ORIGINAL ARTICLE

Assessment of occupational exposure to pesticides in a pooled analysis of agricultural cohorts within the AGRICOH consortium

Maartje Brouwer,[1] Leah Schinasi,[2] Laura E Beane Freeman,[3] Isabelle Baldi,[4,5,6] Pierre Lebailly,[7,8,9] Gilles Ferro,[2] Karl-Christian Nordby,[10] Joachim Schüz,[2] Maria E Leon,[2] Hans Kromhout[1]

▸ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/oemed-2015-103319).

For numbered affiliations see end of article.

Correspondence to Professor Hans Kromhout; Division of Environmental Epidemiology, Institute for Risk Assessment Sciences, Utrecht University; P. O. Box 80.178, Utrecht 3584 TD, The Netherlands; h.kromhout@uu.nl

Received 17 September 2015
Revised 19 February 2016
Accepted 5 March 2016
Published Online First
23 March 2016

ABSTRACT

Background This paper describes methods developed to assess occupational exposure to pesticide active ingredients and chemical groups, harmonised across cohort studies included in the first AGRICOH pooling project, focused on the risk of lymph-haematological malignancies.

Methods Three prospective agricultural cohort studies were included: US Agricultural Health Study (AHS), French Agriculture and Cancer Study (AGRICAN) and Cancer in the Norwegian Agricultural Population (CNAP). Self-reported pesticide use was collected in AHS. Crop-exposure matrices (CEMs) were developed for AGRICAN and CNAP. We explored the potential impact of these differences in exposure assessment by comparing a CEM approach estimating exposure in AHS with self-reported pesticide use.

Results In AHS, 99% of participants were considered exposed to pesticides, 68% in AGRICAN and 63% in CNAP. For all cohorts combined (n=316 270), prevalence of exposure ranged from 19% to 59% for 14 chemical groups examined, and from 13% to 46% for 33 active ingredients. Exposures were highly correlated within AGRICAN and CNAP where CEMs were applied; they were less correlated in AHS. Poor agreement was found between self-reported pesticide use and assigned exposure in AHS using a CEM approach resembling the assessment for AGRICAN (κ −0.00 to 0.33) and CNAP (κ −0.01 to 0.14).

Conclusions We developed country-specific CEMs to assign occupational exposure to pesticides in cohorts lacking self-reported data on the use of specific pesticides. The different exposure assessment methods applied may overestimate or underestimate actual exposure prevalence, and additional work is needed to better estimate how far the exposure estimates deviate from reality.

What this paper adds

- To investigate associations between rare pesticide exposures and rare health outcomes, pooling of data from agricultural cohort studies is a necessity.
- Occupational exposure to 14 pesticide chemical groups and 33 active ingredients was assessed across three cohort studies included in the AGRICOH pooling project on lymph-haematological malignancies. Country-specific crop-exposure matrices (CEMs) were created to assign exposure in the two cohorts that did not collect data on the use of specific pesticides.
- Pesticide exposures were highly correlated where CEMs were applied and agreement between self-reported pesticide use and assigned exposure using a CEM approach was poor.
- Pooling of data from different agricultural cohort studies with distinct designs and detail regarding pesticide exposure is possible. However, results from subsequent epidemiological analyses should be interpreted cautiously due to potentially substantial exposure misclassification.

INTRODUCTION

Agricultural workers are of specific interest in occupational epidemiology as they show decreased risk of some diseases and excess risk for others, possibly due to experiencing a wide range of specific work-related exposures (eg, pesticides, diesel exhaust, dust and endotoxins) and conditions (eg, physical activity, outdoor work).[1–5] Pesticides are one of the most studied exposures for farmers and farmworkers. The biological activity of pesticides may impact both target pests and human health and there are plausible hypotheses on mechanisms through which pesticides could be involved in different adverse health effects.

Accurate assessment of exposure to pesticides is critical for epidemiological studies to further investigate suggested associations with health outcomes, but this is a major challenge. Biological measurements often do not allow quantification of past pesticide exposure, as most pesticides and their metabolites are not persistent in the human body. Many studies have used occupational classifications (eg, farmer, farmworker) as a proxy for exposure to pesticides, or assessed exposure in broad classifications such as 'herbicides'. However, such metrics of pesticide exposure are crude and often not specific enough to offer useful information on the

To cite: Brouwer M, Schinasi L, Beane Freeman LE, *et al*. *Occup Environ Med* 2016;**73**:359–367.

chemicals that represent potential health risks. A few attempts have been made to analyse data considering exposure to chemical groups of pesticides or individual active ingredients, and some interesting findings have emerged from these studies.[6,7] For example, results from the US Agricultural Health Study (AHS) are suggestive of associations between specific pesticides and some cancers, including leukaemia, non-Hodgkin lymphoma and multiple myeloma.[8]

Individual studies often lack statistical power to investigate associations between specific pesticide exposures and health outcomes due to rare exposures (eg, use of infrequently applied pesticides), rare health outcomes (eg, cancer subtypes, specific neurological or autoimmune diseases) or a combination of both.[9] Therefore, the AGRICOH consortium was established with the aim of promoting and sustaining collaboration between agricultural cohort studies and enabling data sharing and pooled analyses.[10] The AGRICOH consortium currently consists of 28 prospective cohort studies from 12 countries.[11] However, the type of pesticide exposures or exposure proxies investigated varies from one study to another. These differences in exposure assessment, and further variation in agricultural practices between and within countries, pose a challenge for pooling of data across studies.

Here, we describe the development of cohort-specific methods to assess exposure to selected pesticide chemical groups and individual active ingredients in three prospective cohort studies from France, Norway and the USA, included in the AGRICOH pooling project on lymph-haematological malignancies. The information on pesticide exposures collected in each cohort is discussed, as well as the harmonisation efforts resulting in a set of common exposures and their prevalence across the cohorts. Furthermore, potential exposure misclassification arising from these cohort-specific exposure assessment methods is explored. The focus on lymph-haematological malignancies guided the selection of pesticide chemical groups and active ingredients. Risk estimates of lymph-haematological cancer and pesticide exposure, derived from the exposure assessment described, will be reported in separate publications. Nevertheless, the exposure assessment methods developed for this project will be applied in other pooling projects within the AGRICOH consortium.

