Polyvinyl chloride (PVC)[1),2)] / chloroethene

MAK Value Documentation

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Abstract

The German Commission for the Investigation of Health Hazards of Chemicals in the Work Area has re-evaluated polyvinylchloride [9002-86-2] since a new maximum concentration at the workplace (MAK value) for poorly soluble dusts was established in 2011.
Polyvinylchloride (PVC) is a biopersistent granular dust. It is therefore classified in Carcinogen Category 4 and a MAK value of 0.3 mg/m³ × material density for the respirable dust is established in analogy to biopersistent granular dusts. This value is valid for PVC containing no additives and having a monomer content of < 1%. The classification is based on animal data that showed increased tumour incidences in rats exposed to biopersistent granular dusts in the high dose range. These tumours are regarded to be a consequence of the inflammatory mechanism of action, for which thresholds can be defined. Direct genotoxic effects appear to be of subordinate relevance for the carcinogenicity of biopersistent granular dusts. In analogy to biopersistent granular dusts, Peak Limitation Category II with an excursion factor of 8 was established for PVC. Since PVC is not distributed systemically and accumulates only locally in the lungs, no developmental effects due to this dust are expected to occur at the MAK value of 0.3 mg/m³ × material density. The assignment to Pregnancy Risk Group C is confirmed.

Keywords

polyvinyl chloride; PVC; chloroethene homopolymer; chloroethene polymer; chloroethylene homopolymer; chloroethylene polymer; vinylchloride homopolymer; vinylchloride polymer; mechanism of action; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; allergenic effects; reproductive toxicity; genotoxicity; carcinogenicity; peak limitation; prenatal toxicity; germ cell mutagenicity; absorption through the skin; sensitization; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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1) Additives must be evaluated separately.

2) Residual monomer content < 1 ppm.

Polyvinyl chloride (PVC)[1),2)]

[9002-86-2]

Supplement 2016

MAK value (2015)	**0.3 mg/m³ R (respirable fraction) × material density[3)]**
Peak limitation (2015)	**Category II, excursion factor 8**
Absorption through the skin	**–**
Sensitization	**–**
Carcinogenicity (2015)	**Category 4**
Prenatal toxicity (2008)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
Synonyms	chloroethene, homopolymer chloroethene, polymer chloroethylene, homopolymer chloroethylene, polymer PVC vinylchloride, homopolymer vinylchloride, polymer
Chemical name	polyvinyl chloride
Structural formula	$(–CH_2–CHCL–)_n$ n = 500–2000
Molecular formula	$(C_2H_3Cl)_n$
Molar mass	30 000 – 130 000 g/mol (technical-grade PVC)
Melting point	212 – 310 °C (Römpp 2013)
Density	1.4 g/cm³
Solubility	practically insoluble in water

1) Additives must be evaluated separately.

2) Residual monomer content < 1 ppm.

3) The effects of pure polyvinyl chloride (without additives, with a monomer content < 1 ppm) are based on the effects of biopersistent granular dusts (BGD). The value of 0.3 mg/m³ for the R fraction is valid for a material density of 1 g/cm³.

Since the documentation from 1985 (documentation "Polyvinyl chloride" 1991) and the supplement on prenatal toxicity from 2009 (supplement "Polyvinylchlorid" 2009, available in German only) several studies have been carried out, the results of which make a reassessment of polyvinyl chloride (PVC) necessary.

Production

As described in the documentation from 1985 (documentation "Polyvinyl chloride" 1991), petroleum, natural gas and sodium chloride are used in the production of PVC. Via the intermediate step naphta, ethylene is obtained from petroleum by thermal cleavage. Chlorine, on the other hand, is obtained electrochemically from sodium salt. The monomer building block vinyl chloride is produced from ethylene and chlorine in a ratio of 43% to 57%. Polymerization of the monomer can be carried out via three different procedures, in which the monomers first assemble into very small PVC primary particles and subsequently aggregate into larger secondary particles at a higher level of monomer conversion. In the case of monomer conversions between 75% and 90%, PVC polymerization is discontinued. The vinyl chloride not converted is removed by distillation and reduced to the permissible residue content by intensive degassing, for example < 1 ppm in PVC foils for food packaging. The three production procedures are: suspension polymerization (80% of the PVC production worldwide), emulsion polymerization (12% of the PVC production worldwide) and mass polymerization (8% of the PVC production worldwide) (Fischer et al. 2014). Depending on the production procedure employed, different additives are used directly during PVC production to initiate polymerization (initiators), to control granule size (protective colloids), to control the adsorption of plasticizers (protective colloids) and to regulate dispersion properties (emulsifiers). In the subsequent production and processing stages, plasticizers are added to the white, odourless powder (raw polymer). The latter make processing easier, and determine the properties of the product. Granular PVC is available in two different particle sizes with diameters of 100 to 180 μm and 0.1 to 3 μm. The porosity of the PVC particles is produced under controlled conditions and is important for further processing (Fischer et al. 2014).

