

# Power Considerations in Studies of Reproductive Effects of Vinyl Chloride and Some Structural Analogs

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We review the evidence examining the relation of reproductive function and exposure to vinyl chloride and selected structural analogs. Investigation of these compounds for possible reproductive effects has focused on paternal exposure, a much less well studied route than maternal exposure. Drawing on animal models, we discuss what is known about the possible reproductive consequences of exposure to the father as well as to the mother. In evaluating the studies of reproductive outcome in relation to vinyl chloride or analogs, we consider what biologic model may have been tested and whether there was statistical power to detect moderate increases in risk. Parameters influencing statistical power are reviewed, and recommended sample sizes are set out which would insure sufficient power, in future studies, to detect adverse effects.

As a setting for research on the relations between exposures and adverse reproductive events, the workplace has both strengths and limitations. A first advantage is that exposures in the occupational setting are usually at higher dose levels than those in the general environment. Since higher levels of exposure are often associated with greater risks, studies of occupationally exposed individuals may facilitate the detection of modest effects. A second advantage is that it is usually possible to distinguish which parent is exposed, since most parents do not share a common work environment. A limitation of studies set in the workplace is that frequently the number of exposed subjects is too few to yield a valid test of the association being sought.

This problem of small numbers revolves around

the question of power, the statistic that guards against the observer reporting no association, when in fact one does exist. The smaller the study population, the greater the chance that an association between an exposure and an effect will not be detected. False negative results can lead, in turn, to erroneous inferences about the safety of the workplace.

In this evaluation of the studies where exposure to vinyl chloride and structural analogs has been examined in relation to adverse reproductive outcomes emphasis will be placed on considering whether the statistical power in studies reporting negative results was sufficient to justify strong inferences from the findings. Conversely, we will also evaluate whether results reported as demonstrating an association truly support this conclusion.

The paper is divided into three sections. First we briefly consider the types of effects which may follow on either exposure to the mother or to the father. Second, we outline the parameters which influence statistical power. Third, we review the evidence with a view to summarizing current knowledge of the relation of vinyl chloride exposure to reproduction.

This work was supported by NICHD Grant No. 5T32-1D-07040.

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## Types of Reproductive Effects

The birth of a child with malformations is only one of many outcomes that may follow on exposure to a reproductive hazard. So too, maternal exposure during pregnancy is just one of the routes through which an agent may affect reproduction (1). We consider below, several outcomes and routes of exposure.

### Paternal Exposure

The route of exposure may be through the father, in which case possible reproductive effects include: sterility, infertility, reduced sperm production or mobility, alterations in sperm morphology and genetic damage to the germ cell. Work in the laboratory lays the necessary foundation for our thinking about these processes, but it is unfortunately often less precise, particularly in descriptions of outcomes, than we would now wish. Thus we would ask not only that experimental work distinguish between types of agent, dose, age at administration and duration of exposure, and the supposed action on spermatogonia, spermatocytes, spermatids and sperm; but also that outcomes be distinguished in the offspring, in terms of chromosome structure and function, as well as morphology and morbidity.

With few exceptions, such specificity is available on almost none of the exposures with which we are concerned in the workplace. Given that there are known interspecies variations in tolerance levels which must be considered to act not only in absolute terms, but also in terms of stage of development and tissue affected, it is unlikely in any event that studies in animals can substitute fully for studies in man.

When the route to the conceptus is through the father, exposures prior to conception must be considered. The interval between exposure and conception that is relevant in regard to potential effects of exposure is not known, and it may vary with the type of exposure and mechanism. The period is sometimes specified as three months, roughly corresponding to the 75-80 days it takes for sperm to regenerate. However, it may be that some agents act not on the spermatids, spermatocytes and spermatozoa, but rather on the spermatogonia, which give rise to the sperm. In that case, judging from the experimental work, all subsequent populations of sperm might be affected, and not simply the generation present at the time of the exposure. Such an example is found in mice, where paternal irradiation exposure is associated with an excess of mutations in all litters conceived after exposure (2); we do not know of a similar example in humans.

