Case-control Study of Childhood Cancers in Dover Township (Ocean County), New Jersey

Volume V: Response to Public Comment

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Division of Epidemiology, Environmental and Occupational Health
New Jersey Department of Health and Senior Services

in cooperation with

Agency for Toxic Substances and Disease Registry
U.S. Department of Health and Human Services

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PREFACE
RESPONSE TO PUBLIC COMMENTS

This volume presents the comments received from interested parties on the public comment draft of the report "Case-control Study of Childhood Cancers in Dover Township (Ocean County), New Jersey," together with the responses to these comments by the New Jersey Department of Health and Senior Services (NJDHSS) and the federal Agency for Toxic Substances and Disease Registry (ATSDR).

The draft report was released on December 19, 2001. The public comment period began on that date, and was originally scheduled for two months (to end on February 19, 2001). However, after requests from commenters, the period was extended one month until March 19, to allow sufficient time for the preparation and submission of comments on this complex report.

Eleven persons or institutions submitted comments on the draft report. Multiple individuals contributed comments from some institutions. On the following pages, comments (in italics) are grouped by commenter, without personal identifiers. In general, comments are presented in full; in some cases, however, minor editing was done to some comments. (Copies of original comments may be obtained from the NJDHSS.)

Responses by the NJDHSS and ATSDR (in plain font) are interspersed with the comments. Note that page numbers in the comments and responses refer to the public comment draft, not the final version of this report.

Commenter: United States Environmental Protection Agency (Multiple Reviewers)

Summary of the General Comments of the Reviewers

Comment:

"In general, the report payed careful attention to case and control selection. Additionally, the expert panel gathered to advise study investigators appears to have been well qualified to provide technical advice in the area of epidemiologic studies assessing environmental exposures; many individuals on this panel have previously carried out epidemiologic investigations into environmental factors.

In reviewing this report, a number of concerns were identified and details are provided in the attached comments. For example, while Volume I noted limitations based on low statistical power, several reviewers recommended the need to more fully describe these limitation in the report and the impact the limitations have on the conclusions."

Response:

We followed that advice which was provided before release and as a result we stated repeatedly that the results should be interpreted carefully, particularly due to the relatively small number of study subjects in the analyses (i.e., low power). The conclusions have been made taking into account the limitations in the data.

Comment:

"Another limitation of the report, is the limited discussion on the uncertainties of the air and water models and the weights placed by the authors on particular exposure metrics. EPA recommends that Volume I be expanded to include a discussion of these uncertainties. This information will allow the reader to place observations from the various analyses into perspective."

Response:

Uncertainties in the models were discussed in Volume I (Environmental Factors). The air and water models were conducted by the Environmental and Occupational Health Sciences Institute (EOHSI) and the Agency for Toxic Substances and Disease Registry (ATSDR), respectively. Both of these groups issued their own reports on the modeling efforts, which include extensive discussions and/or evaluations of uncertainty in their models.

Comment:

"Clarification on the statistical methods used in the report is warranted. Specifically, Volume II or Volume IV should contain a Statistical Methods Section which describes the statistical methods used (e.g., definition and computation of OR and its SE), and how the results (e.g., significance of odds ratios and C.I.) were interpreted by the authors. This will enhance the readability of the report and ensure consistency. In addition, the presentation of statistical analyses should be modified to present the information with a maximum of one significant figure. For example, with only four or five cases it is inappropriate to provide an Odds Ratio of 5.02."

Response:

Additional language was added in Volume II (Interview Study Methods) to clarify the analytical methods. Although use of only one significant figure for the presentation of data has merit, we prefer to maintain current data presentation for consistency with earlier report presentations.

Comment:

"The draft report lacks information on the logic as to why certain covariates were examined in the analyses. EPA suggests the inclusion of more detailed discussion on these analyses and the inclusion of parameter estimates for the regressed variables be provided to aid the readers understanding."

Response:

Bivariate analysis was performed on non-environmental factors for which associations with leukemia were observed. However, it should be noted that given the population study size, our ability to adjust for potential confounding was limited. The Expert Panel indicated that the univariate analyses would likely be the most we could do with the data. One member suggested that we should place less emphasis on confounding, because he felt that confounding was "unlikely to be a major limitation, given the lack of established risk factors for the childhood cancers of concern."

Comment:

"Finally, Dr. Ed Bresnitz discussed the importance of considering that a statistical association alone does not demonstrate biological plausibility and that there is a big difference between an association and a causal association. It is recommended that the final report should expand on this concept and more fully discuss the fact that

while an association has been established this does not necessarily establish causality."

Response:

Biological plausibility was discussed in Volume II (Risk Factor Evaluation)). As stated in the Report, "The potential causal association of a risk factor with an outcome was evaluated using a combination of criteria, including: strength of the association, statistical significance, consistency of findings of multiple measures for an exposure, apparent dose response effect, and evidence of a completed exposure pathway."

Reviewer 1:

Comment:

"*Overall, this is a well-designed and conducted study, with many strengths, including: careful attention to case and control selection (which should minimize selection bias); comparison of Interview and Birth Certificate studies with different approaches to case and control definition (the consistency of results is reassuring); objective reconstruction of exposure indices from residential histories that are unlikely to be affected by recall bias; and sensitivity analyses using alternatives methods to construct exposure indices, again the consistency of results using a variety of methods is reassuring.*

The study is severely limited by the small number of cases available for study. Consequences include: an inability to study joint results of multiple correlated exposures; inability to adequately explore potential confounding; and unstable and imprecise estimates of association, whose importance is difficult to assess.

The conclusions reached by the study are very cautious. However, four exposures were associated with leukemia, particular in young females and for exposure during the prenatal period; these include Parkway well field water; water from a private well in regions known to have contaminated groundwater; ambient air pollution from the Ciba-Geigy plant; and proximity to the Ciba-Geigy pipeline. The last of these was discounted because of lack of association with proximity to known breaks in the pipeline; although the latter measure might appear to be a more accurate surrogate for exposure, there are no data to support this assumption. The association with exposure to Parkway well field water was strengthened by accounting for tap water consumption and likely period of contamination, reinforcing the importance of this relationship. Most of these four exposures were not correlated, suggesting that they are not simply surrogates for one another. Similar chemicals - many of which are animal carcinogens - were involved in the different exposures. Thus, although the study was limited by its low power, it might be appropriate to give more weight to its results."

Response:

We believe the cautionary language expressed in the reports to describe the results is appropriate because of the limited number of study subjects. This limitation lead to generally wide confidence intervals for the odds ratios, and impacts the precision of our analyses. These issues are inherent in, and problematic for, any cluster study.

Comment:

"The limited ability of the study to reach firm conclusions suggests that the value to communities of studies of this type is severely restricted. In general, it is almost impossible to prove that a particular exposure in a particular community is responsible for a particular health effect. It may be more useful to establish (i) that particular exposures are related to health effects by conducting larger studies in independent settings chosen to provide sufficient power; and (ii) that the relevant exposure exists in a particular community. Together, these points should be considered sufficient evidence to warrant remediation and perhaps compensation. Although communities often request that their particular situation be studied, they should be helped to understand that studies of limited power may not provide them with the information they need and may in fact do harm if their findings are considered to support a lack of association."

Response:

Prior to initiating a case-control study in Dover Township, the NJDHSS and ATSDR, in cooperation with the Citizen Action Committee for Childhood Cancer Cluster and other Stakeholders, developed a systematic process of addressing the environmental and childhood cancer issues. The systematic process was detailed in the Public Health Response Plan, which included a cancer incidence update of the cancer statistics, environmental assessments of the two Superfund sites (Reich Farm and Ciba-Geigy) and the Dover Township Municipal Landfill in order to evaluate potential for past exposure pathways in the community, and extensive sampling of the community water supply for evidence of contamination. These initial activities confirmed that childhood cancer incidence was elevated in Dover Township and that there had been completed exposure pathways. It was only after laying this groundwork that we decided that there were environmental hypotheses which could be evaluated through a case-control study. Furthermore, through regularly monthly interaction with the public at Citizen Action Committee meetings we extensively described the limitations of our work and what could be expected.

Comment:

"Exposure, for example to Parkway well field water, was apparently quantified as average exposure over the relevant time period (prenatal, postnatal, total). However, the length of the postnatal period was variable; children were diagnosed at any point from birth to age 19. It would be interesting to see the effects of cumulative exposure to the various sources."

Response:

In the evaluation of childhood cancer, the time period of exposure was considered very important. In fact, the potential prenatal exposure window may be the most critical period for some of the early diagnosed cancers. Cumulative and average exposure estimates during the prenatal time period are equivalent.

Cumulative (the sum of the monthly exposure estimates over the postnatal period) and average exposures during the postnatal period (or total time period) are very different given that subject ages ranged from 0 to 19. Consequently, nearly all older children would be assigned a higher exposure value simply by having lived longer prior to diagnosis.

Comment:

"Use of odds ratios and conditional logistic regression is completely appropriate.

The small number of cases severely limits the study, making it difficult to determine whether the detected associations are meaningful. It should be emphasized that the unstability and imprecision of the estimates are likely a consequence of limited power, and that the study is also not able to draw negative conclusions, i.e., prove that the exposures are not associated with the outcomes. Limited power should have been obvious before the study was undertaken, and calls into question the rationale for conducting the study in the first place."

Response:

Power considerations were discussed in the Study Protocol which received extensive peer and public review. As discussed above, the decision to conduct the case-control epidemiologic study was based on the outcome of a number of activities specified in the Public Health Response Plan. All "cluster" studies are limited by low study power. However, based on the documented evidence of elevated childhood cancer incidence and past environmental exposure pathways in the community, it was judged that an epidemiologic study was appropriate and warranted.

Comment:

"Uncertainties regarding positive findings are clearly identified. It would be valuable to also stress that any negative findings (lack of association) are also uncertain."

Response:

We made numerous statements in the Report that the results (all results) should be interpreted carefully and that due to the limited number of study subjects the analyses are sensitive to random fluctuations, which can result in substantial imprecision in the odds ratios.

Comment:

"There are no obvious explanations for the finding of associations in female but not in male children. Regarding criteria to evaluate the likelihood of causality, the study addressed specific hypotheses; the findings are internally consistent (similar between Interview and Birth Certificate studies, and robust to various methods of calculating exposure); they are coherent with the epidemiologic literature; and they are biologically plausible given that animal carcinogens were involved. Some of the measured associations were quite strong. Their imprecision and lack of dose-response are likely a consequence of limited power. On balance, this provide weak (as opposed to no) evidence for causality."

Response:

Because of the uncertainty in the findings, we were cautious in our interpretation of the results. We believe that the findings support certain environmental exposure hypotheses during the prenatal period for leukemia in females.

Although there is no obvious explanation for differences in the sexes, the etiology of childhood leukemia is little understood. In both New Jersey and nationally, childhood leukemia incidence rates are 20-30% higher for males than females. While there is no scientific explanation for this sex differential, it is a fact that the differential exists and there are likely biological reasons for the difference, yet it remains unexplained at this point. In Dover Township (Berry and Haltmeier, 1997), childhood leukemia incidence in females was significantly elevated, while incidence in males was not elevated, relative to the State of New Jersey.

Comment:

"Given the limited power of the study, it is equally difficult to evaluate the importance of inverse and positive associations. In cases where there was a strong positive association for prenatal and no association or an inverse association for postnatal exposure, it would be useful to discuss potential biological explanations for the findings."

Response:

Prenatal and postnatal analyses focused on two distinct exposure windows: first, when the child was in utero, and second, after the child was born. It is known that exposures during different time windows in development may have different effects. Language has been added in Volume II (Interview Study Methods) to the text to make this point more clear.

Reviewer 2:

Comment:

"The assessment of the past environmental exposures by study subjects (cases and controls) is probably the most difficult task in an epidemiological Case-Control Study (often used for rare diseases). This exposure assessment is typically conducted using reconstruction computer modeling. The various exposure factors listed above have been discussed in volumes II and IV of the Case-Control Study.

Computer-based reconstruction modeling as conducted by ATSDR (ATSDR, 2000, 2001) and EOHSI (2001) was used to assess the exposure to drinking water and ambient air in Dover Township. These computer simulation models are briefly described in Appendices D and F of Volume IV. The computer models used appear to be adequate for the intended purpose of computing estimates of water consumption by the study residences from the various well fields. Specifically, computer models were used to derive monthly estimates (water source/ consumption indices) of percent of water from each of the public well fields (including Parkway and Holly Street well fields) delivered to each study residence. Similarly, atmospheric dispersion modeling was performed to estimate the potential exposure to the two air pollution point sources, Ciba-Geigy facility and the Oyster Creek Nuclear Generating Station at the study residences during the study time period (EOHSI, 2001). Computer modeling was used to obtain monthly estimates of potential exposure to air emissions from the two point sources. Adjustments were made in case of missing data (e.g, for Ciba Geigy).

These monthly modeled data (using ATSDR modeling for well fields, and EOHSI monthly air pollution estimates) were then used to derive average water and air pollution exposure indices (computed as the arithmetic average of the monthly percentages) for each study subject (case or control). For the Interview Study, these exposure indices (water source/ consumption indices) were derived for the three time periods- prenatal, postnatal, and total time period. For Birth Record Study, these indices were computed for the prenatal period. For water supply factor, these exposure indices were qualitatively categorized in low (e.g., <10% supply), medium (10% to 49.9%), and high (50% or more) exposure categories. Similarly air exposure indices were categorized in three categories separately for Ciba-Geigy and Oyster

Creek sites. Exposure indices for ever (rather than % of time a child lived near the site) having lived near (within ½ mile) the sites (seven of them) of concern were also computed for the one (prenatal) to three (prenatal, postnatal, and total) study time periods.

These categorized modeled exposure indices were used to determine associations (odds ratios) between the exposure pathways and subject status (having or not having the disease). Thus, the statistical results (correlations, OR, SE) are sensitive to random fluctuations in data and depend upon the accuracies of the modeled exposure source/consumption indices. Several confounding factors consistent with the literature (e.g., parental occupation, family medical history etc.) were also considered. These factors represent the confounding variables to the environmental exposure factors (e.g., air, water).

Computerized distribution models and exposure indices as computed and categorized in the Case-Control Study represent reasonable approaches for the intended purpose of exposure assessment. Approaches used are consistent with the literature as discussed in Appendix I, Volume IV. Models used and data thus generated (e.g., exposure indices) seem to be adequate to characterize the degree of exposure by the various exposed populations.

Data (e.g., monthly % estimates, average exposure indices) generated from these air and water computer modeling are presented in Appendices D and F of Volume IV. The assumptions made in the development of the historic reconstruction water models are summarized in Appendix D, Vol IV (and in ATSDR, 2000 and 2001 documents). Similarly, the results of the EOHSI study (EOHSI, 2001) were used to obtain monthly air emission exposure estimates. The assumptions made are summarized in Appendix F, Vol IV. The computer modeling studies as conducted by ATSDR and EOHSI are quite thorough and consistent with the literature. After reviewing the four volumes provided, the reviewer believes that the models used and data thus generated (exposure indices) seem to be adequate to characterize and capture the degree of exposure by the various exposed populations (children under 19 in Dover Township).

However, some inconsistencies in the interpretation of statistical results have been observed. For example, in Table F4 (page 95, Volume IV) for the Autumn season, a correlation of 0.16 has been reported to be statistically significant (with p-value <0.001) which seems to in error. A low correlation of about 0.16 should be insignificant at most levels (e.g., 0.01, 0.05) of significance."

Response:

The statistical significance of a correlation is not just a function of the magnitude of the correlation coefficient (r^2), but also on the number of points being correlated. In the example given, Table F4 shows the Oyster Creek gas exposure correlation to

particulate matter (0.5 and 15, separately). These correlations are based on all Ocean County study locations for cases and controls in both the Interview and Birth Records Studies for each month over a 24 year period. The number of exposure estimates at these locations makes it feasible that a correlation coefficient of 0.16 could be significant.

Comment:

"Also on pages 29-30 (Volume II), it is stated that all environmental index correlations (correlations between environmental risk factors) are significant at p<0.01 level. These index correlations (for Interview Study) range from -0.37 to 0.81 (Table 21). How one should interpret negative correlations between the environmental indices? It is not clear how was it determined that all correlations (listed In Table 21, Volume III) are significant at levels p<0.01. Some inconsistencies observed in the interpretation of odds ratios (OR) are discussed below."

Response:

All environmental index correlations were not significant at the p<0.01 level. Table 21 presents only the statistically significant correlations. A negative correlation indicates that as the value of one variable increases, the value of the other variable decreases. For example, the total amount of water reaching all homes sum to 100%. As water from one well field decreases its percent, water from other well fields increases in percent to compensate for the loss from the first well field.

Comment:

"Since the conclusions derived are based upon the strengths (values of OR), significance or insignificance of correlations and associations (odds ratios), it is desirable to include a section explaining the statistical significance or insignificance of the various association statistics (odds ratios, correlation coefficients) used. What level of significance was used? How were the p-values determined and used? Were the p-values copied from the computer outputs?"

Response:

A combination of criteria were used to evaluate the potential casual association of a risk factor with an outcome. These include strength of the association, statistical significance, consistency of findings of multiple measures for an exposure, apparent dose response effect, and evidence of a completed exposure pathway.

A 95% confidence interval (p<.05) was used to determine the statistical significance of an odds ratio. The p values were generated by the Stata statistical software. Additional language has been added to Volume II (Interview Study Methods) on

statistical significance, as suggested.

Comment:

"Also, it is stated that the statistical power of the study is low (page 69, Volume II), and imprecision and uncertainties (standard errors (SE) of OR) in estimates of OR are high. The statistical results (correlations, OR, SE) are sensitive to random fluctuations in data and depend upon the accuracies of the exposure source/consumption indices. It is desirable to include the power study analysis in the report."

Response:

Power calculations were presented in Volume II (Interview Study Strengths and Limitations and Birth Records Study Strengths and Limitations), and also discussed in the Study Protocol.

Comment:

"The Case-Control study design (matched analyses- controls matched by age, sex, and other criteria) used to compute the associations between risk factors and select cancer groups (disease) represents a well thought design for both the Interview Study and the Birth Records Study. Odds ratios (OR), logistic regression, conditional logistic regression (matched analyses), and relative risks are often used in Case-Control and Cohort Studies (e.g., see Daly and Bourke, 2000, Hosmer and Lemeshow, 2000) to determine the magnitude of association between exposure factors (e.g., air emission) and a specific disease (e.g., leukemia). An odds ratio close to 1 (=null value, the value under the null hypothesis) suggests insignificant association between exposure to a risk factor and the specific disease. Higher values (>1) of odds ratio are indication of association between exposure to a risk factor and the disease under study. Uncertainty in an odds ratio is usually determined by its SE, the length of the associated 95% confidence interval (C.I.), or an upper confidence limit (UCL) of the OR. Higher SE and wider C.I. intervals are indication of uncertainties in the OR estimates.

Some clarification on the statistical methods used is warranted. Specifically, it will be useful to include a Statistical Methods section in Volume II or in Volume IV giving details of the statistical methods used (e.g., definition and computation of OR and its SE), and how the results (e.g., significance of odds ratios and C.I.) should be interpreted. This will enhance the readability of the report and make the derived conclusions statistically sound. Matched analyses and conditional logistic regression have been performed to compute odds ratios for the cancer groups considered. For environmental exposure factors (e.g., air, water, proximity) considered, odds ratios were computed for one (birth record study) to the three (for interview study) time periods (prenatal, postnatal, and total study time). These statistical methods are suitable for the case-control epidemiological studies. It is observed that the statistical

results of the study have been presented in Volume III. However, criteria used to determine the significance or insignificance of statistical results are missing from the report. Also, it is observed that some of the results have not been interpreted adequately (e.g., see 2 above and 6 below)."

Response:

Additional language has been added to Volume II (Interview Study Methods) on the analytical analyses.

Comment:

"An explicit power analysis about the significance of the observed association between prenatal Ciba-Geigy air emissions exposure factor (modeled) and prenatal time-specific Parkway well field water exposure factor (modeled) and leukemia in female children is missing from the report. Based upon the results provided, it will be difficult to assess the robustness on the observed associations.

