Edmonds, L.D., Anderson, C.E., Flynt, J.W.Jr. and Heath, C.W. Jr. (1976). Congenital central nervous system malformations, Kanawha County, West Virginia. Public Health Service - CDC-Atlanta, EPI-76-60-2. Manuscript. ("Not for publication").

(Note: I have not seen this manuscript published but know that it has been submitted to at least one journal for consideration for publication. It was not accepted by that journal but will probably be published somewhere in the near future).

During 1970-74 there were 7 U.S. counties in which (a) a PVC production plant was located, and (b) hospitals representing more than 50 percent of the births participated in the birth defects monitoring program (BDMP) of the Center for Disease Control, Atlanta, Ga. Two of these seven counties had rates of central nervous system defects significantly in excess of national rates for hospitals reporting to the BDMP; one was Lake County, Ohio (Painesville) which was studied previously by Edmonds et al. (1975); the other was Kanawha County, West Virginia. There are two relevant aspects of this paper-patterns in the rates for Kanawha County and a case-control study of the cases themselves and their parents.

Rates of CNS defects are based on two sets of data - the BDMP and the state vital record system. For the former, national BDMP rates are used for comparison; no comparison rates are presented for the latter. The rates are highest in BDMP data in 1971 and in the state data in 1970. The state data show a marked decline in 1973 and 1974; in the BDMP data the rate in 1974 (and in preliminary data for 1975) was similar to the total U.S. rate. The high rate in 1970-73 was manifested by all three major CNS defects - anencephaly, spina bifida and hydrocephaly - as well as by the category "other CNS" defects.

For the case-control study, two controls were selected from vital statistics records for each confirmed CNS defect in a resident of Kanawha County (n = 47). It is not clear why two controls were selected since only the case parents and one of the controls (randomly selected) were interviewed. No information on the other control is used. The interviews were by telephone. There were no differences between case and control parents in frequency of working in the PVC plant or in location of work-place or residence in respect to distance from the plant. Only two of the fathers of cases, five of the fathers of controls and none of the mothers in either group had ever worked in the PVC plant.

Comment

This study uses simple and standard epidemiologic procedures and provides little on which to comment. It would be of interest to know the reason why 59 cases in Table 1 is reduced to 47 in Table 3. If this was primarily because of misdiagnosis or miscoding it would raise questions as to the accuracy of the BDMP data. If, on the other hand, the 12 excluded cases were mostly non-residents of the county it would appear that rates for non-residents (born in the county) were as high as those for residents. One can estimate from the numbers of cases and rates in the three tables that the number of births to non-

residents in the county was about 980. It would require only 3 of the 12 excluded cases to be non-residents for the rate for non-residents to be as high as that for residents.

Whatever the reason for the high rate of CNS defects in Kanawha County in 1970-73, the results of the case-control study indicate that it is not the presence of the polymerisation plant.

Edmonds, L.D., Falk, H. and Nissim, J.E. (1975). Congenital malformations and vinyl chloride. (Letter to the Editor) Lancet, ii: 1093.

Following the report of Infante (1976) (reported in 1975 but published in 1976), data from the birth defects monitoring program (BDMP) of the Center for Disease Control were examined. Two hospitals participating in the BDMP are located in cities with vinyl chloride polymerisation plants - one in Pennsylvania and one in Painesville, Ohio., one of the three cities studied by Infante. Congenital malformation rates reported from these two hospitals during 1970-74 are compared with rates from all the reporting hospitals in the respective states.

No increase in rates was seen in the Pennsylvania hospital.

In the Painesville hospital it is stated that "an increase, primarily in anencephaly and spina bifida, was noted...". Data are given only for anencephaly and spina bifida, the rate for each malformation being a little over twice the rate for the state.

In Painesville, two "control" (normal) infants were selected for each of the 15 known cases and information on residence and occupation of parents of cases and controls obtained from medical records. In addition, parents of 14 of the 15 cases were interviewed. None of the interviewed parents of cases had ever worked at either of the two polymerisation plants. None of the parents of cases or controls lived within 2 miles of the plants. A significantly higher proportion of mothers of controls than of cases lived within 10 miles of a PVC plant, but this is attributed to a chance finding among multiple comparisons.

