VINYL CHLORIDE AND BIRTH DEFECTS

In the late summer of 1974, a researcher in Ohio reported that vinyl chloride gas might be contributing to a higher than normal incidence of birth defects among children born in communities where such gas is produced or where it is used in the manufacture of polyvinyl chloride resin. In early 1976, an excess of stillbirths and miscarriages among the wives of heavily exposed vinyl chloride workers also was reported. Much misinformation and misunderstanding has resulted from these two reports. The purpose of this paper is to put forth the facts and to set the record straight.

This paper documents three key points:

- Research conducted in Ohio purporting to show a relationship between vinyl chloride emissions and an excess of birth defects has been roundly criticized by experts in the field and has been refuted by a series of studies conducted by the Federal Center for Disease Control.
- According to experts from Harvard University and the University of Texas, the single study alleging an excess of stillbirths and miscarriages among the wives of heavily exposed vinyl chloride workers is "inadequate," "misleading" and essentially "worthless."
- Two separate animal studies found that even at extremely high levels of exposure, vinyl chloride did not produce mutagenic or teratogenic effects in the test animals even though it has been found to be capable of producing a mutagenic reaction in salmonella bacteria.

Background

In January 1974 three cases of angiosarcoma, an extremely rare type of liver cancer, were discovered among long-term workers exposed to high concentrations of vinyl chloride monomer (VCM), the gaseous industrial chemical used to produce polyvinyl chloride (PVC) resin. Ultimately, over a period of 16 years, 23 deaths were confirmed in four U.S. plants, and approximately 48 in other countries. The workers' jobs principally involved cleaning residue of PVC resin from the polymerization reactors in which it was produced from VCM.

As a result of these findings, the U.S. Occupational Safety and Health Administration in 1974 announced standards to drastically reduce worker exposure to vinyl chloride. In 1976 the Environmental Protection Agency issued regulations limiting emissions of VCM into the atmosphere around vinyl chloride and PVC resin plants. The Food and Drug Administration currently is considering regulations on the use of PVC food and beverage packaging materials.

Because of these regulations and through industry efforts, VCM exposures in the workplace have been reduced a hundred-fold or more in the past four years. Emissions into the atmosphere have been decreased by over 90 percent. Similarly, new and better PVC packaging materials have been developed to eliminate the possible migration of residual vinyl chloride from the PVC into finished food and beverage products.

Additional Research Conducted

As a consequence of the angiosarcoma discovery, a wide range of scientific research projects have been undertaken or expanded in the past few years to investigate further the possible health effects of vinyl chloride exposure. Among other findings of this research, VCM was shown to be capable of producing a mutagenic reaction in salmonella bacteria; and an increase in chromosomal breakage was found in a small number of heavily exposed PVC polymerization workers although, in another study, no chromosomal changes were seen in workers exposed at lower levels. Because of these findings, concern was raised that VCM might also cause malformations or birth defects in humans.

Study of Ohio VCM Plant Towns Undertaken

To investigate this supposition, Dr. Peter F. Infante, then of the Ohio Department of Health, examined the birth records of children born between 1970 and 1973 in three towns in northern Ohio -- Painesville, Avon Lake and Ashtabula -- that contained vinyl chloride polymerization plants.

In a preliminary report released in August 1974 and in a paper subsequently published in 1976, Dr. Infante reported that the rate of birth defects, based on hospital records, in each of the thre Ohio towns was significantly higher than the average for both the state of Ohio and for the balance of the three counties in which the towns were located.

Dr. Infante further reported a major excess in birth defects of the central nervous system (CNS), which he considered to be "the greatest cause for concern," and also in adult deaths from CNS cancer.

These reports attracted wide press attention and speculation, even though Dr. Infante, in his Academy of Sciences paper, had warned:

> "These preliminary findings do not link polyvinyl chloride production facilities with the increased occurrence of congenital malformations and CNS tumors in adults, but indicate the need for further study of possible contributing factors."