However, limited sample size can result in wider uncertain (with negative values) intervals of odds ratios for the various hypotheses tested. A chisquare approximation (used in the computation of SE of OR and a 95% C.I. for OR) assumes that the expected number of observations (individuals) in each cell (e.g., factor-disease cell) should be at least 5 (Daly and Bourke,2000). Due to limited number of samples (cases), this assumption may not have been satisfied which in turn might have contributed to larger uncertainties (SE) and C.I. for odds ratios.

The uncertainties pertaining to the study findings have been identified by using the 95% confidence intervals of the odds ratios. Wider confidence intervals of the odds ratio suggest greater uncertainties in the odds ratios (which represent associations between risk factors and disease). This has been recognized in the report, for example on page 69, Volume II. These uncertainties can result due to several reasons including small sample sizes, recall bias in the Interview Study, and other confounding risk factors (e.g., family history etc.). Typically data presented in a contingency table is used to compute the association (odds ratio) between risk factor and subject status. For results (OR.) with adequate accuracy and precision (reduced uncertainty and SE), it is recommended that the expected cell frequencies be at least five (e.g., page 241 Daly and Bourke, 2000) for the computation of chisquare statistic. Note that chisquare statistic is used in the computation of the SE and C.I. of an OR. The standard error (SE) of an OR also represents a measure of uncertainty in the OR estimate. Since, SE of an OR is used in the computation of a 95% C.I. of OR, there is no need to directly report the SE in the report."

Response:

Odds ratios were calculated using Stata software and conditional logistic regression for matched case-control data. Standard errors were not presented for odds ratios in the Report. Only 95% confidence intervals were reported. Power calculations were presented in Volume II (Interview Study Strengths and Limitations and Birth Records Study Strengths and Limitations), and discussed in the Study Protocol.

Comment:

"It is observed that there are some inconsistencies in the interpretation of results. Subjective judgements have also been used to derive some of the conclusions. For example, it is observed that the while the OR are not elevated (e.g., Tables 7-9, Vol III), the associated C.I. of the odds ratio are wide and the upper confidence limits (UCLs) of the OR are elevated exceeding 5, 10, 20 etc. It is desirable to elaborate on the interpretation of such results. For example on page 22, Volume II (first paragraph last sentence), it is stated that time-specific well (for both Holly Street (prior to 1976) and Parkway (after 1982)) field exposure did not appear to be associated with case status (Tables 9a-9d). This statement needs statistical justification. How is the significance or insignificance of an OR determined? What makes an OR elevated?

Why are the OR of 4.99 (prenatal high exposure category, all ages combined for females, time-specific Parkway well field, page 22, Vol II) and 3.23 (prenatal high exposure category, females prior to age 5, time-specific Parkway well) not statistically significant? Why are these elevated?

The OR for postnatal time-specific medium exposure Parkway well field-brain and central nervous system cancer for age<5 is as high as 3.46 with the associated C.I. = (0.27, 43.9) - Table 9d, page 8/8 (Vol III). If this result is considered to be insignificant and not elevated, then what is the justification of concluding that for the prenatal high exposure period for time-specific (1982-1996) Parkway well field, OR is elevated for females diagnosed with leukemia before age five (OR=3.23, 95% C.I. = (0.52, 20.1)) - page 22, Volume II. This limits the credibility of the derived conclusions. Similar subjective statements and inconsistencies were observed in other conclusions as described in Volume II.

The association (measured by OR and UCL of the OR.) between mothers inhaling modeled air from Ciba Geigy site during pregnancy and the incidence of leukemia in their female offspring appear to be high (page 27 Volume II). The results are given in Tables 17a through 17d. Again some inconsistencies have been observed in the interpretation of results. On page 27, it is stated that the medium prenatal Ciba-Geigy air exposure category was significantly associated with leukemia in female for all ages combined (OR=6.42; 95% C.I. = 1.09, 37.8). At the same time on the same page it is stated that, " although not significantly associated, the odds ratios for the medium (OR=5.21; 95% C.I..= 0.48, 56.5) and high (OR=18.9; 95% C.I. = 0.90, 397) Ciba-Geigy prenatal exposure categories were elevated for leukemia in female

children diagnosed before age 5. It is not clear how was it determined that association was significant for prenatal medium exposure category for all ages combined (OR=6.42), and not significant in the other medium (OR=5.21) and high (OR=18.9) prenatal exposure categories for female offsprings before age 5.

Furthermore, it is concluded that (page 15, Volume I), exposure to Oyster Creek ambient air emissions did not appear to be associated with any childhood cancer groups evaluated in either the Interview or Birth Record Studies. However, for leukemia and nervous system cancers, elevated OR and UCL of OR are observed (e.g., Table 16, page 2 of 8, Vol III) for prenatal Oyster Creek Gas exposure in ages 0-4 (males and females combined) in medium and high exposure categories. For medium category, the OR=6.37, 95% C.I.=(0.62, 65.3), and for high category, OR=1.55 with 95% C.I.= (0.02, 99.9). The later interval is quite wide suggesting high uncertainty in the estimates. This is due to the availability of only 2 cases in this category. None the less, statistically these UCLs (65.3 and 99.9) represent elevated OR suggesting some association between prenatal exposure and Leukemia and Nervous System Cancers for Oyster Creek source. Similarly, for Oyster Creek source, elevated OR was observed between (Table 16, page 5/8) prenatal medium exposure and brain and nervous system cancers. Similar elevated OR pattern was observed for Oyster Creek air prenatal exposure in both males and females when these statistics were computed separately (Table 17a, page 1/8) for males and females for the medium exposure gas category.

It appears that some subjective statements have been made about the significance or insignificance of odds ratios. As mentioned before, some justification is needed for the interpretation of results. It is very well possible that some of the conclusions derived may not be accurate due to the limited availability of study subjects. A small sample does result in wide C.I. (e.g. for Oyster Creek, prenatal high category, the number of case =2, and a 95% C.I. = 0.02, 99.9). A statistical section giving details of the methods and criteria used to determine the significance or insignificance of a result should be included in the report."

Response:

In the Results sections of the Report, statistically significant and select elevated odds ratios were highlighted. Interpretation of the results was presented in the Discussion section. An odds ratio was considered to be statistically significant if the confidence interval did not include the value 1.0.

Our Expert Panel cautioned that we should not focus too much on statistical significance. As discussed by Rothman and Greenland (in Modern Epidemiology: Approaches to Statistical Analysis, 1998):

> the preoccupation with significance testing derives from the research

> interests of the statisticians of the early 20th century whose research problems were primary industrial and agricultural typically involving experiments intended to facilitate decision making. Much of the popularity of significance testing stems from the apparent objectivity and definitiveness of the pronouncement of significance. Declarations of significance or its absence can supplant the need for more refined interpretations of the data; the declarations can serve as a mechanical substitute for thought. It is preferable to view the confidence limits as only a rough guide, and a minimum estimate, of the inherent uncertainty in an epidemiologic result. An interval estimation procedure does more than assess the extent to which the null hypothesis is compatible with the data. It provides simultaneously an idea of the likely magnitude of the effect and the random variability of the point estimate. Points nearer the center of the confidence interval are more compatible with the data than points further away from the center. Results that are not significant may be compatible with substantial effects, while lack of significance alone provides no evidence against such effects. The confidence limits could indicate that the data, although statistically compatible with no association, may be even more compatible with a strong association.

Consequently, as stated in Volume II (Interview Study Methods), the association of a risk factor with an outcome was "evaluated using a combination of criteria, including: strength of the association, statistical significance, consistency of findings of multiple measures for an exposure, apparent dose response effect, and evidence of a completed exposure pathway." As our Expert Panel pointed out, these criteria are used in all epidemiologic studies to evaluate exposure disease relationships.

Comment:

"Negative associations (represented by the lower limit of C.I. of an OR) between environmental exposures and incidences of childhood cancer should be explained in the final report. By definition, odds ratios should take only positive values. Occurrence of negative values of OR clearly suggest that the uncertainties associated with odds ratios are high. This could be due to several reasons namely, the underlying assumptions may not have been satisfied. A chi square approximation used in the derivation of the SE and C.I. for an OR requires that the expected number of individuals in each cell (factor-disease) should be at least 5. Violation of this statement can lead to imprecise results. Negative OR (represented by the lower limit of its 95% C.I.) are observed due to large SE of the OR estimates. These negative OR values have no physical interpretation."

Response:

None of the odds ratios presented in the Report have a negative value. The term "negative association" could be used to mean either an absence of statistical significance (i.e., no association) or an indication that a factor is inversely associated with the disease outcome (i.e., protective). We have used it to mean an inverse association.

Comment:

"It is desirable to include a Statistical Methods section in the report. This section should briefly define and describe how the association statistics (odds ratios, correlation coefficients) and the associated 95% confidence intervals are computed and how to interpret them. How and when is it determined that an OR is statistically significant or elevated? What are the sample size requirements? What if the requirements and assumptions are not met? For example, it should be documented why a relationship is considered statistically significant (or insignificant) and at what level of significance (e.g., 0.05, or 0.01 etc.). For example, how was the decision derived that a correlation of -0.25 is statistically significant (page 29, Volume II)? How one should interpret negative associations (OR) in the present context? How was the decision (page 28, second paragraph, Vol II), " Ever living within ½ mile of the Ciba-Geigy pipeline was found to be significantly associated with leukemia during total time period for all ages combined (OR=2.63; 95% C.I. = 1.03. 6.67)," derived?

It is also desirable to include the power analysis in the report. It is stated (page 16, Volume II) that potential causal association of a risk factor with an outcome was evaluated using strength of the association and statistical significance. It is desirable that the definitions of strength of association and statistical significance be provided in the Statistical Methods section. Inclusion of such a section will enhance the report and make the study findings statistically sound."

Response:

A presentation of the analytical methods appears in Volume II (Interview Study Methods and Birth Records Study Methods). Power analyses were presented in Volume II (Interview Study Strengths and Limitations and Birth Records Study Strengths and Limitations). Additional language has been added to Volume II (Interview Study Methods) concerning the analytical methods, as suggested.

Reviewer 3:

Comment:

"This draft report contains several strengths. Much thought appears to have gone into the design of the study and the investigators are to be commended for collecting as much information on the many variables of interest. Additionally, the expert panel

gathered to advise study investigators appears well qualified to provide technical advice in the area of epidemiologic studies assessing environmental exposures; many individuals on this panel have previously carried out epidemiologic investigations into environmental factors. Study investigators have, also, taken great care to obtain information from both the child and mother on important variables for the interview portion of the study which, by definition, could not be obtained for the analysis of birth records. Last, study investigators apply standard statistical methodology, conditional logistic regression analysis, to evaluate the relationship between exposure and outcome.

The New Jersey draft report draws conclusions of an association between maternal prenatal exposure to Parkway well field water and childhood leukemia in female offspring and of an association between maternal prenatal exposure to ambient emissions from a Ciba-Geigy facility and leukemia in female children diagnosed prior to age five. The findings in this study appear to support the first conclusion of an association between Parkway well field water and leukemia risk in female offspring. The association is best depicted in Figure 6a (Volume III) of the report where odds ratios from the interview study increase with what appears to be more specific information from the mother; however, see my comment below on the weight I attach to a particular exposure metric. This observation is consistent with the presence of exposure misclassification bias in exposure measures that do not include consumption information of the mother; measures biased by exposure misclassification would be closer to the null or a risk of 1.0. In fact, the lower confidence interval is above 1.0 for the association between leukemia in females and one measure that includes information on maternal consumption and for the time period associated with the greatest probability of water contamination, suggesting chance as an unlikely explanation. Furthermore, results from the birth records study add support to the observations in the interview portion of this study.

Less clear is the support for the conclusion on ambient emissions. A strong but imprecise association was observed in both the interview study and in the birth records study between leukemia in female offspring who were less than 5 years of age and high maternal exposure to emissions. The association between leukemia and medium exposure is less than the odds ratios for high exposure, with the point estimate still above an odds of 1.0. These observations are suggestive of an exposure-response relationship; however, study investigators do not provide evidence in the report that they carried out a statistical test for trend and I recommend this information be added to the text."

Response:

We did not do tests for trend. Instead we presented odds ratios for each category separately.

Comment:

"Ambient modeling of emissions is highly correlated to other exposure measures, for example, living within 1/2 of the Ciba-Geigy facility for which the correlation coefficient was r=0.81 (p. 30, Volume II). Given the high degree of correlation between several variables in this study and a single source, I would expect analyses assessing the relationship between these variables and leukemia to support the findings of the relationship with ambient air modeling. This does not appear to be the case, however (see Table 20 and Table 55, Volume III). Additionally, Table 20 shows larger and statistically significant risks for other variables, for example, living with 1/2 mile of the Ciba-Geigy pipeline. The draft report needs to more clearly articulate the support for their conclusion on ambient emissions and its consistency with other findings in this study."

Response:

While the indices for modeled Ciba-Geigy emissions and residential distance from Ciba-Geigy are correlated (based on the total time period), the variable "lived within ½ mile of Ciba-Geigy" is a cruder measure of exposure than the modeled estimates because it merely relies on linear distance without incorporating important meteorological data to characterize where the emissions were going. In fact, that is why we conducted the ambient air modeling. However, it is important to note that as presented in Volume III (Table 20b.), the odds ratio for females diagnosed with leukemia (all ages combined) and prenatal residential distance from Ciba-Geigy was 6.0, while the odds ratio for females diagnosed under age five with leukemia could not be calculated due to loss of an exposed control subject. This, perhaps, provides additional support that Ciba-Geigy emissions are associated with female leukemia.

Comment:

"The presentation of many odds ratios in the current draft makes it difficult to follow the consistency of findings over a number of exposure variables that are intended to measure a similar source. The report would benefit from the inclusion of a discussion of the weight placed on a particular exposure metric; this way, the reader can place observations from the various analyses into better perspective. For example, do study investigators place greater weight on an exposure metric that is defined as average percentage of water distribution or a metric that incorporates specific information on the mother's or child's water consumption pattern? This is not well defined in the draft for public comment."

Response:

The variables "water source" and "water source/consumption" describe two separate methods to estimate exposure to water from a particular well field. While addition of

the consumption information was an attempt to modify "water source" by incorporating quantity into the second metric (considered an improvement), the consumption information was self-reported and, therefore, could be incorrect due to recall bias (lessening the improvement).

In the Risk Factor Evaluation component of the Discussion section, we discuss the interpretation of all the data for a factor. In general, important considerations include whether there was a known exposure pathway, specific exposure time windows (e.g., prenatal), and more homogeneous cancer groupings (e.g., leukemia). Additional language has been added to Volume II (Interview Study Methods).

Comment:

"Second, the report needs to place into context similarities or differences in observed results from the interview study and the birth records study. The figures contained in Volume III are a good starting point since odds ratios and their 95% confidence intervals for a number of analyses examining a similar exposure source are presented for the interview study and the birth records study. However, this is only a limited presentation and not all odds ratios are presented for all analyses. For example, Figure 6a nicely displays odds ratios for the interview study, however, the analogous information for the birth records study is missing and its inclusion would provide more information to the readers. Additionally, resultant odds ratios from analyses examining the relationship between leukemia in female offspring diagnosed before age 5 and ambient air model and residential proximity to the Ciba-Geigy facility are also not presented for either the interview study or the birth records study. The lack of an integrated synthesis of the various exposure metrics and of observations from the interview study and birth records study makes it difficult for the reader to fully judge the validity of the draft's conclusions."

Response:

In the Risk Factor Evaluation component of the Discussion section we discuss the interpretation of all the data for a factor. Odds ratios and their 95% confidence intervals were presented graphically for leukemia and for brain and central nervous system cancer in all ages combined where there was at least two cases in the exposed or unexposed categories. All odds ratios and their 95% confidence intervals were presented in tabular form.

Comment:

"Study investigators appear to place greater weight on observations from univariate analyses (analyses of only one exposure metric), as judged from the lengthy discussion in the draft report, than on observations from bivariate analyses (where overall risk is a function of two risk factors), for which few details are provided. The draft report

lacks even basic information on these analyses such as the point estimate and 95% confidence interval, in addition, to the logic as to why certain covariates were examined. I suggest the inclusion of more detailed discussion on these analyses and the inclusion of parameter estimates for the regressed variables. Several variables were shown to be statistically significantly associated with leukemia risk and a thorough presentation of the bivariate analysis is important so as to judge the overall conclusions. Univariate analyses only consider one variable and not effects from multiple variables that may contribute to the overall association; hence, univariate analyses are quite limited. Additionally, I recommend that study investigators consider a multivariate analysis of leukemia risk and exposure to sources of interest where the model includes the effects of other several pre-determined important covariates. While a multivariate analyses will have reduced power and the 95% confidence interval may include an odds ratio of 1.0 for this reason, these analyses can provide some insight as to how a particular source may contribute to overall risk. This also begins to address cumulative risk, an emerging issue in risk assessment, since a number of exposures may potentially contribute to the elevated leukemia risk."

Response:

While bivariate analyses were performed, it should be noted that given the relatively small study size, our ability to adjust for confounding was extremely limited. In fact, the Expert Panel cautioned us that the univariate analyses would likely be the most we could do with the data. One member suggested that we should place less emphasis on confounding than we did, because he felt that confounding was "unlikely to be a major limitation, given the lack of established risk factors for the childhood cancers of concern."

Comment:

"The number of cases did not remain a constant over all analyses. For example, Tables 11c and 11d (Volume III) note 18 cases of nervous system cancers for analyses examining water distribution from the Brookside source well fields, however, all other analyses in this table are based on 17 nervous system cancer cases. I would like to see a discussion in the text as to why these analyses are based on differing numbers of cases."

Response:

In this particular instance, there was missing data for one of the cases because we were not able to interview one of the mothers. Hence, we had address information, but did not have consumption data.

Comment:

"Birth records became electronically available in 1966 (Volume II, p. 49), and I have difficulty placing into perspective the implication of this date with respect to identifying births as possible controls. The draft report does not identify the time period for births to be considered as a possible control. Given the earliest possible date of birth for a case was 1959, it is important to discuss how the control population was identified for cases whose births occurred between 1959 and 1965."

Response:

The electronic birth record files were used to match against childhood cancer cases from select state cancer registries, in an attempt to identify Dover Township births that had been diagnosed with cancer after moving out of Dover Township. Controls were selected from Dover Township birth records, using electronic files or, when necessary, paper files. Language was added to clarify this point in Volume II (Birth Records Study Methods).

Comment:

"*In conclusion, the study described in the draft for public comments is very similar to a recent analysis of childhood leukemia and possible associations with solvent contaminated well-water (Ma DPH, 1997). The Ma DPH (1997) study suggested that the relative risk of developing childhood leukemia was greater for those children whose mothers were likely to have consumed water from wells contaminated with trichloroethylene, perchloroethylene, chloroform, and other organic compounds. Like that found in the New Jersey study, the Ma DPH study observed the highest risk with maternal exposure during pregnancy. These studies together are suggestive of an increased susceptibility to the fetus and pregnancy as a critical window of exposure. The lack of a discussion that places into perspective findings from multiple exposure metrics for a source, in addition, to the need for more detailed information on bivariate or multivariate analyses limits my ability to fully judge the validity of the NJDOHSS draft report conclusions. The incorporation of the suggestions identified above should help with this determination.*"

Response:

Responses to these suggestions are discussed above.

Commenter: New Jersey Department of Environmental Protection

Comment:

"Overall, the study appears well designed, well executed, and reasonably interpreted. While the implications of the findings appear (given protective measures already in place) to be historical rather than current, the findings of the study suggest a relatively coherent and, for the most part, plausible picture of associations between pre-natal exposure to Parkway water and possibly to air emissions from the Ciba-Geigy facility, and leukemia in females. Importantly, the study does not appear to provide any explanatory associations for nervous system cancers. As indicated in the following, however, we have questions regarding the air modeling and the exposure estimates derived from the air modeling. We do not believe, however, that our questions significantly impact the overall conclusions of the study.

