Occupational Exposures to Plant Protection Products and Associated Health Effects in Agricultural Workers

STATE OF THE EVIDENCE

Submitted to
State Secretariat for Economic Affairs (SECO)
the funding agency

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December 2017

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au Travail

Executive Summary

Recent epidemiological studies have shown increasing evidence of a presumed link between occupational exposure to plant production products (PPPs) and certain pathologies in adult agricultural workers. However, significant challenges currently exist in regards to the interpretation of such studies, and the application of results into regulatory risk assessment. The objective of this investigation was to provide a comprehensive summary of existing epidemiological data on health effects related to occupational PPP use among agricultural workers. The results of this investigation will to assist in the development of evidence-based policy making for occupational PPP exposures among agricultural workers in Switzerland.

Due to the extremely broad scope of this research question, an iterative methodology was employed, which allowed the research to be conducted in five distinct stages. Each stage assessed a different aspect of occupational PPP exposures and resulting health effects, and in some cases analysed different types of sources. This iterative process made it possible to recognize patterns among results from various sources and through different procedures.

In regards to evidence from Switzerland, it is clear that a lacuna of information exists for the amount of active substances used, PPP exposure scenarios and exposure levels for different types of agricultural workers, and resulting health effects due to such exposures. These findings highlight the need to develop targeted research campaigns in order to more clearly understand the nature of this health risk for the agricultural population in Switzerland.

Nevertheless, evidence from international studies provides a foundation of knowledge that can be applied for future investigations. Thousands of peer-reviewed epidemiological studies on occupational PPP exposure and resulting health effects have been published. The results of these studies, when taken together, reveal an important link between occupational PPP exposures and adverse clinical health effects in exposed agricultural populations.

From the exposure side, this investigation found that there are more than 330 active substances authorized as PPPs currently in Switzerland. Several of these active substances, including the herbicides 2,4-D, MCPA, mecoprop, glyphosate, the insecticide chlorpyrifos, and the foliar fungicide mancozeb, have a demonstrated moderate or strong association with chronic health effects. More specifically, these six active substances were found to have a presumed moderate or weak association with hematopoietic cancers. In addition, mancozeb had a presumed weak association with Parkinson's disease (PD), and the insecticide chlorpyrifos and the herbicide glyphosate had a presumed moderate association with non-Hodgkin lymphoma (NHL).

In addition, one of our key research findings allowed for a precision of a commonly cited notion regarding the overall health of agricultural workers: that these workers are often healthier than other non-farming populations. Our findings indicate that although the *general* health status of agricultural workers appears to be better than comparison populations, their *occupational* health appears to be one

of the worst among all occupations. Agriculture in every industrialized country is one of the most hazardous occupations.

This report highlights the crucial point that even if agricultural workers exhibit generally lower mortality rates than the general population, they also demonstrate a distinct pattern of specific disease prevalence. This pattern has been widely associated with exposures to PPPs. Evidence from the literature demonstrates disease pattern trends for two types of clinical health endpoints types: selected carcinogenicity and neurotoxicity.

While agricultural populations may have a lower *overall* cancer mortality rate than the general population, significantly lower lung cancer rates explain about 60% of this difference. Given the much lower smoking rates and generally healthier lifestyle of agricultural populations, this precision remains imperative to the understanding of epidemiological trends among this population. Aggregated findings from prospective cohort studies revealed that agricultural workers have an increased risk for hematopoietic cancers (leukemia, NHL, multiple myeloma), as well as skin, soft tissue sarcoma, prostate, testicular, stomach, and brain cancers.

In regards to neurotoxicity endpoints, and specifically PD, there is strong evidence in favour of a generic link between occupational exposure to PPPs and PD. The most recent, and the most scientifically reliable meta-analysis found that exposure to *any* PPP involves a ≥50% increased risk for developing Parkinson's disease in occupationally exposed populations. In addition, there is strong evidence in favour of a link between occupational exposure to herbicides and insecticides and PD. More evidence is needed for occupational exposure to specific classes of PPPs and for active ingredients. However, there is strong evidence in favour of occupational exposure to organochlorines and PD; and moderate evidence in favour for occupational exposure to paraquat and rotenone and PD.

One of the main successes of this investigation was the ability to reduce the scope of the research question to more precise exposures (i.e., active substances), and to specific clinical health outpoints. These findings provide a focused and evidence-based starting point for future epidemiological investigations. Due to increasing evidence of a presumed link between PPP exposure and chronic health effects, and a general lack of data for the situation in Switzerland, it is imperative that increased research efforts are undertaken to address this occupational health concern. The recommendations provided in this report would assist in evidence-based policymaking and would promote a safer and healthier agriculture workforce in Switzerland, as well as the population at large.

Résumé

De récentes études épidémiologiques ont mis en évidence un lien de présomption entre l'exposition professionnelle aux produits phytosanitaires et certaines pathologies chez les adultes actifs dans le domaine de l'agriculture. Il est toutefois difficile d'interpréter de telles études et d'en utiliser les résultats dans le cadre d'analyses de risque réglementaires. Le but de cette étude est de présenter un aperçu des données épidémiologiques disponibles relatives aux effets sur la santé des produits phytosanitaires utilisés par les professionnels agricoles. Les résultats de cette étude contribueront au développement d'une politique orientée sur des données factuelles en matière d'exposition professionnelle aux produits phytosanitaires des travailleurs du domaine agricole en Suisse.

En raison de l'étendue du thème étudié, nous avons eu recours à une méthode itérative, c'est-à-dire à une méthodologie de recherche effectuée en cinq étapes. Chaque étape a évalué un aspect différent de l'exposition professionnelle aux produits phytosanitaires et de leurs effets sur la santé. Plusieurs sources de littérature scientifique ont parfois été analysés selon les cas. Ce processus itératif a permis d'identifier des tendances dans les résultats en fonction des différentes sources de littérature et des procédures sélectionnées.

Les données recueillies en Suisse révèlent un manque évident d'information en ce qui concerne la quantité de substances actives utilisées, les scénarios et les niveaux d'expositions aux produits phytosanitaires des travailleurs agricoles et les effets potentiels sur la santé. Ces observations soulignent la nécessité de développer des campagnes de recherche ciblées visant à clarifier la nature de ce risque pour la population agricole suisse.

Les données rapportées par les études internationales apportent une base de connaissances importante et sur laquelle de futures études pourront s'appuyer. La littérature répertorie des milliers d'études épidémiologiques examinées par les pairs et publiées sur le thème de l'exposition professionnelle aux produits phytosanitaires et de leurs effets sur la santé. Les résultats de ces études révèlent dans leur globalité une association importante entre l'exposition professionnelle aux produits phytosanitaires et certains effets sur la santé des populations agricoles exposées.

En ce qui a trait spécifiquement à l'exposition, cette étude a identifié plus de 330 substances actives actuellement autorisées en tant que produits phytosanitaires en Suisse. Plusieurs de ces substances actives, dont les herbicides 2,4-D (acide 2,4-dichlorophénoxyacétique), MCPA (acide 2-méthyl-4-chlorophénoxyacétique), mecoprop et glyphosate ainsi que l'insecticide chlorpyrifos et le fongicide mancozeb, se sont révélés avoir un lien de présomption modéré à élevé avec certains effets chroniques néfastes pour la santé. Plus précisément, il a été constaté que ces six substances actives présentaient un lien de présomption faible à modéré avec les cancers hématopoïétiques. De plus, le mancozeb présente un faible lien de présomption avec la maladie de Parkinson (MDP), et le chlorpyrifos et le glyphosate auraient un lien de présomption modéré avec le lymphome non-Hodgkinien (LNH).