METHODS

Description of the cohort studies

The three prospective cohort studies included in this pooling project on lymph-haematological malignancies were: the US Agricultural Health Study (AHS),[12] the French Agriculture and Cancer Study (AGRICAN)[13] and the Cancer in the Norwegian Agricultural Population (CNAP) Study[14] (table 1). These three cohort studies were selected within the AGRICOH consortium because of available data on the incidence of lymph-haematological malignancies, and the opportunity to assess exposure to individual pesticides within these cohorts.

AHS

AHS is a prospective cohort study which collected data on 52 394 licensed private pesticide applicators and 32 346 of their spouses in Iowa and North Carolina, USA, and on 4916 commercial applicators in Iowa. Details of the AHS design have been described elsewhere.[12] In brief, pesticide applicators were

Table 1 Characteristics of the prospective agricultural cohort studies

	Agricultural Health Study (AHS)	Agriculture and Cancer Study (AGRICAN)	Cancer in the Norwegian Agricultural Population (CNAP)
Cohort characteristics			
Number of participants	57 310 applicators seeking pesticide licenses and 32 346 spouses	181 747 members of the French health insurance for agriculture (MSA)	147 134 farm holders and 98 759 spouses, identified in the agricultural censuses from 1969 to 1989
Participants selected for this pooling study	51 167 private pesticide applicators* (farmers)	127 282 farmers*,† (49 698 farm workers, 37 474 farm owners and 40 110 who held both functions during their life)	137 821 farm holders*
Geography	Iowa and North Carolina, USA	11 departments, France (Doubs, Gironde, Côte d'Or, Isère, Loire-Atlantique, Manche, Bas Rhin, Haut Rhin, Somme, Tarn, Vendée)	Norway
Gender: male (%)	49 831 (97)	71 358 (56)	116 128 (84)
Year of birth: median (range)	1949 (1901–1983)	1939 (1900–1985)	1942 (1925–1971)
Year of enrolment (range)	1993–1997	2005–2007	1969–1989
Reference	12	13	14
Pesticide exposure data			
Crop cultivation	NA‡	Self-reported lifetime cultivation of 13 crops§ and years of cultivation	Self-reported cultivation of crops at the farm in the year preceding the censuses of 1969, 1974¶, 1979, 1985¶ and 1989
Pesticide application information	Self-reported mixing or application of pesticide products (ever use, duration and first decade of use)	Self-reported pesticide treatment tasks on 11 crops** and start/end years performing tasks	Farm-level pesticide use indicators: money spent on pesticides (1969 census) and presence of pesticide spraying equipment on the farm (1979 census)

*For cohort-specific exclusions, see online supplementary figure S1.
†Farmers were defined as participants who indicated ever cultivating any of 13 types of crops or ever having any of the five types of animals, and/or had an indication of being a farmer based on the data in their occupational history.
‡Crop cultivation was collected in AHS (current income producing crops in phase I and crops cultivated during the reference year in phase II), but this information was not used to assign pesticide exposure in this pooling project, except for comparing CEM assignments and self-reported use in a subset of phase II participants.
§Grassland, vineyards, corn, wheat or barley, field peas, beets, sunflower, rape, tobacco, orchards, potatoes, other vegetables and greenhouses.
¶The 1974 and 1985 censuses were specific for horticultural crops and only administered to part of the cohort (3636 and 6588 participants, respectively).
**For all the crops listed previously, except for other field-grown vegetables and greenhouses.
NA, not applicable.

enrolled between 1993 and 1997 by completing self-administered questionnaires[15] that asked, among other things, about past and current personal use of 50 commonly used pesticide products based on a predefined list of chemicals (phase I). Five years following enrolment, a follow-up questionnaire was administered (phase II) asking about crops cultivated, animals raised and pesticides used (in an open-ended question) during the reference year, which was the most recent year a participant was farming.

AGRICAN

AGRICAN is a prospective cohort study of 181 747 participants affiliated with the *Mutualité Sociale Agricole* (MSA), the French agricultural health insurance. Details of the AGRICAN cohort have been described previously.[13] In brief, participants were enrolled between 2005 and 2007 by completing a mailed self-administered questionnaire. Participants were asked about the cultivation of 13 crops and different tasks, including pesticide treatment, performed on 11 of these crops.

CNAP

The CNAP prospective cohort study of Norwegian farm holders and their families was compiled by linking data on farm characteristics and production from the compulsory agricultural censuses (between 1969 and 1989). Details of this cohort have been described elsewhere.[14] In brief, a total of 147 134 farm holders and 98 759 spouses have been included in the cohort. Eligibility criteria for participation in the censuses have changed over the years. In each census, information on the cultivation of different crops at the farm during the preceding year was collected, using a prompted list. In addition, the 1969 census collected data on pesticide purchases and the 1979 census on the presence of pesticide spraying equipment at the farm.

Selection of participants

To harmonise the participants included in the pooled analysis, male and female private pesticide applicators and/or farmers (active or retired) were selected from each of the three cohorts. After exclusions, 51 167 participants from AHS, 127 282 from AGRICAN and 137 821 from CNAP remained (table 1). Participants in AHS were younger at enrolment than participants in AGRICAN. In AHS and CNAP, respectively, 3% and 16% of the cohort were female, compared to 44% in AGRICAN.

Chemical groups and active ingredients

For this pooling project, pesticide chemical groups and active ingredients were selected that were potentially used in more than one of the three countries, and prioritised if there was evidence from the scientific literature for an association with lymph-haematological malignancies. For this purpose, International Agency for Research on Cancer (IARC) monograph evaluations, US Environmental Protection Agency (EPA) assessments of carcinogenicity and the published epidemiological literature were reviewed. In total, 14 pesticide chemical groups and 33 individual active ingredients were selected (table 2). Active ingredients were classified into chemical groups on the basis of their main function (insecticide, fungicide, herbicide) and the classifications listed in the Wood's[16] compendium of pesticides and the 1991[17] and 2009[18] British Crop Protection Council pesticide manuals. The complete list of the active ingredients contributing to each of the chemical groups per cohort varied, since the registration and use of specific active ingredients differed by country (see online supplementary table S1).

