were examined at the time of their spontaneous death. Statistically significant increases were noted in the incidence of mammary gland carcinomas, Zymbal gland carcinomas, nephroblastoma, and liver angiosarcoma. Exposure of Swiss mice to 50 ppm VCM for 4 hours/day, 5 days/week for 30 weeks also appeared to increase the incidence of liver angiosarcoma and angioma. Some variation in the target organs that developed tumours was observed when different species were exposed to VCM.⁷⁴ Whereas angiosarcomas of the liver were reported to occur in rats, mice, and hamsters, mammary gland carcinomas were found only in rats and mice; Zymbal gland carcinomas, neuroblastomas, and nephroblastomas were found only in rats; lung tumours were found only in mice; and melanomas, acoustical duct epithelial tumours, and leukemias were found only in hamsters.⁴ In their review of the Maltoni study, ATSDR noted that limited histopathological data were presented and cancer incidences were presented only in summary tables. Also, survival of control animals was poor in some of the experiments. Furthermore, statistical analyses, where present, appear to be based on a compilation of data from several individual studies.⁶

Overall, mice seem to be more sensitive to the acute and chronic effects of VCM exposure than rats and golden hamsters. In mice, increase in tumour incidence was found at all tested concentrations, already at the lowest test concentration of 130 mg/m³ and exposure for one month. Most studies were performed with rats, with concentration ranges differing greatly: between 2.6 mg/m³ and 78 g/m³.^{73,77} Basically, all these studies report increased tumour incidence at all test concentrations.

Conclusions of the animal studies

Based on the available data it can be concluded that tumour incidence (number of rats with a tumour) and multiplicity (number of tumours/ rat) following VCM in rats was clearly related to exposure concentration and duration. It can therefore

be concluded that the carcinogenic effects of VCM in animals and humans are similar .

3.3 Selection of the suitable study for risk estimation in the occupational situation

VCM has been shown to induce cancer in both humans and experimental animals. As the epidemiological data are of sufficient quality, the Committee prefers to estimate the health-based occupational cancer risk value using human data rather than animal data.

The risk calculations on human data are given below. For comparison however, risk calculations on animal data are performed and summarized in Annex I.

In human studies VCM has been consistently associated to liver cancer, in particular the subtypes ASL and HCC. The highest relative risks were observed for ASL. Two large multicentre cohort studies together incorporate most of the evidence available from independent cohorts in which the association between VCM and liver cancer (subtypes) was assessed.^{30,34} Boffetta et al. combined the two multicentre cohort studies with several other independent studies, but did not report on ASL.³⁸

The study by Ward et al.³⁰ is the only multi-centre study that reported results from quantitative exposure response analysis for cumulative exposure to VCM. Two more recent publications report on exposure response analysis for cumulative exposure to VCM and HCC based on an Italian cohort.^{31,32} This cohort was included in the Ward analysis and preference was given to base the calculation of the HBC-OCRv on the multi-centre analysis. Ward et al.³⁰ sufficiently describe the methods that were used to assess exposure levels and to model the exposure-response relationship. The Committee concludes that the Ward et al.³⁰ report provides the best data to estimate health-based occupational cancer risk values.

Study quality limitations and uncertainties potentially affecting the study on which the HBC-OCRv will be based

Several study quality limitations and uncertainties in Ward et al.³⁰ have a potential effect on the calculated HBC-OCRv. Considerable uncertainty exists in the historical exposure levels that had to be estimated to allow estimation of

cumulative exposure to VCM. It may be likely that the historical exposure levels are underestimated eventually resulting in an increase in the HBC-OCR_V. A limitation pertaining primarily to the HCC results is the modest number of cases observed in the study population, increasing the uncertainty of the estimated relative risks [direction of effect on HBC-OCR_V unclear]. Finally, Ward et al. controlled only for age and calendar period as confounding factor in their study but were not able to control for other potential confounders (e.g. thorotrast treatment).

3.4 Calculation of the HBC-OCR_V

The risk analysis for VCM is based on the assumption that VCM is a genotoxic carcinogen with a stochastic mode-of-action as described in section 2.3 and Annex G. Consequently, it is not possible to determine a threshold level for the observed carcinogenicity.

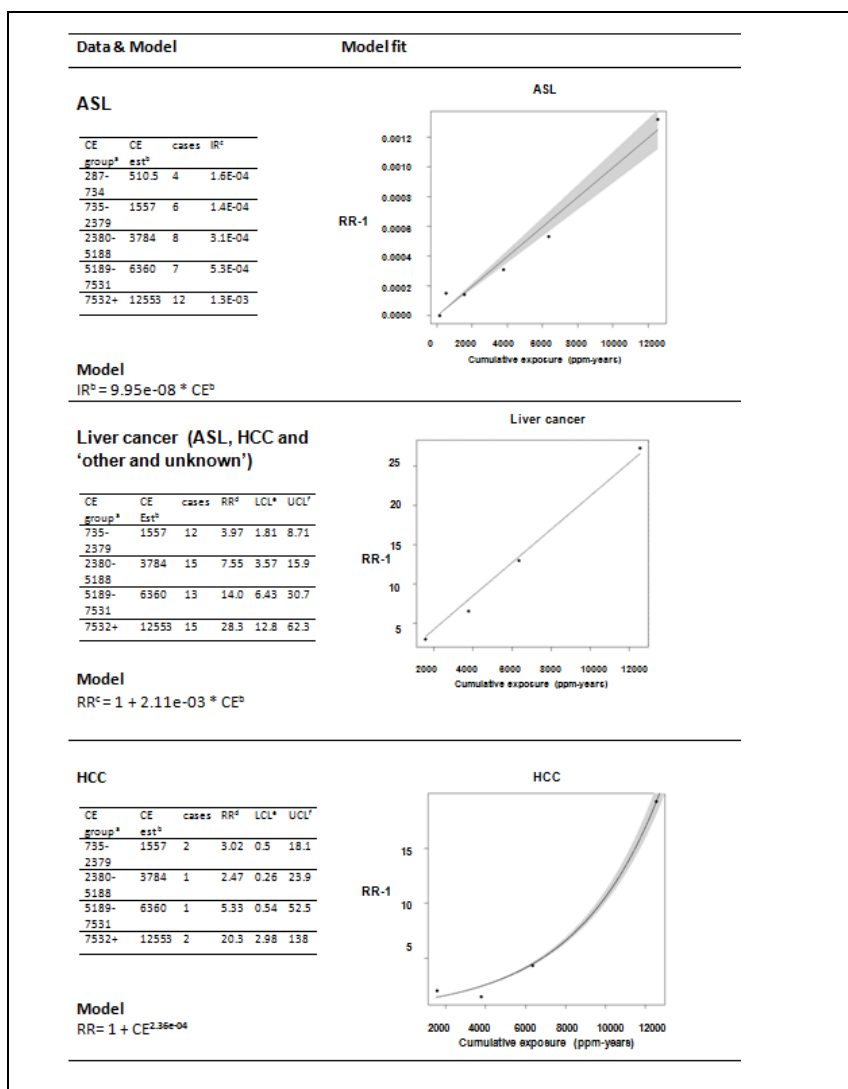
The Committee used the quantitative exposure-response relationships for VCM and ASL, liver cancer (including both ASL, HCC and ‘cancer of other and unknown histology’), or HCC reported by Ward et al.³⁰ to derive unit risk estimates. For ASL the regression model to derive a unit risk estimate was fit on reported exposure group specific incidence rates, while for liver cancer and HCC the model was fit on the reported exposure group specific relative risks. For ASL and liver cancer a linear model fit the data best, while for HCC an exponential model fit the data best. The data and regression models are summarized in Table 3.

The exposure levels corresponding to the relevant occupational health and safety standards were calculated using life tables derived from Dutch mortality data.

The following assumptions were made for the life table analysis:

- Workers were assumed to be exposed for 40 years (between 20 and 60)
- Workers were followed until age 100
- Excess risk for ASL was calculated using an absolute risk model (linear):
$$IR(X=1) = IR(X=0) + AR$$
- Excess risk for liver cancer (linear) and HCC (exponential) was calculated using a relative risk model:
$$IR(X=1) = IR(X=0) * RR.$$

Table 3 Regression models used to derive unit risk estimate from Ward et al. (2001).³⁰



^a Reported cumulative exposure group (in ppm-years).

^b Estimated mean cumulative exposure (in ppm-years), for the highest exposure group the mean was estimated as 5/3*lower bound, for the other categories the midpoint was used.

^c Incidence rate.

^d Relative risk.

^e Lower confidence limit.

^f Upper confidence limit.

Based on the life table analysis the Committee estimated an excess ASL incidence of

- 4 per 1,000 (4×10^{-3}) for 40 years of exposure to 65.5 mg VCM/m³
- 4 per 100,000 (4×10^{-5}) for 40 years of exposure to 0.65 mg VCM/m³.

Based on the life table analysis the Committee estimated an excess liver cancer incidence of

- 4 per 1,000 (4×10^{-3}) for 40 years of exposure to 57.5 mg VCM/m³
- 4 per 100,000 (4×10^{-5}) for 40 years of exposure to 0.57 mg VCM/m³.

Based on the life table analysis the Committee estimated an excess HCC incidence of

- 4 per 1,000 (4×10^{-3}) for 40 years of exposure to 127 mg VCM/m³
- 4 per 100,000 (4×10^{-5}) for 40 years of exposure to 2.4 mg VCM/m³.

The Committee agrees that ASL is causally related to VCM exposure and that a risk assessment based on human ASL is the most appropriate. ASL incidence is however low in the general population potentially resulting in unstable risk extrapolations. Therefore, the Committee has performed additional analyses using the broader disease definition of 'liver cancer' recognizing that the disease category is not necessarily causally related to VCM to address the potential limitation of low incidence rates in ASL. The Committee observes that the calculated risk numbers for both ASL and 'liver cancer' are similar. Therefore the Committee is of the opinion that the issue of the low ALS background does not seem to be a significant methodological problem, and expresses a preference for the risk estimate based on ASL.

For comparison (see Annex I for details) the Committee performed a number of risk calculations based on animal data (rat angiosarcoma) published by Maltoni et al. (1981).⁷⁴ The best fitting dose-response curves on the data from three respective experiments were established, bench mark doses (BMD10) were derived, and health- based calculated cancer risk values were calculated for the human situation. Although the calculated values were different per animal experiment, they were all in the same order of magnitude (approx. between 1 and 10 VCM mg/m³ at an extra risk level of 4 per 1,000, and between 0.001 and 0.1 at 4 per 100,000). The results from the animal data were slightly more conservative than the above calculated results from the epidemiological study. The Committee is of the opinion that the risk assessment based on the human

data should be preferred, and that the animal data may be considered supportive to the risk numbers established based on human data.

3.5 Groups with increased risk

A higher susceptibility for developing HCC due to exposure to VCM among workers that are infected with hepatitis B virus, or that report high levels alcoholic beverage consumption has been reported.^{32,78} This information is not (and can not be) used in the calculation of the occupational cancer risk values based on epidemiological evidence for the association between VCM and HCC. However, if there are large differences between the population of the epidemiological study that was used for derivation of the occupational cancer risk values and the current population of the Netherlands in the incidence of hepatitis B virus or alcoholic beverage consumption this could lead to an over- or underestimation of the actual risk of HCC due to exposure to VCM. A downward trend in hepatitis B virus infection in the European Union has been reported for the period 1995 - 2007⁷⁹, indicating that current risks for HCC due to exposure to VCM might currently be lower than at the time of the study by Ward et al.³⁰

3.6 Conclusions and recommendation

The Committee endorses the conclusions of the DECOS Subcommittee on the Classification of Carcinogenic Substances (see Annex G) that VCM is a human carcinogen and that a stochastic genotoxic mechanism underlies its carcinogenicity. In addition, the Committee considers cancer of the liver as the most critical effect of VCM.

The Committee is of the opinion that health-based occupational cancer risk values (HBC-CRVs) should be calculated for VCM. Therefore, the Committee performed a number of risk calculations based on human and animal data using different risk models and end-points for liver carcinogenicity.

The Committee concludes that human angiosarcomas of the liver (ASL) relate specifically to VCM exposure and that a risk assessment based on ASL is the most appropriate.

The Committee estimated that the concentration of VCM in the air, which corresponds to an excess cancer risk of

- 4 per 1,000 (4×10^{-3}), for 40 years of occupational exposure, equals to 65.5 mg/m³
- 4 per 100,000 (4×10^{-5}), for 40 years of occupational exposure, equals to 0.65 mg/m³.

References

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- 1 Gezondheidsraad. Leidraad berekening risicogetallen voor carcinogene stoffen. Den Haag: Gezondheidsraad; 2012: Publicatie nr. 2012/16.
 - 2 Health Council of the Netherlands. Guideline for the calculation of occupational cancer risk values. The Hague, The Netherlands: 2012; publication no. 2012/16E.
 - 3 International Agency for Research on Cancer (IARC). Chemical Agents and Related Occupations. IARC Monogr Eval Carcinog Risk Chem Man 100F. 2012.
 - 4 World Health Organization (WHO). Environmental Health Criteria. 1999.
 - 5 NTP (National Toxicology Program). Report on Carcinogens, Thirteenth Edition. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service.; 2014. Internet: <http://ntp.niehs.nih.gov/pubhealth/roc/roc13/> consulted: 3-11-2016.
 - 6 U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service Agency for Toxic Substances and Disease Registry. Toxicological profile for vinyl chloride. 2006.
 - 7 ChemIDplus Advanced. online source. <http://chem.sis.nlm.nih.gov/chemidplus/> consulted: 3-11-2016.
 - 8 International Agency for Research on Cancer (IARC). Some anti-thyroid and related substances, nitrofurans and industrial chemical. IARC MonogrEval Carcinog Risk Chem Man 1974; 7: 1-326.
 - 9 International Agency for Research on Cancer (IARC). Some monomers, plastics and synthetic elastomers, and acrolein. IARC MonogrEval Carcinog Risk Chem Man 1979; 19.
 - 10 International Agency for Research on Cancer (IARC). Summaries & Evaluations. IARC MonogrEvalCarcinogen Risk Chem Man 1987; Supplement 7: 373.
-

- 11 International Agency for Research on Cancer (IARC). 1,3-Butadiene, ethylene oxide and vinyl
halides (vinyl fluoride, vinyl chloride and vinyl bromide). IARC MonogrEval Carcinog Risk Chem
Man 2008; 97.
- 12 Merck Index. 2013.
- 13 European Parliament and Council. REGULATION (EC) No 1272/2008 OF THE EUROPEAN
PARLIAMENT AND OF THE COUNCIL of 16 December 2008 on classification, labelling and
packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and
1999/45/EC, and amending Regulation (EC) No 1907/2006. 2008.
- 14 Ministerie van Sociale Zaken en Werkgelegenheid. SZW-lijst van kankerverwekkende stoffen en
processen. 2016: 43.
- 15 Health Council of the Netherlands. Advies inzake vinylchloride. Toetsing van een criteriadocument
en voorstel risico-evaluatie. The Hague, Netherlands: 22-5-1986.
- 16 Ho SF, Phoon WH, Gan SL, Chan YK. Persistent liver dysfunction among workers at a vinyl chloride
monomer polymerization plant. J Soc Occup Med 1991; 41(1): 10-16.
- 17 Du CL, Kuo ML, Chang HL, Sheu TJ, Wang JD. Changes in lymphocyte single strand breakage and
liver function of workers exposed to vinyl chloride monomer. Toxicol Lett 1995; 77(1-3): 379-385.
- 18 U.S.Environmental Protection Agency. Toxicological Review of Vinyl Chloride. Washington, DC:
U.S.Environmental Protection Agency; 2000.
- 19 RIVM, National Institute for Public Health and the Environment. online source. www.rivm.nl
consulted: 3-11-2016.
- 20 SER, Social and Economic Council of the Netherlands. online source. www.ser.nl
consulted: 3-11-2016.
- 21 SCOEL, Scientific Committee on Occupational Exposure Limits. Risk Assessment for Vinyl
Chloride. 2002: SCOEL/SUM/109.
- 22 Collins JJ, Jammer B, Sladeczek FM, Bodnar CM, Salomon SS. Surveillance for angiosarcoma of the
liver among vinyl chloride workers. J Occup Environ Med 2014; 56(11): 1207-1209.
- 23 Heath CWJ, Falk H, Creech JLJ. Characteristics of cases of angiosarcoma of the liver among vinyl
chloride workers in the United States. Ann N Y Acad Sci 1975; 246: 231-236.
- 24 Mark L, Delmore F, Creech J, Ogden L, Fadell E, Songster C et al. Clinical and morphologic features
of hepatic angiosarcoma in vinyl chloride workers. Cancer 1976; 37(1): 149-163.
- 25 Delorme F, Theriault G. Ten cases of angiosarcoma of the liver in Shawinigan, Quebec. J Occup Med
1978; 20(5): 338-340.
- 26 Forman D, Bennett B, Stafford J, Doll R. Exposure to vinyl chloride and angiosarcoma of the liver:
a report of the register of cases. Br J Ind Med 1985; 42(11): 750-753.
- 27 Lee FI, Smith PM, Bennett B, Williams DM. Occupationally related angiosarcoma of the liver in the
United Kingdom 1972-1994. Gut 1996; 39(2): 312-318.
- 28 Pirastu R, Comba P, Reggiani A, Foa V, Masina A, Maltoni C. Mortality from liver disease
among Italian vinyl chloride monomer/polyvinyl chloride manufacturers. Am J Ind Med 1990; 17(2):
155-161.
-

