Supplemental Material 1 – Details on pesticide exposure assessment for the InterLymph pooled analysis of herbicides

Details of the data collected and coded by the original studies (i.e., by the individual study investigators as part of the conducting the original study) and subsequent exposure assessment/ coding for the InterLymph pooled study are described in this document.

We requested data from each participating study on occupational history, farming, and occupational pesticide use. In addition to the questionnaire data, we requested any variables coded from these data, such as those resulting from expert assessment of pesticide exposures by an industrial hygienist or other exposure expert. Details on the relevant data from each individual study data are listed below.

In summary, five of the studies queried all participants about chemical and/or pesticide use in any type of job, and five of the studies administered questions about pesticides to persons with a history of farming or those who ever worked in other jobs with probable exposure, such as pest control, gardening and forestry. Two questionnaires asked about chemicals without distinguishing between work and home (LACCMM & Yale), although in both of these studies, participants were also queried separately about occupational and/or farming exposures.

Occupational use of pesticides was coded directly from questionnaire responses (i.e., self-report, 6 studies) or from reviews conducted by local experts in the individual studies (i.e., expert assessment, 4 studies), as follows:

Self-Reported Use was based on responses to either closed-ended (LAMMCC, Mayo) or open-ended (LANHL, Yale, NCI-SEER, BCMM) questions (detailed above); these were coded as a specific pesticide if either the active ingredient, or a product that contained the active ingredient, was named. One exception is that Agent Orange, a formulation which contained both 2,4,5-T and 2,4-D, was coded in the categories for 'all phenoxy herbicides' and 'other phenoxy herbicides', but was not coded as '2,4-D' as we wished to distinguish these exposures. Only personal handling of pesticides (i.e., mixed/loaded/applied) was coded as exposed from the questionnaires that provided this level of detail (all except LAMMCC and LANHL, which queried about substances to which the person was 'exposed' or 'directly exposed'). Self-reported responses to open-ended questions were reviewed for this InterLymph analysis (blinded to case status) by the principal investigator (AJD) and an industrial hygienist (TH), and were coded as a broad pesticide class or active ingredient by matching reported pesticide names to information from product labels, EPA registration materials, manufacturer documentation, and pesticide classification databases; discrepancies between AJD and TH were resolved through discussion and reevaluation.

Expert Assessments of pesticide exposure were previously conducted by four of the studies – the Italian Multicenter Study (Miligi et al. 2003), New South Wales (Fritschi et al. 2005), ENGELA (Orsi et al. 2009), and Epilymph (Cocco et al. 2013), as described for each study, below. Coded pesticide exposures (ever-use) from these expert assessments were accepted, as is, without recoding. However, specific pesticides coded in the expert assessment were grouped, when appropriate, into broad pesticide categories for the pooled analysis (the converse of coding specific active ingredients from expert-assessed broad pesticide categories was not done).

Cocco P, Satta G, Dubois S, et al. Lymphoma risk and occupational exposure to pesticides: results of the Epilymph study. Occup Environ Med 2013;70:91-98.

Fritschi L, Benke G, Hughes AM, et al. Occupational exposure to pesticides and risk of non-Hodgkin's lymphoma. Am J Epidemiol 2005;162:849-857.

Miligi L, Costantini AS, Bolejack V, et al. Non-Hodgkin's lymphoma, leukemia, and exposures in agriculture: results from the Italian multicenter case-control study. Am J Ind Med 2003;44:627-636.

Orsi L, Delabre L, Monnereau A, et al. Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study. Occup Environ Med 2009;66:291-298.

Following ever/never coding of the pesticides of interest by either self-report or expert assessment, additional data coding and cleaning was conducted to harmonize the data. Duration of use was coded from reported duration or reported years of use, and cross-checks were conducted to make sure these reported items corresponded to each other (if in disagreement then the lower duration value was retained). Reported years of use were also recoded if they exceeded the study reference year (in this case, the year of use was set to the reference year). Finally, years of use were restricted to plausible years after the chemical was registered for use (for example, glyphosate was first marketed for use in 1974; therefore, we did not count reported use during earlier years).

Duration of use for each pesticide was summed across all use periods, for each participant (e.g., across multiple jobs). If reported duration or years of use was not collected in the study or if the data were missing, then duration was calculated from job years for exposures linked to a particular job. The earliest and latest years of use (out of all uses of the pesticide) were used for calculation of lagged exposures, exposure windows prior to diagnosis, and decades of use.