Table 2 Selected pesticide chemical groups and active ingredients

Chemical group	Number of active ingredients that contributed to the chemical group*	Active ingredients selected for individual assessment
Insecticides		
Carbamate insecticides	19	Aldicarb, carbaryl, carbofuran, pirimicarb
Organochlorine insecticides	15	DDT, lindane
Organophosphate insecticides	76	Chlorpyrifos, dichlorvos, malathion, parathion, terbufos
Pyrethroid insecticides	31	Deltamethrin, esfenvalerate, permethrin
Herbicides		
(Phenyl) urea herbicides†	16	Isoproturon, linuron
Chloroacetanilide herbicides	6	Alachlor, metolachlor
Dinitroaniline herbicides	8	Trifluraline
Thiocarbamate herbicides	9	Butylate, EPTC
Phenoxy herbicides‡	9	2,4-D, MCPA, mecoprop
Triazine herbicides	12	Atrazine, simazine
Triazinone herbicides	2	Metribuzin
Individual active ingredients	2	Dicamba, glyphosate
Fungicides		
Dithiocarbamate fungicides	12	Mancozeb, thiram
Phthalimide fungicides	3	Captafol, captan
Other		
Arsenicals	10	Only the chemical group is considered; no individual active ingredients from this group were selected

*This refers to the number of active ingredients considered within each chemical group, as these were used or potentially used (registered and sold in the country) by participants in one or more of the cohorts.
†Restricted to the phenylurea herbicides (Weed Science Society of America (WSSA) 7).[19]
‡Excluding the WSSA 1 and WSSA 25 phenoxy herbicides.[19]
DDT, dichlorodiphenyltrichloroethane; EPTC, S-ethyl-dipropylcarbamothioate; MCPA, 2-methyl-4-chlorophenoxyacetic acid; 2,4-D, 2,4-Dichlorophenoxyacetic acid.

Crop cultivation

In AGRICAN and CNAP, no self-reported information on the use of individual pesticides was collected. Available data on crop cultivation and indicators of personal pesticide use were used as the basis for the exposure assessment. A number of crops were selected for developing country-specific crop exposure matrices (CEMs), to assign exposures to chemical groups and individual active ingredients. These crops were considered relevant because they were commonly produced in at least two of the three countries, or were major commodities in any of the countries, irrespective of the frequency of cultivation in the other cohorts (eg, vineyards in France).

For AGRICAN, grassland, corn, grains, potatoes, tobacco, orchard crops and vineyards were selected, and for CNAP, grassland, grains, potatoes, orchard crops and greenhouses. The prevalence of cultivation of these crops in each of the cohorts is shown in table 3. Although crop cultivation was not used to assign exposure in AHS, it is presented in table 3 to illustrate differences between the cohorts. In AGRICAN, 276 participants exclusively cultivated other crops than the ones selected for the CEM. Similarly, in CNAP, 33 834 participants

Table 3 Participants per cohort who ever cultivated the selected crops

	AHS* (n=51 167)		AGRICAN† (n=127 282)		CNAP‡ (n=137 821)	
Crops selected for AGRICAN and CNAP	N	Per cent	N	Per cent	N	Per cent
Grassland, Hay, Meadows	19 062	37	89 168	70	34 656	25
Corn	38 046	74	54 815	43	NS	–
Grains	15 031	29	73 774	58	34 838	25
Potatoes	2222	4	52 025	41	43 458	32
Tobacco	8473	17	17 730	14	NS	–
Orchard crops	1421	3	49 743	39	7683	6
Vineyards	655	1	57 160	45	NS	–
Greenhouses	–	–	NS	–	23 719	17
Soya beans§	36 281	71	NS	–	NS	–

NS, the crop is not selected in this cohort for pesticide exposure assessment in the pooling project.
*Counts are based on reports of ever producing the crop at phase I or phase II. Grassland/meadows include hay and alfalfa, corn includes field and seed corn, grains include barley, wheat, rye and oats, vineyards are represented by grape production and orchard crops include apples and peaches. No data on crop cultivation in greenhouses were collected.
†Counts are based on ever cultivating the crop, and these are the average of five imputation data sets, calculated using Rubin's rules for combining data from multiple imputed data. Corn includes corn produced for grain or silage, grains include wheat or barley, and orchard crops include apples.
‡Counts are based on reports of ever producing the crop in any of the agricultural and horticultural censuses (1969–1989). Since no information on grassland (or meadows or hay) is available from the censuses, production of silage was used as a proxy for grassland cultivation. Grains include barley, oats, wheat, rye and oil seeds, orchard crops include apples, pears and plums, and greenhouses include all crops cultivated in greenhouses.
§Soya beans are listed to illustrate their relevance as a major commodity in AHS, but were not included in the country-specific CEMs developed for AGRICAN and CNAP.
AHS, US Agricultural Health Study; CEM, Crop-exposure matrix; CNAP, Cancer in the Norwegian Agricultural Population.

were farm-holders who did not cultivate any of the selected crops. These participants were considered unexposed to any of the selected pesticide chemical groups and active ingredients.

Assessment of exposure to pesticides

AHS

For AHS, exposure to the specific pesticide active ingredients and chemical groups was based on participants' self-reported use of pesticides. In phase I, participants could indicate the period in which they first used the active ingredient as well as the duration of use of each pesticide product. If a participant reported the use of one of these active ingredients in phase II, the reference year of that participant was used as the last year of use, and the duration of use was recalculated accordingly. If a pesticide was only reported at phase II, then duration of use was calculated as the period between the enrolment year and the reference year. For the chemical groups, ever use, first year of use and duration of use were determined by the self-reported use of any active ingredient considered within the group (see online supplementary table S1).

AGRICAN

A country-specific CEM was developed for seven main crops in France (table 3), covering the period 1950–2009, as the last day of follow-up for AGRICAN was 31 December 2009 in this pooling project. This CEM lists the first and last years the chemical groups and active ingredients were potentially used on each crop in France (see online supplementary table S2). For the development of this CEM, data were drawn from an existing French matrix, PESTIMAT,[20] which contained information on the registration, sales and recommended use of a selection of chemical groups and active ingredients. For the crops and chemical groups and active ingredients not present in PESTIMAT at the time of the present study, additional work was performed to extract the first and last years of potential use from the data sources underlying PESTIMAT.[20] For grassland, only herbicides were considered in the CEM.

