

## GUERNSEY TASK 3B CFB Gagetown Reports – RESPONSE TO PEER REVIEW COMMENTS

*Unless otherwise noted, all comments have been addressed.*

### *Responses to comments made*

Section	Major Comment	Response
<b>Recommendations Epi Study:</b>	discuss migration influences in more detail	p.7-8 text has been expanded on this issue.
	stratification of results by calendar time period is not explained and may not be necessary- provide more detail	included in introduction
	imprecision is a pervasive concern - aggregation seems warranted across time and gender - justify approach	rationale introduced in introduction
	no strong a priori reason to believe herbicide effects would differ by gender or time	Task 2A report strongly suggests this; rationale explained more fully in report
	use of exclusion of the GSR from the 95% confidence interval of NB results is somewhat unusual - test for differences comparing GSR to NB using p value = 0.2	approach has been modified; 95% CI for SIRs and SMRs were used to draw conclusions
	Tables 5-8 should include the total number of cases of the condition of interest as a clear reminder to the	number of cases included

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	reader of the imprecision	
	how capable are these data of implicating herbicides but also of exonerating herbicides?	text clarified to provide context for study- that it is an exploratory study and can only look at general health experience of a region that has been sprayed with herbicides compared to NB
	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, etc to provide context	not possible given difficulties of getting access to NB and timelines to get this done
	more descriptive information on the demography, sociology, and environment would be helpful	not enough time to conduct this comparison between GSR and NB
	data discrepancies between NB and CCS data should be resolvable	more recent data were obtained from NB and issues were resolved
	calculation of attributable risk seems like inappropriate use of the data - not clear the value of the comparison	this was a deliverable that was requested by PHAC; however the fact that we did not have true herbicide exposure information, the value is not as great compared to studies where one could truly evaluate the attributable risk of the exposure.
	definition of exposed population- discuss rationale - different potentially exposed groups - according to mechanism of exposure - military vs agricultural and forestry applications- occupational vs environmental	expanded introduction and methods sections to provide rationale
	relatively high population mobility- and those exposed during experimental spray period likely represent only a small fraction of the study population etc. - reduce the chance of detecting any increased risks attributable to CFB Gagetown	this issue is addressed in the discussion of study limitations

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	low statistical power- the numbers of cases were too small to draw any statistical conclusions - author recognizes point but makes a few inferences that go beyond the data	text has been modified to provide greater clarity to this issue and not overstate spurious findings
	maps- include a map that shows boundaries of study population and areas where experimental applications were conducted during 1966 and 1967- if not possible, add semi-quantitative/qualitative statements on extent of such uses	this map is available in Task 2 and Task 3A report
	add 95% CI for all SIRs and SMRs; add numbers of cases/deaths in tables 5-8	done
	recommendations section needs to be expanded -	this was done
	r1: assess feasibility of using data in enhanced cancer surveillance system to identify risk factors	added to recommendations section
	r2: reimplement enhanced cancer surveillance with major focus on residential, occupational and bystander exposure	added to recommendations section
	r3: assess feasibility of record linkage cohort study of CFB Gagetown military personnel and families	added to recommendations section
	specific comment on page 7 about size of study area	edited methods text to provide rationale
	comment on formula for calculation of variance that a statistician should be consulted on formula	we consulted with Dr. Pan Andreou who is an Assistant Professor of Biostatistics on this prior to conducting the analysis. He assisted us to find the appropriate reference.

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	comment on interpretation of direct vs indirect methods of standardization and interpretation of resulting information	text was revised from initial version of the report and data presented more clearly
	comment: include total number of cases; also include summary measure; clarify title of table	total number of cases added; summary measure were not done as explained in introduction, table heading clarified
	mortality tables should be clarified to all cancer causes not all causes	done
	numerous text comments on remaining pages	these comments were extraordinarily helpful; the report author accepted these comments and report text was revised accordingly
<b>Lit Review</b>	clarify discrepancies where review differs from IOM findings	these differences are already discussed in the document text; the discrepancies are now highlighted (bolded) in the tables included in the executive summary
	how much evidence is needed to justify classification	only one study is needed to justify limited or suggestive association provided the study is of high quality with sufficient sample size; for the higher categories (e.g. sufficient evidence of a positive association), consistency becomes more important
	clarify distinctions between agent classes and specific agents with more careful grouping or delineation of exposure category	edited text in exposure considerations section to clarify agent classes vs specific agents and clarified the ways this classification was created
<b>Specific</b>	S4 - p.1 clarify focus of review	added research question to first paragraph
	S5 - General - reduce confusion about Gagetown situation	text edited to be more explicit about situations where Gagetown is specifically studied
	S6 - p.13 clarify different populations and exposure	comment added in introduction about different cohorts exposed to

