Appendix A

Ashland Nyanza Health Study
External Peer Review Committee Comments and MDPH Response

Listed below are the comments received from the External Peer Review Committee regarding the *Ashland Nyanza Health Study*. The study was sent to the peer review committee on January 26, 2005 and final comments were received on June 7, 2005. The External Peer Review Committee members were:

Van Dunn, M.D., MPH
Senior Vice President/Chief Medical Officer
New York City Health and Hospitals Corporation

Thomas J. Mason, Ph.D., Professor
Department of Epidemiology & Biostatistics
College of Public Health
University of Southern Florida

Thomas Long, M.S.
Program Manager/Toxicologist
The Sapphire Group

This section addresses all of the comments received by the Massachusetts Department of Public Health (MDPH). Each member of the External Peer Review Committee was asked to answer eight questions and provide their opinion and/or comment on the study objectives, overall study design, methodology, analysis and interpretation of study results, as well as the study conclusions and recommendations. Each committee member was then asked to select a category for recommending the report for public release. The categories included 1) Recommend, 2) Recommend with Required Changes or 3) Not Recommend. The External Peer Review Committee members also had the opportunity to provide additional comments if desired. Each of the questions and peer review comments received are presented below followed by the MDPH response. The comments are provided exactly as stated in written correspondence to MDPH. Copies of the actual peer review comments are included in this Appendix.

Peer Review Committee Questions and MDPH Response

Question 1: Are the study objectives clearly stated and appropriate?

Comment 1:
Yes. The 'goal' or primary objective of the study stated in the paper as the primary aim of the study was to examine exposure opportunities associated with the site to former residents as a

risk factor for development of cancer, particularly sarcoma. It would be interesting if the goal of the study could be to examine exposure to the site as an 'independent' risk factor for development of cancer, particularly sarcoma.

The hypothesis of the study is that exposure to 'contamination' at the site increases the risk of developing cancer among children residing in the area for a particular time period could be stated as a null hypothesis.

The 'objective' of the study which is to determine and compare the incidence of cancer among exposed and non-exposed individuals in the cohort may be taken as a simplistic approach of putting all cancers together and assigning risk of exposure to all 'contaminants' in the site as the cause (or not) of these cancers.

Comment 2:
Yes. The authors present a thoughtful well-written background and introduction section. The historic perspective facilitates an appreciation of the "exposures of interest" and the "biologic plausibility of the outcomes" under consideration.

Comment 3:
Yes and No. The study objectives are themselves clear enough and the desire for such a study plain, but the means of carrying out the study (at least one half of it) introduces a high potential for error in assessing exposure that I cannot easily see a resolution to. See attached memo for expansion on this point; however, I think that a serious discussion of the uncertainties and potential problems (lack of independent means of verification) need to be identified and clearly discussed.

Response to Comment 1:

The MDPH agrees that it would be interesting if the goal of the study were to examine exposure to the Nyanza Chemical Waste Dump as an independent risk factor for the development of cancer. In order to accomplish this, one would need to evaluate exposure to the Nyanza site as a separate factor while accounting for any and all factors that could be related to the development of cancer. However, cancer is a complex disease and can be caused by a variety of factors acting either alone or in concert over time. In addition, some factors that may cause cancer are still unknown. Therefore, it would difficult to assess the effects of Nyanza site exposure as an independent risk factor for cancer in this setting (i.e., while accounting for all other possible factors that could be related to cancer development).

However, data analysis for the study involved the use of multiple logistic regression as a means to evaluate the independent effects of a number of different factors on the association of cancer diagnosis and contact with the Nyanza Chemical site. By employing logistic regression as part of the statistical analyses for the study, the MDPH was able to evaluate the relationship between exposure to the Nyanza site as a factor in the development of cancer while accounting for other known risk factors for cancer as well as factors that could confound or distort the association between cancer development and exposure to the Nyanza site. These include factors such as gender, family history of cancer, smoking and occupation. Unfortunately, it was beyond the scope of this study to assess whether or not exposure to contaminants at the Nyanza site was

the only factor related to cancer development among this cohort of Ashland residents. Rather the study assessed the relationship of Nyanza site exposure as one possible factor or determinant related to cancer development among this group.

The study hypothesis could be stated as a null hypothesis. The MDPH has revised the Final Report to include the study hypothesis stated as the null hypothesis. (Please refer to page 6 of the Final Report for the Ashland Nyanza Health Study.) It is also true that the objective of the study as stated can be viewed as a simplistic approach to evaluating the primary study question. However, the study was designed to investigate the primary question asked by residents of the Ashland community. That is, "Is activity at the Nyanza site in the past related to the development of cancer among children and young adults who lived there when the site was operational?" Due to the retrospective nature of this study and the inability of the study to determine precise exposure measurements, the study has some limitations by design. While it may appear simplistic, the MDPH attempted to answer the question about Nyanza site exposure and cancer incidence among this cohort of Ashland residents initially at the broadest level and then depending upon the quality and specificity of the data collected during interviews with study participants, expand upon the initial analyses to be more specific in investigating site exposures (e.g., types of contaminants, specific types of exposures/activities, frequency and duration of exposure). Therefore, the analysis of study data focused initially on whether study participants had any contact with defined areas on the Exposure Map B depicting known areas of chemical contamination at the Nyanza Chemical site and any associations observed with reported cancer diagnoses and then focused on what types of activities were reported by study participants in these areas.

Response to Comment 3:

As a result of reports of a possible cluster of rare cancers among former Ashland residents, the Ashland Board of Health and residents of the Ashland community requested that the MDPH investigate if there was a relationship between the development of cancer among residents of Ashland who played or engaged in activities at the Nyanza Chemical Waste Dump when they were children and/or young adults. Because these individuals were former residents of the town and did not necessarily live in Ashland at the time of their diagnosis, it was difficult to confirm whether a cluster of rare cancers may exist without some type of further study. In an attempt to answer the question posed by the Ashland community, it was necessary to determine the cohort of individuals who were children and/or young adults living in Ashland at the time the Nyanza site was operational and accessible to the public (1960s to 1980s). After establishing the study population, it was then necessary to determine who among this population was diagnosed with cancer as well as who had contact with the site, what types of activities these individuals engaged in, and at what frequency and duration these activities took place so that potential exposure to the Nyanza site could be assessed.

Measuring exposure to environmental contaminants depends on a number of factors. In the absence of biologic measures (i.e., biologic samples measuring chemical concentrations), at a minimum, it is necessary to know the amount or concentration of a contaminant in the environment as well as the frequency (how often) and duration (how long) an individual is in contact with that contaminant. This information is then used to estimate or determine an

exposure dose. However, environmental epidemiologic studies, particularly those that are historical in nature, are often limited in their ability to create precise measures of exposure. This is typically due to the fact that little or no data is available to determine chemical concentrations that existed at a particular hazardous waste site in the past. Further, there are generally no data available related to biologic measures with which to determine more precise exposure measurements for study participants. In the face of this challenge, epidemiologists must therefore rely on estimates of exposure either through modeling or the use of proxy measures to approximate actual exposures. This was the case for the Ashland Nyanza Health Study where given the historical nature of the site, there was little or no environmental sampling data describing contaminant levels present during the 1960s through the 1980s. This is the time period described by an Expert Panel, who reviewed the available exposure information for the Nyanza Chemical site, as the critical period when the greatest opportunity existed for Ashland residents to be exposed to contaminants present the site (MDPH 1990). Therefore, the exposure assessment portion of the Ashland Nyanza Health Study used proxy measures to estimate what the true exposure to Nyanza site contaminants might have been in the past for each study participant. This was accomplished by using self-reported information collected from study participants about activities that they were involved in and could have brought them in contact with certain areas of the Nyanza Chemical site where chemical contamination was known to be present during the study period of interest (i.e., 1965 to 1985).

As previously stated, due to the historical nature of the Nyanza Chemical Waste site, the exposure assessment for the Ashland Nyanza Health Study was limited. That is, prior to 1982, when the Nyanza site was closed and investigations into to the extent and nature of contaminants present at the site took place, little or no data existed that could be used to empirically measure exposure from site contaminants. For that reason, it was necessary to estimate exposure based on reported information from study participants about the nature and types activities they engaged in at the site and pair that with information about locations at the site where contaminants were known to have been present.

In any observational study, some degree of inaccuracy in assessing exposure is inevitable. Although using exposure estimates, as was the case in the Ashland Nyanza Health Study, likely introduced some misclassification of exposure status to the study, the MDPH disagrees that there was a high potential for error as suggested by the above comment. Given that the study design was a retrospective cohort and the exposure assessment relied on self-report from study participants of activities at the Nyanza site, the most likely source of error was introduced in the form of recall bias. Recall bias is a systematic error that can occur in studies due to differences in the accuracy or completeness of recall to memory of prior events or experiences (Last 1988).

The MDPH attempted to minimize any effect this type of bias may have had by using consistent and replicable methods to assess exposure. Two maps were provided to all study participants. The maps provide a standard source of information from which study participants could respond to questions about locations and activities they engaged in at the Nyanza Chemical site in the past. A standard script was used during the interview process to allow study participants to familiarize themselves with the map locations and orient themselves to specific exposure areas defined on the map. Therefore, although study participants were asked to recall events that occurred possibly 20 to 40 years ago, because standard methods and prompts were

used, recall of events should be similar among both the exposed and unexposed groups. Also, during the study period of interest (1960s to 1980s), the Nyanza site was a large uncontrolled hazardous waste site. If exposures occurred, conditions at the site during this period of time were such that study participants would have specific recollections of exposure events. For example, Chemical Brook was an intermittent stream where the Nyanza Company discharged waste from its dye manufacturing processes. Chemical Brook was named for the fact that that the brook would change colors according to the chemical processes that took place at the Nyanza facility. Therefore, if a study participant had fallen into Chemical Brook as a young child or teen and emerged with discolored skin or clothes, they were likely to have remembered this type of event even though it may have occurred 20 years prior. These were the types of exposure events that were reported frequently at the Nyanza site.

Further, Map B (the exposure map used in the study) was developed using a geographic information system based on historical aerial photographs of the site taken during the 1950s through the 1970s. The Exposure Map B was created to accurately depict historical features and landmarks of the Nyanza site during the time period of interest so as to minimize any potential misclassification of exposure. The specific site areas labeled as Areas A through I on Map B were shown as discrete areas so that reports of activities or contact with these locations would be with some degree of accuracy in terms of actual location. Recall bias for the most part would then be non-differential because it likely occurred equally between the two study groups. This type of bias tends to underestimate the observed association between exposure and disease.