For this pooling project, AGRICAN participants were considered potentially exposed to an active ingredient during a year if (1) they declared cultivating a crop, (2) reported personally performing pesticide treatment tasks on this crop and (3) the active ingredient was registered and recommended for use on the crop during that year according to the CEM. Participants who did not report any pesticide treatment tasks were considered unexposed to any pesticide for that crop. All active ingredients classified within a chemical group were considered for determining ever use, first year of use and duration of use for that group (see online supplementary table S1).

CNAP

A country-specific CEM was developed for five main crops in Norway (table 3), covering the period 1950–2011, as the last day of follow-up for CNAP was 31 December 2011 in this pooling project. This CEM provided the first and last years each chemical group or active ingredient was sold and registered for use on each of the selected crops (see online supplementary table S2). In Norway, the available historical data on farmer pesticide use was restricted to pesticide registration and sales data, which were obtained from the Norwegian Food Safety Authority, and supplemented with expert input if the first year of registration or sales was unknown. All active ingredients classified within a chemical group were considered for setting the first and last years of potential use for a chemical group. For grassland, only herbicides were considered in the CEM (see online supplementary table S1).

Census data on crop cultivation on the farm was restricted to a maximum of five points in time. If a crop was cultivated at the farm in one census as well as the follow-up census, it was assumed that the crop was cultivated for the whole period between the censuses. Otherwise, the median year between the two censuses was assigned as the end or start year for cultivation of that crop (see online supplementary table S3). No crop cultivation was assigned to a participant for the years he/she was under 18 years of age. In the Norwegian census data, two pesticide use indicators were available at the farm level: (1) the amount of money spent on purchasing pesticides (1969 census) and (2) the presence of pesticide spraying equipment on the farm (1979 census). When either of these two indicators was positive, the participant was considered a likely pesticide applicator. Participants who only participated in the 1989 census (n=5852) or the horticultural censuses (n=421), and thereby lacked either of these pesticide use indicators, were also considered likely pesticide applicators.

For this pooling project, CNAP participants were considered to be potentially exposed to an active ingredient during a year if (1) they cultivated a crop, (2) were considered pesticide applicators and (3) the active ingredient was sold and registered on the crop during that year according to the CEM. All active ingredients classified within a chemical group were considered for determining ever use, first year of use and duration of use for that group (see online supplementary table S1).

Imputation of missing data

The imputation of missing data in AHS has been described previously.[21] For AGRICAN, missing data on crop cultivation and pesticide treatment tasks on crops were imputed using multiple imputation by chained equations (MICE).[22] All imputations were performed five times and the imputed data were combined using Rubin's Rules.[23] No data were imputed in CNAP as the agricultural censuses were mandatory and thereby complete.

Comparison of exposure assessment methods

No external data were available to validate the exposure assessment methods used in this pooling project. However, we did attempt to compare exposure estimates generated using the different methods applied. In the AHS phase II questionnaire, participants provided information on both pesticides applied and crops cultivated during the reference year. These data allowed for a comparison between pesticide exposure assigned using a CEM approach based on crop cultivation and self-reported pesticide use in the reference year.

For the purpose of this comparison, a CEM was developed on the basis of pesticide registration data from the USA, for the period corresponding to the phase II reference years (1992–2002). This CEM will not be used in the epidemiological analyses, as for AHS exposure is based on the participants' self-reported use of pesticides. Eight crops were selected on the basis of cultivation in either of the other two cohorts (grassland, corn, grains, potatoes, tobacco, orchard crops and vineyards). Soya beans were added as they are a major crop in Iowa and North Carolina, USA. Eleven pesticide active ingredients with relatively low, medium and high self-reported use among AHS participants were selected for this CEM (see online supplementary table S4).

In AGRICAN, participants were considered exposed to the active ingredients in the CEM for a specific crop, when cultivating the crop and performing crop-specific pesticide treatment tasks. To approximate this approach, AHS phase II participants were classified as exposed to active ingredients registered for use on the crop cultivated during the reference year, if they reported having applied any pesticide to the relevant crop (approach 1). For CNAP, exposure to pesticides was assigned on the basis of purchase of pesticides and/or the presence of pesticide spraying equipment on the farm. AHS phase II participants who reported any pesticide application were considered exposed to all active ingredients registered on the crop during the reference year according to the CEM (approach 2).

For each active ingredient, agreement between the self-reported use and the two CEM exposure assignments was estimated by the percentage raw agreement and Cohen's κ score.[24]

RESULTS

Prevalence of pesticide exposure

In AHS, 99% of the participants reported ever using any pesticide. In AGRICAN, 68% of the participants reported performing pesticide treatment tasks on any of the selected crops, and in CNAP, 63% of the participants were considered a likely pesticide applicator based on the available farm-level pesticide use indicators. The prevalence of exposure could differ substantially between the cohorts, depending on the chemical group or active ingredient (table 4). For example, organophosphate insecticides were used by 93% of AHS participants, but exposure was assigned to only 64% of AGRICAN participants and 42% of CNAP participants. In contrast, exposure to dithiocarbamate and phthalimide fungicides was highly prevalent in AGRICAN (64% and 60%, respectively), while fewer AHS participants (12%) reported using either of these chemical groups. However, for some chemical groups, the overall prevalence of exposure was relatively similar. Exposure prevalence among women participants was lower than among male participants in all cohorts (see online supplementary table S5). In AHS, for some pesticides data were only collected in phase II (eg, MCPA) and the prevalence therefore referred to the phase II reference year only, and is lower than the (lifetime) prevalence of exposure in AGRICAN and CNAP. The distribution of exposure duration in the cohorts can be found in the online supplementary table S6.