- 29 Simonato L, L'Abbe KA, Anderson A, Belli S, Comba P, Engholm G et al. A collaborative study of cancer incidence and mortality among vinyl chloride workers. *Scand J Work Environ Health* 1991; 17(3): 159-169.
- 30 Ward E, Boffetta P, Andersen A, Colin D, Comba P, Deddens JA et al. Update of the follow-up of mortality and cancer incidence among European workers employed in the vinyl chloride industry. *Epidemiology* 2001; 12(6): 710-718.
- 31 Pirastu R, Baccini M, Biggeri A, Comba P. Epidemiologic study of workers exposed to vinyl chloride in Porto Marghera: mortality update. *Epidemiol Prev* 2003; 27(3): 161-172.
- 32 Mastrangelo G, Fedeli U, Fadda E, Valentini F, Agnesi R, Magarotto G et al. Increased risk of hepatocellular carcinoma and liver cirrhosis in vinyl chloride workers: Synergistic effect of occupational exposure with alcohol intake. *Environmental Medicine* 2004; 112(11): 1188-1192.
- 33 Cooper WC. Epidemiologic study of vinyl chloride workers: mortality through December 31, 1972. *Environ Health Perspect* 1981; 41: 101-106.
- 34 Mundt KA, Dell LD, Austin RP, Luippold RS, Noess R, Bigelow C. Historical cohort study of 10 109 men in the North American vinyl chloride industry, 1942-72: update of cancer mortality to 31 December 1995. *Occup Environ Med* 2000; 57(11): 774-781.
- 35 Ott MG, Langer RR, Holder BB. Vinyl chloride exposure in a controlled industrial environment. A long-term mortality experience in 594 employees. *Arch Environ Health* 1975 B.C.; 30(7): 333-339.
- 36 Tabershaw IR, Gaffey WR. Mortality study of workers in the manufacture of vinyl chloride and its polymers. *J Occup Med* 1974; 16(8): 509-518.
- 37 Wong O, Whorton MD, Foliart DE, Ragland D. An industry-wide epidemiologic study of vinyl chloride workers, 1942-1982. *Am J Ind Med* 1991; 20(3): 317-334.
- 38 Boffetta P, Matisane L, Mundt K, Dell L. Meta-analysis of studies of occupational exposure to vinyl chloride in relation to cancer mortality. *Scand J Work Environ Health* 2003; 29(3): 220-229.
- 39 Beaumont JJ, Breslow NE. Power considerations in epidemiologic studies of vinyl chloride workers. *Am J Epidemiol* 1981; 114(5): 725-734.
- 40 Belli S, Bertazzi PA, Comba P, Foa V, Maltoni C, Masina A et al. A cohort study on vinyl chloride manufacturers in Italy: study design and preliminary results. *Cancer Lett* 1987; 35(3): 253-261.
- 41 Buffler PA, Wood S, Eifler C, Suarez L, Kilian D. Mortality experience of workers in a vinyl chloride monomer production plant. *J Occup Med* 1979; 21(3): 195-203.
- 42 Byren D, Engholm G, Englund A, Westerholm P. Mortality and cancer morbidity in a group of Swedish VCM and PCV production workers. *Environ Health Perspect* 1976; 17: 167-170.
- 43 Carreon T, Hein MJ, Hanley KW, Viet SM, Ruder AM. Coronary artery disease and cancer mortality in a cohort of workers exposed to vinyl chloride, carbon disulfide, rotating shift work, and o-toluidine at a chemical manufacturing plant. *Am J Ind Med* 2014; 57(4): 398-411.
- 44 Du CL, Wang JD. Increased morbidity odds ratio of primary liver cancer and cirrhosis of the liver among vinyl chloride monomer workers. *Occup Environ Med* 1998; 55(8): 528-532.
- 45 Duck BW, Carter JT, Coombes EJ. Mortality study of workers in a polyvinyl-chloride production plant. *The Lancet* 1975; 306(7946): 1197-1199.
-

- 46 Fox AJ, Collier PF. Mortality experience of workers exposed to vinyl chloride monomer in the
manufacture of polyvinyl chloride in Great Britain. *Br J Ind Med* 1977; 34(1): 1-10.
- 47 Gennaro V, Ceppi M, Montanaro F. [Reanalysis of mortality in a petrochemical plant producing vinyl
chloride and polyvinyl chloride]. *Epidemiol Prev* 2003; 27(4): 221-225.
- 48 Gennaro V, Ceppi M, Crosignani P, Montanaro F. Reanalysis of updated mortality among vinyl and
polyvinyl chloride workers: Confirmation of historical evidence and new findings. *BMC Public
Health* 2008; 8: 21.
- 49 Hagmar L, Akesson B, Nielsen J, Andersson C, Linden K, Attewell R et al. Mortality and cancer
morbidity in workers exposed to low levels of vinyl chloride monomer at a polyvinyl chloride
processing plant. *Am J Ind Med* 1990; 17(5): 553-565.
- 50 Heldaas SS, Langard SL, Andersen A. Incidence of cancer among vinyl chloride and polyvinyl
chloride workers. *Br J Ind Med* 1984; 41: 25-30.
- 51 Heldaas SS, Andersen AA, Langard S. Incidence of cancer among vinyl chloride and polyvinyl
chloride workers: further evidence for an association with malignant melanoma. *Br J Ind Med* 1987;
44(4): 278-280.
- 52 Hsieh HI, Chen PC, Wong RH, Du CL, Chang YY, Wang JD et al. Mortality from liver cancer and
leukaemia among polyvinyl chloride workers in Taiwan: an updated study. *Occup Environ Med*
2011; 68: 120-125.
- 53 Infante PF, Wagoner JK, Waxweiler RJ. Carcinogenic, mutagenic and teratogenic risks associated
with vinyl chloride. *Mutat Res* 1976; 41(1 spel. no): 131-141.
- 54 Jones RD, Smith DM, Thomas PG. A mortality study of vinyl chloride monomer workers employed
in the United Kingdom in 1940-1974. *Scand J Work Environ Health* 1988; 14.
- 55 Langard S, Rosenberg J, Andersen A, Heldaas SS. Incidence of cancer among workers exposed to
vinyl chloride in polyvinyl chloride manufacture. *Occup Environ Med* 2000; 57(1): 65-68.
- 56 LaPlanche A, Clavel F, Contassot J-C, Lanouziere C. Exposure to vinyl chloride monomer: report on
a cohort study. *Br J Ind Med* 1987; 44: 711-715.
- 57 LaPlanche A, Clavel-Chapelon F, Contassot J-C, Lanouziere, French VCM group. Exposure to
vinyl chloride monomer: results of a cohort study after seven year follow up. *Br J Ind Med* 1992; 49:
134-137.
- 58 Lewis R. Use of rank-order analysis of ordinal exposure data: application to vinyl chloride exposure.
Appl Occup Environ Hyg 2001; 16(2): 188-191.
- 59 Lewis R, Rempala G. A case-cohort study of angiosarcoma of the liver and brain cancer at a polymer
production plant. *J Occup Environ Med* 2003; 45(5): 538-545.
- 60 Molina G, Holmberg B, Elofsson S, Holmlund L, Moosing R, Westerholm P. Mortality and cancer
rates among workers in the Swedish PVC processing industry. *Environ Health Perspect* 1981; 41:
145-151.
- 61 Monson RR, Peters JM, Johnson MN. Proportional mortality among vinyl chloride workers. *EHP,
Environ Health Perspect* 1975; 11: 75-77.
-

- 62 Nicholson WJ, Hammond EC, Seidman H, Selikoff IJ. Mortality experience of a cohort of vinyl
chloride-polyvinyl chloride workers. *Annals New York Academy of Sciences* 1975.
- 63 Pirastu R, Bruno C, De SM, Comba P. An epidemiological study of workers exposed to vinyl
chloride in the plants of Ferrara, Rosignano and Ravenna. *Epidemiol Prev* 1998; 22(4): 226-236.
- 64 Scelo G, Constantinescu V, Csiki I, Zaridze D, Szeszenia-Dabrowska N, Rudnai P et al. Occupational
exposure to vinyl chloride, acrylonitrile and styrene and lung cancer risk (europe). *Cancer Causes
Control* 2004; 15(5): 445-452.
- 65 Smulevich VB, Fedotova IV, Filatova VS. Increasing evidence of the rise of cancer in workers
exposed to vinyl chloride. *Br J Ind Med* 1988; 45(2): 93-97.
- 66 Swaen GMH, Duijts SFA. Epidemiologic evidence for the carcinogenicity of vinyl chloride
monomer. *Scand J Work Environ Health* 2005; 31(3): 233-235.
- 67 Theriault G, Allard P. Cancer mortality of a group of Canadian workers exposed to vinyl chloride
monomer. *J Occup Med* 1981; 23(10): 671-676.
- 68 Waxweiler RJ, Stringer W, Wagoner JK, Jones J, Falk H, Carter C. Neoplastic risk among workers
exposed to vinyl chloride. *Annals New York Academy of Sciences* 1976.
- 69 Weber H, Reinl W, Greiser E. German investigations on morbidity and mortality of workers exposed
to vinyl chloride. *EHP, Environ Health Perspect* 1981; 41: 95-99.
- 70 Wong RH, Chen PC, Du CL, Wang JD, heng TJ. An increased standardised mortality ratio for liver
cancer among polyvinyl chloride workers in Taiwan. *Occup Environ Med* 2002; 59: 405-409.
- 71 Wu W, Steenland K, Brown D, Wells V, Jones J, Schulte P et al. Cohort and Case-Control analyses
of workers exposed to vinyl chloride: An update. *J Occup Med* 1989; 31(6): 518-523.
- 72 Hong CB, Winston JM, Thornburg LP, Lee CC, Woods JS. Follow-up study on the carcinogenicity
of vinyl chloride and vinylidene chloride in rats and mice: tumor incidence and mortality subsequent
to exposure. *J Toxicol Environ Health* 1981; 7(6): 909-924.
- 73 Drew R, Boorman G, Haseman J, McConnell E, Busey W, Moore J. The effect of age and exposure
duration on cancer induction by a known carcinogen in rats, mice, and hamsters. *Toxicol Appl
Pharmacol* 1983; 68: 120-130.
- 74 Maltoni C, Lefemine G, Ciliberti A, Cotti G, Carretti D. Carcinogenicity bioassays of vinyl chloride
monomer: a model of risk assessment on an experimental basis. *Environ Health Perspect* 1981; 41:
3-29.
- 75 Maltoni C, Lefemine G, Chieco P, Carretti D. Vinyl chloride carcinogenesis: current results and
perspectives. *Med Lav* 1974; 65(11-12): 421-444.
- 76 Maltoni C, Lefemine G, Ciliberti A. Experimental research on vinyl chloride carcinogenesis. In:
Maltoni and Mehlman, editor. *Archives of Research on Industrial Carcinogenesis*. Princeton, New
Jersey: Princeton Scientific Publishers Inc., 1984:
- 77 Maltoni C, Lodi P. Results of sputum, cytology among workers exposed to vinyl chloride monomer
and to poly(vinyl chloride). *Environ Health Perspect* 1981; 41: 85-88.
- 78 Wong RH, Chen PC, Wang JD, Du CL, Cheng TJ. Interaction of vinyl chloride monomer exposure
and hepatitis B viral infection on liver cancer. *J Occup Environ Med* 2003; 45(4): 379-383.
-

- 79 European Centre for Disease Prevention and Control. ECDC INFORMATION SHEET Hepatitis B
and C Current situation in the EU/EEA. European Centre for Disease Prevention and Control. [http://
ecdc.europa.eu/en/press/news/Documents/110524_Hepatitis_info_sheet.pdf](http://ecdc.europa.eu/en/press/news/Documents/110524_Hepatitis_info_sheet.pdf) consulted: 2-11-2016.
- 80 Van Everdingen J. From consensus to CBO guideline (Van consensus naar CBO-richtlijn).
Nederlands Tijdschrift Geneeskunde 1999; 143(12): 2086.
- 81 Mark L, Delmore F, Creech JLJ, Ogden LII, Fadell EH, Songster CL et al. Clinical and morphologic
features of hepatic angiosarcoma in vinyl chloride workers. *Cancer* 1976; 37(1): 149-163.
- 82 Prince MM, Ward EM, Ruder AM, Salvan A, Roberts DR. Mortality among rubber chemical
manufacturing workers. *Am J Ind Med* 2000; 37(6): 590-598.
- 83 Klimisch H. A systematic approach for evaluating the quality of experimental toxicological and
ecotoxicological data. *Regul Toxicol Pharmacol* 1997; 25(1): 1-5.
- 84 Suzuki Y. Neoplastic and nonneoplastic effects of vinyl chloride in mouse lung. *EHP, Environ Health
Perspect* 1981; 41: 31-52.
- 85 Suzuki Y. Neoplastic effect of vinyl chloride in mouse lung - lower doses and short-term exposure.
Environ Res 1983; 32(1): 91-103.
- 86 Holmberg B, Kronevi T, Winell M. The pathology of vinyl chloride exposed mice. *Acta Vet Scand*
1976; 17(3): 328-342.
- 87 Winell M, Holmberg B, Kronevi T. Biological effects of vinyl chloride: an experimental study.
Environ Health Perspect 1976; 17: 211-216.
- 88 Adkins BJ, Van SEW, Simmons JE, Eustis SL. Oncogenic response of strain A/J mice to inhaled
chemicals. *J Toxicol Environ Health* 1986; 17(2-3): 311-322.
- 89 Lee CC, Bhandari JC, Winston JM, House WB, Peters PJ, Dixon RL et al. Inhalation toxicity of vinyl
chloride and vinylidene chloride. *Environ Health Perspect* 1977; 21: 25-32.
- 90 Lee CC, Bhandari JC, Winston JM, House WB, Dixon RL, Woods JS. Carcinogenicity of vinyl
chloride and vinylidene chloride. *J Toxicol Environ Health* 1978; 4(1): 15-30.
- 91 Hehir RM, McNamara BP, McLaughlin J, Jr., Willigan DA, Bierbower G, Hardisty JF. Cancer
induction following single and multiple exposures to a constant amount of vinyl chloride monomer.
EHP, Environ Health Perspect 1981; 41: 63-72.
- 92 Viola PL, Bigotti A, Caputo A. Oncogenic response of rat skin, lungs, and bones to vinyl chloride.
Cancer Res 1971; 31(5): 516-522.
- 93 Caputo A, Viola PL, Bigotti A. Oncogenicity of vinyl chloride at low concentrations in rats and
rabbits. *IRCS Libr Compend* 1974; 2(9): 1582.
- 94 Radike MJ, Stemmer KL, Brown PG, Larson E, Bingham E. Effect of ethanol and vinyl chloride on
the induction of liver tumors: preliminary report. *Environ Health Perspect* 1977; 21: 153-155.
- 95 Groth DH, Coate WB, Ulland BM, Hornung RW. Effects of aging on the induction of angiosarcoma.
Environ Health Perspect 1981; 41: 53-57.
- 96 Maltoni C, Cotti G. Carcinogenicity of vinyl chloride in Sprague-Dawley rats after prenatal and
postnatal exposure. *Ann N Y Acad Sci* 1988; 534(Living Chem. World): 145-159.
-

- 97 Feron V, Spit B, Immel H, Kroes R. One-year time-sequence inhalation toxicity study of vinyl chloride in rats. III. Morphological changes in the liver. *Toxicology* 1979; 13: 143-154.
- 98 Til H, Feron V, Immel H. Lifetime (149-week) oral carcinogenicity study of vinyl chloride in rats. *Fd Chem Toxic* 1991; 29(10): 713-718.
- 99 Health Council of the Netherlands. Guideline to the classification of carcinogenic compounds. The Hague, The Netherlands: 2010: Publication no. A10/07E.

A	Request for advice
B	The Committee
C	Letter of submission (in English)
D	Comments on the public review draft
E	Human studies
F	Animal experiments
G	Evaluation of the carcinogenicity by the Subcommittee on Classification of carcinogenic substances
H	Carcinogenic classification of substances by the Committee
I	Calculation of the HBC-OCR _V based on animal data (Maltoni et al., 1981)

Annexes

A

Request for advice

In a letter dated October 11, 1993, ref DGA/G/TOS/93/07732A, to, the State Secretary of Welfare, Health and Cultural Affairs, the Minister of Social Affairs and Employment wrote:

Some time ago a policy proposal has been formulated, as part of the simplification of the governmental advisory structure, to improve the integration of the development of recommendations for health based occupation standards and the development of comparable standards for the general population. A consequence of this policy proposal is the initiative to transfer the activities of the Dutch Expert Committee on Occupational Standards (DECOS) to the Health Council. DECOS has been established by ministerial decree of 2 June 1976. Its primary task is to recommend health based occupational exposure limits as the first step in the process of establishing Maximal Accepted Concentrations (MAC-values) for substances at the work place.

In an addendum, the Minister detailed his request to the Health Council as follows:

The Health Council should advice the Minister of Social Affairs and Employment on the hygienic aspects of his policy to protect workers against exposure to chemicals. Primarily, the Council should report on health based recommended exposure limits as a basis for (regulatory) exposure limits for air quality at the work place. This implies:

- A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as part of a specific request for advice.
- If possible this evaluation should lead to a health based recommended exposure limit, or, in the case of genotoxic carcinogens, a 'exposure versus tumour incidence range' and a calculated concentration in air corresponding with reference tumour incidences of 10^{-4} and 10^{-6} per year.
- The evaluation of documents review the basis of occupational exposure limits that have been recently established in other countries.
- Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
- Reporting on other subjects that will be specified at a later date.

In his letter of 14 December 1993, ref U 6102/WP/MK/459, to the Minister of Social Affairs and Employment the President of the Health Council agreed to establish DECOS as a Committee of the Health Council. The membership of the Committee is given in annex B.

B

The Committee

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- RA Woutersen, *chairman*
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The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the chairperson and members of a Committee and for the President of the Health Council. On being invited to join a Committee, persons are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the Health Council to assess whether or not someone can become a member. An expert who has no financial but another clearly definable interest, can become a member under the restriction that he will not be involved in the debate on the subject to which his interest relates. If a person's interest is not clearly definable, he can sometimes be consulted as an expert. Experts working for a ministry or governmental organisation can be structurally consulted. During the inaugural meeting the declarations issued are discussed, so that all members of the Committee are

aware of each other's possible interests. For permanent committees, possible conflicts of interest are considered for each topic of advice.

C

Letter of submission (in English)

Subject : presentation of advisory report *Vinyl chloride monomer*
Your reference : DGV/BMO/U-932542
Our reference : 1090448/JR/jh/459-A74
Enclosure(s) : 1
Date : February 22, 2017

Dear Minister,

I hereby submit the advisory report on the effects of occupational exposure to vinyl chloride monomer.

This advisory report is part of an extensive series in which carcinogenic substances are evaluated for the possibility to establish health-based occupational cancer risk values. It involves substances to which people can be exposed under working conditions.

The advisory report was prepared by the Dutch Expert Committee on Occupational Safety of the Health Council. The advisory report has been reviewed by the Health Council's Standing Committee on Public Health.

In this report, the Committee concludes that vinyl chloride monomer is a carcinogenic substance with a stochastic genotoxic mechanism. The Committee estimated that the concentration of VCM in the air, which corresponds to an excess cancer risk of

- 4×10^{-5} for 40 years of occupational exposure to 0.65 mg/m^3
- and 4×10^{-3} for 40 years of occupational exposure to 65.5 mg/m^3 .

I have today sent copies of this advisory report to the State Secretary of Infrastructure and the Environment and to the Minister of Health, Welfare and Sport, for their consideration.

Yours sincerely,
(signed)

Prof. dr. J.L. Severens
Vice President

D

Comments on the public review draft

A draft of the present report was released in April 2016 for public review. The following organizations and persons have commented on the draft document:

- Kort JH, Shin-Etsu PVC B.V., Rotterdam
- Lentz TJ, Rice FL, Schubauer-Berigan MK, National Institute for Occupational Safety and Health (NIOSH), Cincinnati OH, USA.

E

Human studies

If no statistical significance is given, the result was not statistically significant, if statistical analysis was performed.

In parallel to the historical decrease of the worker exposure concentrations, the reports are summarized chronologically.

