DRAFT TLV DOCUMENTATION FOR POLYVINYL CHLORIDE (PVC) DUST

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February 4, 2002

PVC Dust

CAS Number 9002-86-2

Synonyms chloroethene polymer, ethylene chloro-polymer, chloroethene homopolymer, polychloroethylene, vinyl chloride polymer

Molecular formula $(C2\text{-}H\text{-}Cl)_n$

Structural formula $(-CH=CCl-)_n$

TLV-TWA To be determined

A4 - Not Classifiable as a Human Carcinogen

Summary

PVC dusts are particulates generated from PVC resin prior to compounding with other agents The size of the particulates, which determines its deposition, clearance, and ultimately its toxicity in the lung, is strongly dependent upon the polymerization process used during resin synthesis The majority of the PVC produced in the U S occurs by a suspension polymerization method which results in particle sizes that are generally too large to be respired Animal and epidemiology data indicate that the lung is the primary target organ affected by exposures to respirable dusts Prolonged exposures to high concentrations of PVC dusts can overwhelm the clearance mechanisms of the lung, resulting in a benign pneumoconiosis In this condition, PVC dust particles can be found in alveolar macrophages, and may be associated with small decrements in pulmonary function, an increased frequency of coughing or wheezing, and an increase in the prevalence of small opacities visible upon chest radiography

Chemical and Physical Properties

At room temperature, PVC is an odorless solid plastic that can be colorless to amber in color Chemical and physical properties for PVC dust are listed below (HSDB, 2001, Harris and Sarvadi, 1994)

Molecular weight 60,000-150,000 (average)
Melting Point 212-310 °C
Density 1 406
Refractive index 1 54
Solubility High molecular weight PVC soluble in cyclohexanone, methylcyclohexanone, dimethyl formamide, nitrobenzene, tetrahydrofuran, isophorone, mesityl oxide, low molecular weight PVC soluble in dipropyl ketone, methyl amyl ketone, methyl isobutyl ketone, acetonylacetone, methyl ethyl ketone, dioxane, methylene chloride
Decomposition products When heated to decompose, PVC can emit toxic fumes of hydrogen chloride and phosgene

One of the key properties that impacts its kinetics and toxicity of PVC dust is particle size The particle size distribution for PVC dusts differs greatly from one resin to another, and depends upon the polymerization process used to make PVC resin The two primary polymerization methods include (1) suspension polymerization, which accounts for approximately 96% of U S production, and (2) emulsion polymerization, which accounts for approximately 4% of U S production (VI, 2000) Resin particles generated by the suspension methods are generally large in diameter (50 to 200 um) (Harris and Sarvardi, 1994), and as such the majority are not considered to be respirable Resin particles generated by the emulsion method generally have a much smaller diameter (0 05 to 30 um) (Harris and Sarvardi, 1994), and are therefore more easily respired [VI ANY ADDITIONAL INFO ON PARTICLE SIZE DISTRIBUTIONS WOULD BE USEFUL, KEEP IN MIND 0 1 UM SERVES AS ACGIH'S REDLINE VALUE FOR ULTRAFINE PARTICLES IN THEIR PNOS GUIDELINE]

PVC dusts may contain one or more additives or impurities that may affect its toxicity For example, vinyl chloride monomer (VCM), a known human carcinogen, is present in PVC resin However, the levels of VCM contained in PVC resin has changed substantially over the past 30-40 years Prior to 1975, residual VCM levels of 1,000 to 2,000 ppm were commonly detected in PVC resin (Clayton, 1977, Burgess, 1982, USFDA, 1986) Efforts to reduce the levels of residual monomer by improved stripping techniques resulted in levels below 5 to 10 ppm in 1975-1976 A recent survey of four PVC resin types revealed residual VCM monomer concentrations ranging from 0 09 to 3 ppm, with arithmetic means ranging from 0 32 to 1 45 ppm (VI, 2000) PVC dusts may also contain one or more surfactants used to facilitate the polymerization process, such as sodium lauryl sulfate [VI ARE THERE OTHERS WE SHOULD CONSIDER SPECIFYING? SHOULD WE INCLUDE INFORMATION ON RESIDUAL LEVELS & HOW THEY HAVE CHANGED OVER TIME?] Some in vitro studies have suggested that extractable components (*i e* , surfactants) can contribute to the cytotoxicity of PVC dusts at relatively high concentrations (Richards et al 1975, Pigott and Ishmael, 1979) Regardless, it should be noted that the contributions to toxicity from either residual VCM or surfactants are intrinsically included in the toxicity and epidemiology studies that have evaluated PVC dusts In this way, PVC dusts may be viewed as a simple mixture