Comment

It is not surprising that a high rate of anencephaly and spina bifida was found in Painesville, since the data cover almost the same years as those of Infante (1976). For 1970-73 (for the whole city)Infante found 13 cases of "central nervous system" defects, while for 1970-74 (in this one hospital) Edmonds et al. found 15 cases, suggesting that most of the births to residents of the city occur in this one hospital and that there is considerable overlap between the two series.

The fact that no link could be found between cases of anencephaly and spina bifida and either of the two VC polymerisation plants, as well as the lack of increased rates in the Pennsylvania hospital, indicates that it is not the presence of the two plants which is responsible for the high malformation rate in Painesville. The most likely explanation seems to me to be random fluctuation.

There is a small numerical error in this letter. The total of 15 cases includes one that was not reported to BDMP but was identified by search of birth certificates. Since this search was not undertaken for the entire state data (or, at least, it is not stated that it was) the state data in the table relate

only to cases reported to the BDMP, and a more accurate comparison would be with the Painesville cases similarly identified - i.e. 14 cases. The effect of this error is trivial.

The controls are stated to have been selected as "normal white" infants. It is not stated that all the cases were white, but presumably this was so. (The rates in the table are given per 10,000 white births.)

The declining rate of neural tube defects (anencephaly and spina-bifida) in the state data given in the table - from 1.6 per 1,000 in 1970 to 1.0 per 1,000 in 1974 - is of some interest, though not directly relevant to the matter under review.

Infante, P.J. (1976). Oncogenic and mutagenic risks in communities with polyvinyl chloride production facilities. Ann. N.Y. Acad. Sci., 271: 49-57.

Data are presented on rates of congenital malformation and of certain neoplasms in three communities in Ohio containing polyvinyl chloride production facilities. Only the congenital malformation data are relevant to this review.

The three communities and the number of livebirths during the four years studied (1970-73) are Ashtabula (1,900), Painesville (1,381) and Avon Lake (738). The sources of information on congenital malformations are the routine reports on certificates of birth. Most of the data are limited to livebirths but some information is given on neural tube defects in stillbirths.

The author notes that the total reported malformation rate for the three index cities combined is almost twice as high as for the state as a whole or for the balance of the three counties in which the index cities are located. In two brief paragraphs at the top of page 52 it is stated that the differences "did not appear to be" related to race or maternal age, that the differences were observed for children born in the same hospital but to parents not resident in the city (seeming to rule out reporting bias) and that urban-rural differences were not "significant" in three other county-city combinations matched to the index areas on population size. However, no data are given on these three points.

The three index cities are then compared with 10 other cities located in the same three counties. Two of the other cities had higher malformation rates than the index cities. One of them (North Ridgeville) was "proximate to" one of the index cities (Avon Lake) and the data for that city were therefore combined with those for the three index cities to give observed and expected numbers of malformations by site, expected values being based on state averages. Observed values exceed expected in 13 of the 17 categories of malformation.

Data for central nervous system defects are given for stillbirths as well as livebirths. For stillbirths and livebirths combined, CNS defects were approximately three times as frequent in the four communities (3 index cities plus North Ridgeville) as in the state as a whole. Type of CNS defect is given for stillbirths but not for livebirths.

Comment

There are several potential sources of error in this study, but it is not easy to see how any one of them could account for the principal finding of a high malformation rate in the three index cities. I am fairly well convinced that the finding results from a combination of chance, reporting differentials and epidemiologic gerrymandering.