Quality criteria⁸⁰:

Evaluation of therapeutic or preventive studies:

A1: meta-analysis with at least some A2-level studies with unambiguous results from individual studies

A2: randomised clinical trials (double blind, controlled) of good quality and scale

B: randomised clinical trial of moderate quality or limited scale, or other comparable study (non-randomised study, cohort study, case-control study)

C: non-comparative study

D: expert opinion

Evaluation of diagnostic studies:

A1: study on the diagnostic effects of clinical results of a prospective well-defined group of patients with a defined policy based on test results from clinical tests of A2-level, taking into account mutual dependency of the diagnostic tests

A2: study with reference test, with well-defined criteria for test and reference test, with a good description of the test and included clinical population; with an adequate number of successive patients and well-defined cut-off values and independent assessment of results from test and reference standard (in case of multiple diagnostic tests analysis needs to be adjusted for mutual dependency, by using e.g. logistic regression)

B: comparison with a reference test, description of the test and population excluding the A-level characteristics

C: non-comparative study

D: expert opinion

Table 4 Retrospective/ prospective cohort studies, case reports and nested case-control studies.

Study design and population	Data on exposure and health assessment	Results	Remarks
Retrospective mortality study; USA; Vinyl chloride plants; 1930s -1972; 7,128 participants (workers exposed for ≥ 1 year); control group is US male population; Tabershaw et al., 1974 ³⁶	No exposure measurements; Exposure Index (duration (months) x intensity (low, medium or high) resulting in <1.5 and ≥ 1.5); Mortality and cause of death recorded; standard deviation; SMRs adjusted for deaths with cause unknown	EI >1.5 : Total malignant neoplasms SMR: 134 (41 obs./32.7 exp.); digestive organs and peritoneum SMR:141 (12 obs. /9 exp.); respiratory system SMR: 135 (13 obs. /10.3 exp.); other/ unspecified sites SMR: 190 (8 obs./4.52); EI <1.5 : SMR146 (9 obs./6.57 exp.); leukemia and aleukemia SMR: 136 (2 obs./1.6 exp.); lymphomas SMR: 212 (5 obs./2.54 exp.)	Basic study with sufficient number of participants, no exposure measurements; limited study (only supportive). Quality score: B
Case report; USA; PVC industry (4 different plants, total number employees not reported); 13 diagnosed cases; Heath et al., 1975 ²³	No exposure measurement data; worker in PVC production; 0.0014 cases ASL/100,000 in entire population; no statistical analyses; 1 case increased alcohol intake, 1 case exposure to arsenic insecticides as teenager; no exposure to other hepatotoxicants	Diagnosis of ASL; Average age 48.2 years, length of time between first VC work and diagnosis ASL: 12-29 years, mean total duration of VC work: 18 years; calculated risk ratio for VC workers $>400:1$ based on estimate of 20,000 VC workers in USA; suggestion of dose-response relation with latency period	Case study, unclear how many undiagnosed VC-related ASL occurred among VC workers of these plants; no exposure measurements; Limited study (only supportive). Quality score: C

Retrospective mortality study; USA; VC industry (5 plants); 1942-1960; 1974; 594 participants; controls = US white males (age-specific); Ott et al., 1975 , partly overlaps with Tabershaw et al., 1974 ^{35,36}	Four levels of exposure defined based on continuous stationary measurement (1950-59) in 2 plants and job classification (assigned to highest level for at least 1 month), low (TWA < 25 ppm), intermediate (25-200 ppm), high (>200 ppm) and unmeasured; statistical analysis of high-exposure vs all other exposure groups with conditional distribution of independent Poisson random variables; arsenic workers were excluded	Significant increase cases of malignant neoplasms (>200 ppm: 9 obs/ 5.1 exp, $p<0.025$); 15 yr after initial exposure to >200 ppm: 8 obs/ 3.2 expected, $p<0.01$; no deaths due to angiosarcoma or hepatic malignancies	Well-documented study, limited number of cancer cases; well-documented estimation of exposure concentrations (in part based on sampling); potential bias/confounding addressed (healthy worker effect; smoking; family cancer risk; co-exposure to arsenic). Limited study only supportive Quality score: B
Case report; USA and Canada; PVC industry; 15 diagnosed cases; Mark et al., 1975 , partly overlaps with Heath et al., 1975 ^{23,81}	No exposure measurement data (estimated to be high); workers in PVC production; primary angiosarcoma incidence is 20-25 in the US per year; no statistical analysis	Diagnosis of angiosarcoma; Average age 47.5 years, average exposure: 16.9 years; 3-22 months survival after onset	Case study; no exposure levels estimated; Limited study (only supportive) Quality score: C
Retrospective cohort mortality study; South Wales (UK); PVC plant; 1948-1968; study performed Feb, 1975; 2,120 male workers; controls: males aged less than 75 years in England and Wales in 1955-1972; Duck and Carter, 1975 ⁴⁵	No exposure measurement data; Subgroups based on occupation, duration of exposure or time of first exposure; Analyses by a "man years at risk" computer program	No increased SMR for cancer related deaths in the different subgroups (observed 35, expected 36.4) nor for specific cancers; No ASL cases	Study with limited number of participants, no exposure levels estimated; limited study (only supportive) Quality score: B
Retrospective cohort mortality study; New York State, USA; 1 PVC plant; 1946-1963; 255 participants (exposed for ≥ 5 years, latency period of ≥ 10 years); control data based on mortality in New York State; Nicholson et al., 1975 ⁶²	Peak exposures of $\geq 1,000$ ppm estimated based on symptoms experienced (up to 10,000 ppm); no statistical analysis; no other risk factors taken into account	All cancers: 9 observed, 3.9 expected; 3 persons with haemangiosarcoma; no relationship cancer incidence with duration of exposure.	Study with limited number of participants; no exposure measurements; potential bias/confounding not addressed; no statistical analyses; study contains several flaws. Quality score: B
Proportional mortality analysis; Kentucky and Louisville, USA (2 (poly)vinyl chloride plants); late 1947-1973; 161 participants (deceased white males); controls USA white males; Monson et al., 1975 ⁶¹	No exposure measurement data; cause of death based on death certificate; no other risk factors taken into account	SMR all cancers 1.5 (obs 41, exp 28), SMR cancer of liver and biliary tract 11 (8 obs, 0.7 exp), SMR lung cancer 1.6 (13 obs, 8 exp), SMR brain cancer 4.23 (5 obs, 1.2 exp); 5 cases of angioasarcoma	Study with limited number of participants; no exposure measurements; potential bias/confounding not addressed; no statistical analyses Quality score: B

Retrospective mortality study; Sweden; 1 PVC plant; 1940-1971; 750 participants; control is population of Sweden (1969); Byren et al., 1976 ⁴²	No exposure measurement data (peak exposures of up to 10,000-15,000 ppm estimated for autoclave cleaners based on unconsciousness); one-tailed Poisson distribution	Brain cancer SMR 612 (2 observed /0.33 expected; p 0.043); cancer of liver/ pancreas SMR 413 (4 obs. / 0.97 exp.; 0.017); no relationship with time of exposure	Study on mortality of total PVC employee group (number of cases too limited), no refinements, no exposure measurements; Limited study (only supportive)
Retrospective cohort mortality study; USA; Vinyl chloride polymerization industry (4 plants); follow-up from time of termination of employment 1941 to Dec 1973; 1,294 participants (≥ 5 years exposure and latency period of at least 10 years); control = US white males (same age, calendar year of death and cause of death); Waxweiler et al., 1976 and Infante et al., 1976 ^{53,68}	VC exposure determined by survey, review of company process, engineering control, and air-sampling data (not further specified); Mortality, cause of death and histopathology were recorded; type of statistical analyses not described	SMR (all malignant neoplasms) increased significantly (35 obs/ 23.5 exp, $p<0.05$); Hepatic system ≥ 10 -y latency SMR: 1,155 (7 obs/0.6 exp, $p<0.01$) and ≥ 15 -y latency SMR: 1,606 (7 obs/0.4 exp, $p<0.01$); Brain and CNS ≥ 15 y latency SMR: 498 (3 obs/0.6 exp, $p<0.05$); Respiratory system ≥ 15 y latency SMR: 194 (11 obs/5.7 exp, $p<0.05$); Lymphatic and hematopoietic system (≥ 15 y latency SMR: 176, not significant); 11 cases of angiosarcoma within 14 cases of confirmed liver cancer (average latency = 19 years)	Quality score: B Well-documented study with intermediate cohort; no exposure measurements; no potential bias/confounding taken into account, statistical analyses not described; only supportive study. Quality score B
Retrospective cohort mortality study; UK; VCM industry (including 4 PVC plants); 1940-1974; 7,409 workers; sex and age standardized death rates for England and Wales; Fox and Collier, 1977 ⁴⁶	No exposure measurements, exposure estimated based on job history (>200 ppm "high", 25-200 ppm "medium", >25 ppm "low", constant or intermittent); statistical analyses not described; no other risk factors taken into account	SMR primary liver cancer 141 (1 obs/ 0.71 exp); SMR other liver cancers 323 (3 obs (2 angiosarcomas)/ 0.93 exp); both liver angiosarcoma cases at high/constant exposure (SMR: 1,538 (2 obs/0.13 exp))	Study on large cohort, differentiated for exposure estimate; Number of cases too limited; No potential bias/confounding taken into account; Limited study only supportive Quality score B
Case report; Canada; 10 cases of ASL diagnosed between 1955-1974 in Shawinigan, Quebec; study in 1974; Delorme et al., 1978 ²⁵	No exposure measurements, exposure in PVC plant is estimated as very high in the past, in 1974 <3 ppm; Questionnaires on occupational history of patients, past and present residence, medical history, smoking and drinking habits; no statistical analyses; authors have taken into account smoking and alcohol intake	All cases worked in VC polymerization plant with direct contact with VC for 5-26 years (average 17 years), average age at death 50.5 years; latency time 11-28 years from first exposure (average 20.5 years)	Well-documented case study. Clear experimental set-up. No exposure measurements performed. Quality score C

Retrospective cohort mortality study; Canada; VCM/ PVC industry (1 plant); 1948-1972; study performed in 1977; 451 participants (exposed to VCM for >5 years); control = entire population of the Province of Quebec (age- and sex-matched; Theriault et al., 1981 ; Delorme and Theriault 1978 ^{25,67}	No exposure measurement data; job and exposure history assessed via questionnaires; statistical analyses via “man-years-at-risk” method	SMR all cancers 122 (20 obs/ 16.4 exp); SMR cancer of digestive system: 259 (14 obs/ 5.4 exp, $p<0.01$); SMR cancer of bone, skin and connective tissue 526 (2 obs/ 0.4 exp); SMR respiratory cancer 187 (6 obs/ 3.2 exp); 8 angiosarcomas/ 20 total cancer cases	Well-documented study, limited number of participants/ limited number of cases; No exposure levels. Limited study only supportive Quality score B
Retrospective cohort analyses of mortality patterns; USA; VCM production plant; 1948-1975; 464 participants (white males, ≥ 2 consecutive months of exposure); control population is age-matched, white males from Texas; Buffler et al., 1979 ⁴¹	No exposure measurements, exposure estimated based on company personnel records: job and exposure history; jobs classified in 7 exposure groups; one-sided test of significance, based on Poisson distribution; corrected for effects of smoking, duration and level of exposure (combined or separate)	Respiratory system cancer: SMR: 289 (5 obs/1.73 exp, $p=0.032$); latency period 5 years: SMR: 268 (4 obs/ 1.49 exp ($p=0.06$)); group longer exposed SMR: 381 (4 obs/1.05 exp, $p=0.023$); high average level of exposure SMR: 441(3 obs/0.68 exp, $p=0.032$); 4/5 persons with lung cancer smoked	Well-documented study, limited number of participants. Limited number of cases; Exposure levels only based on estimation. Limited study only supportive. Quality score B
Retrospective cohort study; Sweden; PVC processing industry; 1945-1974; study in 1976; 1,970 workers (at least 3 months employed); control = national population; Molina et al., 1981 ⁶⁰	No exposure measurements, exposure estimated based on job history: high (mixing department), medium (heat treatment machines) or low (other departments), exposure time subcohorts based on individual employment history; endpoints: mortality and morbidity; no details on type of statistical analyses; other risk factors not taken into account	Workers >2-y exposure (10 y latency): SMR: malignant tumours 1.51 (9 obs/6 exp), SMR: digestive organ tumours 1.85 (4 obs/2.2 exp); workers > 6 months exposure: SMR: digestive organ tumours 1.29 (11 obs/8.5 exp); all SMRs not significant	Too many subcohorts; number of cases too small; no potential bias/confounding taken into account in analysis; only supportive study Quality score B
Retrospective cohort study; USA (mainly South USA); PVC/VCM industry (37 plants in total, 11 produced only VCM, 18 only PVC, 3 both and 5 produced homopolymers and copolymers, with or without VCM and PVC); start VC production; 1978; 9,677 male workers (>1 year exposure to vinyl chloride before 31 Dec 1972); controls were age-matched males from USA general population; Cooper, 1981 ; Tabershaw, 1974 ^{33,36}	No exposure measurements, exposure estimated based on job history (high/ medium/ low); Statistical significance calculated following Chiang (1961); not corrected for other risk factors	SMR brain and CNS malignant neoplasms 203 (12 obs / 5.9 exp, $p<0.05$); SMR leukemia and aleukemia 143 (9 obs/ 6.7 exp); 8 cases of liver angiosarcoma in cohort (4-23 years of exposure, 16-24 years from first exposure to death)	Number of cases too small; other risk factors not taken into account limited study only supportive. Quality score B

Retrospective cohort study; Germany (West); PVC processing industry; from beginning of VCM/PVC production industry-1974; date study not mentioned; 7,021 male workers, German or Austrian, VCM/ PVC production; 4,910 controls (West German male population); Weber et al., 1981 ⁶⁹	No exposure measurement data; statistical method: Poisson test; other risk factors by additional cohort of PVC processing workers not exposed to vinyl chloride (4,007 participants)	Malignant tumours of: Lymphatic and hematopoietic tissues: SMR 214 (15 obs/6 exp, p<0.01; SMR decreased in PVC processing); GI tract and peritoneum SMR 149 (45 obs/27 exp, p<0.05; SMR decreased in PVC processing); Liver SMR 1,523 (12 obs/4 exp, p<0.01; no increase in PVC processing); Brain: SMR 162 (2 obs/2 exp); for PVC processing: SM 535 (5 obs/2 exp, p<0.05); Latency period taken into account: Lymphatic and hematopoietic tissues, GI tract and peritoneum and brain: no significantly increased SMR for any latency period); Liver SMR 874 for 13-16 months (p<0.05), 1,525 for 61-120 months and 2,528 for >121 months exposure (both p<0.01)	No exposure measurements or estimations included, number of cases too small; Limited study (only supportive) Quality score B
Cohort study; Norway (Telemark county); Vinyl chloride industry; 1953-1979; 454 participants (employed ≥ 1 year, before 1970); age-matched control cohort from Norwegian population; Heldaas et al., 1984 ⁵⁰	No exposure measurements, exposure estimated based on interviews and sporadic 'explosion meter' measurements: 2,000 ppm (1950-1954), 1,000 ppm (1955-1954), 500 ppm (1960-1967), 100 ppm (1968-1974, <1 ppm (since 1975, monitored)); study differentiates nine job classifications based on estimated exposure level; no statistical analyses; 53% of the workers was estimated to smoke (comparable to control: 42%)	All cancers: SMR 114 (23 obs/20 exp); For high VC exposure (VC/PVC production, autoclave cleaning, maintenance, packing/drying): Malignant melanoma of the skin: SMR 590 (3 obs/0.51 exp); Cancer of thyroid gland: SMR 1820 (2 obs/0.11 exp); Bronchial cancer: SMR 220 (4 obs/1.82 exp); Colon cancer: SMR 330 (3 obs/0.92 exp); data indicate dose-related effect on risk of cancer; For group with ≥ 500 ppm-years: all cancers 23 obs/ 20 exp	Number of cases too small, exposure levels estimated, no statistical analyses performed. Supporting study Quality score B
Case reports: register of all cases of angiosarcoma in the liver (histologically confirmed); 118 cases in total, all men working in the PVC industry; worldwide; 1974-1984 (dates back to 1955); Forman et al., 1985 ²⁶	Principal occupation; no statistical analyses	Angiosarcoma incidence peaks 20-29 years after exposure: Production worker/ operator and autoclave cleaners most at risk	Descriptive study with only limited data per case. Supporting study Quality score C

<p>Cohort study; Norway (Telemark county); Vinyl chloride industry; 1953-1984; 430 participants (employed ≥ 1 year, before 1970); age-matched control cohort from Norwegian population; Heldaas et al., 1987; Heldaas et al., 1984^{50,51}</p>	<p>Study set-up essentially the same to Heldaas et al., 1984 (only extended study period)</p>	<p>High exposure: Colon cancer (5 obs/1.4 exp); Bronchial cancer (6 obs/2.5 exp); Malignant melanoma of skin (4 exp/0.7 obs), 1 additional case in each high and medium group compared to Heldaas et al., 1984, cases equally divided between 3 latency groups in workers employed between 1950 and 1964</p>	<p>Number of cases too small, exposure levels estimated, no statistical analyses reported. Supporting study</p> <p>Quality score B</p>
<p>Prospective exposed/non-exposed cohort study; France; 12 VCM polymerization plants; 1980-1985; 1,100 participants (40-55 years old); 1,100 controls (non-exposed, age-matched, same plant and physician); LaPlanche et al., 1987⁵⁶</p>	<p>No exposure measurements, exposure estimated high before 1970, moderate 1970-1976, low since 1976, data combined resulted in 7 exposure levels; data collected on job history, amount of exposure and medical history, smoking and drinking habits of participants and controls; Data analysed by PIGAS system; confounding factors (smoking, alcohol consumption and socio-economic status) were controlled for by Mantel-Haenszel procedure</p>	<p>No significant change in cancer incidence related to Vinyl chloride exposure; One case of angiosarcoma was found, in the group of exposed workers</p>	<p>Number of cases too small No exposure measurements; Several potential bias/confounding taken into account ; Limited study (supportive only)</p> <p>Quality score B</p>
<p>Retrospective cohort study; Italy; VC/PVC industry (3 plants included); 1953/1959-1983/1984; 437+181+638 workers employed ≥ 6 months); controls (Italian population, age-, cause of death- and calendar time-specific); Belli et al., 1987⁴⁰</p>	<p>No exposure measurements, exposure levels estimated (> 1,000 ppm in '50s en '60s to 1-5 ppm mid '70); vital status/ cause of death from administrative sources (when available, clinical and pathological data collected); statistical analyses not described, performed per plant (confidence intervals calculated by procedure by Liddel); other risk factors, not taken into account</p>	<p>Ferrara cohort: All tumours: SMR 155 (23 obs/14.8 exp, 90% CI 106-220); Lung cancer: 217 (9 obs/4.1 exp, 90% CI 113-379); other two plant cohorts showed no increased risk for any malignant tumour</p>	<p>Number of cases too small; no potential bias/confounding taken into account; Limited study (only supportive)</p> <p>Quality score B</p>

