# I. Purpose and Objectives

The purpose of this review is to critically assess the recent scientific literature, using the US National Academy of Sciences Institute of Medicine[1] (IOM) evaluation criteria, in order to establish the current level of evidence associated with possible human health effects that may have resulted from exposure(s) to herbicides and any herbicide-related contaminants purportedly used at CFB Gagetown from 1952 to 2004. Key to this analysis is the question: "Are the herbicides known to have been applied at CFB Gagetown potentially capable of causing adverse health effects?". Of particular interest are the health effects associated with exposure to Agent Orange. Agent Orange was an herbicide mixture containing 2,4-D, 2,4,5-T, and its industrial contaminant, dioxin, and picloram and cacodylic acid. The recent literature (published since 2004) has received special emphasis in this review but pertinent studies, dating back to the 1980's, are included where appropriate. An entire synthesis was not feasible due to the vastness of the complete literature.

The primary sources for forming initial conclusions were the original published reports. Published, peer-reviewed scientific reviews of herbicides and health were accessed as secondary sources to assist identification of gaps in our analysis and to help to identify studies which we had not found through our systematic search of the published literature. An important source was a report series resulting from a ten-year, international study of evidence pertaining to Agent Orange and Health that focused on the health effects of exposure to Agent Orange; the most recent report was released in early 2005[1]. This series was overseen by the Institute of Medicine (IOM).

The scope of the IOM reviews included consideration of evidence associated with the spectrum of chlorophenoxy herbicides, because, as noted in the 2004 document[2], the body of evidence was sufficient for reaching conclusions about statistical associations between herbicide exposures and health outcomes. The lack of adequate data on

Vietnam veterans themselves, however, complicated consideration of specific health effects associated with exposure to Agent Orange. Hence, while the IOM Committees examined over 9000 studies related to the biochemistry, toxicity and epidemiology of herbicide exposures and human health, many of the epidemiological studies were of occupational cohorts that were involved in the manufacture of chlorophenoxy herbicides, in the application of pesticides, or of community populations who were exposed to the agents of interest. Therefore, the IOM report series was seen as providing important background information for the analysis of chlorophenoxy herbicide exposures, and not solely Agent Orange. Nevertheless, three years have passed since the release of the last report and it was important to assess recent scientific evidence. The IOM report series also did not include consideration of all the agents reportedly used at CFB Gagetown.

The prioritization scheme for assessment of evidence that has been developed by the Institute of Medicine [Sufficient Evidence of a Causal Relationship; Sufficient Evidence of an Association; Limited or Suggestive Evidence of an Association; Inadequate or Insufficient Evidence to Determine Whether an Association Exists; Limited or Suggestive Evidence of No Association; Sufficient Evidence of No Association] was adopted for this review. These categories build upon Hill's[3] well known epidemiological criteria for assessing causal associations in epidemiology and the International Association for Research on Cancer (IARC) Monograph Series scientific criteria[4] for assessment of evidence. These categories will be discussed in greater detail in the next section on Evaluating the Evidence. As will be discussed, robust, high-quality case-control or cohort epidemiological research findings are ranked more highly than descriptive or cross sectional epidemiological studies. The latter investigations are of interest, however, provided concerted efforts have been made by the study authors to identify specific herbicides and to reduce research bias from influencing the reported outcomes. In general, case series or case reports were excluded from this review in so much as they lacked proper control or comparison groups.

## II. History of Herbicide Spraying Practices at CFB Gagetown, NB

Herbicides have been used for many years at CFB Gagetown for the primary purpose of minimizing secondary growth of trees and bushes. This has ensured that the training area is maintained at an acceptable level to allow ongoing military exercises and training at the base. As noted in the CFB Gagetown Task2A report[5], chemical application of herbicides has been seen as the most effective means by which to achieve this objective. Almost all herbicides used at CFB Gagetown were for this purpose; in only a few instances, were experimental sprays applied at the base.

Annual herbicide applications began in 1956 and were applied throughout the base, usually between May and August of each year, and ending in 2004. The CFB Gagetown Task Force Task2A report[5] provides a comprehensive summary of all herbicides that were applied on the site, some occasionally, others repeatedly, based upon historical records and files, during this fifty year period. During 1966, 1967, and 1970, CFB Gagetown was host to three herbicide experimental trials designed to test the efficacy of different products and mixtures of active ingredients (AIs), including Agent Orange (Agent Orange is a mixture of 2,4-D, 2,4,5-T), Agent White (mixture of 2,4-D and picloram) and Agent Purple (mixture of 2,4-D and 2,4,5-T).

Herbicides that were used at CFB Gagetown are provided in Table 1. The Task2A report, which provided a detailed summary of the nature, amounts and dates of applications of herbicide agents used at CFB Gagetown, served as a useful document to verify this list. This document was peer reviewed. The authors observe that, in the cases where information regarding product application rates could be determined, the actual application rates of products appear to fall within the recommended application rates; this provides some guidance about the level of exposures that occurred there. They also report that actual application rates were often lower than the recommended dosage rates. The authors also determined that herbicide applications at the Base were regulated by the Federal and Provincial governments and by DND (base and NDHQ)

policies and science of the day. Also, as noted and documented in the report, most of the herbicides used at the Base for vegetation control, with exception of the agents tested in the experimental trials, have been commonly used across Canada for the past fifty years.

**Table 1: List of herbicides and industrial impurities used at CFB Gagetown between 1956 and 2004**

**Agents**

2,4-D
2,4-DP (dichloroprop)
2,4,5-T (2,4,5-Trichlorophenoxyacetic acid)
2-(2,4,5-T) Trichlorophenoxy propionic acid
Ammonium sulfamate
Bromacil
Dicamba
4,6-dinitro-o-sec-butylphenol (Dinitro)
1,1'-ethylene-2,2'-dipyridinium dibromide (Diquat)
Diuron
Fosamine ammonium
Glyphosate
Hexachloroacetone
Hexazinone
Imazapyr
Mecoprop
Paraquat (1,1'-dimethyl-4,4'-dipyridinium dibromide)
Pentachlorophenol
Picloram
Sodium cacodylate (Cacodylic acid)
Sodium trichloroacetate (Trichloroacetic acid)
Tebuthiuron
Triclopyr
2,3,6-Trichlorobenzoic acid

**Potential industrial impurities associated with CFB Gagetown agents**

Polychlorinated dibenzo-p-dioxins & furans
Tetrachlorobenzene
Pentachlorobenzene
Hexachlorobenzene

# III. Examining the Evidence

Identification and classification of herbicide categories

The list of CFB Gagetown herbicides identified in Table 1 comprises a spectrum of agents with diverse physical and chemical properties and acute and chronic toxicological activity[6]. In order to more appropriately group these agents into useful categories, a US Environment Protection Agency pesticides classification scheme[7] which assigns individual agents to categories according to toxicity, chemical structure and activity, was applied. A summary of the herbicide agents, their commercial names, the pesticide class to which they belong, the WHO hazard level[8], and an indication of whether they were included in the IOM analysis is presented in Table 2.

Finding relevant publications

A combined keyword search of PubMed, EMBASE, CISTI, Toxline and other relevant bibliographic electronic databases was conducted using the chemical and commercial names and agent classifications of all the CFB Gagetown herbicides, as identified in Table 2. Citations, including titles, abstracts, and the main text were scanned to identify epidemiological, exposure assessment and human biomonitoring studies and to exclude the large number of laboratory and field biology studies of herbicides that were uncovered.

As a second level scan, the following terms were added as single search terms in combination with each herbicide term as single, separate searches: *(human health, mortality, morbidity, cancer, diabetes, congenital anomalies, reproductive outcomes, neurology, Parkinson's Disease, epidemiology, exposure assessment).* Studies that did not assess human health outcomes or human biological monitoring were excluded and not reviewed further.

Thirdly, those publications in which exposure to pesticides was identified generically (e.g. studies which asked study participants if they had ever been exposed to 'pesticides' but without identifying or probing for which agents) were excluded. Inclusion of such

generic studies would have been uninformative for the purposes of this review, given the varied toxicity of the range of herbicides and pesticides generally.

Search Results

The MEDLINE search dated back to 1996; the rationale was that this would allow for identification of relevant publications for the past ten years. As identified in the original request for proposal from the Public Health Agency of Canada, emphasis was placed on the most recent two years. 628 new citations were identified for 2004-2006. These abstracts were scanned by two members of the research team in an independent, blinded review and 22 were found to be highly relevant. Due to the smaller size of TOXLINE, this search encompassed the entire years for the database (1977-2006) but only yielded ten references. The EMBASE search focused on recent literature (2004-2006) and provided 12 additional references. Two other internet sources were examined as potential sources of literature. The IRIS website provides a toxicological profile of each chemical but does not specifically identify relevant human health studies. A hand search for frequently-referenced citations were also obtained and independently reviewed to determine if these contained additional evidence pertinent to the review. Other key references from earlier years were selected and included in this review in order to provide overall context to the review of evidence.

Comment on Cochrane Review Process

The search methodology criteria for selecting studies to be included in the literature review was initially based upon an assessment of the Cochrane Collaboration of Methodology Reviews strategies[9] to determine if a particular approach might be applied to this particular review. The emphasis on evidence from clinical trials was deemed not exceedingly useful for this examination of primarily observational epidemiological studies. The IOM report's authors similarly concluded it would be inappropriate to use quantitative techniques, such as meta-analysis, to combine individual study results into a single summary measure of statistical association. The many differences between studies related to definitions of exposure, health outcomes,

**Table 2: List of CFB Gagetown agents by Herbicide Class, Commercial Names and WHO Hazard Level**

| IOM review | Agent | Herbicide Class | Commercial names | WHO Hazard Level[10] |
|---|---|---|---|---|
| | Sodium trichloroacetate (Trichloroacetic acid) – TCA [CAS: 76-03-9] | Aliphatic acids | | II: moderately hazardous |
| ▪ | Sodium cacodylate (Cacodylic acid), {Dimethylarsinic acid) [CAS: 75-60-5] | Arsenical | Bolate, Bolls-Eye, Bophy, Dilie, Kack, Rad-E-Cate 25, Salvo, Ansar 138, Arsan, Broadside, Check-Mate, Cotton Aide HC, Dilic, Moncide, Montar, Phytar, Silvisar,Sylvicor | III: slightly hazardous |
| | Dicamba [CAS: 1918-00-9] | Benzoic acid compound ( Chlorophenoxy) | Banvel, Banfel, Banvel CST, Banvel D, Banvel XG, Dianat, Dicazin, Fallowmaster, Mediben, Metambane, Tracker, and Trooper | III: slightly hazardous |
| ▪ | 2,4-dichlorophenoxyacetic acid [CAS: 94-75-7] | Chlorophenoxy | 2,4-D, Aqua-Kleen, Barrage, Lawn-Keep, Malerbane, Planotox, Plantgard, Savage, Salvo, Weedone, and Weedtrine-II | II moderately hazardous |
| | 2,4-DP (dichlorprop) [CAS: 7547-66-2] | Chlorophenoxy | Butoxone, Butyrac, Butirex, Embutone, Embutox, and Venceweed | III: slightly hazardous |
| | Mecoprop (MCPP) [CAS: 7085-19-0] | Chlorophenoxy | MCPP, Kilprop, Mecopar, Triester-II, Mecomin-D | III: slightly hazardous |
| ▪ | 2,4,5-T (2,4,5-Trichlorophenoxyacetic acid) [CAS: 93-76-5} | Chlorophenoxy | 2,4,5-T | Discontinued for use as pesticides; subject to prior informed consent procedure |
| | 2-(2,4,5-T) Trichlorophenoxy propionic acid | Chlorophenoxy | 2,4,5-TP, Fenoprop | |
| | 2,3,6-Trichlorobenzoic acid (2,3,6 TBA) [CAS: 50-31-7] | Chlorophenoxy | TCBA, Tribac, 2,3,6-TBA | III: slightly hazardous |
| | Triclopyr [CAS: 55335-06-3] | Chloropyridinyl (pyridine) | Garlon, Access, Crossbow, ET, Grazon, PathFinder, Redeem, Rely, Remedy, and Turflon | III: slightly hazardous |
| | 2,3,7,8-tetrachlorodibenzo-p-dioxin | Dioxin (Chlorophenoxy) | Dioxin | Contaminant of 2,4,5T |
| | 1,1'-ethylene-2,2'-dipyridinium dibromide (Diquat dibromide) [CAS: 2764-72-9] | Dipyridines | Reglone, Aquacide, Dextrone, Aquakill, Diquat, Reglone, Reglox, Reward, Tag, Torpedo, Vegetrole, Weedtrine-Dt | II: moderately hazardous |
| | Paraquat (1,1'-dimethyl-4,4'-dipyridinium dibromide) [CAS: 1910-42-5] | Dipyridines | Cekuquat, Crisquat, Dextrone, Esgram, Goldquat, Gramocil, Gramonol, Gramoxone, Cyclone, Dexuron, Herbaxone, Ortho Weed, Spot Killer, Sweep | II: moderately hazardous |

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| IOM review | Agent | Herbicide Class | Commercial names | WHO Hazard Level[10] |
|---|---|---|---|---|
| | Hexazinone (thiocarbamates) [CAS: 51235-04-2] | Dithiocarbamate herbicide (triazine) | DPX 3674, Pronone, Velpar | III: slightly hazardous |
| | Hexachloroacetone {CAS: 116-16-5] | Halogenated aliphatic herbicide | | No longer considered to be in use; no toxicity details |
| | Imazapyr [CAS: 1071-83-6] | Nicotinic acid isopropylamine | Contour, Hammer, Overtop, Passport, Pivot, Pursuit, Pursuit Plus, and Resolve | Unlikely to present acute hazard in normal use |
| | 4,6-dinitro-o-sec-butylphenol | Nitrophenolic and nitrocresolic herbicides | Dinitro | |
| | Hexachlorobenzene [CAS: 118-74-] | Organochlorine | hexachlorobenzene is a manufacturing impurity associated with the production of picloram. | I(a) extremely hazardous[11] |
| | Glyphosate [CAS: 1071-83-6] | Phosphonate | Roundup, Glyfonox, Gallup, Landmaster, Pondmaster, Ranger, Rodeo, and Touchdown | Unlikely to present acute hazard in normal use |
| | Pentachlorophenol [CAS: 87-86-5] | Pentachlorophenol | Chlorophen, PCP, Penchlorol, Penta, Pentcon, Penwar, Sinituho | I(b) highly hazardous |
| | Fosamine ammonium [CAS: 25954-13-6] | Phosphonate | Krenite | Unlikely to present acute hazard in normal use |
| | Picloram [CAS: 1918-02-1] | Picolinic acid | Tordon, Pinene, Access, Grazon, Pathway | Unlikely to present acute hazard in normal use |
| | Tebuthiuron [CAS: 34014-18-1] | Urea derivatives | Brush, Bullet, Bushwacker, EL-103, Graslan, Herbec, Herbic, Perflan, Reclaim, Scrubmaster, Spike, Sprakil, and Tebusan | III: slightly hazardous |
| | Diuron [CAS: 330-54-1] | Urea derivatives | Cekiuron, Crisuron, Dailon, Direx, Diurex, Diuron, Karmex, Unidon, Vonduron, Diater, Di-on | Unlikely to present acute hazard in normal use |
| | Ammonium sulfamate [CAS: 7773-06-0] | Sulfamate | | Unlikely to present acute hazard in normal use |
| | Bromacil [CAS: 314-40-9] | Uracils | Borea, Bromax 4G, Bromax 4L, Borocil, Cynogan, Hyvar X, Hyvar XL, Isocil, Krovar, Rout, Uragan, Urox B, and Urox HX | Unlikely to present acute hazard in normal use |

2 Tordon 101: 2,4-D and Picloram dioxin (for 2,4-D); Hexachlorobenzene (from Picloram)

the criteria for identifying populations, correction for confounding factors, and degree of detail in the reporting of results[1] form the basis for this conclusion.

To ensure the completeness of the literature review, the Institute of Medicine *Veterans and Agent Orange 2004*[1] report and a recent Public Health Agency of Canada review [12] were examined for pertinent references. In addition, reference lists from reviewed articles were crosschecked against search results. Only new, significant studies are presented as separate tables in this report which include details of study populations and key findings. All articles were entered into Endnote. The final Endnote Library contained 260 references (see Appendix 1).

Evaluating the Evidence

The IOM prioritization scheme for ranking of evidence [Sufficient Evidence of a Causal Relationship; Sufficient Evidence of an Association; Limited or Suggestive Evidence of an Association; Inadequate or Insufficient Evidence to Determine Whether an Association Exists] was adopted for assessing evidence related to each agent group. Details of this approach may be found in the IOM Agent Orange report[1] and other IOM documents[13]. These categories build upon the Hill's criteria for assessing causal associations in epidemiology and the IARC classification rankings to assess cancer risk and rank robust, high-quality analytical epidemiological research findings more highly than descriptive and cross sectional studies, or case series and case reports.

In essence, the strength of each investigation was assessed using Hills criteria (temporality, strength (based on strength of association, usually determined by the size of the relative risk or odds ratio and supported by a statistically significant finding), dose-response, coherence, consistency, biological plausibility, specificity). Well-conducted cohort studies and case-control studies were viewed as having the greatest ability to identify an association between herbicide exposure and disease. Cross sectional studies are potentially useful to elucidate exposure disease associations if individual level information has been collected and they include relevant exposure and health outcome

[1] IOM report, see page 25.

information. Ecological studies were also included in the review but were deemed to have less capability to assess the association. Adequate sample size, potential for bias, confounding and disease misclassification were examined in each study. In many instances, the number of study subjects was small and, in these studies, this created statistically unstable estimates of risk with wide confidence intervals in the assessment between exposure and disease. A 95% confidence interval provides the range in which the investigators are 95% confident that the true value of the risk estimate lies within. If this range spans 1.0, the null value, then one generally concludes that the estimate of risk is not statistically elevated or decreased.

As previously noted, studies that did not specifically examine the herbicides of interest were largely excluded from this review. Articles that analyzed relevant classes of herbicides were included. Exposure assessment techniques were evaluated for ability to examine individual exposure to specific herbicides, include latency period between exposure and diagnosis in analysis, efforts to minimize recall bias, and minimize exposure misclassification. Studies that employed biomarkers known to be highly correlated with the exposure indicators of interest or which used carefully documented exposure records were regarded to have higher exposure validity than those that employed unsubstantiated measures of exposure (e.g. self reported history of exposure).

Consideration of classification of disease outcome

To help focus the descriptive epidemiological study, each study was examined for how the health outcome(s) was classified. In some investigations, only clinical symptoms were studied; this is more common, for example, in studies of respiratory diseases. The challenge of investigations of clinical symptoms is that they are not diagnoses of disease. The international consensus standard for classifying and coding clinical outcomes is the World Health Organization International Classification of Diseases (ICD). This is reviewed periodically and updated as new diseases are discovered or as disease etiologies are explained. When a person is diagnosed with a disease, this information is recorded in medical records, hospital records, or surveillance surveys or, for deaths, on a death certificate. For most diseases, a confirmed diagnosis, supported by clinical and laboratory documentation, is the best means for tracking patterns of health outcomes.

Etiological investigations, thus, are strengthened if they include validated cases of disease or validated prognostic indicators.

Cancer is unique in the quality of information we have about this class and this has largely been driven by the significant public concern for this disease. In Canada and in many countries, if someone is diagnosed with cancer, this incident must be reported to the provincial health authorities. In this way, cancer is a 'notifiable' disease. This triggers an enhanced reporting system which ensures that proper information about the case, including the ICD code and any pathological diagnostic information, is recorded in an anonymous, unique population-based database that is separate from the regular health system database. Care is taken to ensure that the report is either the result of an initial diagnosis (primary site) or a possible metastatic tumour resulting from another primary site. The purpose of this reporting system is to help to identify better ways to prevent cancer and to provide improved cancer care.

This system is in contrast with other disease diagnoses. For most diagnoses, the only record that indicates when a person has been diagnosed with a disease is when the physician or hospital submits a claim to the provincial health authorities to be paid for services related to the care of the patient. There is often little data about whether the claim is for an initial diagnosis or for a follow-up visit. The net impact of this situation is that better epidemiological surveillance information exists for cancer than for most other diseases. Congenital anomalies and other birth outcomes are the exception to this rule, with improved perinatal outcomes surveillance systems being implemented. It is easier to accurately describe a community's experience with a disease with such systematic disease surveillance systems.

Exposure considerations

This review examines the evidence associated with exposure to major herbicide categories separately. In reality, most pesticide applicators and others working with, or exposed to herbicides, are exposed to a combination of compounds over their lifetime. The exceptions are those industrial settings, where, in highly controlled conditions, employees are exposed to a single agent class only. The second issue to keep in mind is

that when these herbicides are manufactured in industry, there is the possibility that, in addition to the primary products of interest, impurities will be produced in small quantities that are included as part of the final product that goes to market. In this manner, industrial by-products, such as various dioxins and furans, may have been present in industrial grade pentachlorophenol, 2,4-D and 2,4,5-T, especially in earlier years. In more recent years, efforts were made to remove this by-product from the commercial grade product. Exposure to these compounds in the early years may have caused the observed health effects identified by the researchers, and in this way, are epidemiological 'confounders'. This and other technical terms are defined in the Glossary (Appendix 2).

Presentation of Findings

The results of this review are presented according to major herbicide class, as provided in Table 2. Chlorophenoxy herbicides have been studied to far greater degree than any other class of herbicide; the other relevant categories for which there is some information include: dipyridines, phosphonates, pentachlorophenol and hexachlorobenzene. For most of the herbicides listed in Table 2, very few or no epidemiological studies have been published about health impacts associated with exposure. These herbicides are not discussed in this document due to the lack of evidence. The order in which the health outcomes are presented within each section reflects the order in which they appear in the International Classification of Diseases, 9$^{th}$ revision.

# IV. Principal Findings

## Section 1. CFB Gagetown Herbicide Compounds included within the Institute of Medicine Review

This initial section presents findings from our review of the current literature pertaining to compounds that were covered within the US Institute of Medicine review of Agent Orange and associated herbicides. The conclusions of the IOM 2004 Committee are presented in the text following discussion of each disease. This is followed by a synthesis statement which incorporates the findings from more recent studies upon which the conclusions of the current reviewer are based. The second section of this part of the report will follow and will present the summary of our review of the epidemiological evidence for the other herbicide classes.

## A. Chlorophenoxy Herbicides

### 1. Cancers

a *Oral, Nasal and Nasopharygeal cancers*

Nasal sinus cancers are anatomically distinct from nasopharygeal cancers and have distinct risk factors. The occurrence of nasopharyngeal cancers is very rare (less than 1 per 100,000 person-years)[14] which make investigations of the etiology of this disease more difficult. Nevertheless, associations between exposures to chlorophenoxy and chlorophenolic compounds and the development of nasal and nasopharyngeal cancers have been suggested by researchers since the 1960's[15,16]. Scientists have theorized that these cancers arise from inhalation and deposition of large droplets or particles from agricultural or forestry spraying or from wood dust that has been impregnated with these compounds resulting from wood preservative applications. In a frequently cited case-control study in Sweden, a suggestive association between nasal sinus and nasopharyngeal cancer and chlorophenoxy herbicide exposure (grouped together) was found (OR 2.1; 95% CI: 0.9-4.9)[15] though the confidence interval included the null value and the analysis did not adjust for smoking status. The most widely used chlorophenoxy herbicide in Sweden at that time was MCPA[17].

In a study of 1341 herbicide applicators in the Netherlands[18], no fatal cases of pharyngeal or buccal cancers were observed in the exposed cohort which prevented calculation of an SMR and highlighting the challenges of studies with small numbers of health outcomes. Herbicides to which the applicators in this study were exposed included paraquat, mecoprop, glyphosate, diuron, diquat, and 2,4-D among others. Investigators, in a recent US study, adjusted for smoking status in their analysis and observed significant associations for sinusoidal cancer [OR 5.9; 95% CI: 1.5-24.0] and a non-significant trend for nasopharyngeal cancer [OR 1.8; 95% CI: 0.2-15.0] in relation to exposure to chlorophenoxy compounds[19]. The researchers attributed the increased risk to exposure to 2.4.5-T and concluded, on the basis of the results of other covariates in the study, that the risk factor profiles for the two different cancer types were different. This is supported by results from the IARC cohort study[20], which followed 21,863 male and female workers in 36 cohorts exposed to chlorophenoxy herbicides, chlorophenols, and dioxins in 12 countries, and found a similar and slightly elevated but non-significant nasopharyngeal mortality risk for those workers and applicators who were exposed to any chlorophenoxy herbicide (SMR 1.6, 95% CI: 0.33-4.66) but this report was based upon only three cases. Nasal sinus cancer and nasopharyngeal cancers were not included on the list of cancer types in a 2005 report of cancer incidence from the US Agricultural Health study[21], involving 89,678 private and commercial pesticide applicators and their spouses.

Studies which have examined the specific experience of Vietnam Veterans suggest that there is no association (either positive or negative) between exposure to the Agent Orange chlorophenoxy herbicides and nasal sinus cancer. A report from the Selected Cancers Study[22], which was a population-based, case-control study to examine associations between Agent Orange exposure, military service in Vietnam, and several cancers had inadequate statistical power to determine if exposure to Agent Orange was associated with nasal cancer risk. Nasal cancer was not found to be associated with self-reported prior exposure to chlorophenoxy herbicides (nasal cancer: OR=1.2; 95% CI: 0.4-3.3). A strong relationship was observed, however, for cigarette smoking in this study. This is consistent with a US study by Vaughan, et al.[9] which showed that

nasopharyngeal cancer was strongly associated with smoking. Those who had reported living or working on a farm were found to be at reduced risk for developing nasal sinus cancer. The authors identified significant challenges in obtaining proper control subjects for this study but chose not to use proxy-derived data on control subjects. They also acknowledged the small number of nasal sinus cancer cases and the paucity of experience with certain exposures as limitations to their findings.

In a more recent study, Ahktar et al[23] examined cancers of the buccal cavity as part of their investigation of health outcomes in Operation Ranch Hand veterans who were involved in the aerial spraying of herbicides. This study included measurement of dioxin levels in serum (in 1987) and a physical examination. No differences between the observed and expected incidence of buccal cavity cancer in either the Ranch Hand veterans or in a comparison group who did not spray herbicides were found. This study only involved six exposed cases which imposed limitations on the analysis. No other new studies (since 2004) of nasal or nasopharyngeal cancers and chlorophenoxy herbicide exposures were identified in our search of the literature.