Additives in the industrial production of PVC

PVC is used in a wide range of variants. The PVC variants need various additives in order to obtain the different properties required by the product, such as its morphology, flexibility, durability, surface texture and chemical properties. Several additives to which the workers in industrial PVC production can also be exposed are given below. In the production of PVC granules, however, these substances are used only in very small quantities (initiators: 0.03% to 0.08%, protective colloids: 0.05% to 0.15%) and are present only in minute traces in the final product as a result of the reactions during production of the PVC raw polymers and the subsequent purification (Fischer et al. 2014).

Additives in the production of the raw polymer

Initiators

In the suspension polymerization process, diacyl peroxides, peroxydicarbonates, alkyl peroxyesters and azo initiators such as azobisisobutyronitrile are commonly used.

In the emulsion polymerization process, usually ammonium or potassium peroxosulfates containing copper or iron are used (Fischer et al. 2014).

Protective colloids

To regulate the particle size of the granules and to enhance the adsorption capacity of plasticizers, polyvinyl alcohols and polyvinyl acetates are very commonly used in the suspension polymerization process (Fischer et al. 2014).

Emulsifiers

As emulsifiers in the emulsion polymerization process, sodium salts of alkyl sulfates, alkyl sulfonates, alkyl benzene sulfonates, dialkyl sulfosuccinates, alkyl ethoxy sulfates, fatty acids, alkylphenol ethoxylates and fatty acid ethoxylates are very commonly used (Fischer et al. 2014).

Additives for the further processing of the raw polymer

Softening agents

A distinction is made between two types of added plasticizers: a) internal plasticizers, whose molecules are to a slight extent covalently bound to the PVC macromolecule during copolymerization, such as vinyl acetate, maleic acid, ethylene, methyl vinyl ether, vinylidene chloride and acrylonitrile; b) external plasticizers, which react with the PVC macromolecules via intermolecular forces, such as certain phthalates and certain esters. As a result of the external plasticizers, the spaces between the macromolecules become larger, improving the flexibility of the material. The external plasticizers are not bound covalently and can slowly escape from the PVC by evaporation, migration or extraction. The plasticizer content can amount to as much as 70% (hard PVC: 0–12%; soft PVC: > 12%) (Römpp 2013).

Internal lubricants

To obtain specific slide and flow characteristics, polar and transparent substances, and those which have a tendency to exudate, such as fatty acid amides or polyesters, can be added to the PVC. The internal lubricants are added to the polymer melt during copolymerization to reduce the friction between the PVC molecular chains and the smelt viscosity. Subsequent processing steps are optimized as a result. In contrast, the mostly non-polar external lubricants, such as paraffins and

polyethylenes, act only on the surface and reduce adhesion between PVC and metal surfaces.

Plasticizers

These substances are added to the raw polymer to optimize the properties of the material during subsequent production steps (Fischer et al. 2014). They include heat and UV stabilizers, dyes, fillers, chemical foaming agents, antistatics, external lubricants, acid scavengers and flame retardants (Römpp 2013).

1 Toxic Effects and Mode of Action

PVC particles are taken up by inhalation and ingestion. Absorption through the skin is not known.

In the case of exposure to PVC at the workplace, it is difficult to estimate whether and to what extent exposure is to a mixture of substances. This can result from exposure to the additives cited above and to residual monomers and decomposition products.

PVC particles occur in the form of poorly soluble dusts, and lead to the general particle effects expected from biopersistent granular dusts. As with other inhaled poorly soluble dusts, these particles can accumulate in the lungs and lymph nodes and cause impairment of the clearance function of the lungs (see supplement "General threshold limit value for dust (R fraction) (Biopersistent granular dusts)" 2014).

PVC does not induce mutations in Salmonella typhimurium.

As PVC particles occur in the form of poorly soluble, granular, biopersistent dusts, particle-induced tumour formation is to be expected in rats at high exposure levels.