Some of the terminology of the draft report and, in particular, the frequent use of statistical terminology may not be readily understood by the general public ("temporal adjustments" and "a priori hypothesis" were two terms that were cited). We suggest consideration of more explanation when such terminology is used."

Response:

Volumes II-IV are written as technical reports. We have used lay language in Volume I, the Citizen's Guide, and other communications about the report's findings that targeted the general public. These are available on the NJDHSS website (www.state.nj.us/health).

Comment:

Executive Summary - "The presence of the SAN trimer is briefly noted, and it is appropriate that it is not given particular attention given that this study focuses on epidemiological rather than strictly environmental findings. However, since the issue of the trimer is well known in the community, and it is likely to be an underlying issue in the public's interpretation of the report, it should be noted that it has been determined that the trimer (with environmentally irrelevant impurities removed) has been found to be negative in mutagenicity tests with and without metabolic activation, and was not highly toxic in fourteen day studies in rats and mice. It should further be noted that while lack of mutagenicity does not preclude carcinogenicity by other mechanisms, it calls into question the potential for the trimer to be responsible for observed associations."

Response:

The trimer was only one of many potential Reich Farm contaminants in the groundwater. Historically, the groundwater was not well characterized during much of the exposure period of interest. Available data provided little information on the specific chemical composition of these contaminates given the nature of the waste dumped at Reich Farm. Additionally, NIEHS is currently pursuing extensive testing to determine the heath implications of the trimer at this time, and no definitive information is yet available from these studies. Hence, we decided to examine "exposure" to the drinking water sources through time, rather than specific contaminants that may have been present.

Comment:

"In addition, in the Executive Summary (as well as in the Technical Report) the implications of the non-environmental associations with the cancer cases (e.g., antibiotic use, diagnostic x-rays) is not discussed. While some of the odds ratios (ORs) for the exposure variables relating to the a priori hypotheses are adjusted relative to each other, this is not the case for the non-environmental factors. Thus, there does not appear to be any attempt to determine whether these non-environmental factors may be confounding the observed associations with environmental factors. It is not clear whether such confounding can be addressed directly given the nature of the interview data for these factors, but this issue should at least be discussed."

Response:

Bivariate analysis was performed on non-environmental factors for which associations with leukemia were observed. As noted in Volume II (Other Factors), non-environmental factors evaluated in the bivariate analyses include: child's antibiotic use, mother's consumption of cured meats during pregnancy, child's exposure to household appliance EMF, mother's prenatal tap water consumption, mother's prenatal occupational exposure to dyes and pigments or solvents, mother's use of prenatal vitamins, number of mother's live births, and father's prenatal occupational exposure to petroleum products. However, it should be noted that given the population study size, our ability to adjust for confounding was limited. The Expert Panel indicated that the univariate analyses would likely be the most we could do with the data. One member suggested that we should place less emphasis on confounding than we did, because he felt that confounding was "unlikely to be a major limitation, given the lack of established risk factors for the childhood cancers of concern."

Comment:

"In general, the conclusions as stated in Executive Summary are clear and defensible. However, the conclusions regarding associations with ambient exposure to air emissions from the Ciba-Geigy plant *may not be expressed with sufficient caveats and uncertainty given the lack of statistical significance in the relevant ORs. This is discussed in more detail in the following comments on the Technical Report."*

Response:

These general comments are addressed in the more detailed comments below.

Comment:

"In general, the Technical Report is not as clearly written as the Executive Summary. While it deals in more detail with technical issues, it is largely inaccessible to even those with scientific, but not epidemiological, backgrounds. Little or no attempt has been made to explain technical terms or concepts, such as conditional logistic regression, and bivariate adjustment, with the result that even those members of the public who seriously attempt to read and evaluate the Technical Report will become frustrated. This is unfortunate as the conclusions highlighted in the Executive Summary rely on the analyses in the Technical Report."

Response:

Volumes II-IV are written as technical reports. We have used lay language in Volume I, the Citizen's Guide, and other communications about the report's findings that targeted the general public. These are available on the NJDHSS website (www.state.nj.us/health).

Comment:

"While the focus on a prior hypotheses is appropriate, the Introduction of the Technical Report should explain why it was necessary for the study design to test specific a priori hypotheses rather than to generate conclusions from examination of all possible variables."

Response:

Before embarking on any epidemiological study, it is important to have specific testable hypotheses. As stated in the Study Objectives, "While no single risk factor was the focus of the study, the study was designed to examine specific hypotheses about certain environmental exposure pathways identified in the community."

Comment:

"The designation of two age categories for examination of age at diagnosis is not adequately justified other than to state that "These are the age groups in which elevated rates were previously found." The nature of this previous determination is unclear. In addition the significance of age at diagnosis does not appear to be adequately addressed."

Response:

The peer-reviewed Study Protocol designated separate evaluation of these age groups. We considered it important to examine the youngest children separately since there may be different risk factors which result in cancer developing at an earlier age.

Comment:

"It is not clear from the explanation of the Interview and Birth Record study designs why there were 4 controls for each case in the Interview Study, but 10 controls for each case in the Birth Records Study. Since the number of controls increases the power of the study, one would, of course, want to maximize the number. It appears likely that because of the necessity of actually interviewing all the controls, the number of controls in the Interview Study was dictated by logistical, time and resource considerations, but this should be explicitly discussed."

Response:

The original study protocol proposal specified four controls for both the Interview Study and the Birth Records Study. However, during the Stakeholder review process, a consensus of the Stakeholders recommended the use of ten controls per case for the Birth Records Study due to the relative ease of collecting the data. Although more than four controls per case could have been used in the Interview Study, very little additional increase in the precision of the odds ratio would have been gained with more controls.

Comment:

"While uncertainties are discussed in terms of sensitivity analyses and reference to standard engineering practices, the relative uncertainties in the exposure estimates for water and air should be explicitly stated. Without such a statement it is impossible to judge the probability of misclassification of exposure estimates for the cases and controls."

Response:

We attempted to address this issue in Volume II (Discussion Introduction), where we discussed both ATSDR's and EOHSI's sensitivity analyses. ATSDR concluded that their "sensitivity analysis found that estimates did not vary greatly, with the annual standard deviation of the differences always less than ten percent and frequently less than five percent (ATSDR, 2001)." EOHSI concluded in their sensitivity analyses that the "use of a different model or the use of closer weather data each produced higher exposure estimates compared to the data used for the exposure assessments...but similar relative patterns (EOHSI, 2001)."

Comment:

Environmental Exposure Pathways - "On page 5 it is stated that the Oyster Creek Nuclear Generating Station was identified as a site of potential environmental contaminants that were of concern to the community. The plant is located 10 miles to the south of Dover Township and even a simplistic calculation quickly demonstrates that any radiation exposure to the public from Oyster Creek could not even reach 0.1 % of the annual background exposure. The nature of the citizen concern expressed and the method by which the concern was solicited or expressed should be cited. On page 5 of the report Atmospheric Dispersion Modeling Analysis to Support the Dover Township Childhood Cancer Epidemiologic Study (Chandrasekar, A., et. al., Technical Report CCL-TR01-02, Revised May 2001, Environmental and Occupational Health Sciences Institute, UMDNJ, Rutgers, The State University of New Jersey) it is noted that the basis for selecting Oyster Creek was "community concerns" but no further information is given."

Response:

During the early stages of planning the epidemiological study, the issue of Oyster Creek emissions were repeatedly discussed during community meetings in Dover Township. "Simplistic calculations" were not considered sufficient to address these concerns. Consequently, we felt that the most direct approach to address this community concern was to evaluate Oyster Creek via an air dispersion model.

Comment:

"It is stated (pp. 8 – 9 Exposure to Pollution from Point Sources) that monthly air pollution estimates from the Oyster Creek Nuclear Generating Station for each study residence were calculated. Appendix F of Volume IV and the previously cited EOHSI report on air dispersion modeling (see p. 7 of the report) indicate that exposure estimates were obtained using an "EPA-approved" computer model titled "Industrial Source Complex model Short-Term version (ISCST3)". We have been unable to locate anyone in the nuclear industry, or a regulatory agency that deals with the nuclear industry, that uses the ISCST3 code for assessing exposure to air emissions from nuclear power plants. Codes that are widely accepted for this purpose by the nuclear

industry and nuclear regulatory agencies include CAP88-PC, XOQDOQ and MIDAS. Since an industry standard model was not selected, the use of the ISCST3 code should be discussed in terms of the advantages it provides over existing industry standard models or, alternatively, the limitations of the ISCST3 code for modeling exposure to nuclear power plant emissions should be discussed."

Response:

The EOHSI modeling report was independently peer reviewed by modeling experts. Two of the three peer reviewers felt that the ISCST3 model used by EOHSI was an appropriate and valid model for this application, while the third reviewer was unsure and suggested that the CALMET/CALPUFF model might be better. The ISCST3 model has been used extensively in regulatory risk assessments and has proven useful for a variety of applications.

Comment:

"As one example of our concern for the accuracy of the exposure estimates provided by the ISCST3 code, we note that iodine-131 was treated as a gas. At a distance of 10 miles from Oyster Creek, it is likely that little, if any iodine would arrive in Dover Township in gaseous form. Most of it would have plated out on intervening surfaces, been adsorbed on particulates in the air, attached to water vapor or washed out by precipitation. Does the ISCST3 model account for these losses? If not, what effect would this have on exposure estimates at the various residence locations?"

Response:

The ISCST3 model does not take into account loss by the methods mentioned. The monthly exposure estimates generated by the ISCST3 model for Oyster Creek were all extremely low, far below any level for health conern. The affect of such a loss would be to decrease the exposure estimates even lower. However it should be noted that although iodine emission concentrations were modeled, iodine was not the only radioactive gas emitted from the facility. EOHSI recommended using iodine because it was the most frequently reported gas emission in the quarterly NRC reports. Also, separate model runs were conducted for gaseous and particulate dispersion, which displayed high correlation between results.

Comment:

"As a second example, the air dispersion analysis report notes (see p. 14 of the report) that the input emission parameters for modeling exposure to particulates were the

sum of the reported emissions of cesium-137, cobalt-60 and strontium-90. What was the necessity to aggregate these three parameters? A technical concern we have with this aggregation is that while Cs-137 and Co-60 are generally measured in effluent releases, Sr-90 is not. The concentration of Sr-90 is typically inferred from Cs-137 and Co-60 measurements. The reason for this is that both Cs-137 and Co-60 are gamma emitters and measurements of their concentrations are relatively easily made by gamma spectrometry. Sr-90, on the other hand, is a beta emitter and not directly measurable in the effluent stream. Further, given the age of the plant, the methods by which these concentrations were obtained (measurement, inference, or other techniques) may have changed with time. These issues and their effects on the exposure estimates should be discussed and explained."

Response:

The underlying idea was to use a relative measure of potential overall exposure to emissions from Oyster Creek. EOHSI identified three isotopes of particular concern in the NRC data.

Comment:

Appendix F - "Point Source Air Pollution Assessment in Volume IV (p. 80) notes that "This model did not include the effects of sea breezes typical of coastal areas." Reference to the original EOHSI report (Chandrasekar, et al., Atmospheric Dispersion Modeling Analysis to Support the Dover Township Childhood Cancer Epidemiologic Study, p. 12) notes that "It is not possible to precisely determine the influence of sea breezes across the Dover Township area since the area of interest stretches from the coast to twenty miles inland." First, while influence of sea breezes is difficult to "precisely" determine, their potential affects on the exposure estimates that were calculated should be discussed. In particular, the effect the wind shift created by the sea breeze should be addressed. Second, it is unclear as to why the area of interest extends to twenty miles inland. Dover Township extends approximately 10 miles inland from Barnegat Bay and approximately 13 miles inland from the eastern shore of the barrier island. Further, due to the shallowness of the bay, it behaves more like a landmass than water. The rationale for the statement that the area of interest extends 20 miles inland should be clearly explained."

Response:

The study area for the air modeling was all of Ocean County, which extends well inland. The Atlantic City meteorological data were used to characterize weather in

the study area. The Atlantic City data incorporates a sea breeze effect. We consider that this information is the most complete and reasonable data for use.

Comment:

"This section (p. 16, last paragraph – Analytical Methods) is unclear, particularly as it relates to the basis for grouping and cut points."

Response:

We believe the bases for grouping and establishing cutpoints are sufficiently described; the identical language was used in the peer-reviewed Interim Report released in December 1999.

Comment:

"Even for the initiated, more explanation of conditional logistic regression is needed (p. 17 – Analytical Methods)."

Response:

Additional language has been added to Volume II (Interview Study Methods) to explain conditional logistic regression.

Comment:

"The accounting of the control recruitment is confusing (pp. 18 – 19, Interview Study Results), particularly regarding apparent contradictions between the first two full paragraphs (i.e., in the first paragraph 159 were eventually interviewed, while in the second paragraph, 132 were interviewed)."

Response:

The first paragraph of the control recruitment focuses on the overall success of recruitment. The second paragraph focuses on the success of recruiting the original four controls selected per case. Of the 159 controls interviewed, 132 of these were original controls (i.e., originally selected as one of the four controls per case) while the other 27 were selected only after an original control refused to participate or could not be found. The issue addressed by this information relates to possible selection bias and representativeness of the control population to the overall Dover Township childhood population. The two paragraphs are nearly identical to the language released in the peer-reviewed December 1999 Interim Report. Language has been added to the second paragraph.

Comment:

"While some care was taken in the Executive Summary to explain the nature and significance of Odds Ratios, no explanation is given in the Technical Report. This is not necessarily a well known or intuitive concept even for (non-epidemiologist) scientists."

Response:

As discussed earlier, Volume II is a technical report. However, additional language has been added to the Methods section to further explain some of these concepts.

Comment:

"While the occurrence of (apparently only one) significant negative association (postnatal exposure to Parkway water for source/consumption data for female leukemia with diagnosis before age 20) is pointed out, its implications for interpretation of positive associations is not discussed in terms of the multiple hypothesis fallacy. In addition, it seems that based on chance alone, there should have been more such seemingly spurious associations. The possibility, therefore, that some seemingly reasonable associations are also spurious should be discussed.

What is the significance of finding significant positive associations for leukemia and nervous system cancers combined, but for neither separately in Tables 11-13?"

Response:

The rationale for interpretation goes beyond statistical significance. Statistical significance is a function of the magnitude of the odds ratio and the number of study subjects. We discuss at length our rationale for interpretation in the report. The issue of multiple comparisons is discussed in Volume II (Interview Study Strengths and Limitations and Birth Records Study Strengths and Limitations).

Comment:

"That significant and near significant ORs occur almost exclusively prenatal exposures is striking, as is the increase in OR with increasing temporal, water consumption, and sex specificity. This lends strong support to the implication of Parkway water in a causal association."

Response:

As stated in our conclusion, we believe that this evidence supports the primary hypotheses tested.

Comment:

"The nature of "Relative Air Impact Units" (pp. 26 – 27 and Table 15) does not appear to be defined or discussed anywhere. It is, therefore not clear how to interpret these data. There is a general lack of explanation of how the air exposure index was derived and what uncertainties may underlie its use. This becomes particularly important in assessing the lack of statistical significance in the elevated ORs for modeled exposure to Ciba-Geigy air emissions."

Response:

Relative air impact units are discussed in Volume IV (Appendix F: Point Source Air Pollution Assessment). As mentioned above, we were cautioned by our Expert Panel not to over emphasize statistical significance because of the relatively small study size. Consequently, a combination of criteria, including: "strength of the association, statistical significance, consistency of findings of multiple measures for an exposure, apparent dose response effect, and evidence of a completed exposure pathway" were all used to evaluate the potential association of a risk factor with an outcome.

Comment:

"The Ciba-Geigy air assessment, while suggestive of a pre-natal association for leukemia in females (which would be consistent with associations observed for drinking water), is not entirely convincing. The general lack of significance (as opposed to elevated ORs) deserves more discussion. This is particularly the case since the only OR which does achieve significance (pre-natal exposure for female leukemia diagnosed before age 20) is for medium estimated exposure, but not for high exposure. While significance testing relies on a largely arbitrary cut point (the a value) lack of statistical significance has historically been treated as indicating uncertain conclusions at best. The overall pattern of elevated ORs for exposure to Ciba-Geigy air emissions, on the other hand, does suggest a robustness to the association. Perhaps this dichotomy between strength of association and significance could be put into better perspective of more discussion of the air exposure model and its potential for exposure misclassification were provided."

Response:

As discussed above (Rothman and Greenland: Modern Epidemiology Approaches to Statistical Analysis, 1998):

> It is preferable to view the confidence limits as only a rough guide, and a minimum estimate, of the inherent uncertainty in an epidemiologic

> result. An interval estimation procedure does more than assess the extent to which the null hypothesis is compatible with the data. It provides simultaneously an idea of the likely magnitude of the effect and the random variability of the point estimate. Points nearer the center of the confidence interval are more compatible with the data than points further away from the center. Results that are not significant may be compatible with substantial effects, while lack of significance alone provides no evidence against such effects. The confidence limits could indicate that the data, although statistically compatible with no association, may be even more compatible with a strong association.

Consequently, we stated in Volume II (Interview Study Methods)lytic methods, and in the discussion, the "potential causal association of a risk factor with an outcome was evaluated using a combination of criteria, including: strength of the association, statistical association, consistency of findings of multiple measures of an exposure, apparent dose response, and evidence of a completed exposure pathway."

Comment:

"It is stated that with the exception of the Ciba-Geigy pipeline (pp. 27 – 28), few children lived within 1/2 mile of any site of concern. However, 12.5% of cases and 7.6% of controls lived within 1/2 mile of the Ciba-Geigy plant. These proportions, while not large, are not as negligible as implied."

Response:

Agreed, however these numbers are for the total time period. Each percent decreases further when only the prenatal or postnatal period were evaluated. However, we have modified the language (Volume II, Interview Study Results) to reflect this point.

Comment:

"There appears to be a robust association for female pre-natal leukemia and proximity to the Ciba-Geigy pipeline, and a somewhat less strong (but significant) association with proximity to the pipeline breaks. Presumably, these two variables are highly correlated, although this does not appear to be reported. It would be useful to report the results of bivariate adjustment between these variables as a means of understanding the potential significance of pipeline breaks, or perhaps undocumented emissions from the pipeline."

Response:

As discussed in Volume II (Risk Factor Evaluation), no known exposure pathways were identified for the pipeline (or pipeline breaks) during the earlier environmental assessments. However, if there were exposures related to known pipeline breaks, we believe the variable "living within ½ mile of a pipeline break" was a refinement of the cruder variable "living within ½ mile of the pipeline," because it limits the definition of "exposure" to residence in areas near the breaks, and only after each pipeline break occurred. But odds ratios tended to decrease with the more refined measure.

Comment:

"The terminology "environmental index correlations" is unclear, especially to the uninitiated reader (pp. 29 – 30)."

Response:

The term refers to correlations among environmental exposure indices. We believe the meaning of the term is apparent in the text.

Comment:

"It is not clear why bivariate adjustment was not attempted between environmental (a priori hypothesis) variables and non-environmental variables. It would seem, however, that if that were not feasible because of the nature of those variables, that at least cross-reference of cases which were positive for non-environmental variables with significant associations (e.g., antibiotic use) and for environmental variables (e.g., Parkway water use) could be investigated as a means of investigating potential confounding. This would seem to be particularly relevant given the small number of cases and the large number of variables.

The nature of the adjustment procedure for ORs needs more explanation."

Response:

Bivariate conditional logistic regression was used to adjust for potential confounding. This was conducted for the two exposure pathways of the primary study hypotheses and the non-environmental factors for which associations with a specific cancer type (leukemia) was observed as noted in Volume II (Interview Study Results). As noted earlier, given the population study size, our ability to adjust for confounding was extremely limited. The Expert Panel indicated that univariate analyses would likely be the most we could do with the data. One member suggested that we should place less emphasis on confounding than we did, because he felt that confounding was "unlikely to be a major limitation, given the lack of established risk factors for the childhood cancers of concern."

Comment:

"It is interesting that co-adjustment of Parkway water use and Ciba-Geigy air emissions exposure suggests some overlap, but does not eliminate either as a significant association with pre-natal female leukemia."