Conclusions of IOM 2004 Report:

The committee concluded on the basis of the currently available epidemiological evidence that there is still inadequate or insufficient information to determine an association between exposure to 2,4-D. 2,4,5-T, TCDD, picloram or cacodylic acid and oral, nasal, and pharyngeal cancers.

Synthesis of Agent Orange and other chlorophenoxy herbicide exposures and oral, nasal and pharyngeal cancers

The few recent studies that have been published suggest that the environmental etiologies of nasal cancer and nasopharyngeal cancer are different. Whereas nasal cancer appears to have a stronger association with smoking history, a chlorophenoxy herbicide exposure history might more possibly increase the risk for the development of nasopharygeal cancer. Because this disease is so rare, it has been extremely difficult

for scientists to gather enough information about this disease to explore these hypotheses. For the present, there remains inadequate or insufficient evidence of an association between these agents and oral, nasal and pharyngeal cancers and further research is needed.

b Laryngeal cancer

Laryngeal cancers are also rare and are almost exclusively squamous cell carcinomas[14]. Both tobacco and alcohol remain as the best established risk factors for this disease. An early study by Wynder[24] noted that laryngeal cancer cases were more likely to report having worked in a woodworking occupation than matched controls. This was counter to other studies[25,26] that found no associations. Other environmental agents that have been implicated are nickel exposure, fiberglass insulation production, alcohol manufacturing and diethyl sulphate[14]. A multi-centre case-control study[27] of occupational exposures and the risk of laryngeal cancer, published in 2006, was conducted in four European countries and a significant association with exposure to chlorinated solvents (OR = 2.18, 95% CI: 1.03-4.61), as a general category, was observed. Wood dust exposure was inversely associated with laryngeal cancer in this study. Chlorophenoxy herbicides were not specifically mentioned in this study.

Fingerhut[28] conducted a historical cohort study of 5172 US male workers who were exposed to 2,3,7,8-TCDD (dioxin) between 1942 and 1984. Because laryngeal cancer is a rare disease, the probability of occurrence is low and the cohort size was likely not sufficient to develop stable estimates of incidence in the cohort. The researchers did report an SMR of 2.7 for those who had more than one year of occupational exposure but this finding was not significant due to the broad confidence intervals (95% CI: 0.6-7.8) that span the null value of 1.0. Occupational exposure was documented in this study by reviewing job descriptions and by measuring TCDD in blood serum. The Saracci et al[29] report on the IARC cohort study also indicated a non-significant mortality risk of 1.5 (95% CI: 0.6-2.9), involving small numbers of cases. In the larger multinational IARC[20] study in 1997, involving 26,976 male and female workers, an increased risk of laryngeal cancer mortality (RR= 1.62; 95% CI: 1.0-2.5) was found in

workers exposed to TCDD compared to national rates. When this analysis was stratified by TCDD or higher chlorinated dioxin versus no exposure to these agents, a slight dose-response effect was observed (SMR= 1.72 vs SMR = 1.22 for low level exposures).

Conclusions of IOM 2004 Report:

On the basis of the epidemiological evidence reviewed from the current literature and in previous Veterans and Agent Orange reports, the committee concluded that there is limited or suggestive evidence of an association between exposure to at least one compound of interest (2,4-D. 2,4,5-T, TCDD, picloram or cacodylic acid) and laryngeal cancer.

Synthesis of Agent Orange and other chlorophenoxy herbicide exposures and laryngeal cancers

This reviewer agrees that there is limited or suggestive evidence of an association between exposure to at least one of the Agent Orange compounds of interest (especially dioxin) and laryngeal cancer. This is supported most strongly by evidence provided by the multinational International Agency for Research on Cancer study, discussed above. No recent studies were identified that have examined this particular outcome and chlorophenoxy herbicides.

c Stomach cancer

The US National Cancer Institute Fingerhut study[28], discussed previously, showed no significant overall association between dioxin exposure and stomach cancer among US workers. In the highly exposed subcohort with greater than 20 years of latency in which subjects had greater than one year of exposure, the standardized mortality ratio (SMR) was not significantly higher for stomach cancer (1.38; 95% CI: 0.38-3.53). The 1997 IARC multinational cohort study[20] revealed a non-significant risk for stomach mortality (overall SMR= 0.88; 95% CI: 0.69-1.11) in relation to exposure to dioxin exposure. An ecological study of cancer mortality in four US northern wheat producing states by Schreinemachers[30] found no association between wheat acreage (as

a surrogate for chlorophenoxy exposure) and stomach cancer mortality. When the data were stratified by wheat acreage per county, an elevated mortality risk was observed for women less than 65 years of age living in counties with greater than 111,000 acres (SRR= 2.39; 95% CI: 1.48-3.88) but no significant associations were observed for women of 65 years of age or older. No significant associations were observed for males in this study. Information on smoking, alcohol consumption, and ethnic background was not available for the international studies nor was information about migration rates or when or how exposures might have occurred.

Lee et al[31] reported a population-based case control study of men and women in Eastern Nebraska in which individual classes of insecticides and herbicides were examined as risk factors. There was no association with self-reported 'ever use of herbicides' (OR= 0.9; 95% CI: 0.5-1.4) and stomach cancer. In an agent class-specific analysis, exposure to dicamba (benzoic acid) was reported to be associated with a reduced risk of stomach cancer (OR= 0.3; 95% CI: 0.1-0.8) though this finding only involved 4 cases. It is important to note that N-nitroso compounds are under suspicion as potential causes of stomach cancer; these agents are commonly found in agricultural environments as a by-product of fertilizer application and from manure runoff in rural groundwater drinking water sources. Non-farmers were used as the reference category in all analyses. The authors propose that this suggests a non-causal interpretation due to lack of biological plausibility but may actually be the result of low prevalence of smoking, alcohol use and associated risk factors in farming populations. Of special interest in this study was the manner in which agents were classified by their capability to form N-nitroso compounds. Nevertheless, no associations were observed for this grouping of agents and stomach cancer. Wang et al.[32] reported a 2002 historical cohort study of female Farm Bureau members who were also farm residents from New York State, and noted significantly lower cancer rates for all cancers combined compared to rural, non-farm female residents. The standardized incidence ratio for stomach cancer was 0.43 (95% CI: 0.05-1.88) and was not significant. This study was limited by the lack of individual data on cancer risk factors, including smoking and alcohol use, and by the lack of information about specific pesticide exposures.

These investigations contradict an earlier Swedish study of railway workers[33] that found an increased risk of stomach cancer among workers exposed to chlorophenoxy acids. In a 2004 report by Ahktar[23] of US Air Force Vietnam Veterans, the incidence digestive system cancers were found to be significantly lower in this group compared to the general US population.

Conclusions of IOM 2004 Report:

The IOM concluded that on the basis of previous IOM Committee assessments and on the basis of its current evaluation of epidemiologic evidence, that there is still limited or suggestive evidence of ***no*** association between exposure in the compounds of interest and gastrointestinal cancers. The Committee did not draw separate conclusions on specific gastrointestinal cancer types (e.g. stomach, colon, rectum).

Synthesis of Agent Orange and other chlorophenoxy herbicide exposures and stomach cancer

This reviewer believes that the current evidence indicates that there is inadequate or insufficient evidence to determine if an association between exposure to at least one of the Agent Orange compounds of interest or other chlorophenoxy herbicides and stomach cancer exists, based upon evidence provided in the earlier studies as well as the more recent studies identified above. Most of the studies published to date are based upon agricultural producers with comparisons with the general underlying populations and with limited capacity to control for lifestyle, dietary and activity levels or other modifiable risk factors. More research involving carefully collected information about individual exposure and risk factors are needed, especially given that a few studies have found increased risks for stomach cancer associated with exposure.

d Colorectal cancer

A recent study of male US Air Force Veterans by Akhtar et al[23] found significantly lower incidence rates for digestive system cancers (SIR=0.61; 95% CI: 0.36-0.96) in those who were exposed to Ranch Hand compared to the US national incidence rates

for this cancer site, whereas, for a comparison non-spraying veterans cohort, no such observation was noted. The study did not stratify by digestive system cancer types. A similar, statistically significant reduced association was observed for mortality from digestive system cancers. Other studies have reported varying results in risk of colon cancer resulting from chlorophenoxy herbicide exposure. A study by Hoar and co-workers observed an increased risk of colon cancer associated with chlorophenoxy herbicide use (OR= 1.9) but no dose-response relationship was found[34]. In contrast, the IARC 12-country study[20] reported no increased risk of colon cancer death among the subgroup of chlorophenoxy/chlorophenol manufacturing workers exposed to TCDD and related dioxins (SMR=1.0; 95% CI: 0.75-1.31) or the unexposed subgroup (SMR=1.16; 95% CI: 0.80-1.63). Rectal cancer mortality was also not significantly elevated in the exposed group (SMR=1.32; 95% CI: 0.88-1.89). Fifteen-twenty years after the industrial explosion, rectal cancer mortality was found to be two fold higher in exposed Seveso residents[35] but this was based upon 4 observed and 2 expected cases and was not significant (RR=2.0; 95% CI: 0.7-5.5). No significant associations were observed for colon cancer in this study. The Seveso studies were also limited due to the fact that they were based upon an analysis of fatal cancers and could not adjust for potential confounders, such as diet and smoking.

A recent analysis[36] of dicamba exposure in the US Agricultural Health Study found suggestive trends of increasing risk for colon cancer for both lifetime exposure days and intensity-weighted lifetime days when the referent group comprised applicators with low levels of exposure. However, only relative risks for the highest exposure category were significant (lifetime days RR = 3.29; 95% CI: 1.40–7.73; *p*-trend = 0.02; intensity-weighted lifetime days RR = 2.57; 95% CI: 1.28–5.17; *p*-trend = 0.002). These increased risks were not observed when the referent group was comprised of applicators that had never used dicamba.

A hospital-based case-control study in Spain of colorectal cancer risk by Howsam et al[37], used interviews to capture dietary history and other lifestyle factor information and blood serum to measure levels of organochlorine compounds as an indicator of body burden. The investigators also looked at mutations in the *K-ras* and *p53* genes. This

investigation did not specifically examine chlorophenoxy herbicides. Statistically significant positive associations were observed between colorectal cancer risk and medium levels of DDE, detectable levels of PCB-28, high levels of PCB-118 (both mono-ortho PCBs) and non significant but elevated risks for medium levels of DDT, HCB, and HCH. Mutations conferred additional risk. They suggest that chemical-specific analyses, which take into account molecular structure, are needed to understand mechanisms of organochlorine exposures and colorectal cancer risk. Validation studies are needed, however, to assess the meaningfulness of current body burden of organochlorine levels as indicators of lifetime exposures to chlorophenoxy herbicides.

Significantly lower cancer rates for colorectal cancer were reported in a 2002 historical cohort study of female Farm Bureau members, by Wang et al.[32]. Subjects who were also farm residents from New York State were compared to rural, non-farm female residents (OR=0.65; 95% CI: 0.45-0.90). This is further supported by recent findings from the US Agricultural Health Study[38] which reported inverse but non-significant cancer incidence ratios for both colon and rectal cancer in male and female private pesticide applicators compared to respective underlying state populations. Slightly elevated, but non-significant, rates were observed in the commercial applicators in this study, however. The lower prevalence of smoking and higher levels of physical activity observed in farmers were offered as reasons for the suggested protective effects that were found.

Conclusions of IOM 2004 Report:

The IOM concluded that on the basis of previous IOM Committee assessments and on the basis of its current evaluation of epidemiologic evidence, that there is still limited or suggestive evidence of ***no*** association between exposure in the Agent Orange compounds of interest and gastrointestinal cancers.

Synthesis of Agent Orange and other chlorophenoxy herbicide exposures and colorectal cancers

Based upon recent evidence, this reviewer concludes that that there is inadequate or insufficient evidence to determine if an association exists between colorectal cancer and chlorophenoxy herbicide exposure. The IOM Committee did no assess evidence for specific GI cancers and the studies cited in this review revealed odds ratios with point estimates ranging from 0.61 to 3.29. Additionally, the findings reported by Howsam et al[37] raises the question of whether there is a need for more detailed chemical-specific analyses in understanding mechanisms of disease and chlorinated herbicide exposures. This is further supported by the increased risks relating to dicamba exposure associated with colon cancer by Samanic et al.[36] based on data from the US Agricultural Health Study. Many of the other studies which have indicated either no association or an inverse association (i.e. high levels of exposure are associated with a reduced risk for disease) have relied upon general population rates for comparison and have not incorporated consideration for individual dietary, lifestyle, and activity- associated factors into the analyses. Carefully designed studies with rigorous documentation of past herbicide exposures and other potential risk factors are needed in relation to fully understanding the etiology of digestive cancers.

e Lung Cancer

A recent population-based case control study of 273 cases and 187 controls in Sasketchewan[39] did not find significant associations between use of specific herbicides and the risk of lung cancer. Exposure was based on self-reported duration of use of specific herbicides, including phenoxyacetic herbicides. The study investigators were able to adjust for smoking and other lifestyle factors, and to assess risk related to specific chemicals.

A1997 hospital based case control study of Vietnam veterans by Maher et al.[40] analyzed lung cancer risk using two control groups, one with a colon cancer diagnosis,

and one of patients with no history of cancer. In this study, surrogate measures derived from military service records were used to estimate Agent Orange exposure (branch of service, history of combat service, and location of service unit). There was an increased risk of lung cancer among individuals with a history of service in Vietnam (OR=1.39; 95 % CI: 1.01-1.92), a history of combat duty (OR=1.96; 95% CI: 1.16-3.25), and a history of being in the army in Vietnam (OR= 1.53; 95% CI: 1.05-2.21) when the non-cancer patient comparison group was used. Statistical significance was not maintained when the colon cancer control group was the comparison group. The study was significantly limited by the use of a surrogate measure of exposure and the inability to control for the influence of smoking. Akhtar et al[23], in contrast, did not observe an increased risk of lung cancer incidence (SIR=1.13; 95% CI: 0.79-1.57) in US Air Force Veterans compared to the general US population. They were not able to adjust for smoking status in this investigation.

The International Agency of Research in Cancer (IARC) cohort study[20] examined mortality associated with exposure to phenoxy herbicides, chlorophenols and dioxins in 21,863 workers. Among the total cohort of workers, there was a slightly elevated risk of lung cancer mortality rate (SMR=1.09; 95% CI: 0.98-1.20). Similarly, among the subgroup of the population (13,831) who were exposed to TCDD or higher chlorinated dioxins, the risk of death from lung cancer was found to be slightly elevated (SMR=1.12; 95% CI: 0.98-1.32). In the mortality study of 2,187 Dow Chemical company workers exposed to dioxin, mortality due to lung cancer did not differ from expected[41]. In the US 12 plant study of 3,538 manufacturing employees exposed to TCDD, there was no excess mortality due to lung cancer (SMR=1.06; 95% CI: 0.88-1.26). In the analysis of cumulative exposure and lung cancer mortality, however, there was indication of a dose-response trend between increasing exposure and lung cancer mortality (p=0.05). The significance of this trend did not persist when the analysis included a 15 year lag time[42].

Mortality rates for of lung cancer among residents exposed to TCDD following the Seveso explosion were not significantly elevated (RR=1.3; 95% CI: 0.7-2.6 - Zone A), (RR=1.2; 95% CI: 0.9-1.6)[43]. Higher rates were found for men (RR=1.3; 95% CI: 1.0-

1.7) when a 15-20 year latency period was considered. The investigators for the Seveso study were not able to adjust for smoking or other lifestyle factors in their analyses, which may partially explain these results. Among residents of the heavily dioxin-exposed Chapevsk region of Russia, there was an elevated rate of lung cancer (SMR=3.1; 95% CI: 2.6-3.8). This ecological study assessed dioxin contamination via soil and breast milk samples and did not control for individual level risk factors for lung cancer[44].

Researchers for the US Agricultural Health Study[45] analyzed lung cancer risk and pesticide exposure among a cohort of 57,284 pesticide applicators. Study participants provided exposure histories on 50 specific pesticides. The study reported an overall significantly decreased standardized incidence ratio of lung cancer (SIR=0.44; 95% CI: 0.39-0.49). This finding is likely largely attributable to the lower smoking rate among the study participants compared to the underlying general populations in the two states. A significantly increased risk of lung cancer (OR: 3.1; 95% CI: 1.2-7.7) and evidence of a dose response trend (p=0.04) was found among applicators with the highest level of dicamba (a chlorophenoxy compound) exposure when the referent group were applicators with the lowest level of exposure but not when the referent group were applicators with no exposure. The large sample size, prospective design, link to tumour registries, use of an exposure intensity matrix, and ability to assess specific pesticides are notable strengths of this study. A further analysis[36] of the US Agricultural Health Study dicamba data showed a trend of increasing lung cancer risk with increasing lifetime exposure days when the referent group was low-exposed participants (*p*-value for trend = 0.02) but noted that the number of nonsmoking, dicamba-exposed lung cancer cases ($n$ = 5) was too small to assess risk among nonsmokers.

Wang et al[32] reported a significantly reduced risk of lung cancer amongst New York State female Farm Bureau members (SIR= 0.33; 95% CI: 0.20-0.51) compared to rural, nonfarm residents. The authors suggest that the study cohort might have experienced some of the same factors that reduce cancer incidence for male farmers, and acknowledge that farmers generally are protected by their physically active work and nonsmoking lifestyle, reducing the overall risk for lung cancer. The overwhelming

positive contribution of these particular lifestyle factors poses challenges for understanding the contribution of herbicide exposures especially for the etiology of lung cancer.

Conclusions of IOM 2004 Report:

The IOM concluded that on the basis of previous IOM Committee assessments and on the basis of its current evaluation of epidemiologic evidence, that there is limited or suggestive evidence of an association between exposure in the compounds of interest and lung cancer. This was a consistent observation in all of the Committee assessments. Strongest evidence in favour of this decision comes from Saracci et al, 1991.

Synthesis of Agent Orange and other chlorophenoxy herbicide exposures and lung cancer

This reviewer believes, based on recent evidence, that there is inadequate or insufficient evidence of an association between exposure in the compounds of interest and lung cancer. The studies which have carefully controlled for herbicide exposures and which have appropriate reference groups show a consistent trend towards a decreased risk for lung cancer (e.g. the Saskatchewan study). Many studies which have indicated either no association or a protective association have examined agricultural populations and their exposures and relied upon general population rates for comparison. These studies, for the most part, have not adjusted at the individual level for dietary, lifestyle, and activity- associated factors that would have likely have contributed to higher lung cancer rates in the comparison groups. The data from the dicamba-specific analysis of the US Agricultural Health Study show higher risk of lung cancer in the most highly exposed subjects compared to the lower exposed group and are perhaps the exception. Studies of dicamba are few and more work needs to be done to determine whether this is a particularly hazardous herbicide. The divergent findings for lung cancer thus suggest that associations between lung cancer and chlorophenoxy herbicide classes may be driven by the specific toxicity of each individual chemical agent. More research is needed that includes meticulous collection of information

about smoking life history and other factors as well as exposure to the specific herbicides.

f Soft tissue sarcomas

Soft-tissue sarcoma (STS) is a condition with varied characteristics, making accurate diagnosis and classification challenging. Thus, in reviewing the literature on STS and chemical exposures, it is important to bear in mind the potential for significant misclassification of cases through the use of death certificates or absence of pathologically review of tumors. Moreover, STS is a rare disease. As a result, many of the sample sizes in studies of STS are small, with cohort studies being particularly susceptible to a lack of adequate number of cases for sufficient statistical power to assess the relationship between chemical exposures and STS.

Eriksson et al.[46] conducted a study of a Swedish population-based case-control study of STS in men, in which they attempted to identify the chlorophenoxy agents which were responsible for the higher rates of soft tissue sarcomas (STS). Like previous studies, they found an association between exposure to chlorophenoxy compounds and STS (OR 1.8; 95% CI: 1.02-3.18). Furthermore, the authors observed that STS use during the 1950s was associated with any exposure to chlorophenoxy compounds and to 2,4,5-T, in particular, [chlorophenoxy compounds (OR=2.36; 95% CI: 1.02-5.44), 2,4,5-T (OR=2.94; 95% CI: 1.08-7.98)]. They also observed a median latency period of 29 years for development of the disease. The authors conclude that their results suggest exposure to dioxin-contaminated chlorophenoxy compounds may account for the excess risk of STS.

A Canadian population-based case-control study assessed the relationship between phenoxyherbicide exposure and soft tissue sarcoma. This study, a further analysis of the research conducted by McDuffie et al[47], examined how DEET exposure and use of personal protective equipment impacts the association between phenoxyherbicides and STS risk. While no significant associations between self reported exposure to ‘any phenoxyherbicide’, ‘2,4-D’, ‘mecoprop’, or ‘any dicamba-containing herbicides’ and

soft tissue sarcoma were observed, use of rubber gloves was associated with a significantly decreased risk of STS (OR= 0.56; 95% CI 0.33-0.95). This finding persisted when the analysis was restricted to individuals who worked or lived on a farm (OR=0.57; 95% CI: 0.31-1.06) but was no longer statistically significant due to small numbers.

A series of cohort studies have observed an association between STS mortality and exposure to chlorophenoxy herbicides, including those contaminated by dioxins. These studies have reported greater mortality from STS than expected, with SMR estimates ranging from 2.00-3.38 [20,42,41,28]. The associations in the generally exposed cohorts were not statistically significant, however, with the point estimates being unstable due to small number of cases (i.e. 2-4 cases). The IARC study, an international mortality cohort of workers exposed to chlorophenoxy herbicides (IARC cohort) which included those contaminated with TCDD, in which exposure ascertainment was based upon job records and company questionnaires, investigators reported a STS mortality rate double that of the expected rate[29,48,20] . When the analyses were restricted to workers with 10-19 years of exposure, the excess mortality from STS was observed to be statistically significant (SMR=6.06; 95% CI: 1.65-15.52)[29,48].

In the NIOSH historical mortality cohort of workers from 12 manufacturing plants in the US (NIOSH cohort), Fingerhut et al.[28] reported three times more STS deaths than expected but this was based upon very few cases (n= 4) (SMR 3.38; 95% CI: 0.92-8.65). When this analysis was restricted to employees with greater than one year of exposure, the risk for STS mortality was observed to be elevated (SMR 9.22; 95% CI: 1.90-26.95), but this observation was based upon 3 observed and 0.3 expected cases.

Another mortality cohort study of manufacturing workers[42] that investigated the risk of death from STS following TCDD exposure reported a nonsignificant risk of mortality (RR 2.32; 95% CI: 0.63-5.93). In a sub-analysis of workers with chloracne, they observed a statistically significant increased risk (RR=11.32; 95% CI: 2.33-33.10); however this was based on sparse data (3 deaths). Bodner and colleagues[41] also report an excess number of deaths from STS in a cohort of chemical production workers

exposed to dioxin especially among those with very high exposure (SMR 21.8; 95% CI: 2.7-80.2).

Unlike the above studies, a mortality cohort study of Finnish men exposed to 2,4-D and 2,4,5-T [49] while spraying brushwood, found no elevated standardized mortality or incidence rates of STS. Again, a small number of cases were the basis for this analysis, and the authors note the results may have been influenced by a 'healthy worker effect'.

Two historical cohort studies have looked at the risk of diagnosis of STS from occupational exposures to chlorophenoxy herbicides. One study[50] examined the risk of occupational exposure to these chemicals in paper mills and found an increased risk of STS in women [SIR=3.98; 95% CI: 1.71-7.84, cases = 9), and a slightly elevated risk in men (SIR=1.15; 95% CI: 0.96-2.01). As most of the female cases of STS were packers and sorters who had little direct exposure to chemicals other than glue, the authors conclude that the observation for women may be due to chance. Lynge[51] observed that, in a cohort of Danish manufacturing workers exposed to phenoxy herbicides, the incidence of STS in exposed workers (SIR=2.0; 95% CI: 0.7-4.8) was suggestively but not significantly higher, based upon five exposed cases. A significantly elevated rate of STS (SIR=3.67, 95% CI: 1.0-9.39) was found after accounting for a ten year latency period among exposed workers.

Several case-control studies have found elevated risks of STS associated with exposure to chlorophenoxy herbicides, reporting statistically significant risk ratios ranging from 1.8-5.7 [52,53, 54, 46]. Limitations common to these studies are the small number of exposed cases in some of the analyses. An earlier population-based case-control study of STS and chemical exposure Sweden was reported by Hardell and Sandstrom[52]. Incorporating a 5-year latency period, they observed a significant association between self-reported exposure to chlorophenols and phenoxyacetic acids and STS (OR=5.7; 95% CI: 2.9-11.3). These findings were replicated by Eriksson[53], who also found a significantly elevated risk of STS from chlorophenoxy exposure with a 5-year latency period (OR 5.1; 95% CI: 2.2-10.2) in a case-control study. Hardell[54] also noted that self-reported exposure to phenoxyacetic acids was statistically significantly associated

with STS when compared to population-based controls (OR=4.1; 95% CI: 1.7-10.0). Similarly, Kogevinas[55] examined the risk of STS in a nested case-control study of workers exposed to phenoxy herbicides, chlorophenols and dioxins. They observed elevated odds ratio estimates, yet the estimates were unstable due to small sample sizes [2,4-D/DP: OR= 10.32; 95% CI: 1.18-90.56]; [2,4,5-T/TP: OR=5.72; 95% CI: 1.14-28.65]; [Any dioxin/furan: (OR=5.56; 95% CI: 1.12-27.7].

Not all case-control studies of soft tissue sarcoma and chlorophenoxy exposure have reported positive associations. A population-based case-control study by Woods[56] used cases identified through a tumor registry and population-based controls matched for age and vital status. No association was found between exposure to chlorophenoxy compounds and chlorophenols and STS (OR=0.9; 95% CI: 0.4-1.9). However, an elevated risk of STS was observed in the sub-analysis restricted to those with self-reported chloracne, although this association was not statistically significant (OR=3.3; 95% CI: 0.8-14.0). Similarly, Smith and Christophers[57] found no association between any exposure to chlorophenoxy herbicides and STS (OR=1.0; 95% CI: 0.3-3.1). In a sub-analysis of those with greater than 30 days of exposure, a non-significant risk was observed (OR=2.0; 95% CI: 0.6-3.7). A particular strength of their design was the use of both hospital and population-based controls but they were challenged by the few numbers of cases available. Two other case-control studies did not find associations between STS and chlorophenoxy exposure. A case-control study of STS in Kansas by Hoar et al.[58] reported no association between STS and any farm use of herbicides (OR=0.9; 95% CI: 0.5-1.6).

