



TECHNICAL INFORMATION

POTENTIAL EFFECTS OF VINYL CHLORIDE ON HUMAN OFFSPRING

Associations
CMA
Vinyl Chloride Panel

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SUMMARY

Vinyl chloride monomer (VCM) is one of the most intensely studied chemicals that is used in industry today. Although it is a known human and animal carcinogen, many other alleged health concerns are not supported by animal or human data. Early or preliminary studies of offspring by some investigators have suggested that VCM causes birth defects and miscarriages. However, critical peer review and subsequent research have shown that there is no basis for such fears.

What we do know from decades of research on VCM is that studies with pregnant animals have shown that VCM can undergo placental transfer and, at high levels, cause cancer in their offspring. Other animal studies have indicated that VCM does not produce any mutations in subsequent generations.

Furthermore, numerous animal and human studies have shown that VCM does not cause birth defects or reproductive effects. While some human studies have claimed that VCM causes birth defects and miscarriages, close examination by numerous experts have found these early reports to be seriously flawed and not supportive of an effect.

Transplacental Carcinogenicity

The carcinogenic potential of VCM is well recognized. Many studies have shown that it causes cancer in a number of different animal species and conditions (Viola et al., 1971; Maltoni and Mehlman, 1984; Keplinger et al., 1975). The fact that VCM causes angiosarcoma in man is evidenced by numerous studies (Creech and Johnson, 1974; Delorme and Theriault, 1978; Fox and Collier, 1977; Noria et al., 1976). Studies by Maltoni (1974) and Maltoni and Mehlman (1984) also have shown that VCM is transplacental carcinogen. When pregnant rats were exposed to high levels of VCM, an increased incidence of cancer was observed in the offspring.

Animal Studies of Developmental and Reproductive Effects

The exposure of males and/or females to toxic chemicals prior to or following conception may provide an opportunity for

deleterious effects to occur. Because VCM has been found to cause mutation in some non-reproductive cells (Bartsch et al., 1976); McCann et al., 1975; Rannug, 1974; Drevon and Kuroki, 1979; Basler and Rohrborn, 1980), studies have been conducted to determine whether VCM can cause mutations in germ cells (egg, sperm) that could effect viability or produce body anomalies.

In 1976, Anderson et al. examined VC mutagenicity in fertile male mice using the Dominant Lethal Assay. These investigations exposed mice to VC for 6 hours per day for 5 days in concentrations of 3,000, 10,000 and 30,000 ppm. To assure that their test system was functional, this study employed two known mutagens as positive controls (cyclophosphamide and ethyl methane sulphonate). No mutagenic effects were observed with VCM at any stage of spermatogenesis while dominant lethal effects were observed with the positive controls.

This early work of Anderson et al. (1976) was later confirmed by Himeno et al. (1983) in a dominant lethal study using two different exposure conditions. One group of CD-1 mice was exposed for four hours per day during five consecutive days to 10,000 ppm of VC, and the second group of mice was exposed four hours per day, five days per week over a 10 week period to 5,000 ppm VC. Again, no dominant lethal mutations were observed following VC exposure.

Using another approach, Peter and Ungvary (1980) studied the germinal mutation potential of VCM in the mammalian spot test. Following the mating of inbred females with rotated-bred males, they exposed groups of females on the 10th day of pregnancy to 0 or 4,600 ppm of VCM for 5 hours or to cyclophosphamide, the positive control. Cyclophosphamide caused a significant increase in the number of white or colored spots, while VCM did not cause an increase in color spots. Also, there was no effect on litter size at birth or at the end of the 3-5 week observation period. The authors concluded that although gene mutation had been reported in fruit flies exposed to VCM, there is no evidence that VCM causes mutations in mammals.

Other studies have focused on the potential effects of maternally inhaled VCM on embryonal and fetal development. In studies by John et al. (1977 and 1981) groups of rats and rabbits were exposed to 0, 50, 500 or 2,500 ppm VC for 7 hours per day during the critical development phase (organogenesis) for each species (days 6 to 15 for mice/rats and days 6 to 18 for rabbits). Additional groups of pregnant females were simultaneously exposed to VCM (2,500 ppm for rats and rabbits and 50 and 500 ppm for mice) plus 15% ethanol in their drinking water over the same period. Ethanol, a known reproductive toxin, was used because it is known to block the primary metabolic pathway for VCM. Although high levels of VCM caused

frank maternal toxicity, no significant embryonal toxicity, fetal toxicity or teratogenic effects were observed. Greater maternal embryonal and fetal toxicity but not teratogenic effects were observed following exposure to ethanol and VCM. Because of the limited control data which was provided, it could not be determined whether this increase in toxic response was largely due to ethanol alone or the inhibition of VCM metabolism (detoxification) of VCM. However, these studies have further underscored the concerns associated with ethanol consumption during pregnancy.