The epidemiological studies of the carcinogenicity of PVC are difficult to interpret as both the exposure data and the presence of additives were not recorded in detail.

There are no studies available for the sensitizing effects and developmental toxicity of PVC.

2 Mechanism of Action

See supplement "General threshold limit value for dust (R fraction) (Biopersistent granular dusts)" 2014.

3 Toxicokinetics and Metabolism

In two studies, groups of 14 female rats were exposed to polyvinyl chloride (diameter of primary particles 1.3 µm, aerodynamic diameter 1.3 µm, density 1.3 g/cm^3, no other details) in concentrations of 0, 3.3 ± 0.5, 8.3 ± 0.9 and 20.2 ± 1.8 mg/m^3 daily for 25 hours a week, for 7 and 8 months, respectively. The controls were ex-

posed to pure air. At the end of the exposure, the retained masses were 0.45 ± 0.10, 2.00 ± 0.16 and 6.22 ± 0.77 mg/lung (Muhle et al. 1990 a) and 0.56 ± 0.16, 2.09 ± 0.29 and 7.24 ± 1.10 mg/lung (Muhle et al. 1990 b) and the retained volumes were 0, 0.35, 1.53 and 4.78 µl/lung (Muhle et al. 1990 a) and 0, 0.43, 1.61 and 5.57 µl/lung (Muhle et al. 1990 b). The half-times for alveolar clearance, determined with the aid of ^{85}Sr-labelled polystyrene particles, were 57 days in the control group and 71, 122 and 184 days in the groups exposed to PVC, respectively (Muhle et al. 1990 a, b). Overloading of the lungs was already demonstrated at the low exposure concentration of 3.3 mg PVC/m^3. Lower exposure concentrations were not tested (Muhle et al. 1990 a). The alveolar clearance in the high PVC concentration group was slower by a factor of 3.3 than that in the low PVC concentration group. There was a dose-dependent increase in polymorphonuclear neutrophils in the bronchoalveolar lavage fluid (Muhle et al. 1990 b).

4 Effects in Humans

4.1 Single exposures

There are no data available.

4.2 Repeated exposure

In a study, the lung function parameters (FEV_1/FVC and $V_{max}75$) of 70 workers from a PVC production plant, and those of 48 control persons from a vegetable packing plant were determined. In addition, respiratory symptoms such as wheezing were determined by means of a questionnaire. The mean exposure concentration was 21 mg PVC/m^3 (no other details). Compared with the values in the control persons, the FEV_1/FVC and $V_{max}75$ values were considerably lower in the workers exposed to PVC. The numbers of complaints of shortness of breath and coughing were increased in this group (Ernst et al. 1988). In the authors' opinion, employment in PVC production appears to be associated with both obstructive and restrictive ventilatory effects.

In a longitudinal study, the lung function of workers from plants producing PVC, cement or asbestos was investigated by means of standardized questionnaires and spirometry. The geometric mean value of the total dust concentration in the PVC production unit was 3.3 ± 1.3 mg/m^3 (0.9–16.1 mg/m^3). In non-smokers working at this production plant, the decline in the FVC and FEV_1 accelerated slightly with the length of employment (Siracusa et al. 1988). It is not clear from the exposure data given whether the workers in the PVC production unit were exposed to PVC only.

In a plant producing PVC mixtures, 24 of 72 workers were exposed to high PVC concentrations while filling PVC granules and powder together with different additives into hoppers heated to around 135 °C. Another 24 workers were exposed to low PVC concentrations (workplace not described). As controls, 24 workers not

exposed to PVC were examined. Investigation of the persons included determination of the PEFR (peak expiratory flow rate) and spirometry, in addition to which a questionnaire had to be filled in. The mean respirable dust concentration in the air inhaled by the highly exposed workers was 1.6 mg PVC/m^3 (range: 0.2–2.9 mg PVC/m^3). In the workers exposed to low levels, the workplace concentration of the respirable fraction was 0.4 mg PVC/m^3 (range: 0.1–1.0 mg PVC/m^3). The mean diurnal variation in the PEFR of 6.5% in the highly exposed group was significantly higher than that in the low exposure group (4.8%, not statistically significant compared with the values for the control group) and in the control persons (4.3%). Some of the exposed workers (29% of the high exposure group, 4.2% of the low exposure group) complained of wheezing. The FEV_1 in the highly exposed persons was 10% below the predicted values, compared with 2% in the non-exposed controls (Lee et al. 1991). The authors conclude that occupational exposure to PVC dust can result in acute airway constriction.

