Developing Research Priorities and Disseminating Knowledge about Pesticides, Agricultural Exposures, and Select Cancers

Workshop Final Report

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November 8, 2013

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ACKNOWLEDGEMENTS

This workshop and report was made possible thanks to the following organizations and individuals:

- The CIHR knowledge dissemination grant team and supporters, including:
  - Shelley Harris, PI (Cancer Care Ontario, University of Toronto-Dalla Lana School of Public Health, Occupational Cancer Research Centre);
  - Manisha Pahwa, Co-I (Occupational Cancer Research Centre), John J. Spinelli, Co-I (BC Cancer Agency, University of British Columbia), and Desre Kramer, Co-I (Occupational Cancer Research Centre);
  - Laura Beane Freeman (U.S. National Cancer Institute), Aaron Blair (U.S. National Cancer Institute), and Paul A. Demers (Occupational Cancer Research Centre), Collaborators;
  - Maria Trainer (CropLife Canada), Gary Liss (Ontario Ministry of Labour), and Michelle Tew (Occupational Health Clinics for Ontario Workers Inc.), who wrote letters of support for the grant proposal;
- Shelley Harris, Laura Beane Freeman, and John J. Spinelli, who comprise the Executive Committee of the North American Pooled Project;
- Manisha Pahwa, Project Manager for the North American Pooled Project;
- Janet Brown (JD Brownfields), who helped to develop the workshop agenda, facilitated the workshop, and provided ongoing technical support to produce the workshop report;
- Aaron Blair, Manisha Pahwa, Laura Beane Freeman, Angela Hofstra (Syngenta Canada Inc.), Amy Brown (University of Maryland-Department of Entomology), and Catherine LePrevost (North Carolina State University-Department of Environmental and Molecular Toxicology), for giving presentations at the workshop;
- Garthika Navaranjan (Occupational Cancer Research Centre), Linda Kachuri (Cancer Care Ontario), Desre Kramer, and Nancy Deming for note taking and administrative support;
- The Principal Investigators of the U.S. National Cancer Institute case-control studies and of the Cross-Canada Study of Pesticides and Health, who generously allowed us to use data from these studies for the North American Pooled Project; and,
- The Canadian Institutes for Health Research (CIHR), which provided funding for the workshop and associated knowledge dissemination activities.
- The authors wish to thank Laura Beane Freeman, Aaron Blair, Angela Hofstra, Maria Trainer, and Garthika Navaranjan for their detailed review of the draft workshop report.

EXECUTIVE SUMMARY

The prevalence of certain cancers is elevated in farmers and agricultural populations. It has been hypothesized that exposures to pesticides and other agricultural factors may increase some cancer risks. These potential risks were examined in four case-control studies in the U.S. and Canada during the 1980s and 1990s. Over the past 20 years, there have been numerous publications detailing the results of the individual studies, and now, data from these studies is being combined or "pooled" to better understand the effects of exposures to pesticides and other farm-related substances on the risks of lymphatic and hematopoietic cancers. This combined effort, called the "North American Pooled Project" (NAPP), is large in scope. Therefore, it is important for researchers to share knowledge with relevant stakeholder groups and collaboratively identify knowledge needs that can be addressed using information in the NAPP.

On May 27, 2013, Cancer Care Ontario and the Occupational Cancer Research Centre (OCRC) hosted a workshop in Toronto, Ontario, Canada. The objectives of this workshop were to identify research priorities using data available in the NAPP and to brainstorm potential inputs for a future knowledge translation and exchange (KTE) strategy for the NAPP (Appendix 1). This workshop was funded by knowledge dissemination grant from the Canadian Institutes for Health Research.

Twenty-two participants attended the workshop with expertise in broad areas including cancer epidemiology, agricultural extension, pesticide exposure assessment, toxicology, risk assessment, regulation, KTE, and policy (Appendix 2) and were from government and advocacy organizations, academia, industry, and extension. In the morning, stakeholders were briefed on the case-control studies and NAPP, and then discussed knowledge needs on the topic of pesticides, agricultural exposures, and cancer. An iterative, facilitated process was used to help participants identify research priorities specifically using data in the NAPP. In the afternoon, representatives from industry discussed the limitations of using epidemiologic research currently in risk assessment and regulation and the potential for improvement. Agricultural extension specialists described how they communicate pesticide risk information to farm workers in the field. Researchers shared the methods used to translate findings from the Agricultural Health Study to members of this cohort. All workshop participants then discussed possible elements of a future KTE strategy for the NAPP. The day wrapped up with a roundtable of next steps and ways to stay engaged in knowledge generation and translation efforts. Altogether, participants emerged with a greater understanding of the NAPP, a set of research priorities, a greater appreciation of how epidemiologic research is applied in different contexts, direction for a prospective KTE strategy, and strengthened researcher-stakeholder partnerships.

This workshop report is intended to summarize the day's presentations and discussions as a resource for participants and the groups that they represent. This report will subsequently inform the public and the Canadian Institutes for Health Research about the NAPP and methods used to engage stakeholders early in the research and KTE process. It articulates the approaches used, outcomes achieved, and next steps to be taken by the researcher and stakeholder team. Thank you to everyone who contributed to the workshop presentations and to the participants for the rich discussion and input.

ABOUT THE NORTH AMERICAN POOLED PROJECT (NAPP)

It is well known that the prevalence of certain cancers (e.g. lung, colorectal) is lower in agricultural populations primarily due to healthier lifestyle factors. However, the prevalence of certain cancers is elevated. The exact causes are not known, and many studies have been conducted to identify potential risk factors. A series of studies was conducted in the U.S. and Canada during the 1980s and 1990s. The U.S. National Cancer Institute (NCI) led three case-control studies in four states to assess the effects of agricultural exposures, including pesticides, on the risks of four different types of cancer: non-Hodgkin lymphoma, Hodgkin lymphoma, soft tissue sarcoma, and multiple myeloma. A similar case-control study, called the Cross-Canada Study of Pesticides and Health (CCSPH), was subsequently completed in six Canadian provinces.

Researchers from the OCRC and U.S. NCI are currently combining, or pooling, data from the CCSPH and U.S. case-control studies. This effort is called the North American Pooled Project (NAPP). The NAPP is unique compared to other studies of pesticides and cancer because of the large number of cancer cases (e.g. over 1000 cases of non-Hodgkin lymphoma) and the high prevalence of pesticide use in the study population. The large sample size of the NAPP makes it possible to re-evaluate specific pesticide exposures with greater statistical power, assess rare exposures not possible in the individual studies, examine interactions between multiple pesticides and other exposures, and assess risks for cancer sub-types. For these reasons, the NAPP is a valuable research endeavour that will build upon previous work and make important new contributions to our understanding about the potential causes of these cancers.

Fairly extensive information on pesticide use and agricultural exposures is available from studies in the NAPP. For example, detailed data were collected on participants' previous use of specific pesticides (self-reported individually and as groups of chemicals), methods used to apply pesticides, use of personal protective equipment (PPE), and length of use (number of years and number of days per year). Information was obtained about other occupational exposures, such as diesel engine exhaust, as well as other potential risk factors for the four types of cancers like age, medical conditions, and smoking history. Further details about the case-control studies and NAPP are in Appendices 3-5.

WORKSHOP OBJECTIVES AND FORMAT

The aims of the workshop were to: 1) summarize and share key findings from the individual case-control studies comprising the NAPP; 2) identify stakeholder knowledge needs; 3) incorporate these knowledge needs to inform a set of research priorities using data available in the NAPP; and, 4) brainstorm the inputs for a future KTE strategy. To achieve these goals, the workshop was generally divided into two parts: research prioritization (morning) and KTE of epidemiologic evidence among various stakeholder groups (afternoon). The day began with each participant introducing themself and sharing how they were connected to the NAPP or research on the topic of agriculture and cancer. The remainder of the workshop alternated between presentations and facilitated discussions (Appendix 1).