Ugvary et al. (1978) also carried out a detailed study in rats of the potential of VCM to cause birth defects. In their initial experiments, they exposed females on the 18th day of pregnancy to either 2,000, 7,000 or 12,000 ppm VCM for 2.5 hours. Analyses of the maternal blood, amniotic fluid, and fetal tissue demonstrated that VCM could be transferred across the placental barrier from the mother to the fetus. In subsequent experiments they exposed females to 1,500 ppm VCM 24 hours per day over three different periods of their pregnancy and looked for fetal effects. No birth defects occurred as the result of VCM exposure. Fetal toxicity was evident in only one of the three groups.

All of these studies cited above are remarkable in two ways. First, the exposure levels used in these experiments are for the most part several orders of magnitude above levels of VCM in the workplace and many orders of magnitude above that in the community. Such exposure would only be encountered under rare, catastrophic situations and would likely be short-lived relative to these studies. Secondly, even though the females were exposed to very high levels of VCM, the evidence indicates that VCM does not cause dominant lethal mutations or birth defects. Furthermore, these data indicate that the levels of VCM in the workplace and the ambient air are not of concern to the mother, embryo or developing fetus.

Human Studies of Mutagenic, Developmental and Reproductive Effects

Numerous studies of human populations have been conducted to evaluate the potential of VCM to cause birth defects or other reproductive effects. The studies in humans have been carried out with workers employed in polyvinyl chloride (PVC) production or fabrication facilities, and other studies have examined communities in which a PVC production or fabrication facility is located. In contrast to the well controlled conditions of the animal studies in the laboratory, these human studies have had to contend with many confounding factors such as smoking, alcohol, maternal age, maternal infections, lack of exposure information, etc. The ability or inability of the author to deal with these variables has frequently affected the utility of the study and the validity of the authors' conclusions. Many of these problems have been encountered in studies of the effects of VCM on human reproductive outcome.

One of the earliest studies of the potential of VCM to influence human reproductive outcome was conducted by Infante et al. (1976a). Fetal loss among wives of VCM exposed workers was studied by interviewing husbands employed in VCM polymerization and PVC fabrication facilities in Ohio. No interviews were conducted with wives and no maternal age information was obtained. Among the workers potentially exposed to VCM, fetal loss was observed to be 15.8% compared to 8.8% among the unexposed controls. This effect was observed in men younger than 30 years old.

The above study by Infante et al. (1976a) has been reviewed by a number of investigators and has been found to be inadequate and misleading (Stallones, 1987; Clemmensen, 1982; Haas and Schottenfeld, 1979). This credibility and validity of the conclusions from this survey have been imposed by the absence of maternal interviews and information on maternal age, smoking or alcohol consumption and inappropriate statistical treatment of the data. Furthermore, it was presumed that all workers had a significant exposure to VCM.

In addition to the above problems, Paddle (1977) asked for clarification of the age adjustment procedure used by Infante et al. (1976a). The response given by Infante et al. (1976b) tried to explain the age adjustment procedure, but the response also revealed that there were four different age-based categories in the original study. The alleged effect upon fetal loss could only be detected in the 25-29 year old age group. Such a specific response is hard to explain on any basis since one normally expects the overall incidence in fetal defects to increase with increasing observation for the presumed effect in the 25-29 year age group by pointing out that the fetal loss in the unexposed group was substantially lower than for any other age group within the unexposed population. The conclusion of Stallones was that the study was seriously flawed by the lack of internal consistency, and the study should be discarded on that basis alone.

A recent study was conducted by Lindbohm et al. (1985) which examined spontaneous abortions among women employed in the plastics industry. The study was conducted in Finland during the years of 1973 to 1980 on workers who belonged to the Union of Chemical Workers, and whose potential exposure were to a variety of plastics materials including VC, styrenes, butadienes, acrylonitriles, and polyurethanes. Cases were selected from women who had been union members during their first trimester of pregnancy, and selections were done so that a given case was primarily exposed to only one type of plastic or monomer. Controls were selected from women not having a spontaneous abortion. Exposure (yes or no only, no quantitation) was determined by having the physicians who treated a given patient fill out a questionnaire.

When the data from Lindbohm et al. (1985) was examined, no difference in the rate of spontaneous abortions could be determined between the case and control populations for women working with PVC or PVC thermal degradation products. Although the number of women in the study was low, the statistical power of this study was sufficient to detect a two-fold increase in fetal wastage. Therefore, this study indicated that there was no association between VCM exposure and the occurrence of spontaneous abortion.