Recall bias is more of a concern to the validity of the study if it results in differential misclassification of exposure. That is, if exposure is classified differently as a result of recall for individuals in the study who reported a cancer diagnosis as opposed to those who did not, then the association between exposure and disease may be exaggerated or overestimated. This is because those who have a diagnosis of cancer may tend to remember or recall events in their past more specifically and attribute these events to their diagnosis. As a result, these study participants are disproportionately classified as exposed. However, if exposure or disease is classified incorrectly for equal proportions of study participants in the two groups being compared, then this type of bias results in non-differential misclassification. If the exposure truly increases the risk of disease then non-differential misclassification will bias the observed risk estimate towards the null value (i.e., no association between exposure and disease). Therefore, non-differential misclassification bias is a lesser concern to the study validity because the bias is always in the direction of an underestimate of the association between exposure and disease. That is, the estimate of the effect without the misclassification would always be greater than that observed in the study. Some may argue that poor exposure data (or poor disease classification) invalidates study results, but this argument is incorrect if the results indicate a nonzero effect (Rothman 1986). In the Ashland Nyanza Health Study differential misclassification bias is probably not an issue because the study results for most types of exposure related activities at the site did not show a strong effect of exposure on the incidence of cancer and the impact of differential misclassification would only tend to overestimate the true effect of exposure on disease.

In the Discussion section of the Draft Final Report of the Ashland Nyanza Health Study, the MDPH included discussion of potential sources of bias that could influence the study results

and acknowledged on page 40 that reliance on self-reports of contact with Nyanza site areas as the primary assessment of exposure could result in imprecise measures of exposure. However, in light of this comment, the MDPH has included in the Final Report additional discussion to more clearly illustrate the impacts of any potential bias to the study as a result of the exposure assessment methodology. Please see the revised Discussion section on page 37 of the Final Report for the Ashland Nyanza Health Study.

Question 2: Is the overall study design appropriate for the study objectives?

Comment 1:
Yes, the study design, a retrospective cohort survey, is appropriate for the study 'objective.'

Comment 2:
Yes. The study design is the design of choice to address the objectives. The definition of the cohort identifies those persons with the greatest potential for exposure. The authors are to be commended for their presentation/discussion of their recruitment procedures and standardization of the questionnaire. Studies such as this require clear replicable methods for case confirmation, as well as, determination of exposure status. The authors have done this.

Comment 3:
Yes and No. Same basic comment, I applaud the initiative and large effort, but basing the exposure assessment on 20 to 40 year old memories of yes/no trespass is so fraught with error that I cannot easily see a way to address the potential biases. Again see attached memo.

Response to Comment 3:

As previously stated, the use of self-report of activities and thus proxy measures to assess exposure in the Ashland Nyanza Health Study likely introduced some misclassification of exposure due to inaccurate recall of exposure events. However, the MDPH disagrees with the comment that the exposure assessment for the study is "fraught with error." Although the exposure assessment relies on self-report of contact with Nyanza site areas and reports of activities in known areas of contamination on the Nyanza site, the exposure assessment was based on clear and replicable methods which are necessary in any epidemiologic study. Again, due to the retrospective nature of the Nyanza Chemical site and the study question under investigation, the choice of study design as well as the available information with which to determine exposure and disease among this cohort of Ashland residents was limited. While it is true that studies such as the Ashland Nyanza Health Study have certain inherent limitations due to their retrospective nature, the goal of this study was to address questions raised by the Ashland community regarding past exposures at the Nyanza site and the possible relationship to cancer diagnoses. The MDPH believes it has accomplished this objective while attempting to minimize any potential bias introduced to the study as a result of the methods used for exposure assessment. See the response to comments on Question 1 of this Appendix for further clarification and discussion of the impacts of potential bias on the study.

Question 3: Are the methods and analysis plan appropriate for the study objectives?

Comment 1:
Yes, the methods of collecting data from participants is appropriate for the study objectives. The high participation rate ensures good comparison between the 'exposed' and 'non-exposed' individuals.

As in any survey, particularly with the use of a very long questionnaire, participants may not totally recall events, particularly those that happened close to three decades ago, thus responses may not always be accurate. Another recall bias to consider would be among those that have been diagnosed with cancer or suffer from other conditions that they may blame directly from being at the site.

Comment 2:
Yes. The methods and analysis plan are quite appropriate! As a matter of fact, the methods and the sequence which was followed are "textbook approaches" to these issues. This approach is widely accepted by practitioners of "environmental epidemiology".

Comment 3:
Yes. The type of analysis and techniques employed seem appropriate (and MDPH always does good work), but if the data (exposure, especially) is poor to begin with, there isn't much the best analysis can do. The issue of multiple comparisons and the generation of false positives (or negatives) is also of concern, but again the data is what it is. See attached memo.

Response to Comment 1:

The MDPH acknowledges that like all retrospective studies, recall bias is an issue of some concern to the Ashland Nyanza Health Study. As previously stated in the response to comments for Question 1, the area in which recall bias has the most potential to impact the study results is the possibility for misclassification of exposure. This means that study participants who may actually have been exposed as a result of contact with areas of the Nyanza Chemical site or participated in certain activities at the site do not recall these events accurately because of the length of time that has passed since the events occurred. So those who have actual exposure are then misclassified as unexposed due to poor memory of events in the past. It can also be argued that individuals with a cancer diagnosis are more likely to recall certain events in their life as related to their cancer diagnosis and therefore respond differently to questions about activities and contact with the Nyanza Chemical site. Therefore, the bias due to recall leads to misclassification of the exposed and unexposed groups by incorrectly classifying exposure status.

As described in the response to comments for Question 1, while it is entirely possible that recall bias had some impact on the study results, the real issue is whether recall of events differed significantly between those with and without a cancer diagnosis. If the recall occurred evenly or in a comparable way among both groups then the bias is non-differential and would not have a large impact on the observed associations. However, if the cases were more likely to report exposure than non-cases then the result would be a bias in the direction of a positive association (differential bias). The Ashland Nyanza Health Study used a standard method of assessing

exposure for all study participants regardless of whether they had a diagnosis of cancer. A standard map was used as a memory prompt for participants to locate areas of the Nyanza Chemical site. These steps were taken to establish a standard method for assessing exposure for all study participants and therefore minimize any effect that recall bias may introduce to the study results. However, it is difficult to say with certainty whether recall bias resulted in differential misclassification of exposure. Viewing the study results in their entirety suggests that any impact of recall bias was not in biasing the observed associations towards an increased risk of cancer since most analyses did not result in a statistically significant association between reported activities at the Nyanza site and an increased risk of cancer diagnosis.

Response to Comment 3:

The MDPH disagrees with the comment that multiple statistical comparisons and the generation of false positive results is a concern to the Ashland Nyanza Health Study. The goal of the study was to attempt to investigate whether exposure to the Nyanza Chemical site in the past was associated with cancer development in a specific cohort of Ashland residents. In order to test this study hypothesis, there was a standard method of data collection and analysis that focused on "exposure to the site" as defined by self-reported site activities. Although a large volume of data was collected during interviews with study participants, the statistical analysis followed a clear and well defined data analysis plan. The initial and primary analyses consisted of tests of association comparing broad categories of exposure (e.g., ever had contact with defined areas of the Nyanza Chemical site versus never had contact with Nyanza Chemical site) as determined by self-reported responses to the question, "looking at Map B, in which area or areas did you play or spend time?" The analyses were then expanded where indicated based on initial results to then assess more specific questions about possible exposure and disease (such as the types of activities that occurred in the depicted areas on Map B) and whether they may have an association with cancer development. Depending on the results from these analyses, where possible, questions related to the frequency and duration of activities corresponding to each area of the Nyanza site were then explored.

The basis for concern over multiple comparisons in epidemiologic data analysis is the premise that there are no real associations in the collected data and if statistical significance testing is performed at the five percent level of significance (i.e., the 95% confidence interval), there would be significant associations in the data all representing Type I errors or false positive results (Rothman 1986). The issue lies in the thought that chance guarantees a certain proportion of statistically significant associations and when many associations are studied (i.e., multiple comparisons) many false positive results will occur by chance alone. The multiple comparisons issue centers around the assertion that the explanation for all the "significant" results is chance stemming from a larger theoretical null hypothesis.

Multiple comparisons are typically not an issue of concern for epidemiologic studies that evaluate associations because in conducting these studies one does not typically make definitive decisions about true causal relationships. The approach to hypothesis testing in such studies is usually viewed as "could an association be found, given the definitions of exposure and outcome?" In this context, it is important to understand and appreciate that the 0.05 probability value (p-value) is indicative of how "reality" could be, and not as the sole conclusion about the reality studied. Multiple comparisons are particularly an issue of concern when one collects

information on many exposures and many outcomes. That is, multiple comparisons are not an issue unless the data are subjected to a dredging procedure as a result of searching for significant contrasts which would not have been thought of initially (Poole 1991). However, if scrutiny is restricted to those comparisons which the data were designed to investigate, as indicated by the study hypothesis, then multiple comparisons are not an issue for such studies.

The Ashland Nyanza Health Study was a focused study that investigated a reasonable study hypothesis stated prior to the collection and analysis of study data. The analyses followed a well-defined data analysis plan that compared exposure through contact with Nyanza site areas among those with and without a cancer diagnosis. There was not a random mix of variables studied ad infinitum or continual parsing and re-analyzing data. The statistically significant results observed in categorical table analysis were also validated and confirmed using logistic regression. This implies that the observed associations were less likely the result of chance or random associations that arose by chance. For exposure involving any type of water contact at both Areas D (Megunko Hill area) and Area H (the Sudbury River near Myrtle Street), statistically significant increased risks of cancer were consistently observed when the analyses included all participants who self-reported a cancer diagnosis as the case group as well as the smaller sunset of study participants with a medically confirmed cancer diagnosis. The increased risks were typically two to three times greater than the risks observed for study participants who reported no contact with these areas of the Nyanza site. These results stand in contrast to comments about false positive observations and the validity of study results as a result of multiple comparisons or continually re-analyzing the study data. Therefore, the MDPH believes that the issue of multiple comparisons and the generation of false positive results is not a concern to the study.