<p>Retrospective cohort study; UK; VC industry; 1940-1974; 5,498 participants (males, employed for ≥ 1 year with VCM exposure for $\geq 25\%$ of work shift); controls from England and Wales, same five-year age group; Jones et al., 1988; Fox and Collier 1977^{46,54}</p>	<p>No exposure measurements. Four occupational categories with estimated and measured VCM exposure levels (not further specified): Autoclave operators (500-800 ppm and 150-500 ppm), baggers and driers (<400 ppm and <40 ppm), craftsmen (240 ppm-440 ppm and 50-300 ppm) for 1940-955 and 1956-1974 resp., and other workers (<100 ppm); mortality and cause of death via death certificate; mortality analysis by OCMAP computer program (Poisson distribution assumed); other risk factors not taken into account</p>	<p>Nonsecondary liver cancer: SMR 567 (11 obs/1.9 exp; 95% CI 283-1,015, 7 angiosarcoma); Highest exposure group (autoclave operators): Liver malignant neoplasm (prim or sec): 6 obs/ 0.1 exp ($p<0.5$), in this group incidence non-secondary liver cancer increased with latency (2 obs/ 0.16 exp for 10-19 years and 4 obs/0.13 exp for ≥ 20 years, both $p<0.05$) and length of exposure (2 obs/ 0.08 exp ofor 5-9 years and 4 obs/ 0.15 exp for ≥ 10 years); other cancers not increased</p>	<p>Number of cases small; no potential bias/confounding taken into account; Limited study (supportive)</p> <p>Quality score B</p>
<p>Retrospective cohort study; Soviet Union; VC industry; 1939-1977; 3232 participants (2,195 male and 1,037 female VC workers (> 1 month employed)); control (mean death rates in city where relevant plant was located for years 1959, 1969 and 1975 (15-74 y old)); Smulevich et al., 1988⁶⁵</p>	<p>No exposure measurements, exposure estimated (> 300 mg/m³ (high), 30-300 mg/m³ (moderate), <30 mg/m³ (low); significance determined by confidence limits of the variation of cancer frequency, effect of duration and level of treatment calculated by factorial dispersion technique</p>	<p>Leukaemia/ aleukaemia in both sexes: SMR 500 (5 obs/1 exp; $p<0.05$); Other malignancies of lymphatic and haematopoietic tissue: both sexes: SMR 417 (both 5 obs /1.2 exp, $p<0.05$); females: SMR 2,000 (4 obs/0.2 exp; $p<0.05$); Both sexes high level group: Lymphomas/ leukaemias: SMR 636 (7 obs/1.1 exp, $p<0.05$); Females in high level group: (Stomach cancer: SMR 385 (5 obs/1.3 exp; $p<0.05$); Lymphomas/ leukaemias SMR 4,000 (4 obs/0.1 exp, $p<0.05$)</p>	<p>Number of cases small, exposure levels only estimated; no potential bias/ confounding taken into account; Limited study (only supportive.</p> <p>Quality score B</p>

Retrospective cohort mortality study; USA; vinyl chloride polymerization industry; 1974-1986; total cohort 4835 (VCM subcohort 3635) participants (whites, employed between 1942-1973); control (US white men); Wu et al., 1989 ; Waxweiler et al 1976 ^{68,71}	No exposure measurements; vital status determined via administrative records; cause of death via death certificate or hospital records; statistical significance tested assuming Poisson distribution	Total cohort: Liver cancer: SMR 300 (18 obs (12 cases angiosarcoma) / 6 exp; 90% CI 196-449); Lung cancer: SMR 123 (115 obs/ 94.5 exp, 90% CI 104-142); Brain cancer: SMR 162 (15 obs/ 9.2 exp, 90% CI 100-250); supportive)	Number of cases limited except for lung cancer; no exposure measurements, no potential bias/confounding addressed (potential co-exposure to butadiene only mentioned); Limited study (only
		VCM-exposed cohort: Liver cancer: SMR 333 (14 obs/ 4.2 exp, 90% CI 202-521); Lung cancer: SMR 115 (80 obs/ 69.2 exp, 90% CI 95-139); Brain cancer: SMR 145 (10 obs/ 6.8 exp, 90% CI 79-248); risk of mortality due to liver cancer was consistently elevated for all duration categories from 5-25 years of exposure.	Quality score B
Nested case-control study; USA; vinyl chloride polymerization industry; 1974-1986; each death from cause of interest was matched with 5 control subjects by age (whites, employed between 1942-1973, subcohort with workers exposed to VCM); Wu et al., 1989 ; Waxweiler et al 1976 ^{68,71}	No exposure measurements, cumulative exposure/worker was estimated based on level of exposure (0 to 5) job1 x duration of job1 + level of exposure job2 x duration of job2 + ... ; vital status determined via administrative records; cause of death via death certificate or hospital records; Data analyses conditional logistic regression (variables for sex, year of first employment, cumulative dose of VCM, cumulative dose of PVC and butadiene taken into account	Odds ratio cumulative exposure to VCM and liver angiosarcoma (n=12) for 5 years at level 5 exposure: 109.9 (p=0.03); no relationship between VCM and other cancers or PVC and specific cancers or butadiene and specific cancers	Study with limited number of cases; No exposure measurements, PVC and butadiene potential bias/confounding addressed. Limited study (supportive only) Quality score B

Retrospective cohort study; Sweden; PVC processing industry; 1945-1980; 2,031 participants (male, employed ≥ 3 months); about 75,000 controls (males in same county, age-matched); Hagmar et al., 1990 ⁴⁹	No exposure measurements, exposure estimated (none, low (0.1 ppm), moderate (1 ppm), high (10 ppm)); job and exposure history derived from plant records; cause of death from death certificates; two-tailed statistical analyses, assuming Poisson distribution; effects of co-exposure to fibers and plastics were addressed	No stat. significant relationship between mortality and a specific tumour; all tumour morbidity similar with (or without) ≥ 10 y latency: SMR 138 (55 obs/ 39.8 exp, 95% CI 105-181); Respiratory cancer morbidity without ≥ 10 y latency: SMR 213 (17 obs/ 8.0 exp, 95% CI 127-346); no significant liver tumour morbidity (2 liver tumours were not haemangiosarcoma); no significant association between respiratory cancer or total cancer incidence and length of employment, or individual cumulative exposure VCM estimates; only significant increase of SMR respiratory cancers in subcohort exposed to asbestos and plasticizers (not to VCM):1,070 (95% CI 220-3,120)	Low number of observed/ cancer, exposure only estimated; co-exposure to fibers and plastics explained the respiratory cancers Limited study (only supportive)
Case mortality study; Italy; VCM/ PVC industry (3 plants); 253 deaths; Pirastu et al., 1990 ; Belli et al., 1987 ^{28,40}	No exposure measurement data; causes of death (and other personal information) collected from death certificates and/or hospital records (clinical and pathological data collected where available (3 plants only)	14 primary liver cancers were identified: 7 angiosarcoma and 2 hepatocellular carcinoma, others not further specified; For resp. angiosarcoma and primary nonangiosarcoma liver cancer the mean age of death was 48 years and 53 years, mean duration of exposure 16 and 18 years, mean latency 19 and 20 years Note: next to highly VCM exposed angiosarcoma cases	Paper describing causes of death related to liver for VCM/ PVC workers; no comparison to control; Supportive study Quality score C
Retrospective cohort study; USA; Vinyl chloride industry (32 plants); 1942-1982; study in 1990; 9,370 participants (males, exposed for ≥ 1 year prior to 31 Dec 1972 and employed during or after 1942); controls= US population; Wong et al., 1991 ; Cooper, 1981, Tabershaw et al., 1974 ^{33,36,37}	No exposure measurements, exposure estimated by occupation (high/ medium/ low) and duration of employment (<10 years, 10-20 years and >20 years); demographic information, vital status and employment history collected via questionnaires; cause of death collected via death certificates; Statistical analyses with standard computer package (OCMAP; 95% confidence limits)	Cancer of liver and biliary tract: SMR 641 (37 obs/ 5.77 exp, $p=0.01$); 20+ y exposure: SMR 1285 (11 obs; $p=0.01$); <20 y latency: SMR 386 (10 obs, $p=0.01$); 20-30 y latency: SMR 59 0 (11 obs, $p=0.01$); 30+ y latency: SMR 1218 (16 obs, $p=0.01$); Cancer of brain and CNS: SMR 180 (23 obs/ 12.8 exp, $p=0.05$); 20+ y exposure: SMR 386 (6 obs, $p=0.05$); none of latency periods significant	Basic epidemiological study on mortality and cause of death, sufficient number of participants from different plants, but limited number of cases. No exposure measurements (only estimated); healthy worker effect or other factors not taken into account; Study with minor flaws, supporting Quality score B

Prospective cohort study; France; VC industry (12 plants); 1980-1988; 1,100 participants (40-55 y old in 1980); 1,100 controls (age-matched, same plant and same physician); Laplanche et al., 1992 ; Laplanche et al., 1987 ^{56,57}	No exposure measurements, exposure estimated based on employment history; data analysed with the GLIM package	RR malignant tumour 1.3, 95% CI 0.8-2.10); Liver cancer (all angiosarcoma): 3 exposed group/ 0 control group	Small number of cases, exposure estimated; no statistical analyses; limited study (supportive only)
			Quality score B
Case study; United Kingdom; PVC industry; 1972-1994; 20 patients; Lee et al., 1996 ²⁷	Unclear how cases were identified: from public databases or from industry records; incidental exposure of up to 10,000 ppm (19 workers, autoclave operators and polycleaners), moderate exposure up to 200 ppm (1 worker, premix, blow down and stripping operator). Exposure low after 1975 Background level of liver angiosarcoma in UK is around 2-7 cases/ year	Twenty cases of liver angiosarcoma in male VC workers reported (all in 2 plants); Average age 54 years (37-71), average exposure 15 years (3-29), average latency 25 years (9-35), mean survival from diagnosis to death 3.5 months (1.5-13 months)	Twenty case reports from the UK, source unknown Quality score C
Morbidity cohort study, case-control design; Taiwan; PVC industry (5 plants); follow-up 1989-1995; 2,224 participants (current and former male workers); 3,667 and 5,861 male controls (workers from optical equipment and motorcycle industry 1985-1994 resp.); Du et al., 1998 . ⁴⁴	No exposure measurement data; health examinations including 5 liver function tests and interview on occupational and medical history (714 current workers only); information from 1,510 former PVC workers from hospital records; Morbidity odds ratio (MOR) statistically analysed by multiple logistic regression on the SAS package, 6.08 edition; incidence of primary liver cancer in males is 28.4 per 100,000 (Cancer Registry Report Taiwan, 1994); by selecting reference population with similar socio-economic status, effects of smoking, drinking were minimized	Primary liver cancer: MOR 4.5 (vs motor; 95% CI 2.3-18.4) and 6.5 (vs optical; 95% CI 1.5-13.3); Haematopoietic cancer: MOR 3.4 (vs motor, 95% CI 1.0-11.8) and 3.1 (vs optical, 95% CI 0.8-11.8); Incidence haematopoietic cancer related with age (MOR 18.1 for <40 vs >50 (95% CI 2.3-138); In total, 6 cases of primary liver cancer and 6 cases of hepatocellular carcinoma in PVC worker group (latency 8-29 years, age at admission 41-68 years, working duration 5-30 years)	Limited number of cases; no exposure measurements; several potential bias/ confounding taken into account by choice of relevant control group; Limited study (only supportive) Quality score B

Retrospective mortality study; Norway (Telemark county); PVC industry 91 plant); follow-up 1953-1993; 428 participants (employed > 1 year, first employment between 1950 and 1970); age-matched control cohort from Norwegian population; Langard et al., 2000 , Heldaas et al., 1984 and Heldaas et al., 1987 ^{50,51,55}	No regular exposure measurement data (estimated based on measurements with explosion meters in the 50s and 60s, interviews (odour threshold): constant decrease in VC concentration over the years, therefore, cumulative exposure: <1 ppm-years, 1-5 ppm-years, ≥5 ppm-years; nine job classifications based on estimated exposure level; cause of death based on Cancer Registry of Norway (also used to calculate expected incidence of cancers); Poisson distribution	Lung cancer: 11 obs/ 8 exp; Melanomas of the skin: 7 obs/ 2.07 exp (5 cases in highest exposure group ≥5 ppm-years vs 0.7 exp (95%CI 2.3-16.7); Total number of skin cancers, melanomas and spinocellular cancers combined: 12 obs/ 3.7 exp (95% CI 1.7-5.7); during observation period 1985-93 no new cases of liver haemangiosarcoma, thyroid	Study with small cohort, no exposure levels measured; no confounding factors taken into account; Supporting study Quality score B
Retrospective mortality cohort study; Taiwan; PVC industry; 1985-1997; 3,293 participants (male workers, employed ≥ 1 year between 1950-1992, alive on 1 st January 1985)); reference general male population of Taiwan; Wong et al., 2002 ; Du et al., 1998 ^{44,70}	No exposure measurement data; Vital status and/or cause of death via National health Insurance/National Mortality Registry; statistical analyses assuming Poisson distribution; potential hepatitis infection addressed	Malignant neoplasm of the liver (mostly hepatocellular carcinoma, no ASL): SMR 1.78 (25 obs/14.1 exp, 95% CI 1.15-2.62); Cancer of lymphatic and haematopoietic tissue: SMR 2.6 (7 obs/2.6 exp, 95% CI 1.09-5.6); SMR for liver cancer specifically increased in group exposed <10 years (2.45, 95% CI 1.30-4.19), age at first exposure <30 years (4.5, 95% CI 1.07-4.12), year of first exposure before 1970 (4.82, 95% CI 2.41-8.63) and latency period ≥ 25 years (3.13, 95% CI 1.5-5.75), all p<0.05	Well-performed study (sufficient number of participants), no exposure measurements; only one other risk factor addressed (hepatitis infection); well-performed study with limitations Quality score B
Retrospective mortality study; Italy (Venice area, 1 plant); VC industry; 1973-1999; 1,658 participants (from 1950, present in 1956 or successively hired until 1985); Pirastu et al., 2003 (only English abstract, main text in Italian) ³¹	No exposure measurement data (differentiated per job)	SMR for primary liver cancer increased (SMR 2.78 90% CI 1.86-4.14); Mortality rates for liver angiosarcoma (6 cases) increased with latency and cumulative exposure (both p<0.001); Mortality rates for hepatocellular carcinoma (12 cases) showed similar pattern for cumulative exposure	Since only the summary is available of this study in English, the reliability of the data cannot be assessed

Retrospective mortality study; Italy (Venice area, 1 plant); VC industry; 1972-1995; 1,658 participants (males); two reference groups: “technicians and employees” and “other blue collar workers”; Gennaro et al., 2003 (only English abstract, main text in Italian) ⁴⁸	No exposure measurement data (differentiated per job); statistical analyses by Poisson regression, adjusting for age, age at hiring, calendar period, length of exposure and latency	Excess mortality for all tumours (RR=1.53), lung cancer (RR=2.05), liver tumours (RR=4.08), and lymphomas and leukaemia (RR=2.97)	Since only the summary is available of this study in English, the reliability of the data cannot be assessed
Retrospective case-cohort study; USA (Kentucky); VC/PVC industry (1 plant); 1942-2002; 1,817 participants in total, 23 cases of angiosarcoma, 16 cases of brain cancer (white males, hired prior to 1967, employment ≥ 1 year); Lewis and Rempala, 2003 ; Waxweiler et al, 1976, Wu et al., 1989, Lewis et al., 2001 ^{58,59,68,71}	No exposure measurement data, exposure estimated from year, building and job with VC exposure by qualitative ranking system (6 ranks); stratified nonparametric analysis of case exposure ranks (Fisher’s exact), calculations with SAS software or LogXact 2.1 (for small size calculations)	Angiosarcoma incidence related to year of hire and years employed (p=0.09 and p<0.05), all cases worked in PVC building, and all exposed in two highest ranks (p<0.001); Brain cancer incidence related to year of hire (p=0.09); Angiosarcoma and brain cancer cases not exposed to highest levels of acrylonitrile, 1,3-butadiene and styrene	Moderate number of cases, no exposure measurements; potential effects of co-exposure to acrylonitrile, 1,3-butadiene and styrene addressed; control cohort not described; Limited, study (only supportive) Quality score B
Retrospective case- control study; USA (Kentucky); VC industry (1 plant); 1942-2002; 23 cases of angiosarcoma, 16 cases of brain cancer (all white males, hired prior to 1967, employment ≥ 1 year); 160 and 98 controls for angiosarcoma and brain cancer cases resp.; Lewis and Rempala, 2003 ; Waxweiler et al., 1976, Wu et al., 1989, Lewis et al., 2003 ^{58,59,68,71}	No exposure measurement data, exposure estimated from year, building and job with VC exposure by qualitative ranking system (6 ranks); rank order and logistic regression analyses, weighted sum of the case percentile ranks by the van Elteren-Cuzick statistic, calculations with SAS software or LogXact 2.1 (for small size calculations)	Strong association of angiosarcoma with exposure to VC (p<0.001), not with vinyl acetate, vinylidene chloride or PVC; no association of brain cancer with any of the substances used	Moderate number of cases, no exposure measurements; potential bias/confounding for vinyl acetate, vinylidene chloride or PVC investigated; Limited study (only supportive) Quality score B
Retrospective case-control study; Europe (Romania, Hungary, Poland, Russia, Slovakia, Czech republic, UK); 1998-2002; 2,861 cases (recruited from clinical and pathological departments); age- and gender matched controls (total number 3,118); Scelo et al., 2004 ⁶⁴	No exposure measurement data; job and exposure history assessed by questionnaires analysed by industrial hygienists for vinyl chloride, acrylonitrile and styrene for each job held by each subject; stratified statistical analyses (unconditional logistic regression models); effect of smoking, age and gender was taken into account	No significant correlation incidence lung cancer and vinyl chloride exposure	Moderate number of cases, no exposure measurements; several potential bias/ confounding taken into account; limited study (only supportive) Quality score B

<p>Nested case-referent study; Italy; VC industry; 1987-1999; 13 cases of hepatocellular carcinoma and 139 controls (total cohort of 1,658 participants); Mastrangelo et al., 2004.²</p>	<p>No exposure measurement data (cumulative exposure estimated based on job history); cancer cases through hospital records and cancer registry; physical examination of 643 cohort members 1999-2002 (liver sonography or serum biochemistry); interval variables analyzed by Student's t-test and frequency variables by Fisher's exact test; Odds ratio and 95% Confidence Interval by StatXact statistical package; Chi-square test for linear trends; authors addressed effect of alcohol intake and viral hepatitis infection</p>	<p>Hepatocellular carcinoma: odds ratio for VC exposure >2500 ppm years 29.3 (9 cases, 95% CI 3.61-1,298, p<0.001 for trend)</p>	<p>Small number of cases, well-documented statistical analyses; no exposure measurements; Several potential bias/confounding taken into account. Limited study (only supportive)</p> <p>Quality score B</p>
<p>Retrospective case-cohort mortality study; Italy (Veneto area); VC-PVC production plant; 1972-1999; 1,658 participants (male workers, employed between 1950-1985); internal reference group: technicians and clerks (202 workers) or Italian population; Gennaro et al., 2008; Gennaro et al., 2003, Pirastu et al., 2003, Pirastu et al., 1998^{31,47,48,63}</p>	<p>No exposure measurement data, exposure estimated based on work history: autoclave workers (n=210), PVC baggers (n=198), PVC compound workers (n=404), and technicians and clerks (n=202, low to null exposure), other blue collar workers (n=644); ; Internal comparison through two-sided, Poisson regression model, multivariate regression analysis adjusted for age, calendar period, employment duration and latency</p>	<p>Relative risk for liver cancer among autoclave workers (9.57, 95% CI: 3.71-24.7, 7 obs, significant); Increased SMR (compared to Italian population) for haemolymphopoietic system tumours for PVC baggers (3.77, 95% CI 1.03-9.66) and total blue collar workforce (2.27 95% CI 1.24-2.81)</p>	<p>Low number of cases; no exposure measurements; potential bias taken into account by use of internal comparison group; confounding factors not taken into account. Limited study (only supportive)</p> <p>Quality score B</p>
<p>Retrospective cohort study; Taiwan; PVC industry (6 plants); 1980-2007; 3,336 participants (male workers); reference is general Taiwanese population; Hsieh et al., 2011; Wong et al., 1991^{37,52}</p>	<p>No exposure measurement data (estimated TWA: 150 ppm (1973-1974), 25 ppm (1974-1975), 10 ppm (1975-1994), 5 ppm (1995-2002), 3 ppm (203-2007); Vital status, cause of death and other personal information via National Household Registration System or National Mortality Registry; statistical analyses by Byar's approximation of the exact Poisson test, non-parametric test for several risk factors (all two-sided); confounding factors not taken into account</p>	<p>Liver cancer: SMR 1.93 for 1980-1997 (33 obs/16, 6exp, 95% CI 1.37-2.79, p<0.01); Leukaemia: SMR 3.93 for 1908-1997 (6 obs/1.53 exp, 95% CI 1.4-8.5; p<0.01); both SMRs for 1998-2007 non-significant</p>	<p>Moderate/low number of cases; no exposure measurements (only estimated); no potential bias/confounding taken into account; Limited study (only supportive)</p> <p>Quality score B</p>

Table 5 Multi-centric cohort studies and meta-analysis of previously published data on the effects of VCM exposure.

