DR-0114-1986 VINYL CHLORIDE REPT K

TOX FILE NUMBER: K-001711 REVISED: 01/19/90
CAS NUMBER 0000075-01-4
SYNONYMS CHLOROETHENE
VCM
MONOCHLOROETHYLENE

COMPOSITION AND PROPERTIES

NOTE ABOUT MATERIAL:
APPEARANCE: COLORLESS GAS
VAPOR PRESSURE: 2544.4 mm Hg @ 20C
2963.8 mm Hg @ 25C
ODOR DESCRIPTION: sweet, ethereal (threshold varies greatly)
EXPOSURE GUIDELINES:
Vinyl chloride: ACGIH TLV is 5 ppm, A1; OSHA PEL is 1 ppm TWA, 5 ppm excursion limit averaged over any period not exceeding 15 minutes.

COMMENTS

ACUTE ORAL EFFECTS

Under room temperature conditions VCM is a gas so the likelihood of ingestion is essentially nil.

SKIN EFFECTS

If the liquid (under pressure) were to contact skin a frost-bite type burn could result (R-1). Skin absorption unlikely since material is a gas at room temperature.

EYE EFFECTS

If the liquid under pressure were to contact the eye severe injury to the cornea and soft tissues might result (R-1).

ACUTE INHALATION EFFECTS

Early animal experiments were limited to short-term exposures to VCM vapors varying between 50,000 and 400,000 ppm (R-2, R-3, R-4, R-5, R-6, R-7, R-8). In mice, rats, guinea pigs, rabbits and dogs anesthesia, deep narcosis, cardiac arrhythmias and lethal effects were observed in this range of exposure but no relevant organ pathology was noted except for congestive and hemorrhagic changes in lungs, liver and kidneys on fatal events. 2-hour

LC50's are reported as follows: 113,000 ppm in mice, 150,000 in rats, 230,000 ppm in guinea pigs, and 113,000 in rabbits (R-32). The primary acute physiological effect of VCM is depression of the central nervous system which begins to occur at concentrations of 8,000-10,000 ppm in humans (R-7). Two cases of accidental industrial fatalities have been reported (Danziger in R-7). There have been suggestions of a delayed carcinogenic response following massive acute exposures (R-9).

SUBCHRONIC EFFECTS

Torkelson et al (R-10) conducted repeated exposure studies on animals for 7 hrs/day, 5 days/week for 4.5 to 6 months. At 500 ppm rats showed increased liver weights and histopahtology. At 100 and 200 ppm rats showed increased liver weights but no changes were observed in dogs and guinea pigs. All species tolerated 50 ppm for 6 months with no observed adverse effects. Repeated exposures for 1 hr/day at 100 and 200 ppm showed no observable ffects. Liver effects that were observed in this study were mild and apparently reversible since they were not observed in rats kept 6-8 weeks after the 6 month exposures ceased. See CHRONIC section also.

CHRONIC EFFECTS/CARCINOGENICITY

Early pioneer work was conducted by Viola et al (R-11) who exposed rats to 30,000 ppm VCM 4 hrs/day, 5 days/week for a full year. Histopathological examination revealed lesions similar to human acroosteolysis and nontumorous liver disease observed in PVC (polyvinyl chloride) workers 3 yrs later (R-12). Viola was also first to report carcinogenicity in animals (10th Int. Conc. Congress in Houston, Texas, May 1970). In 1970 Maltoni executed a series of studies designed to evaluate the effects of VCM exposure as affected by experimental factors such as route of administration, dose level, length of treatment, species, sex, strain and age of animals. These studies and those of many other investigators produced a wide variety of tumors, particularly at high concentrations. In a summary paper Maltoni states that liver angiosarcoma, carcinoma of the Zymbal glands, nephroblastoma, neuroblastoma, mammary adenocarcinoma, forestomach papilloma and acanthoma, extrahepatic angiosarcoma and hepatoma in the rat were correlated with exposure to vinyl chloride (R-13). Angiosarcomas were observed at 10 ppm by inhalation and 0.3 mg/kg by gavage, but none of the above tumors were seen at lower doses by either route of administration. There appeared to be marked differences between strains and species of animals with mice being more susceptible than rats which are more susceptible than hamsters. Regarding angiosarcomas of the liver, all species appear more susceptible than man. It's of interest that in 1975 Maltoni and Lefemine (R-14) reported a potential transplacental carcinogenic effect suggested by the development of subcutaneous agiosarcomas in the offspring of breeding animals exposed for 7 days during pregnancy (R-15). By far the most significant toxicological property of VCM is that of carcinogenicity. There appears to be no question that angiosarcoma of the liver has resulted from excessive vapor exposure to VCM in industry primarily while cleaning reactor vessels. Angiosarcomas in