Question 4: Were the data analyzed in such a way to address appropriately the objectives of the study?

Comment 1:
Yes. Although it would be informative if there is any information on the type of cancers among those with family history of cancer and with significant risk of exposure. It would also be interesting to determine if the length of exposure in the site is a determinant of outcome, i.e., cancer.

Comment 2:
Yes. The authors have appropriately addressed the objectives of their study.

Comment 3:
Yes. I believe the answer to the previous question applies here as well. Additional points are discussed in the attached memo.

Response to Comment 1:

Information on the cancer types reported among study participants who reported a family history of cancer and had significant risk of exposure to the Nyanza site has been included in the Final Report along with the discussion of study results.

In summary, the results showed that study participants with a family history of cancer who reported contact with areas of the Nyanza Chemical site depicted on exposure Map B such as the Eastern Wetlands (Area B), the Sudbury River near High Street (Area F) and the Sudbury River and Mill Pond area (Area G), had a statistically significant increased risk of cancer. In addition, those individuals with a family history of cancer who reported swimming or wading in the ponds located at Megunko Hill also had a statistically significant increased risk of cancer. The most consistent and significant results occurred among individuals who reported any type of water contact with Nyanza site areas as depicted on Exposure Map B. There were a number of different cancer types reported among individuals who reported contact with these specific areas. Among this exposure group, 32 individuals reported a cancer diagnosis. Of these individuals, the majority of diagnoses were cancer types that are not strongly associated with a family history of cancer or have some association with environmental exposure (e.g., soft tissue sarcoma, brain cancer, Hodgkin's disease). Thirty-one percent of the cancer types that occurred among this exposure group (N=10) can be defined as rare cancers; meaning that the type of cancer itself is considered rare (e.g., certain sarcomas or brain cancers) or the cancer is a more prevalent cancer type in general but rarely occurs at ages that were observed in this cohort. For example, there were three diagnoses of lung cancer that occurred in individuals under age 40 and two diagnoses of soft tissue sarcoma. Information about cancer types among study participants who were defined as having a significant risk of exposure to the Nyanza site and a family history of cancer is included in the Final Report. Specific information about cancer types defined as rare cancers is not included to protect the confidentiality of individual study participants.

The analyses of residential history of study participants included an evaluation of the cumulative duration of years lived in Ashland. These analyses did not show a statistically significant association between the duration of time lived in the exposure area and an increased cancer diagnosis. These results are presented and described on page 36 of the Final Report.

Question 5: Are the study results presented and interpreted appropriately and completely?

Comment 1:
Yes. The study presented the results of the questionnaire, and its limitations, appropriately.

Comment 2:
Yes. The presentation is both appropriate and thorough.

Comment 3:
Yes and No. Generally, I found the discussion clear and the analysis adequate; however, there were a number of areas in which language needed to be refined or clarified, and others in which the choice of words seems to reflect some bias or pre-conceived notions. The attached memo includes specifics on this issue.

Response to Comment 3:

The MDPH disagrees with the comment that the choice of words used in the Discussion section of the Draft Final Report reflects a bias or pre-conceived notions by the study investigators. All studies conducted by MDPH follow standard scientific methodology in study design and data analysis and reporting of the results is presented in an objective manner. In conducting the Ashland Nyanza Health Study, the MDPH strived to present the data in its entirety and interpret the results in the context of known information about the Nyanza Chemical site. The objective in conducting this study was to consider all of the information presented and draw appropriate conclusions about whether the data collected on exposure and disease support an association between these two factors. It is our responsibility to report the results in their entirety and use our best scientific judgment to provide a context for what the results may mean. The MDPH does not discount that some bias as a result of recall and misclassification of exposure were present in the study and this information was discussed in the Final Report. The issue is, to what extent does any bias present in the study impact the study results. In conducting the Ashland Nyanza Health Study, the MDPH believes it has accomplished the goal of further investigating important questions asked by the Ashland community while presenting discussion of the study limitations, the possible biases present in the study and their impact on the study results. Please refer to the response to comments received for Questions 1 and 3 in this Appendix for a further discussion of the impact of bias to the study.

Question 6: Are the study conclusions and recommendations appropriate and complete?

Comment 1:
Yes; see comments under 7.

Comment 2:
Yes and No. The recommendations are appropriate. However, they can be improved upon.

Comment 3:
Yes. Can't complain about recommending that concerned citizens be screened for cancer, etc.; however, the conclusions regarding the site risks and exposures seem over-stated for reasons previously mentioned and expanded upon in the attached memo.

Response to Comment 3:

The MDPH does not agree with the comment that the conclusions regarding site risks are overstated. As with any epidemiologic study, the findings are not intended to be regarded as definitive of a sole cause and effect relationship. Epidemiologic findings either support the

hypothesis that an association exists between exposure and disease or that no association exists. It is beyond the scope of any one epidemiologic study to prove a cause and effect relationship. This is the case with the Ashland Nyanza Health Study. The Conclusions section of the study state that the findings "suggest that contact with specific areas of the Nyanza Chemical Waste Dump as defined on the exposure Map B are associated with an increase risk of cancer diagnosis." However, the Conclusions also stated that "the study was limited in its ability to draw conclusions about cause and effect relationships between specific contaminants and risks of cancer among this population."

Additional analyses were conducted in response to comments received by the Peer Review Committee. The additional analyses involved evaluation of contact, specifically water contact, with certain areas the Nyanza site while restricting the case group to study participants for which cancer diagnoses were confirmed through medical records or the Massachusetts Cancer Registry (N=40) rather than the entire case group of all self-reported cancer diagnoses (N=73).

The results of these additional analyses showed that for cases with a confirmed diagnosis of cancer, there were no statistically significant associations with Nyanza site activities. Although no statistically significant associations were observed for contact with general areas of the Nyanza Chemical site defined on exposure Map B (i.e., Areas A through I), and confirmed cancer diagnoses, when specific exposure locations were evaluated, significant associations occurred with overall water contact exposures at Chemical Brook and the two ponds located on Megunko Hill. These results were also statistically significant among individuals whose diagnosis could be defined as a rare cancer type. Again, the results were confirmed and remained statistically significant when a family history of cancer was considered in the analyses. Therefore, even though the analyses restricting the case group to only those study participants who had a confirmed cancer diagnosis did not consistently confirm the associations initially observed between areas defined on Map B and self-reported cancer diagnoses, the results for overall water contact exposures at the site were consistent for specific site areas.

The MDPH believes that these results lend support to and tend to strengthen the overall study conclusions that certain reported exposures at the Nyanza site appear associated with an increased risk of cancer development among this study cohort and that the observed associations between site exposures and family history of cancer possibly suggest a gene-environment interaction among this group.

Question 7: Are there any other comments on the final report?

Comment 1:

Yes. The study addressed the limitations of the study such as the recall bias of the respondents, the lack of data on exposure or potential exposure to specific contaminants and others. It would also be interesting to know which types of cancer were present in the same family and found to be associated with exposure to the site. One may argue that regardless of exposure, certain cancers like breast and prostate may be more prevalent among those who have such in other family members. It could also be possible that those who have cancer may have bias towards

reporting more exposure to the site, as they have been proven by the study to be more likely to report a cancer diagnosis.

The study did not present any data on the number of years of exposure; respondents may have attended school, or resided in the community, but did not state the length of stay in either. It would be interesting to know if the extent of length of exposure, i.e., starting elementary through completion of high school, is a determinant of risk.

Comment 2:
Yes. An additional analysis is recommended restricted to those individuals for whom the diagnosis was confirmed either by medical record review or through the Massachusetts Cancer Registry. This should be done for those with "any type of water contact (e.g., lagoons on Megunko Hill) with a family history of cancer". The authors' finding is consistent with a potential "gene-environment" effect, and should be clarified by this analysis. These findings should be incorporated into the recommendations section.

Comment 3:
See memo attached.

Response to Comment 1:

Regarding information about which types of cancer occurred among study participants who reported a family history of cancer, please see the response to comments on Question 4. Also, please refer to the response to comments for Question 1 and Question 3 for a further discussion of potential bias and its impact to study validity. Information on the length of exposure and residential history for study participants is discussed on page 37 of the Final Report.

Question 8: Select the appropriate category below. – Recommend, Recommend with Required Changes, or Not Recommended

Comment 1:
Recommend.

Comment 2:
Recommended with required changes.

Comment 3:
Recommend with Required Changes. I think some critical re-writing is necessary in terms of the exposure assessment/measurement and its potential weaknesses. The potential biases and their impacts need to be expanded on, and I don't think it would hurt to compare these findings in terms of the Hill criteria to assess their significance before drawing any conclusions.

Response to Comment 3:

As stated in the response to comments received on Question 1, the Discussion section of the Final Report for the Ashland Nyanza Health Study includes further discussion of the potential biases present in the study and their implications for interpreting the study results. The MDPH believes the revisions to the Discussion section will clarify the study findings and provide a more objective context in interpreting the study results. In response to the comment that the findings of the study should be compared to the Hill Criteria to assess their significance, the MDPH believes it is not appropriate in this instance. The Hill Criteria outline conditions to establish a causal relationship between two items. These criteria were originally presented by Sir Bradford Hill as a way of determining a causal link between a specific factor and a disease. The criteria that Sir Bradford Hill referred to as viewpoints, serve as a general guide and are not meant to be an inflexible list (Hill 1965). Again, it was beyond the scope of the Ashland Nyanza Health Study to determine a true causal relationship between Nyanza site exposure and cancer diagnoses among the study cohort. Rather the goal of the study was to assess whether a relationship between these two factors may exist as supported by the data examined. The study found that for some reported exposures, such as water contact in certain areas of the Nyanza site, the data suggests a relationship exists between Nyanza site contact and the incidence of cancer among this group of study participants. As with any association noted in an observational epidemiologic study, the findings are suggestive of a relationship between the outcome and exposure of interest beyond the role of chance or random error. In making decisions based on epidemiologic data, the MDPH tries to avoid overemphasis on statistical significance testing alone. The suggestion that the study findings should be compared to the Hill Criteria assumes that these criteria are a checklist for inferring causation. Sir Bradford Hill himself emphasized that his nine viewpoints were neither necessary nor sufficient for establishing causation (Phillips and Goodman 2004). This approach eliminates scientific reasoning or judgment in considering all sources of information to reach appropriate conclusions. While it is true that the Ashland Nyanza Health Study lacks an independent means of validating the exposure measurement and this is a limitation to the study nevertheless, the data available were the data used and we must therefore rely on scientific judgment in the context of all of the information presented, not just a single measure of association and whether it meets statistical significance or a certain list of criteria. The MDPH believes it is our responsibility as a public health agency to review all of the information in its totality to draw appropriate conclusions in attempting to address environmental health questions from communities such as Ashland, Massachusetts.