Les résultats de cette étude apportent une précision à la notion communément admise selon laquelle les travailleurs agricoles seraient globalement en meilleure santé que le reste de la population. Même si la santé des travailleurs agricoles paraît *globalement* meilleure que celle des autres populations, nos résultats indiquent leur santé *professionnelle* est en revanche considérée comme l'une des plus précaires de toutes les professions confondues. En effet, l'agriculture dans l'ensemble des pays industrialisés est l'une des professions les plus à risque.

La présente étude montre que même si les professionnels de l'agriculture affichent un taux de mortalité plus bas que le reste de la population, ils sont néanmoins plus à risque de développer certaines maladies spécifiques associées à l'exposition de produits phytosanitaires. La littérature démontre que cette population a un risque plus élevé de développer deux types d'effets sur la santé: une cancérogénicité spécifique à certains organes et une neurotoxicité.

Les populations agricoles ont un taux *global* de mortalité dû au cancer plus faible que le reste de la population. Toutefois, les taux significativement plus faibles de cancer du poumon dans cette population expliquent à 60 % la différence avec la population générale. De fait, le taux de fumeurs est nettement plus faible parmi les populations agricoles et ces populations ont également un style de vie généralement plus sain. Ces précisions sont essentielles à considérer pour comprendre l'évolution épidémiologique dans cette population. Les résultats groupés d'études prospectives de cohorte révèlent que les travailleurs agricoles encourent un risque plus élevé de développer des cancers spécifiques comme les cancers hématopoïétiques (leucémie, LNH, myélome multiple), le sarcome des tissus mous, le cancer de la peau, de la prostate, des testicules, de l'estomac et du cerveau.

Quant aux effets neurotoxiques, plusieurs études épidémiologiques démontrent la présence d'un lien de présomption générique entre la MDP et l'exposition professionnelle aux produits phytosanitaires. La méta-analyse la plus récente et la plus concluante d'un point de vue scientifique montre qu'un travailleur agricole exposé à un produit phytosanitaire donné a ≥50% de risque de développer la MDP. De plus, un lien de présomption manifeste est également constaté entre la MDP et l'exposition professionnelle aux herbicides et aux insecticides. Davantage de données sont par ailleurs nécessaires pour ce qui est de l'exposition professionnelle à certaines catégories de produits phytosanitaires ou à certains ingrédients actifs. Toutefois, il existe un lien de présomption évident entre la MDP et l'exposition professionnelle aux organochlorés, ainsi qu'un lien de présomption modéré entre la MDP et l'exposition professionnelle au paraquat et à la roténone.
Cette étude a donc permis de réduire l'étendue du champ de la question de recherche à des expositions (p. ex. à des substances actives) et à des effets cliniques plus spécifiques. Les résultats apportent un aperçu précis de la thématique et constituent un point de départ ciblé pour de futures enquêtes épidémiologiques. En considérant le nombre croissant de données attestant un lien de présomption entre l'exposition aux produits phytosanitaires et certains effets chroniques et le manque général de données relatives à la situation en Suisse, il devient primordial d'intensifier les études de recherche sur ce problème de santé au travail. Les recommandations de ce rapport peuvent favoriser l'élaboration de politiques

fondées sur des données factuelles et contribuer à mieux promouvoir la santé et la sécurité des travailleurs agricoles en Suisse et de la population dans son ensemble.

Zusammenfassung

Neueste epidemiologische Studien haben gezeigt, dass immer mehr Hinweise auf einen mutmasslichen Zusammenhang zwischen der beruflichen Exposition gegenüber Pflanzenschutzmitteln (PSM) und bestimmten Erkrankungen bei erwachsenen landwirtschaftlichen Arbeitskräften bestehen. Allerdings bestehen derzeit erhebliche Herausforderungen in Bezug auf die Interpretation solcher Studien und die Anwendbarkeit der Studienergebnisse in der regulatorischen Risikobewertung. Ziel der vorliegenden Arbeit war, alle aktuell vorhandenen epidemiologischen Daten über die gesundheitlichen Auswirkungen der beruflichen Anwendung von PSM in der Landwirtschaft zusammenzufassen. Die Ergebnisse dieser Studie werden die Entwicklung eines evidenzbasierten Regulierungsprozesses für die Beurteilung der beruflichen Exposition von landwirtschaftlichen Arbeitskräfte in der Schweiz gegenüber PSM unterstützen.

Aufgrund des extrem breiten Spektrums dieser Forschungsfrage kam eine iterative Methodik zum Einsatz. In fünf verschiedenen Phasen wurde jeweils ein anderer Aspekt der berufsbedingten Exposition gegenüber PSM und der daraus resultierenden gesundheitlichen Auswirkungen bewertet. Dabei wurden zum Teil unterschiedliche Quellen analysiert. Dieser iterative Prozess ermöglichte es, gemeinsame Muster innerhalb der Resultate aus den verschiedenen Quellen und den verschiedenen Verfahren zu erkennen.

In der Schweiz weiss man wenig über die Menge der verwendeten Wirkstoffe, die PSM-Expositionsszenarien und die Expositionshöhen für die verschiedenen in der Landwirtschaft tätigen Personengruppen und die daraus resultierenden gesundheitlichen Auswirkungen. Es braucht zielgerichtete Forschungsprojekte, um Klarheit über die Art des Gesundheitsrisikos für die landwirtschaftliche Bevölkerung in der Schweiz zu erlangen.

Dennoch liefern Erkenntnisse aus internationalen Studien eine Wissensgrundlage, die für zukünftige Untersuchungen genutzt werden kann. Weltweit gibt es Tausende von epidemiologischen Studien über die berufliche PSM-Exposition und die daraus resultierenden gesundheitlichen Auswirkungen. Die Ergebnisse dieser Studien zeigen insgesamt, dass es einen klaren Zusammenhang zwischen der berufsbedingten Exposition gegenüber PSM und Gesundheitsschäden bei Personen gibt, die in der Landwirtschaft tätig sind.

Die vorliegende Arbeit hat aufgezeigt, dass derzeit in der Schweiz mehr als 330 PSM Wirkstoffe zugelassen sind. Mehrere dieser Wirkstoffe, darunter die Herbizide 2,4-D (2,4-Dichlorphenoxyessigsäure), MCPA (2-Methyl-4-chlorphenoxyessigsäure), Mecoprop, Glyphosat, das Insektizid Chlorpyrifos und das Blattfungizid Mancozeb, haben eine moderate oder starke Assoziation mit chronischen Erkrankungen gezeigt. Konkret weisen diese sechs Wirkstoffe eine vermutlich moderate oder schwache Assoziation mit hämatopoetischen Krebserkrankungen auf. Darüber hinaus zeigt Mancozeb eine vermutete schwache Assoziation mit der Parkinson-Krankheit (PD), das Insektizid Chlorpyrifos und das Herbizid Glyphosat hatten eine vermutete moderate Assoziation mit dem Non-Hodgkin-Lymphom (NHL).