WORKSHOP PARTICIPANTS

Twenty-three participants representing fourteen different organizations from Ontario, Saskatchewan, British Columbia, Maryland, and North Carolina were invited to the workshop by the grant team (Appendix 2). Just under half of the participants had their primary affiliations with a research institution; the others were knowledge translation specialists or affiliated with government, the pesticide industry, advocacy groups, or organizations representing workers (Figure 1).

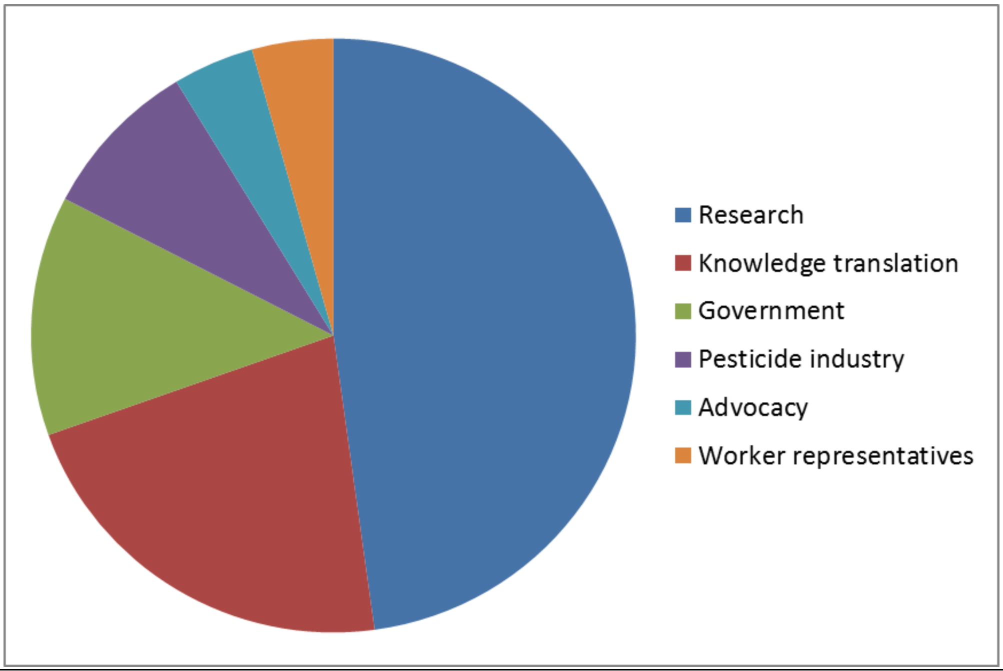

Figure 1: Distribution of workshop participants by area of specialty or primary affiliation

SETTING RESEARCH PRIORITIES

The NAPP has been in development since the beginning of 2012. The NAPP Executive Committee and associated researchers who have conducted analyses on the case-control data have developed research priorities based on their knowledge of the data from their personal research and the literature. However, NAPP investigators welcome suggestions from stakeholders regarding research priorities based on their knowledge. Therefore, researchers sought input to ensure that interests from a wide range of stakeholder communities were considered in planning analyses of the NAPP.

BACKGROUND PRESENTATIONS

Researchers gave three presentations to provide stakeholders with the background information on how the NAPP was formed and what type of data is available for analysis. These presentations were:

1. Case-control studies in the U.S.: Dr. Aaron Blair
2. Cross-Canada Study of Pesticides and Health: Ms. Manisha Pahwa
3. Purpose and status of the NAPP: Dr. Laura Beane Freeman

Various topics were raised by participants during the discussion periods following each presentation. These included:

- The public often has concerns about possible associations between pesticide exposure and cancer risk even if the evidence is inconclusive. The interpretation of the evidence based on older and sometimes less reliable studies should change based on newer, more reliable data. However, once an association is established in the literature, the perception that this association exists often remains regardless of more reliable evidence from newer, more powerful studies. In addition, scientists tend to follow-up positive associations; null findings aren't generally investigated as thoroughly, so false positives are likely to occur.
- Historical maps of leukemia and non-Hodgkin lymphoma mortality in the U.S. show higher rates in agricultural compared to urban areas. This finding led researchers from the U.S. NCI to conduct the case-control studies that comprise much of the NAPP. While pesticides were the focus of these case-control studies, other factors were also evaluated by the U.S. NCI investigators. These include immune suppression (the strongest risk factor for non-Hodgkin lymphoma), diet, lifestyle and other factors.
- Although the relationship with diet was not significant in previous analyses by the U.S. NCI, there was considerable discussion around relationships between nitrates and NHL as well as the role that infectious agents in food might play. These were not looked at historically as significant risk factors but are emerging as potentially important.
- With regards to the status of the NAPP at the time of the workshop, researchers had agreed upon a common definition of non-Hodgkin lymphoma sub-types. This is important because the definition of non-Hodgkin lymphoma has changed over time. Data had been pooled for demographic variables (e.g. age, smoking) and individual insecticides, herbicides, and fungicides. The harmonization of variables for pesticide chemical classes, medical conditions, and other agricultural exposures was in progress.

THE NOMINAL GROUP METHOD

Following the presentations and brief discussions, participants were asked to consider two guiding questions to catalyze discussion about research priorities:

1. What are the broad knowledge needs around pesticides, other agricultural exposures, and cancer?
2. What are your thoughts regarding research priorities for the NAPP, given the data available in the NAPP?

The nominal group process was employed to support this discussion. The following briefly describes the process.

To begin, participants were given approximately 5-10 minutes to reflect on the questions above and to record their thoughts and questions. They were then asked to self-organize into groups of three to share their reflections using an open dialogue process. Participants were asked to listen actively and move toward a shared group understanding of the needs and research priorities.

After approximately 20 minutes, two groups of three were asked to join together into a single group of six and the process of dialogue was repeated. After a further 20 minutes, the groups provided five to ten points on large post-it notes and markers. The full group then reassembled and the facilitator asked one group member at a time to come forward and present an idea. Once presented, the post-it notes were posted on flipcharts on the wall. The facilitator then asked whether any other group had discussed a similar point. If yes, the group was asked to bring forward their item. If not, another post-it note was requested from one of the groups. This continued until all points were presented and themed by the participants.

Once all of the ideas were presented and themed, the entire group was ask to review each theme in turn and provide a summary heading to capture its overall intent. From this process, seven themes emerged and each is summarized below. As the summary below is slightly modified for reporting purposes, the exact photographic record of the flipcharts is provided in Appendix 6. Detailed notes about the discussion that occurred during the theming process were taken to add further depth to the documentation of this exercise.

1. QUANTITATIVE MEASURES OF EXPOSURE

Improving the retrospective assessment of pesticide exposure was among the top priorities identified at the workshop. Participants suggested that assessments of exposure-response to individual pesticides should continue to advance beyond dichotomous categorization (i.e. yes/no) if possible, in order to account for timing, duration, or intensity of exposure on an ordinal scale. The time between putative exposure and disease outcome is critical to evaluating a suggested association. Individual studies in the NAPP have developed exposure scales (e.g. number of days per year) that have been used in past analyses and publications. These semi-quantitative exposure metrics will be continue to be used, or improved, in the pooled analyses. This will allow approximations of dose-response in the NAPP. It is important to note, however, that it is not possible for researchers to contact cases and controls that participated in the NAPP in order to obtain additional pesticide exposure data.