Conclusions of IOM 2004 Report

The IOM concluded that on the basis of previous IOM Committee assessments and on the basis of its current evaluation of epidemiologic evidence, that there is sufficient evidence of an association between exposure of the Agent Orange compounds of interest and soft tissue sarcomas. They note that findings from occupational, environmental, and Vietnam-veteran studies show sufficient evidence to link herbicide exposure to STS. That evidence is supported by long-term follow-up studies of dioxin-

exposed chemical workers. The reports by Bodner et al[41], Comba et al[59] and Tuomisto et al[60] do not change the conclusions from those of previous committees.

Synthesis of Agent Orange and other chlorophenoxy herbicide exposures and soft tissue sarcoma

This reviewer agrees that that there is sufficient evidence of an association between exposure in the Agent Orange compounds of interest and soft tissue sarcomas. This conclusion is supported by highly consistent results in a rather extensive literature examining this hypothesis though it is acknowledged that there are some conflicting findings.

g Breast Cancer

Breast cancer is one of the most common forms of cancer in women. Research on this disease has elucidated a wide range of causal factors, many of which are linked to diet and lifestyle, but also include hormonal-related factors[14]. Because breast cancer occurs predominantly in women and there were few US women exposed to Agent Orange in Vietnam, the availability of studies of this outcome in Vietnam Veterans has been limited. The current evidence is primarily limited to findings from investigations of community exposures (e.g. Seveso, Italy) and studies of industrial and agricultural work force populations. Problems of lack of appropriate control groups or comparison populations have made interpretation of some of these findings especially challenging.

There has been recent considerable interest in TCDD (dioxin) exposure given its estrogen-mimicking properties. The potential to induce expression of one of the cytochrome P450 enzymes that has the ability to metabolize estradiol to 4-hydroxyestradiol, a genotoxic-reactive intermediate possibly involved in inducing breast carcinogenesis, is an example of one metabolic pathway[154]. Furthermore, some studies on breast cancer and polychlorinated biphenyl (PCB) exposure have reported increased risk being limited to exposure to mono-*ortho* PCBs[61], [62]. These data suggest that there may be value in pursuing specific agent-related exposures in the etiology of

**Table 3: Recent Studies of Herbicide Exposures and Breast Cancer**

| *Source* | *Study Design & Population Description* | *Pesticide Type & Exposure Assessment* | *Measures of Association & Outcome* | *Main Findings RR 95% CI* | *Strengths & Limitations* |
|---|---|---|---|---|---|
| **Mills, 2005**[63] **International Journal of Occupational & Environmental Health 11, 123-131.**<br><br>**Breast Cancer Risk in Hispanic Agricultural Workers in California** | Nested case-control study within cohort of Hispanic women farm workers who were members of United Farm Workers of America (1973-2001).<br><br>Cases: newly diagnosed breast cancer cases (128) identified by record linkage of ever members of UFW (1973-2000) and California Cancer Registry (1987-2001)<br><br>Controls: female members of UFW not diagnosed with any cancer (640). 5 to 1 matching by age, Hispanic ethnicity. | Pesticide exposure was based on union records (location, type of crop, number years). Fertility and poverty level (SES) obtained from county-level statistics.<br><br>Pesticide information obtained from Pesticide Databank (1974-1989) and University of California, Davis Statewide Integrated Pest Management Project (1990-1999).<br><br>Variables obtained: county, crop, month and year application, pesticide, number acres treated, pounds of active ingredient applied.<br>Pesticides: diazinon, malathion, captan, methyl bromide, 2,4-D, chlordane, chlorothalonil, maneb, dichloropropane, propargite, triflurin, dicofol, simazine. | Unconditional logistic regression analyses adjusted for age, fertility, SES, date of first contribution to union, duration of union membership.<br><br>Age adjusted ORs showed significant elevation in risk associated with work growing mushrooms, but not other crops.<br><br>Risks of breast cancer increased with increasing use of 2,4-D. | Age adjusted ORs for breast cancer 6.02 (2.01-18.0) associated with growing mushrooms (7 cases, 6 controls).<br><br>Risk of breast cancer related with use of 2,4-D: OR= 2.14 (1.06-4.32) (21 cases, 73 controls).<br><br>Number in ( ) = exposed cases | Limitations:<br>No information about use of protective clothing, re-entry intervals or other practices affecting exposure. Exposure misclassification possible.<br><br>Cases and controls not interviewed, only work histories available. No info on smoking history, diet or medical history. SES and fertility estimated from place of residence.<br><br>Strengths:<br>Includes all cases in farm worker population.<br>No recall bias (interviews not used). |

breast cancer risk. To that end, in 2005 Arbuckle et al[64] reported an interesting study of farm workers exposed to 2,4-D and MCPA (4-chloro-2-methylphenoxyacetic acid) in the Ontario Farm Families study. Those who wore goggles or a face shield during mixing or loading had significantly lower concentrations of 2,4-D in their urine. The results of the MCPA urine analyses did not show this effect but fewer people were exposed to this herbicide. The etiological implications of these biological exposure data are unknown; longitudinal research is needed that links these internal levels to health effects. A general limitation of using biological markers is the inability to determine historical exposure experience and account for the latency between exposure and diagnosis.

A 2005 report from the US Agricultural Health Study by Hoppin et al.[65], which involved the female pesticide applicators in Iowa and North Carolina, including 309 breast cancer cases and 30,145 referent controls, used questionnaires to assess direct and household exposure to 50 specific pesticides. The authors identified increased breast cancer risk among women whose husbands were exposed to certain chlorophenoxy herbicides (2,4,5-TP: OR=2.0; 95% CI: 1.2-3.2), (2,4,5-T: OR=1.3; 95% CI: 0.9-1.9), but not for others (2,4-D: OR= 0.9; 95% CI: 0.6-1.4). There was an indication of a dose-response trend between husbands' cumulative use of 2,4,5-TP (test for trend: $p < 0.001$) and 2,4,5-T (test for trend: $p=0.009$) and wives' breast cancer risk.

A 2005 cohort study of Hispanic farm (128 cases, 640 controls) workers in California[63] reported an increased risk of breast cancer among recently diagnosed women with a history of 2,4-D exposure (OR=2.14; 95% CI:1.07-4.32) [Table 3]. The California Department of Pesticide Regulation (DPR) pesticide use reports provided information on the date, location, and amount of specific pesticides used for each crop. This information was linked with union records to create an index of exposure for each crop location and time period. This study benefits from the extensive pesticide data collected by California DPR though is limited by the lack of individual –level risk factor data.

There have been two mortality cohort studies that examined the association between breast cancer risk among female workers occupationally exposed to chlorophenoxy herbicides and dioxin contaminated products. A 1997 International Agency for Research on Cancer (IARC) study[20] assessed mortality causes among 21,863 workers exposed to phenoxy herbicides and chlorophenols in 12 countries. Among workers who were exposed to TCDD or higher chlorinated dioxins (n= 13,831), the rate of mortality due to breast cancer (SMR=2.16; 95% CI: 0.99-4.10) was higher than the control population though the lower 95% confidence limit bordered 1.0. There was a statistically significant increase for mortality evident in the German cohort (SMR=2.85; 95% CI: 1.30-5.39). An earlier cohort study of Danish manufacturing workers herbicides[51] included 1069 women employed between 1933 to 1981 who may have been occupationally exposed to 2,4-D, MCPA, 2,4,5-T, or 2,4-DP. The observed number of breast cancer incident cases did not differ from the expected number of cases in the Danish population (RR=0.93, no confidence limits reported). An analysis of a subset of female employees who had worked in two factories in the manufacture and packing of chlorophenoxy herbicides revealed a relative risk of 0.53 but this was based on only 2 cases. Job records were used in each of these studies to capture exposure history. The inability to account for individual level heterogeneity in exposures and the lack of information about individual lifestyle behaviours, which might pose as risk factors, are notable limitations in this investigation.

A 2004 population-based nested case-control study of 105 cases and 210 controls who reside in Long Island, New York[66] found no association between 2,4-D exposure and breast cancer risk (OR=1.2; 95% CI: 0.6-2.1). A history of positive exposure was defined as individual residential history in regions with detectable levels of 2,4-D in drinking water. This study was limited by the imprecise nature of estimating exposure and the inability to control for individual breast cancer risk factors.

Follow-up studies of the industrial accident in Seveso, Italy (1976) have examined mortality resulting from dioxin exposure. In the most recent report published in 2001, Bertazzi et al[43] calculated observed and expected rate ratios for causes of death among residents of the most heavily contaminated area (Zone A), the fallout path (Zone B),

and a region with low level, patchy contamination (Zone R). Soil samples of dioxin were used to estimate exposure in these regions. A random sample of serum TCDD levels was obtained from residents to validate the use of soil contamination as a surrogate for individual exposure. Among women in Zone A, there was no indication of excess breast cancer mortality (RR=0.8; 95% CI: 0.2-3.1, observed cases = 2) but the study did not have adequate statistical power for a meaningful assessment of breast cancer risk. Moreover, no elevated risk among Zone A and Zone B residents was observed when the analysis was stratified into four periods for time since exposure [35] (total cases studied = 14). This study had nearly complete follow-up (99%) of residents twenty years after the explosion.

An ecological study of health outcomes[44] in Chapevsk, Russia, a community with high environmental dioxin levels from chemical plant emissions, that was published in 2001, reported significantly higher mortality due to breast cancer among residents compared to the surrounding regions (SMR=3.1; 95% CI: 2.6-3.8). Though individual exposure information was not obtained, the high levels of dioxin contamination in the region were verified by human milk and soil samples. Serum TCDD is an excellent indicator of continuing TCDD exposure or even brief TCDD exposure if measured within 20-30 years after exposure.

Conclusions of IOM 2004 Report:

On the basis of the information reviewed in the report and the previous investigations, the committee concluded that there is inadequate or insufficient evidence to determine an association between exposure to the Agent Orange compounds of interest and risk for breast cancer. They note that the lack of data on the association between exposures to the chemicals of interest and breast cancer, coupled with the lack of exposure information on Vietnam Veterans, precludes quantification of any possible increase in risk.

Synthesis of Agent Orange and other chlorophenoxy herbicide exposures and Breast Cancer

Recent studies and especially those in which past exposure was carefully documented and appropriate controls were involved, this reviewer believes that that there is limited or suggestive evidence of an association between exposure in the Agent Orange compounds of interest and breast cancer. The Engel[65] analysis of chlorophenoxy exposures in US Agricultural Health Study supports this conclusion as does the California Migrant Worker investigation. Other evidence that favours this conclusion suggests that TCDD (dioxin) or specific chemical congeners, rather than chlorophenoxy herbicides generally, are the responsible agents.

h Prostate cancer

The relationship between serum TCDD as a surrogate for historical Agent Orange exposure and prostate cancer risk was recently examined in a 2006 report of the Air Force Health Study[67], a cohort study of 1019 US Air Force veterans responsible for handling and applying herbicides in Vietnam [Table 4]. Prostate cancer rates among Operation Ranch Hand veterans, specifically those who were directly involved in spraying or handling herbicides, were compared to rates among comparison veterans, specifically those who did not directly handle herbicides. While no overall association between TCDD and prostate cancer risk was observed, there were significant findings among two population subgroups. Operation Ranch Hand veterans in the highest exposure category who had served less than two years in Southeast Asia and veterans who served prior to 1969 both had an elevated prostate cancer risk (RR=2.15; 95% CI: 1.03-4.48 and RR=2.27; 95% CI: 1.11-4.66 respectively). In an earlier analysis (2004) of this study population, Akhtar et al[23] compared prostate cancer risk among veterans to risk among the general population. In this study, statistically significantly elevated risks (SIR=1.46; 95% CI: 1.04-2.00 and SIR=1.62; 95% CI: 1.23-2.10 respectively) were found for both Caucasian Operation Ranch Hand and Caucasian comparison veterans. In contrast to the comparison veterans, the Ranch Hand veterans with the

highest dioxin concentrations who spent two years or less in Southeast Asia were observed to have experienced a significantly elevated prostate cancer risk (RR= 6.04; 95% CI: 1.48-24.61)[23]. It is important to keep in mind that, though the use of serum TCDD is a reliable indicator of individual body burden, it is not necessarily an accurate reflection of historical exposure. These findings do suggest that the prognostic significance of this internal marker of TCDD dose is significant.

A 2004 hospital based case-control study of prostate cancer in veterans in Ann Arbor, Michigan[68] found that cases were twice as likely to have a history of exposure to Agent Orange (OR=2.06; 95% CI: 0.81-5.23) than controls but this estimate is not conclusive due to the small numbers of cases and the resulting wide 95% confidence intervals. Exposure was based on a self-reported history regarding whether individuals were ever exposed to Agent Orange.

Cohort studies of dioxin exposure among manufacturing employees and prostate cancer are more ambiguous. The US 12 Plant cohort study[42], published in 1999, used a job exposure matrix to estimate exposure among 5132 workers exposed to dioxin contaminated products. In this population, prostate cancer mortality was not significantly elevated (SMR 1.17; 95% CI 0.78-1.69) when compared to the US population.

The findings from the IARC study of 21,863 workers from 12 countries[20] do not suggest an elevated risk for prostate mortality among employees exposed to TCDD or other chlorinated dioxins (SMR=1.11; 95% CI: 0.81-1.50). The 2003 Dow Chemical company cohort study (n=2187)[41], a subset of the IARC cohort, reported that workers exposed to dioxin did experience an elevated rate of prostate cancer mortality (SMR=1.7; 95% CI 1.0-2.6). Exposure in this investigation was assessed via an industrial hygiene workplace assessment and exposure estimates were verified with environmental dioxin measurements; the results were limited by the use of death certificates as a source of disease classification and inability to account for individual level risk factors.

Research on the health experience of men exposed to TCDD following the Seveso explosion[35] revealed that exposed subjects did not have a elevated risk for prostate cancer mortality (RR=1.0; 95% CI: 0.5-2.2). This finding persisted when a latency period of twenty years was considered. This study benefited from a nearly complete (99%) rate of follow up of subjects, including identifying cause of death for those deceased of the 22,000 men who resided in the exposed zones. The lack of individual level data, however, precluded the ability to control for major prostate cancer risk factors, including family history and lifestyle factors.

The relationship between risk of prostate cancer and chlorophenoxy herbicide exposure resulting from agricultural use has been examined in two recent cohort studies. Data from the US Agricultural Health Study[69] published in 2003, a cohort study of 55,332 private and commercial pesticide applicators in Iowa and North Carolina, indicate a slightly elevated prostate cancer risk among the study population (SIR=1.14; 95% CI: 1.05-1.24). There was also evidence of a dose-response trend (p=0.005) related to exposure to a group of chlorinated pesticides (including 2,4,5-T and 2,4,5-TP) and risk for men over 50 years of age.

A cohort study of 145,383 Canadian farmers from Alberta, Manitoba, and Saskatchewan[70] used estimates of exposure based upon individual- level agricultural census data of the number of acres sprayed with herbicides. The authors reported that number of acres sprayed was associated with a slightly increased risk after adjustment for age and calendar period (RR=1.19; 95% CI: 0.98-1.45). Furthermore, they report evidence of a significant dose-response trend between herbicide exposure and prostate cancer mortality. Though the researchers were not able to distinguish specific classes of herbicides, chlorophenoxy herbicides were reported to be the most commonly used herbicides in the Canadian prairies during the study time period.

**Table 4: Recent Studies of Herbicide Exposures and Prostate Cancer**

| *Source* | *Study Design & Population Description* | *Pesticide Type & Exposure Assessment* | *Measures of Association & Outcome* | *Main Findings* | *Strengths & Limitations* |
|---|---|---|---|---|---|
| **Pavuk, 2006**[67] **J Expo Sci Environ Epidemiol, 16, 184-90** | Longitudinal cohort study (Air Force Health Study)<br><br>Exposed (n=1019, 62 with cancer): US Air Force veterans responsible for handling and applying herbicides (Ranch Hand) in Vietnam from 1962-1971<br><br>Unexposed (n=1497, 89 with cancer): Air Force veterans who served during the same time period but were not involved in herbicide application<br><br>Subjects (n=2516) followed from 1982-2002 | Cumulative TCDD exposure: serum TCDD measurement was done in 1987, 1992,1997, and 2003 then used to calculate total cumulative TCDD level (area under the curve) | Outcome: Time to prostate cancer diagnosis, identified through medical records<br><br>Cox proportional hazard regression, adjusted for age, BMI (on duty), occupation, smoking (pack years).<br><br>Comparison done between high exposed, low exposed and unexposed veterans<br><br>Stratified by time served in Southeast Asia (SEA), and last tour of duty (with 1 Jan 1969 as cutoff, as pre 1969 levels of TCDD were higher) | No overall association between TCDD and prostate cancer was observed<br><br>For specific categories, Ranch Hand veterans in the highest exposure category who served <2 years in SEA had a RR = 2.15 (1.03-4.48), *p* for trend 0.03 (cancer/no cancer = 14/335), those who were in SEA before 1969 had a RR = 2.27 (1.11-4.66), *p* for trend 0.04 (cancer/no cancer = 15/227)<br><br>In the comparison group, time served in SEA was associated with increase risk RR = 2.18 (1.27-3.76) (cancer and greater time n=63) | Authors suggest caution in interpreting associations in Ranch Hand veterans, as they are based on small sample sizes<br><br>Identified strengths include the long period of follow up, and repeated measurement of TCD levels and other covariates.<br><br>Weaknesses involve the use of serum TCDD levels as a proxy for exposure levels some 16-26 years earlier<br><br>Findings in the comparison group point to the need for more comprehensive exposure measurement |

The authors of an ecological study of chlorophenoxy herbicide exposure and cancer mortality in four Midwest US states[30] published in 2000 used tertiles of wheat acreage as a surrogate for herbicide exposure. Residents of regions with the middle and highest tertiles of wheat acreage had elevated prostate cancer mortality (SMR= 1.10; 95% CI: 1.01-1.20, SMR=1.24; 95% CI: 1.14-1.36 respectively) and, while lacking individual exposure and risk factor information, are consistent with the results discussed above.

Conclusions of IOM 2004 Report:

On the basis of its evaluation of epidemiological evidence available to 2004 and the results from previous Agent Orange reviews, the committee concluded that there is limited or suggestive evidence of an association between exposure to at least one of the compounds of interest and prostatic cancer. Although the associations are not large, several studies provide evidence that suggests a small increase in morbidity or mortality.

Synthesis of Agent Orange and other chlorophenoxy herbicide exposures and prostate Cancer

Based upon recent data and especially those studies in which past exposure was carefully documented or appropriate controls were involved, this reviewer agrees that that there is limited or suggestive evidence of an association between exposure to the chlorophenoxy herbicide compounds of interest and prostate cancer.

- Testicular Cancer

Investigators of a mortality cohort study of 23,829 British Columbia sawmill workers[71] reported an elevated rate of male genital cancer among the study population when compared to mortality in the general British Columbia population (SMR=1.19; 95% CI: 1.02-1.39). Mill industrial histories and records of chlorophenateswere used to create exposure scores for each job title. The lack of individual risk factor data and considerable loss-to-follow up in this study (11.2%) are notable limitations. In contrast, another mortality cohort study of 18,390 workers from 10 countries[29]

occupationally exposed to chlorophenoxy herbicides (2,4-D, 2,4,5-T, MCPP) identified suggestive elevated mortality risks due to testicular cancer among exposed workers (SMR=2.20; 95% CI: 0.89-4.54) and production workers (SMR=2.78; 95% CI: 0.90-6.48). The 2005 report[38] on cancer incidence in the US Agricultural Health Study (n = 55,332 male pesticide applicators; 89,658 male and female applicators in total) noted no increased elevation for testicular cancer in private pesticide applicators or in commercial pesticide applicators compared to underlying state populations.

Conclusions of the IOM 204 Report:

On the basis of its evaluation of the epidemiologic evidence and in previous Agent Orange reports, the committee concluded that there is inadequate or insufficient evidence to determine an association between exposure to the compounds of interest and testicular cancer.

Synthesis of Agent Orange and other chlorophenoxy herbicide exposures and testicular cancer

Based upon recent findings, this reviewer agrees that there is inadequate or insufficient evidence to determine an association between exposure to chlorophenoxy herbicides and testicular cancer.

j Brain Cancer

Significant associations between risk of glioma and farming after age 18 and ever use of herbicides were reported (OR=1.7; 95% CI: 1.0-3.0) in a 2005 case-control study of eastern Nebraskan men[72,73] [Table 5]. In this study, chlorophenoxy herbicide exposures were specifically associated with an increased risk of glioma (OR: 1.8; 95% CI: 1.0-3.3). There were no observed associations between glioma and 2,4,5-T exposure[72]. The Upper Midwest Health study, another population-based, case-control study, assessed risk for glioma among women. In this study, there was no observed

association between 'ever use of 2,4-D' and glioma risk[73] [Table 6]. Due to the rapid progression of glioma, the use of proxy (next of kin) respondents was necessary in both of these studies. In the study by Lee[72], 76% of cases were proxies whereas in the Upper Midwest Health study, 43% of cases were proxies. Assessing exposure via proxy may have introduced differential misclassification bias. As such, these results should be interpreted with caution. The Akhtar[25] study observed a standardized incidence ratio of 1.84 (95% CI: 0.68-4.08) [5 vs. 2.7 expected cases] which is suggestive but not significant for an increased risk for brain and nervous system cancers in Operation Ranch Hand Veterans compared to the general US populations; whereas, for the comparison population in this study, the SIR was 0.53 (95% CI: 0.09-1.75) and lower, but not significant.

The 2004 study by Swaen et al[18] of 1341 licensed herbicide applicators in the Netherlands reported a non significant, but increased standardized mortality rate of 1.60 (95% CI: 0.43-4.05) for brain cancer in applicators compared to the underlying Netherlands population; this was based upon 4 deaths versus an expected number of 2.5. Herbicides to which this cohort was exposed also included 2, 4-D, plus diuron, diquat, glyphosate, paraquat, and mecoprop. In the previously described US Midwest case-control study, an increased risk for developing glioma related to past dicamba use was not observed [OR=1.2; 95% CI: 0.5-2.7][72,73] . Two other recent population-based studies[73],[74] [Table 7] of glioma and self reported pesticide exposure do not support the hypothesis of studies that farm residence or pesticide exposure increases the risk of glioma.

**Table 5: Recent Studies of Herbicide Exposures and Brain Cancer**

| *Source* | *Study Design & Population Description* | *Pesticide Type & Exposure Assessment* | *Measures of Association & Outcome* | *Main Findings Continued* | *Strengths & Limitations* |
|---|---|---|---|---|---|
| **Lee, 2005**[72] **Occup Environ Med, 62, 786-792** | Population-based case-control study<br><br>Cases (n=251): residents of Nebraska age 21< with glioma<br><br>Controls (n=503): Recruited through random digit dialing with those 65+ identified through Medicare files, frequency matched to cases by age sex and vital status | Structured interview (via telephone) during 1992-94: Collected data on demographics and lifestyle factors, and for those who worked/lived on a farm collected history of pesticide use prior to 1985 and specific pesticides used, years of farming, and size of farm<br><br>Proxies responded for 76% of cases | Outcome: histologically confirmed incident primary glioma diagnosed between 1988-1993<br><br>Unconditional logistic regression adjusted for age group, sex and respondent type (proxy or not)<br><br>Evaluated potential confounders including history of head injury, marital status, education, alcohol use, diabetes, dietary intake of carotene and fiber<br><br>*Main Findings:* Significant association between farming after age 18 in men and glioma OR = 1.7 (1.0-2.9) (cases/controls = 62/122) and years farmed in men OR = 3.9 (1.8-8.6), *p* for trend 0.001 (24/40) | Association between ever use: herbicides (all) in men OR = 1.7 (1.0-3.0) (38/70); and herbicide categories dinitroaniline OR = 2.9 (1.3-6.6) (17/16); phenoxy OR = 18 1.0-3.3) (32/56), and triazine 2.0 (1.0-3.7) (27/40)<br><br>Association between nitrosatable pesticides (all) (includes 2,4,5-T, 2,4-D, dicamba, glyphosate) in men<br><br>Association between organochlorine insecticides (in men) OR = 1.9 (1.0-3.6) (26/47)<br><br>No significant association between glioma and use of 2,4,5-T, dicamba, or glyphosate<br><br>Significant association with: 2,4-D OR = 1.8 (1.0-3.3) (32/56) Paraquat OR = 11.1 (1.2-101.2) (5/1) | The authors caution that the observed association may be due to differential recall of proxies for cases and for controls, with a major limitation of the study being the high percentage of proxy respondents<br><br>Limitation not identified: the use of self-reported measure of exposure<br><br>Small sample sizes result in unreliable estimates for some associations<br><br>All associations observed in men. No associations in women. |

**Table 6: Recent Studies of Herbicide Exposures and Brain Cancer**

| *Source* | *Study Design & Population Description* | *Pesticide Type & Exposure Assessment* | *Measures of Association & Outcome* | *Main Findings (cont'd)* | *Strengths & Limitations* |
|---|---|---|---|---|---|
| **Carreon et al. [73] Env Health Perspectives 2005** | Population-based case-control study<br><br>Cases (n=341)- 57% alive, female residents of Iowa, Michigan, Minnesota, Wisconsin with glioma<br><br>Controls - (n=528), females, ages 18-80: residents of nonmetropolitan counties of 4 states<br><br>Companion article to Ruder et al.,[74] | Structured interview using modified US Agricultural Health Study questionnaire Collected data on demographics and lifestyle factors, and self reported history of pesticide exposures | Outcome: histologically confirmed intracranial primary glioma diagnosed between 1995-1997 identified through participating medical facilities and neurosurgeon offices.<br><br>Unconditional multiple logistic regression<br><br>Stratified overall versus proxy data in analyses | Association between ever use: herbicides (all) [proxys included] OR = 1.00 (0.6-1.5); Herbicides (all)[proxys excluded]: OR = 1.00 (0.6-1.7);<br><br>Carbamate herbicide showed moderately elevated associations of borderline statistical significance [proxys included] OR=3.0 (0.9-9.5); [proxys excluded] OR= 3.5 (0.9-13.0)<br><br>2,4-D- OR=0.9; (0.5-1.6)<br>Dicamba- OR=0.7, (0.3-1.5)<br>Glyphosate OR=0.7, (0.4-1.3)<br><br>Does not support the hypothesis that farm residence or pesticide exposure increases the risk of glioma | Largest population based case-control study of female glioma and pesticide exposure focusing on non-metropolitan populations.<br><br>Control subjects were older than cases, cases were somewhat less likely to live on a farm than controls<br><br>High proportion of proxy participants |

**Table 7: Recent Studies of Herbicide Exposures and Brain Cancer**

| *Source* | *Study Design & Population Description* | *Pesticide Type & Exposure Assessment* | *Measures of Association & Outcome* | *Main Findings (cont'd)* | *Strengths & Limitations* |
|---|---|---|---|---|---|
| **Ruder,[74] 2004 Archives of Environ Health** | Population-based case-control study<br><br>Cases (n=457)-59% alive, male residents of Iowa, Michigan, Minnesota, Wisconsin with glioma<br><br>Controls - (n=648), males, ages 18-80: residents of nonmetropolitan counties of 4 states | Structured interview using modified US Agricultural Health Study questionnaire Collected data on demographics and lifestyle factors, and self reported history of pesticide exposures | Outcome: histologically confirmed intracranial primary glioma diagnosed between 1995-1997 identified through participating medical facilities and neurosurgeon offices.<br><br>Unconditional multiple logistic regression<br><br>Stratified overall versus proxy data in analyses | Association between ever use: herbicides (all) [proxys included] OR = 0.89 (0.63-1.26); Herbicides (all)[proxys excluded]: OR = 1.51 (0.92-2.48);<br><br>None of the specific herbicide categories showed significant associations<br><br>Observed statistically significant associations between reduced glioma risk and involvement in farm activities; suggesting healthy farm worker effect | Largest population based case-control study of glioma and pesticide exposure focusing on non-metropolitan populations. Control subjects were older than cases, cases were somewhat less likely to live on a farm than controls<br><br>High proportion of proxy participants |

Two historical cohort studies did not identify increased brain cancer mortality among workers occupationally exposed to dioxin contaminated products. The IARC cohort study of workers exposed to TCDD reported no indication of elevated rates of death due to brain cancer (SMR=0.63; 95% CI: 0.33-1.10)[20]. Similarly, there was no evidence of elevated brain cancer mortality reported in study of 12 US manufacturing plants (SMR=0.81; 95% CI: 0.35-1.60)[42] or of elevated cancer incidence in the US Agricultural Health Study (SIR=0.80; 95% CI: 0.55-1.12)[38].