Ausserdem erlaubte unsere Forschung, die häufig zitierte Aussage zu präzisieren, dass der Gesundheitszustand der in der Landwirtschaft tätigen Personen oft besser sei als derjenige, der nicht in der Landwirtschaft tätigen Bevölkerung. Unsere Ergebnisse deuten darauf hin, dass der allgemeine Gesundheitszustand der landwirtschaftlichen Arbeitskräfte zwar besser zu sein scheint als der von Personen, die nicht in der Landwirtschaft beschäftigt sind. Jedoch kommen gewisse aus der landwirtschaftlichen Tätigkeit resultierende Gesundheitseffekte im Vergleich zu den anderen Berufsgruppen häufiger vor. Die Landwirtschaft ist in allen Industrieländern einer der gefährlichsten Berufe.

Eine der Kernaussagen dieses Berichts ist, dass selbst wenn die Sterblichkeitsrate von landwirtschaftlichen Arbeitnehmern im Allgemeinen niedriger ist als die der Allgemeinbevölkerung, bei diesen jedoch ein ausgeprägtes Muster an spezifischen Krankheiten vorkommt, die deutlich mit der Exposition gegenüber PSM zusammenhängen. Aus der Literatur geht hervor, dass sich Trends für zwei Arten von klinischen Krankheiten zeigen: selektive Karzinogenität und Neurotoxizität.

Die landwirtschaftliche Bevölkerung weist generell eine geringere Krebssterberate als die Allgemeinbevölkerung auf; eine deutlich geringere Lungenkrebsrate macht rund 60 % dieses Unterschieds aus. Die Tatsache, dass die landwirtschaftliche Bevölkerung viel weniger raucht und generell gesünder lebt, ist von grosser Bedeutung, um die epidemiologische Tendenzen dieser Bevölkerungsgruppe zu verstehen. Die aus prospektiven Kohortenstudien zusammengetragenen Erkenntnisse zeigen, dass die in der Landwirtschaft tätigen Personen ein erhöhtes Risiko für hämatopoetische Krebserkrankungen (Leukämie, NHL, Multiples Myelom) sowie Haut-, Weichteilsarkome, Prostata-, Hoden-, Magen- und Gehirntumoren haben.

Was die Neurotoxizität, insbesondere Parkinson betrifft, gibt es eindeutige Belege für einen generischen Zusammenhang zwischen der berufsbedingten Exposition gegenüber PSM und Parkinson. Die jüngste und wissenschaftlich zuverlässigste Meta-Analyse ergab, dass Menschen mit berufsbedingter Exposition gegenüber *irgendeinem* PSM, ein mehr als 50 % höheres Risiko haben, an Parkinson zu erkranken. Darüber hinaus gibt es eindeutige Belege für einen Zusammenhang zwischen der beruflichen Exposition gegenüber Herbiziden und Insektiziden und Parkinson. Es bedarf weiterer Indizien bezüglich der berufsbedingten Exposition gegenüber spezifischen Klassen von PSM und Wirkstoffen. Es gibt jedoch klare Indizien, dass die berufsbedingte Exposition gegenüber chlororganischen Verbindungen mit Parkinson in Zusammenhang steht; mittlere Indizien liegen vor, die einen Zusammenhang zwischen der berufsbedingten Exposition gegenüber Paraquat und Rotenon sowie Parkinson zeigen.

Einer der Haupterfolge der vorliegenden Arbeit war, den Umfang der Forschungsfrage auf Expositionen gegenüber bestimmten Wirkstoffe und auf bestimmte klinische Krankheiten zu reduzieren. Diese Ergebnisse bieten einen fokussierten und evidenzbasierten Ausgangspunkt für zukünftige epidemiologische Untersuchungen. Aufgrund der zunehmenden Hinweise auf einen vermutlichen Zusammenhang zwischen der Exposition gegenüber PSM und chronischen Erkrankungen und einem allgemeinen Mangel an Daten zur Situation in der Schweiz, ist es unerlässlich, verstärkte Forschungsanstrengungen zu unternehmen, um diesem Anliegen des Gesundheitsschutzes zu begegnen. Die in diesem Bericht enthaltenen Empfehlungen könnten einen evidenzbasierten Regulierungsprozess unterstützen und dazu beitragen, dass die landwirtschaftliche Bevölkerung - und schliesslich auch die Allgemeinbevölkerung - der Schweiz sicherer und gesünder ist.

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1. Introduction

Plant production products (PPPs) are extensively used in agriculture worldwide to control harmful pests and prevent crop losses or plant damage. PPP is a generic term that includes thousands of different products used to prevent, destroy, or control harmful organisms or diseases, and to protect plants or plant products during production, storage and transport (EU, 2017). The term PPP is often used interchangeably with "pesticide", however, PPP is the preferred term among most regulatory bodies. Pesticide is a broader term that also covers non plant/crop uses as biocides and veterinary drugs (EU, 2017). Despite the beneficial actions of PPPs for agricultural production, their widespread use and inherent toxicity has posed long-recognized threats to human health. Improper handling of certain PPPs may result in severe acute poisonings and adverse health effects may also result from long-term, low-level exposures (INSERM, 2013).

Of potential human PPP exposures, those that occur in the workplace are of particular epidemiological importance due to the likelihood of chronic or long-term exposures (Damalas and Koutroubas, 2016). Agriculture in every industrialized country is one of the most hazardous occupations, based on occupational fatality and injury rates, as well as occupational illness rates (Donahan and Thelin, 2016). From an occupational health perspective, chronic health effects potentially induced by PPPs, such as cancers and neurodegenerative diseases, are more important than acute effects due to their severity, impact on the quality of life of workers and their families, as well as their incurred costs to the public health system. The scientific literature includes a significant number of studies on occupational PPP exposures and associations with chronic health outcomes. One of the most comprehensive meta-analysis was conducted by the Institut national de la santé et de la recherche médicale (or French National Institute of Health and Medical Research in English; INSERM) in 2012 to 2013. Based on a scientific literature analysis, the experts found a presumed link between occupational exposure to PPPs and certain pathologies in adult agricultural workers, including Parkinson's disease, prostate cancer, and hematopoietic cancers (non-Hodgkin's lymphoma, and multiple myeloma) (INSERM, 2013).

1.1 Occupational exposure to PPPs

In general, exposures arising from occupational PPP exposures are considered to be greater than those from residential or wider environmental exposure (Arcury et al., 2014). Workplace exposures are also of particular epidemiological importance due to the likelihood of chronic or long-term exposure scenarios. Moreover, some PPPs that are banned for residential uses may be still in use in workplace, suggesting a considerable difference between occupational exposure and residential PPP residues over a period of time.

In professional environments, the dermal route is the main route of exposure, accounting for roughly 80% of exposures (INSERM, 2013). Skin absorption of organophosphate PPPs is especially efficient in areas of thin skin with high blood supply, such as the head, axilla, and groin (Figure 1). While protective clothing may reduce contact with skin, if they become contaminated with PPPs it will provide a continued source of exposure until it is removed. Exposure through the respiratory tract occurs to a lesser degree, and for specific work tasks, such as during fumigation, during mixing-loading tasks (especially for powder formulations) or when PPPs are used in closed spaces. Exposure can occur at different times and is largely dependent on the types of work tasks conducted. It is generally accepted that the types of work tasks conducted and therefore potential exposure scenarios depend on whether an individual is an operator (i.e., sprayer) or a re-entry worker. Operators often handle the PPPs, and are usually responsible for mixing/loading the product into application machinery; operation of application machinery; repair of application machinery whilst it contains PPPs; and emptying/cleaning machinery/containers after use. On the other hand, re-entry workers may be exposed when re-entering to a field/agricultural area to conduct various tasks after PPP application, such as pruning, cutting, harvesting, etc.