The potential for exposure can sometimes be assumed even if details are lacking by using surrogate information. For example, field crop data can be used to approximate exposure if exposure to certain pesticides has not been reported or if there is a large proportion of missing data. For instance, if it is known that certain pesticides are used on apples but information for these pesticides is missing in the NAPP dataset, apples (as a crop) can be used to model the effects of these pesticides. Statistics Canada field crop data provides information on land use that could be used to infer likely pesticide uses in a given area during the time of reported exposure. Sales data, dates of pesticide registration, and recommended agricultural practice at the time of reported exposure can also be used to verify pesticide use.

Furthermore, data gaps (e.g. intensity, duration, frequency) can be addressed using surrogate information. Direct information on specific pesticide exposure, however, is the goal.

In addition, there was a need for evaluation of exposure to individual pesticides and to combinations of pesticides and other agricultural risk factors with respect to sub-types of each cancer site, where relevant (e.g., Non-Hodgkin and Hodgkin lymphoma). Participants also stated that the pattern of pesticide use in controls could be used to provide information on pesticide use that would be valuable for other case-control studies and for communication purposes.

2. OTHER AGRICULTURAL EXPOSURES, CONFOUNDING, AND INTERACTIONS

Participants agreed that associations between pesticide exposure and cancer are complex and that other factors need to be considered in statistical analyses. These factors include other (i.e. non-pesticide) agricultural exposures, confounding exposures, and co-exposures/interactions.

With regards to other agricultural exposures, there was a specific need to evaluate diesel engine exhaust, solar ultraviolet radiation, and grain dust. Participants were interested in knowing how many cases and controls were exposed to these and other types of non-pesticide substances included in the NAPP dataset. In addition to being evaluated as a main exposure, these substances may be evaluated as confounding and effect modification variables with pesticides as the main exposure variables.

Smoking was suggested as both a potentially confounding variable and interaction variable in analyses, although a number of studies indicate that smoking does not appear to be involved in the development of NHL. Participants expressed a need for analyses that stratify by age. Age is related to decade of pesticide use and is most relevant for Hodgkin lymphoma, which has a bimodal age distribution. Interactions between different pesticides can also be evaluated. Participants specifically mentioned organochlorine insecticides, but interaction analyses should not be restricted to this chemical group. There was an interest in re-assessing the impact of immune conditions on the link between pesticide exposure and the risk of non-Hodgkin lymphoma in the NAPP.

Participants requested that sensitivity analyses be conducted by excluding proxies from statistical models. It is known that proxy respondents cannot provide as much detail regarding pesticide use as the subjects themselves, which would tend to bias estimates of relative risks downward, but results could be biased in unpredictable ways using proxy respondents. Although it was noted that proxy respondents for farmers tend to have higher agreement with each other compared to proxy respondents for other occupations, sensitivity analyses will help to determine if the use of proxy respondents has an appreciable effect on risk estimates.

Lastly, gene-environment interactions emerged as an area of interest. Although these analyses are not possible in the NAPP, they should be considered for future studies. This type of analysis is intended to tease apart the effects of a family history of cancer from living in a shared agricultural area over several generations (i.e. underlying genetic versus shared environmental exposures).

3. NON-OCCUPATIONAL PESTICIDE EXPOSURE

Cases and controls in the NAPP were previously recruited from agricultural areas in the U.S. and through provincial cancer registries and hospitals (cases) and random samples of the population (controls) in Canada. Therefore, not all subjects in the NAPP were from agricultural areas or would have experienced occupational exposures to pesticides. It's reasonable to assume that farmers and their families would also be exposed to pesticides in residential settings since they would use products in their homes and gardens. Occupational and non-occupational exposures may differ in terms of the type, frequency, duration, and intensity of pesticide use. Participants stated that analyses should separate work versus home exposure to account for these potential differences, where possible. In addition, it was suggested that analyses parse out “bystander” exposure if possible, i.e. persons who were inadvertently exposed to pesticides, e.g. through the drift of pesticide spray on fields. This theme was represented as “bystander exposure” in the workshop but has been expanded to non-occupational exposure here since there was discussion of home versus work use. Although it will not be possible to evaluate “bystander” exposure in the NAPP, this point has been noted for consideration in future studies.

4. Factors that modify exposure

There are several ways that exposure to pesticides can be influenced. For example, the formulation of the pesticide, its use in combination with other pesticides, application method(s), safety handling information on the package, and use of PPE can affect how, and to what extent, individuals are exposed. These factors may or may not mitigate corresponding cancer risks but should be evaluated where possible.

With regards to formulation, for example, exposure to a pesticide as a dust may confer greater exposure through inhalation relative to liquid, wettable powder, or granular formulations. The use of two or more pesticides simultaneously, or at different time points during the same growing season, can occur and exposure to combinations of pesticides may have different effects on cancer risks compared to exposure to individual pesticides. Exposures can be influenced if users follow safety and use instructions on pesticide packages. Some may use historical application methods learned from the farm family. Various PPE may be used to reduce exposure, and PPE use can vary based on the pesticide in question. Pesticide formulations, combinations, packages, and PPE have changed over time. For example, one participant remarked that old pesticide labels did not even recommend PPE, and another commented that farmers commonly used their hands and arms to mix pesticides in the 1960s. It is worth noting that awareness of the importance of following label instructions and using precautionary measures has increased tremendously in recent years in farm owner/pest control operators.

Participants suggested that these factors be taken into consideration in analyses if possible. Particularly, participants expressed an interest in knowing how PPE may modify exposure and associated cancer risks, what type of PPE was used for different pesticides, and general use of PPE in the NAPP. The use and impact of PPE was identified as a knowledge gap. Participants also wanted to know about other factors that may modify risk by reducing exposure to pesticides, e.g. clothes washing, enclosed cabs in vehicles or planes used to apply pesticides, etc. This knowledge can be used to better inform risk communication and risk reduction strategies.

5. Communication/KTE/Advocacy

There are many reasons to provide effective communication regarding NAPP findings. Some participants noted that there is international consciousness around the effects of pesticides on human and environmental health. Pesticides that were banned decades ago in the U.S. and Canada may still be used elsewhere in the world. Uncontrolled unlicensed use of pesticides may still occur in the U.S. and Canada. In addition, cancer may take decades to develop (i.e. long latency period) and there are many other known and suspected causes of cancer. Participants acknowledged the importance of continued research in this area and of communicating findings to previously and currently exposed communities.

Since the case-control studies that make up the NAPP were conducted in the 1980s and 1990s, some of the pesticides that were reported by cases and controls at that time are no longer registered for sale or use and may be different from pesticides that are commonly used today. However, many are still the same. Participants noted that knowledge translation efforts should address both historic- and current-use pesticides.

6. CROSS-CUTTING

There were a few knowledge needs that were found to cut across different thematic areas. There was discussion, for example, about using knowledge from other disciplines to help inform epidemiologic research and using results from epidemiologic studies to inform our knowledge about potential mechanisms of pesticide carcinogenesis. Some participants stressed that epidemiologic associations observed in individual studies do not establish causation.

7. FUTURE RESEARCH NEEDS

Numerous questions were raised with regards to future research needs. Historically Caucasian males have constituted the majority of participants in occupational cancer research studies. Workshop participants identified a need to better understand potential risks to underrepresented groups such as minority populations and female applicators. In general, participants wanted to know what protective measures are useful for reducing pesticide exposures and/or cancer risk. A larger pooled sample was recognized as essential for examining the effects of individual pesticides and cancer sub-types with even greater statistical power than the NAPP, and participants inquired if there are other case-control data that can be harmonized with the NAPP.