Additional External Peer Review Comments and MDPH Response

1. *While the observation that cancer appears to be elevated among younger residents in a small community is alarming, making an assumption that this is due to some single cause (environmental or otherwise) is probably fallacious (page 7).*

   § In conducting the Ashland Nyanza Health Study, the MDPH did not make the assumption that cancer diagnoses among younger residents of Ashland are due to some single cause as suggested by this comment. This would assume an a priori conclusion of cause and effect, which is neither the intent of nor the scope of an epidemiologic study. As stated previously, the intent of an epidemiologic study is to test a hypothesis of whether some association exists between a defined exposure and an outcome of interest. The MDPH used standard study design and epidemiologic methods to test the hypothesis that exposure to the Nyanza Chemical Waste site is associated with an increase in cancer diagnoses among former residents of Ashland and then assessed the results of statistical analyses to draw conclusions about whether the data collected support the study hypothesis. As stated in the response to comments for Question 6 of this Appendix, the conclusions of the study state that the findings "suggest that contact with specific exposure areas of the Nyanza Chemical Waste Dump is associated with an increase risk of cancer diagnosis." However, the Conclusions also stated that "the study was limited in its ability to draw conclusions about cause and effect relationships between specific contaminants and risks of cancer among this population."

   § These results were observed when Nyanza site exposures were evaluated using all individuals who self-reported a cancer diagnosis as the case group. Additional analyses were conducted that restricted the case group to study participants for which a cancer diagnosis was confirmed either through medical records review or the Massachusetts Cancer Registry. Although the results of the additional analyses for cases with a confirmed diagnosis of cancer did not consistently confirm all of the associations initially observed for contact with Nyanza site Areas B, F, and G, the results demonstrate a consistent pattern in the direction of an increased risk of cancer for individuals in this study population who reported water contact exposures in specific locations both on and off the Nyanza site property. The MDPH concludes that as a result of this information about reported exposure activities at the site, the findings suggest that a gene-environment may exist among individuals who reported water contact in certain areas of the Nyanza site in the past and who have a family history of cancer.

2. *Cancer is a conglomeration of over 80 different diseases, each with their own etiology and prognosis. It is highly unlikely that low level exposure to residual chemicals in the local environment would account for them all even if past exposure was certain to have occurred, and was of sufficient frequency and duration (the exposure assessment in this study is the weakest part as it usually is in such cases).*

   § The above comment is incorrect in assuming that contamination at the Nyanza Chemical Dump constituted low level exposure to residual chemicals in the local environment. The point is taken that grouping all cancer types as was done in the initial analysis likely

combined cancer types that could be of both environmental and non-environmental etiology. However, additional analyses were conducted restricting the case group to study participants with a medically confirmed cancer diagnosis as well as study participants with a rare cancer. Again, it is beyond the scope of this study to draw conclusions about specific cause and effect relationships but rather to determine whether a particular factor (in this case contact with the Nyanza site) is associated with cancer diagnoses among this population of Ashland residents. The results of our analyses show that there is a statistically significant association between certain types of exposure to the Nyanza site as defined by the study and cancer diagnoses. Please see response to comments for Question 6 in this Appendix.

3. *I note that the two most frequent (self-reported) cancer types (Figure 5) were basal cell carcinoma and cervical cancer. Aside from some potentially iatrogenic cancers associated with hormones, I know of no convincing evidence that cervical cancer is associated with exposure to environmental chemical residues. Likewise, the largest risk factor for basal cell carcinoma (in young adults) is sunlight. Although exposure to compounds like arsenic have been associated with skin cancer, such cancers are usually accompanied by significant skin changes in advance of the cancer as well as requiring a relatively high (internal) exposure. If these are eliminated from consideration, along with others that are not potentially "environmental" in origin (i.e., breast, colon, uterine/ovarian), are known to be strongly associated with other risk factors like tobacco use (i.e., long/bronchus, tongue), or were previously eliminated as unassociated with the situation under consideration (i.e., the referenced kidney and bladder cancers?), would the excess in total cancers remain? If not, the need to pursue such a health study is not persuasive.*

   § The above comment is incorrect regarding the information that prompted the MDPH to further investigate cancer incidence and environmental exposures in Ashland. The Ashland Nyanza Health Study was prompted by a number of factors but primarily the report of a suspected cluster of young adults with similar rare cancer types who had contact with the Nyanza Chemical Waste Dump in the past. Please refer to the Background/Introduction on pages 1-6 of the Final Report for a more detailed explanation of factors that prompted the Ashland Nyanza Health Study. The comment is also incorrect that bladder and kidney cancer were eliminated as unassociated with the situation under consideration. Bladder and kidney cancer were not considered unassociated with contaminants detected at the Nyanza Chemical Waste Dump. A previous review of the pattern of bladder and kidney cancers among current Ashland residents during 1982 through 1986 did not show a pattern that appeared associated with the site (MDPH 1990). However, the individuals included in the study of bladder and kidney cancer in Ashland would not have been considered as part of the study cohort included in the current Ashland Nyanza Health Study. Only one individual who was included in the previous study of bladder and kidney cancer would have met the age criteria for the current study. Therefore, the conclusions reached in the previous study did not apply to the current study cohort of the Ashland Nyanza Health Study or the population of individuals that the expert panel, convened to review the studies of bladder and kidney cancer as well as health and environmental data for the Nyanza site, concluded had the greatest opportunity for exposure to the Nyanza site (i.e., younger

children and adults who resided in Ashland during the late 1960s and 1970s, the critical time period of interest).

§ Contrary to the reviewer comments above, the expert panel recommended to local health officials that, if possible, information on individuals who resided in Ashland during the 1960s be identified. The panel believed the 1960s to be a critical time period of interest based on possible population changes in the town during the 1970s and 1980s and the latency period of diseases, such as cancer, that could be associated with exposures from the Nyanza site. Consequently, in the conclusion of the Public Health Assessment, the Health Activities Recommendation Panel (HARP) recommended that should the pattern of cancer among Ashland residents change, a retrospective epidemiological study be conducted to evaluate increased adverse health outcomes to residents of the town (MDPH 1994).

§ In 1999, residents of Ashland reported to the MDPH that children who lived in the town and played on the Nyanza site in the past developed similar types of rare cancers as young adults. Of greatest concern was the report of five men in their early 20's that developed various types of soft tissue sarcoma. These individuals were in the general age range identified in the Public Health Assessment as the population with the greatest opportunities for exposure to Nyanza site contaminants. Further, the reported individuals were school-aged residents of Ashland during the time period that was described by the expert panel as a critical period of interest in terms of possible exposures from the Nyanza site. Although the previous health studies of bladder and kidney cancer in Ashland concluded that the pattern of these two cancer types did not appear associated with the Nyanza Chemical site, the studies reviewed the pattern of bladder and kidney cancer among current Ashland residents during the period 1982 through 1986. The age range at the time of diagnosis for the majority of individuals in the investigations was between 50 and 85. Only one individual who was included in the previous studies of bladder and kidney cancer was younger than age 45. Further, none of the individuals had attended school in Ashland.

§ An additional review of cancer incidence data for the town of Ashland available from the Massachusetts Cancer Registry at the time the suspected cluster of soft tissue sarcoma was reported indicated that there was an overall increased incidence of cancer among younger residents of the town (i.e., those under the age of 40 years). The increase occurred among individuals who were residents of Ashland at the time of diagnosis during the years 1982 to 1994 and was for all cancer types combined. The incidence of all cancers combined was statistically significantly elevated among both males and females during this time period. Please refer to Table 1 of the Final Report for a summary of these data. While the cancer registry data indicated an increase in the incidence of cancer among younger residents of the town through 1994, there was no way to determine the pattern of cancer incidence among former residents who resided in Ashland during the critical period of interest with respect to opportunities for exposure form the Nyanza site. All of these factors contributed to the decision to further investigate the incidence of cancer among former Ashland residents.

4. *Apparently, the self-reported excess in total cancers was confirmed by a review of cancer incidence data from the state tumor registry; however, it would be useful to have this information presented in tabular form along with the statistics in order to be able to judge the issue raised.*

   § The above comment is incorrect in stating that "the self-reported excess in cancers was confirmed by a review of cancer incidence data from the state tumor registry." Again, the Ashland Nyanza Health Study was initiated based on a number of factors. Previous investigations of the site determined that exposures to residents of Ashland likely occurred. An expert panel that reviewed health and environmental data for the Nyanza Chemical site concluded that exposure opportunities in the past to site contaminants were likely high. This panel further concluded that the population who had the greatest opportunity for exposure were children and young adults who lived in Ashland during a critical period of time when the site was in operation and accessible. Given the types of contaminants detected at the Nyanza site, exposures likely resulted in a variety of health effects including cancer (MDPH 1990). When information was reported to the MDPH about a suspected cluster of rare cancer diagnoses among young adults who were former residents of Ashland and reported playing on the site as young children, as previously stated, it was difficult to confirm and verify this information without further study. However, the MDPH reviewed cancer incidence data for Ashland available from the Massachusetts Cancer Registry at the time. This information showed that the incidence of all cancers diagnosed among current Ashland residents under age 40 during the period 1982 to 1994 was more than twice the expected rate and was elevated at a statistically significant level. These data have been included in the Final Report and are presented in Table 1. Therefore, it was a variety of information that prompted the MDPH to conduct further study of the Nyanza site exposures and cancer incidence among former residents of Ashland.