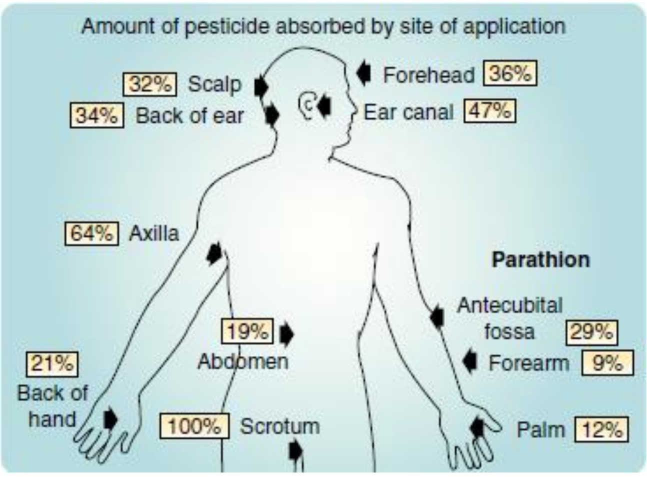

Figure 1. The most common systemic exposure to PPPs is through skin contact. Different parts of the body have different absorption rates based on dermal characteristics (from: Dohanan et a., 2016).

Operators are often at risk for PPP exposure in a variety of tasks. Firstly, mixing and loading are tasks associated with the greatest intensity of PPP exposure, as farmers are exposed to the concentrated product, and at risk for face splashes and spills. The risk of inhaling aerosols during mixing and loading is minimal in relation to overall exposure (Wolf et al., 1999). Ideally the PPP is transferred to the sprayer by a closed transfer system to reduce exposures. In applications where tractors are used, the operator's level of exposure is dependent on various scenarios. Operators will be generally less exposed when operating the tractor with a cabin that is tightly sealed and the charcoal filters are properly maintained. The exposure situation is quite different when a hand sprayer is used, and varies widely based on the specific type of hand sprayer. Cleaning the spraying equipment may also be an important source of exposure. The time given to equipment cleaning may occupy a considerable part of an operator's activities. Despite variation among operators, equipment cleaning has been found to contribute greatly to workers' daily dermal exposure (Lebailly et al., 2009).

In regards to re-entry, it is known that physical contact with branches, leaves, or fruit in previously treated crops is responsible for the transfer of PPPs to the worker's skin in agricultural tasks such as harvesting, pruning, thinning, cutting or sorting (INSERM, 2013). In the PESTEXPO study of vineyards, Baldi et al., (2014) found that the type of task conducted by workers was the parameter most strongly associated with the level of dermal PPP contamination. The highest dermal contamination was observed during moving of wires and cutting of branches; while during the harvest, dermal contamination was highest for grape-picking. The authors further found that the delay since the last PPP treatment and the rate of active ingredient per hectare, together with other factors such as meteorological factors, crop and farm characteristics, gloves and clothes, were important in determining the dermal contamination level of the workers.

1.2 Understanding the epidemiological evidence

In its classic definition, epidemiology describes the study of the distribution and determinants of health-related states or events (including disease), and the application of this study to the control of diseases and other health problems (Bonita et al., 2006). However, it is important to note that epidemiology is a dynamic science that is not limited to only "the study of" health in a population; it also involves the application of evidence-based judgement to research results. Epidemiology uses the scientific methods of descriptive and analytic research as well as experience, epidemiologic judgment, and understanding of local conditions in diagnosing the health of a sub-population and developing appropriate public health interventions to control and prevent disease. Moreover, epidemiology has the power to ascertain patterns *suggestive* of cause and effect, before the mechanisms underlying the associations are understood.

1.2.1 Types of epidemiological studies

Epidemiological studies can be divided into two main types: experimental studies, which place in a controlled setting (e.g., randomised control trials); and observational studies, which are carried out in a non-controlled natural setting. In regards to human PPP exposures and resulting health effects, we are concerned only with observational epidemiological studies, as experimental studies of PPP exposures to humans face inherent ethical barriers (Olesky et al. 2004). Nevertheless, a major strength of observational epidemiological studies is their ability to study health effects in the same population about which conclusions are to be drawn, rather than a proxy species. Designs of observational epidemiological studies are classified as either ecological, cross- sectional, case-control or cohort studies. Information on cases of disease occurring in a natural setting can also be collected through clinical case reports. Although clinical case reports do not compare study groups according to differing exposure, they provide important information on specific details related to exposure and health outcome. Such case reports prove highly important to risk assessment by highlighting adverse effects that may occur after marketing.

Type of study	Description
Ecological studies	• Examines the relationship between exposure and outcome by examining population-level data rather than individual-level data. Can be subject to ecological fallacy, which infers association at the population level whereas one may not exist at the individual level.
Cross-sectional studies	Examines relationship between exposure and outcome prevalence in a defined population at a single point in time. Difficult to determine temporal relationship between exposure and outcome (lacks time element).
Case-control studies	• Examines multiple exposures in relation to an outcome; subjects are defined as cases and controls, and exposure histories are compared. Difficult to establish clear chronology of exposure and outcome.
Cohort studies	• Examines multiple health effects of an exposure; subjects are defined according to their exposure levels and followed over time for outcome occurrence. Most reliable as such studies can directly measure incidence, and provide a clear chronological relationship between exposure and outcome.

Table 1. Description of observational epidemiological studies

When epidemiological studies are assessed individually, there may be some uncertainties related to interpretation of risk estimates, mostly due to a limited number of subjects exposed, or the measures of exposures and resulting health effects. For these reasons, individual epidemiological studies may sometimes prove problematic in assessing an association between PPP exposure and health effects.

Of the different types of observational epidemiological studies, prospective cohort studies have several advantages when compared to the other types of studies. Prospective cohort studies can evaluate multiple effects of a single exposure, and can be more efficient for rare exposures and outcomes with long induction and latency periods. In addition such studies can directly measure incidence, and can provide a clear chronological relationship between exposure and outcome. In addition, as prospective cohort studies usually involve the collection of large amounts of exposure and health data over time, multiple investigations can be conducted to increase the power of the risk estimates for certain health endpoints, thereby providing more reliable results than the assessment of one individual study.

Systematic reviews are a type of investigation performed to collect and review individual epidemiological studies and involve a reproducible and thorough search of the literature and critical appraisal of eligible studies. When combined with a meta-analysis (quantitatively pooling of results of individual studies), a rigorously conducted systematic review provides the best available knowledge for informing evidence based policies (Sriganesh et al. 2016). Systematic reviews and meta-analysis of observational epidemiological studies can provide information that strengthens the understanding of the potential hazards of PPPs, exposure-response characterization, exposure scenarios and methods for assessing exposure, and ultimately risk characterization.