After synthesis, PVC resins may be shipped as pellets, powders, or liquid latex to other facilities where the PVC resin undergoes compounding with plasticizers, stabilizers, filling agents, flame retardants, biocides and/or pigments to modify the properties of the resin prior to forming a final product For this reason, compounded PVC may be viewed as a mixture that is considerably more complex than the original PVC resin The potential interactions of these agents on the toxicity of PVC dusts are not known For the purposes of documenting a TLV, the term "PVC dust" is defined here to refer specifically to dusts generated from PVC resin, prior to compounding Therefore, any TLV value derived for PVC dust is not necessarily protective of dusts generated from compounded PVC The need to assess individual additives within compounded PVC, by comparing concentrations to their individual TLV values, should be considered on a case by case basis

Major Uses

The annual production of PVC in North America has been estimated to be approximately 15 billion pounds, and has generally been increasing at a rate of 5 to 6% per year (Lewis, 1999) PVC resins are used in a wide variety of applications Major uses of PVC resin (as a percentage of North American consumption) include pipes and fittings (47%), siding (15%) windows and doors (9%), flexible film and sheeting (7%), wire and cable coverings (4%), rigid film and sheeting (3%), flooring (3%), bottles (1%), and miscellaneous products (11%) (VI, 2001)

Animal Studies

Acute

Information regarding the acute toxicity of PVC dust following inhalation exposure is limited, and suggest that the respiratory tract is the principal target of toxicity following exposure to high concentrations of dust In rats exposed to 50 to 60 mg/m^3 for one hour/day, for one to three days (geometric mean diameter = 1 2 um), some evidence of cellular proliferation was observed in the lungs (Srivastava et al 1980) This effect was resolved following a 30-day recovery period These results are in sharp contrast to the more severe effects (interstitial fibrosis and granulomatous lesions) which were observed in rats receiving the same delivered dose of PVC dust via intratracheal instillation (Agarwal et al 1978), suggesting that intratracheal instillation is not a suitable model for PVC dust delivery to the lung

Dermal application of PVC dust to rabbit ears, five days/week for two weeks, did not produce dermal lesions (Goh and Ho, 1988)

Subchronic

Limited information suggest that subchronic inhalation exposures to high concentrations PVC dusts are associated with effects on the lung Small lung lesions were observed in rats exposed to 10 mg/m^3 PVC dust for six hours/day, five days/week for 15 weeks (Richards et al 1981) The authors concluded that PVC

dust at this concentration was best characterized as a "nuisance" dust with weak biological activity

Chronic

Rats and guinea pigs exposed to PVC dusts (concentrations not specified) continuously for two to seven months at a facility where workers were exposed (Frongia et al 1974) developed lung lesions The response in exposed animals was characterized initially as an alveolar-lobular macrophagic reaction, more so in guinea pigs than rats, followed by the formation of granulomatous foci and septal thickening in the lungs

No indication of significant pulmonary disease was evident in rats exposed to 12 mg/m^3 PVC dust (average diameter = 0 15 um) for seven hours/day, five days/week for seven months (Wagner and Johnson 1981) However, a slight proliferation of reticulin fibers was observed, and PVC dust particles were found in macrophages

Several species (rat, guinea pig, monkey) were exposed to 13 mg/m^3 PVC dust (90% of particles with a diameter less than 1 5 um) 6 hours/day, five days/week for up to 22 months (Groth et al 1981) No fibrosis, cellular infiltration, or deficits in pulmonary function were observed in any species Aggregates of PVC dust particles were found in macrophages in all three species, but were more numerous in monkeys The authors concluded that PVC dust produces a benign pneumoconiosis under the conditions tested

Lung inflammation and hyperplasia were observed in some rats exposed to either 3 2, 8 0, or 20 mg/m^3 PVC dust (mean diameter = 1 31 um) five hours/day, five days/week for eight months (Takenaka et al 1981) The lack of specific information regarding the dose-dependency of the incidence or severity of these effects precludes defining a NOAEL or LOAEL value from this study

Genotoxicity Studies

No data were located regarding the potential genotoxicity of PVC dust

Reproductive Toxicity Studies

No data were located regarding the potential reproductive toxicity of PVC dust However, a few epidemiology studies have evaluated reproductive endpoint in PVC workers (see Human Studies below)

Pharmacokinetic/Metabolism Studies

In rats exposed to 50 to 60 mg/m^3 PVC dust (geometric mean diameter = 1 2 um) one hour/day, for one to three days, the authors noted that the lung retention rate was approximately 21 to 25 mg/hour (Srivastava et al 1980) PVC dust was present in the airways immediately following exposure However, the airspaces were free of dust following a 30-day recovery period Some infiltration of PVC dust into lymphatics and epithelial lining of the bronchioles was evident