LACCMM

Original study. An occupational work history included all jobs held for at least two months. All participants were asked about occupational exposures in two different sections of the questionnaire: a) up to 3 unprompted exposures in the occupational history section; b) up to 8 chemical exposures in response to the interviewer reading a list of substances (these exposures seemed to include both workplace and non-workplace exposures, although the participant could link the exposure to a particular job). Each participant’s reported exposures were then summarized into codes by the study investigators.

Pooled study. Investigators received questionnaire data including coded occupational history (standard job codes) and chemical exposures. Chemical exposures were, in some cases, further grouped for the pooled analysis (e.g., grouping “agent orange” and “2,4,5-T; 2,4-D” as phenoxy herbicides). Exposure years and duration were coded from self-reported exposure years for the prompted exposures and, otherwise, as job years.

LANHL

Original study. An occupational work history included all jobs held for 6 months or longer "since the age of 15 up until 12 months ago". Participants were also asked, separately, about work in farming. All participants were asked if they were ever "directly exposed" to particular types of exposures, prompted by the questionnaire, including, for pesticides: a) "Weed killers or herbicides like agent orange or other phenoxy-acids such as MCP, or 2,4-D, 2,4,5-T"; b) "Insecticides or pesticides"; c) "Rodent or vermin poisons". For each reported exposure, the interviewer elicited more details according to the questionnaire on 'what kinds?" of the chemical (e.g., 2,4-D), whether the participant mixed or applied it themselves, ages exposed, length of exposure (years), total (cumulative) hours exposed, and whether the exposure occurred at work, school, or in leisure.

Pooled study. Investigators received questionnaire data including coded occupational history (standard job codes). Reported chemical exposures were provided as the raw text responses, which investigators coded using the approach described above for self-reported exposure. Participants were coded as exposed if they indicated that they were exposed at work and they mixed or applied the chemical themselves. Exposure years and duration were coded from self-reported exposure ages. If ages were missing then duration was coded from self-reported length of exposure. A measure of frequency was coded from total hours exposed divided by the duration in years, then divided by 8 for estimation of the number of days per year.

Italian Multicenter

Original study. Data were collected through an in-person interview. Occupational history included every job held for more than 6 months and included basic information such as the job title, type of company or business, job description, and years. A job-specific questionnaire was administered to any participant who had ever worked in farming. The questionnaire was designed explicitly for crops commonly grown in the study areas, and elicited crop-specific information on crop diseases and pesticide use. Detailed data were also collected on the years and frequency of treatment and means of application.

Expert agronomists (one for each agricultural or mixed study area) reviewed information from the job descriptions and agricultural questionnaire in order to assess chemical exposures. To ensure a standardized approach, the assessors were centrally trained prior and during their independent evaluation of questionnaires. Experts examined the information on crop diseases, treatments carried out, field acreage, geographical location, and reported the use of specific pesticides. The agronomists developed a crop exposure matrix (Miligi et al., 1993) that was used as a baseline for the individual exposure assessment and to create a common resource in order to reduce exposure assessment variability among the different experts. The agronomists also based their judgments on their personal local experience, national statistics on pesticide use per year and administrative unit, available records of local pesticide suppliers, records of pesticides purchased by the major farms, and on professional consultants for the different crops. Pesticides were assessed by the type of treatment (e.g., herbicides), chemical families used (e.g., phenoxy acid), and active ingredients (e.g., 2,4-D).

Miligi L, Settimi L, Masala G, Maiozzi P, Alberghini Maltoni S, Seniori Costantini A, Vineis P. Pesticide exposure assessment: a crop exposure matrix. The Working Group on Pesticide Exposure Assessment. Int J Epidemiol. 1993;22 Suppl 2:S42-45.

Pooled study. Investigators received coded data including coded occupational history (standard job codes) and pesticide exposures from the expert assessment. Coded exposure and years of use were taken directly from data specified in the expert-assessed data for each exposure. In some instances, exposures coded as mixtures by the experts were coded in a particular category or active ingredient for the pooled analysis (e.g., “MCPA + DICAMBA” expert assessment was coded for the pooled analysis as both ‘phenoxy herbicides’ and ‘other phenoxy herbicides’, and as dicamba use).

Yale

Original study. Questionnaires were administered by an interviewer. An occupational work history included all jobs held for 1 year or longer and collected information on job title, job duties, the type of company or industry, and the years and hours worked. Information on pesticide exposure was collected in two sections of the questionnaire. First, farm and agricultural pesticide use was elicited from participants who had ever lived or worked on a farm. This section asked separately about insecticides and herbicides used on the farm, eliciting details such as the chemical name, years used and total duration, frequency (days/year), personal handling, application methods, and personal protective equipment/clothing. Participants were shown cards with the names of commonly-used insecticides and herbicides to aid in recall. In a separate section of the questionnaire, participants were asked about a list of chemicals to which they may have been exposed at work or at home. They were asked if they “ever had repeated contact for a period of a year or more” with any of the substances listed on the provided prompt cards “apart from exposure on farms”. If yes, they were asked for the names of the substances, years exposed, total duration (years), frequency, personal handling, and protective equipment/clothing.