humans are consistent with the results of animal studies in which these tumors have been produced in various species in several independent studies. However, epidemiological evidence is inconsistent from one study to another regarding other cancers and chronic toxic effects such as liver injury, splenomegaly, blood changes, respiratory injury, etc. Effects most consistently reported in workmen exposed to VCM vapors industrially are: acroosteolysis, scleroderma, Raynauds syndrome or phenomenon, and angiosarcoma of the liver. VC is an A1/R45 material (confirmed human carcinogen) under MAK and in Austria, an R45 material (may cause cancer) in Norway and Sweden under EEC and a 2R/S103 material (restricted in use) in Finland. A citation relative to cancers other than angiosarcomas concerns melanoma in PVC workers (R-35). A Russian epidemiology study reported an increase in a number of tumors in workers employed in VC and PVC operations, but no cases of angiosarcoma were found (R-36). Doll, in a review article, concluded that angiosarcoma of the liver is the only d finite cause for increased mortality among VC workers (R-37).

TERATOGENIC EFFECTS

VCM appears not to be teratogenic in laboratory animals. John et al (R-16) exposed mice, rats and rabbits to 500 ppm VCM 7 hrs daily during organ ogenesis. Mice were also exposed to 50 ppm and rats and rabbits to 2500 ppm. Maternal toxicity was observed mostly in mice, but the exposur produced no significant embryonal or fetal toxicity or teratological effects. Ungvary et al (R-17) exposed pregnant rats continuously to 1500 ppm during first, second or third trimesters of pregnancy with no t ratogenic effects. Exposure during the 1st trimester only resulted in fetal mortality and other fetotoxic effects, but no teratology. Epidemiological studies have reported increases in congenital malformations in areas where vinyl chloride polymerization plants were located, but evaluation of the data did not show a cause-effect relationship (R-39,41).

REPRODUCTIVE EFFECTS

A study of wives of VCM-exposed workers reported an increase in miscarriages (R-38). However, inadequacies in the methodology prevent the determination of a cause-effect relationship (R-39).

MUTAGENICITY

Several studies have been conducted that demonstrate a mutagenic r sponse to VCM or its metabolites in bacterial and yeast systems. Point mutations due to base pair substitution have been produced in various strains of S. Typhimurium by VCM in the presence of animal and human liver microsomes as a system of metabolic activation (R-18,19,20,21,22). Mutagenicity of VCM metabolites has also been demonstrated in yeast strains (R-23,24,25) and in mammalian cells (R-26). In agreement with a number of other studies, Purchase, et.al. (R-27) reported that 57 workers occupationally exposed to vinyl chloride had an increase in the incidence of chromosomal

abnormalities in their lymphocytes by comparison with 24 control workers. Since that time (July 1974) threshold limit values for vinyl chloride and plant exposure levels have been reduced. In a study by Anderson et al (R-28), 2 further samples from the same population of workers have been analyzed for chromosomal aberrations 18 and 42 months after the initial sampling. At 18 months, 21 VCM workers and off-site controls were investigated as were 23 workers on 8 on-site controls at 42 months. In the second sampling there was a tendency to an increase in chromosomal abnormalities of VC-exposed workers except in those people who had changed occupation. By the third sampling, however, there was a decrease by comparison with previous samplings and the levels of abnormalities had returned to values similar to those of the controls. Thus, reduction in exposure to vinyl chloride is accompanied by a reduction in the chromosomal abnormalities to levels indistinguishable from those of controls. Levels of VC as high as 30,000 ppm in the inspired air produced no dominant lethal mutations in mice, indicating that chromosomal changes in humans would not reach the germ cells.(R-27) Mutagenic risk to humans, especially r garding exposure to males, has been reviewed, but no conclusions could be drawn.

PHARMACOKINETICS/METABOLISM

Numerous studies indicate that probably a reactive metabolite, not vinyl chloride per se, is responsible for its toxicity. Although some inhaled vinyl chloride is excreted unchanged, depending on the dose, a varying amount is metabolized. The metabolism of vinyl chloride has been the subject of numerous recent studies which need confirmation and interpretation. Currently it is thought that vinyl chloride is metabolized by epoxidation with subsequent production of chloroacetaldehyde. Further oxidation and conjugation with glutathione are responsible for the metabolites found in urine. Gehring et al. analyzed the metabolic and carcinogenic data from man and laboratory animals. Using several models to predict the incidence in man from animal data, they found that all models overpredicted unless corrections were made for rates of metabolism and for surface area of the different species (R-33).