Study design and population	Data on exposure and health assessment	Results	Remarks
Re-analysis of retrospective mortality studies; original studies from USA (Texas), UK, Sweden, Germany; Vinyl chloride industry; studies published 1974-1978); studies differed in number of participants (255-9,677), exposure time of participants (1 day - >5 years), age of participants, different control populations (standard population of Texas or study's country was conducted); Beaumont and Breslow, 1981; Tabershaw et al., 1974, Ott et al., 1975, Nicholson et al., 1975, Byren et al., 1976, Waxweiler et al., 1976, Fox and Collier, 1977, Buffler et al., 1979 ^{35,36,39,41,42,46,62,68}	Statistical power of median SMRs found in the studies were calculated with respect to liver, brain or lung cancer to relate positive (excess risk for a specific cancer at $p=0.05$) and negative findings to power; One- sided Poisson test	Combined relative risk for liver cancer 5.17 ($p<0.00001$), for brain cancer 1.74 ($p<0.01$)	Well-documented re-analysis of historical data sets Quality score B
Multicentric cohort study; Italy, Norway, Sweden, United Kingdom; VCM/ PVC industry; 1955-1986; 12,706 participants from 19 plants (males with ≥ 1 year employment); controls are national incidence of mortality rates (men only) specific for age and 5-year calendar periods; Simonato et al., 1991; Byren et al., 1976, Molina et al., 1981, Heldaas et al., 1984, Belli et al., 1987, Pirastu et al., 1990 ^{28,29,40,42,50,60}	No exposure measurements, exposure estimated based on industrial hygiene sources and occasional air measurements (regular measurements from mid-1970s (low: <50 ppm; intermediate: 50-449 ppm; high: ≥ 500 ppm); background data through nation-based cancer registries or WHO databases; Poisson distribution; authors mentioned possibility of co-exposure to other compounds	All malignant neoplasms: SMR 104 (445 obs/ 428 exp, 95% CI 95-114) Cancer of liver and intrahepatic bile ducts: SMR 286 (24 obs/ 8.4 exp, 95% CI 183-425); ≥ 15 y latency: SMR 445 (95% CI 285-663); 16 confirmed angiosarcoma/ 17 histologically identified; Duration of exposure, level of exposure, and cumulative exposure related to increased mortality from liver cancer ($p<0.001$, $p<0.01$ and $p<0.001$ resp.), risk unaffected by age of first exposure and calendar period of exposure; Liver and intrahepatic bile cancer: SIR 303 (7 obs/ 2.3 exp, 95% CI 122-623, Norway and Sweden only, 2643 participants); Data show clear dose-dependency for liver cancer incidence	Well-documented study with sufficient number of participants, from 4 different countries and several plants; no exposure measurements; possible co-exposure to other substances only mentioned; Well-performed study Quality score B

<p>Retrospective cohort study; USA/ Canada (1 plant, Ontario); VCM or PVC industry (37 plants); 1942-31 Dec 1995; 10,109 participants (males employed for ≥ 1 year in 1942-1972); reference rates for white men, SMRs calculated both nation-wide and state-specific by NIOSH;</p> <p>Mundt et al., 2000; Tabershaw et al., 1974, Cooper, 1972, Wong et al., 1991^{33,34,36,37}</p>	<p>No exposure measurement or estimates; vital status/ cause of death from National Death Index and the death records of the Social Security Administration; for Canada from Ontario Office of the Registrar General; Standardized mortality ratio (SMR) analyses and 95% confidence intervals were done with ProSMR (ProQuest database system). Cox's proportional hazards models and stratified log rank tests were used to further assess occupational factors</p>	<p>Liver and biliary tract cancer: SMR 359 (95%CI 284-446); Brain and CNS cancer: SMR 142, (95%CI 100-197); Connective and other soft tissue cancer: SMR 270 (95%CI 139-472); Lung cancer: SMR 82 (95% CI 73-92); Cancer of lymphatic and haematopoietic tissue: SMR 86 (95% CI 67-108); Stratified log rank analyses identified duration of exposure as the strongest predictor of hazard ($p < 0.001$, controlling for age and controlling for year of first exposure); 80 deaths from liver cancer, 41% due to angiosarcoma; All deaths due to cancer of connective and other soft tissue in workers first exposed before 1960</p>	<p>Study with large number of participants; statistical analyses to identify variables of influence; no exposure measurements or estimates; potential bias/confounding taken into account; Limited study (only supportive)</p> <p>Quality score B</p>
<p>Retrospective cohort study; Europe (Italy, Norway, Sweden, UK); VCM/PVC industry (19 plants); 1955-1996 (except for 2 plants in Italy (from 1972 and 1974) and 1 plant in Sweden from 1961), 80% of cohort has been traced ≥ 15 years); 12,700 participants (male workers, employed ≥ 1 year); control data from WHO data base (age-, calendar period and country-specific);</p> <p>Ward et al., 2001; Simonato et al., 1991^{29,30}</p>	<p>No exposure measurement data, quantitative estimates per worker based on interviews (smell threshold of 400 or 500 ppm), air measurements since 1970s and job history for 9,775 participants resulting into categories: <1 ppm-years, 1-5 ppm-years and ≥ 5 ppm-years; Vital status and cause of death from death certificates, cancer registry records, medical records, and listings of angiosarcoma cases from several registries; estimated incidence angiosarcoma 0.1 per million population per year; Statistical analyses by internal Poisson regression, 95% CIs calculated using a Poisson distribution</p>	<p>Liver cancer: SMR 2.4 (53 obs, 95%CI 1.8-3.1); Thyroid cancer: SIR 2.21 (7 obs, 95%CI 0.89-4.55); Malignant melanoma: SMR 1.6 (15 obs, 95%CI 0.9-2.65); Among 71 cases of liver cancer were 37 angiosarcomas (for autoclave workers: 25 liver cancers, 16 angiosarcomas); Risk for angiosarcoma 200 times greater than for reference population; Liver cancer correlates with time since first employment, duration of employment, and cumulative exposure. For liver angiosarcoma strong relation with cumulative exposure and duration of employment (≥ 21 y).</p>	<p>Well-described study (sufficient number of participants); no exposure measurements; confounding factors not taken into account; well-performed study</p> <p>Quality score B</p>

<p>Meta-analysis of two multi center cohort studies (Italy/Sweden/Norway/UK and US/Canada) and 6 smaller studies (Former USSR, France, Canada, Germany, China, Taiwan); VC/PVC industry; variable follow-up, 1940 and 1997; 43,810 participants; Boffetta et al., 2003;</p> <p>Ward et al., 2001; Mundt et al., 2000; Smulevich et al., 1988, Laplanche et al., 1992; Theriauld and Allard, 1981; Weber et al., 1981; Wong et al., 2002^{30,34,38,57,65,67,69,70}</p> <p>Re-analysis of meta-analysis of two multi center cohort studies (Italy/Sweden/Norway/UK and US/Canada) and 6 smaller studies (Former USSR, France, Canada, Germany, China, Taiwan); VC/PVC industry; variable, between 1939-1997; Swaen and Duijts, 2005;</p> <p>Boffetta et al., 2003^{38,66}</p>	<p>For details see studies summarized in this table individually; meta-analysis based on random-effects modeling, if heterogeneity ≥ 0.01. Meta-SMR values and their 95% CI were calculated</p> <p>Meta-analysis using fixed effects modeling, when heterogeneity $p \geq 0.01$; using random effects modeling, when heterogeneity $p \leq 0.01$</p>	<p>Meta-SMR for liver cancer increased (based on 2 multi center cohort studies): 2.96 (133 cases, 95% CI 2.00-4.39) and 1.35 (68 cases, 95% CI 1.04-1.77) if ASL is excluded; Increased meta-SMRs for brain cancer 1.26 (95% CI 0.98-1.62), soft tissue sarcomas 2.52 (95% CI 1.56-4.07), non-Hodgkin lymphoma 1.23 (95% CI 0.70-2.19)</p> <p>Based on all studies: meta-SMR for liver cancer 4.95 (95% CI 2.32-10.65), without ASL 2.37 (95% CI 1.27-4.44), soft tissue sarcomas 2.52 (95% CI 1.66-3.82), skin cancer 1.20 (95% CI 0.86-1.68), brain cancer 1.28 (95% CI 1.01-1.61), neoplasms of the lymphatic and hematopoietic systems 1.61 (95% CI 0.96-2.70), non-Hodgkin lymphoma 1.31 (95% CI 0.71-2.41), leukemia 1.43 (95% CI 0.67-3.02)</p> <p>Hepatobiliary cancer mortality was elevated among workers ever exposed to VCM (11 observed deaths, of these 5 were defined as 'liver primary', 5 as 'liver unspecified', and 1 as 'intrahepatic bile duct'). Over all SMR=3.80; (95% CI 1.89-6.80)</p> <p>No significant associations between VCM and non-Hodgkin lymphoma or pancreatic cancer</p>	<p>Well-documented meta-analysis of multiple previously published data. Well-performed analysis</p> <p>Quality score B</p> <p>Well-documented meta-analysis of previously published data. no exposure measurements. Limited study (only supportive)</p> <p>Quality score B</p> <p>Well-described study Moderate number of participants. No exposure measurements , only estimated exposure</p> <p>Quality score B</p>
<p>Retrospective cohort mortality study: New York plant manufacturing rubber and plastic. Production of VCM and PVC from 1946. 1,874 participants employed at the plant between 1946 and 1994 and 2006. Control mortality data from US population rates. (Carreon et al., 2014 update of Prince et al. 2000 ('NIOSH cohort'))^{43,82}</p>	<p>No exposure measurement data available. Exposure was estimated by duration of employment (yrs). Any worker assigned to the PVC, VCM department prior 1995 was considered exposed. In addition employees in several jobs assigned to other departments were also considered exposed</p>		

Animal experiments

Quality criteria⁸³:

1: Reliable without restriction (This includes studies or data from the literature or reports which were carried out or generated according to generally valid and/or internationally accepted testing guidelines (preferably performed according to GLP) or in which the test parameters documented are based on a specific (national) testing guideline (preferably performed according to GLP) or in which all parameters described are closely related/comparable to a guideline method)

2: Reliable with restriction (This includes studies or data from the literature, reports (mostly not performed according to GLP), in which the test parameters documented do not totally comply with the specific testing guideline, but are sufficient to accept the data or in which investigations are described which cannot be subsumed under a testing guideline, but which are nevertheless well documented and scientifically acceptable)

3: Not reliable (This includes studies or data from the literature/reports in which there are interferences between the measuring system and the test substance or in which organisms/test systems were used which are not relevant in relation to the exposure (e.g., unphysiologic pathways of application) or which were carried out or generated according to a method which is not acceptable, the documentation of which is not sufficient for an assessment and which is not convincing for an expert judgment)

4: Not assignable (This includes studies or data from the literature, which do not give sufficient experimental details and which are only listed in short abstracts or secondary literature (books, reviews, etc.)

Study design and animal species	Data on exposure and effect endpoints	Results	Remarks
Preliminary repeated dose study; CD1 mice (male); 30/group; 30/ control group; Suzuki, 1981 ⁸⁴	Inhalation; 0, 1, 10, 100 ppm (corresponds to appr. 0, 2,6, 26, 260 mg/m ³); 5 hr/day, 5 days/ week, 4 weeks; 0 (10/group), 12 (10 animals found dead/group) or 40 weeks (survivors); gross pathology; no statistical analyses	Pulmonary tumours: found only at 40 weeks after exposure; 0/10, 1/9, 2/9 and 5/9; 1, 1, 2 and 4 mice (at 0, 1, 10 and 100 ppm, resp.) found dead during observation time.	Limited study (only supportive). Klimisch score 4
Repeated dose study; CD1 mice (male); 30/ all groups except 600 ppm, 40/ 600 ppm; 60 controls/ group; Suzuki, 1983; Suzuki, 1981 ^{84,85}	Inhalation; 0, 1, 10, 100, 300, 600 ppm (corresponds to appr. 0, 2,6, 26, 260, 767, 1,534 mg/m ³); 6 hr/ day, 5 days/ week, 4 weeks; sacrifice at 0 (10/ dose, 20 of control group), 12 (6-9/dose, 18 of control group), 40-41 (7-9/ dose, 17 of control group) or over 41 weeks after exposure (4 at 600 ppm and 2 control); Histopathology and electron microscopy of tumours; no statistical analyses	Alveologenic tumours; no tumours directly after exposure, first tumour 10 weeks post exposure, after 12 weeks tumour incidence 8/9 and 6/9 at 600 and 300 ppm, resp., after 40/41 weeks: 6/7, 5/7, 6/9, 3/9, 1/9for 600, 300, 100, 10 and 1 ppm, resp. (0/17 in controls; m ortality due to Vinyl chloride cannot be deduced from data; dose-related increased incidence of pulmonary (alveologenic) tumours, inverse relation dose to latency period; size of tumours related to dose; no metastases into other organs	Limited study (only supportive). Klimisch score 4
Repeated dose study; NMRI mice (male and female); 12/sex/group; Holmberg et al., 1976 ⁸⁶	Inhalation; 0, 50 or 500 ppm (corresponds to appr. 0, 130 or 1,300 mg/m ³); 6 hr/day, 5 days/ week; 26 weeks (0, 500 ppm), 52 weeks (0, 50 ppm, except 4/sex/ group killed at 26 weeks); gross pathology and histopathology; no statistical analyses	Alveologenic adenoma: none in controls; 13/24 at 50 ppm, first 26 weeks after start exposure; 24/24 at 500 ppm; Haemangiosarcoma: none in controls; 15/24 at 50 ppm (subperitoneal, subcutaneous and/or lungs); 8/24 at 500 ppm (subperitoneal, liver); Mammary carcinoma: none in controls; 1/24 at 50 ppm; 4 at 500 ppm; Overall tumour incidence 3/48, 18/24 and 24/24 for 0, 50 and 500 ppm resp	Well-documented study. Klimisch score 2

Repeated dose study; NMRI mice (male and female); 12/sex/group; 24 controls/sex; Winell et al., 1976; Holmberg et al., 1976 ^{86,87}	Inhalation; 0, 50 and 500 ppm (corresponds to 0, 130 and 1,300 mg/m ³); 6 hours/ day, 5 days/ week, 52 weeks (50 ppm) or 26 weeks (500 ppm); life time observation; histopathology; no statistical analyses	After 6 months: Lung adenoma: 0/8, 2/8 and 8/8; no haemangiosarcoma found; After 12 months: Lung adenoma: 0/24, 13/24 and 24/24; Haemangiosarcoma (subperitoneal, subcutaneous, pulmonary, hepatic and renal): 0/24, 14/24 and 8/24; mean time of death: 46 and 35 weeks resp. at 50 and 500 ppm (no further data on mortality)	Limited study (only supportive). Klimisch score 4
Repeated dose study; A/J mice (male and female); 70-72 sex/group; 70 controls/sex; Adkins et al., 1986 ⁸⁸	Inhalation; 0, 50 and 500 ppm (corresponds to 0, 130 and 1,300 mg/m ³); 6 hr/day, 5 d/week, 6 months; mice killed at end of exposure; lung histopathology; one-way analysis of variance of Kruskal-Wallis test, Duncan's new multiple-range test	Pulmonary tumours; no sex-difference observed; 50/140, 115/142 and 140/140 (average male/female, for 0, 50 and 500 ppm resp.); mortality at 500 ppm higher (43% vs 1 and 3% in other groups); male mice had significantly more tumours at 50 ppm than females (p<0.001)	well-performed study. Klimisch score 2
Repeated dose study; A/J mice (female); 30/group; 30 controls; Adkins et al., 1986 ⁸⁸	Inhalation; 0, 50 and 200 ppm (corresponds to 0, 130 and 520 mg/m ³); 6 hr/day, 5 d/week, 6 months; mice killed at end of exposure; lung histopathology; one-way analysis of variance of Kruskal-Wallis test, Duncan's new multiple-range test	Pulmonary tumours: 8/30, 26/30, 30/30; no substance-related mortality	well-performed study Klimisch score 2
Repeated dose study; Fischer-344 rats (female); 56-76/group; 112 controls; Drew et al., 1983 ⁷³	Inhalation; 0 or 100 ppm (corresponds to 0 or 260 mg/m ³); 6 hr/ day, 5 days/ week, exposed for 6 (starting at t=0, 6, 12 or 18 months), 12 (starting at t=0, 6 or 12 months), 18 or 24 months; up to 24 months observation time; gross pathology and histopathology; statistical analyses by life table analyses and contingency tables	As incidence of tumours was higher if exposure started earlier in life, only results with start of exposure at t=0 are given: 0, 100 ppm (0-6, 0-12, 0-18, 0-24 months): haemangiosarcoma (liver), 1/112 (4/76, 11/55, 13/55, 19/55); haemangiosarcoma (all sites), 2/112 (4/76, 12/56, 15/55, 24/55); mammary gland adenocarcinoma 5/112 (6/76, 11/56, 9/55, 5/55), hepatocellular carcinoma 1/112 (3/75, 4/56, 8/54, 9/55), all p<0.01	well-performed study. Klimisch score 2