While the press totally ignored this statement, a careful analysis of the data contained in the report lends credence to the reservations expressed in the paper's conclusion. In addition, serious questions as to the quality of the research and the value of the findings of the study have been raised by two eminent scientists -- Dr. Brian MacMahon, chairman of the department of epidemiology, Harvard University Graduate School of Public Health, and Dr. Thomas D. Downs, professor of biometry, University of Texas Health Science Center. The two scientists were engaged by The Society of the Plastics Industry to conduct independent critical reviews of all known literature relating to vinyl chloride and birth defects.

For comparison purposes, the Infante study examined the birth defects rates in nine communities without PVC facilities, but which were located in the same general geographical area as the three plant towns. Two of them were found to have birth defects rates higher than any of the communities with PVC facilities.

Not only was this discrepancy unexplained, but the report also combined cases of CNS malformations from one of these two communities -- North Ridgeville -- with those from the three plant towns in developing the basic statistics. This unusual procedure was explained in the report by stating that North Ridgeville was "proximate" to one of the plant towns. In reality, the two are nearly 10 miles apart -- approximately twice the distance that the Environmental Protection Agency has determined, through extensive air monitoring, as the maximum that vinyl chloride gas can travel through the air before decomposing into other, non-toxic, materials.

The inclusion of North Ridgeville data in the Infante study is both misleading and inappropriate. Dr. MacMahon, in his critique of the study, called the addition "completely unjustified." Dr. Downs said "in our judgment the inclusion...is reprehensible."

In addition, if one examines the data from the four towns separately, rather than in combination, the fact emerges that while one of the plant towns -- Painesville -- did have over half of the observed CNS birth defects, the non-VCM town had 25 percent of the total. Another of the plant towns -- Avon Lake -- which has had a VCM facility in its midst for the longest period of time of all three communities, had no CNS defects at all.

Nearly the same situation applied in the case of CNS cancers among adults. The report, once again, added cases from North Ridgeville to the three plant towns. When examined separately, only Painesville and North Ridgeville, which has no VCM facility, showed an excess of adult CNS cancer deaths. The other two VCM plant towns showed no excess.

When the hard data from the three VCM plant towns and North Ridgeville are examined individually, more unexplained differences than similarities in CNS malformation and adult cancer rates emerge. The procedure of "combining" data from three widely separate communities -- Painesville is located about 30 miles to the west of Ashtabula and Avon Lake lies another 50 miles west of Painesville -- plus a town without a VCM facility, effectively obscured these significant differences.

The sources Infante used for information on birth defects are routine reports of birth. Dr. MacMahon points out in his critique that birth certificates are "a notoriously poor source of information on congenital malformations." He states that the rate for the state of Ohio as a whole suggests that only about half the medically significant malformations are being reported.

Equally as important as the manner in which the data was compiled and presented is the fact that no attempt was made to determine whether any of the mothers involved (or their husbands) had ever been exposed to vinyl chloride, either by working in one of the VCM plants or by living in close proximity to them. Nor were any measurements made to determine if there was any vinyl chloride at all in the ambient air in these communities. Furthermore, interviews were not conducted of any of the subjects to determine, for example, if there was a history of birth defects in the family or if the mothers might have been exposed during pregnancy to some other toxic substance. Also, no attempt was made to compare the current birth defects rate with those existing before the VCM facilities were constructed.

Dr. MacMahon in his critique states that while Infante focuses attention on the central nervous system defects because of their unusual severity, 13 of the 17 categories examined are in excess and several such as oral clefts and club foot are in substantial excess. Since known teratogenic agents in humans and experimental animals produce specific malformations, it is unlikely that any agent would produce the variety of malformations found in excess in these cities, Dr. MacMahon says. A more likely explanation, he states, is some artifact, such as reporting differentials, that would apply to all categories of malformation.

Dr. MacMahon cites numerous shortcomings in the Infante research and sums up his critique by stating: "I am fairly well convinced that the finding results from a combination of chance, reporting differentials and epidemiologic gerrymandering." Dr. Downs, also highly critical of the research procedures, concluded his review with the comment: "It does not seem possible to salvage anything from this study."