In a cross-sectional study with 171 workers, the relationship between exposure to PVC and lung function was investigated. The control group consisted of 48 persons not exposed to PVC. The exposure concentration was between 0.06 and 2.90 mg PVC/m^3. The exposed workers were divided into two groups: those with cumulative exposures < 10 mg/m^3 × years were designated as the "low exposure group" and those with cumulative exposures > 10 mg/m^3 × years as the "high exposure group". The lung function was examined by spirometry and radiography of the thorax was carried out. A subjective estimate of respiratory function was determined by means of a questionnaire. The highly exposed group had a cumulative exposure of 18.0 mg PVC/m^3 × years (1.22 mg/m^3 × 14.7 years), the low exposure group of 2.9 mg/m^3 × years (0.39 mg/m^3 × 7.5 years). The workers were not exposed to vinyl chloride monomers or products from the thermal degradation of PVC, although they were exposed to calcium and barium compounds and to other additives. The highly exposed persons were found to have significantly lower FVC and FEV_1 values than expected, a higher prevalence of pulmonary opacities in the radiographic pictures, and they complained more frequently of respiratory distress. The authors reported that vinyl chloride monomer (VCM) could not be detected at the mixers and extruders (Ng et al. 1991).

In a study, in which 104 workers occupied in PVC production and 43 employees in the administration of the same production plant were investigated, the pulmonary effects following exposure to PVC were determined using HRCT (high resolution computed tomography) and a questionnaire. In 7 exposed workers, isolated pleural thickening without parenchymal involvement was present. Parenchymal lung changes were found in 49 workers and 13 administration employees. Round opacities, heterogeneous attenuation and ground-glass opacities in the lungs were found in the workers only. The questionnaire revealed a significant increase for coughing only. The findings from HRCT did not correlate with the symptoms. No details are available regarding exposure levels (Süyür et al. 2012).

Case reports

A patient who complained of daily coughing attacks and progressive dyspnoea had worked in a PVC production factory between 1974 and 1986, where he had been exposed to concentrations of 0.3 to 42 mg PVC/m^3 (particle size < 1 µm) and 0 to 3 ml vinyl chloride/m^3. Although the values obtained by spirometry were normal, the carbon monoxide transfer factor T_{LCO} and the Krogh factor K_{CO} were reduced (T_{LCO} 45%, K_{CO} 36% of the nominal value). Histological examination revealed an accumulation of macrophages and an increase in elastic and collagenous fibres. In the bronchoalveolar lavage fluid 82% of the cells were macrophages (Antti-Poika et al. 1986). These findings constitute a stress reaction and clearly indicate irritation of the lungs as a result of the effects of PVC particles.

Another case report described the simultaneous occurrence of pneumoconiosis and secondary systemic sclerosis in a 58-year old patient. He had smoked five cigarettes a day for 30 years and had been working in a plastic reutilization plant for the preceding 10 years. Data for the composition of the particular components in the air at the workplace and their concentrations are not available. Radiographic and computed tomographic examinations showed pneumoconiosis and scleroderma-like lesions in his lungs. Histological examination of a biopsy sample from the patient's skin revealed a picture similar to that of systemic sclerosis. Transbronchial biopsy showed a pronounced thickening of the alveolar walls. The authors suggested in their discussion that the dust-laden macrophages might stimulate fibroblasts in the lungs and the skin to produce excess collagen by releasing growth factors (Studnicka et al. 1995). The demonstration of scleroderma-like lesions suggests possible exposure to vinyl chloride (documentation "Vinyl chloride" 1993).

In July 1993, a mild restrictive lung disorder with lung function values at the lower limit of normal was found in a 35 year-old worker who had never smoked and also had no allergies. Since 1985 he had been working with fine PVC powder and had worn a simple face mask only. Using HRCT, nodular changes in the lungs were found. In June 1994, after the worker had not been exposed to PVC for 10 months, no symptoms of airway disease were detected (White and Ehrlich 1997).

4.3 Local effects on skin and mucous membranes

There are no data available.