KTE

RISK ASSESSMENT AND REGULATION

Dr. Angela Hofstra opened the afternoon session on KTE by giving two presentations titled, “The use of epidemiological research in risk assessment and regulation” and “Industry perspectives.” As we live in a “chemical soup”, Dr. Hofstra stated the need for accurate dose measurements and accurate measures of the amount and extent of exposure to a particular chemical to allow both regulators and industry to utilize epidemiology studies. Currently, in the absence of accurate dosimetry, while regulators consider epidemiological literature, it is infrequently used inform risk assessment and/or regulatory decisions. Regulators want a comprehensive outlook with evidence of biological plausibility that demonstrates a link between animal studies and epidemiological findings. She indicated that exposure to pesticides in modern agriculture is at low levels on an intermittent basis in generally well controlled situations making epidemiology studies difficult to interpret; however, high quality well designed epidemiology studies can be used to inform toxicity assessment and vice versa. Dr. Hofstra presented a weight of evidence approach using both disciplines to assess human relevance. Epidemiological research on specific chemicals, rather than groups of chemicals, supports risk assessment and enables additional mode of action work to determine if an observed effect has biological plausibility and relevance in humans.

Participants agreed that both toxicology and epidemiology data are needed to obtain a fuller picture of pesticide health effects and that stronger links need to be established between both disciplines. Animal models of pesticide exposure are useful because the dose administered is many times higher than what is usually encountered in occupational or environmental settings. Unfortunately, these models do not capture chronic exposure very well. Biologic differences between the animal model and humans introduce uncertainty regarding the utility of bioassays and experimental findings. Epidemiological studies are valuable because they reflect individual variation and directly measure risk in humans. It was recommended that a metric can be developed for evaluating the quality of epidemiological studies so that toxicologists can have a better frame of reference for using data from human studies. In addition, participants suggested using data from toxicological studies to estimate exposure levels that would be expected to have an effect in humans. Epidemiologic studies would be much more relevant for risk assessment if they included an environmental or biological sampling component in all or some subjects to obtain more accurate exposure estimates.

PESTICIDE SAFETY EDUCATION AND AGRICULTURAL EXTENSION

Dr. Amy Brown spoke about “Incorporating epidemiological research results in pesticide safety education” and Dr. Catherine LePrevost presented on “Engaging stakeholders from North Carolina’s rural and agricultural communities.” These presentations provided a glimpse of what communicating epidemiological research looks like on the ground. For example, Dr. Brown empowers pesticide users with information by drawing upon data from the Agricultural Health Study and providing practical, motivational, and evidence-based advice on how to reduce pesticide exposure. Users are encouraged to adopt safe handling or “best” practices for all pesticides at all times so that special measures to reduce exposure do not need to be taken for the more toxic pesticides or agents perceived to be more dangerous than others. In the U.S., heat is a major issue, and extreme temperatures in the warm season make it challenging for users to comply with PPE. Nevertheless, the importance of following instructions on pesticide containers is emphasized.

Dr. Brown also noted that the credibility of the messenger is a key component of pesticide safety education. Credibility can be enhanced by the responsible and accurate reporting of research that reflects "real life" exposure situations and by not scaring or threatening farm workers' livelihoods by communicating *only* significantly elevated risks. Flaws in exposure assessment of pesticides can be acknowledged without disregarding the relevance of findings.

Dr. LePrevost described the "train the trainer" approach that is applied with farm workers, farmers, stage agencies, and various other groups in North Carolina. Because of the diversity of these groups, Dr. LePrevost underscored that messaging needs to focus on the specific audience. During her presentation, it was suggested that store owners who sell pesticides should be targeted with research information so that they can educate buyers about potential health risks of pesticides and measures to reduce exposure. She stated that agricultural extension specialists need more information on PPE to develop relevant guidance and encouraged researchers on the NAPP to try to design analyses to meet this data gap.

AGRICULTURAL HEALTH STUDY

The Agricultural Health Study is a prospective cohort study designed to identify occupational, lifestyle, and genetic factors that may affect the rate of diseases in farming populations. It evaluates many health outcomes that are potentially associated with pesticide exposure, and not just cancer. Dr. Laura Beane Freeman presented how findings from the Agricultural Health Study are communicated to farming communities. Up-to-date information about the Study is maintained on its website, http://aghealth.nih.gov/. This website serves as an interface between researchers, farming community stakeholders, and the public, who can use it to easily learn more about the Study in plain language and obtain contact information for Study researchers. Various groups have been targeted for translating knowledge, including State Advisory Panels and the U.S. National Institute for Occupational Health and Safety. KTE strategies have evolved over time; currently, notices for new publications are emailed to stakeholders on a monthly basis. Dr. Beane Freeman provided an example of how the U.S. Environmental Protection Agency used a recent publication from the Study to evaluate atrazine in 2011, which demonstrated the need for researchers to notify regulators as soon as studies are published.

GUIDANCE FOR A KTE STRATEGY FOR THE NAPP

The prior presentations and discussions were highly informative. To close the meeting, participants were asked to provide advice to the NAPP initiative. The facilitator asked each in turn to respond and their thoughts are noted below. Participant's ideas built one from the other and that there was significant agreement in the room about the ideas being generated. Four general categories of advice emerged and each is briefly described below.

1. Think strategically about the broad pesticides and health agenda and consider how best the NAPP project fits within this context. The pooled project is one important step and other efforts to align and integrate may be possible to strengthen the impact of the research. Integration was viewed as important, since the ability of one study (i.e. the NAPP) to address the many questions about pesticides and health is limited. The NAPP probably should not be strictly viewed as one study because it is composed for four investigations from two different countries. Participants identified the importance of considering the scope of both the NAPP and KTE efforts, since communication of findings can occur through many channels and the OCRC and U.S. National Cancer Institute have stronger capacities in some forums (e.g. conferences, peer-reviewed literature) while the other researchers and stakeholders around the table exchange knowledge in ways distinct to their respective communities. To assist with this, the group was advised to leverage the expertise and contacts around the table and to keep participants engaged.

2. Work closely with stakeholders to understand how best to develop and target messaging arising from findings from the NAPP. Recommended activities included:
   - Hold public meetings/forums with stakeholders on a regular basis to understand their needs and capture their knowledge and experience
   - Include health care providers to discuss potential links between exposures and the health effects
   - Identify a liaison to exchange epidemiological findings with pesticide educators in the US and Canada
   - Make links with government or regulatory agencies such as Health Canada and the U.S. Environmental Protection Agency
   - Remain aware of the political nature of communications to farmers and consult with experts in risk communication
   - Develop communications in partnership with stakeholders
   - Discuss whether to position PPE as a measure to reduce exposure to potential carcinogens or as a way to reduce health risk overall

3. Develop lay summaries that:
   - Emphasize behaviours that mitigate risks
   - Focus on the health effects and how to protect oneself from exposure
   - Discuss and clarify strength of the evidence regarding various issues
   - Use language that motivates behaviour change rather than generating a sense of fear of doing work involving pesticides
   - Make sure that communication documents are not too technical and use simple graphics and metaphors
   - Include sound bites
   - Contextualize summaries where possible to be meaningful to specific audiences e.g. down to the individual crop specific stage

4. Distribute findings through a variety of formats:
   - Post studies and lay summaries on the OCRC website
   - Develop interactive formats, e.g. a website dedicated to the NAPP
   - Develop online courses
   - Develop an annotated slide deck for use by researchers and the stakeholder groups represented at the workshop