5. *Although the study cites over 100 chemicals found on or near the site (page 5…and the attached Health Assessment references some quantitative maximum concentration data for some), I would find it instructive if descriptive statistics on the frequency of detection, range, mean etc. on accessible chemical residues (carcinogens would suffice) were provided somewhere in the body of the report. If 99 were infrequently and at low levels (or in areas in which exposure was unlikely like subsurface soil), then the qualitative statement is a bit misleading.*

6. *Additionally, I found the statements regarding the issue of mixtures toxicology to be a bit too general and one-sided (page 7). Humans have evolved a complex series of generalized defense and repair mechanisms to deal with the mixtures that they encounter daily. A meaningful risk of exposure to mixtures seems to be a high dose effect in which one component is at a high enough dose to alter pharmacokinetics of another component. In the absence of such an occurrence, the components of a mixture would likely act, at most, in an additive fashion or independently. It is equally important to recognize that, while a child's physiology, metabolism, diet and chemical specific response may increase a child's sensitivity to chemicals (page 7)," the same factors may also act to decrease a child's sensitivity to chemicals.*

- The above comment regarding mixtures of chemicals and that "humans have evolved a complex series of defense and repair mechanisms to deal with the mixtures that they encounter daily" is a simplistic view of the contamination and types of exposures at the Nyanza Chemical Waste Dump. The site was an unrestricted and uncontrolled industrial site for decades before it was proposed to the National Priorities List in 1981. The site is located in a residential setting and the site boundaries abut the Ashland High School. Children and high school students frequented the site regularly, including the use of a short cut path that transversed the site extending from the Ashland High School to the residential areas of Pleasant and Cherry Streets. Given its classification as a Superfund site, the types and nature of chemical contaminants present at the Nyanza site can hardly be described as chemical mixtures that one might encounter daily as suggested in the above comment.

- There is still uncertainty in assessing the risks of chemical mixtures among humans as it is difficult to simulate the types of real world exposures that can occur in settings such as hazardous waste sites. Exposure to mixtures can produce unpredicted effects including enhanced acute and chronic health effects, health impacts at low-level concentrations, and effects on unexpected target organs (Zeliger 2003). A recent study reviewing several cancer clusters and exposure from chemical mixtures found that previously unexplained cancer clusters have common characteristics in that they can be attributed to exposures to mixtures that contain at least one lipophilic and one hydrophilic chemical (Zeliger 2004). In particular the study found that the specific combinations of lipophilic and hydrophilic chemicals present in the exposure mixtures act as individual entities and produce cancers not associated with exposure to any of the individual chemicals contained in the mixture. The cancers that result can be in the form of single cancer types per cluster or specific multiple cancer types per cluster (Zeliger 2004). Therefore, the MDPH believes that it is a reasonable hypothesis that the conditions and mixtures of contaminants at the Nyanza site could be related to increased cancer diagnoses (not necessarily any one cancer type) among individuals who had contact with the site in the past.

7. *The "recent epidemiological studies" linking mixtures to soft tissue sarcoma ought to be cited (page 8) if they persuaded the researchers of a link.*

   - The MDPH has included in the Final Report citations for the epidemiologic studies related to soft tissue sarcoma.

8. *I am not sure that "anecdotal reports" can provide "evidence" by definition (page 8), but the point is taken.*

   - The text of the Final Report describing anecdotal reports from Ashland residents has been revised to state, "Reports from the Ashland community describe instances where children playing in the Megunko Hill area would often return home with blistered hands and discolored clothing."

9. *Discussion should be limited to those chemical residues (again carcinogens to exclusion of others) to which exposure was likely. Discussion of contaminated groundwater (unless ingested), underground vaults, sub-surface soils, etc. are not instructive. In reviewing the limited amount of such data, I would be more concerned with the neurotoxic risks (from mercury and lead) than the potential cancer risks on the face of it.*

   § Information on page 5 of the Final Report under the heading *Nyanza Site History* is provided as background information about the Nyanza site. The information consists of one paragraph that summarizes some of the primary sources of contamination at the Nyanza Chemical Waste Dump. This information is intended as background information to provide some context for the reader about the nature and conditions of the site. It is not intended as a "discussion" of site exposures likely related to cancer risk as suggested by the above comment. For a more complete discussion of chemical constituents detected at the Nyanza site and a review of exposure pathways, the reader is referred to the Public Health Assessment for the Nyanza Chemical Waste Dump (MDPH 1994).

10. *The desired study hypothesis is understood, but I am not sure it can be accomplished as stated. While it is perhaps possible to determine whether someone would resided in Ashland as a child (1965-1985) has a higher risk of developing cancer, the addition of exposure to contamination at the Nyanza Chemical Waste Dump" cannot be independently verified at the time and creates a large source of bias (i.e., recall) that would be difficult to control under the best of circumstances.*

   § Please see the response to Question 1 of this Appendix for further discussion on the impact of bias to the study.

11. *The years of interest is also understood although the age restriction (i.e., 10 to 18) seems a bit too artificial, especially since the site contaminants reportedly escaped off-site, and I doubt seriously if only 10 to 18 year olds were the only group to regularly trespass on the property. I would be curious what happens to the observed disease trends if the range examined is widened a bit (i.e., 5 to 25). Do the cancer trends strengthen or weaken?*

   § As explained on page 7 of the Final Report, the age restriction of study participants to those who were between ages 10 to 18 was based on opportunity for past exposure to the Nyanza Chemical Dump. By restricting the study participants to individuals who were ages 10 to 18 during the years 1965 to 1985, the study targets those Ashland residents who had the greatest opportunity for exposure to the Nyanza site not necessarily individuals with the only opportunity for exposure. Based on the study hypothesis and the initial reports about a suspected cluster of cancer diagnoses among young adults who grew up in Ashland when the site was operational, other than site workers, the study appropriately targets the population of individuals who had the most potential to be in contact with the Nyanza site. It logically follows that if any relationship exists between exposures from the Nyanza site and cancer diagnoses, then one would expect to see that relationship among the individuals who had the most frequent contact with the site. As further described in the Final Report, the 1994 Public Health Assessment for the Nyanza Chemical Waste Dump provided a complete assessment of exposure pathways from the

site and concluded that although opportunity for exposure to site contaminants for young children and adults may have occurred, exposure to these individuals as a group was considered low (MDPH 1994).

12. *Subject to the above stated concern, the identification and recruitment of study participants appears to been as thorough an effort as might be expected under these conditions. The statement that the current and former Ashland residents that could not be reached through local recruiting efforts had an "equal opportunity" to participate in the study is probably overstated.*

    § The primary recruitment of study participants was not based on "local recruiting efforts alone." As stated on page 8 of the Final Report, recruitment of study subjects was based on a number of efforts. The primary recruitment was through individual mailings to each member of the Ashland High School classes 1972 through 1992. The mailings were accomplished by using current contact information from high school class reunion lists. Therefore, a standard method of recruitment was employed for all potential study participants. With the exception of individuals for whom current address or contact information was unknown, both current and former residents had an equal opportunity to participate in the study. Current address information was unknown for a portion of the eligible or target study population (22%).

13. *Questionnaire development and use appears standard and the incorporation of maps or visual aids as a means to prompt memory is understandable. The difficulty remains in developing an adequate measure of exposure in light of the publicity over the study and the idea that an excess of disease existed in this community. In this case, I am not confident that any meaningful exposure information can be derived from the questionnaire or 20 to 40 year old memories. I am of similar age to the study participants and would be hard pressed to remember exactly where and when I played during that period. I am not sure that there is not significant potential for exposure misclassification between and among the exposed and non-exposed groups because of the potential biases likely present in the population.*

    § The MDPH acknowledges that there are limitations to the exposure assessment portion of the study due to the necessary reliance on proxy data to estimate individual exposures. As a result, it is likely that some misclassification bias was introduced to the study due to poor recall of exposure activities. Again, see response to Question 1 of this Appendix for a further discussion of the potential impact of misclassification bias to the study. When few or no past measurements of the environment are available, any characterization of study subjects according to their likely past exposure to environmental contaminants will be crude and at the level of broad groups rather than individual observations. Although the exposure assessment for the Ashland Nyanza Health Study may be considered crude by some, the MDPH believes that potential error in exposure measurement was reduced by quality control in the design of the study questionnaire, interview procedures, and standardization of response. The questionnaire included all items needed to compute an exposure dose (i.e., timing of exposure in terms of location, frequency, and duration). Instructions to study participants were clear and data collection items unambiguous. Mutually exclusive response categories were provided for close-ended items. Further,

the survey instrument was peer reviewed by other researchers and pre-tested on volunteers from the Ashland community so that appropriate revisions could be made before its implementation. Again, please see the response to Questions 1 and Questions 3 of this Appendix for further discussion of the exposure assessment and the potential impact of bias on the study.

14. *The description of the data analysis and control for confounding seems standard enough although I worry that making multiple statistical comparisons such as was done in this case (and virtually every similar study) generates a high likelihood of false positives at the 95% Confidence Interval.*

    § Please see response to Question 3 of this Appendix for further discussion of multiple comparisons as an issue of concern to the Ashland Nyanza Health Study.

15. *In terms of study participation, I came up with a response rate of 65.9% (1387/2054) rate than the 67.5% cited. It is also a question as to whether the response rate shouldn't be based on the original population estimate (2751) or the sample population identified (2618).*

    § The response rate is defined as the number of completed or returned survey instruments (questionnaires, interviews, etc.) divided by the total number of persons who would have been surveyed if all participated (Last 1988). The sample population identified from the target study population was 2,618 individuals. The response rate was determined as the number of individuals in the sample population who completed the study interview (1,387) divided by the total number who would have participated (2,054). That is, the total number of study participants identified (2,618) less those individuals for which there was no contact information (564). Therefore, the response rate as reported in the Final Report was 67.5% (or 1,387/2,054).

16. *While the reasons for refusals didn't vary by gender of year, the high number of refusals for various reasons suggests the potential for selection bias that ought to be discussed.*

    § Again, please see the response to Question 1 for further discussion on the impact of bias to the study.