4.4 Allergenic effects

There are no reports available for contact allergy to pure PVC. Several cases have been reported in which reactions to PVC products in the form of contact allergy or urticaria, in particular to gloves, occurred. In these, however, not the PVC itself, but probably the additives in it, for example plasticizers, stabilizers or preservatives, were responsible for the reaction. However, in some cases, the substances respon-

sible could not, or not clearly, be identified (Larsson et al. 2010; Park et al. 2008; Sasseville and Theriault 2012).

4.5 Reproductive and developmental toxicity

In the case–control studies of the reproductive and developmental toxicity described below, it is difficult to assess whether and to what extent exposure was to a mixture of substances.

In one case–control study, no increase in spontaneous abortions in female workers exposed to PVC in Finnish PVC production plants was found. As the study comprised only 13 workers exposed to PVC and was thus very small, only strong effects could have been evaluated as statistically significant. Also, no data for the exposure levels at the individual workplaces of the female PVC workers were given (Lindbohm et al. 1985).

In contrast to this, a case–control study revealed significantly increased risks for the combined end points stillbirth, malformation and low weight at birth (< 2 kg in the Swedish cohort, < 1.5 kg in the Norwegian cohort) of the children (odds ratio (OR): 2.2; 95% CI: 1.1–4.5) of women in Swedish and Norwegian PVC production units exposed to the substance (Ahlborg et al. 1987). From a group of 1397 and 288 pregnant women who worked in plastics processing companies in Sweden and Norway, respectively, 54 women were selected. An increased risk for the combined end points mentioned above was determined for women who had been exposed to vinyl chloride monomers during the processing of PVC. The OR for the processing of "non-heated" PVC (OR: 3.6; 95% CI: 1.4–8.7) was higher than that for the processing of "heated" PVC (OR: 1.5; 95% CI: 0.7–4.0). In the Swedish production plants, vinyl chloride concentrations of 0.5 to 2.5 mg/m^3 in the air were determined at the workplaces for injection moulding processes and during the processing of "cold" PVC. As a result of the vinyl chloride concentration determined and possible exposure to various additives such as phthalates, fillers, pigments, stabilizers and to other materials that are present in gaseous form at processing temperatures between 140 and 220 °C and that could have been inhaled, the findings cannot be clearly attributed to exclusive exposure to PVC. Data for lifestyle factors such as smoking and alcohol consumption, and data for the socioeconomic status of the workers were not given. These studies are therefore not suitable for the assessment of potential toxic effects of PVC on reproduction and development.

4.6 Genotoxicity

In a study, the peripheral lymphocytes of 52 workers in PVC production plants were analysed. A value of 6 mg PVC/m^3 was given (without further data) as the mean exposure concentration. Compared with the values for control persons, the frequency of cells with chromosomal aberrations was significantly increased in those exposed to PVC (6.1% compared with 2.45% in the control persons) (Suskov and Sazonova 1982). As the data for exposure are inadequate, and as exposure to

vinyl chloride monomer cannot be excluded, this study cannot be included in the evaluation of the genotoxic potential of PVC.

4.7 Carcinogenicity

4.7.1 Cohort studies

The updated mortality data for 1658 male workers employed in a production plant for petrochemicals in Italy between 1950 and 1985 were reanalysed using the Poisson regression. Relative risks (RR) were determined for the entire group of PVC workers who had been active in the areas of packing, production and autoclaving. Technicians and clerks from the same production plant served as a reference group. The relative risk was determined for all causes of death, death resulting from tumours and especially for mortality from lung tumours, lymphoid and haematopoietic tumours, brain tumours, liver tumours, liver cirrhosis and cardiovascular diseases. A significant increase in mortality from all causes of death was found for all workers (RR: 1.55; 95% CI: 1.03–2.35, 229 deaths), for PVC workers in packing (RR: 1.72; 95% CI: 1.04–2.83, 49 deaths) and for PVC workers in production (RR: 1.71; 95% CI: 1.09–2.67; 72 deaths), compared with the mortality in the control group. The relative risk for liver cancer was increased in autoclave workers (RR: 9.57; 95% CI: 3.71–24.68, 7 deaths). In PVC workers from packing, the number of cases with cardiovascular diseases was increased (RR: 2.25, 95% CI: 1.08–4.70, 12 deaths). The occurrence of liver cancer suggests exposure to vinyl chloride monomers (Gennaro et al. 2008).