There is some evidence (3-5) that various drugs may be carried in the human semen. If this is indeed the case, then the developing conceptus may also be affected by exposures to the male parent during gestation. Certainly Naeye (6) has now presented evidence suggesting that intercourse during late pregnancy can cause amniotic fluid infection and abruptio placentae.

### Maternal Exposure

When the mother is exposed, events occurring during pregnancy as well as prior to conception can influence the outcome. In the female the germ cells are present at birth; thus any postnatal exposure, and possibly exposures encountered when the mother-to-be is still an embryo, may affect the germ cells. There is some evidence that the germ cells are more vulnerable to exposures at some stages (perhaps during follicular development) than at others.

Adverse outcomes from maternal exposure before conception include infertility, and conception of a zygote with anomalies in either chromosome number or structure and/or with a gene mutation. Exposure to the mother during pregnancy can result in anatomic malformations in the conceptus (a teratogenic effect), it may lead to disability in the conceptus but without patent malformation (a fetotoxic effect), or it may lead to premature expulsion of a normal conceptus (an abortifacient effect). A carcinogenic effect on the offspring is also possible (7, 8).

Experimental models to distinguish these effects in mice are elegantly displayed in the work of Maudlin and Fraser (9).

Tentative though our understanding may be, at this stage, of the processes involved, we would still argue for researchers to spell out, at the outset of their investigations, the likely hypothetical model they are testing. In the discussion of statistical issues and in the critique of papers that follows, we have had in most cases to superimpose the model that we assumed was the one being investigated. By so doing, we may sometimes have been less than just to the investigator, and we will point up this type of problem when it arises.

### Issues Relating to Statistical Power

Although studies evaluating the effects of occupational exposure often permit specification of the parent exposed and the timing of exposure, firm answers to important questions about effects on the

fetus may be impossible to give, because of the small number of individuals exposed. Sample size affects the power of the test. Formally, power can be defined as the probability that, in any study, a raised risk of a specific size will be detected, if it is present (10). Other determinants of power are: the research design, the test statistic, the level of statistical significance established, the size of the increase in risk, and the prevalence of the condition under study in the unexposed population. Some of these relationships are illustrated in the next two tables.

Table 1 illustrates the relation between the prevalence of a condition in an unexposed sample and sample size, fixing the relative risk to be detected, the statistical power, and the significance level. In the first column, we set out the frequencies of an outcome among the unexposed; these vary from 0.1% to 45%. In the second column we show a doubling in the risk. (Throughout, we define a relative risk of 2, or a doubling, as a nontrivial effect that one would wish to detect.) In the third column we set out the sample size needed in each study group in order to have 80% power to detect the doubling in relative risk (at  $\alpha = 0.05$ , two-tailed). It is obvious that the rarer the outcome in the unexposed population, the larger the sample needed to detect a doubling in risk among the exposed. The need to use large samples when studying rare outcomes relates to the fact that a doubling in a rare event—which may result from an additional handful of cases—is far more likely to arise by chance than a doubling of a more common event.

Table 2 illustrates the relation between statistical power and the size of effect (relative risk), fixing the sample size of the two study groups and the frequency of the outcome among the unexposed. In the example, there are 100 individuals in each cohort and a prevalence of 15% for the outcome among the unexposed. It is obvious that statistical power increases with increases in the relative risk. The greater the size of the effect, the smaller the sample required to detect it.

The moral of these two tables is that not all studies with negative results are equal. Some negative studies are more equal than others. In order to interpret a negative finding, we need to determine the probability that a particular increase in risk would have been detected, if present. It is with this in mind that we evaluate the studies which have examined exposure to vinyl chloride and structural anomalies, in relation to reproductive outcomes.