Response:

Agreed.

Comment:

"The issue of potential recall bias on water consumption data is important. It is appropriately addressed by the observation that the strength of the association was consistent with and without the use of the consumption index. This is more clearly the case for female leukemia with pre-natal exposure than it is for pre-natal leukemia and nervous system cancers combined. The implications of this dichotomy are not, however, discussed."

Response:

The significantly elevated odds ratio for high prenatal time-specific Parkway water/consumption exposure seen in females diagnosed with leukemia and nervous system cancers (OR=5.2) appears to be driven by the elevated odds ratio for females diagnosed with leukemia (OR=6.0). Five of the six cases in the high exposure category for the leukemia and nervous system grouping are leukemia cases. This is evident by examining Table 14 in Volume III.

Comment:

"A significantly elevated OR is seen for Brookdale water in the Birth Records Study, but not in the Interview Study. Interestingly, this association, unlike most of those in the Interview Study, is for all cancers. Given the relative inability to obtain specific exposure information in the Birth Records Study, and the fact that this study contains only 20% more cases, it would be expected that the main difference between the findings of the two studies would be increased exposure misclassification and reduced power in the Birth Records Study. Qualitative differences such as elevated ORs for variables without positive associations in the Interview Study, would not a priori be expected. It is not clear what the implications of this are, but this observation is not carried forward to the discussion, and deserves some discussion."

Response:

Although there are 20% more cases in the Birth Record Study compared to the Interview Study (48 vs. 40 cases respectively), only 50% of the cases (24 of 48) in the Birth Records Study are also in the Interview study (as discussed on page 51 of the Technical Report). Therefore, the distribution of exposures may be substantially different in the Birth Records Study compared to the Interview Study. In addition, the control series are different in the two studies. Consequently, differences in results between the two studies is not unexpected.

Commenter: Union Carbide Corporation

Comment:

"Our primary concern is that the report does not adequately convey the limitations inherent in the study design and the uncertainties in the study results, leaving the reader with the false impression that the findings are indicative of a cause and effect relationship."

Response:

In numerous places of the Report the reader is cautioned that the results should be interpreted carefully and that due to the limited number of study subjects the analyses are sensitive to random fluctuations, which can result in substantial imprecision in the odds ratios. However, after carefully weighing the results of our analyses, we believe that that the weight of the evidence indicates that the associations noted in the Report support the a priori hypotheses of an impact from certain environmental exposure pathways identified in the community.

Comment:

"The draft report presents the results of data analysis from a very large number of comparisons (5,256) between types of childhood cancers and possible risk factors. This is consistent with the stated purpose of this exploratory study, 'to identify possible disease risk factors that might explain the elevated rates of select childhood cancers...'. It is not surprising with multiple comparisons, therefore, that a large number of statistically significant positive (52) and negative (26) associations have been observed. Because the study sample size was so small, many cells in the tables were zero and it was impossible to even calculate odds ratios (OR) for many comparisons (1,288).

For the Parkway well field alone, 600 comparisons were attempted, resulting in 10 ORs that were statistically significant, 5 significantly increased and 5 significantly decreased. We are of the opinion, consistent with that of at least one of the State's peer reviewers, that there is no biological rationale for grouping leukemia and nervous system cancers. If this grouping is eliminated from the Parkway related analyses, there remain 480 attempts to calculate ORs, 83 of which did not have sufficient numbers of study subjects. Of the 397 ORs calculated related to drinking water from the Parkway well field, one was significantly greater than 1.0, while four were significantly less than 1.0."

Response:

Our Expert Panel cautioned that we should not focus too much on statistical significance. As discussed by Rothman and Greenland (in Modern Epidemiology: Approaches to Statistical Analysis, 1998):

> the preoccupation with significance testing derives from the research interests of the statisticians of the early 20th century whose research problems were primary industrial and agricultural, typically involving experiments intended to facilitate decision making. Much of the popularity of significance testing stems from the apparent objectivity and definitiveness of the pronouncement of significance. Declarations of significance or its absence can supplant the need for more refined interpretations of the data; the declarations can serve as a mechanical substitute for thought. It is preferable to view the confidence limits as only a rough guide, and a minimum estimate, of the inherent uncertainty in an epidemiologic result. An interval estimation procedure does more than assess the extent to which the null hypothesis is compatible with the data. It provides simultaneously an idea of the likely magnitude of the effect and the random variability of the point estimate. Points nearer the center of the confidence interval are more compatible with the data than points further away from the center. Results that are not significant may be compatible with substantial effects, while lack of significance alone provides no evidence against such effects. The confidence limits could indicate that the data, although statistically compatible with no association, may be even more compatible with a strong association.

Consequently, we stated in Volume II (Interview Study Methods) that "the potential causal association of a risk factor with an outcome was evaluated using a combination of criteria, including: strength of the association, statistical significance, consistency of findings of multiple measures for an exposure, apparent dose response effect, and evidence of a completed exposure pathway." As our Expert Panel pointed out, these criteria are used in all epidemiologic studies to evaluate exposure disease relationships.

In general, analyzing homogeneous disease groups (e.g., leukemia) is preferable to heterogeneous groups (e.g., all cancers combined or leukemia and nervous system cancer combined). This is why we chose to focus our discussion in the report on the two more homogeneous groups, leukemia and brain and central nervous system cancers. However, it is important to note that little is known about the etiology of childhood cancers, including the relatively homogeneous cancer groups.

In terms of the multiple comparison issue, the study was designed to examine specific a priori hypotheses about certain environmental exposure pathways in the

community. A discussion of multiple comparisons can be found in Volume II (Interview Study Strengths and Limitations and Birth Records Study Strengths and Limitations).

Comment:

"The results from two of the Parkway comparisons, including the one that was statistically significant, are highlighted in the report as supportive of the 'a priori' hypothesis that childhood cancer was associated with contamination of drinking water from the Parkway well field by the Reich Farm Superfund site. The summary conclusion related to Parkway are:

> *'Although no associations were detected in analysis of the overall study population, a statistically significant association and consistency in multiple measures of association were seen between the prenatal exposure to time-specific Parkway well water (1982-1996) and leukemia in female children of all ages. This finding seems to support the hypothesis that prenatal exposure to Parkway well water during this interval was a risk factor for childhood leukemia in females. However, it is important to note that there is considerable uncertainty in the findings'.*

We agree with the NJDHSS report that 'there is considerable uncertainty in the findings'. We believe, however, that the uncertainties from these two sets of associations have neither been adequately examined nor discussed in the context of the all the results from the study. This leads the reader to infer stronger conclusions than the data warrant."

Response:

We believe that an association was found between prenatal exposure to time-specific (i.e., contaminated) Parkway water and leukemia in females. As noted in the previous response, evaluation of homogeneous cancer types is preferable when considering etiologic plausibility. This association was not found for males diagnosed with leukemia, and remains unexplained in this study. However, it is important to note that the excess childhood cancer found during our earlier statistical review (Berry and Haltmeier, 1997) was primarily seen for females diagnosed with leukemia.

Comment:

"Inadequate attention is given to inconsistent data, particularly the differences observed between male and female children.

The importance of the results for females in the study report is over emphasized in the study's conclusions. This is not justified for the following reasons: 1) the absence of effects in the analysis of males and females combined, 2) the fact that there is no

evidence in the literature of a risk factor that is gender-specific for leukemia and 3) the apparent inverse relationship for males. One of the State's peer reviewers was of the opinion that there was no biological rationale to conduct gender-specific analyses.

While the report notes the absence of associations with the Parkway well field water when males and females are analyzed together, it focuses on the female results and avoids a clear presentation of the magnitude of the inconsistency between the results for males and females. For example, in Table 10b, all 9 male cases received, on average, less than 10% of their water from Parkway, while 5 of 36 controls received more than 10% of their water from Parkway. Because there were no male cases in the moderate and high exposure categories but there were controls in these categories, the data indicate that male cases are more likely to have received lower percentages of water from Parkway than controls. This should be specifically noted in the report. The results are identical in Table 14b, based on the water source/consumption variable. The findings for male leukemia cases during the prenatal period are, therefore, inconsistent with the 'a priori' hypothesis. Recommendation: The study report should specifically present the results for males that are inconsistent with the results for females and identify this aspect of uncertainty in the conclusions of the study."

Response:

While the scientific literature provides little knowledge for a differential impact of one sex but not the other, it is important to note that little is known about the etiology of childhood cancer or childhood leukemia. It is a common practice in the field of epidemiology to separately evaluate sex differences as a means of understanding the natural history of the disease when conducting descriptive and analytic studies of childhood cancer. Furthermore, in both New Jersey and nationally, childhood leukemia incidence rates are 20-30% higher in males than females. While there is no scientific explanation for this sex differential, the differential does exist and there may be biological, though unexplained at this point, reasons for the differences. However, what we see in Dover Township (Berry and Haltmeier, 1997) is just the opposite, with childhood leukemia incidence in females significantly elevated while incidence in males was not elevated. In addition, our response to the peer review comment mentioned above included: "... The original standardized incidence ratio study of selected childhood cancers in Dover Township found elevated leukemia rates among female children under age five. Thus we had an a priori interest in leukemia among young girls in Dover Township..."

Comment:

"Another important inconsistency, not sufficiently addressed, is the pattern of deficits of cases, male and female, in the moderate exposure category, whether based on water source only or on water source and consumption combined. For example, the report focuses on the one statistically significant excess related to the Parkway associations examined (Table14b), but does not focus on the four statistically significant deficits among this group of associations, when the moderate exposure category is compared to the none/low category (Tables 11, 12, 13, and 14). All of these relate to female leukemia cases or female and male leukemia cases combined, diagnosed 0-19 years of age and postnatal exposure from 1979 or post 1982. These statistically significant ORs range from 0.07-0.17. There are also numerous other such deficits, while not statistically significant, that indicate lower risk at moderate Parkway exposure prenatally than at no or minimal exposure. It is unheard of for a human carcinogen to behave in this manner. These findings would clearly not be consistent with the 'a priori' hypothesis, nor with the positive findings related to high vs. low exposure.

In addition to chance, due to small sample sizes, and the problem of multiple comparisons, exposure misclassification is a possible explanation for these findings, both the positive and negative associations. It has been well documented that even random misclassification can lead to overestimation of risks (Sorahan, T and Gilthorpe, MS. 'Non-differential misclassification of exposure always leads to an underestimate of risk: and incorrect conclusion.' Occupational and Environmental Medicine 1994; 51:839-840).

Recommendation: The report should provide a more balanced discussion of inconsistencies with the 'a priori' hypothesis related to Parkway well field water. Possible explanations related to chance, exposure misclassification, and multiple comparisons should be recognized and discussed in those circumstances where they may apply and specifically in the overall conclusions."

Response:

The four statistically significantly low odds ratios for the medium Parkway exposure category referred to are all for postnatal exposures. Prenatal and postnatal analyses focused on two separate and distinct exposure windows: first, when the child was in utero and second, after the child was born. It is known that exposures during different time windows in development may have different effects. However, language has been added to Volumes I and II (Conclusion) stating that no consistent pattern of association was seen between the a priori exposure hypotheses evaluated postnatally for any cancer groups.

We discussed exposure misclassification in the Strengths and Limitation section of Volume II, stating that nondifferential exposure misclassification can effect the odds ratio in either direction, but is more likely to bias toward the null hypothesis of no

effect. As pointed out by Rothman and Greenland (in Modern Epidemiology: Precision and Validity of Studies, 1998), "it is possible for independent nondifferential misclassification to bias estimates away from the null...such examples are unusual, however, because trend reversal cannot occur if the mean exposure measurement increases with true exposure...if we do not know what errors were in the study, at best we can only say that the observed odds ratio is probably closer to the null than what it would be if the errors were absent."

Comment:

"The associations with drinking water are not examined in the context of possible influences from the remaining associations examined.

There are over 5,200 associations examined in the interview and birth records studies. Of these, 78 were reported to be statistically significant. Of the 480 Parkway well field water-related associations examined, there were only two associations, as described above, that were given prominence in the report, with only one being statistically significant. The two were based on only four and five exposed cases, respectively. The exposure variables for these two associations were highly correlated variables (Parkway as a source of water and the Parkway as a source combined with recall of consumption of water.) They are so correlated that Tables 10b, based on source, and 14b, based on source/consumption are identical for males. Results for females using these two exposure metrics, therefore, cannot be viewed in any way as independently consistent. This issue is discussed in greater detail in an other comment.

An important question is whether these results could be explained by confounding. A confounder would have to be related to exposure to the Parkway well field as well as be a risk factor for the disease of interest. In addition, there might be chance associations of disease and one or more of the possible risk factors examined that may be correlated with percent of water from Parkway well field and explain the Parkway/disease associations observed.

The authors correctly recognized the inability to formally examine this issue, except for a limited number of factors, due to the small number of study subjects. However, analyses of those variables that were found to be associated with leukemia could be examined for correlation with exposure to Parkway well field water. For example, mothers of leukemia cases, diagnosed between 0-19 years of age, were less likely to take multivitamins during pregnancy than were controls (OR=0.23; 95%CI:0.07-0.73). Did these mothers of female cases reside in areas with a high percent of Parkway water? At the very least, more details should be provided about the cases in the 'high' category in Tables 10b and 14b.

We disagree with the position that the numerous other possible risk factors are inconsequential. While they may not have been uppermost in the minds of the community, they were of interest as potential confounders by the investigators, based on the existing childhood cancers published literature. The fact that the known causes of childhood cancers explain only a small portion of cases make it even more imperative not to exclude the possibility of confounding by one or more of the other factors under consideration in this study. The issue of confounding is too readily dismissed in the report and treated as an acceptable limitation. Recommendation: More effort should be made to explore the potential influence of other variables that may be correlated to percent of water from Parkway well field."

Response:

The Report does not state that the other factors were inconsequential. In Volume I (Other Factors) we did state that "In general, most of the other factors displayed no differences between the cases and controls. Study findings related to the other factors were found to be generally consistent with the published literature, with the exception of consumption of cured meat."

Given the population study size, our ability to adjust for confounding was limited. The Expert Panel indicated that the univariate analyses would likely be the most we could do with the data. One member suggested that we should place less emphasis on confounding than we did, because he felt that confounding was "unlikely to be a major limitation, given the lack of established risk factors for the childhood cancers of concern."

Bivariate conditional logistic regression was used to adjust for potential confounding. This was conducted for the two exposure pathways of the primary study hypotheses and the non-environmental factors for which associations with a specific cancer type (leukemia) was observed, as stated in Volume II (Interview Study Results).

Comment:

"The criteria of interpretation of associations that have been referenced in the report and other NJDHSS communications vary and the inconsistency of the Parkway associations with these criteria for judging causation are not clearly described in the report.

In Volume I, Summary of the Final Technical Report, five criteria are described for evaluating the potential for an association to be causal. These are 'strength of the association, statistical significance, consistency of findings of multiple measures for an exposure, apparent dose-response effect, and evidence of a completed exposure pathway.' In the citizen's guide to the study (December 2001), four of the above criteria are stated. However, consistency is stated more generally, i.e., not restricted

to 'multiple measures for an exposure' and there is no mention of statistical significance. Finally, at the town meeting presentation, six criteria were presented, including biologic plausibility and precision of he estimates of relative risks, i.e., the width of the confidence intervals, which is influenced by sample size, Regardless of which criteria are used, there should be a section in the report where they are discussed with respect to the associations related to Parkway. This was also recommended by one of the external reviewers. If this were done, the following criteria would not be supported by the evidence:

1. Dose-response - As described earlier, female leukemia cases, when examined for prenatal exposures and compared to controls, were more likely to be in the 'high' than the 'low' exposure category; but were also more likely to be in the 'low' than the 'moderate' exposure category. There is, therefore, no evidence of increased risk with increasing exposure. The absence of a doee-response argues against the presence of a causal connection. The importance of a does-response trend, in the presence of an elevated overall risk estimate, has been clearly addressed in Breslow and Day's text, Statistical Methods in Cancer Research Volume 2, 1987, p.82 which stated in the context of a cohort study that, 'a much better indicator of causality is the demonstration of a trend in the mortality ratios with degree of duration or exposure.'

2. Biological plausibility - As discussed earlier, male leukemia cases, when examined for prenatal exposures, are more likely to be in the 'low' category. There is no known biological explanation for the observed gender difference. Secondly, the fact that there are no known chemical causes of childhood leukemia in either gender further weakens the biological plausibility that the observed associations are evidence of a cause and effect relationship.

Additionally, contamination from the Reich Farm plume first reached the Parkway well field in 1986 as previously documented in Union Carbides comments (January 13, 2000), on the Public Health Consultation-Drinking Water Quality Analyses (March 1996 to June 1999) United Water Toms River. The Parkway well field drew water from both the shallow Cohansey aquifer that was impacted by the Reich Farm plume and deeper aquifers that were not impacted. The measured levels of contamination in untreated water from the two effected Cohansey wells were low parts per billion (ppb) and this water was then blended with uncontaminated water from up to four or more other wells before distribution to residences. During mid-1988, air stripping treatment was installed on the effected Parkway wells and volatile contaminants were removed to below detectable levels prior to blending with other unaffected wells. The arrival time of Reich Farm contaminants at the Parkway well field in 1986 and the dilution to extremely low levels, even prior to treatment in 1988, makes the inference that Reich Farm contamination is responsible for the reported associations with Parkway water for 1982-1996, biologically implausible.

3. Precision of relative risk estimates - Because the Parkway findings were based on son few study subjects (e.g., 4 or 5 cases in the 'high' category), the 95% CIs are very wide, indicating substantial imprecision or uncertainty about the odds ratios.

4. Statistical significance - The odds ratio (OR) for female cases in the high Parkway consumption category based on water source, 1982 and later, was not statistically significant (Table 10b, OR=4.99; 95%CI: 0.8-31.2). The association for the same group based on water source/self-reported consumption, 1982 and later, was statistically significant (Table 14b. OR=5.96; 95%CI: 1.1-31.7). This is one positive statistically significant result in 480 associations examined. Furthermore, this association derives in part from unverifiable recall by study subjects, often over an extended time period. As discussed earlier, there were 4 statistically significant deficits. With small numbers of study subjects and so many comparisons, chance statistically significant associations are very likely to occur.

5. Consistency (of multiple measures of exposure) - The report describes the inconsistency of these results with other findings in the literature, particularly the Woburn Study that reported greater contaminated drinking water risk for male leukemia cases. This criterion is inappropriate when multiple measures of exposure are used that are highly correlated. The water source/consumption exposure metric is identical to the water consumption metric, except under two scenarios: 1) when water source is 'high' but consumption is 'low/none' and 2) when water source is 'moderate' and consumption is 'high'. The criterion of consistency of multiple measures is appropriately applied when several independent measures of exposure are used in a study and the results are consistent. It should not be considered indicative of consistency when a positive association in one exposure metric virtually assures a possible association in the other.

When the evidence is critically examined in the context of these criteria, it does not fulfill the requirements for being considered adequate to conclude that a cause-effect relationship existed between Parkway well field water and leukemia in female cases. This fact should be stated more clearly in the report since the distinction between association and causation is to often blurred in the public's perception of findings. Recommendation: The report should discuss the Parkway findings in the context of the investigators stated criteria for interpretation and, in so doing, transparently justify their conclusion; 'there is considerable uncertainty in the findings'."

Response:

As stated in the Report, "The potential causal association of a risk factor with an outcome was evaluated using a combination of criteria, including: strength of the association, statistical significance, consistency of findings of multiple measures for an

exposure, apparent dose response effect, and evidence of a completed exposure pathway." Our conclusion that prenatal exposure to time-specific Parkway water was associated with leukemia in females was based on the strength of the association, the consistency of multiple measures of association, a statistically significant association, and a known completed exposure pathway.

While biologic plausibility is important to consider, Rothman and Greenland (in Modern Epidemiology: Causation and Causal Inference, 1998) point out that "it is far from objective or absolute...it is too often not based on logic or data, but only on prior beliefs. This is not to say that biologic knowledge should be discounted when a new hypothesis is being evaluated, but only to point out the difficulty in applying that knowledge." The scientific literature provides little guidance or knowledge into the etiology of childhood cancer or childhood leukemia.