STRENGTHS AND LIMITATIONS OF THE WORKSHOP

Following the workshop, an electronic survey was sent to all participants to assess their level of satisfaction, willingness to stay engaged in KTE, and to welcome their general feedback. Fifteen individuals responded to the survey. The vast majority (93.3%) thought that the workshop met its goal of informing research priorities for the NAPP. Fewer (66.7%) thought that the workshop met its goal of initiating a knowledge dissemination strategy for the pooled project. While most thought that the workshop was well organized, one person commented that "an increased allocation of time to the afternoon discussion regarding dissemination strategies would have been appropriate and useful." Just over half (53.3%) of survey respondents thought that the workshop was effective in providing them with an opportunity to collaborate or network with other researchers and stakeholders. Some examples of the most important learnings that respondents took away were:

- "The goals and research priorities of the pooled project"
- "Better understanding of the complexities associated with the available datasets"
- "How epidemiological research is being used in the field to educate and inform pesticide users about the risks associated with pesticide use. I also learned that there is not much research that has been done on the use of personal protective equipment [PPE], although its use is strongly recommended to pesticide applicators. Thus, it would be interesting to do more work on this topic so see what kinds of PPE are more effective than others."
- "New connections for possible collaboration"
- "…the need for greater communication and collaboration between researchers and science communicators."
- "The workshop was a great opportunity to connect with fellow researchers and meeting individuals in the field who are using this research to help others."

Nine individuals indicated in the survey that they would like to continue to be involved in developing a knowledge translation strategy. NAPP researchers will personally follow up with these individuals, who may serve as advisors to the research team. This may help researchers build relationships with individual stakeholders who are committed to the success of NAPP knowledge translation efforts. Overall, many participants expressed their gratitude for being invited and their support for continued research and knowledge dissemination.

Nevertheless, the workshop had several weaknesses. The agenda was quite ambitious as there were multiple goals for a one-day workshop. The topic in the morning (research prioritization) was somewhat disconnected from the topic in the afternoon (knowledge translation). Some participants commented that the workshop was too short to go in depth in either of these topics, and that it would have been better to have spread the workshop over two days instead of compressing it into one day. Because of the high volume of content and discussion at the workshop, there was not enough time at the end of the day to thoroughly flesh out next steps as a group.

The main strength of the workshop was that it was an inclusive, efficient way to identify research priorities and catalyze KTE efforts. It represented the first time that individuals from a wide range of knowledge user organizations and communities have been involved in the NAPP. Researchers were able to gain input from different perspectives and deepen their understanding of what key health issues farm workers, the pesticide industry, government, and researchers are concerned about and how the NAPP can and cannot address their concerns.

Stakeholders obtained insight on the research prioritization process. They were able to improve their understanding of how the U.S. NCI and OCRC are collaborating on this project and what the merits and flaws are of a pooled approach. By learning what types of research questions can be answered using the data available in the NAPP, stakeholders became more aware of what information they can take back to their communities and apply in the context of pesticide education, regulation, risk assessment, or other purposes.

All participants were able to compare, contrast, and expand their thinking around the workshop topic by listening to the views of the group. Agricultural extension and pesticide knowledge translation specialists from Canada and the U.S. who wouldn’t normally meet had the chance to discuss shared challenges and strategies in their respective contexts. In addition, the workshop facilitator greatly helped participants to identify research priorities and theme them in a logical way.

NEXT STEPS

On May 28, 2013 (the day after the workshop), several NAPP researchers (Shelley Harris, Laura Beane Freeman, Aaron Blair, Punam Pahwa, and Manisha Pahwa, and Joe Barker (the computer programmer from the U.S. NCI who is merging the Canadian and U.S. case-control studies) met to discuss information and ideas obtained from the workshop; to discuss priority analyses for the NAPP; to receive an update on the pooling status; and to think about further funding opportunities.

In the workshop de-brief, it was noted that the analytic priorities identified by researchers and stakeholders were generally aligned with each other. Many ideas for KTE were raised at the workshop and the research team thought that the most feasible and effective activities were publishing articles, presenting at conferences, keeping stakeholders engaged, and developing a website with updates on analyses and results. The group suggested that interested individuals who attended the workshop group can suggest and advise on web content. The website, which the OCRC will develop, can be modeled from the AHS website and provide links to U.S. NCI and other authoritative sources of information. The website may also be used to facilitate communication within the workshop stakeholder group. Lastly, relevant industry groups and regulators can be notified about upcoming publications from the NAPP.

Stakeholder input gave researchers a better sense of what analyses to focus on first with the NAPP data and validated the priorities that researchers had in mind before the workshop. Taking the guidance of workshop participants into account, researchers discussed examining phenoxy herbicides such as 2,4-D, conducting analyses for specific pesticides and non-Hodgkin lymphoma that adjust for and evaluate the impact of PPE, and assessing the relationship between pesticide exposure and the risk of non-Hodgkin lymphoma in the presence and absence of immune conditions. Other priorities identified were to focus on organophosphate insecticides, organochlorine insecticides, and specific chemicals such as butylate and dicamba. It was agreed that the first set of analyses will be cancer-specific. Where applicable, the use of PPE, proxy versus self-report, and home versus work pesticide exposure will be integrated in all analyses. Researchers would like to offer multiple opportunities for trainees (students and fellows) at the U.S. NCI and OCRC to be involved in analyses. Protocols for proposing research ideas and writing abstracts and manuscripts were discussed.

At the time of the workshop, the harmonization of the Canadian and U.S. data was in progress. To support data harmonization, the group agreed to revise a spreadsheet of frequency of pesticide use for three of the four cancer sites in the NAPP, and discussed the best ways to create variables for occupational versus home pesticide exposure and for the use of PPE. To support data analysis, the group discussed creating a user manual to accompany the datasets and a comprehensive data dictionary for posting on the OCRC group website. In addition to pesticide data and demographic information, the other variables that will be harmonized include medical/health variables and family history of cancer.

Funding to support continued research on the NAPP was raised as an important issue. To date, funding has been drawn from “in house” resources at the OCRC and NCI, but in the long run, external funds will be needed. The group identified potential agencies that administer grants (e.g. Canadian Cancer Society Research Institute, CIHR, U.S. National Institutes of Health, and the Ontario Ministry of Labour, lymphoma foundations) and an initial list of NAPP investigators that are eligible to apply for grants.

In terms of this report, the NAPP research team will distribute this draft for final comments from participants. This will ensure that the report accurately reflects the views and content expressed at the workshop.

APPENDIX 1: WORKSHOP AGENDA

Time	Item
8:15 – 8:30	**Registration**
8:30 – 9:00	**Breakfast**
9:00 – 9:20	**Welcome** *Shelley Harris*
9:20 – 10:20	**About the North American Pooled Project (NAPP) on pesticides, agricultural exposures, and cancer** ➢ Case-control studies in the U.S. *Aaron Blair* ➢ Cross-Canada Study of Pesticides and Health *Manisha Pahwa* ➢ NAPP *Laura Beane-Freeman*
10:20 – 10:35	**Break**
10:35 – 12:00	**Setting our priorities** ➢ Knowledge needs and research priorities for the NAPP *All*
12:00 – 1:00	**Lunch (Dining Room)**
1:00 – 2:15	**Research to action** ➢ The use of epidemiologic research in risk assessment and regulation *Angela Hofstra* ➢ Industry perspectives *Angela Hofstra* ➢ Incorporating epidemiological research results into pesticide safety education *Amy Brown*
2:15 – 2:30	**Break**
2:30 – 3:15	**Research to action** ➢ Engaging stakeholders from North Carolina's rural and agricultural communities *Catherine LePrevost* ➢ Agricultural Health Study *Laura Beane Freeman and Aaron Blair* ➢ Lessons learned for developing a knowledge translation strategy for the NAPP *Janet Brown*
3:15 – 4:00	**Wrap-up and next steps** *Shelley Harris and Janet Brown*

APPENDIX 2: WORKSHOP PARTICIPANTS

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Angela Hofstra
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APPENDIX 3: U.S. NATIONAL CANCER INSTITUTE CASE-CONTROL STUDIES

OBJECTIVE

During the 1980s, the U.S. National Cancer Institute (NCI) conducted three case-control studies in four Midwestern states (Iowa/Minnesota, Kansas, and Nebraska) to evaluate pesticides and cancer at multiple sites. Non-Hodgkin lymphoma was evaluated in all three studies. In addition, Hodgkin lymphoma and soft tissue sarcoma were included in the Kansas study; leukemia and multiple myeloma in the Iowa/Minnesota study; and Hodgkin lymphoma, multiple myeloma, and chronic lymphocytic leukemia in the Nebraska study.