In cohort studies, association between a disease or a health outcome and a risk factor or exposure are determined by calculating the risk ratio (or “relative risk”, RR) and the odds ratio (OR). The risk ratio (RR) determine the risk to develop the health outcome (e.g., NHL) in the exposed group (also called incidence, or newly diagnosed cases) compared to the non-exposed group (Viera 2008). The formula to calculate RR is presented in Table 2. If the RR = 1, the risk to develop the health outcome is the same in the exposed (e.g., agricultural workers) and non-exposed (e.g., general population) group; if RR > 1, the risk is higher in the exposed group, and if RR < 1, the risk is lower in the exposed group compared to the non-exposed group (Viera 2008). For instance, a RR of 3 for the association between NHL and occupational pesticide exposure means that workers exposed to pesticide have a risk to develop NHL three times greater than the general population or an excess risk of 200% (3.0 – 1.0 = 2.0 =200%). The OR determines the strength of the association, it is the ratio of the odds and may be equivalent to the probability of an exposed person develops the health outcome compared to the probability of an unexposed person develops the health outcome (Viera 2008). The formula is presented in Table 2. If the OR > 1, there is an association between exposure and health outcome; however, it does not mean this is the cause and it is not a risk measurement. For instance, an OR of 3 for the association between NHL and occupational pesticide exposure means that the NHL odds in agricultural workers is three times higher than the NHL odds in the general population. It could be concluded that there is an association between occupational pesticide exposure and NHL.

		Disease		
		Yes	**No**	
Exposed	**Yes**	a *(number of persons exposed and sick)*	b *(number of persons exposed and non-sick)*	a + b *(total of persons exposed)*
	No	c *(number of persons unexposed and sick)*	d *(number of persons unexposed and non-sick)*	c + d *(total of persons unexposed)*
		a + c *(total of persons sick)*	b + d *(total of persons non-sick)*	

$$RR = \frac{a/(a+b)}{c/(c+d)} = \frac{Incidenceinexposedgroup}{Incidenceinunexposedgroup}$$

$$OR = \frac{ad}{bc} = \frac{Oddsthatanexposedpersondevelopsthedisease}{Oddsthatanunexposedpersondevelopsthedisease}$$

Table 2. Risk ratio (RR) and odds ratio (OR) calculation in a cohort study. Table and formulas based on the manuscript of Viera (2008).

1.3 The state of epidemiology in regulatory risk assessment

In the EU, as well as in Switzerland, each PPP goes through authorization procedures including a risk assessment based on internationally agreed toxicological data. In the EU, the risk assessment includes review of toxicity data related to human health, and may include information from medical reports following accidental, occupational exposure or incidents of intentional self-poisoning; surveillance data if available; and epidemiological studies published in the open literature. In fact, Regulation (EU) No 1107/2009 equally states that, "where available, and supported with data on levels and duration of exposure, and conducted in accordance with recognized standards, epidemiological studies are of particular value and must be submitted" (EU, 2009). According to EFSA (2011), epidemiological studies should be retrieved from the literature according to specific EFSA Guidance of scientific-peer reviewed open literature for the approval of active substances, which follows the principles of the Guidance "Application of systematic review methodology to food and feed safety assessments to support decision making" (EFSA 2010).

Nevertheless, the integration of epidemiological data with toxicological findings in the peer review process of PPPs in the EU is unfortunately still lacking. The application of findings from epidemiological studies into regulatory risk assessment poses a challenge for regulatory authorities. On one hand, evidence from epidemiological studies can be used to assess associations between PPP exposures and health effects, thus providing important knowledge of the potential toxicity of PPPs for humans, and aiding the risk assessment process. However, regulatory agencies, such as EFSA have noted that the term "epidemiological studies" spans an incredibly vast body of research, which includes different methodologies in regards to the type of study, as well as how the studies are conducted, and how they define PPP exposures and resulting health effects. These differences result in various levels of overall scientific quality of studies, and lend to how well the results can be interpreted for human risk assessment. In addition, epidemiologic research is not often conducted with the aim to guide regulatory risk assessment and therefore does not always focus on PPPs that are either coming to market (clearly, studies epidemiological studies cannot be conducted on products that are not yet used), or have only been on the market for some years. Epidemiological studies sometimes retrospectively assess health effects associated with PPPs that have already been removed or banned from the market.

Despite these barriers, it is important to remain cautious about overarching claims dismissing epidemiologic studies because of perceived intrinsic weaknesses. Such suppositions show a very poor understanding of the importance of casual inference. After all, epidemiology allows for the identification of patterns suggestive of causal associations, before mechanisms underlying the precise associations are clearly understood.

1.4 Objective

Recent epidemiological studies have shown increasing evidence of a positive association between occupational exposure to PPPs and certain pathologies in adult agricultural workers (INSERM 2013; EFSA 2013). However, a significant challenge currently exists in regards to the interpretation of such studies, and the application of results into regulatory risk assessment. As such, the objective of this investigation was to provide a comprehensive summary of existing epidemiological data on health effects related to occupational PPP use among agricultural workers. The results of this investigation are foreseen to assist the development of evidence-based policy making for occupational PPP exposures among agricultural workers in Switzerland.

2. Methodology and Rationale

The question of occupational PPP exposure and resulting health effects represents an incredibly vast, and complex, research domain. Due to the broad scope of this research question, an iterative methodology (Guest et al. 2013) was employed, which allowed the research to be conducted in several different stages (figure 2).

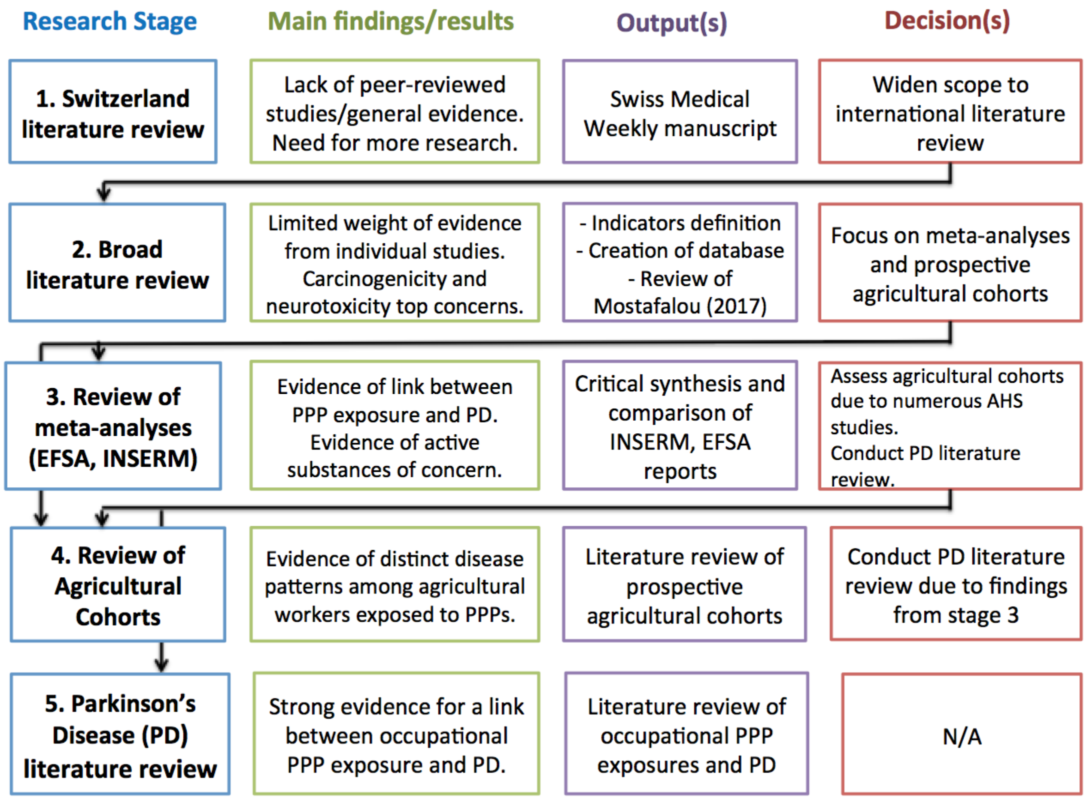

Figure 2. Schematic of methodology. For each research stage, the findings and outputs are listed, as well as the decision taken to move to other research stages.