Overall, low to moderate Pearson correlations were found in AHS between the self-reported duration of use of pesticide chemical groups (median r=0.08) or active ingredients (median r=0.07) (see online supplementary tables S7.1 and S8.1). For AGRICAN and CNAP, where a CEM was used to determine potential exposures, correlations between the assigned duration of exposure were high for chemical groups (median AGRICAN r=0.80, CNAP r=0.77) and active ingredients (median AGRICAN r=0.71, CNAP r=0.55) (see online supplementary tables S7.2, S7.3, S8.2 and S8.3). Correlations were especially high between active ingredients within some the chemical groups, for example, within the phenoxy herbicides (median AGRICAN r=0.91, CNAP r=0.99, AHS r=0.24) and pyrethroid insecticides (median AGRICAN r=0.86, CNAP r=0.95, AHS r=0.51).

Comparison of exposure assessment methods

Generally, <10% of AHS participants reported the use of the active ingredients selected for the CEM comparison during the phase II reference year, except for the herbicides glyphosate and metolachlor (table 5). Using either of the two CEM approaches, the majority of the AHS participants were classified as potentially exposed to the active ingredients during the reference year. Agreement between the self-reported use and the assigned exposure was poor for both approach 1, which resembled the exposure assignment in AGRICAN (κ −0.00 to 0.33), and approach 2, which resembled the exposure assignment in CNAP (κ −0.01 to 0.14). The CEM approaches led to a higher exposure prevalence compared to the self-reports, with minimal differences between approaches 1 and 2.

DISCUSSION

We developed cohort-specific methods to assess exposure to a harmonised set of pesticide chemical groups and individual active ingredients through declared or presumed application in three prospective cohort studies with marked differences in design and detail regarding pesticide exposure. Self-reported pesticide use was used to derive exposure estimates for the AHS participants. In AGRICAN and CNAP, time-specific information on crop cultivation was present and cohort-specific CEMs were developed to estimate pesticide exposures at the active ingredient or chemical group level.

The observed differences in prevalence of exposure to the chemical groups and active ingredients between the cohorts could be due to a wide range of factors, including differences in the (number of) crops being cultivated in each country, the pesticides registered for use over time, the age and gender distribution of the participants in each cohort, or the different exposure assessment methods used for each cohort. The estimated pesticide exposure prevalence in AGRICAN and CNAP was generally higher than in AHS, among participants considered to be pesticide applicators (68% in AGRICAN and 63% in CNAP). In AGRICAN, fruit growing and vineyards were far more common than in the other cohorts, which can in part explain the higher exposure prevalences as many of the selected active

Table 4 Prevalence of exposure to chemical groups and active ingredients (ever exposed yes/no)

	All cohorts (n=316 270)		AHS (n=51 167)		AGRICAN (n=127 282)		CNAP (n=137 821)	
Chemical groups and selected active ingredients	**N**	**Per cent**	**N**	**Per cent**	**N**	**Per cent**	**N**	**Per cent**
Any selected chemical group or active ingredient	198, 492	63	50 547	99	85 898	67	62 047	45
Carbamate insecticides	168 447	53	35 186	69	80 853	64	52 408	38
Aldicarb	80 635	25	6709	13	50 207	39	23 719	17
Carbaryl	115 590	37	29 758	58	80 617	63	5215	4
Carbofuran	42 039	13	13 547	26	28 492	22	NA	
Pirimicarb	111 113	35	NA		60 276	47	50 837	37
Organochlorine insecticides	162 964	52	27 539	54	82 299	65	53 126	39
DDT	108 784	34	13 499	26	57 434	45	37 851	27
Lindane	137 161	43	10 068	20	79 826	63	47 267	34
Organophosphate insecticides	185 950	59	47 414	93	80 943	64	57 593	42
Chlorpyrifos	94 038	30	21 609	42	72 429	57	NA	
Dichlorvos	77 834	25	4800	9	49 315	39	23 719	17
Malathion	144 629	46	36 216	71	51 696	41	56 717	41
Parathion	136 643	43	8560	17	73 460	58	54 623	40
Terbufos	46 181	15	19 115	37	27 066	21	NA	
Pyrethroid insecticides	130 611	41	14 291	28	66 652	52	49 668	36
Deltamethrin*	99 584	31	16	<1	65 542	51	34 026	25
Esfenvalerate*	85 692	27	503	1	53 128	42	32 061	23
Permethrin	103 751	33	8334	16	45 749	36	49 668	36
(Phenyl) urea herbicides†	138 932	44	8561	17	77 434	61	52 937	38
Isoproturon	60 881	19	NA		31 547	25	29 334	21
Linuron	134 845	43	6616	13	75 292	59	52 937	38
Chloroacetanilide herbicides	91 053	29	38 470	75	28 830	23	23 753	17
Alachlor	56 849	18	28 019	55	28 830	23	NA	
Metolachlor	55 877	18	28 162	55	27 715	22	NA	
Dinitroaniline herbicides	83 958	27	36 283	71	47 675	37	NA	
Trifluraline	58 667	19	26 089	51	32 578	26	NA	
Phenoxy herbicides‡	145 609	46	39 834	78	48 608	38	57 167	41
2,4-D	141 465	45	38 608	75	48 608	38	54 249	39
MCPA*	96 883	31	43	<1	40 918	32	55 922	41
Mecoprop*	94 585	30	552	1	38 111	30	55 922	41
Thiocarbamate herbicides	138 536	44	24 311	48	65 848	52	48 377	35
Butylate	41 735	13	17 026	33	24 709	19	NA	
EPTC	72 874	23	13 642	27	27 944	22	31 288	23
Triazine herbicides	159 990	51	41 658	81	74 145	58	44 187	32
Atrazine	85 184	27	39 629	77	45 555	36	NA	
Simazine	62 965	20	4352	9	50 930	40	7683	6
Triazinone herbicides	126 458	40	22 271	44	60 729	48	43 458	32
Metribuzin	126 442	40	22 255	43	60 729	48	43 458	32
Dithiocarbamate fungicides	139 281	44	6392	12	81 985	64	50 904	37
Mancozeb§	135 353	43	5205	10	79 244	62	50 904	37
Thiram	59 540	19	79	<1	51 778	41	7683	6
Phthalimide fungicides	131 267	42	6009	12	76 235	60	49 023	36
Captafol	113 810	36	6	<1	70 649	56	43 155	31
Captan	62 384	20	5896	12	29 775	23	26 713	19
Arsenicals	60 165	19	2118	4	58 047	46	NA	
Individual active ingredients								
Dicamba	103 577	33	26 697	52	42 224	33	34 656	25
Glyphosate	140 318	44	42 243	83	46 147	36	51 928	38