Conclusions of the IOM 2004 Report:

On the basis of its evaluation of the epidemiologic evidence reviewed here and in previous Agent Orange reports, the committee concluded that there is limited or suggestive evidence of **no** association between exposure to the compounds of interest and brain cancer and, though acknowledging recent contributions, they believed that these findings do not overwhelm the previous extensive literature which supports the conclusion of no association.

Synthesis of evidence for Gagetown chlorophenoxy herbicides and Brain Cancer

Based upon data published since 2004 and especially those studies in which past exposures were carefully documented and appropriate controls involved, this reviewer believes that the current level of evidence regarding brain cancer risk and chlorophenoxy exposures is more equivocal. More research is needed that carefully documents previous herbicide exposures as well as individual lifestyle information in relation to brain cancer risk. This reviewer therefore concludes that there is inadequate or insufficient evidence to determine whether there is an association between exposure in the Agent Orange compounds of interest and brain cancer.

k Non-Hodgkin's Lymphoma (NHL)

Studies of agricultural workers, chlorophenoxy exposure and NHL have detected overall relative risks in the range of 1.3-1.6[58,75-77 47,57, 78 79-81,82]. Higher risks have been reported in relation to longer duration of exposure, greater frequency, direct application, lack of protective equipment, or greater acreage treated[58,77,83]. A recent study has shown that the risk for NHL and chlorophenoxy herbicide exposure differs by NHL molecular subtype[84] with t(14;18)-positive NHL being associated with chlorophenoxy herbicides exposure(OR=2.9; 95% CI: l.1-7.9). Zahm[75], in a case control study of NHL in Nebraska, found risks greater than one in a sub-sample of those who ever lived or worked on a farm and who mixed or applied 2,4-D (OR 1.5; 95% CI: 0.9-2.5). Although none of the associations were significant for duration of exposure to mixing and applying 2,4-D, the test for trend was borderline (p=0.051). A limitation was the broad definition of farmer was used to define exposure, likely resulting in misclassification. Hoar[58] found an association between NHL and self-reported phenoxy exposure (OR 2.2, 95% CI 1.2-4.1). In relation to frequency and duration of use of 2,4-D, they observed that the highest exposed (>20 days) had a risk six times greater than those not exposed (OR 6.0, 95% CI 1.9-19.5, test for trend p=0.0002). In a Canadian study, McDuffie[47] found statistically significant associations after controlling for age, province and medical history between self reported use of chlorophenoxy herbicide exposure (OR 1.38, 1.06-1.81), 2,4-D (OR 1.32, 95% CI 1.01-1.73), mecoprop (OR 2.22, 95% CI 1.58-3.44), and, specifically, dicamba (OR 1.88, 95% CI 1.32-2.68).

**Table 8: Recent Studies of Herbicide Exposures and Lymphohematopoetic System Cancers**

| *Source* | *Study Design & Population Description* | *Pesticide Type & Exposure Assessment* | *Measures of Association & Outcome* | *Main Findings* | *Strengths & Limitations* |
|---|---|---|---|---|---|
| **Demers, 2006 Cancer Causes Control 17:749-758**<br><br>**Cancer and occupational exposure to penta-chlorophenol and tetra-chlorophenol (Canada)** | Cohort study<br><br>26, 487 sawmill workers in BC | Pentachlorophenol (PCP) and tetrachlorophenol (TCP)<br><br>Exposure assessed from work history – cumulative dermal hours of exposure based on job title and job history information<br><br>Exposure-year variable created to represent 2000 hours of PCP or TCP exposure. Measure based on mill records of fungicide use. | Standardized incidence and mortality ratios using BC provincial rates as external reference population<br><br>Relative risk calculated using least exposed workers as referent group (Poisson regression)<br><br>No excess mortality or incidence of major causes of death or a priori selected cancers (NHL, soft tissue sarcoma, multiple myeloma, lung, kidney, sinonasal, nasopharyngeal)<br><br>Evidence of dose-response relationships observed with NHL, Multiple myeloma, Kidney cancer and rectal cancer. | NHL: Trend towards elevated mortality among workers with greater cumulative exposure to all chlorophenols ($p<0.07$ mortality). Trend towards elevated mortality ($p<0.06$) and incidence ($p<0.03$) with increasing PCP exposure.<br><br>Multiple myeloma: Significant trend towards elevated mortality ($p<0.03$) and incidence ($p<0.02$) among workers with greater cumulative exposure to PCP. Sig elevated risk among workers with 5+ exposure years (RR Mortality 4.80 (1.39-16.54) 10 cases) (RR Incidence 4.18 (1.36-12.9) 11 cases)<br><br>Kidney cancer: Trend towards inc. mortality ($p<0.02$) and incidence ($p<0.07$) among workers with greater cumulative exposure to PCP. Sig. elevated mortality among workers with highest cumulative exposure to tetrachlorophenol (5+ exposure years RR mortality 2.30 (1.0-5.32 12 cases)<br><br>Rectal cancer: Trend towards elevated incidence with increasing PCP ($p<0.07$) and TCP ($p<0.08$) exposure. Evidence of sig increased incidence among PCP exposed workers (RR 1.70 (1.20-2.61 43 cases) and TCP exposed workers (RR 1.70 (1.06-2.74 22 cases) with greater than 5 exposure-years<br><br>Strength of relationship inc. slightly for kidney, colon, rectum ca, NHL incidence with 20 yr. latency period. | Limitations:<br>Inability to account for non-occupational confounding factors<br><br>Exposure assessment based on jo history<br><br>Limited ability to assess rare can due to small number of cases (so tissue sarcoma, sinonasal, nasopharyngeal)<br><br>Strengths:<br><br>Ability to assess specific exposu specific chemicals.<br><br>Large sample size<br><br>Use of national registry to assess incident cancers<br><br>Good follow-up |

**Table 9: Recent Studies of Herbicide Exposures and Lymphohematopoetic System Cancers**

| *Source* | *Study Design & Population Description* | *Pesticide Type & Exposure Assessment* | *Measures of Association & Outcome* | *Main Findings OR 95% CI* | *Strengths & Limitations* |
|---|---|---|---|---|---|
| **Hartge, 2005[85] Cancer Epidemiology, Biomarkers and Prevention 14:934-937**<br><br>**Residential Herbicide Use and Risk of Non-Hodgkin Lymphoma.** | Population based case control study in Iowa, metropolitan Detroit, Los Angeles, Seattle, 1998-2000.<br><br>Cases: from Surveillance Epidemiology and End Results (SEER) identified 1321 cases 20-64 years old with first primary diagnosis of NHL between July 1998-June 2000.<br><br>Controls: 1057 population controls (20-64 years by random digit dialing; ages >64 years from Medicare files). Controls stratified on age, sex, race and centre. | Personal interview, collected biological and environmental samples.<br><br>Chemicals measured in dust taken from used vacuum cleaner bags: herbicide dacthal and 22 other pesticides, 10 PAHs, 6 PCBs, 4 herbicides (2,4-D, dicamba, MCPA, 2,4,5-T) and pentachlorophenol.<br><br>Interviewer asked about pesticide use, who applied pesticide, application frequency and product form (e.g. fogger). | To estimate RR of developing NHL, used unconditional logistic regression analyses adjusted for geographic location, age, education sex, and race.<br><br>For analyses of selected histological types, used polytomous regression, controlling for family history of lymphoma, current or previous work as farmer, insecticide use. | Residential herbicide use did not result in detectible increase in risk of developing NHL.<br><br>Ever use of weed killers on lawn or garden not associated with increased risk RR=1.02 (0.84-1.23) (708 cases, 565 controls). Duration, frequency, intensity of use did not alter risk significantly.<br><br>Among respondents with carpet dust samples (679 cases, 510 controls), neither 2,4-D nor dicamba was consistently related to NHL risk, even among respondents with highest levels.<br><br>Among African Americans with detectable 2-4 D levels in carpet dust, risk elevated (RR 3.34 95% CI 1.16-9.63) Sample size not given but total number of AA in study is small (cases 8 controls 14) | Limitations:<br>Loss of information from death, nonlocation, or refusal of eligible cases and controls to participate in study.<br>Bias from NHL survivors or willingness to participate in study.<br>Inaccuracy of reporting herbicide use, measurement errors in environmental pesticide samples.<br><br>Strengths:<br>Use of two exposure assessments, personal interviews and carpet dust samples.<br>Population basis of cases and control, study sample size, detailed data on potential confounders. |

**Table 10: Recent Studies of Herbicide Exposures and Lymphohematopoetic System Cancers**

| *Source* | *Study Design & Population Description* | *Pesticide Type & Exposure Assessment* | *Measures of Association & Outcome* | *Main Findings RR 95% CI* | *Strengths & Limitations* |
|---|---|---|---|---|---|
| **McDuffie, 2005**[78] **Journal of Occupational and Environmental Medicine 47, 806-816**<br><br>**Insect Repellents, Phenoxyherbicide Exposure and Non-Hodgkin's Lymphoma** | Population based case control study.<br><br>Cases: 513 men aged >19 years who were residents in one of 6 Canadian provinces and had a first diagnosis of NHL between Sep 1, 1991 and Dec 31, 1994. 235 (45.8%) had lived/worked on a farm..<br><br>Controls: 1506 men aged > 19 who were residents in same province as case and free of cancers of interest. 673 (44.7%) had lived/worked on a farm. Selected at random from provincial health insurance (4 provinces), computerized telephone listing(1 province) or voters' lists (1 province). Stratified by age ± 2 years. | Purpose: tested associations among exposure to specific herbicides, exposure to insect repellents and use of gloves / protective clothing while handling pesticides to explore their relationship to risk of developing NHL.<br><br>Structured pesticide exposure telephone interviews for those who indicated exposure to 10 hours or more per year of pesticide exposure, and a 15% random sample of the remaining cases and controls.<br><br>Telephone interview characterized exposure to individual pesticides by home/garden or occupational use, days/year usage, average acres sprayed/year, details of occupational hygiene practices (use of gloves & protective clothing). | Conditional logistic regression used to assess association between exposure to 'any phenoxy herbicide', 24-D, mecoprop, MCPA. DEET and use of rubber gloves and NHL risk. Controlled for age and province of residence.<br><br>Analysis conducted on whole population and subgroup that lived/worked on a farm (235 cases, 673 controls). | No sig association between any phenoxyherbicide, 2,4-D exposure, or mecoprop exposure and NHL risk in total population<br><br>Exposure to both DEET and mecoprop: total population (OR=2.05 95% CI: 1.30-3.21) (cases 38, controls 61) subgroup who lived/worked on farm and used rubber gloves (OR=3.86 95% CI 1.57-9.49) (cases 12 controls 15)<br><br>Exposure to any phenoxyherbicide, DEET, subgroup who lived/worked on farm and use of rubber gloves (OR 1.99 95% CI 1.06-3.74) (cases 25 controls 58)<br><br>Exposure to dicamba and DEET: total population (OR 1.84 95% CI 1.23-2.75) (cases 52, controls 93) subgroup exposed to DEET, dicamba, lived/worked on farm and used rubber gloves (OR 2.04 95% CI 1.02-4.06) (18 cases, 40 controls) | Limitations:<br>Deficits in type of information collected: did not determine type of rubber gloves used, whether gloves specifically used during mixing / application of 2,4-D.<br>Recall bias during interview.<br>Specific information regarding exposure not included in models<br>Subgroup analysis limited by small numbers<br><br>Strengths:<br>Information on exposure to specific pesticides collected |

**Table 11: Recent Studies of Herbicide Exposures and Lymphohematopoetic System Cancers**

| *Source* | *Study Design & Population Description* | *Pesticide Type & Exposure Assessment* | *Measures of Association & Outcome* | *Main Findings OR 95% CI* | *Strengths & Limitations* |
|---|---|---|---|---|---|
| **Mills, 2005 Cancer Causes and Control 16:823-830**[86]<br><br>**Lymphohematopoietic cancers in the United Farm Workers of America (UFW), 1988-2001** | Nested case-control study embedded in cohort of 139,000<br><br>Cases: Lymphohematopoietic cancer (131) identified by record linkage of ever members of UFW (1973-2000) and California Cancer Registry (1987-2001)<br><br>Controls: members of UFW not diagnosed with cancer (655).<br>5 to 1 matching by age, gender, Hispanic ethnicity<br><br>Pesticide exposure was based on union records (location, type of crop, number years). | Pesticide information obtained from Pesticide Databank (1974-1989) and University of California, Davis Statewide Integrated Pest Management Project (1990-1999). Variables obtained: county, crop, month and year application, pesticide, number acres treated, pounds of active ingredient applied.<br><br>Pesticides: organophosphates (diazinon, malathion, methyl parathion), organochlorines (dichloropropane), fungicides (captan, maneb, mancozeb), phenoxyacetic acid herbicides (2,4-D), triazine herbicides (simazine), other herbicides such as nitrofen and trifluralin, and fumigants (methyl bromide). | Unconditional logistic regression analyses adjusted for age, date of first contribution to union, duration of union membership and sex.<br><br>Outcome:<br>131 cases of LHC (94 male, 37 female). Age and sex adjusted ORs for LHC significantly elevated in workers engaged in vegetable cultivation, in males and females.<br><br>Risk particularly high for leukemia among females working in vegetables.<br><br>Logistic regression models including 15 chemicals (controlling each for all others) and results similar to when each chemical examined separately. | LHC risk for workers in vegetable cultivation (51) 1.67 (1.12-2.48). Male (OR=1.76); female (OR=1.40).<br><br>Risk of leukemia for females working in vegetables OR=4.01 (1.11-14.56).<br><br>NHL risk for workers (60) in high use areas of 2,4-D OR=3.80 (1.85-7.81). Stratified by sex, females (15) OR=5.23 (1.30-20.9) and males (45) OR=3.79 (1.58-9.11).<br><br>Extra-nodal NHL risk for workers (22) in high use areas of 2,4-D OR=9.73 (2.68-35.3).<br><br>Number in ( ) = exposed cases | Limitations:<br>Small sample size limits statistical power.<br>Cases and controls not interviewed, only work histories available. No info on smoking history, diet or medical history.<br><br>Strengths:<br>Includes all cases in farm worker population.<br>No recall bias (interviews not used). |

**Table 12: Recent Studies of Herbicide Exposures and Lymphohematopoetic System Cancers**

| *Source* | *Study Design & Population Description* | *Pesticide Type & Exposure Assessment* | *Measures of Association &Outcome* | *Main Findings RR 95% CI* | *Strengths & Limitations* |
|---|---|---|---|---|---|
| **Pahwa, 2006**[87] **Journal of Occupational and Environmental Medicine 48, 264-274**<br><br>**Hodgkin Lymphoma, Multiple Myeloma, Soft Tissue Sarcomas, Insect Repellents, and Phenoxyherbicides** | Population based case control study.<br><br>Cases: 1015 men aged <19 years who were residents in one of 6 Canadian provinces and had a first diagnosis of HL (n=316), MM (n=342), or STS (n=357) between Sep 1, 1991 and Dec 31, 1994.<br><br>Controls: 1506 men aged <19 years who were residents in same province as case and free of cancers of interest. 673 (44.7%) had lived/worked on a farm. Selected at random from provincial health insurance (4 provinces), computerized telephone listing (1 province) or voters' lists (1 province). Stratified by age ± 2 years. | Purpose: investigate the association between phenoxyherbicide exposure and HL, MM, STS, incorporating use of rubber gloves when mixing or applying pesticides and application of DEET into statistical models.<br><br>Structured postal questionnaire. Structured pesticide exposure telephone interviews for those who indicated exposure to 10 hours or more per year of pesticide exposure, and a 15% random sample of the remaining cases and controls.<br><br>Interviews: demographic data, occupation, occupational exposure history, indoor pesticide application, pattern of use of insect repellents on skin/clothing. | Age and province adjusted analysis of association between HL, MM, and STS risk and self reported exposure to each of following agents: insect repellants containing DEET, any phenoxyherbicide, 2,4-D, mecoprop, MCPA, any dicamba containing herbicides.<br><br>Age and province adjusted analysis of use of protective measures (rubber gloves, rubber moots, masks) and risk of HL, MM, and STS<br><br>Conditional logistic regression used to analyze potential modifying effect of DEET exposure on association between herbicides and HL, MM, and STS risk (adjusted for age and province).<br><br>Subgroup analysis conducted on participants who worked or resided on farm. | HL:<br>Self-reported exposure to any phenoxyherbicides, 2,4-D, mecoprop, or any dicamba containing herbicide not association with sig increased risk. DEET exposure associated with sig decreased risk among total population (OR=0.74, 95% CI: 0.55-0.09) (190 cases, 801 controls)<br><br>MM:<br>Self reported mecoprop exposure associated with sig increased risk among total population (OR=1.66 95% CI 1.02-2.71) (27 cases, 81 controls)<br>No sig risk for any other herbicides<br><br>STS:<br>No association between exposure to any phenoxyherbicide, 2,4-D, mecoprop or dicamba contrion herbicides<br>Use of rubber gloves associated with sig decreased STS risk (0R=0.56, 95% CI 0.33-0.95) (18 cases, 118 | Strengths:<br>Populations based study with large sample size.<br><br>Chance may be responsible for findings of risk associated with Mecoprop. This finding did not persist when analysis was restricted to individuals who lived/worked on farms. |

In a post hoc analysis of the same data, McDuffie[78] [Table 10] analyzed the association between the use of rubber gloves, pesticide exposure and exposure to DEET. While there was no observed association between self-reported exposure to 'any phenoxyherbicide', 2,4-D, mecoprop or dicamba and NHL risk in the total population (cases 513, controls 1506), significant associations were observed in the subgroup of participants who used DEET and rubber gloves and who had lived or worked on a farm. Among participants who lived or worked on a farm, used DEET and used rubber gloves, self-reported exposure to 'any phenoxyherbicides' was associated with a nearly two fold increased risk (OR=1.99; 95% CI: 1.06-3.74, 25 cases, 58 controls). Exposure to mecoprop was associated with increased risk among the population who used both DEET and rubber gloves (OR=2.05; 95% CI: 1.30-3.21, 38 cases 61 controls). This finding was strengthened when the analysis was restricted to those individuals who lived or worked on a farm (OR=3.86; 95% CI: 1.57-9.49, 12 cases, 15 controls). Similarly, self reported dicamba exposure was elevated among both the entire population who had used DEET and rubber gloves (OR=1.84, 95% CI: 1.23-2.75, 52 cases, 93 controls) and the population who reported living or working on a farm (OR=2.04, 95% CI: 1.02-4.06, cases 18 controls 40). These findings are limited, however, by the small number of participants in the stratified data and the lack of detailed exposure information[78]. It is possible that rubber gloves do not provide sufficient protection against exposure to the herbicides, perhaps due to lipophyllic nature of rubber from which these are made.

Miligi et al.[88], in a population-based case-control study of agricultural exposures in Italy, found an overall slight but non-significant association between ever/never exposure to phenoxyacetic acids and NHL (OR=1.1, 95% CI: 0.6-1.8). When the investigators looked at a sub-sample of those who did not use protective equipment, an elevated risk was found (OR=2.4, 95% CI: 0.9-7.6). Additionally, the risk of NHL and chronic lymphocytic leukemia (CLL) of those exposed to 2,4-D and who did not use protective equipment was found to be statistically significantly elevated (OR=4.4; 95% CI: 1.1-29.1). The exposure measure was developed using a detailed questionnaire on agricultural exposure to pesticides that was then analyzed by an expert agronomist and converted into pesticide exposure histories for each subject.

A recent nested case-control study of Hispanic farm workers in California study by Mills et al[86] [Table 11] developed measures of chemical exposure by combining pesticide application records with individual job histories and found a statistically significant association between NHL and 2,4-D (OR=3.8, 95% CI: 1.85-7.81). When decomposed into NHL subtypes, no significant association was observed between nodal NHL and 2,4-D (OR=2.29, 0.09-5.83); however, a strong association with extra nodal NHL was identified (OR=9.73, 95% CI: 2.68-35.3). Limitations of this study include the use of a quasi-ecological measure of exposure, the lack of individual level covariates and small sample sizes. A cohort study of Finnish pesticide applicators exposed to phenoxyacetic acids while spraying brushwood[49] noted a lack of elevated risk for both incidence and fatal NHL; however, the result was based on a small number of cases.

A study published by Schreinemachers[30] explored relationships between wheat acreage and cancer mortality in US states (North Dakota, Minnesota, South Dakota, Montana), using wheat acreage per county as a surrogate for chlorophenoxy herbicide exposure. The risk of death from NHL was not found to be associated with chlorophenoxy exposure (SRR=0.96; 95% CI: 0.8-1.16). A case-control study of NHL by Cantor, et al.[76] matched to population controls by age, vital status and state of residence, found no associations between ever/never use of 2,4-D (OR=1.2, 95% CI 0.9-1.6), 2,4,5-T (OR=1.2; 95% CI: 0.7-1.9), and dicamba (OR=1.2; 95% CI: 0.7-2.0) in relation to risk of NHL. Four other case-control studies did not find significant associations between NHL and exposure to chlorophenoxy herbicides[85], [89], [90], [91], [92]. For most of these studies, a crude exposure metric (ever/never used) was constructed using self-reported exposure data, with the exception of Hartge[85] who also measured pesticide residuals from carpet dust in a sub-sample. Use of such comparisons are less likely to detect true associations than those based upon comparisons of more extreme exposure categories such as highest vs. lowest quintiles. The authors point out that associations between 2,4-D exposure and NHL were based upon small sample sizes.

Another population-based case-control study was conducted in Washington State, with occupational exposure identified by job records[56]. Only those spraying forests with

herbicides were at statistically significantly higher risk of developing NHL (OR 4.8; 95% CI: 1.2-19.4). The investigators also examined latency period, and found the highest risk with those who had been exposed 25 years prior to diagnosis (OR 2.5; 95% CI: 0.5-13.0). They also observed an interaction between organic solvents and chlorophenoxy compounds (OR 1.50; 95% CI: 1.03-2.18). A population-based, Swedish case-control study of NHL conducted by Hardell et al[93] found a non-statistically significant association between hairy cell leukemia and 2,4-D and 2,4,5-T exposure(OR=1.48, 95% CI 0.99-2.2).

Several earlier occupational cohort studies have reported non-statistically significant excess of NHL mortality in workers exposed to chlorophenoxy herbicides during the manufacturing process. A mortality cohort study of 21,863 workers in 36 countries occupationally exposed to chlorophenoxy herbicides, chlorophenols, and dioxins (IARC study)[20] examined the risk of dying from NHL related to exposure. In this study, exposure was based on job records and company questionnaires. A non-statistically significant excess of deaths from NHL was found in those exposed to TCDD or dioxins (SMR 1.39, 95% CI: 0.89-2.06) and for any chlorophenoxy herbicide exposures (SMR 1.3, 95% CI: 0.9-1.8). Similarly, a cohort study of 18,390 workers from 10 countries occupationally exposed to chlorophenoxy herbicides by Saracci et al.[29] found an elevated mortality risk among production workers (SMR 1.49, 95% CI: 0.64-2.94). It should be noted however that this finding is based on 8 deaths. A mortality study of 2187 Dow Chemical Company workers exposed to dioxin[41] also found a slightly elevated but non-statistically significant association between dioxin exposure and NHL (RR=1.4; 95% CI: 0.6-2.7), as did a NIOSH study of mortality in 5172 workers from 12 manufacturing plants in the United States exposed to TCDD[28].

Rix[50] report a study of Danish paper mill workers in which a slightly elevated, but not statistically significant NHL risks among workers exposed to chlorophenoxy herbicides was observed (SIR=1.21; 95% CI: 0.80-1.76). This investigation also found a non-statistically significant elevated risk of NHL in male paper workers involved in stock preparation (SIR=1.96, no confidence interval reported). However, as workers involved in stock preparation are exposed to a wide variety of chemicals including

chlorophenoxy herbicides, the authors suggest that the observed association may be due to other exposure-related factors. The absence of an association between exposure to chlorophenoxy herbicides and NHL is also the conclusion of another mortality cohort of US manufacturing workers[42]. In this investigation, exposure was measured using job description and serum TCDD. No elevated risk of mortality was observed (SMR=1.10; 95% CI: 0.56-1.91). Kogevinas et al[55] conducted a nested case-control study of workers exposed to pesticides and found increased but not statistically significant associations between NHL and 2,4-D/DP: (OR=1.11; 95% CI: 0.46-2.65), 2,4,5-T: (OR=1.85, 95% CI 0.71-4.80), and any dioxin or furan: (OR=1.93, 95% CI 0.74-5.07).