METHODS

Individuals who were diagnosed with these cancers during the study years were identified from area hospitals or cancer registries. All three studies included men; women were only included in the study in Nebraska. Controls were selected from the general population by random digit dialing, listings from Medicare for those older than 65, and from state mortality files for deceased cases. Cases and controls were matched on a variety of criteria such as vital status, age, state, sex, and race.
In each study, participants provided answers to detailed questions about the use of agricultural pesticides, other agricultural exposures, farming practices, and exposure to other known or suspected risk factors, including lifestyle factors, medical history, and non-farm occupations. These interviewer-administered questionnaires were conducted by telephone (Kansas and Nebraska) or in person (Iowa/Minnesota) with cases and controls, or with surrogates if the subjects were deceased. To evaluate possible recall bias of self-reported pesticide use, in the study in Kansas, pesticide suppliers were asked to provide information on crops and pesticide purchases for a sample of subjects with farming experience. In the Nebraska study, case recall bias was assessed by comparing information on pesticides used that was volunteered versus that required probing by the interviewer.

KEY FINDINGS

For non-Hodgkin lymphoma, the individual studies showed increased risks for several individual pesticides. More recently, data from all three NCI studies have been pooled to include approximately 1000 cases of non-Hodgkin lymphoma and 3000 controls. Many analyses have been conducted on the individual studies and on this large, pooled dataset to assess various hypotheses related to pesticides and the development of non-Hodgkin lymphoma. The pooled studies have shown increased risks from exposure to several individual pesticides, including 2,4-D, lindane, malathion, carbaryl, and DDT, as well as from exposure to multiple pesticides. Furthermore, there was some evidence that asthma modified the association between pesticide exposure and the risk of NHL. Papers on the individual studies have demonstrated that pesticides may contribute to the development of non-Hodgkin lymphoma through mechanisms that involve chromosomal abnormalities.

Key findings for other cancer sites suggest potentially important roles for pesticides and other factors on cancer risk. For example, several pesticides were associated with an increased risk of leukemia and the use of insecticides on animals was linked to an increase in risk of soft tissue sarcoma. There was little evidence to support associations between farming or pesticides and the risks of multiple myeloma or Hodgkin lymphoma, although these hypotheses were not examined in as much detail as non-Hodgkin lymphoma, due to a smaller number of cases.

PUBLISHED ARTICLES

Over 50 articles analyzing various exposures and the included cancer sites have been published in scientific journals. While earlier publications in the 1980s and 1990s focused on examining cancer risks from pesticides, non-farm occupations, and non-occupational factors (e.g. hair dyes, alcohol, tobacco), in more recent publications there has also been an interest in assessing these factors in relation to genetic variation of non-Hodgkin lymphoma and in relation to risk from immune system conditions.
For example:

- Baris D, Zahm SH, Cantor KP, Blair A. Agricultural use of DDT and risk of non-Hodgkin's lymphoma: pooled analysis of three case-control studies in the United States. Occupational and Environmental Medicine 1998;55:522-527.
- Blair A, Cantor KP, Zahm ZH. Non-Hodgkin's lymphoma and agricultural use of the insecticide lindane. American Journal of Industrial Medicine 1998;33:82-87.
- Waddell BL, Zahm SH, Baris D, Weisenburger DD, Holmes F, Burmeister LF, Cantor KP, Blair A. Agricultural use of organophosphate pesticides and the risk of non-Hodgkin's lymphoma among male farmers (United States). Cancer Causes and Control 2001;12:509-517.
- Schroeder JC, Olshan AF, Baric R, Dent GA, Weinberg CR, Yount B, Cerhan JR, Lynch CF, Schuman LM, Tolbert PE, Rothman N, Cantor K, Blair A. Agricultural risk factors for t(14;18) subtypes of non-Hodgkin's lymphoma. Epidemiology 2001;12:701-709.
- DeRoos AJ, Zahm SH, Weisenburger DD, Holmes FF, Burmeister LF, Blair A. Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. Occupational and Environmental Medicine 2003;60:art. no. ell.
- Lee WJ, Cantor KP, Berzofsky JA, Zahm SH, Blair A. Risk of non-Hodgkin's lymphoma among asthmatic subjects exposed to pesticides. International Journal of Cancer 2004;111:298-302.
- Chiu B,Dave BJ, Blair A, JS, Gapstur SM, Chmiel JS, Fought AJ, Zahm SH, Weisenburger DD. Cigarette smoking, familial hematopoietic cancer, hair dye use, and risk of t(14;18)-defined subtypes of non-Hodgkin lymphoma. American Journal of Epidemiology 2007;165:652-659.
- Chiu BC-H, Lan Q, Dave BJ, Blair A, Zahm SH, Weisenburger DD. The utility of t(14;18) in understanding risk factors for non-Hodgkin lymphoma. Journal of the National Cancer Institute Monographs 2008;39:69-73.
- Chiu BCH, Dave BJ, Ward MH, Hou L, Fought AJ, Jain S, Evens AM, Zahm SH, Blair A, Weisenburger DD. Dietary factors and risk of t(14;18)-defined subgroups of non-Hodgkin lymphoma. Cancer Causes & Control 2008;19:859-867.
- Chiu BC-H, Blair A. Pesticides, chromosomal aberrations, and non-Hodgkin's lymphoma. Journal of Agromedicine 2009;14:250-255.
- Chang CM, Schroeder JC, Dunphy CH, Baric RS, Olshan AF, Dorsey KC, Huang W-Y, Blair A. Non-Hodgkin lymphoma (NHL) subtypes defined by common translocations: Utility of fluorescence in situ hybridization (FISH) in a case-control study. Leukemia Research 2010;34:190-195.

CURRENT ANALYSES

There are currently no analyses focused on pesticides in progress. Future analyses of these data will focus on pooling of case-control studies from the United States and Canada to evaluate hypotheses related to pesticides and other agricultural exposures.

APPENDIX 4: CROSS-CANADA STUDY OF PESTICIDES AND HEALTH (CCSPH)

OBJECTIVE

The Cross-Canada Study of Pesticides and Health (CCSPH) was conducted between 1991 and 1994 to explore associations between pesticides and four different types of cancer: non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma, and soft tissue sarcoma. The CCSPH included men aged 19 years and older in six Canadian provinces with diverse agricultural practices and a variety of occupational and non-occupational exposures to pesticides.