*Data collected in AHS phase II only.
†Restricted to the phenylurea herbicides (Weed Science Society of America (WSSA) 7).[19]
‡Excluding the WSSA 1 and WSSA 25 phenoxy herbicides.[19]
§In AHS phase I, data were collected for 'maneb/mancozeb' instead of mancozeb separately.
AHS, US Agricultural Health Study; DDT, dichlorodiphenyltrichloroethane; EPTC, S-ethyl-dipropylcarbamothioate; MCPA, 2-methyl-4-chlorophenoxyacetic acid; 2,4-D, 2,4-Dichlorophenoxyacetic acid; NA, not available for the cohort.

ingredients and chemical groups were registered on these crops. A relatively high prevalence of exposure to organochlorine insecticides was found in AGRICAN, which could be due to the type of crops cultivated and the older age of the participants in relation to the years these pesticides were registered. In AHS, a high prevalence of exposure to chloroacetanilide, dinitroaniline

Table 5 Agreement between self-reported pesticide use in AHS phase II (during the reference year) and exposure assigned using two CEM approaches among AHS participants included in this pooling project, who completed the phase II questionnaire (n=32 703)

Active ingredient	AHS PII self-reported Exposed (%)	CEM—approach 1* Exposed (%)	CEM—approach 1* Exact agreement (%)	CEM—approach 1* κ	CEM—approach 2† Exposed (%)	CEM—approach 2† Exact agreement (%)	CEM—approach 2† κ
Insecticides							
Carbaryl	9.3	73.4	30.9	−0.00	74.4	29.1	−0.01
Carbofuran	1.0	66.1	34.9	0.01	65.9	34.9	0.01
Chlorpyrifos	8.5	73.4	33.9	0.05	74.4	32.2	0.03
Permethrin	2.8	69.1	33.2	0.02	69.0	33.1	0.02
Terbufos	3.9	65.1	38.7	0.04	64.9	38.5	0.03
Herbicides							
Glyphosate	51.9	73.4	65.7	0.33	74.4	57.8	0.14
Metolachlor	13.5	70.8	42.1	0.11	71.5	38.5	0.06
Metribuzin	1.9	70.8	31.0	0.01	71.5	30.2	0.01
Fungicides							
Mancozeb	1.3	71.6	29.1	<0.01	72.3	28.3	<0.01
Thiram	0.1	71.2	28.9	<0.01	74.7	25.4	<0.01
Captan	2.2	68.1	33.1	0.01	67.8	33.4	0.01

κ, kappa score comparing self-reported use in AHS phase II (during the reference year) with either of the CEM approaches.
*Approach 1, resembling exposure assessment as performed for AGRICAN: AHS phase II participants who reported having applied any pesticide to the relevant crop were considered exposed to all active ingredients registered on the crop according to AHS-CEM.
†Approach 2, resembling exposure assessment as performed for CNAP: AHS phase II participants who reported any mixing or applying of pesticides (irrespective of the crop) were considered exposed to all active ingredients registered on the crop according to AHS-CEM.
AHS, US Agricultural Health Study; AI, active ingredient; CEM, Crop-exposure matrix; CNAP, Cancer in the Norwegian Agricultural Population.

and triazine herbicides was found, which may be related to the use of these herbicides on corn and soya beans, which were predominant crops in AHS. The higher prevalence of exposure to organophosphate insecticides in AHS might be the result of differences in pesticide registration and the use of these insecticides on livestock, which was part of the self-reported insecticide use in AHS, but was not considered in the CEMs for AGRICAN and CNAP.

In AGRICAN and CNAP, correlations between the exposure estimates were high. Roughly 20% of the correlation coefficients between the active ingredients exceeded 0.80, which will make it difficult to attribute health effects, if any, to exposure to individual agents. Mixed exposures and co-occurring exposures to pesticide active ingredients are given in many agricultural settings.[25 26] However, in AHS, correlations between exposures to the pesticide chemical groups and active ingredients were low overall. This might be explained by the higher specificity of self-reported information compared to CEMs, applicators using only a limited set of pesticides on the crops cultivated, differences in the timing of data collection (which is restricted to phase II for a number of pesticides) or applications on livestock included in the self-reported insecticide use.

CEMs have been successfully applied in epidemiological studies to estimate (potential) exposure to pesticides among agricultural populations.[27–29] These studies generally incorporated detailed data to estimate personal pesticide use, such as the intensity, probability and frequency of use or specific tasks performed. In AGRICAN, data on performing crop-specific pesticide treatment tasks were available, but in CNAP, farm-level variables were used as an indicator for personal pesticide application by the farm holder. The CEMs developed in this project assume a 100% probability of use when an active ingredient was registered and recommended for use on a crop (AGRICAN) or registered for a crop and sold (CNAP). Several studies have indicated that only a fraction of registered pesticides are regularly used by farmers,[30 31] and their use will depend, among others, on weather conditions, prevalence of pests, regional preferences and costs. Recent Norwegian survey data indicated that pesticides were applied to potatoes on only 66% of farms, depending on the potato acreage, and only a fraction of farmers applied any herbicides to grassland.[32] Therefore, including information on the probability of use would be an important improvement of the CEMs developed in this project, to differentiate between active ingredients registered for similar uses during the same time period.

Not all crops cultivated by the participants were included in the CEMs, only those considered most prevalent and relevant in AGRICAN and CNAP. Therefore, some exposures to the selected pesticides, associated with excluded crops or livestock, will not be considered. Data from AHS phase II indicate that the underestimation of exposure from not accounting for livestock or poultry applications seems to be minor. Less than 2% of these participants have only livestock or poultry, and for those having both crops and livestock (50%), exposure profiles of a number of selected insecticides (table 5) appear to be similar. Also, exposure through re-entry tasks is not accounted for in any of the three cohorts. In AGRICAN, where the percentage of female participants is especially high, as well as the cultivation of crops likely involving re-entry tasks, exposure to some pesticides might be underestimated. In this study, we have focused on pesticide active ingredients only. It should be acknowledged that pesticide products can also contain multiple additives and solvents, which we do not take into account. Therefore, we cannot exclude the possibility that these chemicals might contribute to potential effects observed in subsequent epidemiological analyses.