Two studies have investigated the relationship between an ecological measure of chlorophenoxy exposure and NHL. A study of mortality in residents exposed to dioxin from Seveso plant explosion[35] compared three exposure zones were identified based on prevailing winds, soil measurements, and serum dioxin levels taken from sample of population living in three zones. The risk of fatal NHL in residents of the highest dioxin exposed zones was elevated (SMR=1.5; 95% CI: 0.7-3.2) and was highest 15-20 years after exposure (SMR=2.8; 95% CI:1.1-7.0).

Akhtar[23] observed an inverse association (lower risk of death among those more highly exposed) but not statistically significant from lymphopoietic cancers in a 35 to 40 year follow-up of Caucasian Vietnam Veterans (Ranch Hand veterans- 10 cases observed; 11.8 cases expected; SIR= 0.85; 95% CI: 0.4-1.5). The same pattern was observed when the analyses were restricted to veterans whose tour of duty ended between 1966 and 1970, the years when Agent Orange was the predominant herbicide in Vietnam. The authors raise the possibility of a ‘healthy worker’ effect but discount this in favour of an argument that the low level exposures encountered by Vietnam veterans were likely considerably less than those occupationally exposed to these compounds. It might be argued however that US military service personnel must undergo considerable testing to ensure that they are fit to serve and it is this process that selects healthier individuals into the exposed population. Also, an SIR of 0.85 was observed among Ranch Hand personnel while an SIR of 0.55 was identified for comparison personnel. The ratio between these two measures is 1.5 suggesting that, after controlling for this

'healthy worker 'effect, Ranch Hand personnel were at increased risk of developing NHL. These analyses were based on small numbers of cases and is subject to influences of random error.

Conclusions of 2004 IOM report

The Institute of Medicine comments that existing evidence suggests that 2,4-D and 2,4,5-T are responsible for the associations observed between Non-Hodgkin's Lymphoma and chlorophenoxy exposures for occupational cohorts. They also note that the Ahktar[23] study does not provide sufficient detail on specific types of lymphohematopoietic cancers to draw conclusions. The 2004 IOM concluded that there is sufficient evidence to conclude that an association exists between exposure to at least one of the compounds of interest and NHL. The evidence is drawn from occupational and other studies in which subjects were exposed to a variety of herbicides and herbicide components.

Synthesis of evidence for Gagetown chlorophenoxy herbicides and Non Hodgkin's Lymphoma

Recent evidence from the Chiu[84] study which notes risk differences between NHL molecular subtypes will likely foster further research on molecular toxicological mechanisms underlying these associations. This reviewer concurs that that there is sufficient evidence to conclude that an association exists between exposure to at least one of the compounds of interest and NHL.

- Hodgkin's Disease

There was no observed association between self reported exposure to 'any phenoxyherbicide', 2,4-D, mecoprop, or 'any dicamba-containing herbicides' and Hodgkin's Disease in the Canadian case control study by Pahwa et al[87] (cases=316, controls=1506) [Table 12]. This lack of association persisted when the referent group included individuals who had not been exposed to DEET, those who had not been

exposed to any phenoxy herbicides, and those who had used rubber gloves. No cases of Hodgkins Disease were observed in the Swaen et al.[18] cohort study of licensed herbicide applicators in the Netherlands, limiting the ability to draw conclusions. The lack of cases however suggests that chlorophenoxy exposure is not significantly associated with Hodgkin's Disease. Alavanja, et al. 2005[38] report of cancer incidence in the US Agricultural Health Study found an SIR=0.88, 95% CI: 0.44-1.57 for Hodgkin's Disease for private licensed applicators compared to the underlying state populations.

A mortality cohort study of workers at a chlorophenoxy herbicide manufacturing plant[94] in Germany found elevated risks for Non-Hodgkin's Lymphoma but not for Hodgkin's Disease. In contrast, Bertazzi et al.[43] noted an overall elevated risk for Hodgkin's disease in residents of the high exposure area in Seveso, Italy in the first ten year observation period (OR=4.9; 95% CI: 1.2-4.6).

Conclusions of the IOM 2004 Committee:

The IOM 2004 Committee noted the low incidence of this disease and the complications this creates in the evaluation of epidemiologic studies addressing this lymphoreticular tumour. They note however that that earlier studies were well conducted and point to an increased risk. These have been tabulated in their report. The IOM 2004 Committee also commented on the biological plausibility of chlorophenoxy herbicide exposure leading to the development of Hodgkin's Disease, due to its lymphoreticular origin and common risk factors to Non-Hodgkin's Lymphoma. On the basis of its evaluation of the epidemiological evidence for their current review and in previous studies, the committee concluded that there is sufficient evidence to state that an association exists between exposure to at least one of the Agent Orange compounds of interest and Hodgkin's Disease.

Synthesis of evidence for Gagetown chlorophenoxy herbicides and Hodgkin's Disease

This reviewer concludes that there is limited or suggestive evidence of an association between exposure to chlorophenoxy herbicides and Hodgkin's Disease. This is in light of recent studies, especially the investigation by Pahwa, et al. Other recent studies also suggest that current evidence is inconclusive and that further research needs to be done to examine specific chlorophenoxy herbicide exposure and etiology of Hodgkin's Disease.

m Multiple Myeloma

In the Canadian case control study conducted by Pahwa et al[87], self reported mecoprop exposure was associated with a significantly increased risk of multiple myeloma in a univariate analysis (OR=1.66, 95% CI: 1.02-2.71; 27 cases, 81 controls) of the total population. In a conditional logistic regression model where the referent group was individuals with no exposure to either DEET or mecoprop, an increased risk was also observed (OR 2.30; 95% CI: 1.03-5.14, 11 cases, 20 controls). The significance of this relationship, however, was not maintained when the analysis was restricted to the subgroup of the population who had lived or worked on farms (OR=1.21, 95% CI: 0.65-2.27; 16 cases, 51 controls). Moreover, the analysis did not account for individual variation in duration or intensity of exposure. There were no observed increased associations between self reported exposure to 'any phenoxyherbicide', 2,4-D, or 'any dicamba-containing herbicides' and multiple myeloma. Swaen[18] reported an elevated but non-significant risk for multiple myeloma (SMR= 2.14; 95% CI: 0.43-6.14; 3 observed, 1.14 expected cases) in the study of 1341 licensed herbicide applicators in the Netherlands. In another study by DeRoos of 57,311 licensed pesticide applicators in IA and NC, USA (Table 13) associations between 23 different pesticides and multiple myeloma were examined. No significant risks were observed for any chlorophenoxy herbicides.

Conclusions of 2004 IOM report

On the basis of its evaluation of the epidemiologic evidence reviewed here and in previous reports, the committee concludes there is limited or suggestive evidence of an association between exposure to at least one of the compounds of interest and multiple myeloma. The evidence regarding this conclusion is drawn from earlier occupational and other studies in which subjects were exposed to a variety of herbicides and herbicide components.

Synthesis of evidence for Gagetown chlorophenoxy herbicides and Multiple Myeloma

The few recent studies, especially those conducted at the University of Saskatchewan, that have been reported to the literature since the release of the 2004 IOM report support the conclusions of the IOM Committee. This reviewer agrees there is limited or suggestive evidence of an association between exposure to chlorophenoxy herbicides and multiple myeloma.

n Leukemia

In reviewing the scientific literature on chemical exposures and leukemia, a major challenge is that not all studies look at leukemia by subtype. There are four major types of leukemia: acute and chronic forms of lymphocytic leukemia, and acute and chronic forms of myeloid (or granulocytic) leukemia. The lack of type-specific analyses may lead to the inability to observe associations between exposures and particular subtypes.

**Table 13: Recent Studies of Herbicide Exposures and Lymphohematopoetic System Cancers**

| *Source* | *Study Design & Population Description* | *Pesticide Type & Exposure Assessment* | *Measures of Association & Outcome* | *Main Findings RR 95% CI* | *Strengths & Limitations* |
|---|---|---|---|---|---|
| **DeRoos, 2005[95] Environ Health Perspect 113, 49-54** | Prospective cohort study<br><br>57,311 licensed pesticide applicators in IA and NC, USA<br><br>Enrolled from 1993-1997, followed until 2001 | Self-administered questionnaire (at enrollment):<br>Collected data on pesticide application methods, personal protective equipment, pesticide mixing and equipment repair<br><br>Detailed information on the use of 22 pesticides<br>and ever/never used for 28 other pesticides<br><br>Constructed three measures of glyphosate exposure:<br>1) Ever/never used<br>2) Cumulative exposure days<br>3) Intensity-weighted cumulative exposure days | Outcome: incident cancers (ICD-9)<br><br>Poisson regression to calculate RR of cancers with n>30, by comparisons of high exposed subjects to referent category (low or non exposed subjects). Also tested for trend.<br><br>Adjusted for age, demographic and lifestyle factors, and other pesticides | A suggestive association was observed between glyphosate exposure (ever/never and duration/frequency) and multiple myeloma RR 2.6 (0.7-9.4) (cases n=32).<br><br>A suggestive dose-response relationship (across tertiles of cumulative exposure days - tertile 1: RR = 2.3 (0.6-8.9); tertile 2: RR = 2.6 (0.6-11.5); tertile 3: RR = 4.4 (1.0-20.2); *p*-value for trend = 0.09)<br><br>No association between glyphosate exposure and all cancers and most specific cancer subtypes, including NHL | Looked for potential confounding effect of other pesticides<br><br>Absence of recall bias due to study design<br><br>Latency period not accounted for<br><br>Identified limitations include that the observations of increased risk of multiple myeloma with exposure may be due to selection bias due to the exclusion of subjects lacking complete information on covariates, or potential confounding<br><br>Also, due to small numbers, precise estimation of RR of multiple myeloma was not possible<br><br>Given that the sample was 97% male, the results are not generalizable to women |

Two studies[96,97] were identified in our literature search in which the investigators did not use any pesticide-specific exposure information; instead, these case-control studies both report significant associations between farming and leukemia (ORs 1.3-1.9). Multiple hypotheses have been put forward to explain these associations.

The association between leukemia and exposure to chlorophenoxy herbicides has been the subject of several case-control studies published since the IOM VAO report. The nested case-control study of Hispanic farm workers in California by Mills et al[86] [Table 10] employed union records and data from the detailed California Pesticide Databank to assess the association between agricultural exposures and different forms of lymphohematopoietic cancers (131 LHC cases, 655 controls). There were no observed associations between all leukemia cases (n=51) or lymphocytic leukemia (n=28), or granulocytic leukemia (n=20) and 2,4-D exposure. This relationship persisted when the analysis was stratified by gender. Despite this lack of chemical-specific association, the authors noted a significantly elevated risk of leukemia among females who worked with vegetables (OR=4.01, 95% CI 1.11-14.56; sample size not provided). These results must, however, be interpreted with caution due to the lack of other exposure data details, individual level covariate information, use of an ecological measure of exposure, and small sample size in the stratified analysis. Another recent case control by Miligi[88] used an agronomist-verified questionnaire to examine the association between agricultural exposures and risk of hematolymphopoietic cancers among Italian men and women. A slightly elevated, non-significant risk of leukemia from exposure to all herbicides was observed (OR=1.4; 95% CI 0.8-2.3; 28 exposed cases). Similarly, there was an elevated yet non-significant relationship between exposure to chlorophenoxy herbicides and leukemia risk (OR=1.7; 95% CI 0.7-4.2;8 exposed cases). This finding is limited by the lack of specific information on type of herbicide, as well as lack of information on the duration, frequency, and intensity of exposure. Furthermore, neither the Mills nor Miligi study assesses the risk of specific types of leukemia.

Consistent with these recent studies, a recent case-control study by Brown et al[98] (579 cases, 1245 controls) found no association between exposure to specific chlorophenoxy

herbicides and leukemia risk among rural men in Iowa and Minnesota (ever/never mixed handled or applied: 2,4,5,T: (OR=1.3, 95% CI:0.7-2.2), dicamba: (OR=0.7, 95% CI: 0.4-1.4), 2,4-D: (OR=1.2, 95% CI 0.9-1.6). There was, however, a modest increased risk of chronic lymphocytic leukemia among men who reported ever farming (OR=1.4, 95% CI: 1.1-1.9; 156 cases 698 controls) and among men who reported ever use of any herbicide (OR=1.4, 95 % CI: 1.0-2.0; 74 cases, 344 controls). These elevated risks were not present in the analysis of acute non-lymphocytic, chronic myelogenous, or acute lymphocytic leukemia.

Four historical cohort studies that assessed exposure in occupational settings similarly did not find any evidence of a relationship between chlorophenoxy exposure and risk of all types of leukemia. The NIOSH study[28] of 5,172 workers from 12 manufacturing plants in the United States measured 2,4,5-T exposure via industrial hygiene assessment of job site and duties. This estimate was validated through serum analysis of TCDD in a subset of workers. There was no excess mortality due to leukemia or aleukemia among the total cohort (SMR 0.67; 95% CI: 0.24-2.46) or among workers with greater than one year of exposure (SMR 0.77; 0.09-2.77). These findings, however, were based on 6 and 2 observed leukemia deaths respectively and, therefore, have notably wide confidence intervals. In a further analysis of this cohort that included six more years of follow-up, there was no elevated mortality due to leukemia and aleukemia (SMR=0.81, 95% CI: 0.38-1.48; 10 cases)[42]. The IARC cohort study of 26, 976 workers from 12 countries similarly used job records and questionnaires to assess TCDD exposure[20]. There was no indication of mortality due to leukemia among workers exposed any phenoxy herbicide (SMR=1.00, 95% CI: 0.69-1.39; 34 cases) or among workers exposed to TCDD or higher chlorinated dioxins (SMR=0.73, 95% CI: 0.42-1.19; 16 cases) using the World Health Organization mortality data bank to calculate national mortality rates. The Dow Chemical company cohort study assessed cancer mortality among 1567 employees potentially exposed to 2,4-D[99]. There was no excess mortality due to leukemia or aleukemia when the US male population was used as a referent population. There was, however, indication of elevated mortality of all lymphopoietic cancers among workers with the highest levels of exposure in contrast to unexposed workers (SMR= 2.05; 4 observed cases). This relationship was

strengthened when the analysis accounted for a twenty year latency period (SMR= 2.71; 4 observed cases). 95% confidence intervals were not reported. Risk estimates from each of these studies may be biased because of misclassified outcomes based on death certificates and the absenced of data on potential confounders such as lifestyle factors.

A historical cohort study by Rix et al.[50] investigated the association between leukemia and the risk of occupational exposure to chemicals, including dioxins and furans, used in Danish paper mills. An excess incidence of leukemia was not found among men or women employed in paper mills (men OR=0.79; 95% CI: 0.48-1.22; 20 exposed cases); (women OR=1.30, 95% CI 0.52-2.68; 7 exposed cases) nor were elevated rates of leukemia identified for any specific job title. These findings are likely subject to exposure misclassification and there was no adjustment for confounding.

Summary of 2004 IOM Report

The VAO Update 2004 report concluded that there is inadequate or insufficient evidence to determine an association between Agent Orange and leukemia types, other than for chronic lymphocytic leukemia (CLL). They concluded that there is sufficient evidence of an association between CLL and compounds of interest. They note that although considerably more studies support the hypothesis that herbicide exposure can contribute to the development of NHL, exposure to the herbicides 2,4-D and 2,4,5-T also appears to be associated with occurrence of CLL.

Synthesis of evidence for Gagetown chlorophenoxy herbicides and leukemia

The findings of one new study of chronic lymphocytic leukemia are consistent with the IOM position on this cancer. Studies are relatively few, however, and differentiation of leukemia into its subtypes is not often reported in the current literature. This reviewer concludes that there is limited or suggestive evidence of an association, rather than sufficient evidence of an association, between exposure to chlorophenoxy herbicides,

and chronic lymphocytic leukemia but inadequate or insufficient evidence to determine an association for the other subtypes of leukemia.

## 2. Reproductive Outcomes

a Spina bifida and other congenital anomalies

Lawson, et al.[100] studied pregnancy outcomes among wives of male chemical workers who were highly exposed to chemicals contaminated with dioxin compared with wives of non-exposed, neighbourhood referents, controlling for paternal serum TCDD at time of conception as a measure of exposure [Table 14]. Only full term births were included in the analysis. This study relied heavily on self-reported data. Mean birth weights were similar in the two groups even after adjustment for TCDD concentrations. These results are consistent with the findings of another case-control study of Vietnam Veterans' risks for fathering babies with congenital anomalies[101]. The investigators reported that there was no evidence that Vietnam Veterans had a greater risk than other men for fathering babies with all types of serious structural birth defects. In a more recent case-control study[102] of Vietnamese women who were resident in the country at the time of the Agent Orange sprayings, no significant difference was found between cases and controls (OR= 0.7; 95% CI: 0.2-1.8) in relation to a cumulative Agent Orange exposure index and risk for gestational trophoblastic disease, nor was such a difference noted for self-reported possible exposure to agricultural herbicides.

In a study of children of agricultural pesticide applicators[103], where chlorophenoxy herbicides were identified as the most frequent herbicidal agents applied, conceptions in the spring resulted in significantly more children with birth defects than found in any other season (7.6 vs. 3.7%). Patterns of elevated circulatory/respiratory anomalies risk were also identified in association with ecological markers of these compounds.

**Table 14: Recent Studies of Herbicide Exposures and Reproductive Outcomes**

| *Source* | *Study Design & Population Description* | *Pesticide Type & Exposure Assessment* | *Measures of Association & Outcome* | *Main Findings* | *Strengths & Limitations* |
|---|---|---|---|---|---|
| **Lawson, 2004 Environmental Health Perspectives, 112(14), 1403-1408** | Cross-sectional study of paternal dioxin exposure and birth weight and preterm delivery in offspring<br><br>Workers identified from plants in NJ and MO.<br><br>Referents selected from workers neighborhood, matched on age, race, and sex.<br><br>604 referent births<br>221 worker birth conceived prior to exposure<br>292 worker birth conceived post-exposure | TCDD levels analyzed from serum samples<br><br>Demographic, medical, reproductive history obtained from workers and wives<br><br>Pregnancy conceived after fathers first date of exposure considered, workers TCDD serum level at time of conception estimated from pharmacokinetic model | Repeated analysis of variance performed to analyze differences in birth weight and preterm labor<br><br>Number of birth defects too small to permit quantitative analysis | No effect of TCDD concentration (continuous or categorical) on birth weight (controlled for sex, maternal education, parity, smoking, gestation length) for whole population<br><br>Among women whose gestation overlapped husbands exposure, paternal TCDD [] associated with sig increase in birth weight (p=0.03)<br><br>Preterm delivery<br>TCDD exposure protective association with preterm birth<br>OR=0.8<br>95% CI: 0.6-1.0<br>(297 exposed births) | Strengths:<br>Potential confounders controlled for (info obtained in mother's interview)<br><br>Biological measurement of TCDD<br><br>Limitations:<br>Number of preterm births and birth defects low<br><br>Recall bias - mother was source of birth weight when birth certificate not available<br><br>Serum TCDD levels at time of conception estimated (actual measurement done several years afterward)<br><br>Method of referent recruitment precluded ability to assess refusal rate and potential for participation bias |

A similar pattern was reported in a study by Schreinemachers[104] that examined birth malformations and other perinatal outcomes in four wheat producing US states. A significant OR of 1.65 (95% CI: 1.07-2.55) was observed for circulatory/respiratory birth malformations. This association became stronger when heart defects were excluded. In addition, infants conceived during the spring had an increased chance of being diagnosed with these malformations compared to infants conceived at other times of the year. Also, infant death from congenital anomalies significantly increased in high wheat counties for males. Rull et al[155] conducted a pooled analysis of 2 case-control studies in California that revealed a statistically non-significant but elevated NTD risk (OR= 1.4; 95% CI: 0.9-2.4; single pesticide model; OR= 1.5; 95% CI: 0.8-2.7; multiple pesticide model) related to prenatal maternal residence less than 1 kilometre from areas with documented agricultural use of 2,4 D or derivatives. No other relevant studies on the association between parental exposure to 2,4-D, 2,4,5-T, TCDD, and other Agent Orange compounds and spina bifida in offspring were found in our scan of the recent literature. Other agricultural exposures, such as high concentration of nitrates in groundwater, might possibly explain these associations.

Conclusions of 2004 IOM report

As noted in the report, there were no new studies of the Agent Orange compounds of interest and spina bifida in offspring. The committee concluded that the evidence is still limited or suggestive of an association between exposure to the Agent Orange compounds and spina bifida.

Synthesis of evidence for Gagetown chlorophenoxy herbicides and spina bifida

The few new studies summarized above do not add significant evidence for a strong association between exposure to chlorophenoxy herbicides and spina bifida. This reviewer agrees that the evidence is still limited or suggestive of an association between exposure to the Agent Orange compounds and spina bifida.

b Fertility

Fertility is affected by both paternal and maternal reproductive functional factors. A woman is considered infertile if, after a period of 12 months of unprotected intercourse, she fails to conceive a pregnancy. Male infertility may result from interference with normal reproductive hormone production or from sperm immobility. There have been few studies of fertility and chlorophenoxy herbicide exposure since 2004.

Conclusions of 2004 IOM report

The committee concluded that there is inadequate or insufficient evidence to determine an association between exposure to the Agent Orange compounds and decreased sperm counts; or sperm quality, subfertility, or infertility.

Synthesis of evidence for Gagetown chlorophenoxy herbicides and fertility

The lack of studies does not add new evidence for a strong association between exposure to chlorophenoxy herbicides and fertility. This reviewer agrees that there remains inadequate or insufficient evidence to determine an association between exposure to chlorophenoxy herbicide compounds and decreased sperm counts; or sperm quality, subfertility, or infertility.

c Spontaneous Abortions

In a highly informative study by Arbuckle, et al.[105], the investigators examined risk for spontaneous abortion by herbicide class and by exposure period in the Ontario Farm Family Health Study. With more than 2000 farm families participating with 3,936 pregnancies, the authors reported increased risks of early abortions (<12 weeks) associated with general preconception exposures to chlorophenoxy acetic acid herbicides [OR=1.5; 95% CI: 1.1-2.1] and slightly elevated but not statistically significant risks specifically associated with 2,4-D [OR=1.3; 95% CI: 0.9-2.0) exposure. 2,4-DB [OR=1.4; 95% CI: 0.7-2.8] preconception exposures were not statistically elevated. It is noteworthy that increased risks for late spontaneous abortions were observed with preconception exposure to thiocarbamates (OR= 1.8; 95% CI: 1.3-3.0). Exposures occurring within the first 3 months of conception did not show significant associations. Maternal age was a strong risk factor in these analyses. No other relevant studies on the association between parental exposure to 2,4-D, 2,4,5-T, TCDD, cacodylic acid or picloram and fertility were found in our review of the literature..

Conclusions of the 2004 IOM Committee

The Committee concluded that the evidence is still limited or suggestive of an association between maternal or paternal exposure to chlorophenoxy herbicides and spontaneous abortions.

Synthesis of evidence for Gagetown chlorophenoxy herbicides and spontaneous abortion

Data are still limited on the relation between chlorophenoxy herbicide exposures and spontaneous abortions. Nevertheless, the strength of the Arbuckle study provides important information that further supports the conclusion that there is limited or

suggestive evidence of an association between exposure to chlorophenoxy herbicide exposure and spontaneous abortions.

d Stillbirths, Neonatal Deaths, and Infant Death

Wigle and Mao[106] studied health effects resulting from defoliant spraying at CFB Gagetown, New Brunswick, that occurred in the mid 1960's and found that the numbers of deaths by gender and cause of death in Sunbury County in 1966-1976 were similar to or less than those expected based on national rates with the exception of deaths due to accidents and other violence among males. The stillbirths plus neonatal mortality ratio for Sunbury County was observed to be significantly higher than that for Oromocto during the period 1965-1967. This was consistent with other rural-urban trends nationally during the same period. Seasonal fluctuations were also found but attributed to random variation resulting from small numbers. No geographic clustering of stillbirths or neonatal deaths within parishes was observed. The authors concluded that the defoliant tests resulted in no significant increase of adverse pregnancy outcome events in the population adjacent to CFB Gagetown. It should be noted that this report was peer reviewed by several prominent epidemiologists and toxicologists who signed a statement at the end of the report concurring with the conclusions of the authors.

Conclusions of the 2004 IOM Committee

The committee concluded that there is inadequate or insufficient evidence to determine an association between exposure to the Agent Orange compounds and stillbirth, neonatal death, or infant death.

Synthesis of evidence for Gagetown chlorophenoxy herbicides and Stillbirths, Neonatal Deaths, and Infant Death

Despite the interesting findings by Wigle and Mao, the authors noted that the pattern they observed may have reflected regional trends during the same period. This

reviewer concludes that there is still inadequate or insufficient evidence to determine an association between exposure to the Gagetown chlorophenoxy compounds and stillbirth, neonatal death, or infant death.

e Childhood cancers

Chen[107] recently completed a case-control study involving 253 cases and 394 controls to examine the association between parental occupational exposure to pesticides and risk of childhood germ-cell tumours. Information on occupational pesticide exposure was collected using job-specific questionnaires and assessed by an experienced occupational hygienist. Odds ratios for childhood germ-cell tumours associated with maternal exposures prior to pregnancy, during pregnancy, and after the birth of the infant were 1.0, 1.1, and 1.3, all non-significant. Subgroup analyses showed a positive association between maternal exposure to herbicides during the postnatal period and risk of germ-cell tumours in girls (OR=2.3; 95% CI: 1.0-5.2) and an inverse association between paternal exposure to pesticides during the pregnancy and germ cell tumours in boys (OR=0.2; 95% CI: 0.1-1.0).