We have grouped the studies by outcome. For each outcome, we consider whether those studies which appear to produce conflicting results were designed to detect effects of the same magnitude.

**Table 1. Relation of prevalence to sample size requirements.<sup>a</sup>**

Probability of outcome among unexposed group	Probability of outcome among exposed group	Samples sizes of exposed and unexposed groups <sup>b</sup>
0.001	0.002	22,403
0.01	0.02	2,243
0.10	0.20	197
0.15	0.30	123
0.25	0.50	65
0.35	0.70	41
0.45	0.90	28

<sup>a</sup>Illustrated by the need to detect a doubling in relative risk (RR) with 80% statistical power.

<sup>b</sup>Sample sizes were calculated for  $\alpha = 0.05$ , two-tailed test.

**Table 2. Relation of relative risk and statistical power.<sup>a</sup>**

Probability of outcome in unexposed group	Probability of outcome in exposed group	Relative risk	Statistical power to detect increase in risk
0.15	0.19	1.3	0.11
0.15	0.23	1.5	0.29
0.15	0.27	1.8	0.56
0.15	0.32	2.1	0.81
0.15	0.37	2.5	0.95

<sup>a</sup>Illustrated among 100 exposed and 100 unexposed subjects when prevalence among the unexposed is 15%. Power calculated for  $\alpha = 0.05$ , two-tailed test.

## A Review of the Evidence

### Birth Defects

The initial suggestion that vinyl chloride might pose a risk to human reproduction came from a study of birth defects in three Ohio communities housing vinyl chloride production facilities (11). This was an ecological study, comparing malformation rates in the index communities with the statewide rates. Attention focused on the finding of a significant excess of central nervous system malformations, especially prominent in one of the cities, where the risk of neural tube defects relative to the state as a whole was 5.8.

Ecological studies always raise knotty statistical issues so that some biostatisticians and epidemiologists shun them utterly. It was therefore entirely appropriate that, following this first report, the Center for Disease Control (CDC) undertook a case-control study to see if, individually, the cases in this city could be linked to the vinyl chloride facility (12). Occupation and residence data from hospital records were used to explore, first, whether the parents of cases had had direct occupational exposure to vinyl chloride and, second, whether

their homes were located closer to the plant than the homes of controls. No differences in work place exposure or in proximity to the plant were found between the two groups.

In this sample, comprising 15 cases and 30 unaffected controls, the chance of detecting a doubling in the proportion of residents living close to the plant compared to controls was about 70%. It seems certain that power was ample to detect a sixfold relative risk, even a twofold risk, but not a more modest effect.

More recently, CDC reported a second study examining the relation of neural tube defects to parental exposure to vinyl chloride (13). Data from the Birth Defects Monitoring Program were reviewed for other locales with poly(vinyl chloride) facilities, and an intensive investigation was launched in Kanawha County, West Virginia, where rates of CNS defects had also been observed to be significantly higher than in reference populations. In this study, unaffected births (controls) were matched to affected births (cases) on several factors (seasonality, race, social class and maternal age) which may relate to CNS malformations. Reproductive, residential and occupational histories were obtained by telephone interviews with the parents of affected and unaffected births; a matched-pair analysis was performed to test whether the frequency distribution of distances from the plant were similar for cases and controls (Table 3).

The power of this study of 46 matched pairs was the same as in the earlier CDC study; that is, there was 80% power to detect a 2.3 increase in the proportion of cases living close to the plant compared with controls, but only 70% power to detect a doubling in this proportion. Once again, no association was found between either working in or living near a poly(vinyl chloride) plant and central nervous system defects. In fact, the proportion of parents employed at the plant was equivalent (4%) in the case and the control group, and the percentage living close to the plant was similar within a

radius of either one or three miles. When the addresses of the two groups were plotted on a map, the direction of the residences with respect to the plant did differ, with families of affected births living more to the northeast and families of unaffected births living to the south of the plant. Emission and meteorologic data were explored to see if exposure levels varied with direction, but the results were ambiguous.