As noted above, confidence limits provide only a rough guide to the uncertainty of the odds ratio. The magnitude of the odds ratio remains the best estimate of the effect, based on the data.

Dose-response or biologic gradient refers to the presence of a monotonic (unidirectional) dose-response curve. As pointed out by Rothman and Greenland (1998), "We often expect such a monotonic relation to exist...but some causal associations show a single jump (threshold) rather than a monotonic trend (e.g., the association between DES and adenocarcinoma of the vagina)...and a nonmonotonic relation only refutes those causal hypotheses specific enough to predict a monotonic dose-response curve." Nonetheless, all of the associations we interpreted as supportive of an a priori hypothesis displayed odds ratios which were strongest in the highest exposure category.

The lack of precision in the odds ratios is primarily due to the limited number of study subjects, which is inherently a problem in "cluster" studies. Consequently, all of our 95% confidence intervals were at least somewhat large, and especially large for the smaller groupings (e.g., leukemia in young females). The best estimate of the risk of a factor remains the point estimate odds ratio, though considerable uncertainty exists as reflected in the width of the confidence intervals.

The water source/consumption indices were developed as an alternate method of analyzing drinking water exposure. Although water source/consumption indices utilized the monthly water source estimates, it did not assure a similar result in the new index odds ratios. In some cases the odds ratios went up, while in other cases the odds ratios went down or remain about the same. A second method was also used in calculating the source/consumption indices which consisted of multiplying the average number of glasses of water consumed and the average percentage of source water. Consistent results were found for the new time-specific Parkway well field source/consumption index. Additionally, if two separate, accurate, and independent

measures of exposure to the same factor could be constructed (theoretically), and the exposure was truly a risk factor for the outcome, then one would expect that the two independently derived measures would be correlated with each other.

Comment:

"The overall conclusion of the study is not adequately discussed, may be incorrectly understood and is not sufficiently responsive to the questions that gave rise to the study.

As stated in the final study protocol of January 1998, 'specifically, the study aim is to identify possible disease factors that might explain the increased elevations, by evaluating the magnitude of associations between these diseases and various factors using a case-control study design.' As stated in Volume II of the (draft for comment) Final Technical Report:

> *'The overall purpose of this exploratory epidemiologic study was to identify possible disease risk factors that might explain the elevated rates of select childhood cancers, specifically leukemia and brain and central nervous system cancers, in Dover Township.'*

While a multitude of possible risk factors were examined and numerous associations reported, the likelihood that they explain the excesses observed is not adequately addressed. The overall study conclusion is stated in the draft report as follows:

> *'No single risk factor evaluated appears to be solely responsible for the overall elevation of childhood cancer incidence in Dover Township.'*

This appears to address the purpose of the study, i.e., why certain childhood cancers were increased in Dover Township but, in fact, sidesteps the critical question. It even implies, by use of the word, 'solely' is misleading and should be deleted. The reported increases in childhood cancer in Dover Township and Tom's River have not been explained in the study. Recommendation: It should be made clear in the report that the findings related to environmental factors alone or in combination do not account for the reported excess of 23 childhood cancer cases from 1979-95 in Dover Township."

Response:

The Interview Study evaluated the childhood cancer types which were found to be significantly higher than expected based on the 1997 Consultation (Berry and Haltmeier, 1997). Those cancer types included leukemia (elevated in females in the Township and the Toms River section of the Township) and brain and central nervous system cancers (elevated in the Toms River section of the Township, especially in females diagnosed under age five). The excess in leukemia incidence (1979-1995)

in Dover Township was 7.7 cases (22 observed vs. 14.3 expected) for males and females combined and 6.5 cases (13 observed vs. 6.5 expected) for females. Brain and central nervous system cancers were not elevated in the Township as a whole, but were elevated in the Toms River section with an excess of 3.4 cases (4 observed vs. 0.6 expected) for males and females under age five and 2.7 cases (3 observed vs, 0.3 expected) for females under five. The conclusions in Volumes I and II will be reworded to emphasize the identification of multiple risk factors for leukemia in females and the lack of associations for leukemia in males and brain/CNS cancer in both sexes.

Comment:

"ATSDR.s Water Distribution Modeling Report overstates the accuracy of the results that estimate the relative proportion of water from each well field to the cases and controls.

Dr. Jon Sykes and Stefano Normani of the Unversity of Waterloo have reviewed ATSDR's report, 'Historical Reconstruction of the Water-Distribution System Serving the Dover Township Area, New Jersey: January 1962-December 1996'. The ATSDR EPANET models were also made available to them. The review highlighted several areas of concern that could substantially affect estimates of proportionate well field contribution, which were subsequently used as input to the epidemiological study. The direction and extent of the potential impact upon the epidemiological study results could not be determined since information on the geographic location of cases and controls was not available for review.

Dr. Sykes looked at three areas: a) The consistency of EPANET model production volumes, data tables in the Supplemental Data report and raw data from the water company's production records; b) The operation of pumping wells within the EPANET models; and c) The characterization of the sensitivity analysis of the percentage of water predicted to be from each well field at a given receptor location. A brief discussion of each follows.

a. Consistency of well production volumes - The review included a spot check comparison of monthly well field pumping volumes used as input data for ATSDR's EPANET models to those provided in Appendix B of ATSDR's report and to data from actual daily records provided by United Water Toms River. Although the data review was not exhaustive in nature, the review found numerous inconsistencies. In some cases significant differences were found. For example, according to UWTR daily production records, Well 22 produced 16,681,000 gallons of water in December 1976. The EPANET model state that 1,668,003 gallons were produced diagreeing by a factor of 10. During August 1980, Well 20 produced 19,614,000 gallons of water according to the UWTR daily production records compared to 29,613,997 gallons of water in the EPANET model. These errors affect the estimate of the total percentage of water

produced from each well field and therefore the amount of water delivered to both cases and controls. Recommendation: Monthly pumping volumes should be corrected and the affected models re-run to determine whether there is a meaningful impact on the epidemiology analysis for the Parkway well field."

Response:

As stated in Maslia *et al.* (2001, p. 22) (referred to as "the ATSDR report," below), water-production data were obtained from the water utility, annual reports of the Board of Public Utilities (BPU) for the State of New Jersey (1962–1996), and from data searches conducted by staff of the NJDHSS. Production data cited in this comment are not included or referenced in any of the official reports made available to ATSDR. During the course of the investigation, repeated requests were made in the form of written communication, electronic mail, and oral communication to obtain daily production data. Through this effort, ATSDR was able to obtain water utility data solely for 1996. Production data for each of the other years of the historical reconstruction (1962–1995) were not made available to ATSDR. Consequently, data prior to 1996 were derived from BPU reports and from data searches conducted by NJDHSS staff. It was the understanding of ATSDR that data contained in BPU reports represented actual production data that the water utility was required to report. Data contained in BPU reports represent total production by well field, but not by individual well (for well fields that contain multiple wells). Data obtained from the NJDHSS staff searches contained, in many instances, production by individual wells, even for well fields with multiple wells. Additionally, well-specific production for October 1971-–March 1983 were also compared with data contained in a report by ENVIRON Corporation (1986, Appendix B).

With respect to the apparent discrepancy cited for December 1976, ATSDR relied on the well summary report provided by NJDHSS staff for well 22 because it provided single-well production data for wells in the Parkway well field. The BPU report for December 1976 provided a total production for all wells in the Parkway well field. Thus, the production volume for well 22 was set at 1.668 million gallons (Mgal) for the EPANET simulation. This production number is also identical to the value listed in the ENVIRON Corporation report (1986, p. B-2). This report indicates that the information was obtained from water utility records submitted to the New Jersey Department of Environmental Protection (NJDEP).
With respect to the apparent discrepancy in well production for August 1980, the well-specific production data (29.614 Mgal) was derived from the ENIVRON Corporation report (1986, p. B-4). (NJDHSS staff were not able to obtain well-specific production data records for 1980.) Using the production value of 29.614 Mgal for August 1980 produces a much smaller difference in total production between EPANET2 simulation values and total production reported in the BPU report for 1980. If, however, the production value of 19.614 Mgal cited in the comment is assigned to well 20, then a discrepancy of about 11 Mgal exits in comparison with

the total production reported by the water utility in the BPU report for 1980. Thus, the production of 29.614 Mgal assigned to well 20 by ATSDR is more consistent with data listed in the BPU report for 1980.

Comment:

"b. Operation of pumping well in EPANET models - Internal to the EPANET models, ATSDR simulates pumping well operations that are physically impossible to accommodate with the equipment in service. An example of this is pumping individual Parkway wells at rates that are more than six times greater than their capacities (five of six Parkway wells for August 1995 are operated at 4,800 gpm [page C-35 in Supplemental Data report]). While this approach may not affect the estimated overall proportional contribution from entire well fields, this abstraction of the real world can provide a profound error if the EPANET models are used to predict the proportionate contribution of water from individual wells. In several instances, single wells such as Anchorage, Silver Bay, Well 15, Well 20, Well 31, and Well 40 are set to operate in EPANET above their rated capacity. The Agency should verify that these rates respect the actual physical constraints of the equipment. Recommendation: The excessively high pumping rates (above rated capacity) for wells serving Dover Township should be investigated to assess if they are the result of an incorrect pumping volume. The affected EPANET models should be re-run to determine whether there is a meaningful impact on the epidemiology analysis for the Parkway well field."

Response:

The comment cites an example of five Parkway wells being operated at 4,800 gallons per minute (gpm) for the August 1995 simulation (simulation notes are described in Table C-6 of the ATSDR report). The comment states that profound errors may result from the proportionate contribution of water from individual wells using the ATSDR approach. At the Parkway treatment plant (and Holly and Windsor treatment plants), proportionate contribution was not determined from individual wells, but rather, from the supply of water provided by high-service pumps to the distribution system. This is because in the actual operation of the Parkway plant, groundwater wells do not supply the distribution system directly. Rather, groundwater wells supply a ground-level storage tank, and then high-service pumps deliver water to the distribution system, depending on demand conditions (this is referred to as the "well-storage tank-pump" or WSTP simulation method on p. 50 of Maslia *et al*. [2001]).

In the ATSDR report, a detailed explanation of the method by which groundwater wells, storage tanks, and high-service and booster pumps were represented for EPANET2 simulations is provided (p. 49–58). The reason for defining operations of the Parkway treatment plant (and Holly and Windsor treatment plants) in the manner described in the ATSDR report was due to a lack of specific data on the operations of

the plants (p. 50). During the course of the investigation, various requests were made in the form of written communication, electronic mail, and oral communication to obtain more specific operational data. However, these efforts did not produce any additional information. Lacking this information, a surrogate method was developed. In the ATDSR report, the authors demonstrate that the surrogate method (called the "supply-node-link" or SNL simulation method) provides the same quantity of water to the distribution system over a 24-hour period as supplied by the WSTP method (see Figure 19, p. 50, of the ATSDR report). The authors further demonstrate the reliability and applicability of the SNL method by comparing measured supply to the distribution system for August 1998 with simulated supply for August 1998 using both the well-storage tank-pump and supply-node-link methods (see Figure 20, p. 56).

In EPANET2 simulations, supply nodes were located to coincide with locations of groundwater wells in the Parkway treatment plant for convenience. Under the ATSDR application of the EPANET2 model, supply nodes could have been located anywhere within the Parkway treatment plant area. This approach is considered valid because supply nodes delivered an equal amount of water to the distribution system at the location where the high-service pumps delivered water to the distribution system. This was confirmed and verified with field measurements, shown in Figure 20 (p. 56) and listed in Table 16 (p. 57–58).

A close review of Table C-6 of the ATSDR report lists the following entries:

> "Parkway ground-level storage tank in service (closed in EPANET2)
> *(note: Parkway wells pump directly into system and represent high-service pump flows)*
> Parkway high-service pump #1 on [0400 to 0600], [1200 to 1700] and [2200 to 2300] at 3,180 gpm
> Parkway high-service pump #2 on [0600 to 1200] and [1700 to 2200] at 4,800 gpm"

The purpose of this note (and all of Appendix C) was to provide the reader with a step-by-step approach of the method used to conduct the EPANET2 simulations (i.e., the SNL simulation method). In this example, the Parkway ground-level storage tank was not operational in the EPANET2 simulation. Instead, groundwater-supply wells were used as a surrogate mechanism in the model to supply water to the distribution system, rather than using the high-service pumps, as was done in the "real world." However, the required flow from the high-service pumps was delivered to the distribution system. Clearer terminology in the notes of Appendix C for the representation of the surrogate wells, such as supply nodes (described in report pages 50–58) could have prevented this misunderstanding.

The five Parkway wells cited in the comment could have been represented by any number of supply nodes (e.g., 1, 10, 15, etc.) using the surrogate (SNL) method described in the ATSDR report. The only constraint was that the total water supply and hours of operation of the supply nodes needed to be equivalent to the operation

and supply of water from the high-service pumps to the distribution system. With the quantity of water from the supply nodes in the model being equivalent to the supply of water from the high-service pumps in the real world, the proportionate contribution of water to any location within the distribution system was also equivalent.

Using the SNL method developed by ATSDR, the capacities of groundwater supply wells do not need to be considered because any value could have been assigned to the capacity of the well (i.e., supply node). That is, the quantity of water from the supply nodes (located coincident with the groundwater wells, as explained above), was derived by multiplying the rated capacity of the supply node by the demand factor for each hour of a 24-hour simulation. Because the supply nodes were used to simulate supply to the distribution system and **not** to simulate the operation of the groundwater wells, it is not appropriate to compare the capacities of the supply nodes on equivalent bases with capacities of groundwater wells. Rather, the capacities of the supply nodes should be compared with the supply of water to the distribution system from the high-service pumps (Figure 20, Table 16 of the ATDSR report).

Comment:

"c. Sensitivity analysis - ATSDR performed a sensitivity analysis to assess the anticipated error in the predicted percentage of water contribution from each well field at a given receptor location. The authors state the following on page 79:

> *'Output from the source-trace analyses-the simulated proportionate contribution of water-will be considered as one of the risk factors in the epidemiologic case-control investigation. If larger but reasonable variations in model parameters values result in correspondingly large variations in percentage of water contributed by a well or well field to pipeline locations, the estimates of exposure to the different water sources may result in exposure misclassification. On the other hand, if changes in the simulated proportionate contributions are small regardless of the magnitude change in model parameters, then simulation variability will not greatly detract from the confidence assigned to exposure classifications.'*

The authors then proceed to calculate the difference in proportionate contribution between the Manual Adjustment Process (MAP) simulations and various sensitivity simulations (SENS0 through SENS7). These differences or variation among alternate simulations are qualified through a statistical analysis to yield a standard deviation of 3.9 percentage points (page 100). The 3.9 percentage points represents a global error and is not indicative of variation at specific study locations, which can be as high as 30 percentage points (see Figure 31 on page 94 - 1988 and 1996). For example, during 1988, 312 study locations (3% of 10,392 for SENS3) have differences of more than 10 percentage points, with some differences as high as 30 percentage points.

As quoted above, the authors indicate that small differences in proportionate contribution lead to greater confidence in the exposure classification of study locations. In reality, the robustness of exposure classification relates to specific study locations and the proximity of their proportionate contribution estimate to the epidemiological study exposure cut-points. It is misleading to imply that a small global error ensures that misclassification has not occurred. The exposure cut-points between low and medium exposure is at 10 percentage points. The exposure classification of some study locations will be more robust than other study locations. For example, if we consider a 10 percentage point variation in proportionate contribution, a study location whose proportionate contribution changes from 65% to 75% maintains the same exposure classification, while a study location that changes from 15% to 5% will shift from a medium to a low exposure classification. The first study location is considered to have a more robust classification than the second study location.

As a result, it is important for the Agency to characterize the potential variation at each study location and not to condense the entire historical water distribution system analysis into a single global error estimate, which could misrepresent the anticipated accuracy of the study results. The distinction should also be clearly made when expressing error, specifically between percentage point differences in predicted proportionate contribution, and the percent error that would result from such differences.

Further comments regarding the Agency's sensitivity analysis are provided below:

1. The Manual Adjustment Process was the ATSDR's approach to manually develop the 420 monthly EPANET simulations, while simulations SENS0 through SENS7 represent alternative operations of the distribution system as well as variations in the hydraulic constraints used for the models. The absolute value of the differences in proportionate contribution between the Manual Adjustment Process (MAP) and the eight sensitivity runs (SENS0 to SENS7) were used as the basis of quantifying the impact of changes to operational and hydraulic constraints. These differences are plotted in Figure 31 using cumulative percentile graphs for selected years. The values of n on these graphs indicate the number of study locations where the contribution of water from a specified well or well field was greater than zero. If a study location contains a zero value within the time period of interest, the epidemiological study will include that zero value in its calculation of the average proportionate contribution fro a particular source. The zero values should be included in the assessment, for it is possible that for a given study location, the MAP proportionate contribution may be zero, while the SENS0 proportionate contribution may be greater than zero. In this case, the calculated difference should be plotted on the graph. Even if both proportionate contributions are zero, they should also be plotted as this indicates that the value for proportionate contributions did not change for the study location.

2. A statistical analysis of the differences in proportionate contribution was performed

based on six characteristic years (see Table 23). The authors state, 'the statistical analyses assumed that the differences could be characterized by a normal distribution' (page 96). The authors don't prove that the differences are normally distributed. Although the histograms shown in Figure 32 show a great degree of symmetry, the graphs for Figure 31 and Figure 32 don't appear to visually represent normal distributions. Nearly symmetrical histograms result from the fact that the proportionate contributions must sum to 100, whereby any positive increase will be compensated with negative decrease(s). The values for proportionate contribution at all study locations are constrained between 0 and 100 percentage points, and thus form a truncated probability distribution. The subtraction of two such distributions may not yield a normal distribution due to the truncation of the distribution tails.

3. The probability distribution of proportionate contribution at a specific study location over a time period of interest will not be normally distributed due to the fact that the values for proportionate contribution are constrained between o and 100 percentage points. The distribution will be different depending on whether the study location generally obtains a lower versus a higher proportionate contribution of water. Neither the assumption of a normal distribution nor a standard of 3.9 percentage points for all study locations can be applied in characterizing the robustness of exposure misclassification at a specific study location. The 3.9 percentage point standard deviation refers to a variation between alternative simulation strategies for all study locations. It does not account for the variation in proportionate contribution at a specific study location fro month to month within a single simulation, nor does it account for the variation in proportionate contribution at any study location between the alternative simulations SENS0 through SENS7. Both are important factors to consider in assessing the robustness of exposure classification at a specific study location.

4. The authors attempt to argue that (1) the statistics of differences in percent contribution tht result from perturbing model input parameters can be used as a surrogate for the uncertainty in the percent contribution. They also argue that (2) if the global standard deviation of the differences in percent contribution is small, then it can be concluded that the EPANET results will not lead to misclassification. The first argument requires the sampling of the input parameters for all possible combinations. This has not been done. Therefore, the authors cannot show the robustness of their calculated standard deviation of differences, let alone the robustness of their calculated percent contributions. The second argument is not valid as Figure 31 of their report clearly indicates that large differences can occur for specific cases and controls.

5. As previously stated, it is more important to characterize the variation at specific study locations, than to condense the entire historical water distribution system analysis into a single global error estimate. There are two ways of doing this. Since the authors have already created a complete alternate set of EPANET simulations

(simulation SENS0) to the MAP simulations for the entire study period, the differences in predicted proportionate contributions could easily be provided to NJDHSS to assess the variation in proportionate contribution for individual study subjects. A more rigorous approach would be to perform the sensitivity analyses (SENS0 to SENS7) for all study locations (cases and controls) during all months in which a study location is considered for inclusion into the epidemiological study. This would allow seven complete alternate simulations, in addition to SENS0, for determining the robustness of study location classification as well as determining the impact of the variation in proportionate contribution upon the final odds ratios.