In a study published in 2004, Flower et al.[108] examined risk of childhood cancer in offspring of Iowan male pesticide applicators and did not find significant associations in relation to maternal use of chlorophenoxy herbicides, paternal exposure to chlorophenoxy herbicides. The study did not stratify by specific cancer types. Reynolds et al[109] studied risk of childhood cancer in relation to mother's residential proximity to agricultural applications of pesticides at the time of the child's birth, involving 2189 childhood cancers. Over one-third of cases were leukemias and about one-sixth of cases were central nervous system-related tumours. None of the specific agents investigated in this study were part of the Gagetown list, though organochlorines were one of the general categories. Nevertheless, rates of childhood leukemia, lymphoma and other forms of childhood cancer were not observed to be significantly elevated in the higher exposure regions compared to the lower exposed regions. An investigation by Wijngaarden et a[110] examined the risk of childhood brain cancer in relation to parental exposure to classes of pesticides among 154 children diagnosed with astrocytoma and 158 children diagnosed with primitive neuroectodermal tumours

in the US and Canada between 1986 and 1989. Herbicide exposure in fathers was associated with an increased OR of 1.6 (95% CI: 1.0-2.7) for astrocytomas.

Conclusions of the 2004 IOM Committee

The committee concluded that there is inadequate or insufficient evidence to determine an association between exposure to the compounds of interest and childhood cancers.

Synthesis of evidence for Gagetown chlorophenoxy herbicides and Childhood Cancers

Despite recent interesting findings by Chen and Wijngaarden that identifies 'herbicide' exposure as being linked to elevated risk of childhood cancers, the lack of specific herbicide compound data prevent drawing significant conclusions about these results. Further research is needed that examines in greater detail specific herbicide agents. This reviewer concludes that there is still inadequate or insufficient evidence to determine an association between exposure to the Gagetown chlorophenoxy compounds and childhood cancers.

## 3. Neurological outcomes

a. Parkinson's Disease

Although previous research has identified positive associations between Parkinson's Disease (PD) and pesticides[111], there are few studies with detailed exposure data. Pesticide exposure in most of the studies published to date is commonly defined by occupation or residence in an agricultural region and rarely includes information on specific classes or types of pesticides. Summarizing the data from this body of literature is further challenged by the lack of consistent disease identification. Whereas some studies recruit only neurologist-confirmed cases, others rely on self-reported symptoms or diagnosis to identify cases. The multiple manifestations of the disease, variation in case definitions, and lack of detailed exposure assessment data are notable obstacles to understanding the relationship between the herbicides of interest and

**Table 15: Recent Studies of Herbicide Exposures and Parkinson's Disease**

| *Source* | *Study Design & Population Description* | *Pesticide Type & Exposure Assessment* | *Measures of Association & Outcome* | *Main Findings RR 95% CI* | *Strengths & Limitations* |
|---|---|---|---|---|---|
| **Firestone, 2005 Archives Neurology 62, 91-95** | Case control study<br>Cases: HMO Parkinson's Patients (250)<br>Controls: HMO Patients with no history neurlogical disease (388)<br><br>Identified 1992-2002<br><br>Frequency matching on age, sex, HMO clinic location, enrollment year | Structured interview: demographics, medical occupational history, occupational home pesticide use, drinking water source, residential history, smoking history<br><br>Pesticide exposure based on checklist of common agents.<br><br>Cumulative exposure categorized as ordinal variables<br><br>Pesticides assessed by class (any, insecticide, herbicide, fungicide, OP, parathion, diazinon, malathion, paraquat) | Unconditional logistic regression model adjusted for age, sex, and smoking status<br><br>Occupational Exposure: No significant association but trend of risk seen with type of occupation<br><br>Residential: No sig association seen with pesticide exposure. | Occupational Exposure<br>Pesticide Workers (7)<br>2.07 (0.67-6.38)<br>Men exposed to herbicides (9)<br>1.41 (0.51-3.88)<br>Men exposed to paraquat (2)<br>1.67 (0.22-12.76)<br><br>Residential Exposure<br>Herbicide Exposure (116)<br>1.09 (0.77-1.53)<br>Lifelong well water use (28)<br>1.81 (1.02-3.21)<br><br>Number in ( ) = exposed cases | Study population largely urban<br><br>Number of individuals exposed to paraquat (n=4) and herbicides (n=17) may have been too small to assess association<br><br>Recall bias minimized by blinding subjects to study hypothesis<br><br>Pesticide use within 5 yrs of dx discounted<br><br>Did not account for commercial application in residences |

Parkinson's Disease. The next few paragraphs highlight the recent literature but do not assess specific herbicides. Due to the lack of studies that examined the herbicides of interest, these studies are reviewed in order to reveal current research activities and general conclusions.

Two cohort studies and one case-control study in Southwestern France[112,113] and Hawaii[114] identified a significant association between agricultural exposures and Parkinson's Disease. The Petrovitch study[114] identified employment in sugarcane and pineapple plantations as surrogates for exposure among a cohort of individuals in the Honolulu Heart Program . In this study, there was a significant dose-response relationship between number of years worked on a plantation and risk of Parkinson's disease after adjustment for age, pack-years of smoking, and coffee intake, especially with longer term work on a plantation (> 20 years RR=1.9; 95% CI: 1.0-3.5, $p<0.006$). Herbicides, including pentachlorophenol, diuron, and other compounds, constituted more than 90% of the total amount of pesticides used on sugarcane and 32% of all pesticides used on Hawaii during 1945-1970, the exposure period prior to subject enrollment. Exposure was defined as duration of years of employment on a plantation at time of enrollment. Cases were confirmed from medical records and a neurological exam.

In the cohort study of 1026 French men and women aged 65 and older[113], a cumulative exposure index was generated from self-reported occupational and residential histories. Among men with a history of occupational exposure to pesticides, there was a five fold increased risk in neurologist-confirmed Parkinson's Disease (RR=5.63; 95% CI: 1.47-21.58, 24 cases). This relationship was not significant for women. No significant associations were observed between Parkinson's Disease and self-reported occupation in agriculture, rural residency, or residency in a district planted with vineyards. The case-control study by Baldi et al[112] in the same region similarly used a job exposure matrix to assess exposure and reported an elevated risk of Parkinson's Disease among individuals with a history of occupational exposure to pesticides (OR=2.20, 95% CI: 1.11-4.34, 19 cases). Disease diagnosis was confirmed according to the United Kingdom Parkinson's Disease Society Brain Bank clinical diagnosis criteria. Although

the analysis did not include data on specific pesticides, the authors report that fungicides are the dominant chemical used in vineyards.

These findings are consistent with the ecological study by Ritz and Yu[115] that used mortality and county-level pesticide use data to investigate the relationship between Parkinson's Disease and agricultural exposures. The authors reported significantly elevated mortality due to Parkinson's Disease among residents of California counties with the highest levels of pesticide use for the time period of 1984-1988 (OR=1.19; 95% CI: 1.06-1.34) and 1989-1994 (OR 1.45; 95% CI 1.32-1.59).

Another recent study[116] demonstrated an 80% increased risk of neurologist-confirmed Parkinson's Disease among individuals in the Cancer Prevention Study II Nutrition Cohort (cases: 413, non-cases: 143,325) who reported a history of pesticide exposure (RR 1.8; 95% CI 1.3-2.3). Self-reported exposure status did not include any specific information on duration, frequency or type of pesticide exposure.

In contrast to these previous studies, a case-control study by Pals et al[117] in Belgium (cases 205, "spouse"-controls 423) reported no association between pesticide exposure and Parkinson's Disease, confirmed by a neurological exam. Other than a trend towards higher organophosphate exposure among cases, there was no difference in self-reported exposure to any other classes of pesticides nor to any specific chemicals between cases and controls. Important exposure methodological details are lacking in this report, limiting full interpretation of these study findings.

The US Agricultural Cohort study investigators examined associations between pesticide exposure and risk of both incident and prevalent Parkinson's Disease among licensed pesticide applicators from North Carolina and Iowa[118]. Cases were identified as individuals who responded positively to the question 'Has a doctor ever told you that you had been diagnosed with Parkinson's Disease?' at enrollment or during a 5 year follow-up interview. Both cases (incident n=78, prevalent n=83) and controls (n=79, 557 at enrollment n=55,931 at follow-up) completed extensive pesticide exposure questionnaires. A significant association and dose-response relationship between cumulative pesticide use and Parkinson's Disease risk was observed among incident

cases: [highest level of exposure OR=2.3; 95% CI: 1.2-4.5; cases = 24, p<0.009] but not among prevalent cases [highest level of exposure OR=0.8; 95% CI: 0.4-1.5, cases=16, p<0.49]. No associations were observed between Parkinson's Disease risk and exposure to specific chlorophenoxy herbicides: [dicamba: (prevalent cases (26): OR=0.9; 95% CI 0.5-1.6, incident cases (32) OR=1.5; 95% CI: 0.8-2.8*)*, 2,4-D (prevalent cases (47) OR=0.9; 95% CI: 0.5-1.8), incident cases (49) OR=1.0; 95% CI: 0.5-2.1), or 2,4,5, TP (prevalent cases (4) OR=0.8; 95% CI: 0.3-1.9, incident cases (7) OR=0.9; 95% CI: 0.4-1.8)]. However, a borderline association was observed for exposure to 2,4,5-T and incident cases (n=24) OR=1.8; 95% CI: 1.0-3.3 but not for prevalent cases (n=16) OR=0.9; 95% CI: 0.5-1.7. There was a non-significant trend towards decreased risk of Parkinson's Disease among individuals who reported the highest level of personal protection use. This trend was evident for both incident and prevalent cases. Despite the potential recall bias and disease misclassification resulting from the use of self-reported exposure and disease history, this large cohort study is only in the early stages of follow-up and it will be interesting to review study findings with longer periods of analysis.

A Canadian population-based case-control study by Semchuk et al.[119] was one of the initial investigations to examine, in detail, relationships between Parkinson's Disease and agricultural exposures among 130 neurologist-confirmed cases and 260 community controls. The conditional logistic regression multivariate analyses revealed a three-fold increased risk of PD for individuals with a history of herbicide use (OR=3.06; 95% CI: 1.34-7.00). Exposure data, obtained from an interviewer-administered questionnaire, included information on duration of exposure at different ages. This increased risk persisted when the model was adjusted for other exposure variables (insecticide use, fungicide use, agricultural work, crop farming, grain farming, market gardening, wood processing). Previous occupational herbicide use was consistently the only significant predictor of PD in the multivariate analysis including other exposure variables. The study did not have the power to assess the relationship between PD and specific types of herbicides, but interviews were reviewed to identify specific herbicides reported by participants. Among the 41% of cases who could recall the type of chemicals they had

used, all but one had used chlorophenoxy and thiocarbamate chemical compounds exclusively.

Conclusions of the 2004 IOM Committee

On the basis of the epidemiological evidence reviewed in their report, the 2004 IOM Committee concluded that there remained inadequate or insufficient evidence of an association between exposure to the Agent Orange compounds of interest and Parkinson's Disease.

Synthesis of evidence for Gagetown chlorophenoxy herbicides and Parkinson's Disease

This reviewer believes that there is limited or suggestive evidence of an association between exposure to the chlorophenoxy compounds of interest and Parkinson's Disease. This is based upon studies that have been published since 2004. The current evidence is especially lacking in studies that contain specific exposure data though the Semchuk study provided important information to support this finding especially since it adjusted for exposure to other types of pesticides.

b. Peripheral Neuropathy

The ability to assess the relationship between peripheral neuropathy and pesticide exposure is complicated by the multiple manifestations of the disease and the potential for confounding created by highly prevalent diabetes. Past IOM committees have concluded that there is evidence for an association between exposure to at least one of the Agent Orange compounds of interest and acute or subacute transient neurological symptoms[1]. It is difficult, however, to determine whether the peripheral nervous system effects of such exposures persist with time. Researchers who have studied Vietnam veterans and plant workers have attempted to assess these relationships.

The study of Operation Ranch Hand Vietnam veterans by Michalek[120] demonstrated an increased risk of peripheral neuropathy among veterans with the highest level of dioxin

exposure (n= 269). The risk of peripheral neuropathy among Operation Ranch Hand veterans was compared to Comparison veterans, those who had served in Southeast Asia during the same time but were not involved in spraying herbicides. Serum 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,6,8 TCDD) was measured and used to estimate dioxin levels at the time of service in Vietnam. The presence of peripheral neuropathy was determined by completion of standardized neurological examinations conducted in 1985, 1987, 1992 and 1997 by a board certified neurologist. Peripheral neuropathy were based on presence of one or more of the following signs; abnormal light touch, abnormal pin prick, abnormal vibration, abnormal joint position, abnormal equilibrium, abnormal ankle/toe flexor strength, absent Achilles reflex. There was a significant relationship and dose-response trend between peripheral neuropathy and individuals with the highest level of 2,3,7,7 TCDD (> 10 parts per trillion) based on the neurological exams conducted in 1997 (Any symmetrical peripheral neuropathy OR=1.8; 95% CI: 1.2-2.7, 45 exposed p=0.01) but not for earlier years. The analysis adjusted for diabetes. Excluding participants with diabetes resulted in a sample size too small to perform any analysis.

The cross sectional study of by Kim et al[121] reported an increased risk of peripheral neuropathy among Korean Vietnam veterans (n=1,224) compared to Korean non-Vietnam veterans (n=154). Exposure to Agent Orange was estimated using self-reported exposure, service locations, and service duration and validated using serum TCDD levels. Nerve conduction velocity tests and full clinical assessments were conducted by one of two neurologists. Vietnam veterans had an increased risk of peripheral neuropathy (OR= 2.39) compared to non-Vietnam veterans, after adjusting for age, smoking, alcohol, body mass index, education and marital status. Lack of clarity on certain design details and possibility for selection bias due to low participation rates limit drawing significant conclusions from this investigation. Nevertheless, the results provide some limited evidence of an association between chronic peripheral neuropathy and Vietnam exposures.

Sweeney et al[122] reported no association between increasing TCDD levels and peripheral neuropathy in an earlier, cross-sectional study of plant workers potentially

exposed to 2,4,5-T, 2,4-D, and dioxin in New Jersey and Missouri. Plant workers (n=265) were matched to community referents (n=244) on age, race, and gender. Serum TCDD levels were used as a surrogate for occupational exposure that occurred 15-37 years prior to the present study. Peripheral neuropathy was assessed by means of a standardized neurological exam. Workers with peripheral neuropathy did not have significantly different TCDD levels than workers without peripheral neuropathy. In a multiple logistic regression model, serum TCDD was not associated with elevated risk for peripheral neuropathy and these results were not markedly changed after adjustment for diabetes in the model.

Conclusions of the 2004 IOM Committee

On the basis of its evaluation of the available epidemiological evidence reviewed in 2004 and in previous reports, the committee concluded that there is limited or suggestive evidence of an association between exposure to the Agent Orange compounds of interest and early onset transient peripheral neuropathy. However, the committee also concluded that there is inadequate or insufficient evidence to determine an association between exposure to the compounds of interest and delayed or persistent peripheral neuropathy.

Synthesis of evidence for Gagetown chlorophenoxy herbicides and Delayed or Persistent Peripheral Neuropathy

This reviewer concludes, based upon the current state of evidence, that there is inadequate or insufficient evidence of an association between exposure to the chlorophenoxy compounds of interest and Delayed or Persistent Peripheral Neuropathy. No new studies have been reported to the literature since the 2004 IOM report. While the Michalek study is interesting, the significant challenges with establishing a proper diagnosis and the need to differentiate between acute and persistent forms of this disease, the possible influences of diabetic-caused peripheral neuropathy and the general failure to control for diabetes in the current work are

especially problematic. Further research is needed that incorporate these considerations in the study of these exposure-disease associations.

## 4. Diabetes

There is increasing interest in the role of environmental factors in contributing to the onset of Type 2 diabetes mellitus. An analysis of Type 2 diabetes mellitus and exposure to dioxin in Air Force veterans of Operation Ranch Hand found an elevated risk of diabetes in the subgroup with the highest serum TCDD levels (Hendriksen, 1997). A non-statistically significant elevated risk for diabetes (RR= 2.5; 95% CI: 0.53-9.50) was observed in a pooled analysis[123] of the 36 cohorts comprising the IARC study. More recently, Kang et al[124] noted that the odds ratio for self-reported diabetes was elevated (OR=1.5; 95% CI: 1.15-1.95, adjusted for race, BMI, obesity, current smoking status, and age) in those veterans who sprayed pesticides in a recent cross-sectional study of US Army Chemical Corps veterans (n= 1499) compared to 1428 non-Vietnam veterans assigned to chemical operations jobs in the military thirty years after exposure. Blood sera samples were collected from approximately 1000 subjects and analyzed for dioxin levels. While those subjects who reported both Vietnam service and herbicide spraying had the highest concentrations of dioxin 30 years post exposure (geometric mean = 4.3 ppt), those who had the second highest concentrations (geometric mean = 3.1) were those who reported a history of spraying herbicides in the military and not those who served in Vietnam but had no history of spraying (geometric mean = 2.7). Blood levels in this latter category were only slightly elevated beyond baseline (geometric mean = 2.1). All these levels are considerably lower than those levels reported in a study of female residents of Seveso, Italy[125]which ranged from 5 ppt to over 50,000 ppt (geometric mean=306 ppt) in the higher risk zone. There were several limitations to the Kang study, including a potential for selection bias and recall bias, and possible loss to follow-up given the long period between the exposure and the study.

Conclusions of the 2004 IOM Committee

On the basis of its evaluation of the epidemiological evidence reviewed in 2004 and in previous reports, the committee concluded that there is limited or suggestive evidence of an association between one of the Agent Orange compounds of interest and diabetes.

Synthesis of evidence for Gagetown chlorophenoxy herbicides and diabetes

The results from the Kang study support the conclusion that there is limited or suggestive evidence of an association between one of the chlorophenoxy compounds and diabetes despite the low blood levels of dioxin found. More research needs to be done on chlorophenoxy herbicides and diabetes incidence associations to determine if this is a true effect.

## 5. Respiratory conditions

Herbicide-related exposures and their role in contributing to onset of chronic respiratory disease have not received significant attention by researchers to date. In a study of 158 BASF chemical plant workers accidentally exposed to dioxin in 1953, respiratory illness was observed to be positively associated with serum dioxin concentrations. The increased illness rates were observed throughout the 36 year period and not just in the early years after the exposure (Zober, 1994). In addition to their study findings on diabetes described above, Kang et al[124] noted that the odds ratio for self-reported prevalent chronic respiratory conditions (including chronic bronchitis, asthma, emphysema, pleurisy, and tuberculosis) was elevated (OR=1.62; 95% CI: 1.28-2.05, adjusted for race, BMI, obesity, current smoking status, and age) in a follow-up study of those veterans who sprayed herbicides in a cross-sectional study of US Army Chemical Corps veterans (n= 1499), compared to 1428 non-Vietnam veterans assigned to chemical operations jobs in the military. Presence of chronic respiratory conditions was determined by response to a 36-item standardized Medical Outcomes questionnaire but few details are provided about how the respiratory conditions were defined

(including whether they followed standard American Thoracic Society diagnostic criteria).

More attention has been given to acute exposures to herbicides and respiratory disease. The objective of a study by Hoppin, et al[126] was to examine chemical use in the past year and self-reports of wheeze in the past year among the Agricultural Health Study, a group of certified pesticide applicators in Iowa and North Carolina. A total of 20, 468 applicators provided complete data and were included in this study. Of these, 19% reported wheezing in the last year (n=3,838). While eight of 16 herbicides were associated with wheeze in single-agent models; the risk was predominantly associated with the herbicide chlorimuron-ethyl (OR= 1.62; 95% CI: 1.25-2.10), which is a post-emergent herbicide used on peanuts and soybeans. This agent was not among those purportedly used at CFB Gagetown.

Conclusions of the 2004 IOM Committee

On the basis of its evaluation of the epidemiological evidence reviewed in 2004 and in previous IOM reports, the committee concluded that there is inadequate or insufficient evidence to determine an association between exposure to the compounds of interest and non-malignant acute or chronic respiratory disorders.

Synthesis of evidence for Gagetown chlorophenoxy herbicides and non-malignant acute or chronic respiratory disorders

Despite the recent positive findings demonstrating a positive association between Vietnam herbicide experience and self reported chronic respiratory conditions in the study of US Army Chemical Corps veterans, difficulties with the study design and limitations support the conclusion of there is inadequate or insufficient evidence to determine an association between exposure to the compounds of interest and non-malignant acute or chronic respiratory disorders.

## Section II: Other Herbicide Categories Used at CFB Gagetown

The remainder of this section reviews the evidence from the literature relating to other significant herbicide agent classes, besides the chlorophenoxy herbicides, that were purportedly used at CFB Gagetown. The IOM scientific committees did not examine the literature related to these classes of agents, therefore it was not possible to include statements from this group about the epidemiological evidence associated with such exposures. The extent of the evidence for many of these compounds is quite limited; for some agents, there have been several important studies but, for most, only summaries of evidence for general disease classes (such as all cancers taken together) are possible.

## A. Dipyridines (including Paraquat)

### 1. Cancers

There have been few comprehensive epidemiological studies of paraquat exposure and cancers. In the 2005 Eastern Nebraska farm study[72], the authors identified a significantly increased risk for glioma (brain cancer) among those individually exposed to paraquat (OR=11.1; 95% CI: 1.2-101.2). This finding was limited by the small number of exposed cases (n= 1) to paraquat. Only one study has examined the relationship between NHL and paraquat. DeRoos[89], in a pooled analysis of three case-control studies did not find an association between NHL and paraquat exposure. The study relied upon self-reported exposure data.

<u>Synthesis of evidence for Dipyridine (paraquat) herbicides and any form of cancer</u>

There have been very few studies of paraquat herbicide exposures and cancer risk. The Eastern Nebraska study finding about glioma is interesting but is limited by the very few cases that were identified. This reviewer concludes, based upon the current state of evidence, that there is inadequate or insufficient evidence of an association between exposure to Dipyridine (paraquat) herbicides and cancers.

**Table 16: Recent Studies of Paraquat Exposure and Respiratory Outcomes**

| *Source* | *Study Design & Population Description* | *Pesticide Type & Exposure Assessment* | *Measures of Association & Outcome* | *Main Findings* | *Strengths & Limitations* |
|---|---|---|---|---|---|
| **Schenker, 2004 Am J Respir Crit Care Med, 170, 773-779** | Cross sectional<br><br>22 Costa Rican farms (banana, coffee, palm oil) participated<br><br>338 workers | Cumulative Paraquat exposure<br><br>Interviewer administered questionnaire, pulmonary function testing, cardiopulmonary exercise testing<br><br>Index of exposure based on monitoring data, weighted for PPE use | Linear and logistic regression adjusted for age, weight, and smoking status<br><br>Outcomes:<br>• Pulmonary function test<br>• Exercise outcome measures<br><br>Adjusted for age, weight, smoking status | Self-reported chronic cough and SOB sig associated with paraquat exposure<br><br>Cough<br>OR: 1.8<br>95% CI: 1.0-3.1<br><br>SOB<br>OR: 2.3<br>95% CI: 1.2-5.1<br>n not reported<br><br>Cumulative exposure associated with sig increased Ve/VCO2 (p=0.02, B=0.49)<br>(An indicator of respiratory in efficiency)<br>n=200<br><br>*Long term low level paraquat exposure not associated with interstitial lung disease or impaired gas exchange | Limitations:<br>Sample size limited by farms that refused to participate, stated no paraquat use, or had too few workers<br><br>Persons over 40 not included in exercise testing<br><br>Strengths:<br>Use of biological monitoring to assess resp. function<br><br>Response bias minimal – no difference between those who completed PFTs and those who didn't |

**2. Parkinson's Disease**

It is valuable to briefly describe the toxicological evidence regarding paraquat exposure due to the uniqueness of this agent and its apparent associations with Parkinson's disease. The chemical structure of paraquat is notably similar to MPP+, a metabolite of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a neurotoxin known to induce parkinsonism[127]. In addition, paraquat exposure produced selective dopaminergic neurotoxicity, a key feature of Parkinson's Disease, in a mouse study[128]. The biological plausibility of an etiological relationship between paraquat exposure and Parkinson's Disease is supported by these studies.

There has been one cohort and one population based case-control study examining the association between Parkinson's disease and paraquat. The Kamel[118] analysis of the US Agricultural Health Cohort Study reported a significant relationship between "ever use of paraquat" and PD risk among prevalent cases (OR=1.8; 95% CI: 1.0-3.4, 14 cases) but not among incident cases (OR=1.0; 95% CI 0.5-1.9, 11 cases). The relationship between incident PD and paraquat exposure, however, increased when information from a supplemental questionnaire was included in the analysis (OR=1.4) though no confidence interval was provided.

Firestone et al[129], in their study of occupational and residential pesticide exposure among 250 patients of a community health clinic and 388 controls in Washington State, did not find a specific relationship between paraquat exposure and Parkinson's Disease. Subjects were asked to report whether they had exposure to classes of chemicals (herbicides) as well as specific pesticides of particular interest (paraquat). The authors observed a trend of increasing risk associated with likelihood of occupational pesticide exposure, with the most intensely exposed workers being at greatest risk and lower exposed groups at lower risk (pesticide worker: OR=2.07; 95% CI: 0.37-6.38, crop farmer: OR=1.65; 95% CI: 0.84-3.27, animal and crop farmer: OR=1.10; 95% CI: 0.60-2.00, dairy farmer: OR=0.88; 95% CI: 0.46-1.70). There was, however, no association between residential exposure to herbicides (OR=1.09; 95% CI: 0.77-1.53,

cases, 116 controls 175) and risk of Parkinson's Disease. As noted, the relationship between paraquat exposure and Parkinson's disease was not significant but this analysis was limited to only two exposed cases (OR=1.67; 95% CI: 0.22-12.76). Though the use of self-reported exposure data is subject to bias, the authors attempted to minimize this recall bias by blinding participants to the study hypothesis.

A study by Engel, et al.[130], reported in 2001, found no association between paraquat exposure and risk of parkinsonism among a subset of a small Washington state cohort (n=310) investigation of men occupationally exposed to pesticides. Though regarded a subset, Parkinson's Disease was not explicitly studied because of the difficulty of distinguishing it from other parkinsonian syndromes. Parkinsonism was defined by the presence of two or more of the following symptoms; rest tremor, rigidity, bradykinesia, and postural reflex impairments in a nurse-administered neurological exam. There was no observed association between the self-reported pesticide exposure, well water use, farm employment, or paraquat exposure and parkinsonism. Though there was a significantly increased risk of parkinsonism among individuals in the highest tertile of pesticide use (PR=2.0; 95% CI: 1.0-4.2, 51 exposed), there was not a significant dose-response relationship (p=0.17). Also, the relationship between cumulative paraquat exposure and parkinsonism (PR=0.9 95% CI 0.4-2.4, 36 exposed) was not significant and there was no indication of a dose-response trend. The nature of exposure assessment and case definition methods pose considerable potential for recall bias and disease misclassification in this study.