METHODS

The CCSPH is a population-based case-control study. Between 1991 and 1994, men who were newly diagnosed with any of the four included cancer sites (incident cases) were recruited from cancer registries in each province except in Quebec, where cases were ascertained from hospitals. The CCSPH included 513 cases with non-Hodgkin lymphoma; 316 with Hodgkin lymphoma; 342 with multiple myeloma; and 357 with soft tissue sarcoma. All cases were matched by age (±2 years) and province to 1506 men who were *not* newly diagnosed with any of the four included cancer sites (controls). Controls were randomly selected from the Canadian population by health insurance records, computerized telephone listings, or voters' lists.

All participants (cases and controls) were mailed a questionnaire to obtain demographic characteristics, medical history, detailed lifetime job history, and pesticide use, among other important factors that may be related to any of the four cancer sites in the study. Telephone interviews were conducted with subjects who reported using any combination of pesticides for 10 hours or more per year during their lifetime, and a 15% random sample of those who used pesticides for less than 10 hours per year. Pesticide data were collected beginning with the broadest categories (e.g. occupations with potential pesticide exposure), followed by major chemical classes (e.g. herbicides), chemical groups (e.g. phenoxy herbicides), and individual compounds (e.g. 2,4-D). These questionnaires were modified from the telephone interview questionnaires that were used in similar studies of pesticide exposure and rare tumors in Kansas and Nebraska.

The complete methodology of the CCSPH is described in the following article:
McDuffie HH, Pahwa P, McLaughlin JR, Spinelli JJ, Fincham S, Dosman JA, Robson D, Skinnider LF, Choi NW. Non-Hodgkin's lymphoma and specific pesticide exposures in men: Cross-Canada Study of Pesticides and Health. Cancer Epidemiology, Biomarkers & Prevention 2001;10:1155-1163.

KEY FINDINGS

The CCSPH is a rich dataset and numerous interesting associations have been demonstrated. For example, studies have shown links between non-Hodgkin lymphoma and the herbicides dicamba, mecoprop, and 2,4-D, as well as the insecticides malathion, lindane, carbaryl, and DDT. The risk of non-Hodgkin lymphoma was also found to rise with use of an increasing number of potentially carcinogenic pesticides and some commonly used pesticide combinations. Other agricultural exposures, such as diesel exhaust, elevated the odds of non-Hodgkin lymphoma. Analyses of pesticides and Hodgkin lymphoma have generally shown few associations, possibly due to the small number of men with this cancer in the study. However, exposure to certain insecticides was related to higher odds of multiple myeloma and soft tissue sarcoma. Minimal links were observed from contact with farm animals. These studies also assessed non-occupational risk factors; for example, family history of cancer, which was found to increase the risks of all four cancer sites. Overall, these results have contributed to knowledge about the potential etiology of these cancers while paving the way for further research.

PUBLISHED ARTICLES

Nearly twenty scientific articles have been published about analyses of the CCSPH. More recently, the following papers have been published:

- Navaranjan G, Hohenadel K, Blair A, Demers PA, Spinelli JJ, Pahwa P, McLaughlin JR, Dosman JA, Ritter L, Harris SA. Exposure to multiple pesticides and the risk of Hodgkin lymphoma in Canadian men. Cancer Causes Control 2013; 24:1661-1673.
- Kachuri L, Demers PA, Blair A, Spinelli JJ, Pahwa M, McLaughlin JR, Pahwa P, Dosman JA, Harris SA. Multiple pesticide exposures and the risk of multiple myeloma in Canadian men. International Journal of Cancer 201;133:1846-1858.
- Pahwa M, Harris SA, Hohenadel K, McLaughlin JR, Spinelli JJ, Pahwa P, Dosman JA, Blair A. Pesticide use, immunologic conditions, and risk of non-Hodgkin lymphoma in Canadian men in six provinces. International Journal of Cancer 2012;131(11):2650-2659.
- Pahwa P, Karunanayake CP, Dosman JA, Spinelli JJ, McLaughlin JR, et al. Soft-tissue sarcoma and pesticide exposure in men: Results of a Canadian case-control study. Journal of Occupational and Environmental Medicine 2011;53:1279-1286.
- Pahwa P, Karunanayake CP, Dosman JA, Spinelli JJ, McDuffie HH, McLaughlin JR. Multiple myeloma and exposure to pesticides: A Canadian case-control study. Journal of Agromedicine 2012;17:40-50.
- Karunanayake CP, Spinelli JJ, McLaughlin JR, Dosman JA, Pahwa P, McDuffie HH. Hodgkin lymphoma and pesticides exposure in men: A Canadian case-control study. Journal of Agromedicine 2012;17:30-39.
- Hohenadel K, Harris SA, McLaughlin JM, Spinelli JJ, Pahwa P, Dosman JA, Demers PA, Blair A. Exposure to multiple pesticides and risk of non-Hodgkin lymphoma in men from six Canadian provinces. International Journal of Environmental Research and Public Health 2011;8:2320-2330.

CURRENT ANALYSES

The CCSPH continues to be used to evaluate associations between agricultural exposures and the risk of cancer. The following analyses are currently in progress:

- A systematic review: Using previously measured dermal exposure information to develop an occupational pesticide exposure assessment.
  Nicole Garzia, Kay Teschke, Patricia Stewart, John Spinelli

APPENDIX 5: NORTH AMERICAN POOLED PROJECT (NAPP)

Objective
The pooling of the Cross-Canada Study of Pesticides and Health (CCSPH) and the 3 NCI case-control studies of pesticides will allow for detailed investigation of pesticides and cancer risk. In particular, the large sample size will allow for investigation of pesticides that are less commonly reported, and for potential associations with cancer types and sub-types for which there is limited power in an individual study.

Methods
Data from the four studies are being harmonized to facilitate joint analyses. Initial efforts are focusing on the use of specific pesticides, as well as harmonization of lymphoma sub-types. Additionally, demographic and other potential confounding variables are being included in a joint dataset to ensure that comprehensive analyses may be conducted.

The total number of cases and controls from each study is reported in Table 1.

Table 1. Number of cases of cancer types and controls available in the pooled dataset

Cancer type	NCI studies	CCSPH	Total
Non-Hodgkin lymphoma	1174	513	1,687
Follicular	340	74	414
Diffuse	436	132	568
Small lymphocytic	121	26	147
Other	277	281	558
Multiple myeloma	245	342	587
Soft tissue sarcoma	133	357	490
Hodgkin lymphoma	191	316	507
Controls	2,655	1,357	4,012

The percentage of users of pesticides is high, with approximately 30% of cases reporting use of some pesticides in these studies, making this the largest study of pesticides and cancer at these sites to date.

There are various types of information available on farming and pesticide use in the combined datasets. Types of information included are listed below.

Pesticide use information:
1. Ever live/work on a farm
2. Ever apply pesticides (insecticides, herbicides, fungicides)
3. Type of application methods
4. Use of personal protective equipment
5. Years of use of specific pesticides
6. Days/year of use of specific pesticides

Other information available, including:
1. Age
2. Smoking
3. Medical conditions (e.g., asthma, previous and family history of cancer)

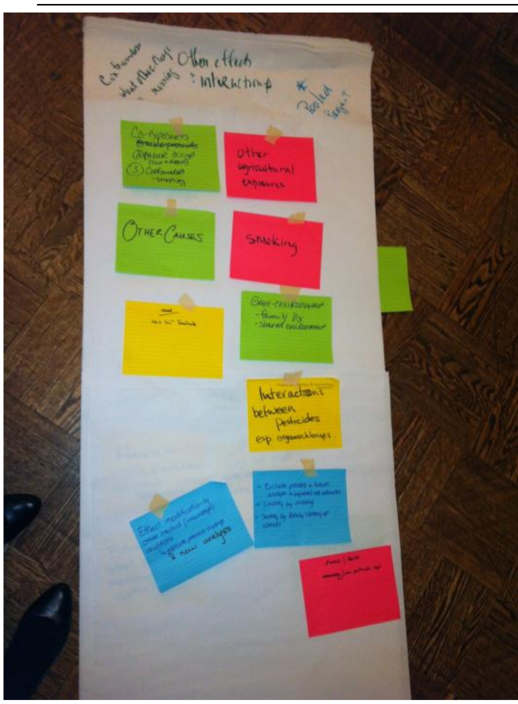
APPENDIX 6: SETTING RESEARCH PRIORITIES: PHOTOS OF THE NOMINAL GROUP METHOD

Please see the separate PDF document accompanying this report.