The alveolar clearance of PVC dust (median diameter = 1 3 um) was found to be increased over control rats (halftime=57 days) in a concentration-dependent manner in rats exposed to 3 3, 8 33, or 20 2 mg/m^3, 25 hours/week for seven months (Muhle et al 1990) Halftimes of 71, 122, and 184 days were reported for the low, medium, and high concentration groups, respectively The authors attributed the impairment of alveolar clearance to dust overload In an analysis of these data, Yu and Rappaport (1996) were able to describe the clearance of PVC dust from rat lung in terms of Michaelis-Menten kinetics with a maximum rate of clearance (kmax) of 0 0089 day^{-1} and a lung burden at which the clearance rate is equal to one half of its maximum value ($M_{1/2}$)of 2 9 mg/lung

Human Studies

A number of epidemiology studies are available for workers exposed to PVC dusts Like many epidemiology studies, interpretation of the results is limited due to the presence of confounders, lack of information on exposure, particularly historical exposures, and small sample size For the few studies in which exposure information is presented, the concentrations generally reflect levels present at the time of study, and do not necessarily reflect historical exposure levels For this reason it is difficult to attribute any of the effects observed to the reported concentrations Collectively the epidemiology studies suggest that prolonged exposures to PVC dusts at high

concentrations are associated with effects on the lung, including decrements in pulmonary function radiographic opacities, and subjective symptoms

Subjective symptoms (complaints of wheezing) were increased and pulmonary function parameters were lower in 70 Canadian PVC wire and plastic wrapping workers exposed to 8-hour TWA concentrations of up to 21 mg/m^3 when compared to 48 controls (Ernst et al 1988) The authors suggested that there may be two different pulmonary reactions associated with exposure, including an obstructive and a restrictive defect

At a facility in Singapore, pulmonary function parameters (forced expiratory volume, FEV, forced vital capacity, FVC) were lower, while radiological opacities and subjective symptoms (wheezing, chest tightness) were more frequent in 171 PVC compounding workers exposed to 0 2-1 55 mg/m^3 PVC dust when compared to 48 controls (Ng et al 1991)

No difference in lung function was reported between 104 PVC coated fabrics and wall coverings workers exposed to 0 2-11 5 mg/m^3 PVC dust when compared to 112 workers exposed to non-chlorinated solvents in the United Kingdom (Chivers et al 1980)

Twenty cases of pneumoconiosis were identified in a health survey of more than 1,216 Italian PVC production workers with exposures estimated to exceed 10 mg/m^3 for at least five years (Mastrangelo et al , 1981)

Subjective symptoms (complaints of wheezing) were more frequent and pulmonary function parameters (FEV) were decreased in 24 PVC compounding mixers (mean exposure = 1 6 mg/m^3) but were not significantly changed in 24 non-mixers (mean = 0 4 mg/m^3) when compared to 24 controls (Lee et al 1991)

Decrements in pulmonary function (FEV, FVC) were associated with PVC dust levels (mean shift levels up to 2 88 mg/m^3), after adjusting for age, height, and smoking habit, in 818 workers at a PVC manufacturing plant (Soutar *et al* , 1980)

Decreases in pulmonary function (forced expiratory flow at 75% of FVC, FEF75) were associated with duration of exposure in 81 U S PVC resin workers (Gamble et al 1976) The authors estimated the rate of diminishing pulmonary function due to PVC exposure to be approximately 1% per year, after adjusting for age, height, and smoking

Duration of employment was associated with decrements in cross-shift lung function in 133 U S vinyl sheeting and wall covering production workers compared to 41 controls (Baser et al 1985)

A significant increase in the prevalence of chest X-ray abnormalities was associated with duration of exposure to PVC dust (concentrations not determined) in U S production plant workers (Lilis et al 1976, 1977)

The prevalence of pulmonary function impairment (decreased maximum mid-expiratory flow, forced expiratory flow) was correlated with duration of exposure in a health survey of 354 U S PVC polymerization workers, regardless of smoking status (Miller et al 1975)

Decrements in pulmonary function (FVC, FEV) were associated with duration of exposure, after adjusting for height, smoking, and age (Siracusa *et al* , 1988)

With respect to reproductive endpoints, an increased odds ratio for spontaneous abortion (95% CI = 1 0-5 1) was observed in Swedish women working in the PVC plastics industry (Ahlborg *et al* , 1987) Conversely, no increased risk of spontaneous abortions was found in Finnish women workers who process polymerized plastics (Lindbohm *et al* , 1985)