Birth certificates are a notoriously poor source of information on congenital malformations. The rate for the state of Ohio as a whole (about 10 per 1,000 livebirths) suggests that only about half the medically significant malformations are being reported. However, incomplete reporting would not account for the findings unless there were bias, as well as incompleteness. The

author's examination of three other city-county combinations and of births in the same hospital to city and county residents suggests that (a) there are no significant urban-rural differentials in other areas of the state, and (b) in the three index cities themselves the difference between residents of the cities and of the balance of the three counties can be demonstrated in infants born in the same hospitals. However, no data are given on these important points. We are not told how the three other city-county combinations were selected, other than that they were matched to the index areas in "population size". Were they the three closest matches in the entire state, or were other criteria used to select among all areas that might be considered a "match"? What were the criteria for a match - i.e. how close must the size be? What is meant by"population size" - the size of the city, the balance of the county or the county as a whole? If the latter, how close was the matching on size of city? Information on urban-rural differences in the state as a whole would be informative. The finding of differential rates among infants born in the same hospital seems superficially quite convincing, since it relates directly to infants in the index cities. In the absence of the data, however, it is hard to believe that a meaningful analysis of this kind could have been undertaken on the numbers of births available for study.

The small numbers of births on which rates in the three index cities are based is also a potential source of misinterpretation. For example, the confidence limits around the point estimates of total malformation rates in the three cities and for the balance of the three counties are as follows:

Community	Point estimate	95% confidence range Uoper	Lower
Ashtabula	17.37	23.37	11.37
Painesville	18.10	25.28	10.92
Avon Lake	20.33	30.73	9.93
All 3 cities	18.16	22.33	13.94
Balance of 3 counties	10.62	11.72	9.52

The lower bound of the 95% confidence interval of the rate for each of the three cities falls well within the confidence interval of the rate for the balance of the counties. Nevertheless, the lower bound for the three cities combined (selected a priori) does exceed both the upper bound of the rate for the balance of the three counties and for the state as a whole. It is unlikely that the high rates for the three cities is due to chance alone, but the wide confidence limits around most of the rates must be kept in mind when interpreting them.

The addition of North Ridgeville to the "exposed" population after noting a high malformation rate in that city is completely unjustified. The fact that it lies "proximate to" (whatever that means) one of the index cities would be reason for combining its data with those of the index cities only if all cities satisfying that criterion were included. It is doubtful that the addition of North Ridgeville makes any qualitative difference to the findings. That this procedure was followed is of concern more because the author gives no indication

of recognizing the error involved and the suggestion it leaves with the reader that similar kinds of selection may have occurred at other steps in assembly of the data.

The feature of the data that is most suggestive that the high malformation rate in the three cities is an artefact is that a wide variety of malformations are involved. The author focuses attention on the central nervous system defects, because of their usual severity, but, as noted above, 13 of the 17 categories examined are in excess and, among the more common groups, oral clefts, club foot and anomalies of the upper alimentary tract and genital organs are all substantially in excess. The known teratogenic agents in humans and in experimental animals have considerable specificity in the malformations they produce. It seems unlikely that any agent would produce the variety of malformations found in excess in these cities. A much more likely explanation is some artefact - such as reporting differentials - that would apply to all categories of malformation. "Clubfoot", which shows a three-fold increase in these data, is a diagnosis whose frequency is particularly dependent on diagnostic and reporting practices and which seems unlikely to be caused by a specific teratogen - much less a mutagen.

There is a good deal of imprecise wording in the paper which does not inspire confidence in the rigor of those parts of the analysis which must be taken on faith. For example:

(1) In the "Discussion and Summary" (page 56) the statement is made that "anomalies of the central nervous system appear to be of the greatest concern". But why? Earlier in the text it is stated that this is because of the "severity of the defects involved". That is, this is not a conclusion that arises from the data. In addition, while most anomalies of the central nervous system are severe, some are not. We are not told what type of CNS malformations occurred among the livebirths, which contributed 17 of the 25 cases.

(2) No distinction is made between mutagenesis and teratogenesis and the text slips from one to the other as though the words were interchangeable, which they are not.

(3) Similarly, the text on page 24 slips from "central nervous system defects" to "anencephaly, spina bifida and hydrocephaly". It is true that these usually constitute the majority of CNS defects, but we are never reassured on this point by a statement as to the types of CNS defect found among the livebirths.

On a more trivial level:

(4) I am unable to square the numbers in Table 3 with those in Table 4. In Table 3 the four communities contribute 105 cases but in Table 4 there are 114. I suspect that Table 3 is based on malformed infants while Table 4 is based on malformations, some infants exhibiting more than one. However, no explanation is given by the author.