Recommendation: The estimated errors and variability in proportionate contribution of water should be determined for each study subject by using alternate proportionate contribution simulations. The impact on the classification of cases and controls into exposure categories and ultimately the odds ratios should be evaluated, as recommended by peer reviewers."

Response:

ATSDR disagrees with the commenter's interpretation of the rationale for conducting sensitivity analyses. The purpose was **not** "to assess the anticipated error in the predicted percentage of water from each well field at a given receptor location," as indicated in the comment. ATSDR acknowledged that the precise nature of historical system operations was unknown (Maslia *et al.*, 2001, p. 59, 1st paragraph). The purpose for conducting the sensitivity analyses was, as stated in the report,

> . . . developing and investigating alternative operating schedules for the historical water-distribution systems and evaluating the effects of these alternative schedules with respect to results . . .

Additionally, the sensitivity analyses were used to assist in answering the following questions (p. 59):

> **!** If a balanced flow operating condition was achieved using the manual adjustment process, was the resulting operating condition the only way the system could have successfully operated?
>
> **!** Could alternative or additional operating conditions be defined such that system operations would also be satisfactory or even "optimal?"

Accordingly, ATSDR stated explicitly that results of the sensitivity analyses indicated that (p. 100):

> (1) only a narrow range of conditions existed within which the historical water-distribution system could have successfully operated and still satisfy hydraulic engineering principles and the "Master Operating Criteria" (Table 4), and (2) daily operational variations over a month did not appreciably change the simulated proportionate contribution of water from specific sources when compared to results from a typical 24-hour day pattern of operation representing the month.

ATSDR believes that given the narrow range of possible operating conditions, **any** of the simulated operating conditions (the manual adjustment process or sensitivity analyses) could have been used as the basis for computing the proportionate contribution of water to locations serviced by the water-distribution system. ATSDR and NJDHSS chose the manual adjustment process.

The commenter also questioned the ATSDR approach of not plotting locations in Figure 31 (of Maslia *et al.*, 2001) where the difference in the simulated proportionate contribution of water was zero. The commenter's reason for questioning this approach states:

> . . . it is possible that for a given study location, the MAP proportionate contribution may be zero, while the SENS0 proportionate contribution may be greater than zero.

ATSDR **did** plot study locations where the proportionate contribution from either MAP **or** SENS0 was zero. ATSDR did **not** plot the study locations when the proportionate contribution from **both** MAP and SENS0 simulations was zero. ATSDR believes that including study locations where the proportionate contribution was zero for **both** the MAP and SENS0 simulations would have biased the plotted results to show less variation than reported to changes in operating conditions.

The commenter concludes that the variations in proportionate contributions of water from all operating conditions (MAP and all sensitivity analyses) should be determined for each study subject since this may impact the exposure category and ultimately the final odds ratios. The proportionate contribution results are available for every simulation (MAP and sensitivity analyses). It is ATSDR's opinion that similar odds ratios would be obtained no matter which simulation method (MAP or sensitivity analyses) is used for the odds ratio computations because of the narrow range of conditions which are needed to successfully operate the historical distribution system.

References for Responses to Union Carbide

ENVIRON Corporation. 1986. Formulation and calibration of a numerical ground-water flow model of the Ciba-Geigy Toms River plant area. Princeton: ENVIRON Corporation, November 1986.

Maslia, ML, Sautner, JB, Aral, MM, Gillig, RE, Reyes, JJ, Williams, RC. 2001. Historical reconstruction of the water-distribution system serving the Dover Township area, New Jersey: January 1962–December 1996. Atlanta: Agency for Toxic Substances and Disease Registry.

Commenter: Ciba Specialty Chemicals Corporation

Comment:

"The most obvious area in which the Final Report may be improved is in a more balanced reporting of the hypotheses that were tested. The key hypotheses relate to environmental factors and the elevated incidence of certain (leukemia, brain, and central nervous system) childhood cancers over a certain period of time. The language in the Final Report should be edited to reflect that the Study results do not support the original hypotheses under investigation, i.e., hypotheses concerning environmental exposures and the incidence of childhood cancer in Dover Township. For example, Table 16 provides evidence that there is no overall association between exposures to Ciba-Geigy air emissions and increased incidence of leukemia and nervous system cancer combined, leukemia alone, or nervous system cancer alone. Analysis by prenatal/postnatal exposures and age at diagnosis similarly show no pattern of increased risk. These findings should be explicitly stated in the text. Indeed, while Ciba recognizes there is always some need to summarize and emphasize some aspects of any study over other aspects, in the case of this Study, if any findings are to be emphasized over any other, they should be the ones that relate most closely to the hypotheses which the Study was designed to evaluate.

Ciba's comment is more than semantic. Even a careful lay reader of the draft Final Report would not realize that the investigator preformed literally thousands of sub-group analyses and that analyses of thousands of possible associations yielded no positive associations. It would be tedious and unnecessary to list all of the thousands of analyses and the null conclusions that were drawn from them, but there is no reason why in the summary of the Report, the public statements accompanying the Report, and in the body of the Report they are not accorded equal weight with the limited and qualified positive associations that the analyses yielded for prenatal exposure of females diagnosed with leukemia under age five."

Response:

We stated in the both Volume I and II that "exposure to Ciba-Geigy ambient air emissions did not appear to be associated with childhood cancers when both sexes were evaluated together." Furthermore, the conclusion in the draft report stated that "no associations were detected in analyses of the overall study population" and exposure to Ciba-Geigy ambient air. Our conclusion that "a consistent elevation in the odds ratios and an apparent dose response effect was seen in both the Interview and Birth Records Studies between prenatal exposure to Ciba-Geigy ambient air and leukemia in female children diagnosed prior to age five" is based on the body of findings for this specific case group. This is consistent with a plausible exposure window (prenatal), and is consistent with our stated hypothesis that exposure to Ciba-

Geigy air emissions was a risk factor. It is important to note that the excess childhood cancer found during our 1997 Health Consultation (Berry and Haltmeier, 1997) was primarily seen for females diagnosed with leukemia.

Comment:

"The manner of presentation of the analyses for females diagnosed with leukemia under the age of 5 with presumed prenatal exposure to Ciba-Geigy air emissions is representative of a focus on one positive finding without reporting other findings that would provide a better balanced Final Report. The Study concludes there is support for the hypothesis that Ciba-Geigy air emissions was a risk factor in childhood leukemia in females. There is no association for male leukemia in this or any other subgroup, which is inconsistent with the association for females diagnosed under the age of 5 with prenatal exposure. Little attention is devoted to the non-conformatory results in the case of males or the inconsistencies among the female leukemia cases. As one Peer Reviewer noted, '[T]he findings are not consistent with knowledge of the etiology of childhood leukemia generally. There are no known risk factors for childhood leukemia or any other childhood cancer that affect only males or only females or one sex to a greater degree than the other.' Comments of Greta Bunin, Ph.D. Recognizing this biological implausibility in the Report is important because the Study authors themselves have recognized it. In the Response to the Expert Panel Comments appears the following:

> *Comment: There is little biomedical reason to stratify on the basis of sex and further rationale is needed for the emphasis of the stratified findings. (Dr. Samet)*
> *Response: We concur that these is little evidence in the scientific literature for environmental exposures to differentially impact males or females for childhood cancer.*

Indeed, the draft Final Report fails to reflect the peer review comments of Dr. Frumkiin that, given the high degree of uncertainty, "the findings are also consistent with an absence of effect."

Response:

While the scientific literature provides little evidence that exposure to environmental pollutants would differentially affect cancer incidence in one sex over another, it is important to note that little is known about the etiology of childhood cancer. Consequently, it is a common practice in both descriptive and analytic epidemiological studies of childhood cancer to separately evaluate sex differences as a means of understanding the natural history of the disease. In both New Jersey and nationally, leukemia and brain and central nervous system cancer incidence rates are

higher in males than females. For example, statewide and national leukemia incidence rates for males are about 20-30% higher than in females. While there is no scientific explanation for this sex differential, it is a fact that the differential exists and there are likely biological, though unexplained at this point, reasons for the differences. However, what we see in Dover Township (Berry and Haltmeier, 1997) is just the opposite, with childhood cancer incidence in females significantly elevated (particularly for leukemia and brain and central nervous system cancers) while incidence in males was not significantly elevated. In addition, our full response to the peer review comment mentioned above included: "... The original standardized incidence ratio study of selected childhood cancers in Dover Township found elevated leukemia rates among female children under age five. Thus we had an a priori interest in findings related to leukemia among young girls in Dover Township..." As to the uncertainty of the findings, in numerous places, in the Report cautions the reader that "it is important to note that there is considerable uncertainty in the findings."

Comment:

"Ciba agrees in general with most of the comments of the Expert Panel of Peer Reviewers who were permitted to review the draft report prior to its December release for public comment. These reviewers generally focused on the considerable uncertainty in the data and findings, imprecision in the modeling and the absence of biological plausibility to support gender-specific findings. Panel members made comments such as:

- *'I would suggest expressing caution in interpreting these findings...' Comments of Howard Frumkin, M.D., Dr.P.H.*
- *'I would give more emphasis to the considerable uncertainty in the findings.' Comments of Howard Frumkin, M.D., Dr.P.H.*
- *'The conclusions concerning the subgroup analyses should be softened since the evidence is not that strong.' Comments of Greta Bunin, Ph.D.*
- *'Readers of the Technical Report are likely to conclude that the research team is pretty sure that Parkway water and Ciba-Geigy air are linked to leukemia in females when the evidence in my opinion is not that strong.' Comments of Greta Bunin, Ph.D.*
- *'[T]oo much is made of the female leukemia findings." Comments of David A. Savitz, Ph.D.*
- *"There needs to be a stronger foundation for interpreting the data.' Comments of Jonathan M. Samet, M.D., M.S.*
- *'[T]he text of the report overly emphasizes 'statistical significance' as a guideline for the interpretation of odds ratios. Power is limited and confidence intervals wide.' Comments of Jonathan M. Samet, M.D., M.S.*
- *'Overall, then, I would conclude that certain findings in the study seem to suggest the hypothesis of exposure-related risks for childhood leukemia, but*

that there is considerable uncertainty in the findings, and the findings are also consistent with an absence of effect.' Comments of Howard Frumkin, M.D., Dr.P.H.

In our opinion, while in most cases the peer review comments were acknowledged by the Agencies as valid, the December public comment draft did not adequately address these comments in the manner in which the findings were finally reported. As was the case of the peer reviewed draft, the language used in the December draft still has 'the overall flavor...of a positive study.' Comments of Howard Frumkin, M.D., Dr.P.H. In order for future researchers and the public generally to fully evaluate the report, and to take advantage of the critiques that have been offered, we suggest that the Final Report set forth in an appendix the original peer reviewed text, the peer reviewers' comments related to that text, the December draft text, and any modifications to the final text as published. In that manner, other investigators and the interested public can gain the benefit of the peer comments in forming their own opinions of the work as a whole."

Response:

The Expert Panel process was an important component of our activities and their input and recommendations were duly considered. This input it provided an independent review and evaluation of all aspects of the study. Comments from the Expert Panel and peer reviewers provided valuable guidance in the development and conduct of the study, as well as interpretation and presentation of the study results. The Expert Panel comments, and our responses, have been released as public documents. In our responses we identify where changes to the report were made.

Comment:

"None of the members of the Expert Panel were air modelers, and no peer review of the air modeling was conducted. Nevertheless, the members of the Expert Panel of Peer Reviewers consistently expressed concern about the considerable uncertainty in the exposure assessment calculated by the air model. Dr. Bunin commented on her impression that the air modeling was less precise, robust and believable than the water modeling.. Dr. Frumkin commented on how the findings were highly dependent on the air modeling exposure reconstruction.

As suggested by these comments, the air modeling results are subject to substantial uncertainty for several reasons, including:

- *Using orders of magnitude difference over time in the emission velocity used in the model, which has a very significant impact on dispersion patterns and potential calculated concentrations of contaminants at any location within the dispersion patten and is counter intuitive (if not down right wrong) considering the plant manufactured its products over time in relatively consistent manner.*

- *The Ciba plant operative as a batch operation. Historically, the Ciba plant shut down for 2 weeks in July and one week in December, when emissions ceased. The model assumes continuous emissions, even during these production shutdowns. This assumption is significant because the analysis assumes continuous pre-natal exposure to females when such exposure never occurred.*
- *Manufacturing operations at the Ciba plant ceased by 1990 after which there were no gaseous emissions and little if any particulate emissions relating to the remaining operations (dye standardization). The model assumes continuous manufacturing through 1996.*
- *The model equates emission levels with production levels, which is highly unreliable. No evaluation was made concerning whether any type of production presented a more significant source of potential air contaminants than others. For example, if one determined that the resins/plastics production at the Site presented a more significant potential source, than the peak emission year and relative percentage of peak emissions would change significantly."*

Response:

While it is true that none of the members of our Expert Panel are air modelers, EOHSI's report, *Atmospheric Dispersion Modeling Analysis to Support the Dover Township Childhood Cancer Epidemiologic Study*, was reviewed by scientists experienced in air modeling. Two of the three peer reviewers felt that the ISCST3 model used by EOHSI was an appropriate and valid model for this application, while the third reviewer was unsure and suggested that the CALMET/CALPUFF model might be better. The ISCST3 model has been used extensively in regulatory risk assessments and has proven useful for a variety of applications.

In conducting the air modeling, EOHSI utilized information on facility characteristics available from Ciba permits located at NJDEP. These facility parameters were used in the modeling.

As stated in EOHSI's report, "Since hourly or annual emissions data needed for the model were available for very little of the study time period, the approach followed in this analysis assumed a nominal emissions rate of 100 grams per second throughout the study period." The production level information, provided by officials at Ciba-Geigy, were then used to annually modify the modeled monthly exposure estimates in order to adjust for changes in operation at the facility over time. Plant shutdowns were not factored into the modified exposure estimates. Sufficient facility emission data over time was not available to evaluate specific potential source emissions impacts.

While uncertainties remain in the modeling, these errors would result in

nondifferential misclassification of exposure which would have tended to bias the results toward seeing no association, not creating associations where none exist.

Comment:

"The air modeling exercise is of highly limited utility for still another different reason. The Study uses exposure units derived from the air model that lack any relationship to actual emissions, concentrations or dose of any specific chemical or group of chemicals. It is impossible to determine the biological plausibility of an association between cancer and potential exposure to arbitrary and non-real world 'exposure units' because the Study does not, and can not, evaluate whether any exposure is below detection limits or below any known human health based exposure levels for any specific pollutants or contaminants."

Response:

Because of the lack of facility emission data available over time, the atmospheric dispersion model estimates where the air (and emissions) from Ciba-Geigy will go in the community. In turn, the modeling estimates the relative impact of pollution over the study area (i.e., higher vs. lower relative potential exposure). Annual facility production information was then used to modify potential exposures as a way of estimating changing activities of the facility over time. We feel that air modeling was a better method for estimating relative exposures than a simple distance measure because wind speed and direction are better predictors of where pollutants will travel.

Comment:

"While the limited utility of the air model should make one extremely cautious about any conclusions related to exposure generally and with respect to any sub-group, an interpretative flaw also permeates the evaluation in relation to females diagnosed with leukemia under the age of five. In the analysis, 'high exposure' is, by the definition given to 'high' by the investigators, the calculated exposure of the highest 25% of all of the controls (of both sexes and of all ages studied). A positive association of the kind reported upon in the Final Report might be justified if it were found that a disproportionate number (compared to all controls) of females under age five with leukemia had been found to have been 'high exposure.'

However, the positive association reported is the result of a deficit of female <u>controls</u> under age five in the high exposure group, not an excess of female <u>cases</u> of leukemia in the high exposure group. As shown in Table 17, the number of females with prenatal exposure and diagnosis of leukemia prior to age 5 presented as 'high exposure' is approximately 25% of this subgroup, 2 of 7 cases. This number of cases is

what one would expect if cases were distributed by exposure in the same pattern as the entire set of controls. (25% of cases and 25% of all controls). The 'elevated' odds ratio arises because there are disproportionately fewer young female controls subject to high exposure. Thus, the strong association that is reported is not due to an excess of exposure among cases. This seriously detracts from a conclusion that leukemia is associated with high exposure."

Response:

We chose to use cut points that were derived using all control data, an approach that was outlined in the Procedure Manual. Because the data were analyzed as matched sets, cases need to be considered with their matched controls. Conditional logistic regression odds ratios for matched sets compares cases with their matched controls, which are matched on age, sex, and exposure time period. The analysis demonstrates that female leukemia cases had, on average, relatively higher exposure estimates than their matched controls.

Comment:

"It would unnecessarily prolong these comments to attempt to list all of the areas in which it would be extremely beneficial to have available the underlying data, assumptions, methodologies, rationales, and judgments employed in the Study. We urge the investigators to disclose and make available all of the data and work product except for that which is truly uniquely personal to the persons who participated in the Study. For example, we see no reason why the Study has not provided any means by which the locations of the cases and controls can be verified to see if one can reproduce the calculations of the odds ratios or other analyses. Moreover, the absence of location data prevents an independent researcher from verifying the analyses or performing alternative analyses. Similarly, judgements were made frequently without explanation in the text. For example, the Study uses as 'cut points' the 25th and 50th percentiles of all of the controls to define 'high' and 'medium' air exposures, but provides no explanation why the analysis was not also conducted on the statistically more usual and more powerful cut points of the one-third and two-third percentiles. We urge that additional information, in the form of open public files, be made available of the data, work papers, calculations, and other information relied upon by the investigators, redacted only to delete clearly personal individual identities."

Response:

Specific requests for study data may be made to the Department. All information within the data set which could be used to identify any individual subject in the study would be removed from the data set for confidentiality reasons.

Tertile cut points were also evaluated and similar results to the 25th and 50th percentile cut points were found. The 25th and 50th percentile cut points were presented in the Report because they permitted a more complete analysis of smaller cancer groupings (specifically brain and central nervous system cancer) by allowing for more stable referent group. We have added language to Volume II (Interview Study Results) concerning the analyses which used tertile cut-points.

Comment:

"To evaluate the Study fairly and objectively, there should be a summary of the effort made to supplement the Cancer Registry data. Especially in light of the small number of cases involved, the effort to supplement the data is important information for scientific reviewers.

As Ciba understands the process, there was an initial study, reflected in a 1995 letter from Michael Berry, summarizing the New Jersey Cancer Registry data from 1979-1991. Between the 1995 Berry letter and the Study, the Department conducted an audit to verify the completeness of the case registration and to include the period through 1995. The audit involved hospital visits and record reviews, but only in Ocean and Monmouth Counties. In the remaining 19 counties, a different methodology , a mail survey, was used. In addition, the audit relied upon the assistance of community groups with a personal and significant interest in the Study. In reviewing the data reported in December 1997, it is evident that the different methodologies used and the differential focus of attention on the case registration effort resulted in disproportionate increases in the number of cases closest to the epicenter of the Study. The audit resulted in a 28.6% (from 14 to 18 cases) increase in the number of cases in Toms River; a 21.4% (from 56 to 68 cases) increase in Dover Township; and a 13.9% (from 230 to 262 cases) increase in Ocean County. It is our understanding that the number of additional cases reported Statewide (exclusive of Ocean County) was de minimis. There is no indication that the Peer Reviewers were apprised of this effort to modify the Official Cancer Registry in this manner. Ciba suggests that the Final Report make explicit mention of this effort to supplement the official Cancer Registry, report the differential additional cases as such, and report on Peer Review comments (to be obtained) on the methodology and potential effects on the findings."

Response:

The activities of updating the State Cancer Registry in 1996 were summarized and reported in another document (*Childhood Cancer Incidence Health Consultation: A Review and Analysis of Cancer Registry Data, 1979-1995 for Dover Township (Ocean County), New Jersey*) which was peer reviewed and released for public comment in 1997. We do not agree that the activities of updating the State Cancer Registry have

a bearing on the current study. The audit did not rely on the assistance of community groups. Our Expert Panel received a copy of the *Childhood Cancer Incidence Health Consultation* report in 1998 while providing comment on the current study protocol. Furthermore, one-third of our Expert Panel were peer reviewers for the protocol and final 1997 Health Consultation on childhood cancer incidence in Dover Township.