In summary, if there is an association between parental exposure to vinyl chloride and CNS defects in offspring, these two case-control studies suggest it is likely to be smaller than the moderate effect exemplified by an odds ratio of 2.3.

The route of exposure was never explicitly specified in these studies of neural tube defects. However, malformations in offspring are often considered to implicate the mother rather than the father as the source of exposure. Hence the study examining effects of vinyl chloride inhalation in pregnant female animals, described elsewhere in this volume, is of interest (14). Since power considerations are as pertinent to the laboratory as to population studies, we calculated, from the published report, the power of the most sensitive test available in this experiment. That comparison could only achieve 80% power if the effect on the treated animals was large; that is, only an increase of more than 4-fold in the incidence of anomaly was likely to have been detected. Reporting such findings as negative is to disregard considerations of power, which are not species-specific.

## Spontaneous Abortion

A later investigation into the reproductive effects of vinyl chloride explicitly proposed the father as the route of exposure and fetal loss as the outcome (15). Using fetal loss data obtained by interview with the fathers, rates of loss were compared in the wives of exposed and unexposed workers, in both the time periods before and after exposure to vinyl chloride. In the time period subsequent to exposure, when mean paternal ages were equivalent (and, by inference, maternal age, a known risk factor for spontaneous abortion), the rate of fetal loss among the wives of exposed workers was 16.5%, and that among wives of unexposed workers was 8.8%, yielding an unadjusted relative risk for fetal loss of 1.8 (Table 4).

A comparison of age-adjusted rates of loss for exposed and unexposed men was carried out by the authors, taking the number of pregnancies to the two groups (412 in total) as the sample size. From this chi-square analysis it was concluded that there

Table 3. Vinyl chloride neural tube defects.

Study		
Study 1	Ecological analysis	RR of CNS defects in community with PVC plant = 5.8
Study 2	Case-control study 15 cases 30 controls	Power to detect a doubling = 70%; RR detectable with 80% power = 2.3
Study 3	Case control study 46 matched pairs	Power to detect a doubling = 70%; RR detectable with 80% power = 2.3

Table 4. Vinyl chloride/fetal loss: comparison of fetal loss rates in wives of exposed and unexposed workers.

	Prevalence in unexposed	N per group	Power
Study 1	0.088	62 exposed 113 unexposed	Power to detect doubling = 31%; RR detectable with 80% power = 2.9
Study 2	0.15	205 exposed 144 unexposed	Power to detect 1.8 RR = 79% RR detectable with 80% power = 1.81
	0.12	205 exposed 144 unexposed	Power to detect 1.8 RR = 65% RR detectable with 80% power = 1.96

was a statistically significant difference between the two groups in the rate of fetal loss. However, there is evidence that women with multiple spontaneous abortions were concentrated in the group which later became exposed (16). Since one spontaneous abortion is associated with a 66% increase in the risk of a subsequent abortion, it is possible that some of the seemingly excessive loss occurring in the wives of men exposed to vinyl chloride is owed to the increased proportion among them of women experiencing previous abortions prior to exposure. Thus the subsequent abortions cannot be considered independent events, and the analysis does not satisfy the assumption which underlies the chi-square statistic, that all observations are independent. If the rates are compared basing sample size on the 62 wives of exposed workers and the 113 wives of unexposed men, then the difference in fetal loss rates is not statistically significant ( $t = 1.43$ , 173 df). However, the power of this test to detect a doubling in the frequency of abortion is only 31%. Thus a negative finding in this analysis does not rule out the possibility of a moderate effect.

The statistic that is appropriate here depends essentially on the explicit model that is being tested. We have noted the chi-square is incorrect, because a woman's first pregnancy and her subsequent pregnancies cannot be considered independent. It could be argued, however, that, if the model to be invoked involves an effect of vinyl chloride on the spermatocyte II layer of the father, then pregnancies that followed within a given period after exposure, and only those, would be affected. In such a case, provided that there was some way of controlling for other risk factors for abortion (like maternal age and previous spontaneous abortion), then the test statistic might legitimately be based on pregnancies rather than on women (although some statisticians will still balk at this procedure).