Birth Defects Questions Studied by CDC

Because of the questions raised by Dr. Infante's Ohio study and the publicity that his results were receiving, the Center for Disease Control (CDC) of the U.S. Department of Health, Education and Welfare undertook an investigation of the possible relationship between vinyl chloride exposure and birth defects in humans.

The results of this investigation were published in the July 19, 1975, issue of Morbidity and Mortality, an official CDC weekly publication. In the first section of the two-part study, a comparison of birth defect rates in hospitals in two widely separated cities with VCM installations -- one in Pottstown, Pennsylvania, the other in Painesville, Ohio (which was included in Dr. Infante's study) -- showed no rate increase in the Pennsylvania community as compared with the state average. The CDC investigation did find an increase in CNS malformations in Painesville, similar to that reported by Dr. Infante.

The second part of the CDC study involved a thorough investigation of the 15 cases of CNS malformation recorded at the Painesville Hospital from 1970-1974. For each malformation case, two normal births were investigated as "controls" for comparison purposes. The results of this research, which covered a number of factors not included in Dr. Infante's study, can be summarized as follows:

- None of the interviewed parents of the children with CNS birth defects ever worked at either of the two VCM polymerization plants in Painesville (one set of parents could not be located, but records show they did not work at the plant at the time of their infant's birth).
- In the "control" group, two of the fathers of "normal" children were working at one of the VCM plants at the time of their infants' births.

Neither of the parents in either group lived within two miles of either of the two plants.

A statistical analysis of the actual distances between the two VCM plants and both residences and workplaces of the parents of "cases" and "controls" showed no difference between either group.

The CDC concluded, on the basis of its own investigations and a thorough analysis of the existing research data, that while the possibility could not be ruled out that VCM might be teratogenic (capable of causing malformations), the evidence to date did "not establish any association between (birth defect) cases and vinyl chloride exposure."

The results and conclusions of the CDC investigation were also published for professional scrutiny in the November 29, 1975, issue of The Lancet, a prestigious British medical journal.

Dr. MacMahon concluded that it is not the presence of the two PVC plants that is responsible for the high malformation rate in Painesville. The most likely explanation, he said, seems to be "random fluctuation."

Second CDC Investigation Undertaken

Despite the publishing of the CDC research, some individuals continued to refer to Dr. Infante's study as the definitive, and indeed the only, investigation into the possibility of vinyl chloride induced birth defects. Dr. Infante, in defense of his own work, argued that there were several methodological errors in the CDC study that could account for its negative findings.

In order to settle the question once and for all, CDC decided to undertake a second, even more definitive investigation. The methodology for the study was modified to take into account Dr. Infante's objections. Charleston, West Virginia, where a vinyl chloride plant had been located since 1938, was selected as the study site. The investigation began in February 1976 and the results submitted in report form to the Director of CDC by the Cancer and Birth Defects Division of the Center's Bureau of Epidemiology on July 26, 1976.

Study Finds "No Relationship"

As in the earlier study in Painesville, Ohio, researchers contacted the parents of all children born with CNS defects in Kanawha County (Charleston and suburbs) from 1970 to 1974. A "control" group, consisting of the parents of "normal" children born in the same hospital immediately before or after a child with a CNS defect, were also interviewed. Air pollution, prevailing wind and other data were also collected.

The results of this investigation can be summarized as follows:

- Except for 1974 (the last year included in the study), rates of CNS birth defects in Kanawha County were higher than total U.S. rates.
- Five "case" parents out of 41 (those with children born with CNS defects) and no "control" parents reported a family history of CNS defects.

- Two "case" fathers and two "control" fathers were employed in the VCM plant at the time their children were conceived. Three additional "control" fathers had worked in the plant on a contract basis for a short time and therefore also had possible exposures.
- No mothers in either group had ever worked at the plant.
- Using sophisticated analytical techniques, no significant differences were found between the two groups as to their places of residence in relation to the plant at the time of their infants' conception.