Comment:

"In summary, ultimately the Final Report must serve two distinct constituencies–the scientific community and the informed and interested lay public. The Final Report can only meet the needs of the scientific community that may in the future look to the Case-Control Study both critically and as a precedent for similar investigations if it makes full and explicit disclosure of all of the underlying data, assumptions, methodologies, rationales, and judgements employed in the Study. The Final Report must also inform and educate the lay public and the media in a manner that is fair and balanced and does not place undue emphasis on some few highly qualified and uncertain findings at the risk of distorting the overall findings. In particular, Ciba was struck by the fact that despite many cautionary and qualified statements made by the Agencies both in the draft Final Report and in the written and oral statements that were released contemporaneously, the media often ignored the cautions and qualifications and distorted the weight and strength of the associations reported. It is important for all involved that the Final Report be as clear as humanly possible about all of the findings, their limitations and qualifications, and not focus unduly on some few of them. In our judgement, further revisions to the Final Report and fuller disclosure of the data, assumptions, methodologies, rationales, and judgements are necessary to make clearer the uncertainties and other limitations pointed out by the Expert Panel of Peer Reviewers. In closing, we urge the Department to revise the Report to clarify for the general public the significant uncertainty, the absence of biological plausibility and limited nature of any conclusions in the Report."

Response:

We agree on the importance of informing and educating the public and media and worked diligently and consistently over the five-year period to accomplish this task. Although we try to work closely with the media regarding important epidemiologic issues and study findings including the most appropriate characterization of the study's contents, we cannot control how the media characterizes any study. Although there appears to be an inconsistent association with regard to the male/female analyses, this is not definitive proof of an absence of biologic plausibility. Much is not known about the etiology of childhood cancer. Mechanisms, unknown to date, may exist to explain the sex differences. As discussed earlier, there are known differences in incidence rates among males and females of certain childhood cancers. As stated in the Report, "The potential causal association of a risk factor with an outcome was

evaluated using a combination of criteria, including: strength of the association, statistical significance, consistency of findings of multiple measures for an exposure, apparent dose response effect, and evidence of a completed exposure pathway." Cautionary statements on interpreting results are repeatedly included in the Report.

Commenter: Eric Rau

Comment:

"The most important outcome are the conclusions that Ciba-Geiegy air emissions and Parkway well field ground water are linked to leukemia and prenatal exposure. Linkage to any cancer condemns the continued use of water from this well field for any human consumption. The decision of the Water Company to replace the source is to be welcomed and supported."

Response:

No response necessary.

Comment:

"The impact on the EPA Trimer Toxicology Test is most significant. Previously I have pointed out that a ground water concentrate should be included in the program. The ground water contains, beside the trimer, many other contaminants such as chlorinated hydrocarbons and unknown compounds of undetermined toxicity. The synergistic impact of this mix on the toxic property of the ground water must be determined. To wait until 2007 for the completion of the current program to learn if a trimer surrogate is the carcinogenic agent is wasteful of time and money. If the results are positive we will know that the trimer mixture is carcinogenic. If the results are negative, we will have spent a decade without knowledge about the toxic properties of the groundwater. To start another series of tests in 2007 will delay final resolution beyond our lifetime. I strongly recommend that a groundwater concentrate specimen be included in the toxicology program. The results will tell us that the groundwater did or did not contain the carcinogenic agent. On page 8 of Volume 1 of the report you recognize this shortcoming, it is high time that the program acted to clear the uncertainty."

Response:

As stated in the Report, the concentration of the contaminants impacting the Parkway Well Field over the years is unknown, therefore the risk potential to the community is not well understood. Consequently, the true carcinogenic potential of the contaminant mixture in this completed historic exposure pathway remains unknown. The approach we took in the epidemiologic study was to examine water source and time windows of potential exposure for the well fields.

Comment:

"It has been said that the linkage between the three childhood cancers and the various parameters cited in the epidemiological study is weak because only two positive correlations were found. Examining the data I find that the primary cause for this opinion is the statistics used in the study. A simple count of Odds Ratios in the report shows that 148 are greater than one, 117 are less. This preponderance of greater than one Odds Ratios makes me question the statistics.

For the above reason I am concerned about the statistical methods used to reach conclusions. It would be desirable if you had presented the statistics in an easier to follow manner. The results should be presented in systematic way to facilitate interpretation. It should include examples of how you fitted the regression model, how you estimated the standard error of the estimated odds ratio, and how you corrected the confidence interval for the finite sample that you were forced to use. If the confidence intervals were shorter than many more Odds Ratios would be significant. Methods for case-control studies are described in 'Statistical Methods for Comparative Studies', Anderson, and et.al. Wylie 1980 pg. 39-44, 120-122, 170-171.

I consider the weakness of the statistics to be most significant. It challenges the validity of the report."

Response:

The major problem encountered in this study concerning the statistical analysis is the limited study sample size. This is a basic problem in any "cluster" study. The wide confidence intervals are a function of this small numbers issue. The statistical methods used are standard and appropriate for the design of the study, and supported by references to epidemiologic texts.

Comment:

"The comments on future monitoring of the parkway wellfield are well taken. It should be made more rigorous. With the determination that the groundwater may well have carcinogenic properties, the exact extent and volume of the plume should be determined. I would suggest that a three dimensional definition of the plume be obtained so that no unexpected diversion of toxic material occurs. Similar comments apply to other waters such as the effluent from the Dover Township Landfill."

Response:

The public health objective is to ensure the continued interruption of the exposure pathway, and that is what we have recommended. How this is accomplished is the province of the environmental regulatory and risk management agencies.

Comment:

"The work done at the EOHSI is not mentioned."

Response:

As mentioned in Volume II, the details of the computer model simulations conducted by EOHSI can be found in their 2001 report, *EOHSI: Atmospheric Dispersion Modeling Analysis to Support the Dover Township Childhood Cancer Epidemiologic Study*. These reports were previously released to the public and we also detail their efforts in Volume IV, Appendix F.

Commenter: Linda Gillick

Comment:

"As the chairwoman of the CACCCC and the mother of one of the children with nervous system cancer included in this study, I am disappointed to say the least. I will not elaborate on the fact that approximately $10,000,000 and six long years was spent to find out an association of just Leukemia in girls was found. I will however point out many of the missing points that were not analyzed and need to be done.

In Volume I page 8. Your first mistake was saying that you ASSUMED the period of 1962-1975 was the exposure for the Holly Street well field. It is documented that shallow wells from this well field remained open and pumping water to the town until approximately 1982. This being a major factor in your analyses on everything pertaining to the Holly street evaluation makes it bogus. You must go back and evaluate the Holly street exposure during the period from say 1976 until the wells that were shallow were closed permanently. You did this for Parkway wells until they were taken off line.

I am not a statistician but try to use common sense when evaluating the data that has been released. In Volume III, Table 8 please take another look at the Holly street numbers...then reanalyze for the time you did not take into consideration for their exposure."

Response:

As stated in the Ciba-Geigy Health Assessment, "The duration of exposure through this pathway cannot be determined, since data are lacking before 1965 and after 1966...Holly Street well #13 was sealed in 1967. Well #14 was in operation until 1975...Well #18 was in operation until 1980." This is also reflected in ATSDR's pumping data available in their modeling report.

We assumed a period of approximately ten years after documented contamination as a way to limit consideration of exposure to the Holly Street water source to a period when it was more likely to have been contaminated. Based on the Commenter's suggestion, and the date of the last use of a previously contaminated well, we have re-analyzed the Holly Street source with an exposure window of 1962 through 1980. The final report now contains analysis of Holly Street water exposures in the periods 1962-1996, 1962-1975, and 1962-1980. The odds ratios for the new time-specific (1962-1980) Holly Street variables were unremarkable and similar to the original time-specific (1962-1975) Holly Street well field analysis. Language has been added to reflect this new analysis in Volume I (Environmental Factors) and Volume II (Interview Study Results).

Comment:

"In Volume III, in the beginning tables, you only analyze for Nervous System cancers in two tables. Why is this, if you are supposed to be doing this for three categories defined, Leukemia's, Central/Brain Nervous Systems and Nervous Systems cancers? I find it even more disturbing when looking at Table II page 1 of 1. It appeared from your findings prenatal exposure and under the age of 4 the most susceptible. Then why do the 5 sympathetic cancers under the age of 4 when added to the brain and central nervous system cancers equal the same amount of children affected for Leukemia in that age group? It is also a known fact that prenatal and young children are more susceptible to chemicals at small amounts; therefore even a blend of contamination from Parkway or Holly Street contaminants could be a contributor."

Response:

Table 2 shows the number of cases by diagnosis age and cancer type. There are no exposure categories associated with Table 2. It is a coincidence that the combined number of sympathetic and brain/central nervous system cases diagnosed under age five equals the number of leukemia cases diagnosed under age five.

All analyses were done for four categories: leukemia and nervous system cancers, leukemia, nervous system cancer, and brain and central nervous system cancer, as set forth in the Study Protocol. The nervous system category includes all sympathetic nervous system cases plus all brain and central nervous system cases.

Parkway and Holly Street well fields were analyzed separately since the exposures involved different contaminants and different contaminant time windows.

Comment:

"I also found the numbers interesting for Brookside Well exposures. Doesn't a red flag get raised when we know that contaminants from the Ciba-Geigy pipeline went right past this well? Isn't it also interesting that an association was found within a distance of the pipeline? Have you also not considered that Mr. Fernicola was arrested with a truckload of drums at the Brookside well site? Isn't it also a fact that some Tic's associated with dyes were found?... You have assumed that since the Brookside well is 'X' amount of feet deep, no exposure could have happened. 1.Have you considered how long that pipeline was leaking? 2.Water seeks its lowest level. 3.Take a look on the maps you have and see where the epicenter of the children radiates from. 4.The sampling done of soil in that area was not done deep enough to get past all the fill and materials brought in for many years after the pipeline break. (We were trying to see PAST exposure as well as PRESENT exposure)"

Response:

We examined the possibility that any water source ever serving the public water system could be associated with cancer risk, though we focused attention on Parkway and Holly because of documented exposures in the past. Analyses from the Interview Study (Tables 7 and 8) provide no support for an association between Brookside exposure and childhood cancers. While some of the odds ratios for Brookside were elevated in the Birth Records Study (Tables 46 and 47), no exposure pathway has been documented for this water source. While leukemia in both sexes combined and males (age 0-19) appeared elevated, no corresponding finding was seen in the Interview Study. No completed exposure pathway associated with the Ciba-Geigy pipeline was identified in the Ciba-Geigy Public Health Assessment.

Comment:

"All through your analyses there are <u>many</u> indications that Neurological cancers were elevated. You did not present this to the public when this report was released. Shame on all of you. The public relies as it has in the past for complete honesty. Your watered down version, which you well know the press reports as you report it, was not completely forthcoming. Even our Dover Township officials have stated they are not going to read the report, but rely on what is reported out. I personally believe this was done so the public wouldn't panic. The facts are there, but only if you read everything presented in all those tables, and know how to read them."

Response:

Expert Panelists with extensive scientific knowledge and experience in the area urged us to focus on the two most homogeneous cancer groupings, 1) leukemia and 2) brain and central nervous system cancers. Furthermore, based on our criteria for assessing association: "strength of the association, statistical significance, consistency of findings of multiple measures for an exposure, apparent dose response effect, and evidence of a completed exposure pathway," we believe that there is no consistent or coherent pattern in the analyses of nervous system cancers.

As an example, we based our rationale concerning Parkway exposure during the prenatal time period and nervous system cancer on the following:

1) while certain odds ratios were elevated for nervous system cancer and prenatal unadjusted Parkway water exposure, little of note was found for the prenatal time-specific Parkway source indices for either nervous system cancer or brain and central nervous system cancer, and
2) no cases from the brain and central nervous system cancer grouping were in the high Parkway source or source/consumption exposure categories and only one of those cases was in the medium Parkway exposure categories.

Therefore, we believe the associations that we focused on in public presentations were those with the most compelling statistical and biological bases.

Comment:

"I know a lot of time and heart went into this for many of you. There are also those that condemned this from the beginning and put the least amount of effort into finding the truth. I also know that so many more lives could have been saved if all of you had been paying attention when these issues were first brought to light.

The above comment brings me to the comments on air exposure. There is such a gap in the data as well as monitoring abilities; I hope a lesson has been learned. With that being said, if you do not demand air monitoring off site during the Ciba clean up, we will be in the same mess we have been in for decades. Should an accident take place, yes we will know how much exposure on the premises, I'm more concerned to the impact of the residents outside the perimeter of the Super Fund site. You are supposed to be protecting our health, you didn't do it for years as was mandated in an agreement between the state and Union Carbide. Are you going to pass the responsibility to someone else's policy. I hope not."

Response:

The USEPA is the agency responsible for developing the plan for remediating the Ciba site. An evaluation of their Proposed Remedial Action Plan for Operable Unit 2 (on-site soils) for the Ciba-Geigy site was prepared by ATSDR in the ATSDR Public Health Consultation (August,2000). Staff from both NJDHSS and ATSDR are reviewing the air monitoring plan developed by USEPA. The results of their evaluation will be included in a subsequent health consultation.

Comment:

"I will leave the detailed comments to the experts, my expertise lies with dealing with all the families you allowed to be affected for too long. Your work is not complete here. You still have a responsibility to the community. Do not allow exposure to chemicals from these sites to happen again to this community. We know contaminants are still in our ground waiting to be removed or in the process of doing so from the water supply. Use common sense and err on the side of caution when decisions have to be made. You have made recommendations to protect us from further exposure by constant monitoring. How will this be carried out? Who will be in charge of this? Will this be another recommendation on paper without teeth?"

Response:

USEPA and NJDEP are the regulatory authorities responsible for implementing and evaluating these activities. As stated above, both NJDHSS and ATSDR are continuing to play a role in the review of remedial and monitoring plans and continue to provide our public health input when warranted.

Commenter: Bruce Anderson

Comment:

"First let me start with my first request, which is all comments should be published un-edited and all comments should be responded to."

Response:

All comments are available to the public upon request. We are incorporating comments (without identifiers unless the comment itself included such information) and responses in the final report as this Volume V. A limited amount of editing to maintain format consistency was done without altering or removing substantive remarks.

Comment:

"As one of the families in the Case-control Study of Childhood Cancers in Dover Township (Ocean County), New Jersey we were very disappointed in the quality of work that went into this study. For the amount of money and the length of time spend on this study a complete and comprehensive study should have been performed.

Please explain how the State of New Jersey is independent and not a principle player in the outcome of this study? I always thought a study had to be independent and unbiased or impartial. Since the State of New Jersey signed an agreement with Union Carbide over Reich Farm, whereas for up to $60,000 the State of New Jersey assumed all responsibility for Reich Farm. Since there is other court sealed documents that we do not have access to, what other unknown agreements are out there?"

Response:

The NJDHSS and ATSDR, took several steps to make our investigation a transparent process. These included, in cooperation with the local Citizen Action Committee for Childhood Cancer Cluster (CACCCC), developing a Public Health Response Plan detailing a systematic process to investigate the elevation of childhood cancer in Dover Township. An Expert Panel of public health and medical professionals provided peer review and guidance for the study. Additionally, stakeholders, including the CACCCC, have been part of the process from the beginning, reviewing protocols, procedures, and providing suggestions throughout the study.

Comment:

"An association was found between maternal exposures to ionizing or low frequency radiation and leukemia and nervous system cancers.

Please explain this association and the source of the radiation? Is the source radiation the radiation found in our drinking water? Low frequency radiation is not a term I am aware of; maybe it should read low energy radiation? What type of particle is this ' low frequency radiation', alpha, beta, or gamma?"

Response:

As part of the parental occupational histories, respondents were asked if they had used certain chemicals/substances at work. These chemicals/substances were grouped into categories with examples provided to help respondents remember. The occupational factor you refer to is maternal exposure to "Radiation, Ionizing and Low Frequency." Examples presented in the questionnaire included radio frequency, heater/sealers, radioactive materials, and x-rays. These are a mix of ionizing and non-ionizing radiation (low frequency). The question does not refer to any contamination of the drinking water.

Comment:

"As previously requested, correct the number of Ciba-Geigy pipeline breaks to five, not the three as reported on Page 3 and elsewhere in the document and update the statistics associated with these other pipe breaks.

1984 Bay & Vaughn Aves
1985 Bay & Vaughn Aves
1986 Oak Ridge Parkway
1988 Bay & Hooper Aves
1989 Mapletree Ave & Old Freehold Road"

Response:

Thank you for bringing this to our attention. We failed to include the1986 pipeline break at Oak Ridge Parkway in our analysis. The second break at Bay & Vaughn Aves. (1985), was taken into account with the analysis of residences within ½ mile of Bay & Vaughn Avenues after the first break in 1984. We have reassessed exposure to the pipeline breaks to include the new break as stated in Volume I (Introduction and Results for Residential Proximity to Sites of Concern) and in Volume II (Environmental Factors and Risk Factor Evaluation). No new study subjects were found within ½ mile of a pipeline break, so the earlier analyses remain unchanged.

Comment:

"Please make the public aware in the future that 'because of the small number of subjects...' this limit was set by the State of New Jersey when the limits were set on who could be included in the cancer cluster and is very limiting. It is a snap shot in time and does not reflect necessarily what has occurred in Toms River, NJ.

Please explain the bases and reason behind selecting only two odds ratio age groups (Page 4) (children diagnosed prior to age 20, and children diagnosed prior to age 5). In the final report please include more age groups."

Response:

The study time period of case ascertainment (1979-1996) reflects the time period of available cancer incidence data from which cases were drawn. The Study cannot address cancer incidence occurring prior to 1979 since the State Cancer Registry did not exist and no systematic collection of cancer incidence information occurred prior to that time.

The age selection was based on the 1997 Health Consultation (Berry and Haltmeier, 1997), which evaluated the two groups (0-4 and 0-19) and found excess cancer incidence in those age groups. The National Cancer Institute publishes data for children aged birth through 14 and birth through 19 years of age. The North American Association of Central Cancer Registries analyzes data of cancers diagnosed among children from birth through 14 years of age. We originally recommended that the case-control study evaluate cancers in children diagnosed prior to age 15, but expanded the age to under 20 in response to Stakeholder comments.

Comment:

"'Weather data used was from a station fifty miles away.' (Page 13.) As I previously mention(ed) at one of the public meetings, weather data should have been taken from Oyster Creek. I was told they only went back as far as 1982. Weather data goes back as far as 1969 when the plant went into operation. Please go back and incorporate this closer area weather data into this report. The information is there if you want to look for it."

Response:

The Oyster Creek Nuclear Generating Station has generally complete and reliable

electronic data from 1982 through 1996. Electronic data prior to 1982 are not available from this station. The Atlantic City weather station has been operational throughout the study time period, 1962 through 1996, with all data available electronically. In Volume IV (Appendix F), we present a correlation analysis of monthly exposure estimates that were generated using the Lakehurst and Atlantic City stations for the years (1973-1989) when data were available at both. The annual exposure estimates were significantly correlated; therefore, we felt that the Atlantic City meteorological data were the best data to use for the entire study period (1962-1996).

Comment:

"The exposure time-specific Parkway well field water (1982-1996) I believe to be inaccurate. The date should be expanded to 1975-1996. I will try to find documentation to support this time period and provide it to you in the future."

Response:

Because of the uncertainty in the travel time of contaminants from Reich Farm to Parkway, alternate time windows were developed for Parkway beginning with 1978-1996, through 1986-1996 as mentioned in Volume II (Interview Study Results and Birth Records Study Results). Analysis was also done for the whole time period that Parkway water was in use (1971-1996).

Commenter: Michael McLinden

Comment:

"Introduction section of the Executive Summary: The Executive Summary digests information contained in three additional volumes. It would be helpful to the reader if an outline or Table of Contents were included in the Executive Summary in order to make the document easier to read and point the reader to a more detailed discussion of a particular topic. A complete Table of Contents in the Executive Summary would also help readers navigate through the other three volumes as well (e.g., page one, paragraph two of Volume II refers to Figure 1, which is located in Volume III)."