OTHER EFFECTS

NOTES

Numerous bibliographics and literature surveys are available including those by von Oettingen (R-27); Warren et al (R-30); NCI (R-31); IARC (R-32). Cancer label according to OSHA standard.

REFERENCES

R-1 Torkelson, T. R., et al. Am. Ind. Hyg. Assoc. J. 22():354 (1961).
R-2 Patty, F. A. et al (1930). V. Vinyl Chloride. Public Health Dep.

45: 1963-1971.
R-3 Peoples, A. S., Leake, C. O. (1933). J. Pharmacol. Exp. Ther. 48:284.
R-4 Schaumann, O. (1934). Med. Chem. (Leverkusen Ger) 2:139-147.
R-5 Oster, R. R., et al, Anesthesiology 8:359-361.
R-6 Carr, J. et al. (1949). J. Pharmacol. Exp. Ther. 97:1.
R-7 Mastromatteo, E. et al (1960). Am. Ind. Hyg. Assoc. J. 5:394-398.
R-8 Sester, D. et al (1963). Am. Ind. Hyg. Assoc. J. 24:265-275.
R-9 Maltoni, C., Ambio. 4, 18 (1975).
R-10 Torkelson, T. R., et al., Am. Ind. Hyg. Assoc. J. (22) 354 (1961).
R-11 Viola, P. L., (1970), Int. Cancer Congr. Abst. 29.
R-12 Marsteller, H. J., Dtsch Med Wochenschr 98:2311-2314.
R-13 Maltoni, C., Proc. Club de Cancerogenese Chim, Paris, Nov. 10, 1979.
R-14 Maltoni, C., Lefemine, G. (1975), Ann. N. Y. Acad Sci, 246:195-218.
R-15 Gricuite, L., (1979), IARC Sci Publ 22:3-11.
R-16 John, J. A. et al (1977). Toxicol. Appl. Pharmacol. 39, 497.
R-17 Ungvary, G. (1978). Toxicology 11:45-54.
R-18 Rannug, V. et al., 1974. Ambio 3/5:194-197.
R-19 Bartsch, H. et al., 1975, Nature 255:641-643
R-20 McCann et al. 1975, Natl. Acad. Sci. 72:3190-3193.
R-21 Malavielle et al. 1975, Biochem, Biophysics Res. Commun. 63:363-370.
R-22 Gano et al., 1976, Mutat. Res. 38:81-88.
R-23 Loprieno et al, (1976) Mutat. Res. 40:85-96.
R-24 Loprieno, et al. (1977), Cancer Res 36:253-257.
R-25 Shahin, M. M. (1976), Mutat. Res. 40:269-272.
R-26 Hubmermon, E. (1975), Int. J. Cancer 16:639-644.
R-27 Purchase, I.F.H., et al (1978), Mutat. Res. 57:325-334.
R-28 Anderson, D. et al., (1980). Mutat. Res. 79:151-162.
R-29 von Oetlingen (1955). U. S. Publ. Health Serv. Publ. No. 414.
R-30 Warren, J. E., et al. (1978). Oak Ridge Natl. Library ORNL/TIRC 78/3, Nov.
R-31 National Cancer Institute, Publ. No. 78-1599 (1978).
R-32 IARC (1978), Vol 19, Lym, France.
R-33 Patty, Vol. 2B, 3540-3541.
R-34 Patty, Vol. 2B, 3537-3442.
R-35 Heldaas, S.S., etal, Brit.J.Ind.Med., 44, 278-280, 1987.
R-36 Smulevich. et al., Brit. J. Ind. Med. 45, 93-97, 1988. In K-1711-100.
R-37 Doll, Scand. J. Work Environ Health 14, 61, 1988.
R-38 Infante et al., Lancet, Apr. 3, p. 734, 1976.
R-39 Vinyl Chloride and Human Reproduction, Review by Brian MacMahon, Aug. 11, 1977. In K-1711-100.
R-40 Uzych, Human Toxicology 7, 517, 1988.
R-41 Rosenman et al., Arch. Environ. Hlth 44, 279, 1989.

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