Repeated dose study; Golden Syrian hamster (female); 56/group; Drew et al., 1983 ⁷³	Inhalation; 0 or 200 ppm (corresponds to 0 or 130 mg/m ³); 6 hr/ day, 5 days/ week, exposed for 6 (starting at t=0, 6, 12 or 18 months), 12 (starting at t=0, 6 or 12 months), 18 or 24 months; 24 months observation time; gross pathology and histopathology; statistical analyses by life table analyses and contingency tables	As incidence of tumours was higher if exposure started earlier in life, only results with start of exposure at t=0 are given: 0, 200 ppm (0-6, 0-12, 0-18 months): haemangiosarcoma (all sites) 0/143 (13/88, 4/52 (both p<0.01), 2/103); mammary gland carcinoma 0/143 (28/87, 31/52, 47/102; all p<0.01); stomach adenoma 5/138 (23/88, 3/50, 20/101; all p<0.01); Skin carcinoma 0/133 (2/80, 9/48 (p<0.01), 3/90)	well-performed study Klimisch score 2
Repeated dose study; B6C3F1 and CD-1 mice (female); 54/group; Drew et al., 1983 ⁷³	Inhalation; 0 or 50 ppm (corresponds to 0 or 520 mg/m ³); 6 hr/ day, 5 days/ week, exposed for 6 (starting at t=0, 6, 12 or 18 months), 12 (starting at t=0, 6 or 12 months), 18 or 24 months; 24 months observation time; gross pathology and histopathology; statistical analyses by life table analyses and contingency tables	As incidence of tumours was higher if exposure started earlier in life, only results with start of exposure at t=0 are given: 0, 50 ppm (0-6, 0-12, 0-18), CD-1 mice: Haemangiosarcoma (all sites) 1/71 (29/67, 30/47, 20/45), mammary gland carcinoma 2/71 (33/67, 22/047, 22/45), lung carcinoma 9/71 (18/65, 15/47, 11/45), all p<0.01; 0, 50 ppm (0-6, 0-12), B6C3F1 mice: Haemangiosarcoma (all sites) 4/69 (46/67, 69/90), mammary gland carcinoma 3/69 (29/67, 37/90), all p<0.01	well-performed study Klimisch score 2
Repeated dose study; Sprague Dawley rats (males and females); 30/sex/group; 68 controls; Maltoni et al and Lefemine, 1974; Maltoni et al., 1981 ^{74,75}	Inhalation; 0, 50, 250, 500, 2500, 6,000, 10,000 ppm (corresponds to 0, 130, 650, 1,300, 6,500, 15,600 or 26,000 mg/m ³); 4 hours/day, 5 days/ week, 52 weeks; total experimental time 135 weeks; complete histopathology; no statistical analyses	0 (50, 250, 500, 2500, 6,000, 10,000 ppm): Liver angiosarcoma 0/58 (1/60, 3/59, 6/60, 13/60, 13/59, 7/60); Extra-liver angiosarcoma 0/58 (1/60, 2/59, 1/60, 3/60, 3/59, 3/60); Nephroblastoma 0/58 (1/60, 5/59, 6/60, 6/60, 5/59, 5/60); Neuroblastoma 0/58 (0/60, 0/59, 0/60, 4/60, 3/59, 7/60); Zymbal gland carcinoma 0/58 (0/60, 0/59, 4/60, 2/60, 7/59, 16/60); Skin epithelioma 1/58 (1/60, 2/59, 1/60, 1/60, 2/59, 3/60); Mammary tumour 0/58 (2/60, 2/59, 1/60, 2/60, 0/59, 3/60)	Well-performed study. Klimisch score 2

Repeated dose study; Sprague Dawley rats (males and females); 119-120/group; 185 controls; Maltoni et al., 1981 ⁷⁴	Inhalation; 0, 100, 150 or 200 ppm (corresponds to 0, 260, 390 or 520 mg/m ³); 4 hours/day, 5 days/ week, 52 weeks; total experimental time 143 weeks; complete histopathology; no statistical analyses	0 (100, 150, 200 ppm): Liver angiosarcoma 0/185 (1/120, 6/119, 12/120); Hepatoma 0/185 (3/120 (only 200 ppm); Nephroblastoma 0/120 (10/120, 11/119, 7/120); Zymbal gland carcinoma 2/185 (1/120, 4/119, 4/120); Skin epithelioma 2/185 (1/120, 4/119, 5/120); Mammary tumour 2/185 (4/120, 6/119, 6/120)	Well-performed study. Klimisch score 2
Repeated dose study; Sprague Dawley rats (males and females); 58-60/ group, 190 controls; Maltoni and Lefemine, 1974; Maltoni et al., 1981 ^{74,75}	Inhalation; 0, 50, 250, 500, 2,500, 6,000, 10,000 ppm (corresponds to 0, 130, 650, 1,300, 6,500, 15,600 or 26,000 mg/m ³); 4 hours/day, 5 days/ week, 17 weeks; total experimental time 156 weeks; complete histopathology; no statistical analyses	0 (50, 250, 500, 2,500, 6,000, 10,000 ppm): Liver angiosarcoma 0/190 (1/60, for 500, 2500 and 6000 ppm only); Hepatoma 0/190 (0/58, 0/59, 0/60, 2/60, 1/60, 1/58); Nephroblastoma 0/190 (3/58, 6/59, 0/60, 2/60, 1/60, 1/58); Neuroblastoma 0/190 (0/58, 0/59, 0/60, 5/60, 12/60, 9/58); Zymbal gland carcinoma 2/190 (0/58, 1/59, 1/60, 7/60, 9/60, 9/58); Skin epithelioma 1/190 (1/58, 0/59, 0/60, 2/60, 5/60, 5/58)	Well-performed study. Klimisch score 2
Repeated dose study; Sprague Dawley rats (males and females); 56-60/group; 150 controls; Maltoni and Lefemine, 1974; Maltoni et al., 1981 ^{74,75}	Inhalation; 0, 50, 250, 500, 2,500, 6,000, 10,000 ppm (corresponds to 0, 130, 650, 1,300, 6,500, 15,600 or 26,000 mg/m ³); 4 hours/day, 5 days/ week, 30 weeks; total experimental time 81 weeks; complete histopathology; no statistical analyses	0 (50, 250, 500, 2,500, 6,000, 10,000 ppm): Liver angiosarcoma 0/150 (1/60, 18/60, 14/60, 16/59, 13/60, 10/56); Extra-liver angiosarcoma 1/150 (1/60, 3/60, 7/60, 8/59, 1/60, 1/56); Lung tumour 15/150 (6/60, 41/60, 50/60, 40/59, 47/60, 46/56); Mammary carcinoma 1/150 (12/60, 12/60, 8/60, 8/59, 8/60, 13/56); Skin epithelioma 2/150 (0/60, 2/60, 4/59, 7/60, 4/56).	Well-performed study. Klimisch score 2
Repeated dose study; Wistar rats (males); 25-28/group; 38 controls; Maltoni et al., 1981 ⁷⁴	Inhalation; 0, 50, 250, 500, 2,500, 6,000, 10,000 ppm (corresponds to 0, 130, 650, 1,300, 6,500, 15,600 or 26,000 mg/m ³); 4 hours/day, 5 days/ week, 52 weeks; total experimental time 165 weeks; complete histopathology; no statistical analyses	0 (50, 250, 500, 2,500, 6,000, 10,000 ppm): Liver angiosarcoma 0/38 (0/28, 1/27, 3/28, 3/25, 3/26, 8/27); Hepatomas 1/25 and 2/26 at 2,500 and 6,000 ppm only; Nephroblastoma 0/28 (1/28, 0/27, 2/28, 0/25, 2/26, 1/27); Neuroblastoma 1/25, 1/26 and 3/27 at 2,500, 6,000, 10,000 ppm only; Zymbal gland carcinoma 2/26, 2/27 at 6,000 and 10,000 ppm only	Well-performed study. Klimisch score 2

Repeated dose study; Golden hamsters (males); 30/group; 60 controls; Maltoni et al., 1981 ⁷⁴	Inhalation; 0, 50, 250, 500, 2,500, 6,000 or 10,000 ppm (corresponds to 0, 130, 650, 1,300, 6,500, 15,600 or 26,000 mg/m ³); 4 hours/day, 5 days/ week, 30 weeks; total experimental time 109 weeks; complete histopathology; no statistical analyses	0 (50, 250, 500, 2,500, 6,000, 10,000 ppm): Liver angiosarcoma 0/60 (2/30, 1/30 and 1/30 for 2,500, 6,000 and 10,000 ppm); Cholangio carcinoma 0/60 (2/30 for 6,000 and 10,000 ppm); Acoustic Duct Epithelioma 3/30, 1/30, 2/30 and 1/30 for 500, 2,500, 6,000 and 10,000 ppm); Skin epithelioma 3/60 (9/30, 3/30, 7/30, 3/30, 1/30, 7/30); Melanomas 0/60 (1/30, 1/30, 0/30, 1/30, 2/30, 1/30); Forestomach papilloma and acanthoma 3/60 (3/30, 4/30, 9/30, 17/30, 10/30, 10/30); Hepatomas 1/25 and 2/26 at 2,500 and 6,000 ppm only; Nephroblastoma 0/28 (1/28, 0/27, 2/28, 0/25, 2/26, 1/27); Neuroblastoma 1/25, 1/26 and 3/27 at 2,500, 6,000, 10,000 ppm only; Zymbal gland carcinoma 2/26, 2/27 at 6,000 and 10,000 ppm only	Well-performed study. Klimisch score 2
Repeated dose study; Sprague Dawley rats (male and female); 294/group; 98 controls; Maltoni et al., 1981 ⁷⁴	Inhalation; 0 or 50 ppm (corresponds to 0 or 130 mg/m ³); 4 hours/day, 5 days/ week, 52 weeks; total experimental time 142 weeks; complete histopathology; no statistical analyses	0, 50 ppm: Liver angiosarcoma 0/98, 14/294; Liver angioma 0/98, 8/294; Extra-liver angiosarcoma 0/98, 11/294; Zymbal gland carcinoma 0/98, 9/294; Skin epithelioma 0/98, 3/294; Mammary gland malignant tumour 10/98, 62/294	Well-performed study. Klimisch score 2
Repeated dose study; Sprague Dawley rats (male and female); 120/group; 120 controls; Maltoni et al., 1981 ⁷⁴	Inhalation; 0, 1, 5, 10 or 25 ppm (corresponds to 0, 2,6, 13, 26 or 65 mg/m ³); 4 hours/day, 5 days/ week, 52 weeks; total experimental time 147 weeks; complete histopathology; no statistical analyses	0 (1, 5, 10 or 25 ppm): Liver angiosarcoma 1/119, 5/120 at 10 and 25 ppm ; Extra-liver angiosarcoma 2/119 at 10 ppm; Zymbal gland carcinoma 2/120 (1/118, 1/119, 2/119, 4/120); Mammary gland malignant tumour 7/120 (15/118, 22/119, 21/119, 17/120)	Well-performed study. Klimisch score 2
Repeated dose study; Wistar rats (male and female); 94/group; 99 controls; Maltoni et al., 1981 ⁷⁴	Inhalation; 0 or 1 ppm (corresponds to 0 or 2,6 mg/m ³); 4 hours/day, 5 days/ week, 52 weeks; total experimental time 134 weeks; complete histopathology; no statistical analyses	0, 1 ppm: Extra-liver angiosarcoma 0/94, 3/99; Hepatomas 0/99, 1/99	Well-performed study. Klimisch score 2

Repeated dose study; CD1 mice (male and female); 36/sex/group; 36 controls/sex; Lee et al., 1977/1978 ^{89,90}	Inhalation; exposure 0, 50, 250, or 1,000 ppm (corresponds to 0, 130, 650 or 2,600 mg/m ³); 6 hr/day, 5 days/week; 4/sex/group sacrificed at 1, 2, 3, 6, 9 and 12 months; gross and histopathological examinations; no statistical analyses	Bronchiolo-alveolar adenoma, liver haemangiosarcoma and mammary gland tumours (females only) increased at all exposure levels; first incidences of bronchiolo-alveolar adenoma in second month of exposure, haemangiosarcoma and mammary gland tumour incidence started 6 th month; dose-related increase in mortality (females more susceptible; most mice died in month 7-9); dose-related increase in tumour incidence	Animal numbers limited due to interim sacrifices; limited study (supportive only). Klimisch score 4
Repeated dose study; CD rats (male and female); 36/sex/group; 36 controls/sex/group; Lee et al., 1977/1978 ^{89,90}	Inhalation; exposure 0, 50, 250, or 1,000 ppm (corresponds to 0, 130, 650 or 2600 mg/m ³); 6 hr/day, 5 days/week; 1, 2, 3, 6, 9 and 12 months; gross and histopathological examinations; no statistical analyses	Mainly hepatic and/or pulmonary haemangiosarcoma in rats at all concentrations; dose-related increase in mortality (females more susceptible; most died month 8-12); dose-related increase in tumour incidence (first incidences in month 6 at 250 and 1,000 ppm)	Animal numbers limited due to interim sacrifices Klimisch score 4
Repeated dose study; CD1 mice (male and female); 8-16/sex/group; 16-28 controls/sex/group; Hong et al., 1981 ⁷²	Inhalation; 0, 50, 250 or 1,000 ppm (corresponds to 0, 130, 650 or 2,600 mg/m ³); 6 hr/ day, 5d/ week, for 1, 3 or 6 months; sacrifice 12 months after exposure; gross and histopathological examinations; one-tailed Fisher exact probability test (compare tumour incidence) and Armitage test for linear trends in proportions	Cumulative incidence (no sex-related difference): Hepatic haemangiosarcoma: 1/120, 2/80, 13/40, 18/76; Bronchioloalveolar sarcoma: 16/120, 18/80, 52/84, 50/76; Mammary gland adenocarcinoma/ carcinoma (females): 4/60, 10/40, 13/40, 6/38; mortality increased dose-dependently	All exposure periods together sufficient animals; well-performed study. Klimisch score 2
Repeated dose study; CD rats (male and female); 4-16/sex/group; 4-16 controls/sex/group; Hong et al., 1981 ⁷²	Inhalation; 0, 50, 250 or 1,000 ppm (corresponds to 0, 130, 650 or 2,600 mg/m ³); 6 hr/ day, 5d/week, for 1, 3, 6 or 10 months; sacrifice 12 months after exposure; gross and histopathological examinations; one-tailed Fisher exact probability test (compare tumour incidence) and Armitage test for linear trends in proportions	Cumulative incidence (no sex-related difference): Neoplastic nodules: 0/72, 0/66, 10/68, 2/36; Hepatocellular carcinoma: 1/72, 0/72, 2/68, 7/72; Hepatic haemangiosarcoma: 0/72, 0/66, 5/68, 14/72; Bronchioloalveolar tumour: 0/72, 0/66, 2/68, 4/72; Pulmonary haemangiosarcoma: 0/72, 0/66, 2/68, 7/72; Malignant lymphoma: 0/72, 0/66, 1/68, 4/36; other tumour incidence comparable to control/no dose-relationship; mortality increase dependent on dose and time of exposure	All exposure periods together sufficient animals; well-performed study. Klimisch score 2

Acute study; ICR mice (both sexes); 90 /sex/group; ≥ 82 controls/sex; Hehir et al., 1981 ⁹¹	Inhalation; 0, 50, 500, 5,000 and 50,000 ppm (corresponds to 0, 130, 1,300, 13,000 and 130,000 mg/m ³); 1 hour; 8 or 18 months observation; clinical signs, weight, (histo-)pathology; no statistical analyses	8 and 18 months combined: Bronchio-alveolar adenoma: 12/120, 14/139, 18/139, 24/143 and 45/137; Bronchio-alveolar carcinoma: 0/120, 0/139, 1/139, 1/143 and 3/137; no substance-related mortality; pneumonitis in all mice at 500 ppm and above	Well-performed study Klimisch score 2
Repeated dose study; A/J mice (both sexes); 90 /sex/group; 40-50 controls/sex; Hehir et al., 1981 ⁹¹	Inhalation; 0, 50 and 500 ppm (corresponds to 0, 130 and 1,300 mg/m ³); 1 hour/ day for 10 days (500 ppm) or 100 days (50 ppm); 8, 16 or 20 months observation; (histo-) pathology, electron microscopy; Z test	For 0 and 100 x 50 ppm, and for 0 and 10 x 500 ppm (8, 16 and 20 month sacrifices combined): Pulmonary adenoma: 29/84, 65/158 (not significant), and 31/90, 124/166 (p≈0.001); Pulmonary carcinomas: 2/84, 7/158 (not significant), and 3/90, 22/166 (p≈0.001)	Well-performed study; A similar experiment with rats were mentioned, but results/ group were not mentioned; mice were stated to be more sensitive to vinyl chloride.
Repeated dose study; Wistar rats (male and female); 150/ group (20,000, 500 ppm groups) or 200/ group (other groups); 200/ control group; no data on sex distribution within groups; Caputo et al 1974; Viola et al., 1971 ^{92,93}	Inhalation; 0, 500, 2,000, 5,000, 10,000 and 20,000 ppm (corresponds to approx. 0, 1,300, 5,200, 13,000, 26,000, and 52,000 mg/m ³); 4 hr/ day, 5 days/ week, 1 year; tumours/ animal; X ² test versus control	Skin squamous cell carcinoma: 0/200, 3/150 (p< 0,01), 0/200, 20/200, 34/200 and 67/150; Liver angiosarcoma: 0/200, 4/150 (p< 0,01), 10/200, 12/200, 16/200 and 18/150 (p < 0.0005); Lung adenocarcinoma: 0/200, 0/150, 8/200, 4/200 (p<0.0005), 14/200 and 21/150; Liver cholangioma: 13/150 at 20,000 ppm; no data on mortality	Klimisch score 2 Limited described study; no mortality data; limited study (only supportive). Klimisch score 4
Repeated dose study; Sprague-Dawley rats (male); 80/group; 80/ control group; Radike et al., 1977 ⁹⁴	Inhalation; 0 or 600 ppm (corresponds to appr. 0 and 1,560 mg/m ³); 4hr/ day, 5 days/ week, for 1 year; 8 weeks observation; Histology of 6 vinyl chloride rats; no statistical analyses	Liver angiosarcoma: 0/80, 2/80; Skin fibroma: 0/80, 1/80; 13 exposed rats died (8 control rats)	Limitedly described study (only supportive). Klimisch score 4