When two CEM approaches, approximating the exposure assessment as conducted for AGRICAN and CNAP, were used to assign pesticide exposure to AHS phase II participants, agreement between self-reported exposures and CEM exposures estimates was poor. The CEM approaches developed for this project appeared to overestimate exposure during the reference year compared to self-reports. The comparison also suggested that assigning exposure exclusively to participants who reported pesticide applications on a specific crop (approach 1) only resulted in small improvements, compared to assigning exposure on an overall pesticide use indicator (approach 2). Self-reported exposure information is not a true gold standard. A study among male applicators participating in AHS indicated their ability to produce reliable and reproducible reports of their pesticide use, but the validity of these reports could not be assessed.[33] Therefore, it remains unclear to what extent the AHS self-reported data may underestimate or overestimate true pesticide use. All AHS participants in this pooling project were licensed private pesticide applicators and the vast majority reported applying pesticides. Most of them cultivated corn and/or soya beans, on which all of the active ingredients selected for this comparison were registered during the consecutive reference years. Therefore, the AHS phase II data might not be comparable to the situation in the AGRICAN and CNAP cohorts, where not all participants are considered pesticide applicators based on their farming activities (AGRICAN 68%, CNAP 63% vs AHS 99%), lifetime crop cultivation is more diverse (table 3), and pesticide registration of active ingredients appears to be more restricted to individual crops.

We acknowledge that the CEM approach may generate false positive exposure assignments. The lack of specificity of the CEMs is, however, less of an issue for assigning exposure to pesticide chemical groups and active ingredients that are relatively frequently applied. It will lead to more substantial exposure misclassification if the actual prevalence of use is low.[34] We assume the misclassification to be non-differential, given that the assignment of exposure is based on occupation and independent of disease status. Non-differential exposure misclassification usually leads to a bias of the estimate towards the null, especially when the strength of the association is modest, as is the case for most pesticide exposures and health effects. This will most likely limit our ability to detect associations, if any, in the two cohorts where CEMs were applied. Results from the epidemiological analyses should be interpreted cautiously.

A strength of this work is that the exposure assessment efforts accommodate the use of information from three different countries and studies, with distinct designs and detail regarding pesticide exposure, in a large pooling project. The large sample size will enable the analysis of associations between rare agricultural exposures and rare health effects. A wide range of chemical groups and active ingredients, selected a priori, have been included, and will allow us to investigate previously studied associations with greater power and other associations for the first time. This is a significant improvement compared to analysing exposure to pesticides as broad categories, or using job titles such as farmer, applicator or farm worker as a proxy for pesticide exposure. Furthermore, the exposure assessment extended back to 1950, thereby covering a substantial fraction of the occupational lifetime of most of the participants.

For future studies applying CEMs, the quality of the exposure estimates will largely depend on the available internally collected exposure data (eg, personal pesticide application on a specific crop) and external information on pesticide registration, sales figures and crop specific usage patterns, which need to be collected separately for each country for the relevant time period. As shown in this study, pesticide registration and sales figures alone are of limited use when the aim is to create CEMs with sufficient specificity to differentiate between exposures to individual active ingredients or chemical groups. More detailed exposure information such as probability and frequency of use is warranted to reduce overestimation of exposure and (non-differential) misclassification. Owing to time constraints and limitations in available resources, these additional factors could not be taken into account in the CEMs in our pooling project at present. Future undertaking of nested case–control studies in AGRICOH would bring the opportunity to collect retrospective exposure data with the necessary depth and in a similar manner in these cohorts. Agricultural studies should work towards more harmonised exposure assessment, using common questionnaires and collecting detailed information on personal application practices, and, given the suspected associations between pesticide exposures and adverse health outcomes, national agricultural censuses would be encouraged to collect more information on the use of (specific) pesticides.

CONCLUSION

We developed methods to assess occupational exposure to specific pesticide chemical groups and active ingredients for the first pooled study within the AGRICOH consortium. Exposure estimates were generated for 14 chemical groups and 33 active ingredients. Our study illustrates the wide range of chemical agents farmers are exposed to or potentially exposed to in the three agricultural cohorts from the USA, France and Norway. The various exposure assessment methods provided exposure estimates that may overestimate or underestimate actual exposure prevalence. Additional work is needed to better quantify how far these estimates deviate from reality. Limitations of the exposure assessment should be taken into account in planning and interpreting results of the subsequent epidemiological analyses.

Author affiliations
[1]Division of Environmental Epidemiology, Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands
[2]Section of Environment and Radiation, International Agency for Research on Cancer, Lyon, France
[3]Occupational and Environmental Epidemiology Branch, National Cancer Institute (NCI), Bethesda, Maryland, USA
[4]Laboratoire Santé Travail Environnement, ISPED, Université Bordeaux, Bordeaux, France
[5]Centre INSERM U897-Epidemiologie-Biostatistique, ISPED, INSERM, Bordeaux, France
[6]Service de Médecine du Travail, CHU de Bordeaux, Bordeaux, France
[7]UMR1086-Cancers et Préventions, INSERM, Caen, France
[8]Cancers et Préventions, IFR146 ICORE, Université Caen Basse-Normandie, Caen, France
[9]Centre de Lutte Contre le Cancer François Baclesse, Caen, France
[10]Department of Occupational Medicine and Epidemiology, National Institute of Occupational Health, Oslo, Norway

Acknowledgements The authors would like to acknowledge the Norwegian Food Safety Authority and Norwegian expert for providing information on the historical registration and sales of pesticides in Norway.