(5) The ICDA codes for CNS defects in Table 4 are incorrect.

In summary, the author himself states that "these preliminary findings obviously do not link polyvinyl chloride production with the increased occurrence of congenital malformations....., but indicate the need for further study of possible contributing factors". I agree with this conclusion. The findings suggest that a second look at the issue is indicated, but these data of themselves would carry very little weight in my mind in evaluating the evidence overall.

Infante, P.F., Wagoner, J.K., McMichael, A.J., Waxweiler, R.J. and Falk, H. (1976). Genetic risks of vinyl chloride. Lancet, i: 734-735.

And related correspondence:
Paddle, G.M. (1976). Lancet, i: 1079
Infante, P.F. et al. (1976b). Lancet, i: 1289-1290

This study is based on data obtained by interviewing 95 workers exposed to vinyl chloride monomer (VCM) and 158 workers ("controls") with no or very little such exposure. The controls worked with polyvinyl chloride or rubber; the proportions from each of these two groups are not given. In addition to broader questions on health status, the interviewees were asked for information on conceptions and fetal deaths experienced by their wives. From employment records, the conceptions were distinguished as occurring "prior to husband's exposure" or "subsequent to husband's exposure". It is not stated how this distinction is made for workers with no exposure, though one can infer that it was in terms of entry into current job category. The question is of some importance because of differences between exposed and control groups in the proportion of conceptions occurring prior or subsequent to "exposure" (see below).

The principal finding is that fetal death rates, adjusted for paternal age, were significantly high among wives of VCM workers after exposure than among wives of controls or among wives of VCM workers prior to exposure. The high fetal death rates were seen only among conceptions occurring to workers aged less than 30 years. The trend persisted when families reporting more than two abortions were excluded and when data collected by individual interviewers were examined separately. The mean interval between fetal loss and time of interview was about two years less for controls than for VCM workers, suggesting that the probability of recall should have been at least as high for the controls as for the exposed workers.

The letter from Paddle (1976) notes the erratic behavior of the fetal death rates when adjusted for paternal age and suggests that additional information be provided. The authors' response (Infante et al., 1976b) gives an important table showing pregnancies and fetal deaths by paternal age. The text of the authors' response provides little additional information.

Comment

It is disappointing to see an article of such poor quality as this published in the Lancet. The data are subject to serious criticism on several counts. These include:

1. The small numbers on which the rates - and particularly the age-specific rates - are based. Although statistical significance is achieved in some comparisons, the general tenor of the article is such that one can have little confidence that this was not the result of post-hoc grouping of data - the "gerrymandering" so evident in another paper by the senior author of this article (Infante, 1976).

2. The fact that reproductive histories were taken from men - not even from the women themselves, much less from written records. The ages of the men are not given, but since they included all VCM workers in a plant they presumably included the range of ages in a working population. It is almost inconceivable that such subjects would remember with accuracy the number of miscarriages experienced by their wives - much less their dates. Evidence of this comes from the data themselves. Studies have shown that the recognized spontaneous abortion rate in a general series of pregnancies is between 15 and 30 percent. In these data the rate for the controls is only 8.1% and among the exposed 13.2%. The difference between exposed and controls results from a deficit in the controls rather than an unusually high rate among the exposed.

3. The evident potential for bias in that VCM workers, because of their known exposure, may more fully report - or even over-report - fetal deaths. To refute this possibility, the authors state "...the workers themselves did not always know into which of our employment categories they were being allocated. For example, several PVC fabrication workers who were included in the control group thought that they had a primary VCM exposure...." (emphasis added). However in order for bias to be introduced in the series, it is not necessary for it to be present in all subjects. If such bias exists in only a small proportion it will affect the results for the entire group.

4. The fact that the exposed and control groups are dissimilar in two relevant characteristics - paternal-age distribution of conceptions and proportion of conceptions occurring after exposure. The difference in paternal-age distribution is marked and is seen in the table on page 1289 - a most revealing table which did not appear in the original paper but was elicited by the letter from Paddle. In the controls, 63 percent of the conceptions occurred after "exposure" but in the VCM exposed group this figure was only 48 percent (Table 1, p 734). These differences are not important per se (the age difference is adjusted for, to some extent, in the analysis) but they are indicative of some fundamental difference between either the demographic characteristics of the exposed and control groups or the criteria of initiation of exposure in the two groups. Because of the inadequate description of the study groups, I am not able to determine what this difference (or differences) could be but many possibilities come to mind that could introduce important differences in rates between the two groups.