17. *The fact that only 68% of the 73 individuals who reported having a cancer diagnosis actually had one (at least a confirmed one) again suggests some bias at work (what happens if those 23 unconfirmed cases are eliminated from the analysis?). It is also unclear whether the number of cases used in the analysis was confined to those that were confirmed (50) or any reported (73).*

    § Page 23 of the Draft Final Report stated that for study participants who self-reported a cancer diagnosis, the diagnosis was confirmed either by medical record review or review of the Massachusetts Cancer Registry data files. The MDPH was able to confirm a cancer diagnosis for 55% (N=40) of the 73 individuals who self-reported a cancer diagnosis. This number was incorrectly reported in the Draft Final Report as 68% (N=50). For the 55% of the 73 study participants who self-reported a cancer diagnosis,

MDPH either received their medical record or was able to locate information in the Massachusetts Cancer Registry files confirming the diagnosis. This does not imply that for the remaining individuals in the self-reported case group that we confirmed they did not have a cancer diagnosis but rather we were unable to obtain the information that would confirm their diagnosis. As described in the Final Report, for these individuals we were either unable to obtain appropriate medical records (i.e., the medical record was not on file or had been purged) or we were unable to obtain participant consent to access medical records. Statistical analyses were initially conducted with all cases of self-reported cancer (both confirmed and unconfirmed) as a group (N=73).

§ Analyses that included all study participants that self-reported a cancer diagnosis as the case group showed that individuals who reported a family history of cancer and engaged in activities in specific areas of the Nyanza Chemical site had a statistically significant increased risk of cancer. The areas that were associated with an increased risk of cancer included the Eastern Wetlands (Area B), the Sudbury River near High Street (Area F) and the Sudbury River and Mill Pond area (Area G). The most consistent and significant results were observed among study participants who reported activities related to water contact. Specifically, swimming or wading at the Megunko Hill area (Area D) showed a significant association with self-reported cancer diagnoses. Further, the relative risk of a self-reported cancer diagnosis increased and remained statistically significant among study participants who reported swimming or wading in the Megunko Hill area and had a family history of cancer. When the analyses considered individuals who reported any activity involving water contact, again there was a statistically significant risk of cancer for water activities that occurred in the Megunko Hill area.

§ Analyses were also conducted with the case group restricted to those individuals with a confirmed cancer diagnosis (N=40). Repeating the analyses above with study participants with a confirmed cancer diagnosis as the case group showed that there was a positive association with confirmed cancer diagnoses for the majority of exposure areas described on Map B. However, the results were not statistically significant and therefore did not confirm the results observed in the initial analyses that evaluated all individuals who reported a self-reported cancer diagnoses. Analysis of overall water contact again did not generally confirm the previous results observed with the complete case group of all self-reported cancer diagnoses. But a statistically significant association was observed between Area H (an area of the Sudbury River near Myrtle Street) and individuals with a confirmed cancer diagnosis. The results show that the risk of a confirmed cancer diagnosis among individuals who reported any type of water contact with Area H was slightly more than twice the risk compared to individuals with no cancer diagnosis (RR=2.07, 95% CI 1.08-3.99). Previous analyses of this area that included all individuals who self-reported a cancer diagnosis showed results that approached statistical significance (e.g., lower bound 95% CI of 0.92, 0.94 etc.). As was also seen in the analyses including all self-reported cancer diagnoses as a group, the relative risk increased and remained statistically significant for those who had any water contact with Area H and reported a family history of cancer (RR=3.63, 95% CI 1.47-8.96).

§ Although no statistically significant associations were observed for contact with the areas of the Nyanza site depicted on Map B (i.e., Areas A through I) and confirmed cancer diagnoses, when specific exposure locations within the defined areas were evaluated, significant associations occurred with overall water contact exposures at Chemical Brook and the two waste lagoons located on Megunko Hill. These results were statistically significant among individuals who had a confirmed cancer diagnosis and those individuals whose diagnosis was considered a rare cancer. Again, the results were confirmed and remained statistically significant when a family history of cancer was considered in the analyses. Therefore, even though the analyses restricting the case group to only those study participants who had a confirmed cancer diagnosis did not consistently confirm the associations initially observed between Areas B, F, and G as defined on Map B and self-reported cancer diagnoses, the results for overall water contact exposures at the site were consistent for specific site areas, such as Chemical Brook and the Megunko Hill ponds. The MDPH believes that these results lend support and tend to strengthen the overall study conclusions that certain reported exposures at the Nyanza site appear associated with an increased risk of cancer development among this study cohort and that the observed associations between site exposures and family history of cancer possibly suggest a gene-environment interaction among this group.

18. *Figure 4 on my copy was not the cancer distribution references (page 23), but the flow chart for the study participation.*

§ The distribution of cancer types for study participants who self-reported a cancer diagnosis is shown in Figure 5. The text of the Final Report has been revised to reflect this correction.

19. *The discussion of the rare cancers ought to be expanded (a table?) in terms of which cancers are being classified as rare, the expected incidence rates, the observed rates in Ashland and Massachusetts, and other salient details.*

- Additional information about rare cancer types observed among the study participants has been included in the Final Report (please refer to page 20). Also, please refer to the response to Question 4 of this Appendix for discussion of rare cancer types.

20. *The sentence starting "The SEER age-specific incidence…" on page 23 also appears to be missing a period (or contains some awkward language).*

§ See the revised text on page 20 of the Final Report.

21. *The exposure analysis is both the most important portion of the study and the weakest. For reasons previously mentioned, I do not believe that a meaningful and unbiased exposure assessment can be constructed out of 20 to 40 years old memories of then children, particularly given the uncertainty introduced by the self-reporting of disease and exposure, the level of participation (or non-participation, if you prefer) on the part of the target population and its influence on response and the fact that virtually everyone in the study is apparently "exposed" by definition (98%).*

- Again, please see response to Question 1 of this Appendix for further discussion of the exposure assessment and the impact of bias on the study.

22. *It is instructive to note that despite the very liberal definition of "exposed" virtually no relative risk was statistically significant in terms of increased cancer risk.*

    - The comment that virtually no relative risk was statistically significant is incorrect. Analyses that included all study participants that self-reported a cancer diagnosis as the case group showed that individuals who reported a family history of cancer and engaged in activities in certain defined areas of the Nyanza Chemical site had a statistically significant increased risk of cancer. The areas that were specifically associated with a statistically significant risk of cancer included the Eastern Wetlands (Area B), the Sudbury River near High Street (Area F) and the Sudbury River and Mill Pond area (Area G). These results pertain to study participants who reported that they ever had contact with areas of the Nyanza site as depicted on the exposure Map B compared with those who reported they never had contact with these areas. The most consistent and significant results were observed among study participants who reported activities related to water contact. Specifically, swimming or wading at the Megunko Hill area (Area D) showed a significant association with self-reported cancer diagnoses. Further, the relative risk of a self-reported cancer diagnosis increased and remained statistically significant among study participants who reported swimming or wading in the Megunko Hill area and had a family history of cancer. When the analyses considered individuals who reported any activity involving water contact, again there was a statistically significant risk of cancer for water activities that occurred in the Megunko Hill area. Additionally, statistically significant relative risks of a cancer diagnosis were observed among study participants who reported occupational exposure to chlorinated chemicals and chemical dyes. Again, the relative risk increased and remained statistically significant among those who reported a family history of cancer. In interpreting the results of the study, the MDPH concludes that this information when considered with known information and reported exposure activities at the Nyanza site in the past possibly suggests that a gene-environment interaction may exist among individuals who reported specific exposures (water contact) in certain areas of the Nyanza site.

23. *I would avoid using phrases like "a nearly statistically significant relative risk" in places [page 27] where there is no statistically significant relative risk unless it is also planned to use "a nearly statistically non-significant relative risk" in analyses where analyses reported a barely statistically significant relative risk.*

    - The MDPH always strives to report the results of its investigations in a consistent and objective manner. In presenting the results of the statistical analyses, attention was drawn to those findings that were notable either because they resulted in a statistically significant increase or decrease in cancer risk or showed a consistent pattern regardless of whether they met the criteria of statistical significance. The objective in conducting the Ashland Nyanza Health Study was to present the study data in its entirety and interpret the results in the context of known information about the Nyanza Chemical site. The

MDPH believes it has accomplished this goal while emphasizing and providing further discussion of results that were more meaningful in terms of their statistical validity and precision.

24. *The use of terms like "more exposed" and "less exposed" to describe individuals based on where they claim to have ventured in the area is a likely source of exposure misclassification since I can easily imagine situations in which the "less exposed" may have a higher actual exposure due to behavior than someone labeled "more exposed." Witness the fact that "discolored clothes or skin" is associated with a self-reported cancer diagnosis for Area K, while the skin irritation/ rashes (an arguably more definitive sign of some exposure) or areas of potentially higher contamination have no such association.*

    § The terms "more exposed" and "less exposed" referred to in the above comment relate to analysis of Nyanza site activities and reported exposures that occurred on the Nyanza property itself versus in areas located not on the Nyanza property. The analyses were conducted to evaluate and compare reported exposures that occurred on the Nyanza site property and those that were reported for other areas associated with chemical contamination from the Nyanza site and in closer proximity to residential areas (on-site versus off-site) to determine if any difference in relative risk of cancer exists between these exposures. These analyses are not representative of areas or activities that may have resulted in more or less exposure among study participants. This distinction has been clarified on page 24 of the Final Report.

25. *The fact that family history of cancer sometimes seems act as an "effect modifier" for exposure to site areas or activities like swimming/wading in Area D (probably should be Area G) is interesting, but raises the question of which factor is the actual confounder (is exposure to the site a confounder for increased risk of cancer due to family history or vice versa?).*

    § An effect modifier, also known as a moderator variable or interaction, is not a confounder. Effect modification addresses the issue of whether exposure and disease relationships vary according to the presence or absence of other variables. It reveals the existing interrelations between the risk factors in the process of producing the disease in the underlying population. A confounder or confounding variable adds its effect to or mixes and distorts its effect with its effect of exposure. Therefore, a confounder will bias the association between exposure and disease. That is, it may overestimate or underestimate the true relationship between exposure and disease. Confounding is a phenomenon that exists but can be controlled for and removed in the statistical analysis usually by stratification of the confounding variable. In other words, when crude and adjusted risk estimates are evaluated, the effect of the confounding variable is eliminated in the stratified analysis and no longer distorts the association between exposure and disease. Because effect modification or interaction is not a bias but rather reveals the existing interrelations between risk factors in the process of producing the disease, its existence is revealed not removed by stratification of the analyses according to the modifying factor. This was the situation when the analyses for the Ashland Nyanza Health Study were stratified according to the presence or absence of a family history of

cancer. In almost all instances, when the analyses considered a family history of cancer, the effect of exposure or contact with the Nyanza site on cancer diagnosis was strengthened and increased not removed as would be the case if family history was acting as a confounding factor between Nyanza exposures and cancer diagnoses.