2.1 Stage 1: The Situation in Switzerland

The original aim of this investigation was to obtain scientific data regarding health effects associated with PPP use in Switzerland. A literature study was planned to summarize existing data on health effects related to PPP use including case reports, focusing on PPPs used in high quantities in Switzerland. It was foreseen that these results could help the State Secretariat for Economic Affairs (SECO) in assessing risks to health effects from PPP exposures among Swiss workers and recommending appropriate safety measures.

As such, stage 1 started with a literature search of occupational exposures to PPPs in Switzerland and resulting health effects. A literature search was conducted in

PubMed, Medline, EMBASE, and Science Direct.[1] A total of nine studies were found, none of which were observational studies on occupational PPP exposure and resulting health effects among Swiss workers. An expanded (i.e., less sensitive) search was then conducted.[2] This time a total of 19 studies were identified; however, again none of the studies were observational studies on occupational PPP exposure and resulting health effects among Swiss workers. The lack of results from a literature search lead to the development of a broader search approach for data in Switzerland, through the use of: 1) mapping study; 2) expert interviews, and 3) clinical records investigation.

The results of stage 1 revealed a general lack of peer-reviewed studies and general evidence for PPP exposures and health effects among agricultural workers in Switzerland. Results from this stage provided a foundation of knowledge from which to work from, and allowed for the development of recommendations on how to more effectively access and collect PPP exposure and resulting health effect data. Nevertheless, based on the limited epidemiological findings for Switzerland, it was decided to conduct a broader literature review of epidemiological studies conducted internationally.

2.2 Stage 2: Broad literature review

The aim of the broad literature search was to systematically collect, review and appraise epidemiological studies carried out to investigate possible links of PPP exposure to health-related outcomes in order to improve understanding of already established or suggested associations with adverse effects in humans. The objectives included:

Objective 1: To collect and compile scientific publications in which a presumed link between PPP exposure and adverse human health effects have been investigated.
Objective 2: To review and evaluate each collected study concerning its qualitative aspects (e.g. the corner points of the investigations).
Objective 3: Provision of a database and a report of epidemiological studies.

To accomplish these objectives, a comprehensive literature search was conducted using the following data sources: Medline, EMBASE, Science direct, PubMed and psycINFO. The following inclusion criteria were established:

1. Studies published from 1990 to the present
2. Crops that are relevant to Switzerland
3. PPPs, or active substances, that are relevant to Switzerland (i.e., currently approved).
4. Clear health endpoint investigated

[1] ("pesticides"[Pharmacological Action] OR "pesticides"[MeSH Terms] OR "pesticides"[All Fields] OR "pesticide"[All Fields]) AND ("occupational exposure"[MeSH Terms] OR ("occupational"[All Fields] AND "exposure"[All Fields]) OR "occupational exposure"[All Fields]) AND ("agriculture"[MeSH Terms] OR "agriculture"[All Fields]) AND ("switzerland"[MeSH Terms] OR "switzerland"[All Fields])

[2] ("pesticides"[Pharmacological Action] OR "pesticides"[MeSH Terms] OR "pesticides"[All Fields]) AND ("switzerland"[MeSH Terms] OR "switzerland"[All Fields]) AND ("occupational health"[MeSH Terms] OR ("occupational"[All Fields] AND "health"[All Fields]) OR "occupational health"[All Fields])

5. Proof of exposure (quantitative), as well as the specific PPP formulation (not just active substance), and form of PPP exposure (powder, liquid, etc.)
6. Scientifically sound approach (i.e., the methodology should be considered, whether case-control, prospective, etc.)

A string sampling methodology was developed through review of the relevant literature and with consultations with the IST librarian (Annex 1). A table was developed with indicators for data extraction and for grading of studies (Annex 2, part a). An excel-based database was created and used to review and extract data from X studies during a pilot test (Annex 2, part b). However, three important conclusions were made mid-process. First of all, it was determined with the research team that the amount of time for the project was too limited to accomplish study grading, extraction and summarization of all studies identified. Secondly, because two comprehensive systematic reviews had previously been conducted using most of the studies identified in this broad literature search (i.e., INSERM and EFSA reports), that it would be more efficient to review in detail the findings of those reports (Stage 3). Finally, it was established that most of the studies identified came from agricultural cohorts, namely the Agricultural Health Study (AHS). As such, it was deemed pertinent to review the collective results of agricultural cohorts (Stage 4).

2.3 Stage 3: Review of Key Systematic Reviews

The European Food Safety Authority (EFSA) published an External Scientific Report in 2013 that consisted of a comprehensive systematic review of all epidemiological studies published between 1 January 2006 and 30 September 2012, investigating the association between PPP exposure and the occurrence of any human health-related outcomes. In the same year, the French National Institute of Health and Medical Research (INSERM) released a systematic literature review on the human health effects of exposure to PPPs, analyzing epidemiological or experimental data published in the scientific literature up to June 2012. As these two systematic reviews represent the most comprehensive bodies of evidence of this subject, they were assessed in detail and summarized. In addition, the two methodologies and results were compared. Finally, summary tables were constructed of the main health findings as well as the PPPs of most concern for Switzerland.

2.4 Stage 4: Review of Agricultural cohorts

Part 4 located international agricultural cohort studies that investigated PPP exposures and health outcomes. The Consortium for Agricultural Health Studies (AGRICOH) was consulted to identify relevant cohorts, seek results of studies, and to summarize the main findings. AGRICOH is a consortium of agricultural cohort studies initiated by the US National Cancer Institute and by the International Agency for Research on Cancer (IARC) in October 2010 (IARC, 2017). As of January 2016, 30 cohorts from 5 continents participate in AGRICOH. The studies are from Australia (2), Canada (3), Chile (1), Costa Rica (2), Denmark (1), France (5), New Zealand (2), Norway (3), Republic of Korea (1), South Africa (2), the UK (1), and the USA (7). All cohorts study health outcomes in relation to environmental and occupational exposures in agricultural settings. However, because not all cohorts assess PPP exposure, or are not specific for agricultural workers exposure, a literature search was conducted to assess the relevance of results.