5. The low response rate - the highest participation rate was 77 percent and the lowest 62 percent - offers further opportunity for serious bias in reporting fetal deaths in the two series.

With respect to statistical analysis, the most remarkable feature is the manner with which the authors utilize rates based on a handful of cases, incorporating significance tests when they suit their purpose and ignoring them when they do not. For example, significance tests are applied to the data in

Table 1 and the differences found to be formally significant. However, when examining the effect of excluding women with more than two abortions (page 735) it is deemed sufficient to note that "the trend was maintained". It is not remarked that the trend was considerably reduced and that the residual difference is almost certainly not significant. (The data are not given actually to permit significance testing after exclusion of repeated aborters.) The table provided in response to Dr. Paddle's letter (page 1289) reveals a most striking difference in the paternal-age distribution for conceptions before exposure. As already noted, this difference is puzzling as to its implications to the definition of the study groups. In addition, the difference is so marked as to make the comparison even of age-adjusted rates almost meaningless. In contrast, the age distributions of conceptions after exposure are quite similar in exposed and control families - a fact which suggests that a difference in the definition of onset of exposure is responsible for at least part of the difference in paternal-age distributions of conception prior to exposure. On page 735, column 1, the authors compare the age-adjusted fetal death rate of 6.1% for VCM workers prior to exposure with that of 15.8% for the same group after exposure. This comparison is not valid since the two rates have been adjusted to different standards - the 6.1% to the controls before exposure and the 15.8% to the controls after exposure. A valid comparison, using the same standard for adjustment of both rates, indicates that the actual difference is less than the 6.1:15.8 comparison suggests. For example, using the age distribution of all control conceptions as a standard, I obtain age-adjusted rates of 9.8% and 14.8% for the VCM group before and after exposure. As the authors would point out, the trend is still present and if the significance test has been carried out correctly it would not be affected. But the authors' lack of recognition that their comparison is not a valid one is disturbing.

The most obvious deficiency in the text of this paper is the inadequacy of the description of sources of data - even after the additional description provided in response to Paddle's letter. We are nowhere told how many eligible workers there were in the various groups or what the response rates were in exposed and control groups. The question of response rates is dealt with in the statement that "Group-participation rates ranged from 62 to 77%". We are not told which ends of the range applied to which groups. In addition, 62 to 77% is a broad range and seems inconsistent with the later statement (page 1289) that "The range for response rates....were similar for the study and control groups". There were two groups of controls (PVC and rubber workers), so some kind of range can be envisaged there, but was there also a range within the "study group" (exposed)? The reader should not be required to puzzle such things out - particularly when no matter how hard he puzzles the answer is not to be found in the paper.

There are other statements which may not have such important implications as definition of the study groups and exposure times but nevertheless give the reader pause for thought. For example, it is stated that a "similar number" of rubber workers were selected for study (page 734), but the context does not indicate what the number is similar to - the number of VCM workers, PVC workers or both (presumably it cannot have been the latter but that is only by implication). There is a sentence on page 734: "Although the underlying distributions differed, mean paternal ages were virtually the same - 30.4 versus 30.2 years". The reference is clearly to the VCM workers subsequent to exposure, yet subsequent to exposure the underlying distributions do not differ - it is prior to exposure

John, J.A., Smith, F.A., Leong, B.K.J and Schwartz, B.A. (1977). The effects of maternally inhaled vinyl chloride on embryonal and fetal development in mice, rats and rabbits. Toxicol. Appl. Pharmacol. 39: 497-513.

In three species the effects on fetal development of maternally inhaled vinyl chloride at several concentrations was studied. Some groups of animals received simultaneously 15% ethanol in their drinking water since the primary pathway of metabolism is thought to be blocked by ethanol. This suggestion is supported by the fact that maternal toxicity was enhanced in nearly all comparisons of animals receiving ethanol with those receiving the same dose of vinyl chloride without ethanol.