26. *The fact that only the nebulous exposure identified as swimming/wading in Area D (or G…which appears to be based on a simple yes/no response on the questionnaire) is associated with a statistically significant risk of self-reported cancer diagnosis makes me suspicious that this is an artifact resulting from making multiple and repeated comparisons (in fact, I am surprised that more analyses were not significant just based on chance).*

§ Swimming or wading in Area D was not the only exposure associated with a statistically significant risk of cancer. Please refer to the response to comments #17 for further discussion the statistically significant observations in the study. Also, as previously explained, the statement regarding suspicious results stemming from multiple statistical comparisons is not a valid comment as it relates to the Ashland Nyanza Health Study. Please refer to the response to comments for Question 3 on page 7 for discussion of multiple comparisons.

27. *Since this type of activity would likely represent the lowest exposure potential, based on frequency, duration, and residue concentrations, it also does not make much sense toxicologically. The actual number of cases and types of cancers self-reported for this observed association would be instructive (as it would for any reported statistically significant finding for site exposure or otherwise).*

§ As described in the response to the above comment #26, swimming or wading in Area D or the ponds located on Megunko Hill is not a nebulous exposure. The Megunko Hill area of the Nyanza site was the location of two waste lagoons where study participants, particularly high school students, reported that they engaged in activities such as swimming or wading. It is difficult to conclude that swimming or wading in a pond that was used as a waste lagoon by a chemical dye manufacturing facility would represent an exposure of low potential.

28. *In terms of the occupational history, I was interested in the negative association reported between paints, etc. and self-reported cancer (cancer is misspelled in the second paragraph, end of the fourth line, page 32).*

§ The misspelling of the word cancer on page 32 has been corrected in the Final Report. In terms of analysis of occupational history and the negative association observed among study participants reporting exposure to paints, paint products, paint thinner or remover, it is uncertain why this type of exposure may have resulted in a negative relative risk of cancer. The observed statistical association indicates that there was a statistically significant decreased risk of cancer among study participants who reported occupational exposure to paints, paint products, or paint thinner or remover. Although the observed negative association implies that a protective effect may exist between occupational exposure to paints and paint products and a self-reported cancer diagnosis, this is not

likely a valid interpretation of this association. This association was observed when the analysis included all study participants who self-reported a cancer diagnosis.

29. *The phrase "is likely a reflection of this sample of participants" requires further explanation in my mind, and begs the question why the same notion could not apply to the weak, although statistically significant, positive associations reported in terms of putative site exposure.*

    - The MDPH does not agree with the above comment that the positive and statistically significant associations observed in the study between reported exposures at the Nyanza Chemical site and cancer diagnoses are weak. While it may be accurate in some instances to describe some of the relative risks observed in the study as small (i.e., increased relative risks in the range of 5% or less), to characterize the observed associations in the Ashland Nyanza Health Study as weak is incorrect. This comment implies that the observed study results are statistically weak and this is a false assumption. In fact, review of the analyses illustrate that the study results are statistically stable. It is known that the estimates least influenced by chance are those with narrow confidence intervals. These are the results that deserve the greatest reliance and are more trustworthy as they are less influenced by random error (Poole 2001). The 95% confidence intervals for the relative risk estimates calculated in the Ashland Nyanza Health Study are narrow. The ratio of upper to lower 95% confidence limits for the majority of risk estimates are low therefore demonstrating statistical strength and precision in the observed risk estimates.

30. *The abbreviation "SR" appears on page 32 as well. I assume this is self-reported cancer diagnoses, but I am unable to find it defined in the text.*

    - The abbreviation "SR" refers to self-reported cancer diagnoses and is defined on page 23 of the Final Report. However, the text on page 32 was revised to clarify that the analyses referred to were analyses that were conducted with the entire case group or the group of study participants who self-reported a cancer diagnosis (N=73).

31. *The association between chlorinated chemicals and dyes is interesting, but the categories are too broad as well as overlapping with other chemicals mentioned (PCE, TCE, etc.) to be a really useful exposure metric. Additionally, this portion of the exposure analysis suffers from the same inherent weaknesses as that seen in the earlier effort.*

    - The associations observed between occupational exposure to chlorinated chemicals and chemical dyes relate to broad exposure categories. The study questionnaire did ask questions regarding occupational exposure to specific chlorinated chemicals such as perchloroethylene (PCE), trichloroethylene (TCE) and polyvinyl chloride (PVC) in an attempt to provide a more precise exposure metric. Unfortunately, the specificity of the questions and poor recall of past occupational exposures resulted in a low frequency of response to these questions rendering statistical analysis impractical. Therefore, the broader categories of occupational exposure to chlorinated chemicals and chemical dyes were used in the evaluation of effect on an increased risk of cancer. While it is true that these categories lack specificity in terms of evaluating specific chemical exposures in an

occupational setting, they do provide some measure of exposure to these types of chemicals in general. As previously stated, given the retrospective aspect of the Ashland Nyanza Health Study, there are limitations to the exposure assessment portion of the study due to the necessary reliance on proxy data to estimate individual exposures. Further, when few or no past measurements of the environment are available, any characterization of study subjects according to their likely past exposure to environmental contaminants will be crude and at the level of broad groups rather than individual observations.

32. *I am uncertain to what the term "cumulative chemical exposure" refers. Is this a means to try to examine if a dose-response (or rather exposure-response) relationship exists for the self-reported cases? If so, does such a relationship actually exist (do individuals with a larger exposure have a higher risk). It may be hard to determine this given the small number of cases, but this characteristic is one of the Hill criteria and needs to be specifically examined if possible.*

- The term cumulative chemical exposure referenced in the discussion of occupational exposures refers to the variable description for the analyses combining as a cumulative response the individual categories of occupational exposure to chlorinated chemicals and exposure to chemical dyes. Statistical analyses that assessed the risk of cancer among those who reported occupational exposure to chlorinated chemicals and chemical dyes as a group resulted in a statistically significant positive association with cancer. Information about the frequency and duration of use of these materials in an occupational setting was also assessed and resulted in a small but statistically significant increase in the risk of a self-reported cancer diagnosis with increasing years of use. These results are presented and described on page 31 and in Tables 44 through 46of the Final Report.

33. *I was also a bit concerned about the phrase (page 34, second paragraph, last line) "…overall water-contact exposure in area D (or G?) is being considered statistically significant at…" That just seems a strange way of stating the findings. It either is or isn't statistically significant. However, in examining Table 29, it appears the 95th CI includes 1.00 in its range and this calls into question whether the result are or remain statistically significant.*

- The text on pages 33 and 34 describes the logistic regression analysis that evaluated the effects of cumulative chemical exposure, overall water contact in Area D, and a family history of cancer on self-reported cancer diagnosis. As stated on page 34, each of these three factors demonstrated a statistically significant association with a self-reported cancer diagnosis. When these factors were combined in logistic regression analysis, the results showed a statistically significant relationship with a self-reported cancer diagnosis. The effects of the individual factors also remained significant with risk estimates comparable to the results observed in analysis of these factors individually. In the logistic regression model, overall water contact in Area D resulted in an odds ratio of 2.44 and a nearly statistically significant effect on self-reported cancer diagnosis (p=0.0531). However, the categorical analysis, which was the primary study analysis, of overall water contact in Area D demonstrated a statistically significant association with a

self-reported cancer diagnosis (RR=2.43, p=0.0411). This distinction has been clarified in the Final Report.

- The above comment also referred to a discrepancy in whether the association of overall water contact with a self-reported cancer diagnosis was related to Area D or Area G. The exposure Map B depicts nine different locations on or near the Nyanza site property. These exposure areas are labeled as Areas A through I and are described in List 1. Area D on Map B refers to the Megunko Hill area, also known as the Hill area where two waste ponds were located. Area G on Map B refers to the Sudbury River and Mill Pond areas and the location of a baseball field north of Pleasant Street. The statistically significant associations described above were observed in Area D (the Megunko Hill area). However, the study questionnaire also asked about activities in more specific areas located within Areas A through I such as Chemical Brook or specifically the two waste ponds located on Megunko Hill. The questions referring specifically to the ponds located at Megunko Hill were numerically marked as question C14 "g" in the study questionnaire and are not intended to mean Area G as depicted on the exposure Map B. This discrepancy has been clarified and corrected in the Final Report.

34. *As mentioned previously, it would be useful to have the number and types(s) of cancer stated in conjunction with the statements regarding the magnitude of the risks associated with various exposures.*

- The Final Report includes information about the number and types of cancers associated with exposures that demonstrated a statistically significant increased risk.

35. *The statistically significant association between pesticide exposure and self-reported cancer is rightly described as small, but is further described as not indicative of "an appreciable increase in risk." Since many of the reported statistically significant positive associations are also small, it would be useful to know how to a measure of "an appreciable increase in risk" in context of this analysis is determined.*

- The above comment stating that "many of the reported statistically significant positive associations are also small" is incorrect. The relative risks for almost all of the statistically significant results observed between Nyanza site contact and individuals with a self-reported or confirmed cancer diagnosis were twice that observed for study participants who did not report Nyanza site contact. That is, the relative risks for these associations were typically 2.0 or greater and were not considered small. There were a number of analyses examining Nyanza site contact and activities that did not result in statistically significant associations. In the discussion of these results in the Final Report, the associations are described as positive associations and can also be described as small. The description of the significant association between pesticide exposure and self-reported cancer as not indicative of an appreciable increase in risk pertains to the specific association observed between the duration in years that tree or agricultural spraying at or near the home was reported. Analysis of this specific exposure using logistic regression showed that the overall cumulative risk for increasing years of exposure resulted in an odds ratio (OR) of 1.05 or an increased risk in self-reported cancer diagnoses of 5%.

36. *The residential history analysis contains too few individuals to draw any meaningful conclusions and might be left out to avoid confusing the issue.*

- In reporting the results of the study, the objective was to present the study data in its entirety and interpret the results in the context of known information about the Nyanza Chemical site. The MDPH believes it has accomplished this goal while emphasizing and providing further discussion of results that were more meaningful in terms of their statistical validity and precision.