Liou et al.[131], in a case-control study, examined cumulative paraquat exposure and risk of PD in Taiwan. Cases (120) were recruited from a movement disorders clinic control and matched by gender and age to controls recruited from outpatient clinics. Univariate analyses demonstrated significant associations between PD and residence in a rural area: (OR=2.04; 95% CI: 1.23-3.38), ever engaged in farming: (OR=1.81; 95% CI: 1.25-2.64), ever use of herbicides: (OR=2.89; 95% CI: 2.28-3.66), and ever use of paraquat: (OR=3.22; 95% CI: 2.41-4.31). There was a six fold increase in risk (OR=6.72; 95% CI: 2.62-17.21, 32 cases) among individuals who reported using herbicides for more than twenty years. Similarly, though individuals with the highest

level of paraquat exposure (> 20 yrs.) experienced a six-fold increase in risk (OR=6.44; 95% CI: 2.41-17.2, 24 cases), there was no indication of a dose-response relationship. By recruiting cases from a movement disorders clinic and obtaining detailed exposure information, this study minimized disease misclassification and increased the capacity to assess specific chemicals. The use of self-reported exposure data does, however, create potential for recall bias.

Synthesis of Findings for Paraquat and Parkinson's Disease

Based upon recent studies by Engel and Liou and supported by earlier data, this reviewer concludes that there is limited or suggestive evidence of Parkinson's Disease resulting from exposure to paraquat, a member of the Dipyridines group of herbicides. The recent research in this area is very interesting but further work, involving larger study populations, is needed.

### 3. Chronic Respiratory Disease

Schenker, et al[132] conducted a study of 338 workers on 22 Costa Rican farms, in which cumulative paraquat exposure was examined in relation to acute and chronic respiratory disease, and observed that long term low level paraquat exposure was not associated with interstitial lung disease or impaired gas exchange. The study was limited by the small sample size.

**Table 17: Diseases or outcomes for which there are no reported epidemiological studies specifically related to dipyridines (paraquat) exposure**

| | |
|---|---|
| Nasal or nasopharyngeal cancers | Hodgkin's Disease |
| Laryngeal cancers | Multiple myeloma |
| Stomach cancer | Leukemias |
| Colorectal cancer | Spina bifida |
| Lung cancer | Fertility Problems |
| Soft tissue sarcoma | Spontaneous Abortions |
| Breast cancer | Stillbirths, Neonatal Deaths, |
| Prostate cancer | Infant Deaths |
| Testicular cancer | Childhood Cancers |

Synthesis of Findings for Paraquat and Other Chronic Disease or Reproductive Outcomes

Apart from investigations of paraquat and Parkinson's Disease, this reviewer concludes there is inadequate or insufficient evidence of other chronic disease resulting from exposure to this group of herbicides.

## II. Phosphonates (Glyphosate)

### 1. Cancers

A 2005 report released by DeRoos et al[95] about glyphosate-exposed pesticide applicators in the US Agricultural Health Study and cancer risk is the most comprehensive investigation to date of this class of herbicides. Few significant associations were observed, however, between glyphosate exposure and the range of outcomes that were assessed. Oral cavity cancer (RR=1.0; 95% CI 0.5-1.8) was not observed to be elevated after adjusting for age, demographic and lifestyle factors in addition to exposure to other pesticides. This particular analysis was based upon 59 cases of which 76% had reported ever using glyphosate. Furthermore, no dose-

response relationships were observed after stratifying by cumulative exposure days or by intensity-weighted exposure days. The report did not differentiate between different types of oral cancers. In relation to gastrointestinal cancer, no associations were observed for both colon and rectal cancers [(RR=1.4; 95% CI: 0.8-2.2) and (RR=1.3; 95% CI: 0.7-2.3) respectively] after adjustment for age, demographic and lifestyle factors and other pesticide exposures. Lung cancer and prostrate cancer, similarly, were not increased (RR=0.9; 95% CI: 0.6-1.3), (RR=1.1; 95% CI: 0.9-1.3; RR=1.1; 95% CI: 0.9-1.3). Significant associations between self-reported glyphosate use and NHL also were not observed. A statistically non-significant elevated risk of multiple myeloma (RR=2.6, 95% CI: 0.7-9.4; cases n=32) among men exposed to glyphosate was found.

DeRoos[89], in another study involving a pooled analysis of three case-control studies that examined the relationship between NHL and glyphosate, found a suggestive association between ever/never used glyphosate and NHL (OR = 1.6; 95% CI: 0.9-2.8) after adjusting for first and second order effects of other pesticide exposures using hierarchical regression analysis. The authors also observed an increased risk for NHL in men exposed to glyphosate after adjusting for exposure to other pesticides (OR=2.1; 95% CI: 1.1-4.0). This study is one of the very few that have adjusted for exposure to other pesticides other than the ones of direct interest. The studies included in this analysis involved the 2001 McDuffie, et al[47] Canadian study and two by Hardell, et al.[91,93]. Hardell et al.[93] conducted a pooled analysis from two Swedish case-control studies and found a statistically significant association between NHL and glyphosate (OR=3.04; 95% CI: 1.08-1.96). After adjustment for study area and vital status, this association was reduced and was no longer statistically significant. Similarly, Lee[90] in an analysis of the same data as DeRoos[89] found a borderline but not statistically significant risk of NHL associated with glyphosate exposure in non-asthmatics (OR=1.4; 95% CI: 0.98-2.1), but not in asthmatics (OR=1.2; 95% CI: 0.4-3.3).

In the previously described US Midwest case control studies, there were no observed associations between glioma risk and glyphosate use[72,73]. The Carreon[73] study did not find an increased risk for women and no data were reported for men in the companion

study. The authors indicate in the text that no increased risks were observed for glyphosate. A case-control study by Brown et al[98] reported no association between self-reported glyphosate exposure and leukemia (OR=0.9; 95% CI: 0.5-1.6). It should be noted that this analysis was only based on 15 cases.

Synthesis of evidence for Phosphonate herbicides and any form of cancer

There have been relatively few studies of Phosphonate herbicide exposures and cancer risk. Apart from the DeRoos et als[89]. and Hardell et al [93] pooled analyses which provide limited or suggestive evidence of an association between NHL and glyphosate, the studies published to date currently suggest that that there are no associations with the risk for cancer. However, more work needs to be done in this area using carefully designed studies. This reviewer concludes, based upon the current state of evidence, that there is inadequate or insufficient evidence of an association between exposure to Phosphonate herbicides and cancers, with the exception of NHL.

2. **Reproductive Disorders**

Arbuckle, et al.[105] examined risk of spontaneous abortions in relation to pesticide exposure in the Ontario Farm Family Health Study, in which retrospective data were collected via questionnaire from farm operators and eligible couples living on selected farms. To be eligible, the couple had to be living year round on the study farm and the wife had to be 44 years of age or younger and at least one member of the couple had to be working on the farm. In this particular study, 2110 women provided information on 3936 pregnancies, including 395 spontaneous abortions. Separate critical exposure windows were identified by trimester. The investigators observed an increased risk (OR=1.7; 95% CI: 1.0-2.9) of late spontaneous abortions associated with self-reported exposure to glyphosate.

Synthesis of evidence for Phosphonate herbicides and reproductive outcomes

Few studies of Phosphonate herbicide exposures and reproductive outcomes have been published. The Arbuckle study finding supports the conclusion that there is an association between exposure to glyphosate and spontaneous abortions. This association needs to be examined in other research studies. This reviewer concludes, based upon the current state of evidence, that there is inadequate or insufficient evidence of an association between exposure to Phosphonate herbicides and reproductive outcomes.

3. **Neurological Disorders**

a. Parkinson's Disease

DeRoos et al[95] did not find a statistically significant association between ever use of glyphosate and Parkinson's Disease (prevalence OR=1.0; 95% CI: 0.6-1.7, incidence OR=1.1; 95% CI: 0.6-2.0) in their 2005 report from the US Agricultural Cohort study.

Synthesis of Findings for Phosphonate Herbicides and Neurological Outcomes

There have been very few studies of this particular agent and the risk for neurological disease. The one recent study that has been reported did not find a significant association with Parkinson's Disease. More research needs to be done to examine the health effects of exposure to glyphosate. This reviewer concludes there is inadequate or insufficient evidence of chronic disease resulting from exposure to this group of herbicides.

**Table 18: Diseases for which there are no reported epidemiological studies related to glyphosate exposure**

**laryngeal cancers**

**stomach cancer**

**soft tissue sarcomas.**

**breast cancer**

**testicular cancer**

**Hodgkin's disease**

## III. Pentachlorophenol

The number of epidemiological studies focusing on this agent remains limited, yet there are sufficient data, especially in relation to cancer, to warrant an outcome-based review. Reproductive outcomes and other chronic diseases are not discussed, due to the lack of published studies.

### 1. Cancers

Perhaps the most significant recent epidemiological investigation about pentachlorophenol and cancer is a study published by Demers et al.[133]. It is a more recent assessment of health effects experienced by a cohort study of British Columbia sawmill workers originally established by Hertzman et al[71]. The investigators for the more recent study developed exposure profiles to pentachlorophenol and tetrachlorophenol, assessed through work history (job title and job history) and examined workers' risk of death from multiple diseases. It should be noted that some of the earlier studies, including Hertzman et al[71], grouped chlorophenoxy herbicides and pentachlorophenol exposures together in their analysis. This is partly due to the nature of the forestry or woodworking industries in which exposures to these agents occur synchronously, the chemical structure similarity of these agent classes and the fact that dioxin compounds were present as industrial by-products in commercial grade formulations of both pentachlorophenol and chlorophenoxy herbicides especially prior

to 1973. Interpretation of the results from these two studies should, thus, be evaluated in this context.

Nasal sinus and nasopharyngeal cancer

In a carefully conducted US study of machinists[16] reported in 2000, which controlled for occupational exposure to wood dust and formaldehyde, the researchers found slightly increased risks for both nasal sinus (OR=1.1; 95% CI: 1.02-1.18) and nasopharyngeal (OR=1.1; 95% CI= 1.01-1.18) cancer and 'substantial' chlorophenol exposure. There was mild evidence of a dose-response trend but the study was limited by the small number of exposed cases. The International Agency for Research on Cancer concluded in 1999[134] that the evidence related to pentachlorophenol for humans was inadequate to draw conclusions, resulting in a 'group 2B classification'. Demers, et al[133], noted that there was insufficient power in their investigation to examine nasal sinus and nasopharyngeal cancers.

Laryngeal cancer

No recent studies of laryngeal cancers and pentachlorophenol exposures were identified in our search of the literature. As noted previously, Demers, et al[133] reported insufficient statistical power to allow examination of laryngeal cancers in relation to pentachlorophenol and tetrachlorophenol exposures in the BC Sawmill workers study.

Digestive cancer

Hertzman et al[71] noted no elevated risk (SMR= 1.02; 95% CI: 1.01-1.20) for digestive system cancer mortality in mill workers exposed to chlorophenates compared to the British Columbia male population at that time. This investigation did not differentiate between chlorophenoxy compounds and pentachlorophenol. Demers, et al[133] did not report results for stomach cancer in their investigation examining chlorophenol risks in this cohort but noted that, in the higher exposed strata, rectal cancer exhibited the most consistent pattern of elevated incidence risk with both pentachlorophenol (RR=1.7; 95% CI: 1.10-2.61) and tetrachlorophenol (RR=1.7; 95% CI: 1.06-2.74) exposures. Conversely, no significant associations were observed for colon cancer.

Lung cancer

The cohort study by Hertzman et al[71], of 23,829 British Columbia sawmill workers exposed to chlorophenates identified a slightly elevated rate of lung cancer mortality (SMR 1.10; 95% CI 1.01-1.20) In the more recent study of the same cohort by Demers, et al[133], no associations between lung cancer and level of exposure to pentachlorophenol, tetrachlorophenol or all chlorophenols were observed nor was there evidence of a dose-response trend. Given that this was a follow-up study of the original Sawmill cohort with a longer time period and more clearly defined exposure data, greater weight should be given to the Demers analysis.

Soft tissue sarcoma

Evidence of excess incidence or mortality for soft tissue sarcoma and pentachlorophenol exposure was not found in the BC Sawmill Workers Study. The relative risk was 0.77 with a 95% confidence interval of (0.23-2.66) after 1-2 years of exposure in total and less for 2-5 years of exposure (OR=0.66; 95% CI: 0.22-1.99).

A case-control study on cancer in persons exposed to chlorophenol-contaminated fish and water supplies in Sweden[79] also did not report an association between exposure to chlorophenol-contaminated water and STS (OR 1.6; 95% CI: 0.7-3.5). A limitation of this study was the use of an ecological measure to indicate exposure to chlorophenol compounds.

Prostate

Overall prostate cancer incidence and mortality risks were not elevated in the Demers report from the BC Sawmill Workers Cohort [133] (SIR= 0.96; 95% CI: 0.89-1.04; SMR= 1.04; 95% CI: 0.88-1.22) compared to British Columbia provincial rates.

Brain

Brain cancer incidence (SIR=1.08; 95% CI: 0.80-1.18) and mortality (SMR= 1.08; 95% CI: 0.73-1.31) were not observed to be elevated in the 2006 Demers study of BC Sawmill Workers[133].

Non-Hodgkin's Lymphoma

Several recent studies have investigated the relationship between pentachlorophenol exposure and risk for NHL. In the analysis of the BC Sawmill Workers Cohort Study using the least exposed workers as a referent group, Demers et al.[133] noted there was an indication of a borderline significant trend towards elevated NHL mortality among workers exposed to all chlorophenols ($p<0.07$) and a trend towards elevated NHL mortality ($p<0.06$) and incidence ($p<0.03$) among workers exposed to pentachlorophenol. The relationship between NHL incidence and pentachlorophenol exposure was strengthened when the analysis was adjusted for a 10 and 20 year latency period ($p<0.02$ for both time periods). With a 20 year latency, the results showed elevated risks with longer periods of cumulative exposures [1-2 exposure years over time (RR=1.83, 95% CI: 0.95-3.50; not significant); 2-5 exposure years (RR=2.05, 95% CI: 1.14-3.68); 5+ exposure years (RR=1.98, 95% CI: 0.97-4.06)].

An earlier case-control study in Sweden[81] also found an evidence of a dose-response trend between self-reported pentachlorophenol exposure and NHL. The investigators report that persons with greater than 1 week straight or more than 1 month total exposure (high grade) had almost 9-fold increased risk of developing NHL than non-exposed (OR=8.8, 95% CI 3.4-24). Persons who had less than 1 week straight or 1-month total exposure were also at significantly elevated risk (OR=3.3, 95% CI 1.6-6.8). In contrast, another population based case-control study[92] of pentachlorophenol and NHL in Sweden reported an odds ratio of 1.2 (95% CI: 0.7-1.8). While this study had a large sample size, it lacked the ability to control for individual-level covariates.

Hodgkin's Disease

Demers et al[133] did not find statistically significant associations for Hodgkin's Disease incidence (SIR=0.94, 95% CI: 0.56-1.49) or mortality (SMR=0.74, 95% CI: 0.32-1.47) in their 2006 study of the British Columbia Sawmill Workers Cohort Study.

Multiple Myeloma

Demers et al[133] report slightly but non-statistically significant risks for both multiple myeloma incidence and mortality in their 2006 study of the British Columbia Sawmill

Workers Cohort Study, with a suggestive dose-response trend in incidence being shown in relation to number of years of exposure [1-2 exposure years: (SIR=1.24; 95% CI: 0.30-5.19); (SMR=2.05; 95% CI: 0.51-8.22), 2-5 exposure years: (SIR=1.52; 95% CI: 0.46-5.07); (SMR=1.82; 95% CI: 0.48-6.90), 5+ exposure years: (SIR=1.80; 95% CI: 0.60-5.40); (SMR=2.83; 95% CI: 0.84-9.52)]. While the 95% confidence intervals listed above all cross the null value, results from the test for trend for both mortality and incidence were significant (p values = 0.03 and 0.02, respectively).

Leukemia

Hertzman et al.[71], in their mortality study of 23,829 sawmill workers in British Columbia, did not identify excess mortality due to leukemia among the exposed population. Conversely, an elevated incidence rate of chronic lymphocytic leukemia was observed (SIR=1.67; 95% CI: 1.16-2.36, 24 cases). There was no elevated risk of disease for the three other leukemia subtypes; acute lymphocytic, acute granulocytic, chronic granulocytic, or other and unspecified leukemia. When the researchers modeled the analysis to examine the association between cumulative hours of exposure and risk of chronic lymphocytic leukemia, no evidence of a dose response relationship was found. The Demers 2006 follow up study[133] did not observe overall increased risks for leukemia. The investigators did not stratify the leukemia results into subtypes.

The Dow chemical company cohort study of 770 workers potentially exposed to pentachlorophenol[135] found no association between pentachlorophenol exposure and leukemia mortality among workers potentially exposed between 1940-1989. The lack of association persisted when the analysis accounted for a 15 year latency period and cumulative pentachlorophenol exposure. Although the investigators' use of industrial hygiene data and pentachlorophenol concentration data to create exposure intensity scores for each job title was a reliable means of estimating occupational exposure, the small number of exposed cases (2) limited extensive statistical analysis.

A Swedish case-control study by Lampi et al[79] estimated pentachlorophenol exposure by using drinking water use, fish consumption, fungicide use, occupation at a sawmill and occupation as a farmer as surrogates for exposure. Cases were identified from the

cancer registry (1967-1986), with population-based controls matched for age, sex and location of residence. No association between any of these exposure surrogates and risk of leukemia was found. The results of this study are limited however, due to the use of exposure surrogates, lack of data on specific types of leukemia, and small number of exposed cases (3 cases exposed to drinking water, 5 cases reported sawmill exposure).

Synthesis of Findings for Pentachlorophenol and Cancers

Based on the results presented above, especially those data from the Demers study, this reviewer believes that there is limited or suggestive evidence of an association between exposure to pentachlorophenol and non-Hodgkin's lymphoma and rectal cancer. Evidence related to pentachlorophenol and other cancers is more equivocal. This reviewer believes, for other cancer outcomes, that there remains inadequate or insufficient evidence of an association resulting from exposure to this herbicide.

## IV. Hexachlorobenzene

Hexachlorobenzene occurs as a manufacturing impurity resulting from picloram production. Due to toxicity concerns, this agent was placed on the conditional prohibition list in 2004 with strict requirements for reporting of products containing more than 10 ppb. This has allowed Environment Canada to identify and address any unanticipated HCB contamination occurrences. Epidemiological research findings related to chronic and reproductive health effects resulting from exposure to this agent are limited.

### 1. Cancers

**a.** Colorectal

Howsam et al[37] conducted a case-control study to assess the risk of colorectal cancer in relation to organochlorine exposure and included consideration of possible interaction

with genetic alterations in tumours. 132 cases and 76 hospital controls were selected from a larger case-control study in Barcelona, Spain. Serum concentrations of hexachlorobenzene were measured in all subjects and the median concentrations were observed to be 1753 ng/g lipid in cases and 1753 ng/g lipid in controls. No increased associations in relation to higher serum concentration levels were observed after adjustment for age, sex, BMI and total energy intake (OR= 1.60; 95% CI: 0.62-4.15).

**b.** Breast cancer

Hexachlorobenzene (HCB), has been examined in several hospital and population based case-control studies. Two hospital-based case-control studies demonstrated that HCB exposure is associated with increased breast cancer risk[136,137]. Charlier et al[136], in their assessment of breast cancer risk among Belgium women reported a five fold increased risk among women with the highest serum HCB levels (OR=4.99; 95% CI: 2.95-8.43) after adjusting for family history, parity, breastfeeding, menopausal status and use of hormone replacement therapy. Because only 11% of samples were considered to be positive for HCB (>0.5 ppb), 29 of the 231 cases were classified as exposed. A Swedish hospital-based case-control study[137] reported a statistically significant association between high levels of HCB in adipose tissue and breast cancer risk among postmenopausal women with estrogen receptor positive tumors (OR=7.1; 95% CI: 1.1-45.0). This analysis is also limited by low numbers as only 11 cases and 6 controls were postmenopausal with estrogen receptor positive tumours.

In contrast, five hospital-based studies in Ontario[61,138], Slovakia[139], Connecticut[140] and Mexico[141] reported no association between breast cancer risk and HCB exposure. The Ontario[61,138] and Connecticut [140] studies employed adipose tissue samples of HCB as a proxies for exposure. The Ontario study by McCready et al[138] reported significantly higher levels of adipose tissue HCB levels among cases than controls. In the adjusted analysis, however, elevated HCB levels were not associated with increased risk. A recent nested case-control study of Slovakian women[139] similarly assessed exposure via adipose tissue levels and reported a trend towards an inverse relationship among women with estrogen receptor negative tumors. Similarly, Lopez-Carrillo et al[141], in

their study of Mexican women reported a trend towards an inverse relationship between serum HCB levels and breast cancer risk.

One identified population based study of Missouri women [142] reported a significantly increased breast cancer risk among women with the highest serum HCB levels. (RR=2.3 95% CI: 1.0-5.0). The authors note that these findings may not be indicative of a relationship between HCB exposure and breast cancer risk. The statistically significant findings were limited to women with a short duration of time from blood collection to diagnosis. Furthermore, the there was no evidence of a dose response trend. Population based case-control studies in New York[143] and Denmark [144,145] reported no association between HCB exposure and breast cancer risk. Hoyer et al[143,144,145] reported no significant associations between serum HCB levels and survival nor between breast cancer when stratified by estrogen receptor status. Among western New York state women, there was no indication of a relationship between serum HCB levels and breast cancer risk. This lack of association persisted when the study population was stratified by women with a history of lactation.

c. Prostate cancer

An investigation by Hardell et al[146]examined concentrations of certain persistent organic pollutants with endocrine-disrupting properties in cases of prostate cancer and controls with benign prostate hyperplasia. In subjects with a PSA level greater than the median level of 16.5 ng/ml, hexachlorobenzene exposure was associated with an increased risk of prostate cancer (OR=9.84; 95% CI: 1.99-48.5). The investigators state that they are not certain as to the significance of this PSA threshold level except to

**Table 19: Recent Studies of Herbicide Exposures and Colorectal Cancer**

| *Source* | *Study Design & Population Description* | *Pesticide Type & Exposure Assessment* | *Measures of Association & Outcome* | *Main Findings RR 95% CI* | *Strengths & Limitations* |
|---|---|---|---|---|---|
| **Howsam[37], 2004 Environ Health Perspect, 112, 1460-1466.** | Hospital-based case-control study Barcelona, Spain<br><br>Cases (n=132): persons with new diagnosis of colorectal cancer recruited from 1996-1998<br><br>Controls (n=76): persons with a new diagnosis (non-colorectal cancer), frequency matched by age, sex and energy intake | Interview: dietary history, BMI, parity and lifestyle factors<br><br>Serum levels of HCH isomers, pe-CB, HCB, PCB congeners, *p,p'*-DDT and *p,p'*-DDE divided into tertiles, with referent category being those values below the detection limit | Outcome: incident colorectal cancer Logistic regression<br><br>Polytomous logistic regression was used to assess risk according to genetic alterations of tumours<br><br>Adjusted for age, sex, total energy intake and BMI at diagnosis. | HCB was present in **98%** of samples<br><br>Non significant associations between HCB and colorectal cancer:<br>Medium serum levels<br>OR = 1.72; (0.83-3.54)<br>High<br>OR = 1.60; (0.62-4.15) | Detailed analysis of molecular factors building biological plausibility for study findings<br><br>Use of hospital controls may introduce information and selection bias;<br><br>Validation of exposure measure (serum concentrations of organochlorine compounds) needed<br><br>High level of exposure in entire population make comparisons difficult |

**Table 20: Recent Studies of Hexachlorobenzene Exposures and Prostate Cancer**

| *Source* | *Study Design & Population Description* | *Pesticide Type & Exposure Assessment* | *Measures of Association & Outcome* | *Main Findings RR 95% CI* | *Strengths & Limitations* |
|---|---|---|---|---|---|
| **Hardell, 2006 J Occup Environ Med, 48,700-707** | Hospital-based case-control study<br><br>Recruited from a university hospital in Sweden between 1997-1999, age (55-84 years)<br><br>Cases (n=58) having a newly diagnostic prostate cancer<br><br>Controls (n=20) having surgery for benign prostatic hyperplasia (no cancer) | Measured levels of PCBs, PBDEs, chlordanes (MC6), *p,p'*-DDE), and HCB from samples of adipose tissue<br><br>Self-administered questionnaire: collected information on occupation, chemical exposure, family history of cancer, BMI | Outcome: levels of prostate specific antigen (PSA)<br><br>Unconditional logistic regression, adjusting for age, BMI (continuous), family history of prostate cancer<br><br>PCBs were analyzed by groupings according to structural and biological activity and to chlorinated status | An association was found between PCB 153 and prostate cancer [OR = 3.15; 95% CI: 1.04-9.54)] (cases/controls = 45/10)<br><br>An association was found between trans-Chlordane and prostate cancer [OR =3.49; (1.08-11.2)]<br><br>In sub-analyses with cases with PSA counts > 10ng/mL, a significant association was found between MC6: [OR = 4.03; 95% CI: 1.13-14.4] and HCB: [OR = 5.21; 95% CI: 1.46-18.6]<br><br>When looking at PCB groupings, the highest OR were found for enzyme-inducing PCBs, phenobarbital inducers and lower and moderately chlorinated PCBs | Strength: analyzed PCBs according to several groupings, and blinded laboratory analyzes<br><br>Also looked at potential confounding by weight loss, family history of prostate cancer<br><br>Identified limitations included small sample size, low number of controls, and potential bias due to the selection of hospital controls |

**Table 21: Recent Studies of Hexachlorobenzene Exposures and Testicular Cancer**

| *Source* | *Study Design & Population Description* | *Pesticide Type & Exposure Assessment* | *Measures of Association & Outcome* | *Main Findings RR 95% CI* | *Strengths & Limitations* |
|---|---|---|---|---|---|
| **Hardell, 2006 Int J Androl, 29, 228-234** | Case-control study<br><br>Enrollment from 1997-2000<br><br>Incident cases (n=58) of testicular cancer recruited from 5 hospitals in Sweden and case's mothers (n=44)<br><br>Controls (n=61) recruited through Swedish population registrar, matched to cases by 5 year age group, and control's mother (n=45), matched to case's mother by age group | Serum levels of PCBs, pp'DDE, HCB, chlordanes and PBDEs<br><br>Self-administered questionnaire on occupations, BMI, and reproductive history of mothers | Outcome: testicular cancer<br><br>Unconditional logistic regression, adjusted for age, BMI | Case mothers had higher levels of PCBs (all types): [OR=3.8; 95% CI:1.4-10] (cases/controls =34/20)<br><br>Association between testicular cancer and case mother's HCB levels was observed: [OR = 4.4; 95% CI: 1.7-12.0] (cases/controls 35/22). This association was strongest in mothers <55: [OR=14.0; 2.8-75] (cases/controls = 19/9)<br><br>Case mothers had higher levels of PBDEs (total): [OR= 2.5; 95% CI: 1.02-6.0] (cases/controls = 31/22)<br><br>No difference in POP levels between cases and controls | Strengths: Use of population-based controls<br><br>Looked for potential confounding by reproductive history, smoking, age and BMI<br><br>Absence of recall bias<br><br>Identified limitations: Uncertainty about whether current body burdens reflect body burdens 30 years prior (to reflect fetal exposure), differences between case and control mothers due to difference in metabolism of POPs |

indicate that PSA levels are correlated with tumour burden. It is possible that the association between prostate cancer and HCB exposure among men with elevated PSA levels could reflect a relationship between HCB and prostate cancer progression rather than to an interaction between HCB and PSA per se. Exposure was identified through a self-administered questionnaire.

d. Testicular cancer

A recent study of testicular cancer by Hardell, et al. in 2006[147] in relation to serum concentrations of chlorinated biphenyls in mothers of cases and controls, noted that the concentration of hexachlorobenzene in the mothers of cases was associated with an increased risk for testicular cancer in their sons (OR= 4.4; 95% CI: 1.7-12.0). No statistically significant association between testicular cancer and serum HCB levels within cases themselves was observed (OR=1.7; 95% CI: 0.8-3.6). The authors did not find significant differences between actual cases and controls in relation to smoking habits or the number of offspring. The investigators chose not to adjust for these covariates, or other self-reported data, in their final analyses. Other chlorinated herbicides were not examined. In a later study of the same population, mothers of cases were found to have higher levels of PBDEs and this was associated with an risk of testicular cancer among sons (OR=2.5; 95% CI: 1.02-6.0)[148]. This suggests that there might be multiple agents acting together in some fashion that is associated with an increased risk of testicular cancer.

e. Lymphopoietic cancers

The few studies that have investigated the relationship between hexachlorobenzene exposure and NHL have yielded consistent findings of no elevated risks. Cantor[149] found no association between NHL and serum measures of organochlorines, including hexachlorobenzene, in a case-control study in US (highest exposed: OR= 1.0, 95% CI 0.3-3.2). Another case-control study in Sweden[150] examined the relationship between the Epstein-Barr early antigen, NHL, and organohalogen compounds including hexachlorobenzene. The investigators found no statistically significant association

(p=0.13) between NHL and self-reported hexachlorobenzene exposure. Similarly, Quintana[151], in a nested-case control study of pesticide levels in adipose tissue and NHL did not find an increased risk of NHL in those subjects in the highest tertile of hexachlorobenzene exposure (OR = 1.29, 95% CI: 0.58-2.83). The controls were hospital patients undergoing abdominal surgery.

