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Review of CFB Gagetown Herbicide Study
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Literature Review

Overall

The authors have thoroughly described and evaluated the range of exposure—disease associations of concern at CFB Gagetown. The literature searching methods are systematic and clearly described. They have made good use of the Institute of Medicine (IOM) reports on Agent Orange for the consideration of possible health effects from chlorophenoxy herbicides, and have incorporated new information that has become available more recently. They have also tried to follow the same strategy in addressing herbicides other than those considered by IOM in a parallel manner. The judgments are, with a few exceptions (mentioned below), clearly explained, and while there is an inherent subjectivity in the assessments, the evaluations are all reasonable. It would be helpful to highlight more directly where the judgment of risk at CFB Gagetown differs from the IOM assessments, perhaps summarized in a table at the beginning of that section, and note whether the different result is due to a judgment about the same body of research or is a product of results from newer studies that shifted the weight of evidence. Both are legitimate but it would be helpful in terms of transparency to know which has occurred when the perspectives differ between the current reviewers and the IOM committees. The amount of explanation or discussion called for is greater when there is disagreement than when the assessments agree.

A recurrent theme is how much evidence is required to fall into the levels of certainty. In a number of cases, a single study was viewed as sufficient to move into the category of “limited suggestive evidence,” and presumably that can be tempered if there are several negative studies of the same issue of similar quality. If there are formal rules to reach such assignments, these should be provided, and if the decision algorithm more subjective and informal than that, it should nonetheless be described.

The distinctions regarding precisely which herbicides and contaminants are addressed needs to be handled more systematically. In some sections, the review notes Agent Orange, chlorophenoxy herbicides generally, and specific chlorophenoxy herbicides as though they were interchangeable. Perhaps a discussion at the outset regarding which is most directly relevant to CFB Gagetown would help, and then a more careful grouping or delineation of the category exposure throughout the document.

Specific comments/questions

Page 1: It is not clear in the first paragraph the exact nature of the question that is to be addressed in the review. Is it “Are the herbicides known to be present at CFB Gagetown potentially capable of causing adverse health effects?” or is it “Did the herbicides known to be present at CFB Gagetown cause adverse health effects to this exposed population?” The first appears to be the one considered here, and should be clarified. However, at times in the report, the authors focus specifically on the Gagetown situation or experience, confusing the issue. The review is a general review of possible health effects from herbicides present at CFB Gagetown and should be clearly stated as such.

Page 13: The issue of exposure assessment appears repeatedly throughout the report. It might be better to present at the outset a discussion of the general categories of studies and what they generate. Occupational cohorts involved in manufacturing, pesticide applicators, community populations, and Vietnam veterans each have certain strengths and limitations for research, and would warrant mention.

Page 46-50: A minor point, but it’s unclear why there are a series of different tables all on the same topic with the same title.

Page 57: It is not clear if there are different implications when the synthesis refers to Gagetown specifically or not, as it does for multiple myeloma and non-Hodgkin’s lymphoma but not for most of the other outcomes.

Page 59: Ranging into studies of environmental chemicals and leukemia in general seems too far afield and not likely to contribute at all to the question regarding specific herbicides.

Page 67: When epidemiologic research on CFB Gagetown specifically is discussed, it is unclear whether that is because such studies happen to add to the body of general information regarding the herbicide and the health outcome or whether it is of special interest because it pertains to the population of concern. This should be clarified at the outset.

Page 87: The conclusions for phosphonate herbicides and reproductive outcomes is based on only one study, which seems rather fallible as a basis for assessment.

Page 93: The one conclusion that is not explained is the judgment of limited or suggestive evidence on pentachlorophenol and nasal and nasopharyngeal cancers. All the results cited on page 89 are not supportive of an association, unless one views ORs of 1.1 as “positive.” Even though ostensibly statistically significant, it seems odd to classify these as positive.

Page 93: The conclusion on pentachlorophenol and rectal cancer is also based entirely on a single study.

Page 101: The conclusion on hexachlorobenzene and estrogen-related cancers is also based on one study only.

Investigation of Potential Health Effects

Overall

This report provides background and documentation of an ecologic study comparing several indices of health between the Gagetown Study Region and New Brunswick as a whole. The technical aspects of the data compilation and analysis are appropriate and the authors recognize the inherent limitations in the certainty that can be attained regarding possible adverse health effects from herbicides. The selection of health outcomes of interest is well reasoned and appropriate. The tables provide thorough documentation of the basis for the reported patterns. A number of concerns are noted below, however, regarding the presentation and interpretation of the data.