In a multicentre study, cancer mortality was recorded in a total of 12 700 workers from 19 vinyl chloride production plants in four European countries (Italy, Norway, Sweden and Great Britain). In 11 production plants, the workers were exposed to a mixture of monomeric vinyl chloride and PVC (no exact data for PVC concentrations). In total, 2664 deaths (standardized mortality ratio (SMR): 0.85; 95% CI: 0.82–0.88) were recorded, including 883 deaths from malignant neoplasms (SMR: 0.99; 95% CI: 0.93–1.06). The SMR was 0.95 (95% CI: 0.84–1.07) for lung cancer, 2.40 (95% CI: 1.80–3.14) for liver cancer, 1.89 (0.69–4.11) for soft tissue neoplasms, 1.60 (0.90–2.65) for melanomas and 1.19 (0.78–1.75) for non-Hodgkin's lymphomas. The relative risks of dying from liver cancer or angiosarcomas were found to be related to the duration of employment and cumulative exposure (Ward et al. 2001). Such findings are to be expected after exposure to vinyl chloride monomers.

In a follow-up study, mortality was determined in 1501 workers from a PVC production plant. Calculations included the standardized mortality ratios for all causes of death, for non-malignant airway diseases, for lung cancer and for ischaemic heart diseases, and their 95% confidence intervals. The workers were mainly exposed to PVC, but also to other chemicals, such as vinyl chloride monomers, asbestos and lead. The mean duration of exposure to PVC was 12.1 years (0.1–32.4 years). The mortality ratio for all deaths in the workers was not increased when compared with the national and local mortality ratios. The results did not reveal any relationship between PVC exposure and non-malignant airway diseases, lung cancer and ischaemic heart diseases. An increased SMR for lung cancer in workers exposed to

PVC can also be attributed to smoking as a confounder, as all lung cancer cases occurred in smokers or ex-smokers. As no adjustment was made for smoking as a confounder, no statement can be made about the risk of developing lung cancer (Graham et al. 2006).

4.7.2 Case–control studies

In a case–control study, 148 patients (age: 30–75 years) with testicular cancer were compared with 315 control persons without cancer (Hardell et al. 1997; Ohlson and Hardell 2000). An increased risk of testicular cancer with an OR of 6.6 (95% CI: 1.4–32) was obtained for patients occupationally exposed to PVC. After excluding the cases of cryptorchidism and orchitis, the risk increased considerably (without cryptorchidism: OR: 14.0; 95% CI: 1.7–14; without orchitis: OR: 10; 95% CI: 1.2–87). From this study, no exact data for PVC exposure can be deduced, neither for exposure levels and duration nor for co-exposure to additives such as phthalates. Furthermore, the exposure data were obtained by means of a questionnaire.

In a case–control study carried out later, 791 patients with testicular cancer were matched with a control person without cancer. The data were obtained from the Swedish Cancer Register from between 1993 and 1997. The OR for all those exposed to PVC was 1.35 (95% CI: 1.06–1.71), increasing to 1.45 (95% CI: 1.06–1.98) after a 10-year latency period. However, no typical dose–response relationship was found, but, paradoxically, a higher OR for those in the lowest exposure category (Hardell et al. 2004).

In a further study, each of these 791 patients with testicular cancer was likewise matched with one control person, whereby 360 persons had been exposed occupationally to PVC for different periods. The workers exposed to PVC were subdivided into four groups; group 1: only indirect exposure (no details), group 2: low exposure, group 3: moderate exposure and group 4: high exposure in the production area (no details of PVC exposure concentration level). The OR for testicular cancer in all workers exposed to PVC was, according to two different exposure estimates, 1.1 (95% CI: 0.82–1.56; questionnaire) or 1.3 (95% CI: 1.05–1.69; exposure assessment by experts). As, however, the risk determined for the high exposure group was lower than that for the low exposure group, this analysis did not reveal a dose–response relationship between exposure to PVC and contracting testicular cancer (Westberg et al. 2005).

In a nested case–control study, 28 patients with pancreatic cancer from a cohort (number of persons in cohort unknown), who had worked in a plastics manufacturing facility for at least 7 months, were compared with 140 control persons without cancer. For workers who had been active in the processing of vinyl resins and polyethylene for more than 16 years, an RR of 7.15 (95% CI: 1.28–40.1) was determined. No relationship between the duration of work and the cancer risk was found when the duration of work was below 16 years. In the case of exposure for more than 16 years, however, the risk was significantly increased. As, in vinyl resin processing, exposure to PVC alone cannot be assumed, the carcinogenic potential of PVC cannot be evaluated on the basis of these findings (Selenkas et al. 1995).