**2. Reproductive Outcomes**

In southeastern Turkey during the period 1955-1957, women were accidentally exposed to hexachlorobenzene (HCB) after eating contaminated seed grain and developed porphyria cutanea tarda. Jarrell, et al.[152] conducted a historical cohort study of women known to be exposed to hexachlorobenzene as children in this episode, which included a cohort with diagnosed porphyria cutanea tarda and two reference cohorts, using both questionnaire and serum HCB levels to compile reproductive histories. They observed a strong relationship between risk for spontaneous abortions and serum HCB levels after controlling for physiological factors (FSH, estradiol), using GEE analysis (coefficient of transformed logistic regression of serum HCB concentration and frequency of reported spontaneous abortions= 2.88 (SE=0.91, $p<0.001$). They concluded that the risk for porphyria cutanea tarda is enhanced by increased body burden for this chlorinated compound and the risk is not limited to only those with known, identifiable, past exposure events. Significantly lower percentages of live births were also observed for those with porphyria cutanea tarda compared to the reproductive experiences of the other two groups. In another study of HCB serum levels and preterm birth in 233 mothers in Mexico City[153], an increased risk was not observed.

**Table 22: Diseases for which there are no reported epidemiological studies related to hexachlorobenzene exposure**

**Nasal or nasopharyngeal cancers**

**Laryngeal cancers**
**Stomach cancer**

**Lung cancers**

**Soft Tissue Sarcomas**

**Brain cancer**

**Hodgkin's Disease**

**Multiple myeloma**

**Leukemia**

Synthesis of Findings for Hexachlorobenzene and Chronic Disease Outcomes

It is noteworthy that the cancers that have been studied to date in relation to hexachlorobenzene exposure and have shown some possible positive associations are known to be modulated by estrogen-related physiological factors. Polymorphisms in the expression of the enzymes associated with estrogen metabolism are increasingly being recognized as having etiological significance for the progression of these diseases. It is possible that some of the inconclusive evidence associated with breast cancer, prostate cancer and testicular cancer may be due to interaction with these polymorphisms. Further work is needed to sort out these covarying effects. Based on the current state of evidence, this reviewer concludes there is limited or suggestive evidence of associations between estrogen-related cancers and exposure to hexachlorobenzene. Furthermore, this reviewer concludes there is limited or suggestive evidence of associations between adverse reproductive outcomes and exposure to this group of herbicides.

# V. Discussion

## A. Overview

This report summarizes the recent epidemiological literature that has provided evidence related to the reproductive and chronic health effects associated with exposure to herbicides that were purportedly sprayed at CFB Gagetown, New Brunswick from the 1950's to 2004. A systematic approach to examining this evidence was applied to all studies that met the selection criteria for review. An electronic keyword search of the major bibliographical health databases was conducted using search terms that were developed by the reviewer based upon the herbicide literature. Emphasis was placed on recent literature, especially those reported since 2000. The abstracts from all citations identified were screened for evidence that the publication was an original epidemiological study and not a review or discussion paper. The shortened list were then accessed and copied and included within this review.

The greatest challenge with the current literature on herbicide use and human health effects is the general lack of studies that incorporate validated exposure assessment methods into the analyses. Many of the studies have relied upon self-reported historical exposure to herbicides or upon ecological community-level measures, rather than capturing individual-level exposure data. Some of the more recent studies have incorporated sophisticated methods for reconstruction of past agent-specific exposures but these are few. This is especially important because pesticides generally constitute a vast array of agents that have a wide range of toxicological and environmental persistence properties. Herbicides, as a subset, also can be described in this way. There is also a need for more studies, such as De Roos et al[88] that adjust for exposure to pesticides other than the principal agent of interest.

Complicating this issue is the fact that, in reality, pesticide applicators, agricultural producers and even members of communities are exposed to multiple pesticides, including herbicides. In some ways, it is artificial to separate the health effects associated with one group of agents from another. Nevertheless, unique situations do present opportunities to

explore single agent relationships, such as the BS Sawmill Workers cohort study that has examined exposure to pentachlorophenol and the experience of Vietnam War Veterans, that have focused on the Agent Orange compounds (2,4-D and 2,4,5-T plus dioxin).
It is reassuring that new analytical methods are being developed that take into account this complexity. Hierarchical modeling provides the capability to assess individual exposures to particular agents in the presence of other agents. Also, markers of internal dosage levels, such as serum levels or urine concentrations, coupled with good records of pesticide applications and who were exposed, may help to further our understanding of the long term effects of exposure to these compounds.

## B. Summary of recent findings

**Figure 1. Summary of the Categories of Evidence Used in This Report**

**Sufficient Evidence of a Causal Positive or Inverse Relationship**
Evidence is sufficient to conclude that a causal (positive or negative) relationship exists between the agent and the outcome. That is, the evidence fulfills the criteria for 'sufficient evidence of an association' and in addition satisfies the following criteria: strength of association, biologic gradient, consistency of association, biologic plausibility and coherence, and temporally correct association.

**Sufficient Evidence of a Positive or Negative Association**
Evidence is sufficient to conclude that there is a positive or negative association. That is, an association between the agent and the outcome has been observed in studies in which chance, bias, and confounding can be ruled out with reasonable confidence.

**Limited or Suggestive Evidence of a Positive or Negative Association**
Evidence is suggestive of a positive or negative association between the agent and the outcome but is limited because of chance, bias, and confounding cannot be ruled out with confidence.

**Inadequate or Insufficient Evidence to Determine Whether an Association Exists**
The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence of an association. Alternatively, no studies exist that examine the relationship.

# 1. Chlorophenoxy Herbicides

**Table 23: Summary of Evidence for Chlorophenoxy Herbicides[1]**

| Sufficient Evidence of a Negative Association | Limited or Suggestive Evidence of a Negative Association | Inadequate or Insufficient Evidence to Determine Whether an Association Exists | Limited or Suggestive Evidence of a Positive Association | Sufficient Evidence of a Positive Association | Sufficient Evidence of a Causal Positive Relationship |
|---|---|---|---|---|---|
| | | **Nasal sinus cancer** | **Laryngeal cancer** | **Soft Tissue Sarcoma** | |
| | | **Nasopharyngeal cancer** | Breast cancer | **Non-Hodgkin's Lymphoma** | |
| | | Stomach cancer | **Prostate cancer** | | |
| | | Colorectal cancer | Hodgkin's Disease | | |
| | | Lung cancer | **Multiple Myeloma** | | |
| | | **Testicular cancer** | Chronic Lymphocytic Leukemia (CLL) | | |
| | | Brain cancer | **Spina bifida** | | |
| | | **Other forms of Leukemia besides CLL** | Parkinson's Disease | | |
| | | **Fertility** | **Type 2 Diabetes** | | |
| | | Spontaneous abortions | | | |
| | | **Stillbirths, Neonatal Deaths, Infant Death** | | | |
| | | **Childhood cancers** | | | |
| | | **Peripheral neuropathy (delayed or persistent)** | | | |
| | | **Non-malignant chronic respiratory disorders** | | | |

[1] bolded diagnoses refer to those categories which are consistent with the conclusions of the IOM.

Results for the five major CFB Gagetown herbicide categories are summarized in separate sections below. The US National Academy of Sciences' Institute of Medicine Classification of Evidence (Figure 1) was used to evaluate each study on the final list.

A synopsis of the summary of evidence for each disease outcome associated with exposure to chlorophenoxy herbicides reviewed in this report is presented in Table 23. There were no disease outcomes for which there was sufficient evidence to support the conclusion that exposure to chlorophenoxy compounds *causes* that disease. Nevertheless, there was sufficient evidence to state that positive associations were found between chlorophenoxy herbicides and Soft tissue Sarcoma and Non-Hodgkin's Lymphoma. These findings were consistent with the Institute of Medicine report. The IOM Committee also identified Chronic Lymphocytic Leukemia and Chloracne as having sufficient evidence to support the finding that there is an association between exposure and disease. The complicated nature of diagnosis of Chronic Lymphocytic Leukemia, combined with the varying accuracy of diagnoses in the studies that were reviewed related to this outcome and including consideration for statistically significant but not overwhelming findings in more recent years, suggest to this reviewer that there is limited or suggestive evidence of a positive association between exposure to chlorophenoxy herbicides and Chronic Lymphocytic Leukemia.

Limited or suggestive associations were identified for a number of disease outcomes and much of the literature in these areas is still emerging. The results for Laryngeal Cancer, Prostate Cancer, Multiple Myeloma, , Spina bifida and Type 2 Diabetes are consistent with the conclusions of the Institute of Medicine Committee. The focus of this review was on chronic health effects, therefore we did not fully examine the transient peripheral neuropathy literature that IOM identified as having limited or suggestive evidence. Similarly, porphyria cutanea tarda was not examined in our review. As discussed in this report, recent studies of Breast cancer, Hodgkin's Disease and Parkinson's Disease support the conclusion that there is limited or suggestive evidence of an association. This is also true for chronic lymphocytic leukemia and spontaneous abortions.

New studies have been published that now support initial evidence in relation to chlorophenoxy herbicide exposure and brain cancer. Other disease outcomes were also examined in relation to chlorophenoxy herbicides exposures and most of these findings suggest that there is still inadequate or insufficient evidence to support establishment of a association for these diagnoses. The results that consistent with the IOM conclusions are: Nasal cancer, Nasopharyngeal cancer, Testicular cancer, Other forms of Leukemia other than CLL, Fertility, Stillbirths, Neonatal Deaths, Infant Death, Childhood Cancers, Peripheral Neuropathy (delayed or persistent), and Non-malignant respiratory disorders. Lung cancer has been downgraded to this category from Limited or Suggestive Evidence of an Association due to identified challenges with selection of control groups in the studies that were assessed. These limitations are discussed in the section pertaining to this outcome. The other outcomes identified by the IOM for this category were not reviewed because of lack of recent studies identified or because of varying disease classification.

Stomach cancer and colorectal cancer, in contrast to the IOM findings, were classified as having inadequate or insufficient evidence to determine if an association exists. There are many risk factors for these gastrointestinal cancers and it is known that poor diet is one major contributory factor. It may be possible that better than average diets in agricultural populations and in military personnel (the two major populations studied to date) may be masking the influences of chlorophenoxy herbicides on these cancer outcomes. Studies that capture dietary history in addition to herbicide and other lifestyle factors are needed to more fully elucidate the possible contribution of herbicide exposures as a risk factor.

## 2. Dipyridine (Paraquat) Herbicides

The dipyridine herbicides have been studied to much less extent. The focus for this agent group has been primarily on paraquat. Paraquat has important neurotoxicological properties that have been demonstrated in animal studies. A synopsis of the summary of evidence for each disease outcome associated with exposure to paraquat herbicides reviewed in this report is presented in Table 24.

There is limited or suggestive evidence of a positive association between paraquat exposure and Parkinson's Disease. Also the 2005 Eastern Nebraska study that identified an elevated risk for brain cancer is interesting but was based upon very small numbers. Other than this study, no recent investigations of paraquat exposure and cancer have been published. There has also been some interest in assessment of chronic respiratory disease in relation to exposure to paraquat exposure. Studies to date have failed to show significant associations between exposure and disease.

**Table 24 Summary of Evidence - Dipyridine (Paraquat) Herbicides**

| Sufficient Evidence of a Negative Association | Limited or Suggestive Evidence of a Negative Association | Inadequate or Insufficient Evidence to Determine Whether an Association Exists | Limited or Suggestive Evidence of a Positive Association | Sufficient Evidence of a Positive Association | Sufficient Evidence of a Causal Positive Relationship |
|---|---|---|---|---|---|
| | | Brain cancer<br><br>Other Respiratory Disease | Parkinson's Disease | | |

3.

## 3. Phosphonate (Glyphosate) Herbicides

There have been several highly informative studies recently published about risk for chronic disease in relation to glyphosate exposures but the evidence for this class of compounds remains severely limited. The Arbuckle study provides interesting findinds but there is still inadequate or insufficient evidence of a positive association between glyphosate exposure and spontaneous abortions. The DeRoos study examined but did not find significantly elevated or decreased associations for a range of cancer outcomes. A synopsis of the summary of evidence for each disease outcome associated with exposure to glyphosate herbicides reviewed in this report is presented in Table 25.

**Table 25 Summary of Evidence Glyphosate Herbicides**

| Sufficient Evidence of a Negative Association | Limited or Suggestive Evidence of a Negative Association | Inadequate or Insufficient Evidence to Determine Whether an Association Exists | Limited or Suggestive Evidence of a Positive Association | Sufficient Evidence of a Positive Association | Sufficient Evidence of a Causal Positive Relationship |
|---|---|---|---|---|---|
| | | Nasal cancer<br>Nasopharyngeal cancer<br>Colorectal cancer<br>Lung cancer<br>Prostate cancer<br>Brain cancer<br>Multiple Myeloma<br>Leukemia<br>Spontaneous abortions<br>Parkinson's Disease | Non-Hodgkin's lymphoma | | |

## 4. Pentachlorophenol

There have been relatively few studies of pentachlorophenol and associated health effects. Two important investigations of the BC Sawmill workers cohort have provided some understanding of chronic diseases, particularly cancers, resulting from exposure to this agent in an industrial setting. This has provided sufficient information, in addition to the other available studies, to have justified a review of individual cancer outcomes. Reproductive outcomes and other chronic diseases were not examined, due to the lack of published studies. A synopsis of the summary of evidence associated with exposure to chorophenol herbicides by disease outcomes reviewed in this report is presented in Table 26.

**Table 26 Summary of Evidence - Pentachlorophenol Herbicides**

| Sufficient Evidence of a Negative Association | Limited or Suggestive Evidence of a Negative Association | Inadequate or Insufficient Evidence to Determine Whether an Association Exists | Limited or Suggestive Evidence of a Positive Association | Sufficient Evidence of a Positive Association | Sufficient Evidence of a Causal Positive Relationship |
|---|---|---|---|---|---|
| | | Nasal cancer<br><br>Nasopharyngeal cancer<br>Colon cancer<br>Lung cancer<br>Soft Tissue Sarcoma<br>Prostate cancer<br>Brain cancer<br><br>Hodgkin's Disease<br>Multiple myeloma<br>Chronic Lymphocytic Leukemia | Non-Hodgkin's Lymphoma<br>Rectal cancer | | |

There is limited or suggestive evidence of positive associations between exposure to pentachlorophenol and Non-Hodgkin's Lymphoma and Rectal cancer. More research is needed to understand the etiological dimensions of how this agent might result in disease.

## 5. Hexachlorobenzene

As noted, hexachlorobenzene occurs as a manufacturing impurity resulting from picloram production. Picloram is one of the two agents in Agent White that was sprayed experimentally at CFB Gagetown. Due to toxicity concerns, hexachlorobenzene was placed on the conditional prohibition list in 2004 by Environment Canada in order to facilitate monitoring of spills and other contamination occurrences. Epidemiological research findings related to chronic and reproductive health effects resulting from exposure to this agent are limited. Perhaps the most well known occurrence was an incident which occurred thirty years ago where unfortunately a bag of grain treated with hexachlorobenzene was unknowingly consumed by a community in Turkey. This resulted in a series of acute adverse health outcomes. A recent study by Jarrell, et al.[152], in which reproductive histories of women who were known to be exposed to hexachlorobenzene as children in this episode, were evaluated for risk for spontaneous abortions in relation to serum HCB levels. Using GEE analysis, they observed significant associations for spontaneous abortions and significantly lower percentages of live births for those with porphyria cutanea tarda compared to the reproductive experiences of two reference groups. Table 27 summarizes the results of this analysis.

**Table 27 Summary of Evidence Hexachlorobenzene Herbicides**

| Sufficient Evidence of a Negative Association | Limited or Suggestive Evidence of a Negative Association | Inadequate or Insufficient Evidence to Determine Whether an Association Exists | Limited or Suggestive Evidence of a Positive Association | Sufficient Evidence of a Positive Association | Sufficient Evidence of a Causal Positive Relationship |
|---|---|---|---|---|---|
| | Non-Hodgkin's Lymphoma | Colorectal cancer | Breast cancer<br><br>Prostate cancer<br>Testicular cancer<br>Spontaneous abortions | | |

## VI. Conclusions

This report presents the results of a comprehensive, structured review of the recent scientific literature regarding the possible increased risk for chronic health effects and reproductive outcomes resulting from exposure to herbicides that were purportedly sprayed at CFB Gagetown from 1952 to 2004. As requested by the contractor, the emphasis was placed upon information that has been published within the last ten years.

This review was an independent assessment based upon the quality of evidence. The US Institute of Medicine criteria for evaluation of evidence were used as the basis for assessment of research findings. The US Institute of Medicine Report Series, entitled Veterans and Agent Orange, especially the 2004 report, proved to be an invaluable document to support this review. The IOM series was an independent scientific review, involving committees of internationally renowned scientists who provided arms-length interpretation of research studies pertaining particularly to the chlorophenoxy herbicides. Conclusions about the quality of evidence were initially drawn by this reviewer and then the IOM documents were examined to determine degree of concordance and to identify key publications that might have been missed by our initial scan.

Most of the evidence, available to-date, pertain to the health effects resulting from exposure to the chlorophenoxy herbicides. Other CFB Gagetown herbicides have been studied much less extensively and more research needs to be completed which examines specific herbicide exposures and reproductive health and chronic disease risks.

There were no instances where sufficient evidence existed to support a causal relationship between exposure to a specific class of herbicides and a specific disease or reproductive outcome. There is sufficient evidence to support a positive association between exposure to chlorophenoxy herbicides and the development of Soft Tissue Sarcoma, and Non-Hodgkin's Lymphoma. There is limited or suggestive evidence of a positive association between chlorophenoxy herbicides and numerous health outcomes but these findings will benefit from further work that will include meticulously collected exposure data.

The dipyridine herbicides (Paraquat) have been the least studied of the herbicide categories reviewed in this report. Paraquat has important neurotoxicological properties that deserve further exploration. Hexachlorobenzene also needs further scrutiny- the capacity for this agent to bioaccumulate in the human body and be associated with increased risks for chronic health effects, as was shown in recent studies, is an important consideration. Environment Canada already has imposed a proposed ban as well as instituted enhanced monitoring programs that will aid in the identification of any future unanticipated release of this agent to the environment.

The other two classes of agents: the glyphosates and the chlorophenolic compounds, might be described as having an emerging scientific literature related to their chronic health effects. While much of the current research supports only a conclusion of inadequate or insufficient evidence of an association related to exposure and disease, there is a need for future work that carefully delineates exposure and disease outcome associations. Much of the initial work that was extraordinarily helpful to sort out some of these preliminary findings were published by Canadian authors.

**In closing, it must be stated that absence of evidence of any exposure-disease relationship does not necessarily imply that there is evidence of absence of such an association. In other words, while the current science may not support such a conclusion at this point in time, it is possible that the future evidence may point more strongly in one direction or another. Furthermore, these findings and the conclusions presented herein, are based upon the collective experience of study groups and populations. Under no circumstances does this reviewer suggest that the experience of a population as a whole, as described in this review, pertain directly to the experience of the individual patient. It is the duty of the patient's physician to sort out the individual circumstances that may have caused a person's disease or impairment, not an epidemiologist.**

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11. Hexachlorobenzene has caused a serious outbreak of porphyria in humans. Hexachlorobenzene is one of the 12 persistent organochlorine pesticides (POPs) banned or

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## Appendix 1: Glossary[2]

**Case-control study** The observational epidemiologic study of persons with the disease (or other outcome variable) of interest and a suitable control (comparison, reference) group of persons without the disease. The relationship of the attribute to the disease is examined by comparing the diseased and non diseased with regard to how frequently the attribute is present or, if quantitative, the levels of the attribute in each of the groups.

**Cohort study** The analytic method of epidemiologic study in which subsets of a defined population can be identified who are, have been, or in the future may be exposed or not exposed, or exposed in different degrees, to a factor or factors hypothesized to influence the probability of occurrence of a given disease or other outcome. The main feature of cohort study is observation of large numbers over a long period (commonly years) with comparison of incidence rates in groups that differ in exposure levels.

**Confidence intervals** The computed interval with a given probability, e.g. 95%, that the true value of a variable such as a mean, proportion, or rate is contained within the interval.

**Confounding** 1. A situation in which the effects of two processes are not separated. The distortion of the apparent effect of an exposure on risk brought about by the association with other factors that can influence the outcome.

[2] Source: Last, John. Dictionary of Epidemiology, 3rd edition.

| | |
|---|---|
| **Confounding** (cont) | 2. A relationship between the effects of two or more causal factors as observed in a set of data such that it is not logically possible to separate the contribution that any single causal factor has made to an effect.<br>3. A situation in which a measure of effect of an exposure on risk is distorted because of the association of exposure with other factors that influence the outcome under study. |
| **Incidence Rate** | The rate at which new events occur in a population. The numerator is the number of new events that occur in a defined period; the denominator is the population at risk of experiencing the event during this period, sometimes expressed as population-time. |
| **Infant mortality rate** | A measure of the yearly rate of deaths in children less than one year old. The denominator is the number of live births in the same year. The numerator is the number of deaths in a year of children less than one year of age. |
| **Latent period** | Delay between exposure to a disease causing agent and the appearance of manifestations of the disease. |
| **Odds** | The ratio of the probability of occurrence of an event to that of nonoccurrence, or the ratio of the probability that something is so to the probability that it is not so. |

**Odds Ratio**

The ratio of two odds. The exposure-odds ratio for a set of case-control data is the ratio of the odds in favour of exposure among the cases *(a/b)* to the odds in favour of exposure among the noncases *(c/d)*. This reduces to *ad/bc*. The odds ratio is *ad/bc*.

| | Exposed | Unexposed |
|---|---|---|
| Disease | *a* | *b* |
| No Disease | *c* | *d* |

**Recall bias**

Systematic error due to differences in accuracy or completeness of recall to memory of past events or experiences. For example, a mother whose child has died of leukemia is more likely than the mother of a healthy living child to remember details of such past experiences as use of x-ray services when the child was in utero.

**Relative Risk**

1. The ratio of the risk of disease or death among the exposed to the risk among the unexposed; this usage is synonymous with **risk ratio.**

2. Alternatively, the ratio of the cumulative incidence rate in the exposed to the cumulative incidence rate in the unexposed, i.e. the **rate ratio.**

3. The term relative risk has also been used synonymously with **odds ratio** and , in some biostatistical articles, has been used for the ratio of forces of morbidity.

**Selection bias** Error due to systematic differences in characteristics between those who take part in a study and those who do not. Examples include subjects in a survey limited to volunteers or persons present in a particular place or a particular time, or hospital cases under the care of a physician.

**Standardized incidence ratio**

The ratio of the incident number of cases of a specified condition in the study population to the incident number that would be expected if the study population had the same incidence as a standard or other population for which the incidence rate is known.

**Standardized mortality ratio**

The ratio of the number of deaths observed in the study group or population to the number that would be expected if the study population had the same specific rates as the standard population, multiplied by 100.

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