A general internet search was conducted using the cohort name in order to locate the cohort homepage (if applicable) to judge inclusion criteria. If a homepage was not available, a Pubmed search was conducted using the cohort name as keywords to locate relevant studies. A review of the methodology was conducted to judge inclusion criteria. Inclusion criteria for assessment of cohorts included: 1) occupational exposure to PPP and associated health effects (as some cohorts investigate other agents, such as dust); and 2) occupational exposure for adult workers, and not for family members (as some cohorts only focus on children of farmers, or environmental exposures in children). Of 30 cohorts, five cohorts met inclusion criteria. These cohorts were summarized for methodology, summary of the main findings and conclusions. Those cohorts with multiple study results are presented in a respective table.

2.5 Stage 5: Focus on Parkinson's Disease

Findings from stages 3 and 4 revealed preliminary evidence of an association between PPP exposures and Parkinson's Disease (PD). In an effort to better characterize this link, a targeted literature review was carried out on occupational PPP exposures and Parkinson's Disease in Medline, EMBASE, Sciencedirect, PubMed and psycINFO[3].

Only meta-analysis were selected for review. A total of 59 articles were located, of which four were meta-analysis that focused on PPP exposures and PD. In addition, the research results of the Agricultural Health Study (AHS) were selected for review as they presented the results of a large scale agricultural prospective cohort study.

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[3] ("pesticides"[Pharmacological Action] OR "pesticides"[MeSH Terms] OR "pesticides"[All Fields] OR "pesticide"[All Fields]) OR fungicid* OR herbicid* OR insecticid* AND occupation [TW] OR worker [TW] OR occupational diseases [MH] OR occupational exposure [MH] OR occupational medicine [MH] OR occupational risk [TW] OR occupational hazard [TW] OR (industry [MeSH Terms] mortality [SH]) OR occupational group* [TW] OR work-related OR working environment [TW]) AND parkinsons OR ("parkinson"[All Fields] AND "disease"[All Fields]) OR "parkinson disease"[All Fields] OR "parkinsons"[All Fields])

3. Results

3.1 Situation in Switzerland

As in other countries, PPPs are widely used in the Swiss agricultural sector to promote crop yield and quality, particularly on vulnerable, but high profit crops such as grapes used for wine making and stone fruits (i.e., apricots in the Wallis area). Almost 400 active substances are currently registered in Switzerland, which are present in more than 1200 different types of marketed PPPs (FOAG, 2017). Almost 2,200 tons of active substances are sold every year (FOAG, 2016). These are mainly fungicides (40%), used in the control of plant diseases, and herbicides (40%), used against weeds. Insecticides used against insect pests account for about 16% of the quantities sold (FOAG, 2016). Despite knowledge of the amounts of active substances sold, more precise information on the utilization of active substances is limited.

What is known is that approximately 1.1 million workers are affected by work-related health problems in Switzerland (SECO, 2014). In terms of the financial repercussions of occupational exposures, this situation for the country is not negligible. It is estimated that the occupational disease costs amount to at least 3% of gross domestic product (equivalent to CHF 20 billion per year (SECO, 2014)).

In regards to chemical exposures, the International Labour Organisation (ILO) reported that in 2003, there were 1000 deaths due to occupational exposure to chemical products in Switzerland (ILO, 2003). However, a critical link between PPP use and subsequent exposures, as well as potential incurred health effects among Swiss workers is currently lacking. What are the incidence rates for PPP-related illness and disease among Swiss agricultural workers? How can we know if an occupational health risk exists among this population?

While this lacuna of occupational health information may be a symptom of a lack of attention for workplace health indicators, which is not always considered the most relevant public health or medical issue; it is also possible that it results from a more generalized problem of transparency and health information management in Switzerland. In fact, Switzerland is one of the countries with the most limited health information systems (OECD, 2015a). Of an analysis of health information systems across 22 OECD countries, Switzerland ranked second to last (before Turkey) in terms of availability and use of health data. This study revealed that only 14% of available health datasets are regularly linked for research, statistics and/or monitoring, highlighting the critical problem that Switzerland lacks connections between different health institutions and organizations when it comes to data sharing and monitoring (OECD, 2015b).

In stage 1 of this investigation, a lack of available data on PPP exposures and possible associated health effects were revealed. This highlighted important knowledge gaps at different–levels of the current institutional information flow system. We found that while there were numerous stakeholders that worked efficiently in their own mandate, there was a clear need for increased collaboration and coordination in order to make use of existing data towards safer PPP use among agricultural workers in Switzerland.

3.2 Broad literature search

As most PPPs contain chemicals designed to be toxic for living organisms, their toxicity for other animal species, including humans is inevitable. In the past decades, this notion has gained footing through the extensive and ever-increasing evidence from epidemiological and experimental studies conducted worldwide. Today, thousands of peer-reviewed studies exist on the potential association between PPP exposures on the incidence of human diseases such as cancers, Alzheimer, Parkinson, amyotrophic lateral sclerosis, asthma, bronchitis, infertility, birth defects, attention deficit hyperactivity disorder, autism, diabetes, and obesity. on the possible role of PPP exposures on the incidence of human diseases such as cancers, Alzheimer, Parkinson, amyotrophic lateral sclerosis, asthma, bronchitis, infertility, birth defects, attention deficit hyperactivity disorder, autism, diabetes, and obesity (Mostafalou and Abdollahi, 2017).

Of peer-reviewed systematic reviews and meta-analysis of PPP exposures and resulting health effects, the most comprehensive and most recent comes from Mostafalou and Abdollahi (2013, 2017). In 2013, Mostafalou and Abdollahi conducted a systematic review on the relation between exposure to PPPs and incidence of different types of human chronic diseases. The results revealed that the largest share was accounted for incidence of cancers and then neurodegenerative, reproductive, and developmental disorders in association with exposure to PPPs.

In 2017, Mostafalou and Abdollahi updated the state of the evidence by conducting the most recent systematic review of PPP exposures and resulting health effects in humans. The systematic review was conducted on 43 human diseases divided into six broad groups of toxicities, and were assessed for occupational or residential/environmental exposure. The results shows that the top two types of toxicities reported were carcinogenicity and neurotoxicity, and carcinogenicity was considered as the most reported toxicity studied in relation to each class of pesticides, including insecticides, herbicides, fungicides, and fumigants (figure 3).

The association of PPP exposure and cancer incidence with human exposure to pesticides was found for 28 cancers sites, divided into nine body organ systems among which the most studied associations are related to the malignancies of the hematopoietic system, notably leukemia and lymphoma. Among studies focusing on the association of cancers with pesticide class, insecticides had the highest prevalence, followed by herbicides, fungicides, and fumigants. However, this may be because insecticides and herbicides are generally considered as the most used classes, which may explain the differences in the rate of their association with cancer incidence.