A new investigation may shed some light. Fetal loss is one of the endpoints currently being evaluated as part of a study of vinyl chloride workers

conducted at the University of Texas (17). The design of this study has been fully described, though results relating to reproduction have not yet been published. Fetal loss data in this investigation will be based on telephone interviews with the wives of workers; interviewers will be blind to the husband's exposure status. Information will also be collected on potentially confounding variables such as cigarette smoking and prior reproductive history.

The Texas group has thus far interviewed 205 wives of exposed men and 144 wives of unexposed men. Does this sample of 349 wives yield sufficient statistical power to detect an effect of the magnitude suggested by the prior study ( $RR \sim 1.8$ )? The statistical power will depend on the rate of abortion in the unexposed wives. If our suspicion that women are more accurate reporters of reproductive history than their mates is correct, then we can expect that the baseline frequency of abortion in this study may be somewhat higher than that of the earlier study based on reports from male workers only. In Table 4 we have computed power based on two different estimates of abortion frequency in the unexposed sample: 15% and 12%. The rate reported will depend partly on the definition of fetal loss and partly on the distribution of risk factors in the population observed. Then if the prevalence of spontaneous abortion among the unexposed is 15%, there will be an adequate test of whether or not paternal exposure to vinyl chloride is associated with a 1.8 relative risk of spontaneous abortion. If, on the other hand, the frequency of abortion among the unexposed is 12%, there is only a 65% chance of detecting this increase in risk.

## Infertility

Also bearing on the question of reproductive risk are investigations of effects on fertility in workers exposed to ethylene dibromide (EDB) and epichlorohydrin (ECH), structural analogs of vinyl chloride shown in animal studies to interfere with spermatogenesis. In studying these compounds, the attempt has been made to demonstrate exposure

effects directly in the male, by examining semen and hormone samples, as well as indirectly, using outcome of pregnancy in wives. Wong and colleagues assessed the fertility of male married workers exposed to EDB, by comparing the number of livebirths to their wives with age-parity-race-calendar year-specific birth probabilities for all U.S. women (18). Effects on single workers were not evaluated, nor was this method able to control for regional differences in fertility rates.

In reporting their negative findings, the authors claimed to have power of 90% to detect a 20% increase in infertility. However, this computation used the number of person-years observed rather than the number of persons as the sample size. Again, whether "men" or "person years" is the correct number to use in the computation depends on the explicit model that is being tested, which is not here spelled out.

## Sperm Counts

The relationship of semen quality to infertility and/or outcome of pregnancy is still imperfectly understood. Men with sperm counts less than ten million have, for instance, been shown capable of impregnating (19), but follow-up studies have not been done to see whether the frequency of adverse pregnancy outcome is greater than among men with normal counts. Kapp et al. have found increased aneuploidy in the sperm of 18 dibromochloropropane-exposed workers investigated (20). Although an increased number of sperm with two Y chromosomes suggests there might be an increased

risk of 47-YYY offspring, this outcome has not been demonstrated.

Milby and Whorton, in a recent paper (21), have summarized results of studies they have conducted on epichlorohydrin in two occupational cohorts. Also Venable and colleagues have recently reported a study of glycerine workers with multiple chlorinated hydrocarbon exposures, including epichlorohydrin (22). Sperm count distribution has been the major focus in these studies comparing semen quality in exposed male volunteers and unexposed controls, although it has been argued that sperm morphology provides a more stable and predictable parameter (23).