The study noted, however, that of the nine "case" parents and ten "controls" who lived within three miles of the plant, most of the "case" parents tended to live east of the plant, while most of the "control" group lived south of the plant.

Because of this curious case "cluster," CDC said it "gave particular attention to the possibility that the cluster may have been caused by increased VCM emissions." While winds in the Charleston area are highly variable, the West Virginia Air Pollution Control Commission reported that suspended particulate matter, a good indicator of wind direction, was heavier in the southwest, thus "suggesting a prevailing wind from the northeast," i.e., away from the "cluster" and the plant.

Furthermore, if the case "cluster" was the result of VCM plant emissions, CDC theorized that "one would also expect an approximate correlation between a decrease in atmospheric VCM levels and a fall in CNS defect rates." According to the report, no such correlation was found.

The report concluded: "The investigation did not reveal an association between the case clustering within three miles of the plant and exposure to VCM or other chemicals."

In its summary of the entire study, CDC concluded that "no relationship between infants with malformations and parents' exposure to vinyl chloride could be established."

The CDC's conclusion was strongly supported by Dr. Downs. After a comprehensive review of the data in the CDC study, he said: "Our conclusion, therefore, is that the available scientific evidence does not indicate any association between vinyl chloride and community birth defects."

No Link in Canadians' VCM Study

In October, 1977, Dr. Gilles P. Theriault, Chairman of the Department of Social and Preventative Medicine at Laval University in Quebec, reported at the annual meeting of the American Public Health Associatic on a preliminary study comparing birth defect rates in two widely separated industrial communities in Quebec. One community -- Shawinigan -- contained a polyvinyl chloride production (PVC) facility. The other community -- Drummondville -- did not have such a plant. The two industrial communities of approximately equal population are more than 50 miles apart.

In his report, Dr. Theriault noted an apparently higher rate of birth defects in Shawinigan, the city with the PVC plant. He pointed out, however, that while the industry in Drummondville is primarily textile, in Shawinigan there is "an aluminum refinery plant, a carbide plant, a chemical factory and a pulp and paper mill."

Referring to the presence of other atmospheric pollutants in the environment of Shawinigan, Dr. Theriault said, "The present study does not permit linking the observed phenomenon to a particular pollutant, be it vinyl chloride or any other teratogenical agent."

To arrive at his conclusion that a higher overall rate of birth defects existed in Shawinigan, Dr. Theriault combined all types of birth defects. But as Dr. MacMahon has pointed out in a review of a variety of birth defect studies, "the known teratogenic agents in humans and experimental animals have considerable specificity in the malformations they produce." Therefore, Dr. MacMahon concluded it would be "unlikely" that any one pollutant would be responsible for the full range of birth defects reported in studies similar to Dr. Theriault's. A more likely explanation is that some artifact is responsible -- such as reporting differentials -- that would apply to all categories of malformations, he said.

Dr. Downs, who also undertook an independent review of birth defect research, also stated that the pattern of birth defects in the Theriault study is consistent with known incidences of the various malformations. If a single teratogen were involved, he concluded, one type of birth defect would most likely be greatly increased, rather than the slight increase observed for most of the deformities on the list.

Even Dr. Theriault found the increase in birth defects in the same order of magnitude in several organ systems "puzzling." The explanation, he said, could be that the chemical (vinyl chloride) in the Shawinigan environment produces by itself or in combination with other air pollutants a broad spectrum of developmental effects.

Or, he said, the apparent influence between Shawinigan and Drummondville can result from an artifact such as ignoring defects diagnosed after hospital discharge, different diagnosis or different reporting criteria used in the seven hospitals contacted.

Dr. Theriault appears to be in agreement with other scientists who have raised serious questions on the significance of the data obtained in this most recent study. In the conclusion of his report, he acknowledges that "further studies are needed to assert that vinyl chloride causes birth defects in the community living near a polymerization plant."

Vinyl Chloride and Fetal Deaths

In early February, 1976, Ralph Nader's Health Research Group released to the press the text of a study scheduled to be printed in the April 3, 1976 issue of The Lancet. The study by Dr. Infante et al., was conducted at a single PVC resin plant in Pennsylvania. It purported to show that the wives of workers exposed to heavy concentrations of VCM had a statistically significant increase in the number of stillbirths and miscarriages compared to the wives of workers exposed to little or no VCM.