Funding This study was funded by a grant from the Office National de l'Eau et des Milieux Aquatique (ONEMA), Plan d'action national ECOPHYTO 2018, Axe 3, Volet 4, France. In addition, this work was funded, in part, by the Intramural Research Program of the National Cancer Institute, National Institutes of Health (Z01-CP010119) and the Ammodo van Gogh travel grant VGP.14/20. We used the following AHS data releases for this analysis: P1REL201209.0 and P2REL201209.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Blair A, Freeman LB. Epidemiologic studies in agricultural populations: observations and future directions. *J Agromedicine* 2009;14:125–31.
2 Hoppin JA, Umbach DM, Long S, *et al*. Respiratory disease in United States farmers. *Occup Environ Med* 2014;71:484–91.
3 Koutros S, Alavanja MCR, Lubin JH, *et al*. An update of cancer incidence in the agricultural health study. *J Occup Environ Med* 2010;52:1098–105.
4 Von Mutius E, Vercelli D. Farm living: effects on childhood asthma and allergy. *Nat Rev Immunol* 2010;10:861–8.

5 Alavanja MC, Ross MK, Bonner MR. Increased cancer burden among pesticide applicators and others due to pesticide exposure. *CA Cancer J Clin* 2013;63:120–42.
6 Weichenthal S, Moase C, Chan P. A review of pesticide exposure and cancer incidence in the agricultural health study cohort. *Environ Health Perspect* 2010;118:1117–25.
7 van der Mark M, Vermeulen R, Nijssen PC, *et al*. Occupational exposure to pesticides and endotoxin and Parkinson disease in the Netherlands. *Occup Environ Med* 2014;71:757–64.
8 Alavanja MCR, Hofmann JN, Lynch CF, *et al*. Non-Hodgkin lymphoma risk and insecticide, fungicide and fumigant use in the agricultural health study. *PLoS ONE* 2014;9:e109332.
9 Beane Freeman LE. Evaluation of agricultural exposures: the agricultural health study and the agricultural cohort consortium. *Rev Environ Health* 2009;24:311–18.
10 Leon ME, Beane Freeman LE, Douwes J, *et al*. AGRICOH: a consortium of agricultural cohorts. *Int J Environ Res Public Health* 2011;8:1341–57.
11 The AGRICOH consortium. Participating cohorts. 2014. http://agricoh.iarc.fr/cohorts/index.php (accessed Aug 2015).
12 Alavanja MCR, Sandler DP, McMaster SB, *et al*. The agricultural health study. *Environ Health Perspect* 1996;104:362–9.
13 Levêque-Morlais N, Tual S, Clin B, *et al*. The AGRIculture and CANcer (AGRICAN) cohort study: enrollment and causes of death for the 2005–2009 period. *Int Arch Occup Environ Health* 2015;88:63–73.
14 Kristensen P, Andersen A, Irgens LM, *et al*. Incidence and risk factors of cancer among men and women in Norwegian agriculture. *Scand J Work Environ Health* 1996;22:14–26.
15 Agricultural Health Study. Questionnaires & Study Data. http://aghealth.nih.gov/collaboration/questionnaires.html (accessed Aug 2015).
16 Wood A. Compendium of Pesticide Common Names. http://www.alanwood.net/pesticides/ (accessed 10 Aug 2015).
17 Worthing CR, Hance RJ. *A world compendium: the pesticide manual*. 9th edn. Hampshire, UK: British Crop Production Council, 1991.
18 Tomlin CDS. *A world compendium: the pesticide manual*. 15th edn. Hampshire, UK: British Crop Production Council, 2009.
19 Mallory-Smith CA, James Retzinger E Jr. Revised classification of herbicides by site of action for weed resistance management strategies. *Weed Technol* 2003;17:605–19.
20 Baldi I, Charles C, Blanc-Lapierre A, *et al*. A French crop-exposure matrix for use in epidemiological studies on pesticides: PESTIMAT. *J Expo Sci Environ Epidemiol* 2015. Published Online First: 23 Dec 2015 doi:10.1038/jes.2015.72
21 Heltshe SL, Lubin JH, Koutros S, *et al*. Using multiple imputation to assign pesticide use for non-responders in the follow-up questionnaire in the Agricultural Health Study. *J Expo Sci Environ Epidemiol* 2012;22:409–16.
22 White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med* 2011;30:377–99.
23 Rubin DB. *Multiple imputation for non-response in surveys*. New York: John Wiley & Sons, 1987.
24 Cohen J. A coefficient of agreement for nominal scales. *Educ Psychol Meas* 1960;20:37–46.
25 Tielemans E, Bretveld R, Schinkel J, *et al*. Exposure profiles of pesticides among greenhouse workers: implications for epidemiological studies. *J Expo Sci Environ Epidemiol* 2007;17:501–9.
26 Kromhout H, Heederik D. Effects of errors in the measurement of agricultural exposures. *Scand J Work Environ Health* 2005;31 1):33–8.
27 Miligi L, Settimi L, Masala G, *et al*. Pesticide exposure assessment: a crop exposure matrix. *Int J Epidemiol* 1993;22 2):S42–5.
28 Young HA, Mills PK, Riordan D, *et al*. Use of a crop and job specific exposure matrix for estimating cumulative exposure to triazine herbicides among females in a case-control study in the Central Valley of California. *Occup Environ Med* 2004;61:945–51.
29 Wood D, Astrakianakis G, Lang B, *et al*. Development of an agricultural job-exposure matrix for British Columbia, Canada. *J Occup Environ Med* 2002;44:865–73.
30 Brouwer M, Huss A, Vermeulen R, *et al*. Expert assessment of historical crop specific pesticide use in the Netherlands. *Occup Environ Med* 2014;71:717–22.
31 Blair A, Zahm SH. Patterns of pesticide use among farmers: implications for epidemiologic research. *Epidemiology* 1993;4:55–62.
32 Statistisk sentralbyrå (statistics Norway). Bruk av plantevernmidler i jordbruket i 2011. Rapporter 42/2012. http://www.ssb.no/a/publikasjoner/pdf/rapp_201242/rapp_201242.pdf (accessed Aug 2015).
33 Blair A, Tarone R, Sandler D, *et al*. Reliability of reporting on life-style and agricultural factors by a sample of participants in the agricultural health study from Iowa. *Epidemiology* 2002;13:94–9.
34 Flegal KM, Brownie C, Haas JD. The effects of exposure misclassification on estimates of relative risk. *Am J Epidemiol* 1986;123:736–51.