These studies vary in the detail with which they have been reported, and in methodology. The focus in the present paper is on issues relating to statistical power; however, several of the methodologic problems in the studies of sperm are important and call into question the value of considering the data in this way. (For instance, in the Milby and Whorton ECH studies, the participation rate among eligible workers was 36% in one cohort and 45% in the other, raising the possibility that the samples were not representative of the exposed populations.)

Negative findings for an association between exposure to ECH and decreased sperm count have been reported for all three cohorts, although the Venable study does note a suggestive reduction in sperm concentration in a subgroup of those exposed (Table 5). For each study, we calculated the size of the relative risk which could be excluded, with a 20% probability of falsely concluding that there was no association between exposure and sperm count;

Table 5. ECH/sperm concentration: semen analyses of exposed and unexposed volunteers.

	Prevalence in unexposed	N per group	Power
Study 1	0.055	44 exposed 90 unexposed	Power to detect doubling = 19% RR detectable with 80% power = 4.1
Study 2	0.055	84 exposed 90 unexposed	Power to detect doubling = 38% RR detectable with 80% power = 3.5
Study 3	0.095	64 exposed 63 unexposed	Power to detect doubling = 35% RR detectable with 80% power = 3.0

Table 6. Recommended sample sizes for future studies.

Outcome	Prevalence in unexposed population	Relative risk to be detected with 80% power <sup>a</sup>	Number required in each study group
Neural tube defects	0.001/livebirths	6.0	1862 livebirths
Spontaneous abortions	0.15/pregnancies	1.8	174 mothers
Sperm counts < 20 million	0.12/pregnancies	1.8	240 mothers
	0.07/males		2.0

<sup>a</sup>Power calculated for  $\alpha = 0.05$ , two-tailed test.

the proportion of men with sperm counts less than 20 million was the index evaluated.

In the first cohort observed by Milby and Whorton, there was an 80% chance of detecting a 4-fold increase over the 5.5% baseline rate observed in the control group; in the second cohort there was an 80% chance of detecting a relative risk of 3.5. The Venable study which observed a 9.5% rate of low sperm count in its control group had power of 80% to detect a threefold increase in risk.

None of these studies had sufficient power to detect a doubling. If we agree that a doubling in the frequency of sperm count depression is not a trivial effect, then these studies are not sufficient to lay fears to rest concerning a possible effect of ECH on sperm count in exposed males.

## Conclusions

What, then, is it possible to infer at this time? At present, there are no data which point unambiguously to a relation between vinyl chloride or analogs and reproductive outcome. On the other hand, there are several studies which report no association where the statistical power to detect a modest association between exposure and outcome, if it should be present, is either insufficient or not able to be calculated from the published data. Certainly there is no evidence to indicate that the fetus is at greater risk from maternal exposure than from exposure to the father. Altogether, one must point to the need for carefully designed and executed studies, where the association of vinyl chloride with reproductive outcome can be examined. In Table 6, we set out some estimates of the sample sizes that would be needed, depending on the outcome under study and its prevalence in an unexposed sample. For different outcomes, we have required that the sample be sufficient to detect effects of the size observed in previous studies. Certainly, we stand a better chance of understanding whether and how vinyl chloride affects reproduction if future studies are designed with the ability to detect these adverse effects.