Major Issues of Concern

- 1) While acknowledging the limitations inherent in trying to study exposures that occurred 40 years ago, the severity of that limitation with regard to migration may be understated both in terms of implicating or exonerating the potential health effects of herbicides. The limited data on migration, which should be expanded, suggests rather rapid turnover due to the military presence in the area. More detail based on census information could be provided and some rough calculations of the fate of the population present at the time of exposure in regard to inclusion in the health outcome analysis. What proportion of those present in 1966-67 would be estimated to still be present in 1980? In 1990? Conversely, of the available population in the years in which health data are available, what proportion are likely to have been in the area when herbicides were sprayed?
- 2) The emphasis on stratification of results by calendar time period is not explained and may not be necessary. In examining the comparison of GSR to New Brunswick, it is unclear what can be learned from the calendar time specific results other than some sense of the random error inevitably generating inconsistencies. It could, I suppose, be argued that the earliest time period is most relevant given the migration issue but that point is not made. Given the severe imprecision and the long passage of time even up to the earliest period covered, summary estimates across the entire time period seem more informative for describing how GSR compares to New Brunswick. Without some basis for isolating time periods, the positive associations limited to specific 5-year intervals seem almost certain to reflect random error resulting from the small numbers of cases involved.
- 3) Imprecision is a pervasive concern, as acknowledged by the authors. In that regard, aggregation across all calendar time and across gender

seems warranted, with subdivision on those attributes a secondary rather than primary interest. If the overall result aggregated across time and gender were masking substantial effect modification, this may be worth noting but there is no strong prior reason to believe herbicide effects would differ by gender or time. To make that assessment, a p-value for interaction should be generated and using loose criteria, e.g., $p < 0.2$, some evaluation made. The use of the exclusion of the GSR from the 95% confidence interval of the New Brunswick results is somewhat unusual. It might be preferable to simply calculate and present a p-value comparing GSR to New Brunswick and let the reader judge what to make of it, providing some guidance. That's not to advocate for statistical testing, but a p-value of 0.2 might generate a very different sense of the strength of the findings as compared to a p-value of 0.8, and I suspect many of the highlighted findings would be more in the latter range. Even though the data are in the Appendices, Tables 5-8 should include the total number of cases of the condition of interest as a clear reminder to the reader of the imprecision.

- 4) The search for glimmers of association and highlighting them may be good public health policy, but inevitably, such glimmers will be found in scanning the data. The cited evidence for nasopharyngeal cancer and soft tissue sarcoma for men and women was not obvious in the tables, including notation based on isolated relative risks on the order of 1.2. Given the concerns noted above, one could ask the question of how capable these data are not just of implicating herbicides (would a positive association provide very strong evidence for a causal association?) but also of exonerating herbicides (how much reassurance of no true health effects is provided by a null finding?). It seems both are limited, the latter even more than the former. It might be useful to include some indices of health of a more global nature, not expected to be related to herbicide exposure, such as total mortality, mortality from cardiovascular disease, life expectancy, etc. to help provide context for the comparison of outcomes potentially related to herbicide exposure.
- 5) Since the study is predicated on comparing one geographic area to another, more descriptive information on the demography, sociology, and environment of GSR would be helpful. Any health-relevant feature of the region that distinguishes it from New Brunswick as a whole is a potential confounder of the comparison, including socioeconomic status, ethnicity, air or water pollution, etc.
- 6) The data discrepancies between the New Brunswick and Canadian Cancer Society results should be resolvable in principle. The differences in reported rates are not trivial, but if only the New Brunswick information is available for GSR (collected in a comparable manner), then there is no basis for comparing GSR incidence rates to Canadian Cancer Society

provincial rates. It seems odd that with a government-mandated study the cooperation of the health authorities would be so limited as to preclude a straightforward resolution of the issue.

- 7) Calculation of attributable risk seems like an inappropriate use of the data. Given that it depends in part on how much of the province is constituted by GSR, the results are not interpretable. It is not clear what the value would be of asking, "how much of the disease risk of a GSR resident is attributable to living in GSR?"