Maternal toxicity(primarily decrease in total weight gain and decrease in liver weight) was found in mice receiving 50ppm vinyl chloride with ethanol or 500 ppm with or without ethanol. In rats and rabbits, no maternal toxicity was evidenced at 500ppm. Rats showed such toxicity at 2500ppm, with or without ethanol, and rabbits at the same level but only with ethanol.

The levels of vinyl chloride concentration at which maternal toxicity is apparent correspond to the levels at which effects on fetal development appear - that is, in mice at 50ppm with ethanol, in rats at 2500ppm with or without ethanol, and in rabbits at 2500ppm only with ethanol. The toxic effects on the fetus were manifested mainly by evidence of fetal detah (decreased litter size, frequency of resorptions) and decrease in fetal weight and length. Decrease in fetal weight or length was not seen in any of the exposed groups of rabbits.

In none of the three species did gross anomalies occur in exposed animals with a frequency significantly greater than in controls. However, some skeletal anomalies occurred significantly more often among mice exposed to 50ppm with ethanol and to 500ppm with or without ethanol and among rats exposed to 2500ppm with ethanol. Although the incidence of skeletal anomalies was high among rabbits exposed at 500ppm, it was not higher than controls among those exposed at 2500ppm. Many statistical comparisons are made in this paper and the significant increase in skeletal anomalies for rabbits exposed at 500ppm is probably a chance finding.

Comment

Although outside the area of this reviewer's expertise, this appears to be an excellent study, the experimental data being meticulously examined and described. In view of the many comparisons made, some of the formally significant differences may be attributable to chance. Nevertheless, a pattern emerges of impaired fetal development at concentrations of vinyl chloride exposure that produce maternal toxicity. Congenital malformations are not a prominent feature of the fetal toxicity. However, the authors' statement (page 513) that "exposure of pregnant mice, rats, and rabbits to vinyl chloride by inhalation was not teratogenic at the concentrations tested", repeated in essence in the Summary

(page 497), seems too strong. While gross anomalies were not induced, minor skeletal abnormalities occurred in excess among exposed mice and rats, although in the latter only when exposure was combined with alcohol. The authors' statement is therefore not literally true.

In interpreting these data it should be recalled that many agents which cause fetal death induce congenital malformations when given in lower dose or to other species. Only two concentrations were tested in each species in this study; in mice the concentrations differed by a factor of 10 and in rats and rabbits by a factor of 5. While fetal toxicity occurred only in the doses associated with maternal toxicity, it is conceivable that there are intermediate concentrations which would produce fetal but not maternal toxicity. It is also conceivable that different kinds of malformation might be produced by different doses, by administration at different stages of gestation (particularly prior to day 6) or in different species. The evidence of fetal death among all three species exposed at the highest concentrations provides grounds for suspicion that vinyl chloride may be teratogenic under circumstances somewhat different from those in these experiments. Effective doses of potential teratogens cannot be extrapolated between species (as evidenced by the data of this study) and I would consider these results as reinforcing the need to prevent exposure of pregnant women to vinyl chloride at significant levels.

Reports of chromosome breakage in workers exposed to vinyl chloride:

Ducatman, A., Hirschhorn, K. and Selikoff, I.J. (1975). Mutation Res., 31: 163-168

Funes-Cravioto, F., Lambert, B., Lindsten, J. et al. (1975). Lancet, i: 459

Purchase, I.F.H., Richardson, C.R. and Anderson, D (1975) Lancet, ii: 410

ibid (1975). Proc. Roy. Soc. Med. 69: 290-291

Fleig, I (1976). Quoted by de Boer, L. Proc. Roy. Soc. Med. 69: 292

Fleig (1976) is said to have reported a study in which chromosome abnormalities were no more common in a group exposed to vinyl chloride than in controls. However, no details are given. The other reports in this series all indicate a higher rate of chromosome breaks in the peripheral lymphocytes of occupationally-exposed subjects than in controls. In addition, Purchase et al. (1976) report briefly on an experiment in which 15 male mice were heavily exposed to vinyl chloride and then mated. There was no evidence of production of dominant lethal mutations, as assessed by fetal death or resorption among the offspring.