Repeated dose study; Sprague-Dawley rats (male and female; 6, 18, 32 and 52 weeks old groups); 110-128/sex/group; 110-128 controls/sex/group; Groth et al., 1981 ⁹⁵	Inhalation; 0 and 948 ppm (corresponds to appr. 0 or 2,465 mg/m ³); 7 hr/day, 5 days/week, for 24,5 weeks (mean); sacrifice at 3, 6, 9 months and 43 weeks; gross pathology and microscopical examination; statistical analyses by Fisher's exact test (compare age groups) or method of weighted least squares regression (determine effect of age on angiosarcoma incidence)	Results for interim sacrifices are considered less relevant and not presented here. Angiosarcomas (liver, spleen, lung) in final sacrifice group: 2 (female)/75 for 6 week-old, 7 (female)/91 for 18 week-old, 26/94 for 32 week-old and 24/109 for 52 week-old compared to one (subcutaneous) in all the control groups; incidence of other tumours comparable to control rats; mean survival was comparable between age groups, age-related response, in older mice tumours appeared earlier and with increased frequency compared to younger mice	Limitedly described study (only supportive) Klimisch score 4
Repeated dose study (chronic); Sprague-Dawley rats (female); 54 exposed and 60 controls; Maltoni & Cotti, 1988 ⁹⁶	Inhalation; 0 or 2,500 ppm (corresponds to appr. 0 or 6,500 mg/m ³); 4hr/day (up to week 7), 7hr/day (week 8-69), 5 days/week, lifetime observation; Full necropsy and histopathology	Malignant tumours in 52/54 (2,500 ppm) and 9/60 (controls); Neuroblastoma 32/54, hepatocarcinoma 5/54, angiosarcoma 27/54 (2500 ppm), all 0/60 (controls)	Well-performed study Klimisch 2
Repeated dose study (including pre-natal exposure); Sprague-Dawley rats (male and female, at start exposure 12-day embryo's); 63 (M) and 64 (F) exposed and 158 (M) and 149 (F) controls; Maltoni & Cotti, 1988 ⁹⁶	Inhalation; 0 or 2,500 ppm (corresponds to appr. 0 or 6,500 mg/m ³); 4hr/day (up to week 7), 7hr/day (week 8-69), 5 days/week; lifetime observation; Full necropsy and histopathology	Malignant tumours in 122/127 (2,500 ppm) and 53/307 (controls); Neuroblastoma 58/127, hepatocarcinoma 65/127, angiosarcoma 82/127 (2,500 ppm), for controls 0/307, 1/307 and 0/307 resp	Well-performed study Klimisch 2
Repeated dose study (including pre-natal exposure); Sprague-Dawley rats (male and female, at start exposure 12-day embryo's); 60/ sex exposed and 158 (M) and 149 (F) controls; Maltoni & Cotti, 1988 ⁹⁶	Inhalation; 0 or 2,500 ppm (corresponds to appr. 0 or 6,500 mg/m ³); 4hr/day (up to week 7), 7hr/day (following 8 weeks), 5 days/week, lifetime observation; Full necropsy and histopathology	Malignant tumours in 114/120 (2,500 ppm) and 53/307 (controls); Neuroblastoma 18/120, hepatocarcinoma 84/120, angiosarcoma 52/120 (2,500 ppm), for controls 0/307, 1/307 and 0/307 resp	Well-performed study Klimisch 2

Repeated dose study; mice (male); 3/2500 ppm, 3/ 6,000 ppm; 4/ control group; Suzuki, 1981 ⁸⁴	Inhalation; 0, 2,500 and 6,000 ppm (corresponds to appr. 0, 6,500 and 15,600 mg/m ³); 5 hr/day, 5 days/week, 5 months ; 6 days; gross pathology, histopathology (light and electron microscopy); no statistical analyses	tumours; proliferation and hypertrophy of bronchiolar epithelium noted in exposed animals (preneoplastic), pulmonary tumours in all exposed mice (none in controls), no metastasis observed, no parenchymal fibrosis nor fibrotic adhesions of the pleura, no data on mortality	Study with focus on histopathology of pulmonary tumours, limited data on other parameters. Low number of animals; no guideline followed, performed before GLP principles were in place; relevant exposure route; observed effects relevant for humans; limited study (only supportive).
Repeated dose study; mice (male); 14/2500 ppm, 7/ 6,000 ppm; 7/control group; Suzuki, 1981 ⁸⁴	Inhalation; 0, 2500 and 6,000 ppm (corresponds to appr. 0, 6,500 and 15,600 mg/m ³); 5 hr/day, 5 days/week, 6 months ; 2 or 37 days; gross pathology, histopathology (light and electron microscopy); no statistical analyses	tumours; proliferation and hypertrophy of bronchiolar epithelium noted in exposed animals (preneoplastic), chronic inflammatory changes particularly after 40 weeks observation, pulmonary tumours in all exposed mice, except 1 at 6000 ppm (none in controls), no metastasis observed, no parenchymal fibrosis nor fibrotic adhesions of the pleura, no data on mortality	Klimisch score 2 Study with focus on histopathology of pulmonary tumours, limited data on other parameters. Adequate number of animals; no guideline followed, performed before GLP principles were in place; relevant exposure route; observed effects relevant for humans; limited study (only supportive).
Repeated dose study; Wistar rats (males and females); 62/ sex/group; 62 controls/sex; Feron et al., 1979 ⁹⁷	Inhalation; 0 and 5,000 ppm (corresponds to 0 and 13,000 mg/m ³); 7 hr/day, 5 days/week, for 52 weeks; 10/sex/group sacrificed at 4, 13, 26 or 52 week; liver effects: light and electron microscopy; no statistical analyses	No tumours were found after 4-26 weeks; Liver angiosarcoma: 3/9 males and 6/10 females after 52 weeks; Hepatocellular carcinoma: 1/9 males and 1/10 females after 52 weeks; no data on final sacrifice	Klimisch score 2 Limitedly described study(only supportive). Klimisch score 4
Repeated dose study; Wistar rats (male); 26/group; 25/ control group; Viola et al., 1971 ⁹²	Inhalation; 0, 30,000 ppm (corresponds to 0 and 78,000 g/m ³); 4 hr/ day, 5 days/ week, 12 months; clinical signs, mortality, histopathology; no statistical analyses	Tumours; all rats showed parenchymal lesions, degeneration of cerebellum, severe chronic hepatitis, interstitial pneumonia, adverse kidney effects, 17 developed skin tumours near the submaxillary and parotid glands, 6 had lung tumours, 5 had bone tumours (none of these effects in controls)	High level of exposure; oral intake may be significant due to licking of fur. Klimisch score 4

Repeated dose study; Wistar rat (male and female); 100/sex/group except highest dose: 50/sex/group; 100 controls/sex; Til et al., 1991 ⁹⁸	Oral (via feed); 0, 0.46, 4.6 and 46 ppm (actual intake 0, 0.013, 0.13 and 1.3 mg/kg bw/day; = oral intake minus faecal Vinyl chloride which was considered to be still enclosed in the PVC granules); lifetime exposure 150 weeks; microscopic examination of liver, all visible tumours in the abdominal cavity, Zymbal and mammary glands and glutathione level in liver; Fisher's exact probability test, one-tailed	Hepatocellular carcinomas: 0/99, 0/99, 0/99 and 3/49 (males, p<0,05), 1/98, 0/100, 1/96 and 3/49 (females); Liver angiosarcoma: 0/99, 0/99, 0/99 and 1/49 (males), 0/98, 0/100, 0/96 and 2/49 (females)	Well-performed study; only liver tumours tabulated. Klimisch score 2
Repeated dose study; Sprague-Dawley rats (male and female); 150/group; 150 controls; Maltoni et al., 1981 ⁷⁴	Oral (gavage); 0, 0.03, 0.3, 1 mg/kg bw/day; 59 weeks; total experimental time 136 weeks; complete histopathology; no statistical analyses	0 (0.03, 0.3, 1 mg/kg bw/day): Liver angiosarcoma 0/150 (0/150, 1/148, 3/149); Zymbal gland carcinoma 1/150 (0/150, 0/150, 5/149); Mammary gland malignant tumour 7/150 (14/150; 4/14; 12/149)	Well-performed study. Klimisch score 2
Repeated dose study; Sprague-Dawley rats (male and female); 80/group; 80 controls; Maltoni et al., 1981 ⁷⁴	Oral (gavage); 0, 3.3, 16.65, 50 mg/kg bw/day; 52 weeks; total experimental time 136 weeks; complete histopathology; no statistical analyses	0 (3.3, 16.65, 50 mg/kg bw/day): Liver angiosarcoma 0/80 (0/80, 10/80, 17/80); Extra-liver angiosarcoma 0/80 (1/80, 0/80, 2/80); Nephroblastoma 0/80 (0/80, 3/80, 2/80); Forestomach papilloma and acanthoma 0/80 (0/80, 1/80, 2/80)	Well-performed study. Klimisch score 2

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Evaluation of the Subcommittee on the Classification of carcinogenic substances

Existing evaluations

IARC (2012), U.S. NTP Report on Carcinogens (2006), and U.S. ATSDR (2014) evaluated the carcinogenic potential of vinyl chloride monomer (VCM). The Subcommittee did not identify human data of a more recent date.¹⁻³

In the present evaluation (September 2015) the DECOS Subcommittee on the Classification of Carcinogenic Substances evaluated the existing and new information regarding human, animal, and *in vitro* studies on carcinogenicity and genotoxicity of VCM based on the reports by IARC (2012), U.S. NTP Report on Carcinogens (2014), and U.S. ATSDR (2006).¹⁻³

Classification and labelling as a carcinogenic substance

IARC classified VCM as carcinogenic to humans (Group 1) in 1974, 1979, 1987, 2008 and 2012.^{1,4-7}

The European Union has classified VCM in carcinogenicity category 1A, (*substance known to have carcinogenic potential for humans*), as listed under index number # 602-023-00-7 in Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation).⁸

VCM is listed in the Dutch SZW-list of carcinogenic substances.⁹

In 1986 a committee of the Health Council of the Netherlands concluded that VCM should be considered a genotoxic carcinogen in humans.¹⁰

Human studies

A considerable number of case reports and epidemiological studies concerning carcinogenicity of VCM is available in the literature and has repeatedly been reviewed by national and international agencies.¹⁻³ All agencies concluded that there was sufficient evidence from epidemiological studies that VCM is a human carcinogen.

The main epidemiological evidence for the carcinogenicity of VCM comes from two large multicentre cohort studies from Europe and North America.

The most recent publication on the European multicentre cohort study is from Ward et al.¹¹ A total of 71 deaths from liver cancer (primary liver cancer, including 37 angiosarcomas, 10 hepatocellular carcinomas, and 24 liver cancers of other and unknown histology) were observed. A strong positive trend for time since first employment, duration of employment, and cumulative exposure was found with relative risks for all liver cancers combined, angiosarcoma, and hepatocellular carcinoma. The highest relative risks were observed for angiosarcoma of the liver, even though workers in the reference group already experienced an estimated 200-fold higher risk of angiosarcoma than the general population (based on 4 cases among approximately 200,000 person-years in the reference group). No other type of cancer was found in excess.

The most recent and complete publication on the North American multicentre cohort study is from Mundt et al.¹² 895 cancer deaths were reported. While total cancer mortality was not elevated, mortality from cancers of the liver and biliary tract was significantly increased. Modest excesses of brain cancer and cancer of connective and soft tissue were also observed. Hazard rates from proportional hazard analyses supported associations with age at first exposure, duration of exposure, and year of first exposure for cancers of the liver and soft tissues, but not the brain. Hazard rates for 'all known angiosarcomas' (n=48) were associated with duration of exposure, though not with age at first exposure or year of first exposure.

Results from the European and North American multicentre studies were combined with six independent studies of cancer among VCM workers (from former USSR, France, Canada, Germany, China, Taiwan) in a meta-analysis by Boffetta et al.¹³. Together these studies include 43,810 vinyl chloride/polyvinylchloride workers with variable follow-up ranging between 1940 and 1997. With SMR values ranging from 1.63 to 57.1, all six studies for which these ratios could be obtained suggested an increased risk of liver cancer, though these results were deemed too heterogeneous to be included in a meta-analysis. A significantly increased meta-SMR was also reported for liver cancers other than ASL (based on the 2 multicentre studies) and for soft-tissue sarcoma, however, these results may have been influenced by the under diagnosis of true ASL. A meta-analysis for ASL was not conducted as relevant SMR values were difficult to estimate due to the extreme rarity of the disease in the general population.

The epidemiological literature indicates a strong association between exposure to VCM and liver cancer incidence and mortality. The elevated risk for liver cancer appears to be primarily driven by ASL. However, studying the association between exposure to VCM and ASL is statistically challenging because this form of liver cancer is extremely rare. Studying the association between exposure to VCM and liver cancer excluding ASL is also difficult because of the risk of misdiagnosis of true ASL. Several other forms of cancer have been associated with exposure to VCM in individual studies, but these associations are not consistent across studies.

Animal studies

The carcinogenicity of VCM has been studied extensively in mice, rats, and hamsters. These studies have been reviewed in depth by U.S. ATSDR, IARC, and U.S. NTP.¹⁻³ All agencies concluded that there was sufficient evidence from animal studies that VCM is an animal carcinogen. The 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.⁵ While studies have assessed the effects of exposure via inhalation, skin, and ingestion, exposure via inhalation is likely the most relevant exposure route for humans. Three large inhalation studies are described below.

Hong et al.¹⁴ reported on an experiment in which rats and mice were exposed to 0, 130, 650 or 2,600 mg/m³ VCM via inhalation for 6 hours/day, 5 days/week

during 1, 3 or 6 months and describe the development and incidence of neoplastic changes and other effects during a 12 month post-exposure follow-up period. Unscheduled mortality increased in both species in a dose-related way, and occurred at earlier time points at higher concentrations. There was no significant sex-related difference in the number of unscheduled deaths (or sacrifices). In mice, cumulative incidence of hepatic haemangiosarcoma during recovery period was increased at higher VCM concentration. The tumour was mostly multiple in site distribution and varied greatly in size. Overall, the incidence of this tumour rose as the concentration and duration of VCM exposure increased. Also the incidence of bronchioloalveolar tumours were greater in mice exposed to increasing levels of VCM and for longer exposure periods. In female mice mammary gland adenocarcinoma/carcinoma was observed. Metastatic adenocarcinoma originating from the mammary gland was also seen in lungs of mice exposed to VCM, but not in lungs of control mice.

Drew et al.¹⁵ observed induced haemangiosarcomas and mammary gland carcinomas in two strains of mice and lung carcinomas in Swiss mice after six months of exposure to 130 mg/m³ VCM. Longer exposure had no significant effect on tumour incidence, while incidence was higher when exposure started earlier in life. In rats, mainly haemangiosarcomas of the liver, mammary neoplasms and hepatocellular carcinoma were found after 6 months of exposure. The incidence of haemangiosarcomas was a function of the duration of the exposure. If the exposure took place early in life, a higher incidence of haemangiosarcomas was noted. In hamsters, haemangiosarcomas, mammary gland carcinomas, stomach adenomas, and skin carcinomas were produced by exposure to 520 mg/m³ VCM. The highest incidence was seen in animals exposed early in life.

A large series of experiments was performed by Maltoni et al. using rats (Sprague-Dawley and Wistar), mice, and hamsters.^{16,17} In one group of studies, Maltoni et al. exposed Sprague-Dawley rats to VCM for 52 weeks at concentrations ranging from 1 to 30,000 ppm. Animals were examined at the time of their spontaneous death. Statistically significant increases were noted in the incidence of mammary gland carcinomas, Zymbal gland carcinomas, nephroblastoma, and liver angiosarcoma. Exposure of Swiss mice to 50 ppm VCM for 4 hours/day, 5 days/week for 30 weeks also appeared to increase the incidence of liver angiosarcoma and angioma. Some variation in the target organs that developed tumours was observed when different species were exposed to VCM.^{16,17} Whereas angiosarcomas of the liver were reported to occur in rats, mice, and hamsters, mammary gland carcinomas were found only in rats and mice; Zymbal gland carcinomas, neuroblastomas, and nephroblastomas were

found only in rats; lung tumours were found only in mice; and melanomas, acoustical duct epithelial tumours, and leukemias were found only in hamsters.³ In their review of the Maltoni study, ATSDR noted that limited histopathological data were presented and cancer incidences were presented only in summary tables. Also, survival of control animals was poor in some of the experiments. Furthermore, statistical analyses, where present, appear to be based on a compilation of data from several individual studies.³

Based on the available data it can be concluded that tumour incidence (number of rats with a tumour) and multiplicity (number of tumours/ rat) following VCM in rats is clearly related to exposure concentration and duration. The effects of VCM in laboratory animals indicate that the effects in animals and in humans are comparable.

Mechanism of genotoxicity

Evidence for the genotoxic properties of VCM has been reviewed by IARC, ATSDR, and NTP. The three agencies concluded that VCM is a mutagen.¹⁻³

VCM caused genetic damage in many test systems, including bacteria, yeast, insects, cultured human and other mammalian cells, rodents, and in humans. The genetic damage included mutations and chromosomal aberrations. Tables 6 and 7 include an overview of the *in vivo* and *in vitro* evidence for the genotoxicity of VCM.

Table 6 Genotoxicity of VCM *in vivo*.^a

Species(test system)	Endpoint	# studies
Mouse	Dominant lethal	0 positive / 1 negative
	Micronuclei	1 positive / 0 negative
Rat	Dominant lethal	0 positive / 3 negative
	Chromosomal aberration	1 positive / 0 negative
Hamster	Chromosomal aberration	1 positive / 0 negative
Human lymphocyte	Sister chromatid exchange	8 positive / 1 negative
	DNA damage	2 positive / 0 negative
	Micronuclei	4 positive / 0 negative
	Chromosomal aberration	21 positive / 1 negative
Rat	DNA alkylation	7 positive / 0 negative
Mouse	DNA alkylation	1 positive / 0 negative
	DNA damage	1 positive / 0 negative
Rat	DNA adduct	6 positive / 0 negative

^a Table modified from Table 3-3 in the toxicological profile for VCM by the U.S. ATSDR³, where references for all studies can be found.

Table 7 Genotoxicity of VCM in vitro.^a

Species	End point	# studies with activation	# studies without activation
Salmonella typhimurium	Reverse mutation	9 positive / 0 negative	7 positive / 2 negative
TA100, TA1535	Base-pair substitution	2 positive / 0 negative	1 positive / 0 negative
TA98, TA1537, TA1538	Frameshift mutation	0 positive / 1 negative	0 positive / 1 negative
Escherichia coli	Frameshift mutation	0 positive / 0 negative	1 positive / 0 negative
Saccharomyces cerevisiae	Frameshift mutation	0 positive / 0 negative	0 positive / 1 negative
	Gene conversion	1 positive / 0 negative	0 positive / 0 negative
Schizosaccharomyces pombe	Forward mutation	2 positive / 0 negative	0 positive / 1 negative
D7RAD yeast	Gene conversion	1 positive / 0 negative	0 positive / 1 negative
Chinese hamster ovary cells	Gene conversion	2 positive / 0 negative	1 positive / 1 negative
Bacillus subtilis	Rec-repair	0 positive / 0 negative	0 positive / 1 negative
Rat liver microsomes	RNA alkylation	0 positive / 0 negative	1 positive / 0 negative
QT6 (avian cells)	Inhibition of DNA synthesis	0 positive / 0 negative	1 positive / 0 negative

^a Table modified from Table 3-4 in the toxicological profile for VCM by the U.S. ATSDR³, where references for all studies can be found.