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	assessment methods	herbicides; rest of text edited to reflect this comment
	S7 – p.46 – 50 table labels are confusing	tables are grouped according to the section to which they correspond; they have been renumbered
	S8 – p. 57 different implications when synthesis refers to Gagetown? (similar to comment S5)	the literature review supporting the synthesis includes consideration for the chlorophenoxy herbicides that were listed in the Task 2A report only; there was no attempt to examine ALL chlorophenoxy herbicides; also revised text in synthesis statements to differentiate between Agent Orange solely and chlorophenoxy herbicides more generally.
	S9 – p.59 ranging into studies of environmental chemicals and leukemia seems too far afield..	paragraph edited to elucidate possible role of herbicides
	S10 – p.67 clarify at outset nature of research at CFB Gagetown (same as comment S5 and S8)	text was clarified that the focus was on adverse pregnancies and was the only study of the region
	S11 – p.87 conclusions based on only one study - seems rather fallible	as noted, only one good study is needed for this category of limited or suggestive evidence
	S12 – p.93 conclusion of limited or suggestive evidence for pentachlorophenol and nasopharyngeal cancer is not explained- clarify	point well taken, the text has been revised accordingly
	W1 – p.3 provide Task2A reference	added citation
	W2 – p.3 add citation	added citation
	W3 – p.6 provide total number of citations and studies identified from lit scan	total number of citations by source are provided in text on page 6
	W4 – p.7 suggest consistent use of phosphonates in table	revised text in table to be consistent

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	W5 – p.9 clarify cross sectional studies as being stronger than ecological studies	revised text
	W6 – p.10 clarify biomarkers are superior only if highly correlated with exposure	revised text
	W7 – p.12 clarify text about TCDD and confounding	edited text
	W8 – p.13 modify title of section to include oral cancers	revised title; point taken about suggested edit; problems with endnote prevent adding citations
	W9 – p.13 modify text to include small numbers	revision made
	W10 – p.13 – 15 edit text to ensure consistent use of nasal sinus vs nasopharyngeal cancer	revised text for clarity
	W11 – p.14 rewording - studies of Vietnam vets had inadequate statistical power	checked and inserted Vaughn reference; added edit.
	W12 – p.14 clarify indicator of AO exposure	corrected and revised text to indicate exposure was chlorophenoxy herbicides
	W13 - p.14 add Vaughan reference with clarification	checked reference and added
	W14 – p.15 add hyphen	revised
	W15 – p.16 reword sentence	revised
	W16 – p.16 helpful to define exposure categories	edited text to add exposure category; no smoking data available-clarified in last sentence of this paragraph
	W17 – p.17 suggest specific definition of dioxin exposure, edit text	revised text
	W18 – p.17 suggest rewording	revised text

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	W19 – p.18 clarify N-nitroso compounds are under suspicion for stomach cancer	revised text
	W20 – p.19 suggest changing level of evidence for stomach cancer	text revised
	W21 – p.20 reword to suggest statistical significance of trend test is more important	reviewed current text and made slight revisions
	W22 – p.20 suggest rewording	revised
	W23 – p.20 suggest rewording	revised
	W24 – p.21 suggest rewording	revised
	W25 – p.21 suggest changing level of evidence for colorectal cancer	revised
	W26 – p.22 adjust interpretation of lower 95% confidence limit	edited entire document for CL interpretation
	W27 – p.24 Wang suggest active work may reduce risk of lung cancer?	text revised slightly to clarify meaning
	W28 – p.25 suggest rewording	revised
	W29 – p.26 suggest rewording	revised
	W30 – p.26 suggest stating the number of observed deaths	text edited to add number of cases
	W31 – p.27 suggest rewording as per W22	revised