A large number of cancer mortality studies have been conducted on PVC production workers, but have generally been focused on exposures to VCM rather than PVC dust For this reason, these studies are not summarized here, but are included in the TLV documentation for VCM (ACGIH, 1997) Relative risk of breast cancer mortality was not significantly increased in female workers from 17 PVC fabrication factories (Chiazze and Ference 1981)

TLV Recommendation

[TO BE DETERMINED]

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TLV Recommendation

The quantitative data available for PVC dusts, including epidemiological and toxicological studies, from which a TLV could be derived are extremely limited Epidemiology studies, while providing suggestive evidence of pulmonary function changes, radiographical abnormalities, and subjective symptoms, generally do not provide adequate information regarding exposures to provide an adequate characterization of an exposure-response relationship Two animal studies which serve as potential candidates for deriving a TLV include (1) a study in rats, guinea pigs, and monkeys that identifies a chronic LOEL of 13 mg/m^3 for benign pneumoconiosis without change in pulmonary function (Groth et al 1981), and (2) a study in rats that reports a concentration dependent increase in lung inflammation and hyperplasia following chronic exposure to 3 2-20 mg/m^3 (Takenaka et al 1987) The strengths of the former study include its use of primates as one of the test species, thereby making the results potentially of greater relevance to human exposures The primary weakness of this study, however, is that only a single test concentration of PVC dust was examined The strengths of the latter study include the testing of three dust concentrations and the availability of kinetic information in a companion study (Muhle et al 1990), which could be used to assess the importance of lung burden and clearance in toxicity [VI WE HAVE ORDERED A FEW STUDIES CITED IN MUHLE ET AL , WHICH MIGHT CONTAIN ADDITIONAL TOXICITY DATA WE EXPECT TO RECEIVE SHORTLY IF ADDITIONAL TOXICITY DATA FOR THE TAKENAKA STUDY ARE AVAILABLE, IT COULD IMPACT TLV RECOMMENDATION] The critical weaknesses of this study, however, include the lack of specific information regarding the incidence and/or severity of the lung effects observed at each concentration, and the difficulties encountered when attempting to extrapolate information from rats, whose respiratory tract and breathing patterns (obligate nose breathers) are fundamentally different from humans In our opinion, neither of these studies are well suited for deriving a TLV

A tentative TLV value could be derived from the results of Groth et al (1981), however, confidence in the value would be considered low The LOEL value of 13 mg/m^3, when divided by an uncertainty factor of 3 (3 for LOEL to NOAEL extrapolation, 1 for interspecies extrapolation), could be used to support a TLV of 4 3 mg/m^3 An uncertainty factor of 3 for LOEL to NOAEL extrapolation is justifiable since no decrease in pulmonary function was reported in the exposed animals (Groth et al 1981) An uncertainty factor of 1 is considered to be appropriate for interspecies extrapolation since the architecture of the respiratory tract and breathing patterns (ability to mouth breathe) in monkeys is similar to that for humans For this reason, depositional processes for PVC dusts are expected to be similar between the two species However, differences may exist between non-human

primates and humans with respect to clearance rates A potential indicator of relative clearance between mammalian species can be made by comparing the relative volume occupied by macrophages in the alveolar region Macrophages comprise approximately 2 3% of the lung cell population in non-human primates (baboon), compared to 9 4% of the lung cell population in humans, indicating a 4-fold difference in favor of humans (CRC, 1995) Furthermore, the average volume of lung macrophage in humans is approximately 2 5 times higher than the corresponding volume in non-human primates (2,492 versus 1,059 um^3) (CRC, 1995) Together, these two factors suggest that when compared to non-human primates, pulmonary clearance of dust is expected to be greater in humans by a factor of approximately 10 (4x2 5) In this case, application of an uncertainty factor of 1 for interspecies extrapolation can be considered conservative However, at least one review of lung clearance data across species has suggested that particle overloading might occur at lower concentrations in humans than other species (Kreyling et al , 1990) [VI WE HAVE ORDERED THIS REFERENCE, WHICH IS CITED ACGIH PNOS DOCUMENTATION, SINCE IT COULD IMPACT THE TLV RECOMMENDATION] Under this alternative assumption, an uncertainty factor for interspecies extrapolation greater than 1would need to be considered

Currently ACGIH recommends a TLV of 10 mg/m^3 for inhalable particulates and 3 mg/m^3 for respirable particulates not otherwise specified (PNOS) (ACGIH, 2001) These TLV values are considered to be protective of "*toxicity caused by physical overloading of the normal clearance mechanisms of the respiratory tract*" (ACGIH, 1997) As such, use of these TLV values for exposures to PVC dusts is considered to be appropriate, and is supported by the tentative value of 4 3 mg/m^3 derived above from the data of Groth et al (1981)

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