Conclusion

Based on a review of the literature and existing evaluations by IARC, ATSDR, and NTP, the Subcommittee concludes that VCM induces cancer in humans and experimental animals (rodents) via a mutagenic mode-of-action. Consequently, DECOS Subcommittee reconfirms the decision by the Health Council of the Netherlands in 1986 that a stochastic genotoxic mechanism underlies the carcinogenicity of VCM. The Subcommittee follows the classification of VCM in category 1A (substance *known to have carcinogenic potential for humans*) by the European Union (Annex H).

References (for Annex G)

- 1 International Agency for Research on Cancer (IARC). Chemical Agents and Related Occupations. IARC Monogr Eval Carcinog Risk Chem Man 100F. 2012.
- 2 NTP (National Toxicology Program). Report on Carcinogens, Thirteenth Edition. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service.; 2014. Internet: <http://ntp.niehs.nih.gov/pubhealth/roc/roc13/>. Consulted: 03-11-2016.
- 3 U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service Agency for Toxic Substances and Disease Registry. Toxicological profile for vinyl chloride. 2006.
- 4 International Agency for Research on Cancer (IARC). Some anti-thyroid and related substances, nitrofurans and industrial chemical. IARC MonogrEval Carcinog Risk Chem Man 7, 1-326. 1974.

- 5 International Agency for Research on Cancer (IARC). Some monomers, plastics and synthetic
elastomers, and acrolein. IARC MonogrEval Carcinog Risk Chem Man 19. 1979.
- 6 International Agency for Research on Cancer (IARC). Summaries & Evaluations. 1987:
Supplement 7.
- 7 International Agency for Research on Cancer (IARC). 1,3-Butadiene, ethylene oxide and vinyl
halides (vinyl fluoride, vinyl chloride and vinyl bromide). IARC MonogrEval Carcinog Risk Chem
Man 97. 2008.
- 8 European Parliament and Council. REGULATION (EC) No 1272/2008 OF THE EUROPEAN
PARLIAMENT AND OF THE COUNCIL of 16 December 2008 on classification, labelling and
packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and
1999/45/EC, and amending Regulation (EC) No 1907/2006. 2008.
- 9 Ministerie van Sociale Zaken en Werkgelegenheid. SZW-lijst van kankerverwekkende stoffen en
processen. 2016: 43.
- 10 Health Council of the Netherlands. Advies inzake vinylchloride. Toetsing van een criteriadocument
en voorstel risico-evaluatie. The Hague, Netherlands: 22-5-1986.
- 11 Ward E, Boffetta P, Andersen A, Colin D, Comba P, Deddens JA et al. Update of the follow-up of
mortality and cancer incidence among European workers employed in the vinyl chloride industry.
Epidemiology 2001; 12(6): 710-718.
- 12 Mundt KA, Dell LD, Austin RP, Luippold RS, Noess R, Bigelow C. Historical cohort study of
10,109 men in the North American vinyl chloride industry, 1942-72: update of cancer mortality
to 31 December 1995. Occup Environ Med 2000; 57(11): 774-781.
- 13 Boffetta P, Matisane L, Mundt K, Dell L. Meta-analysis of studies of occupational exposure to vinyl
chloride in relation to cancer mortality. Scand J Work Environ Health 2003; 29(3): 220-229.
- 14 Hong CB, Winston JM, Thornburg LP, Lee CC, Woods JS. Follow-up study on the carcinogenicity of
vinyl chloride and vinylidene chloride in rats and mice: tumour incidence and mortality subsequent to
exposure. J Toxicol Environ Health 1981; 7(6): 909-924.
- 15 Drew R, Boorman G, Haseman J, McConnell E, Busey W, Moore J. The effect of age and exposure
duration on cancer induction by a known carcinogen in rats, mice, and hamsters. Toxicol Appl
Pharmacol 1983; 68 (1): 120-130.
- 16 Maltoni C, Lefemine G, Ciliberti A, Cotti G, Carretti D. Carcinogenicity bioassays of vinyl chloride
monomer: a model of risk assessment on an experimental basis. Environ Health Perspect 1981;
41: 3-29.
- 17 Maltoni C, Lefemine G, Chieco P, Carretti D. Vinyl chloride carcinogenesis: current results and
perspectives. Med Lav 1974; 65(11-12): 421-444.
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Carcinogenic classification of substances by the Committee

The Committee expresses its conclusions in the form of standard phrases:

Category	Judgement of the Committee (GR _{GHS})	Comparable with EU Category	
		(before 16 December 2008)	(as from 16 December 2008)
1A	The compound is known to be carcinogenic to humans. <ul style="list-style-type: none"> • It acts by a stochastic genotoxic mechanism. • It acts by a non-stochastic genotoxic mechanism. • It acts by a non-genotoxic mechanism. • Its potential genotoxicity has been insufficiently investigated. Therefore, it is unclear whether the compound is genotoxic. 	1	1A
1B	The compound is presumed to be carcinogenic to humans. <ul style="list-style-type: none"> • It acts by a stochastic genotoxic mechanism. • It acts by a non-stochastic genotoxic mechanism. • It acts by a non-genotoxic mechanism. • Its potential genotoxicity has been insufficiently investigated. Therefore, it is unclear whether the compound is genotoxic. 	2	1B
2	The compound is suspected to be carcinogenic to man.	3	2
(3)	The available data are insufficient to evaluate the carcinogenic properties of the compound.	not applicable	not applicable
(4)	The compound is probably not carcinogenic to man.	not applicable	not applicable

Source: Health Council of the Netherlands. Guideline to the classification of carcinogenic compounds. The Hague: Health Council of the Netherlands, 2010; publication no. A10/07E.⁹⁹

Calculation of the HBC-OCRV based on animal data (Maltoni et al., 1981)

The Committee is of the opinion that the epidemiological studies on VCM provide a reliable starting point for quantitative risk assessment. There is sufficient epidemiological evidence that VCM is carcinogenic for humans; the majority of the studies shows increased cancer risks. Based on the currently available human data a reliable calculation can be made. In addition however, for comparison the Committee calculated risk values based on animal data.

The Committee considers the data from the long term inhalatory exposure experiments in rats, as reported by Maltoni et al. (1981) as experiments BT1, BT2 and BT15 (see also paragraph 3.2), suitable for the estimation of cancer risk values.⁷⁴ The exposure in experiment BT1 ranged from 0 to 10,000 ppm, in BT2 from 0 to 200 ppm and in BT 15 from 0 to 25 ppm. The Committee decides to perform a quantitative risk assessment based on angiosarcomas of the liver (ASL).

The Committee derives a bench mark dose (BMD10) after applying the EPA software (2.6) to establish a dose-response on the data from the three respective experiments. As a rule, a series of quantitative models (gamma multi-hit, logistic, loglogistic, probit, logprobit, multistage, Weibull, quantal-linear) is used to fit the dose-response on the data from each experiment. Then, the statistical acceptability is established for each model applied. From all accepted models the

Committee uses the model with the lowest BMD10 value as point of departure for further risk calculation.²

The Committee observes that the animal data from experiment BT2 and BT15 allow reliable modelling of a dose-response relationship over the whole dose range (see Table 1 and Figures 2 and 3). The BMD modelling on the data from the BT1 experiment was reliable up to 500 ppm (=1,300 mg/m³) exposure (see Table 1 and Figure 1).

The BMD10 derived from the BT1 experiment (up to 500 ppm, gamma multi hit model) was used below as a point of departure for further calculation of cancer risk values. First, the incidence per unit concentration (mg/m³) was calculated (I_{conc}).

$$I_{\text{conc}} = \frac{\text{BMR}}{\text{BMD} \times (X_{\text{po}}/L) \times (X_{\text{pe}}/L) \times (\text{exposure hrs per day}/24) \times (\text{exposure days per week}/7)} =$$

$$= \frac{0.1}{(1,255 \text{ mg/m}^3) \times (364/1000) \times (945/1000) \times (4/24) \times (5/7)} = 1.95 \times 10^{-3} [\text{g/m}^3]^{-1}$$

Where:

- I_{conc} is the carcinogenic activity that may be ascribed to exposure to the compound per unit of air concentration, expressed in mg per m³
- BMR, the bench mark response, expressed as 10 % increase in tumour incidence
- X_{po} and X_{pe} are the exposure and experimental periods, respectively
- L is the standard lifespan for the animals in question (L rat is assumed to be 1000 days).

Subsequently the extra cancer risk per unit concentration (HBC-OCR_V) was calculated for humans occupationally exposed during a working life.

$$\text{HBC-OCR}_V = I_{\text{conc}} \times \frac{40 \text{ years}}{75 \text{ years}} \times \frac{48 \text{ weeks}}{52 \text{ weeks}} \times \frac{5 \text{ days}}{7 \text{ days}} \times \frac{10 \text{ m}^3}{18 \text{ m}^3} = 3.79 \times 10^{-4} [\text{mg/m}^3]^{-1}$$

Where it is assumed:

- that biological availability of VCM is 100% after inhalatory dosing
- that no difference exists between rats and man with respect to toxicokinetics, mechanism of tumour induction, target, susceptibility etc., unless specific information is available which justifies a different approach
- that the average man lives 75 years, weighs 70 kg and is exposed 24 hours per day, 7 days per week, 52 weeks per year for lifetime
- that the average man is occupationally exposed for 40 years, 48 weeks per year, 5 days per week, 8 hours per day, and inhales 10 m³ air per 8-hour-working day.

The Committee estimated that the concentration of VCM in the air, which corresponds to an excess cancer risk of

- 4 per 1,000 (4×10^{-3}), for 40 years of occupational exposure, equals to 10.55 mg/m³
- and 4 per 100,000 (4×10^{-5}), for 40 years of occupational exposure, equals to 0.11 mg/m³.

Similar calculations were performed on the data from the two other experiments (see Table 8 and Figures 1, 2 and 3). For experiments BT2 and BT15 a BMD10 was derived of 511 and 82 mg/m³ respectively using a logistic model. For data from experiment BT2 this resulted in VCM concentrations of 4.54 and 0.05 mg/m³ at risk levels of 4 per 1,000 and 4 per 100,000. For experiment BT15 the respective results were 0.75 and 0.01 mg/m³.

Although the calculated values differ per experiment, they are of the same order of magnitude nonetheless. The results from the animal data are slightly more conservative than the results from the epidemiological study (65.5 and 0.65 mg/m³ at 4 per 1,000 and 4 per 100,000). The Committee is of the opinion that the risk assessment based on the human data should be preferred, and that the animal data may be considered supportive to the risk numbers established on human data.

Table 8 Quantitative risk assessment based on the study by Maltoni et al. (1981).

Exposure (4 h per day, 5 days per week, for 1 yr) mg/m ³ (ppm)	Rats	Number of ASL cases	Number of animals in group	BMD10 mg/m ³ (ppm)	BMDL10 mg/m ³ (ppm)	I _{conc} [mg/m ³] ⁻¹	HBC-OCRV [mg/m ³] ⁻¹	Exposure at risk of 4 per 1,000 mg/m ³	Exposure at risk of 4 per 100,000 mg/m ³
<i>Experiment BT1 (Maltoni)</i>									
0(0)	Sprague- Dawley/ M&F	0	58						
130 (50)	Sprague- Dawley/ M&F	1	60						
650 (250)	Sprague- Dawley/ M&F	3	59						
1,300 (500)	Sprague- Dawley/ M&F	6	60	1,255 (482)	778 (299)	1.95x10 ⁻³	3.79x10 ⁻⁴	10.55	0.11
<i>Experiment BT2 (Maltoni)</i>									
0 (0)	Sprague- Dawley/ M&F	0	185						
(260)100	Sprague- Dawley/ M&F	1	120						
390 (150)	Sprague- Dawley/ M&F	6	119						
520 (200)	Sprague- Dawley/ M&F	12	120	511(196)	471 (181)	4.51x10 ⁻³	8.8x10 ⁻⁴	4.54	0.05
<i>Experiment BT15(Maltoni)</i>									
0(0)	Sprague- Dawley/ M&F	0	120						
26 (10)	Sprague- Dawley/ M&F	1	119						
62,5(25)	Sprague- Dawley/ M&F	5	120	82(32)	68(26)	2.73x10 ⁻²	5.33x10 ⁻³	0.75	0.01

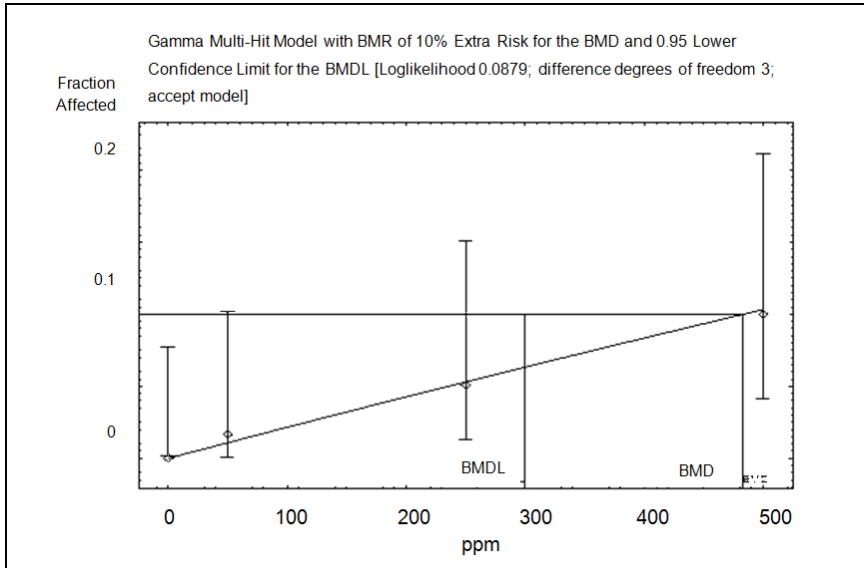


Figure 1 BMD analysis on data from experiment BT1 (0 - 50 - 250 - 500 ppm), Maltoni et al. (1981).

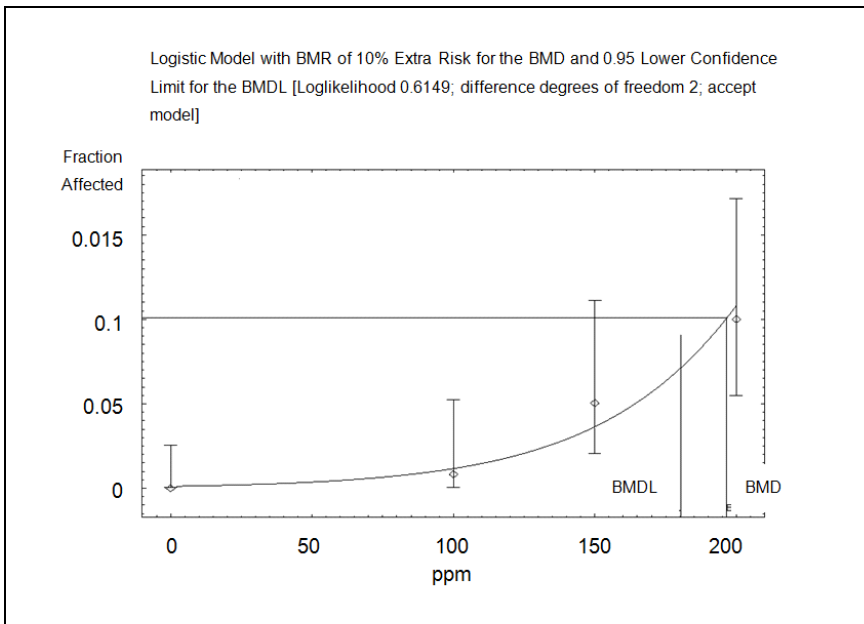


Figure 2 BMD analysis on data from experiment BT2 (0 - 100 - 150 - 200 ppm), Maltoni et al. (1981).

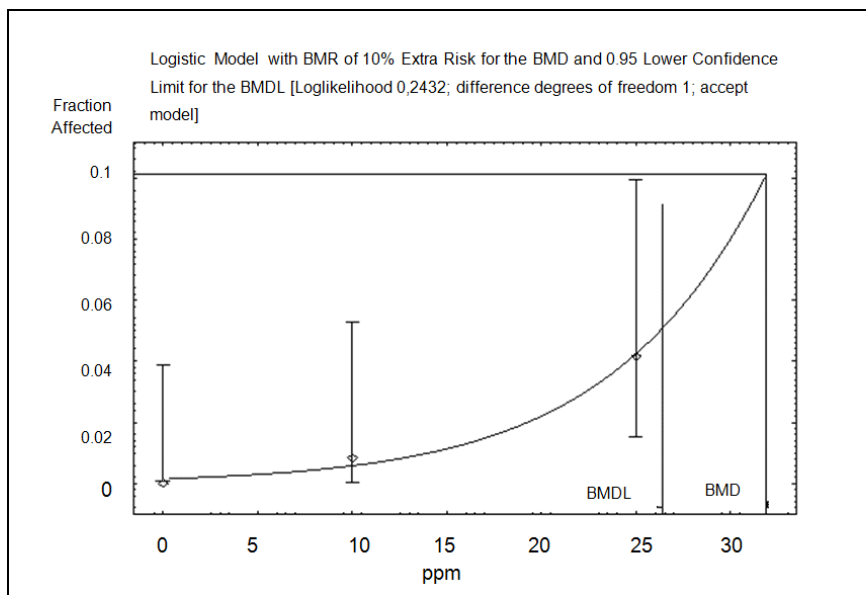


Figure 3 BMD analysis on data from experiment BT15 (0 - 10 - 25 ppm), Maltoni et al. (1981).

Health Council of the Netherlands

Advisory Reports

The Health Council's task is to advise ministers and parliament on issues in the field of public health. Most of the advisory opinions that the Council produces every year are prepared at the request of one of the ministers.

In addition, the Health Council issues unsolicited advice that has an 'alerting' function. In some cases, such an alerting report leads to a minister requesting further advice on the subject.

Areas of activity



Optimum healthcare
What is the optimum result of cure and care in view of the risks and opportunities?



Prevention
Which forms of prevention can help realise significant health benefits?



Healthy nutrition
Which foods promote good health and which carry certain health risks?



Environmental health
Which environmental influences could have a positive or negative effect on health?



Healthy working conditions
How can employees be protected against working conditions that could harm their health?



Innovation and the knowledge infrastructure
Before we can harvest knowledge in the field of healthcare, we first need to ensure that the right seeds are sown.