37. In the discussion (page 38), the first sentence needs to be re-written "…engage in activities that would result in actual exposure to Nyanza site contaminants that were likely to result in a cancer diagnosis." This is incorrect on the face since it assumes that "actual" exposure took place in those areas and that exposure to site contaminants are "likely to result in a cancer diagnosis." Neither statement is certain nor supported by the study results per se.

- The first sentence in the Discussion section has been revised to provide a clearer description of Nyanza site exposure as defined and assessed in this study.

38. Reference is also made to Megunko Hill and environs as Area G (pages 27 and 38) whereas it was previously identified as Area D in the text (page 28). This needs to be clarified and corrected if necessary. Although the impression is given that there is an elevated risk associated with this area based on skin rashes/irritation (RR=4.02), the 95th CI for these analyses all include 1.00 in their range, suggesting that the results are as likely due to chance as any effect from exposure to the site. This kind of information and its implication for the conclusions needs to be included in the discussion.

§ As explained in the response to comment #33, Area D on Map B refers to the Megunko Hill area also known as the Hill area where two waste ponds were located. Area G on Map B refers to the Sudbury River and Mill Pond areas and the location of a baseball field north of Pleasant Street. However, the study questionnaire also asked questions about activities in more specific areas located within Areas A through I as described on Map B, such as the two waste ponds located on Megunko Hill. These questions were numerically marked as question C14 "g" in the study questionnaire and are not intended to mean Area G as depicted on exposure Map B. The results described on page 27 of the Draft Final Report referred specifically to the ponds located on Megunko Hill and were incorrectly referenced as Area G. The results on page 38 referred to Area G of the Exposure Map B (Sudbury River and Mill Pond areas and the location of a baseball field north of Pleasant Street). This discrepancy has been clarified and corrected in the Final Report. Further, the Draft Report correctly described the observed association between discolored skin and clothing resulting from contact in the woods behind Ashland High School (not Area D or Area G as referenced in the above comment) and a self-reported cancer diagnosis as statistically significant. The text provided the relative risk estimate of 4.21 and 95% confidence interval (1.71-10.38) as was presented in Table 4.

39. *The issue of rare cancers (or cancer occurrence) needs further discussion in terms of the types identified and what their known risk factors or associations are as well as whether these cancers occurred in the individuals with highest exposure to site residues or not.*

- Additional information about rare cancer types observed among the study participants has been included in the Final Report. Also, please refer to the response to Question 4 of this Appendix for discussion of rare cancer types.

40. *I am also not sure that selection bias is not an issue. Although the definition of selection of bias was provided, no information was given to assure one that some selection bias did not take place. In fact, if the people who chose to participate did so because they had illnesses or health concerns and worries over their presumed exposure that may have biased the results in one direction or the other. The issue of recall bias is also a concern for the same reason.*

- The Discussion section of the Final Report was expanded to include additional evaluation of the impact of bias to the study. Again, please see the response to Question 1 of this Appendix for further discussion on the impact of bias to the study.

41. *For some reason, the potential for bias due to selection, recall or exposure misclassification seems to be understated in the conclusions whereas I think they are critical issues and need to be more fully explored (or the position taken better defended).*

- Again, please see the response to Question 1 of this Appendix for further discussion on the impact of bias to the study.

42. *The first line of the second paragraph (page 40) appears to be missing a word or to be inelegantly phrased and the last sentence of the same paragraph ought to be deleted as anecdotal information that adds nothing to this analysis or its interpretation.*

- The text referred to on page 40 was revised to provide a clearer explanation of selection bias and its potential impact on the study results.

43. *The single most important statement made is "reliance of self-report of contact with general exposures on Map B as the primary assessment of exposure could yield imprecise exposure estimates and potential misclassification of exposure." I could not agree more. It would be a disservice to the community not to fully and clearly explain why this is such a difficult issue and why it renders most of these types of studies as useless in determining cause and effect, even in cases where disease excesses are present (same disease in the same population in the same time frame).*

- Again, please see the response to Question 1 of this Appendix for further discussion on the impact of bias to the study.

44. *Exposure (even if it did occur) is also not the same as effect, which requires a sufficient absorbed dose for a sufficient period at the target tissue. I am not convinced that occasional*

wading (or swimming) in what sound like intermittent ponds on a (waste) hilltop would result in significant exposure given that the likely residue concentrations in water, sediment, and soil are low or not especially carcinogenic (based on maximum on- and off-site surface water and sediment/soil concentrations referenced in the attached Health Assessment document).

- The MDPH understands that without more detailed knowledge of the history of the Nyanza Chemical site, it may be difficult to appreciate the types of exposures that were reported to have occurred there. Large volumes of industrial wastewater generated by the textile dye operations at the site were discharged to the Sudbury River through Chemical Brook and a small unnamed stream. Large volumes of sludges as well as barrels of solvents and chemical wastes were disposed of on the site (MDEQE 1980). The wastewater discharge resulted in chemical contamination of the waters, sediment and fish. The on site disposal practices caused contamination of top soils and groundwater. Sludge was pumped from a filled lagoon into a pit on the top of Megunko Hill. Thus, the ponds located on top of Megunko Hill were not intermittent ponds as suggested in the above comment but actual waste lagoons. Therefore, if exposures occurred in this area of the site, as reported by study participants, it was not likely to have been to low-level concentrations of contaminants.

45. *The potential for recall bias in this situation given the attached concern and publicity seems high as does the potential biases introduced by self-reporting of disease and exposure.*

- Again, please see the response to Question 1 of this Appendix for further discussion on the impact of bias to the study.

46. *In sum, this is a substantial effort that attempts to address a difficult and challenging problem. One that has not been solved by any investigator in any similar study to date. It takes an interesting approach to the problem, uses local resources to their advantage, and an innovative approach to the critical issue of exposure assessment. Unfortunately, I also believe that the weaknesses in the study results and interpretation are understated and the positive associations overstated. This may be because the findings represent some preconceived notion of what the findings are or should be, but this needs to be closely examined and biases in the presentation of the study results rooted out. In my limited view, this is a small city with the perception of an increased cancer burden among younger residents. This may be true based on cancer registry information for total cancer incidence, but if cancers that are likely unrelated to "environmental' causes (i.e., skin, cervical, uterine, etc.) or have other risk factors are eliminated, does the excess remain?*

- The MDPH does not agree with the comment that the weaknesses in the study results and interpretation are understated and the positive associations overstated. Further, MDPH disagrees that "the findings represent some preconceived notion of what the findings are or should be" as stated in the above comment. The objective in conducting the Ashland Nyanza Health Study was to present the study data in its entirety and interpret the results in the context of known information about the Nyanza Chemical site. The MDPH believes it has accomplished this goal while presenting discussion of the study limitations, possible biases present in the study and their impact on the study results.

Please see the response to comments for Question 5 of this Appendix and the response to comments for Question 6 regarding the interpretation of study results and the study conclusions.

47. *The issue of excess rare cancers should be more fully explored in terms of timing and type and association with site exposures as defined. As it stands, this is a relatively small population of which only around 50% to 65% (depending on how one counts) participated. The small number of cancer cases are self-reported (and only 66% confirmed) as are the potential exposure. Exposure in this sense means does one remember ever being in or near a particular location (at least once), and has little relevance to true exposure (meaning dose to a toxicologist), and less still to biologically significant exposure.*

    - Additional information about rare cancer types observed among the study participants has been included in the Final Report. Also, please refer to the response to Question 4 of this Appendix for discussion of rare cancer types.

48. *Because of the technique used because of necessity, there is a very high potential for both exposure mis-classification and recall bias influencing the results (recreating the behavior of a child from 20 to 40 year old memories filtered through current events is not a trivial issue).*

    § Again, please see the response to Question 1 of this Appendix for further discussion on the impact of bias to the study.

49. *Multiple analyses found few statistically significant (albeit weak) associations between "exposure" as defined and effect (although some unfortunate shading of words that may confuse the issue), but I am concerned that these may be artifactual (the result of continually parsing and re-analyzing the data) and the may be over-stating the true nature of the associations and possible risks. I am afraid I do not the conclusions regarding exposure and risk persuasive for that reason.*

    - The MDPH does not agree that the Ashland Nyanza Health Study found few statistically significant associations between site exposures and cancer risk. Further, the description of the observed positive findings as weak is incorrect. Please see the previous response to comment #22 and comment #29 for a discussion of statistically significant study results and the strength of these associations. Also, as previously stated, the statistical analyses followed a well defined data analysis plan in order to evaluate whether the data collected from study participants support the study hypothesis. The issue of artifactual study results or results arising by chance due to multiple statistical comparisons is not an issue to the Ashland Nyanza Health Study and is discussed in the response to Question 3 on page 9 of this Appendix for a discussion of multiple comparisons.

50. *I applaud the effort, ingenuity, and the interaction with the citizens that this study obviously entails, but trust that undertaking this type of study and its final outcome did not raise false expectations in them or disappoint because it does not and cannot show a definitive cause and effect relationship between the "exposure" to the Nyanza site and the health effects of concern. Thank you for allowing me the opportunity to review and comment on this study.*

- As stated in the response to Question 5 of this Appendix and in the response to Question 6 on page 11, the objective in conducting the Ashland Nyanza Health Study was to present the study data in its entirety and interpret the results in the context of known information about the Nyanza Chemical site. It is true that the Ashland Nyanza Study lacks an independent means of validating the exposure measurement and this is a limitation to the study. Nevertheless, the data available was the data used and we must therefore rely on scientific judgment in the context of all of the information presented, not just single measures of association and whether they may meet the criteria of statistically significant. As public health researchers it is important that we review all of the information in its totality to draw appropriate conclusions. The MDPH believes it has accomplished this goal while presenting discussion of the study limitations, possible biases present in the study and their impact on the study results. Further the MDPH has a long history of positive collaboration with Massachusetts communities to address community concerns about environmental exposures and possible health effects. At the start of this study the MDPH established a Community Advisory Committee. The Community Advisory Committee was composed of residents of the town of Ashland as well as the Ashland Board of Health and representatives from both the USEPA and Massachusetts Department of Environmental Protection (MDEP). Throughout this investigation, the advisory community provided input into the study design and approach and engaged in numerous discussions about epidemiologic methods and their application to environmental health questions. Further, the MDPH will continue to work in partnership and maintain an open dialogue with the Ashland community in the public release of the study results.

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