## REFERENCES

1. Strobino, B., Kline, J., and Stein, Z. Chemical and physical exposure of parents: effects on human reproduction and offspring. *Early Human Dev.*, 1: 371-399 (1978).
2. Russel, W. L. Studies in mammalian radiation genetics. *Nucleonics*, 23: 53-62 (1965).
3. Manson, J. M., and Simons, R. Influence of environmental agents on male reproductive failure. In: *Work and the Health of Women*. V. R. Hunt, Ed., CRC Press, Florida, 1980.
4. Lutwak-Mann, C., Schmid, K., and Keberle, H. Thalidomide in rabbit semen. *Nature*, 214: 1018-1020 (1967).
5. Eriessson, R. J., and Baker, V. F. Transport of oestrogens in semen to the female rat during mating and its effect on fertility. *J. Reprod. Fertil.*, 12: 381-384 (1966).
6. Naeye, R. L. Seasonal variations in coitus and other risk factors, and the outcome of pregnancy. *Early Human Dev.*, 4: 61-68 (1980).
7. Kline, J., Stein, Z., Susser, M., and Warburton, D. Environmental influences on early reproductive loss in a current New York City study. In: *Human Embryonic and Fetal Death*, I. H. Porter and E. B. Hook, Eds., New York, 1980, pp. 225-240.
8. Stein, Z., Kline, J., Levin, B., Susser, M., and Warburton, D. The concept of low risk exposure in relation to pregnancy outcome. Paper presented at the Thirteenth Rochester International Conference on Environmental Toxicity, Rochester, June 2, 1980.
9. Maudlin, I., and Fraser, L. R. Maternal age and the incidence of aneuploidy in first-cleavage mouse embryos. *J. Reprod. Fertil.*, 54: 423-426 (1978).
10. Cohen, J. *Statistical Power Analysis for the Behavioral Sciences*, rev. ed. Academic Press, New York, 1977.
11. Infante, P. F. Oncogenic and mutagenic risks in communities with polyvinyl chloride production facilities. *Ann. N. Y. Acad. Sci.*, 271: 49-57 (1976).
12. Edmonds, L. D., Falk, H., and Nissim, J. E. Congenital malformations and vinyl chloride. *Lancet*, ii: 1098 (1975).
13. Edmonds, L. D., Anderson, C. E., Flynt, J. W., Jr., and James, L. M. Congenital central nervous system malformations and vinyl chloride monomer exposure: a community study. *Teratology*, 17: 137-149 (1978).
14. John, J. A., Smith, F. A., Leong, B. K. J., and Schwetz, B. A. The effects of maternally inhaled vinyl chloride on embryonal and fetal development in mice, rats, and rabbits. *Toxicol. Appl. Pharmacol.*, 39: 497-513 (1977).
15. Infante, P. F., Wagoner, J. K., McMichael, A. J., Waxweiler, R. J., and Falk, H. Genetic risks of vinyl chloride. *Lancet*, i: 734-735 (1976).
16. Infante, P. F., Wagoner, J. K., and Waxweiler, R. J. Carcinogenic, mutagenic and teratogenic risks associated with vinyl chloride. *Mutat. Res.*, 41: 131-142 (1976).
17. Buffler, P. A. Some problems involved in recognizing teratogens used in industry. *Contr. Epidem. Biostatist.*, 1: 118-137 (1979).
18. Wong, O., Utidjian, M. D., and Karten, V. S. Retrospective evaluation of reproductive performance of workers exposed to ethylene dibromide (EDB). *J. Occup. Med.*, 21: 98-102 (1979).
19. Sherins, R. J., Brightwell, D., and Sternthal, P. M. Longitudinal analysis of semen of fertile and infertile men. In: *The Testis in Normal and Infertile Men*. P. Troen and H. R. Nankin, Eds. Raven Press, New York, 1977.
20. Kapp, R. W., Jr. Picciano, D. J., and Jacobson, C. B. X-Chromosomal nondisjunction in dibromochloropropane-exposed workmen. *Mutat. Res.*, 64: 47-51 (1979).
21. Milby, T. H., and Whorton, D. Epidemiological assessment of occupationally related, chemically induced sperm count suppression. *J. Occup. Med.* 22: 77-82 (1980).
22. Venable, J. R., McClimans, C. D., Flake, R. E., and Dimick, D. B. A fertility study of male employees engaged in the manufacture of glycerine. *J. Occup. Med.* 22: 87-91 (1980).
23. Wyrobeck, A. J., and Bruce, W. R. The induction of sperm-shape abnormalities in mice and humans. In: *Chemical Mutagens*, Vol. 5. A. Hollaender and F. J. deSerres, Eds., Plenum Press, New York, 1978.