Comment

These studies must be regarded as suggestive of the potential of vinyl chloride for producing visible chromosome damage and therefore, by implication, of invisible genetic mutation at least in somatic cells. However, even the accumulated evidence from all three positive studies leaves much to be desired and a more definitive study is clearly needed. Only in the study of Purchase et al. are the numbers at all convincing (56 exposed and 24 controls). The study of Ducatman et al. is based on only 11 exposed subjects and 10 controls; that of Funes-Cravioto et al. on 7 exposed and 3 controls. None of the four reports (data from one of the studies are reported twice) describes how the study subjects - either exposed or control - were selected from among the many who could presumably have satisfied the criterion of being exposed or not. From only one study (Ducatman et al.) are data on age given and in that study the mean age of the controls was substantially lower than that of the exposed subjects. In one study (Funes-Cravioto et al.) the highest frequency of abnormal cells was found in subjects with the shortest duration of exposure, and in another (Purchase et al.) the frequency of abnormalities is only slightly, and not significantly, higher in the group with the greatest intensity of exposure.

The negative result of the lethal dominant mutation experiment reported

by Purchase et al. has limited implication. Each of the 15 exposed males was mated 16 times. Assuming 10-12 conceptions per mating this gives a total of only approximately 2600 conceptions observed. The confidence limits of the resorption and fetal death rates are not given - nor are the rates themselves - but it seems likely that a substantial increase in mutation rates - even to dominant lethal genotypes - could have occurred without being detected in a study of this size. Lethal dominants would comprise only a small proportion of the genotypes induced by an effective mutagen.

Appendix. Documents sent by Dr. Torkelson but not reviewed in this report.

(Numbers refer to the list of documents accompanying Dr. Torkelson's letter to Mr. John Lawrence, dated May 12, 1977)

1. Infante (1975). This is the manuscript of a report which was subsequently published. The published version is reviewed (Infante, 1976). There are no substantive changes from the manuscript to the published report.

3. Infante et al. (1976). Subsequently published (item #10) and reviewed.

5. John et al. (1977). Subsequently published (item #8) and reviewed.

7. An earlier version of Edmonds et al. (1975) (item #2), which is reviewed. The text of this version differs a little from the published report but the data are identical. This is probably also reference #2 in Edmonds et al. (1975),but I have not been able to locate the original of this reference.

August 11, 1977

1. The oral toxicity of vinyl chloride monomer (VCM) was examined in a sub-chronic (90-day) study with weanling albino rats as the experimental animals. VCM dissolved in soyabean-oil was administered by gavage, once a day, six days a week, to groups of 15 males and 15 females at levels of 0, 30, 100 and 300 mg VCM/kg body weight.

2. General condition, behaviour, growth and food intake and survival were not adversely affected at any of the VCM-levels.

3. The total numbers of white blood cells and the blood sugar contents were slightly decreased at the two highest dose levels. The serum activities of glutamic-oxalacetic and glutamic-pyruvic transaminases were slightly decreased at the top dose level in males only. All values were, however, fully within the normal range, and the differences with the controls are, therefore, considered to be of minor, if any, toxicological significance. The other haematological and biochemical blood values determined did not show important differences between groups.

4. The results of the urinary analyses did not show treatment-related changes with the possible exception of a slight decrease in glutamic-oxalacetic transaminase activity in males of the top-dose group.

5. The relative weights of the livers increased with increasing levels of VCM, but the differences with the controls were statistically significant only at the highest dose level.

6. Gross autopsy findings were essentially negative.

7. Microscopic examination did not reveal distinct treatment-related abnormalities. Minimal liver changes, seen as one or a few foci of hyperbasophilic hepatocytes, occurred in two animals of both the intermediate and high dose group. The significance of this finding in terms of a treatment-related response was not clear.

8. From the results of the present study it was concluded that 30 mg VCM/kg body weight/day was a no-effect level. The 100 and 300 mg/kg dosage levels did not appear to be distinct toxic-effect levels.