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	W32 – p.30 suggest adding citation for role of TCDD induction	added reference 154
	W33 – p.32 suggest rewording	revised
	W34 – p.33 suggest rewording	Added suggested clarification
	W35 – p.33 suggest adding a sentence to clarify issue of statistical power	edited; number of cases added
	W36 – p.35 suggest rewording	revised
	W37 – p.36 suggest rewording	revised
	W38 – p.38 suggest including statistical measures of dose response	revised
	W39 – p.39 include discussion of Hardell 2006	Hardell 2006 was moved to HCB section; the results do not directly pertain to chlorophenoxy herbicides
	W40 – p.40 exposure misspelled	revised
	W41 – p.42 Table 3B suggest rewording	revised
	W42 – p.45 check manuscript for consistent use of 'chlorophenoxy'	edited text
	W43 – p.46 consider adding discussion of kidney cancer to text	decided to eliminate this outcome due to sparseness of literature and in interest of time!
	W44 – p.51 suggest adding sentence to interpret findings from subgroups that used DEET	revised
	W45 – p. 51 – 52 clarify quasi-ecological	text clarified
	W46 – p. 52 suggest changing chlorophenoxy to wheat acreage; other clarifications	added and text revised
	W47 – p.52 clarify exposure categories with this OR	checked text; not clear what is being asked



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Section	Major Comment	Response
	W48 – p.54 suggest rewording	revised
	W49 – p.54 suggest rewording	revised
	W50 – p.54 avoid use of protective SIRs	revised
	W51 – p.55 suggest rewording; also suggest deleting last few words	revised
	W52 p. 56 consider changing evidence to limited/suggestive	changed level of evidence
	W53 – p.57 include text discussion of De Roos study	discussion of DeRoos study included in text
	W54 – p.60 did study include data based on internal comparison	not clear what is being asked
	W55 – p.61 suggest rewording	revised
	W56 - p.61 suggest rewording	revised
	W57 – p.57 simply state findings are consistent with IOM	revised
	W58 – p.62 sentence out of context	the text was edited to clarify
	W59 – p.63 suggest adding findings of Rull	added reference (155)
	W60 – p.65 clarify definition of fertility	text edited to clarify definition; definition now consistent with Wigle and others
	W61 – p.66 suggest rewording	revised text
	W62 – p.67 consider recent Chen et al reference;	checked reference; did not stratify into different herbicide compounds; also results for overall herbicide exposure were not

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		significant; decided not to add
	W63 – p.67 also other references could be checked. Listed here	scanned these references, some are dated; as stated in introduction, it was not possible to examine every reference; decision was made not to incorporate all of these. The Heacock article was relevant but the results were not significant. The Reynolds reference is included already. As noted in introduction, the author of this report made no attempt to examine every reference that has ever been published but to capture the current evidence regarding health effects of herbicides
	W64 – p.68 reword end of sentence	sentence reworded
	W65 – p.72 suggest rewording (CL issue)	reworded
	W66 – p.74 mention Semchuk study	Semchuk study included
	W67 – p.75 revise text to emphasize serum TCDD as indicator	text was revised after another examination of the article to highlight significance
	W68 – p.76 add sentence - no new studies	sentence added
	W69 – p.76 would be informative to know prevalence of serum TCDD	added this number to text
	W70 – p.81 suggest rewording	reworded
	W71 – p.81 suggest rewording	reworded
	W72 – p.84 suggest separate sentence	sentence added
	W73 – p.85 suggest including results of logistic regression analysis	text revised
	W74 – p.86 consider pooled analysis from DeRoos	included mention of DeRoos in text

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<b>Section</b>	<b>Major Comment</b>	<b>Response</b>
	W75 – p.90 suggest including RRs and not just p values	text modified
	W76 – p.90 note stat significant results from Demers	text modified, last sentence deleted
	W77 – p.91 limited evidence for association given results of Demers study	point well taken, synthesis statement has been modified to more accurately reflect findings
	W78 – p.92 define highest serum HCB category	details were refined about this study and the serum HCB value was added
	W79 – p.93 assoc btwn prostate cancer and HCB could reflect rel'p btwn HCB and prostate cancer progression	text revised to include this consideration
	W80 – p.100 suggest rewording	text revised