In addition to these studies of workers, a number of investigators have examined the occurrence of birth defects in communities surrounding plants which use VCM to make PVC. Infante (1976) has published a study of birth defects in a number of communities in Ohio which contained PVC production facilities. He has reported that the rate of birth defects in the communities producing PVC was greater than in neighboring communities that did not produce PVC.

One obvious problem with this Infante study was the total lack of any quantitative exposure data as in his previous study. Besides the lack of exposure data, no effort was made to correlate the rate of defects with distance from production facilities. If the defects were correlated with VC exposure, then one might expect a greater frequency of birth defects closer to the production sites with lower frequencies away from a given facility. When Edmonds (1976) examined the Infante data as frequency of defects vs. distance from a given facility, he could find no difference between the exposed and unexposed populations, and that observation weakens any putative link between observed birth defects and VC exposure.

Bias is a major concern in the Infante (1976) study because of the way he examined and combined populations for analysis. There are three communities in the study which contained PVC plants, and those cities are Painesville, Ashtabula, and Avon Lake. For comparison communities without PVC plants, 10 cities were chosen for their proximity to the exposed communities. Of the 10 control communities, two of them (Geneva and North Ridgeville) had higher malformation rates than the exposed communities containing PVC facilities. Since North Ridgeville was proximate to Avon Lake, according to Infante, the North Ridgeville data were combined with data from Painesville, Ashtabula, and Avon Lake even though it did not contain any VC operations within its boundary. This combination of data made a more striking difference between the exposed and unexposed groups whereas the difference would have been diminished if North Ridgeville was properly placed with the unexposed data. This gerrymandering in the case of North Ridgeville is of particular concern since it is 10 miles from the nearest plant and since its southwest location is not in the line of typical prevailing winds.

Another point to examine in the Infante study is the question of the CNS defects compared to the control population. Edmonds' (1976) examination of the data could not find an association between VC exposure and reported CNS defects. Edmonds also believes that localized increases can occur sporadically, but these localized increases do not always signal a potential problem. Moreover, Oakley (1981) examined CNS defects nationwide as part of an ongoing activity of the Center for Disease Control (CDC). Oakley found that the frequency of CNS defects has been decreasing in all regions of the country at a steady rate, and the decrease has been occurring since the 1930's.

Since CNS defects were a major concern of the Infante study, Edmonds et al. (1978) examined the presumed relationship of this defect to VC exposure in offspring of Hanawha County, West Virginia residents. In contrast to Infante et al. (1976a) and Infante (1976), Edmonds examined geographic distribution of CNS malformations in relationship to the PVC plant and attempted to quantitate ambient VC levels in the community. When Edmonds examined the malformation rates from matched pairs of exposed and unexposed residents, he could find no correlation with distance from the plant site. He did find some suggestive patterns in which more exposed were northeast and more unexposed south of the plant, but the correlation did not remain when wind and particulate deposition patterns were examined. VC was measured in the community after one large release, and levels of 0.1 to 0.2 ppm VC were found in grab samples to the northeast of the plant site. He was also able to determine emission data during his study period (1970-1974). He found that the rate of CNS malformations was declining during the study period, and the decline in CNS defects preceded the decrease in VCM emissions from the plant sites by about nine months. Edmonds concluded from his study that he could not find any correlation between any wind-borne pollutants and the incidence of CNS defects in Kanawha County, West Virginia.

Theriault et al. (1981 and 1983) also examined the presumed relationship of community VC exposure and the appearance of a variety of birth defects. Their study was conducted in Shawinigan, Canada during the period of 1966 to 1979. In addition to examining the geographic distribution of defects and attempting to quantitate ambient VC levels in the air like Edmonds et al. (1978), this study also examined the seasonal variations in VC levels and malformation rates.

Geographic distribution of malformation rates were examined in Shawinigan and comparison communities by using school district boundaries. The rate of defects was constant for each school district in Shawinigan as well as the comparison areas, and the ratio of observed to expected defects was always close to one (1). The ratio of observed to expected defects was approximately one (1) for the school district with the PVC plant as well. Further comparisons were made between school districts

with high and low VC levels, and no correlation could be found between the exposed and unexposed groups for CNS or any of the other malformations. One group, however, did show an increase in malformation rates, but it was located furthest from the plant and would have had the lowest degree of exposure. Consequently, no association was found between the geographic distribution of malformations and VCM exposure.

Although Theriault et al. (1983) reported that seasonal variations in birth defects corresponded with variations in atmospheric concentration, they concluded that a causal association between VCM and birth defects was not supportable. VCM concentration did not correlate with the distribution of birth defects and malformation rates were not high near the plant or in areas where VCM levels were the highest. Furthermore, districts with the highest rates were farthest from the plant.

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