Response:

A comprehensive guide to the contents of all volumes has been added to Volume I.

Comment:

"Introduction section of the Executive Summary: The second paragraph on page 1 discusses the results of the Childhood Cancer Incidence Health Consultation: A Review and Analysis of Cancer Registry Data, 1979-1995 for Dover Township (Ocean County), New Jersey (1997). This report'confirmed that the overall childhood cancer incidence rate in Dover Township was statistically significantly elevated for the period 1979 through 1995...' The sentence goes on to say that the elevated rate was 'primarily due to excesses leukemia and brain and central nervous system cancer in females residing in the Toms River Section of the Township.' This raises two concerns;

Was the cancer incidence investigation focused on all of Dover Township or a so-called 'Toms River' section of the township?

If the study focused on a 'Toms River section' of the township then that area should be defined in the report.

The majority of residents in Dover Township have a mailing address of Toms River and would generally consider themselves residents of Toms River (rather than Dover Township). Isolating a section of the township, defined by a group of census tracts, may prove helpful to researchers analyzing population data but may not be of much use to residents trying to evaluate which locations pose a higher risk of exposure. Figure 1 'Locations of Ocean County, Dover Township, and Toms River' attempts to define the 'Toms River' section but this map may be difficult for many people to interpret, especially for those unfamiliar with the township."

Response:

The *Childhood Cancer Incidence Health Consultation: A Review and Analysis of Cancer Registry Data, 1979-1995* evaluated childhood cancer data for Ocean County, Dover Township, and an aggregate of four census tracts (228, 231, 232, and 236) within Dover Township representing the Toms River section of the Township. As a result of the findings of elevated cancer incidence in select types of cancer throughout the Township, NJDHSS and ATSDR, in consultation with the CACCCC and the Expert Panel, recommended that further epidemiological evaluation of the elevated childhood cancer groupings was warranted for the entire Township.

Comment:

"Exposure to Air Pollution from Point Sources section of the Executive Summary: The second paragraph on page 13 indicates that there is some concern over the quality of data used in the modeling of Ciba-Geigy air emissions, particularly for weather data taken from a station fifty miles away. Weather data from Lakehurst Naval Air Station (located approximately seven miles west of the Ciba-Geigy plant) or the Oyster Creek Nuclear Generating Station (approximately ten miles south) might improve the input data quality. Was this data considered during the development of the model?"

Response:

Computerized meteorological data for the Naval Air Engineering Center in Lakehurst were only available for 1973 onward. Additionally, a reduction in the number of hours of operation of this station in the late 1980s led to decreased data quality and reliability. Consequently, the Naval Air Engineering Center station only had consistently complete hourly data for the years 1973 through 1987. The Oyster Creek Nuclear Generating Station had generally complete and reliable electronic data from 1982 through 1996. Data prior to 1982 were not available from this station. The Atlantic City weather station operated throughout the study time period, 1962 through 1996, with all data available electronically. In Volume IV, Appendix F, we present a correlation analysis of monthly exposure estimates that were generated using the Lakehurst and Atlantic City stations for the years (1973-1989) when data were available at both. The annual exposure estimates were significantly correlated; therefore, we felt that the Atlantic City meteorological data were the best data to use for the entire study period (1962-1996).

Comment:

"Recommendations section of the Executive Summary: Recommendation number two states that 'Efforts should be continued to cease or reduce exposure to hazardous substances...' The first bullet goes on to state 'The effort to ensure that the Reich Farm groundwater pollution does not cause contamination of additional Parkway well field wells should be continued in order to guarantee that this exposure pathway is not

completed.' The recommendations also call for the need to maintain private well restriction zones in order to eliminate the private well exposure pathway. What the recommendations do not call for is for the contaminated wells to be taken off line in order to eliminate the exposure pathway, instead they call for monitoring of the treatment system that removes the contaminants.

Allowing public water supply wells to continue to be contaminated, especially after finding an association between exposure to these wells and leukemia, is inconsistent with the other recommendations to eliminate exposure pathways and the NJDHSS should reconsider this recommendation. Eliminating the contamination, either by shutting down the contaminated wells or by installing interceptor wells between the Reich Farm plume and the Parkway well field, is the only effective means of ensuring that the exposure pathway has been eliminated. Severing the link between the Reich Farm plume and the public wells would also provide a sense of confidence in the water supply, something that has suffered greatly over the past five years. Reducing exposure through filtration does not guarantee the exposure has been abated and wastes resources on monitoring and maintenance that could more effectively be spent on solving the exposure problem."

Response:

The contaminated wells in the Parkway well field continue to operate with the treated effluent being pumped to waste. The wells, therefore, are "off line", but treated water may be used as a last resort to meet the supply demand of the community. The public health objective is to ensure the continued interruption of the exposure that may be of health concern, and that is what we have recommended. How this is accomplished is the province of the environmental regulatory and risk management agencies.

Commenter: Donald Hassig

Comment:

"Based upon an analysis of large numbers of children's cancer records from the time period 1954-1998, the Cancer Research Campaign, a United Kingdom NGO, has concluded that rates of incidence have risen steadily for certain common cancers, including: brain cancers and acute lymphoblastic leukemia. Such is also the case for cancers of reproductive organs. These increases do not appear to be the result of expanded screening, but rather are indicative of actual increased levels of disease.

Childhood cancer rates have also risen in the United States. Due to the similarities of exposure sources: cigarette smoke and environmental pollutants of heavily industrialized economies, it is reasonable to suspect that the US numbers also represent real increases.

By viewing cancer from a population perspective greater clarity can be obtained. The genetic damage, which leads to decontrol of cell division, is not confined to somatic tissue. When such lesions occur in germ tissue, the damage is heritable. As successive generations are exposed to carcinogens, the amount of inherited damage predisposing the individual to cancer increases. It takes a shorter amount of time for the more highly predisposed person to experience the quantity of exposure sufficient to bring about decontrol. This is due to the cumulative and conserved nature of the initiation stage of carcinogenesis. Put another way, cancer incidence rises among children as cancer persists in human populations at significant levels, such being the case for post-industrial levels.

Cancer as a clinically diagnosable disease is merely a window upon one stage of chromosomal aberration in an individual. Once we begin to take into consideration the many degrees to which damage to the genes of cell division control exist throughout a human population, the need to rethink risk evaluation becomes apparent. Children, predisposed to cancer by the inheritance of damaged DNA, are at a greater risk of developing cancer than individuals, whose chromosomal cell division control is more fully intact.

The most important causal factor of childhood cancer is the degree to which the child is predisposed to developing cancer. When this feature of a child's health is not taken into account, the results of a study such as the one conducted in Toms River can provide little insight into the underlying causes of incidence elevations. Can your office seek to determine the degree to which the cancer cases in the Dover Township study were predisposed to developing cancers? I would suggest that you attempt to include a quantification of genetic damage extant in the children's parents in this study? Could an estimate of this parameter be made by assessing the number of DNA

adducts extant in the genetic material of the parents?"

Response:

The Dover Township study was designed to evaluate specific environmental risk factors. Other factors, that are frequently evaluated in studies of childhood cancer were also collected by interview. While genetic characterization may have wide acceptability and use one day, there is currently insufficient scientific information or agreement on markers of genetic damage which could result in increased predisposition to developing cancer and childhood cancer causality to warrant this type of activity. Even if there were generally agreed upon markers, current characterization of "genetic damage" in parents may have little meaning with respect to possible exposures prior to a child's birth (as long ago as 35 years). Consequently, the study design did not include a genetic screening component.

Comment:

"The cancer risk for modern children is unarguably higher than that which existed among the adults upon whom risk models are based. For example, in the USEPA's dioxin reassessment, cancer risk is estimated using data primarily from factory workers exposed to dioxin contaminants of pesticide manufacture. Therefore, children's cancer risk is higher than the 1 in 1000 to 1 in 100 risk repoted by the Agency.

Elevated incidence of certain childhood cancers in a given area indicates that children, with no as yet clinically diagnosable cancer in this population, are at heightened risk of developing these same cancers. To address this health threat, efforts need to be made to educate residents upon avoidance of carcinogenic exposures. This responsibility falls squarely within the domain of the county, state and federal public health agencies. Childhood cancer prevention education should cover the significant sources of avoidable exposure: internal combustion engine exhaust, cigarette smoke, open waste burning emissions, indoor radon elevations, volatilization from pesticide application, and consumption of animal fats (milk fat, beef fat, fish fat) contaminated with persistent organochloride pollutants (POPs). The message from health professionals to the public should be: 'Make a practical attempt to greatly reduce exposure to carcinogens, with an eventual goal of elimination of same'. Without the reduced exposures, which could result from such education, it would be expected that incidence rates for the population would be excessive throughout the lifetimes of those involved, thus leading to increasing incidence rates among all age groups."

Response:

We agree that educational efforts are important, both in Dover Township and throughout the State. There are ongoing initiatives to educate the general public regarding cancer prevention by various public and private agencies, such as National Cancer Institute, Centers for Disease Control and Prevention, and the American Cancer Society.

Specifically for Dover Township, ATSDR and NJDHSS have been involved in a number of health education activities. Extensive effort and resources have been dedicated to this effort and programs range from a community-based environmental health school curriculum to various health-care professional education seminars and workshops.

Commenter: Mark Cuker

Comment:

"The EPI study has developed an interesting and important body of information which can serve as a critical building block towards better understanding of the cause of childhood cancer in Toms River. Our comments on the study are directed to those portion of the data which were not highlighted in the press statements which accompanied its release.

Principally, we're concerned that the evidence of causation of nervous system cancer was not highlighted in statements accompanying the release of this study. This evidence appears in a number of tables as set forth below:

Table 7 showed an elevated odds ratio between prenatal exposure and nervous system cancers diagnosed ages 0-4 and Parkway Well field prenatal exposure. The odds ratios raised from 2.61 (for all nervous system cancers) to 3.42 (for brain and CNS cancer). Although not statistically significant, they are elevated.

Table 8 shows an odds ratio of 4.53 between prenatal exposure and nervous system cancer in females ages 0-4. Again, not statistically significant, but elevated.

Table 11, page 9 of 16 shows an odds ratio of 5.0 between prenatal exposure and nervous system cancer ages 0-19. This is almost identical to the odds ratio and confidence interval between Parkway Well field exposure and female leukemias that <u>was</u> highlighted in the press. Yet this finding was largely ignored.

Table 11, page 11 of 16 shows five cases versus eight controls among prenatally exposed nervous system cancer of victims diagnosed age 0-4. This should be an elevated odds ratio, but no odds ratio or confidence intervals are given.

Two pages later, Table 11, page 13 of 16 with only three cases and seven controls, the odds ratio is 3.46 for brain or central nervous system cancers.

Table 12, page 9 of 16, there's an odds ratio of 11.3 between prenatally exposed females and nervous system cancers diagnosed ages 0-19. The odds ratio for males is also elevated at 1.9.

Table 13, page 5 of 8, showed an odds ratio of 4.51 between prenatal exposure and nervous system cancers diagnosed age 0-19, looking at Parkway exposure in 1982 and later.

Table 13, page 6 of 8, focuses on nervous system cancers diagnosed age 0-4 among

Parkway well field exposure late 1980 to later. No odds ratio is given, but it is the same number of cases and one fewer control than in the table at page 5, suggesting an even higher odds ratio should be present."

Response:

We acknowledge that others may derive their own conclusions from the patterns they perceive within the vast body of information found in the Report. This is not unusual for studies such as ours and is often the source of much discussion among the scientific community and lay public. As stated in Volume II (Interview Study Methods), we evaluated the association of a risk factor with an outcome using a combination of criteria, not just the odds ratio. These include: strength of the association, statistical significance, consistency of findings of multiple measures for an exposure, apparent dose response effect, and evidence of a completed exposure pathway. This procedure was not only recommended by our Expert Panel but is also considered a standard process of epidemiologic studies that evaluate exposure and disease relationships.

Tables 7 and 8 present the Parkway indices for the whole time Parkway water was in use (1971-1996). While there are elevated odds ratios (ORs) for the nervous system cancer category found in these Tables for prenatal medium and high Parkway exposure, we believe that the time-specific (1982-1996) Parkway indices are a better estimate of potential exposure to contaminates in the drinking water because they incorporate a transit time for the contamination to migrate from Reich Farm to the Parkway Well Field. The corresponding OR's from Tables 9 and 10, which display the time-specific indices, show no elevations for nervous system cancer or brain and central nervous system cancers in the high time-specific Parkway exposure category. Also, none of the brain and central nervous system cancer cases are in the high Parkway exposure category and only one of these cases is in the medium Parkway exposure category.

Tables 11 and 12 present the unadjusted Parkway source/consumption indices. Again while there are elevated ORs for the prenatal Parkway (1971-1996) source/consumption exposure indices for the nervous system cancer grouping, the corresponding OR's from Tables 13 and 14, which display the time-specific Parkway (1982-1996) source/consumption indices, present a less clear picture. Nervous system cancer (all ages and all sexes combined) remained elevated (OR=4.5). However, if one examines the brain and central nervous system grouping, there is only one case in either the medium or high exposure category.

As mentioned in the comment, in certain analyses odds ratios were not presented. This occurs in limited situations because the software, Stata, was unable to calculate an odds ratios primarily due to the small number of subjects and inherent nature of

the matched analysis.

Comment:

"Looking at the water source consumption factor, shows that the relationship between female exposure, prenatal exposure and leukemia is even greater than highlighted in the press. For instance, Table 14, page 3 of 8, shows an odds ratio of 5.96 with a more significant confidence interval of 1.12-31.7."

Response:

The New Jersey Department of Health and Senior Services press release for the Report did not identify any specific odds ratios. The odds ratio you mention was used as one example of our findings during our presentations and in the Report.

Comment:

"Also, overlooked in the press reports was the very strong relationship found between parental occupations, especially occupations of fathers, and childhood cancer. This was discussed at pages 32 and 33 of Volume II, and there were odds ratios of up to 16.0. One would think that this information would be of great interest to the families who worked at the Ciba-Geigy plant. Yet, almost none of its was highlighted in the press reports."

Response:

This information was not part of the Department's press release. However, the elevated odds ratios were discussed in the Risk Factor Evaluation in the Discussion section of the Report. As noted, the odds ratio for father's occupational exposure to dyes or pigments was 12, with three case fathers and 1 control father exposed.

Commenter: Kim Pascarella

Comment:

"Point 1: The report should reflect and give a firm conclusion that public drinking water wells that are impacted by super fund sites and show any sign of chemical contamination should be looked at very closely and if at all possible should be taken out of service immediately. I realize that this could create some difficulty in supplying drinking water to the public, however, the cost on both human and financial terms of supplying tainted water to the community is far outweighed by temporary inconveniences. What is clear is that there was a contamination in Toms River in the early 1970's, this contamination being in close proximity to a public drinking supply. Why that supply was not more closely monitored is a mystery to me. We relied upon self reporting and self inspection of these wells, but it is clear that there should have been some governmental intervention in monitoring that drinking supply.

It is a mystery to me, why upon finding chemical contamination affecting the well field, the government agencies did not more closely monitor or remove the well field from the drinking water supply.

A conclusion and a commitment must be made for the following:

1. Any substantial contamination near or in close proximity to a public drinking supply should be dealt with in an immediate and comprehensive fashion. If possible, those wells must be taken off line and if it is not possible, those wells must be subjected to extensive comprehensive and state of the art testing.

2. We should not rely on the current science as being the only and best conclusion that a well is not contaminated. We should always allow that our current science is limited and because of that always err on the side of caution.

3. The phrase 'meets all state and federal standards' should be eliminated from our vocabulary when it applies to wells impacted by super fund sites, since the testing for such standards are very limited and do not apply to specific contaminations."

Response:

Decisions about the methods and technologies to apply for exposure reduction are primarily the responsibility of environmental regulatory and risk management agencies. In New Jersey, the NJDEP is the responsible agency, operating under specific authorities granted in state and federal laws. Many water supplies, both in New Jersey and across the country, have experienced contamination. Contaminants may be naturally occurring or come from a variety of sources related to human

activities, including agriculture, sewage and septic systems, industrial discharges, and improper waste disposal. The challenge is to protect water supplies from contamination first, and to develop and use effective treatment systems when prevention efforts fail. At the same time, a sufficient supply of water must be maintained to meet short-term demands for water distribution and fire protection, and long-term demands of an expanding population.

In our Report, we have recommended that efforts be continued to remediate environmental hazards associated with the Reich Farm and Ciba sites. Although our recommendations are specific to the Dover Township problems, we agree that any potential contamination of a public drinking water supply in New Jersey should be effectively addressed to ensure that residents are not exposed to hazardous chemicals at levels of health concern. The NJDEP maintains programs to regulate the quality of public water supplies, ensure the quality of laboratory data, clean up contaminated groundwater supplies, and protect water sources.

While the NJDEP is the state agency responsible for regulation of public water supplies, the NJDHSS provides support to the NJDEP through participation in the Drinking Water Quality Institute, which advises the NJDEP on the health and technical basis of State standards for drinking water quality. Also, through a formal memorandum of agreement with the NJDEP, the NJDHSS conducts epidemiologic studies and develops informational materials related to drinking water quality and public health.

Comment:

"Point 2: Federal and drinking water standards need to be enlarged and specifically identified to public drinking water supplies that have been contaminated by super fund sites. The one mystery that has been confusing to most of the public is the question, how can our water be contaminated when it 'meets all state and federal drinking water requirements'. The answer to this question is very simple and very clear, and that is that the drinking water standards are so generic that they do not include many of the chemicals which have impacted on our drinking water supply in the parkway well field area. This situation was easy since it was well within the knowledge of the governmental regulators and corporate entities what chemicals were in fact disposed of in the parkway well field area. The mystery is why these specific chemicals were not tested and only a generic testing protocol was used. This was a definite mistake on the part of the governmental agencies that must not be repeated.

Solution: all well fields that are impacted by super fund sites or any other contamination must be tested for the specific chemical that is known to have contaminated the adjoining area. If the chemical is not known, every resource must be used to identify the potential chemical that impacts the drinking water supply."

Response:

Under state and federal drinking water regulations, there are maximum contaminant levels (MCLs) or other action levels for over 90 chemical or radiologic substances. The USEPA and NJDEP develop standards for drinking water based on frequency of occurrence, toxicity information, and testing capability. A much broader list of chemicals may be tested for during hazardous waste site investigations. However, there are chemicals or classes of chemicals that are not measurable using standard laboratory methods. For this reason the NJDEP and USEPA are engaged in research projects to develop and apply methods that may be used in the future for routine or targeted testing. The NJDEP Division of Science, Research and Technology is conducting a study of selected drinking water wells in New Jersey affected by hazardous waste sites. The purposes of the study are to identify whether non-regulated classes of chemicals are present, and if so, to determine the effectiveness of existing treatment systems at removal of these chemicals. A report of this research project is expected to be completed in 2003.

Comment:

"Point 3: The governmental agencies must have oversight by an independent entity when the governmental agency is the responsible party for the public water clean up and for contamination of a site that could affect the public drinking water supply. The little discussed fact of this investigation reveals that through an agreement that was unusual, the State of New Jersey became the responsible party for clean up to the R(e)ich Farm Site, thus placing itself in a position where the governmental agency was the responsible party as well as the regulatory party for this clean up. This represented a substantial conflict of interest which eventually led to the public not being properly protected. It should be acknowledged that any time a governmental agency is responsible for a clean up with public funds, an independent oversight authority should be appointed to eliminate any conflict of interest. "

Response:

With respect to this investigation of childhood cancer, the NJDHSS and ATSDR took several steps to make our investigation a transparent and inclusive process. These included, in cooperation with the local Citizen Action Committee for Childhood Cancer Cluster (CACCCC), developing a Public Health Response Plan detailing a systematic process to investigate the elevation of childhood cancer in Dover Township. An Expert Panel of public health and medical professionals provided peer review and guidance for the study. Additionally, stakeholders, including the CACCCC, have been part of the process from the beginning, reviewing protocols and procedures, and providing suggestions throughout the study.