In another nested case–control study, 38 patients with lung cancer from a cohort of 1658 vinyl chloride workers who had been exposed to vinyl chloride monomers as well as other substances were compared with 224 control persons without cancer. A 20% increase in the risk (OR: 1.20, 95% CI: 1.07–1.35) of contracting lung cancer was determined for each extra year of work as a PVC packer. Age and smoking status were taken into account in the study. However, no dose–response relationship could be established (Mastrangelo et al. 2003).

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Intratracheal instillation

In a study it was demonstrated that intratracheally instilled PVC (resin grade GEON-121, no other details) is eliminated mainly via the tracheobronchial lymph nodes. A group of 100 female rats were given intratracheal doses of PVC of 25 mg suspended in saline solution. The control animals were given saline solution only. The activities of acid phosphatase, β-glucuronidase, ribonuclease and deoxyribonuclease were determined in the tissue homogenates of tracheobronchial lymph nodes 30, 60, 120, 180, 270 and 375 days after instillation. The tracheobronchial lymph nodes were examined histopathologically. PVC-laden macrophages were found in the vicinity of dust agglomerates 270 days after instillation. The activities of all investigated enzymes were increased. However, a fibrotic reaction was not found (Agarwal et al. 1991).

Groups of 18 Wistar rats were given intratracheal doses of a PVC-E3 or PVC-W3 sample of 10 or 50 mg/kg body weight. The PVC-E3 sample contained 1% sodium lauryl sulfate and 0.04% anti-foaming agent. The PVC-W3 sample was obtained from PVC-E3 by washing four times with boiling methanol and subsequent drying at room temperature and at 40 °C. Over 92% of the additive to PVC-E3 was removed by this process. The animals were killed 2, 7, 28 or 90 days after instillation. The body weight gains were about the same in all animals. Analysis of the bronchoalveolar lavage fluid revealed in all treated animals increases in the lactate dehydrogenase activity, the protein concentrations and the total cell count on day 2. On day 90, there was no significant difference in the parameters between the controls and treated animals. Histopathological examination revealed thickening of the alveolar walls in the treated animals on day 2. No significant fibrosis could be found in these animals on day 90, however. There was no difference in the effects of these two samples (Xu et al. 2004 a).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

Groups of 10 female F344 rats (subgroup from the experiment carried out by Muhle et al. 1990 a; see Section 3 "Toxicokinetics and Metabolism") were exposed nose-only to 0, 3.2, 8 and 20 mg PVC/m^3 for 6 hours a day, on 5 days a week, for 7 months. The controls were exposed to pure air. The mean diameter of the PVC aerosol was 1.31 µm, its density was 1.3 g/cm^3. For comparison, rats were exposed to titanium dioxide and powdered iron in the same exposure concentrations. Histological examinations of the lungs from the rats exposed to PVC revealed the accumulation of particle-laden macrophages distributed throughout the entire lung. In addition, interstitial inflammation, slight proliferation of the connective tissue and lymphoid hyperplasia were found. These effects were more pronounced in the rats exposed to PVC (no quantification, no statistical evaluation) than in the animals exposed to titanium dioxide or powdered iron. The authors explained the somewhat more pronounced effects in the animals exposed to PVC as resulting from the higher number of PVC particles deposited at the same exposure concentration, as these have a lower density than titanium dioxide particles (Takenaka et al. 1987).

5.2.2 Intratracheal instillation

Wistar rats (number of animals not specified) were given intratracheal doses of PVC particles (PVC-E3 and PVC-W3) of 7 × 1.4 and 7 × 7.1 mg/kg body weight within 3 weeks. The PVC-W3 sample was prepared as described in Section 5.1 "Acute toxicity". The cumulative doses were 10 and 50 mg/kg body weight. The PVC-E3 sample contained 1% sodium lauryl sulfate and 0.04% of an anti-foaming agent. The rats were killed on day 28 and on day 90 after the first instillation. In all treated animals, analysis of the bronchoalveolar lavage fluid revealed an increase in neutrophils and macrophages, and on day 28, but not on day 90, in the lactate dehydrogenase activity. The CD4/CD8 ratio from the bronchoalveolar lavage determined using monoclonal antibodies was increased in all treated animals both on day 28 and on day 90. The CD4/CD8 ratio indicates the numerical relationship between the CD4 and CD8 lymphocyte subpopulations as well as the ratio of T helper cells to cytotoxic T suppressor cells. Histopathological examinations revealed mild inflammation of the lungs in all treated animals. These findings, in combination with the increased CD4/CD8 ratio, indicate beginning alveolitis, in which the activated $CD4^+$-T cells appear to play an important role. No significant difference was found between the effects of the two different samples (Xu et al. 2004 b).