Pooled study. Investigators received questionnaire data including coded occupational history (standard job codes). Reported chemical exposures were provided as the raw text responses, which investigators coded using the approach for self-reported exposure, described above. Participants were coded as exposed only if they reported that they personally handled the chemical. Exposure years, duration, and frequency were coded from the self-reported information.

NCI-SEER

Original study. Questionnaires were administered by telephone using a computer-assisted structured interview. An occupational history section elicited information on all jobs held for 1 year or longer, including the job title, years worked, hours worked, the type of business/industry, job duties, chemicals or materials handled, and tools and equipment used. The question on chemicals asked, specifically, for each job, “What kinds of chemicals or materials, if any, did you handle?” The questionnaire did not contain any questions to specifically elicit occupational pesticide use.

Pooled study. Investigators received questionnaire data including coded occupational history (standard job codes). Reported data on chemicals handled on the job were provided as the raw text responses, which investigators coded using the approach described above for self-reported exposure. Exposure years and duration were coded from the years worked in the job.

Epilymph

Original study. In-person interviews were conducted using a structured questionnaire. Lifetime occupational history was collected, including all full-time jobs held for 1 year or longer. Participants who reported that they had ever worked in farming were given a job-specific module questionnaire to elicit detailed information about tasks and exposures. Occupational physicians and industrial hygienists from each participating center attended several meetings to share and upgrade their expertise in retrospective exposure assessment and to harmonize the exposure criteria. Local agronomists reviewed the available information to identify broad pesticide group (e.g., phenoxy herbicides) and individual formulations (e.g., 2,4-D), whenever possible. Their assessment was based on review of the questionnaire data regarding the type of crop, pest to be treated, frequency of treatments, and exposure circumstances, including personal preparation of the pesticide mix. A crop-exposure matrix was also available to support the assessment (Miligi et al. 2003). Frequency was expressed as days per year.

Miligi L, Settimi L, Masala G, Maiozzi P, Alberghini Maltoni S, Seniori Costantini A, Vineis P. Pesticide exposure assessment: a crop exposure matrix. The Working Group on Pesticide Exposure Assessment. Int J Epidemiol. 1993;22 Suppl 2:S42-45.

Pooled study. Investigators received coded questionnaire data including occupational history (standard job codes) and pesticide exposures from the expert assessment. Exposure years, duration, and frequency were taken directly from that specified in the expert-assessment-coded data.

NSW

Original study. Questionnaires were administered over the telephone by interviewers blinded to case or control status of the subjects. A lifetime occupational history was obtained that included the job title, industry, and years of each job. In addition, job-specific modules with detailed sets of questions were administered for several types of jobs with possible pesticide exposure, including farmers, gardeners, janitors, and laborers. The modules included questions about specific tasks performed in that occupation, and the number of hours per week and weeks per year spent performing each task. The questions in the relevant modules were asked in a customized computer-assisted telephone interview. An occupational hygienist (blind to case status) reviewed the occupational histories and the answers to the module questions and determined exposure to various substances, including organophosphates, organochlorines, phenoxy herbicides, other herbicides, and specific active ingredients (e.g., 2,4-D, glyphosate). Participants were coded as exposed in a particular job, only if they had personally handled (mixed or applied) the chemical. A pesticide-crop matrix was developed for assistance with exposure assessment, that included information on the kinds of pesticides known to be used (or recommended by the Australian Department of Agriculture) for each combination of crop or animal raised and pest type (insect, weed, etc.) (Benke et al. 2001). A table was also prepared for assistance with identification of chemical composition from trade names reported by the subjects. Former Department of Agriculture employees, environmental scientists, and pesticide manufacturers assisted with construction of the matrix. Frequency of exposure was allocated as number of 8-hour days per year and was calculated using responses to the task questions.

Benke G, Fritschi L, Hughes AM, et al. Combining job specific modules (JSMs) and exposure matrices for retrospective ex exposure assessment. In: Hagberg M, Knave B, *Lillienberg L, et al, eds. X2001—exposure assessment in epidemiology and practice. Stockholm, Sweden: National Institute for Working Life, 2001:169–171.*

Pooled study. Investigators received coded questionnaire data including coded occupational titles (standard job codes) and pesticide exposures per job. Exposure years and duration were based on the years the job was held for farming, janitor, and laborer jobs. Exposure years and duration were based on the reported years of pesticide use for gardener/groundskeeper jobs.