QUANTITATIVE MEASURES OF EXPOSURES – DOSE AND TIMING

- Formulation and exposures
- Exposure response
- Combinations and sub-types e.g. subtypes of Hodgkins Lymphoma
- Patterns of use in controls
- Exposure – “surrogate back and improve forward”
- Identify future and present exposures that have chronic effects
- Use of information on crops to a proximate exposure
- Dose response – pooled data set – developing measures of dose/response
- Duration/intensity information for individual pesticides
- Need larger polled sample to allow examination of separate effects of individual pesticides

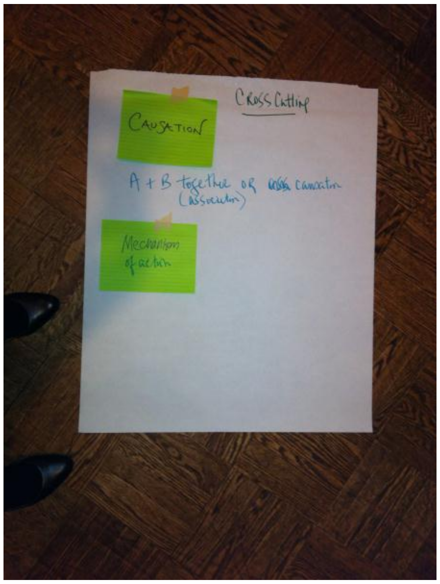
OTHER EFFECTS AND INTERACTIONS



(Confounders and what other things are missing)

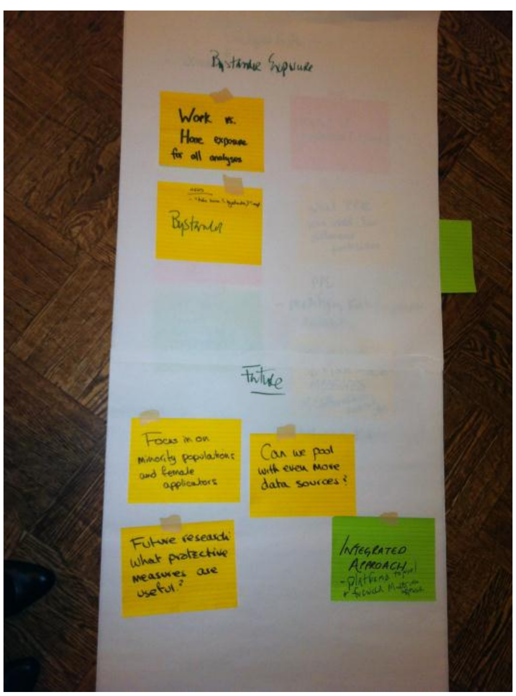
- Co-exposures e.g. other occupational exposures e.g. sun and diesel, confounder such as smoking
- Other causes
- Other agricultural exposures
- Interactions between pesticides (exposure related to outcomes i.e. disease) especially organochlorines
- Gene-environment – family history, shared environment
- Formulations and packaging - mixtures, temporal issues
- Need information in pooled data on non pesticide exposures
- Exclude proxies in future analyses – improved risk estimates
- Stratify by smoking and family history
- Effect modification by other medical (immunological) conditions – replicate previous findings with new analyses

CROSS CUTTING



- Mechanisms of action
- Causation
- A+B together (association) or causation

BYTANDER EXPOSURES

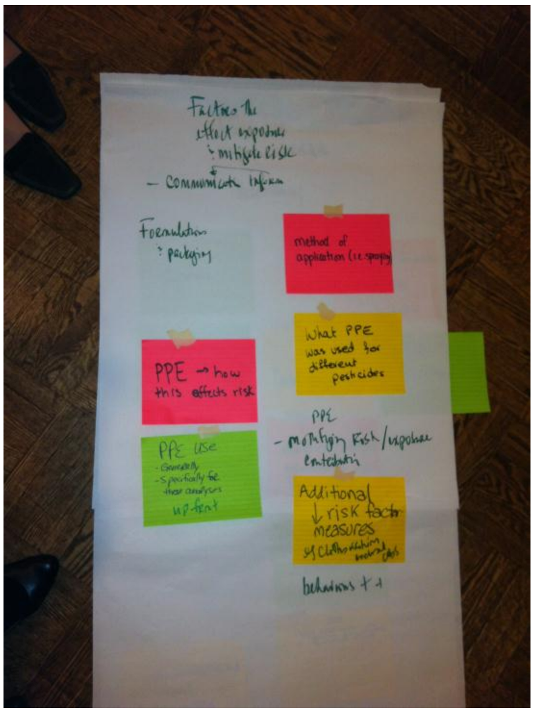


- Work versus home exposure for all analyses
- Need – "take home (bystander)" exposure

Future Research Needs

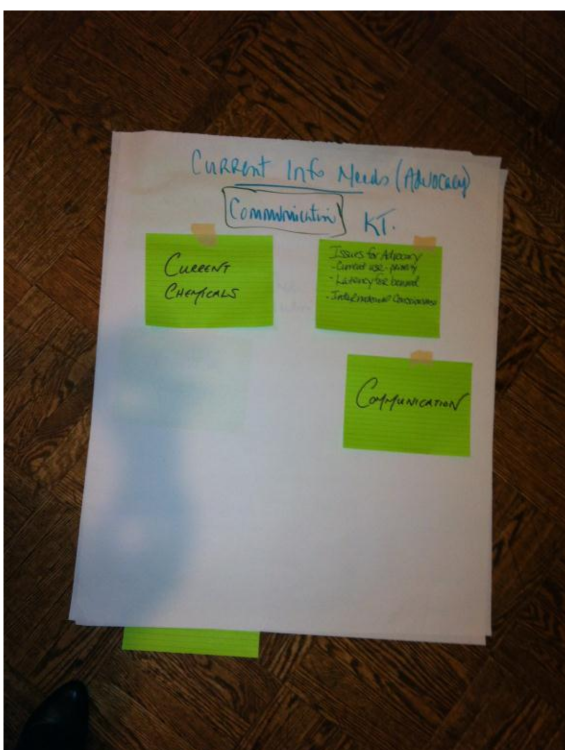
- Focus on minority populations and female applicators
- What protective measures are useful?
- Can we pool with even more data sources?
- Integrated approach – platforms to pool and forward multiple approach

Factors that Effect Exposure and Mitigate Risk - to Inform Communication



- Formulations and packaging
- Methods of application
- PPE use
  - How it affects risk
  - How contributes to modifying risk/exposure
  - Generally <u>and</u> specifically for these analyses (upfront)
  - What PPE was used for different pesticides
  - Behaviours
- Additional reducing risk factors measures e.g. clothes washing, enclosed cabs, etc

Current Information/Communication/KT/Advocacy Needs



- Latency for banned products
- International consciousness
- Current chemicals
- Current use priorities
- Individual exposures – any one thing?
- Issues for advocacy