While the research results certainly merit further investigation, there are a number of factors in the study that have raised some doubts concerning the sweeping conclusions that have been reached from the research.

For example, the number of families participating in the study -- only 62 in the "exposed" group -- is quite small. Second, the wives themselves were not interviewed by the researchers, nor were their ages at the time of conception obtained. All data in the study was based solely on the "recall" of the husbands. Similarly, hospital or other medical records were not checked, nor was any attempt made to contact the wives' doctors for their possibly valuable input.

Even more importantly, there is no indication in the report that any attempt was made to correlate fetal death rates with either length or degree of exposure. This is especially vital in light of the fact that the husbands in the "exposed" group who were 30 years of age and older (and who presumably had the greatest accumulated exposure), did not report an excess of fetal deaths when compared to those 30 and older in the "control" group.

In addition, when women with chronic stillbirth and miscarriage problems were eliminated from the study (standard procedure in research of this type), the difference in fetal death rates between the "exposed" and "control" groups was not reported as statistically significant by the authors.

Both Dr. MacMahon and Dr. Downs, after separate reviews of the study, were highly critical of the analytical methods used. Dr. Downs said that the "misleading conclusions" drawn by the authors were brought about through the "selection and use of their control group." Dr. MacMahon called the data "worthless," the analysis "naive" and the test "inadequate and misleading." "In short," he said, "this paper is strewn with evidence of carelessness and incompetence and deserves, in my opinion, no consideration whatsoever in weighing the

question of whether there is or is not a genetic risk associated with exposure to VCM."

Animal Studies Show No Teratogenic Effects From VCM

In 1977, J.A. John, et al., conducted animal studies on rats, mice and rabbits to determine the effects on fetal development when the subjects inhaled vinyl chloride. Groups of mice were exposed to 50 ppm and rats and rabbits were subjected to 2,500 ppm of vinyl chloride. In the summary of their report, which was published in Toxicology and Applied Pharmacology, the authors said, "While maternal toxicity was observed, vinyl chloride alone did not cause significant embryonal or fetal toxicity and was not teratogenic in any of the species at the concentrations tested."

Two years earlier in 1975, I. Purchase, et al., carried out an animal study in England on the chromosomal effects from inhalation of vinyl chloride. Fifteen male mice were exposed to VCM levels of 30,000, 3,000 and 1,000 ppm of vinyl chloride for six hours a day for five consecutive days. Examinations were carried out after each male was mated with a female. In their report, which was published in the August 1975 The Lancet, the authors said: "There was no significant increase in the number of early deaths per implantation compared with the control group exposed to air alone, indicating that VCM does not produce dominant lethal mutations in mice at these exceptional high levels. It appears, therefore, that the mutagenic effects of vinyl chloride, expressed as chromosomal aberrations in lymphocytes, do not occur in the germ cells...The potential danger of mutagenic effects on the fetus via the sperm does not, therefore,

seem to exist." Unfortunately, the details of this animal study have not been published. This same report did suggest that increased chromosomal changes could be seen in highly exposed workmen.

Conclusion

Since 1974, a number of studies have been undertaken to determine the potential mutagenic or teratogenic hazard of vinyl chloride exposure. Extensive experiments conducted by the U.S. Center for Disease Control have failed to discover any relationship between birth defects in children and their parents' exposure to vinyl chloride. This research refutes an earlier, less definitive study conducted in three towns in Ohio, and a more recent one conducted in Canada. Animal studies have likewise failed to find a link between VCM exposure and either mutagenic or teratogenic effects.

One study undertaken at a single plant in Pennsylvania, which reported that the wives of workers exposed to heavy concentrations of vinyl chloride had a greater number of stillbirths and miscarriages than the wives of workers exposed to little or no VCM, has raised numerous questions by experts about the methodology and conclusions drawn from this study.

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