5.3 Local effects on skin and mucous membranes

There are no data available.

5.4 Allergenic effects

There are no data available.

5.5 Reproductive and developmental toxicity

There are no data available.

5.6 Genotoxicity

PVC did not induce mutations in the Salmonella typhimurium strains TA97, TA98, TA100 and TA1535 in either the presence or absence of a metabolic activation system (Zeiger et al. 1988).

There are no other data available.

5.7 Carcinogenicity

After intraperitoneal injection of a high and (as a result of the low density of the PVC) voluminous dose of 5 × 100 mg PVC (PVC granules from Chemische Werke Hüls AG, particle diameter < 2.5 µm, no data regarding possible additives) a slight, significant increase in the number of tumours in female Wistar rats was found. The surviving animals were killed 2.5 years after the injection. The controls were given a sodium chloride solution. A total of 51 rats were treated, 102 animals served as controls. Most tumours were sarcomas in the abdominal cavity (no data for size and number per animal). Gross-pathological examination revealed tumours in the abdominal cavity in 5 of 51 of the treated rats and in 2 controls. As, however, a very high and voluminous dose was administered, no analytical data were given for the PVC used, and the findings were not based on histopathological examinations, the study cannot be used to assess the carcinogenic potential of PVC. The authors draw attention to the fact that the effects could also be a reaction to the foreign bodies (no other details; Pott et al. 1987).

6 Manifesto (MAK value/classification)

MAK value. Polyvinyl chloride particles (without additives, with a monomer content < 1 ppm) are poorly soluble dusts which act as a result of the general particle effect of biopersistent granular dusts. Therefore, a MAK value at the level of the general threshold value for dust of 0.3 mg/m^3 has been established for a material density of 1 g/cm^3. Multiplied by a PVC density of 1.4 g/cm^3, a value of 0.4 mg/m^3 is obtained. The threshold limit value applies for the respirable fraction (R), as only this fraction was investigated in the available studies. It must be noted that any

copolymers and additives are to be evaluated separately. Such additives can also modify the density of the PVC material.

Peak limitation. The critical effects are those on the lungs. Like other biopersistent granular dusts, PVC is therefore classified in Peak Limitation Category II. The clearance half-time of biopersistent granular dusts is about 400 days, for which reason an excursion factor of 8 has been established.

Prenatal toxicity. There are no studies available for the developmental toxicity of PVC in animals. Biopersistent granular dusts are not systemically available, and accumulate locally in the lungs. They produce adverse effects only in this organ. When the MAK value for biopersistent granular dusts of 0.3 mg/m^3 at a material density of 1 g/cm^3 is observed, which at a PVC material density of 1.4 g/cm^3 amounts to 0.4 mg/m^3, no embryotoxic and/or foetotoxic effects are to be expected. Classification in Pregnancy Risk Group C has therefore been retained.

Carcinogenicity. As the exposure was mainly to a mixture of substances and the exposure data were not described in detail, the available epidemiological studies are difficult to interpret.

The positive tumour finding after intraperitoneal injection into rats cannot be included in this evaluation because the methods used were outdated and a very high dose was administered. This tumour formation is probably attributable to a particle overload-related effect and is not substance-specific. As PVC is a poorly soluble biopersistent granular dust, particle overload-related tumour induction after inhalation is to be expected in rats. Inflammation in the alveolar or bronchial region accompanied by the release of reactive oxygen species is mainly responsible. The respirable fraction of PVC is therefore classified in Carcinogen Category 4, in analogy to other biopersistent granular dusts.

Germ cell mutagenicity. From the data available for genotoxicity, no germ cell mutagenicity is to be expected for PVC. PVC is therefore not classified in one of the categories for germ cell mutagens.

Absorption through the skin. Dermal absorption of PVC is not known. PVC is therefore not designated with an "H" (for substances which can be absorbed through the skin).

Sensitization. There is no evidence of sensitizing effects of pure PVC on the skin or airways. The substance is therefore not designated with "Sh" or with "Sa" (for substances which cause sensitization of the skin or airways).

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