ENGELA

Original study. Data collection was conducted in several phases. First, participants were asked to complete a self-administered questionnaire to collect information on sociodemographics, and residential and work histories. Occupational work history included all jobs held longer than 6 months, for which the participant was asked to report the job title, start and end dates, specific tasks performed and products personally handled. A face-to-face interview was then conducted with each participant to elicit further information on personal and familial medical histories, lifestyle characteristics, leisure activities, and non-occupational exposures. Finally, a specialized questionnaire was administered to each participant who had reported ever working as a farmer or gardener – designed to allow standardized case-by-case pesticide exposure assessment by experts. Participants were asked questions about each farm they had ever worked on, including specific crops and animals, pesticides applied (including whether they had personally prepared or sprayed the chemical), spraying equipment, frequency, and years of use. Repeat interviews for the specialized questionnaire were conducted for more than 80% of the subjects because the reported information was insufficient. All administered interviews were blind to case-control status.

Two persons, one industrial hygienist and one agronomist individually reviewed all the questionnaires to assess pesticide exposures. The experts reviewed the consistency of the subjects' statements with respect to product availability dates, type and size of the crops, geographic location of the farm and frequency of treatment. A database constructed using the annual directories of phytochemicals published by the Association de Coordination Technique Agricole was used to facilitate the process – including recommendations for use of the products (identified by their chemical and brand names) by crop and pest. When information on pesticides was missing or unreliable, the experts allocated a list of chemicals that may have been used based on the crops treated, method of spraying, period and frequency of treatment and pests targeted. Pesticide exposures were primarily coded in broad categories such as organophosphate insecticides, phenoxy herbicides and triazine herbicides, and there was also specific coding for glyphosate. The exposure years and duration were based on the years of pesticide use for each exposure, reported in the specialized questionnaire.

Pooled study. Investigators received coded data including coded occupational history (standard job codes) and pesticide exposures from the expert assessment. Exposure years and duration was coded from the years specified in the expert-assessed data.

Mayo

Original study. Questionnaires were self-administered. Information was collected on the longest-held job and up to 5 additional jobs held for longer than 5 years, including the job title, age first worked, and the total number of years worked in the job. An additional questionnaire based off the Agricultural Health Study private applicator questionnaires (https://aghealth.nih.gov/collaboration/questionnaires.html) was given to participants who reported during the enrollment protocol that they ever worked on a farm or with pesticides for longer than 1 year. Participants who ever personally mixed or applied any pesticides as part of their job were asked about use of 48 active ingredients or pesticide groups; they were asked, separately for each pesticide, to report personal handling, duration (years) of use, frequency (days/year), and the year of first use. Other parts of the questionnaire asked about pesticide application methods and additives used, size of the farm, and crops and animals.

Pooled study. Investigators received questionnaire data including coded occupational history (standard occupational codes) and responses from the farming questionnaire. Reported pesticide uses were considered exposed if the participant reported personal handling of that specific pesticide. Specific active ingredients were coded directly from the self-reported information, and active ingredients were also grouped to code broad categories of pesticides (such as grouping “atrazine” and “cyanazine”, reported separately, as triazine herbicides). Exposure duration and year of first use also were coded from the questionnaire responses.

BCMM

Original study. Questionnaires were self-administered. An occupational work history included all jobs held for 2 years or longer and collected information on job title, job duties, the type of company or industry, and the years and hours worked. Additional questions were given to participants who had ever lived on a farm or worked in agriculture, gardening, parks, golf courses, or forestry. Participants were asked about use of pesticides in these settings, including the name of the product or active ingredient, the target pest, application method, duration of use, and frequency (days/year). Other parts of the questionnaire asked about personal handling of herbicides, insecticides, and fungicides, as broad categories, protective equipment and clothing, and crops and animals.

Pooled study. Investigators received questionnaire data including raw text responses from the occupational history and reported pesticides. The investigators coded jobs of a priori interest for possible pesticide exposures including farming, forestry, gardener/groundskeeper, janitor/cleaner, and laborer. Reported pesticides were provided as the raw text responses, which investigators coded using the approach described above for self-reported exposure. Participants were coded as exposed only if they reported personal handling of the corresponding types of pesticide (out of herbicides, insecticides, and fungicides). Exposure years, duration, and frequency were coded from the self-reported information for each pesticide exposure.