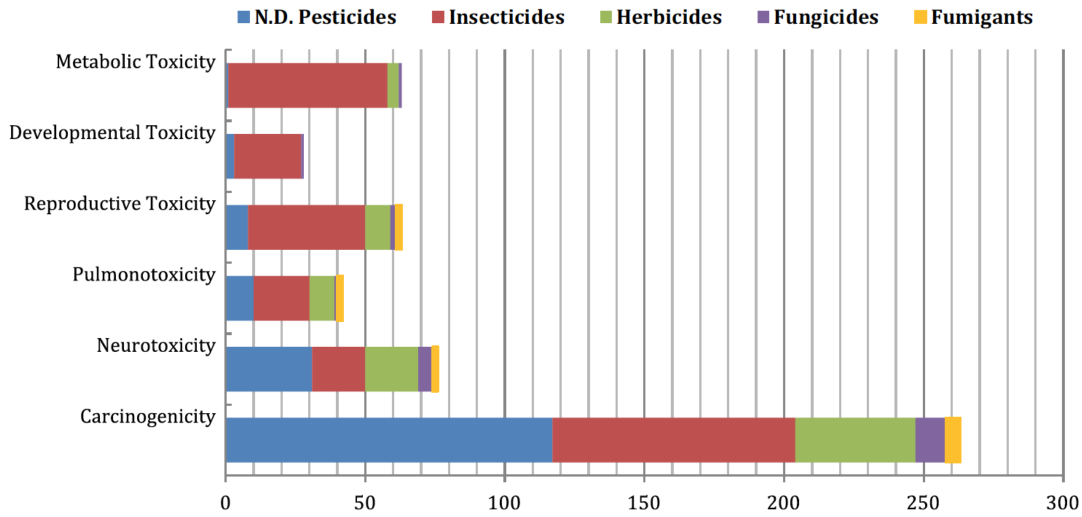

Figure 3. Schematic diagram showing the weight of evidence on the toxicities of pesticides. Horizontal axis legend = Number of significant associations.

Neurotoxicity was found to be the second most prevalent type of toxicity related to PPP exposure according to the associations scrutinized in the review, derived from evidence related to the link of pesticides with three neurodegenerative disease: Parkinson, Alzheimer's and amyotrophic lateral sclerosis (ALS).

Overall, the authors of this most recent systematic analysis conclude that an extensive body of evidence exists on the possible association between PPP exposures and the incidence of human diseases such as cancers, Alzheimer, Parkinson, amyotrophic lateral sclerosis, asthma, bronchitis, infertility, birth defects, attention deficit hyperactivity disorder, autism, diabetes, and obesity. The authors found that the most studied association of health effects was with insecticides and herbicides most notably organophosphorus, organochlorines, phenoxyacetic acids, and triazine compounds.

3.3 Summary of systematic reviews (EFSA and INSERM)

Several epidemiological studies carried out at international level in population groups from the agricultural sector highlight, with varying degrees of proof, links between exposure to PPPs and certain chronic diseases. These statistical associations have been compiled as part of a collective expert appraisal by INSERM and a study commissioned by EFSA analysing the literature on the epidemiological data.

3.3.1 EFSA report

The European Food Safety Authority published an External Scientific Report in 2013 that consisted of a comprehensive systematic review of all epidemiological studies published between 1 January 2006 and 30 September 2012, investigating the association between pesticide exposure and the occurrence of any human health-related outcomes.

The methodological assessment of eligible studies (to evaluate risk of bias associated with each study) was focused on study design, study population, level of details in exposure definition and methods of exposure measurement and the specificity of the measurement. Efforts undertaken to account for confounders through matching or multivariable models, blinded exposure assessment and well-defined and valid outcome assessment were considered. Quantitative synthesis of the results was attempted when there were five or more eligible studies per examined outcome and when there was no substantial heterogeneity among the published evidence. Publication bias was assessed using funnel plots that allowed to visually inspect asymmetry when more than 10 studies were included in the meta-analysis.

The review included cohort studies, case-control studies and cross-sectional studies. Toxicological data was not reviewed or discussed. Each study underwent an assessment of its eligibility based on a method including 12 criteria including study design, description of the inclusion/exclusion criteria, level of detail in describing exposure, robustness in the measurement of exposure, adjustment for potential confounding factors, method of assessment of the health outcome, and sample size. Among these 12 criteria, three were related to the degree of precision in the description/measurement of exposure, which may explain why a large number of epidemiological studies were not selected.

Overall, 602 individual publications were included in the scientific review. These 602 publications corresponded to 6,479 different analyses. A large majority of evidence came from retrospective or cross-sectional studies (38 and 32% respectively) and only 30% of studies had a prospective design. Exposure assessment varied between studies and overall 46% measured biomarkers of pesticides exposure and another 46% used questionnaires to estimate exposure to pesticides. Most studies examined associations between occupational exposure to pesticides and health effects. The entire spectrum of diseases associated with pesticides has not been studies before. The report examined a wide variety of outcomes. The largest proportion of studies pertains to cancer outcomes (N=164) and outcomes related to child health (N=84).

Despite the large volume of available data and the large number of analyses available, strong conclusions were not made for the majority of the outcomes studied. This was due to several limitations of the data collected as well as to inherent limitations of the review itself. As the review studied a whole range of health outcomes examined in relation to pesticides during 5 years' period, only recent evidence was reviewed and the results of the meta-analyses performed should be cautiously interpreted as they do not include all the available evidence. It is therefore capable of highlighting outcomes which merit further in-depth analysis in relation to pesticides by looking at the entire literature (beyond 5 years) and by focusing on appraising the credibility of evidence selected. The limitations of the studies itself are in line with other filed of environmental epidemiology and focus around the exposure assessment, the study design, the 3096 statistical analysis and reporting.

Despite the limitations, the review showed consistent evidence of a link between exposure to pesticides and Parkinson's disease and childhood leukemia, which was also supported by previous meta-analyses. In addition, an increased risk was also found for diverse health outcomes less well studied to date, such as liver cancer, breast cancer and type II diabetes. Effects on other outcomes, such as endocrine disorders, asthma and allergies, diabetes and obesity showed increased risks and should be explored further.

Parkinson's disease and childhood leukemia marked the two outcomes for which a meta-analysis after 2006 was found consistently showing an increased risk associated with pesticide exposure. However, there was limited indication of the effect of specific pesticide classes or individual pesticides.

3.3.2 INSERM report

In 2013, INSERM released a literature review carried out with a group of experts on the human health effects of exposure to pesticides. Epidemiological or experimental data published in the scientific literature up to June 2012 were analyzed. The report was accompanied by a summary outlining the literature analysis and highlighting the main findings and policy lines, as well as the recommendations.

The INSERM report is composed of four parts:

1) exposure assessment, with a detailed description of direct and indirect methods to assess exposure in epidemiological studies;
2) epidemiology, with an inventory and analysis of epidemiological studies available in the literature up to 2012, and a scoring system to assess the strength of presumed association;
3) toxicology, with a review of toxicological data (metabolism, mode of action and molecular pathway) of some substances and assessment of biological plausibility;
4) recommendations.

An inventory and analysis of epidemiological studies available in the literature was carried out, examining the possible association between pesticide exposure and health outcomes: 8 cancer sites (Non-Hodgkin lymphoma, leukemia, lymphoma, multiple myeloma, prostate, testis, brain, melanoma), 3 neurodegenerative diseases (Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis), cognitive or depressive disorders, effects on reproductive function (fertility, pregnancy and child development) and childhood cancers. Epidemiologic studies addressing primarily farmers, pesticide applicators and workers of the pesticide manufacturing industries, as well as the general population when it was relevant, were selected.

A hierarchy was established in regards to the strength of the study based on its methodology, starting with meta-analysis, then systematic review, then the cohort study and finally the case-control study. Based on this hierarchy, a scoring system was defined to assess the strength of presumption of the association between exposure and the occurrence of health outcomes from the analysis of the study results. For each disease or pathological condition investigated, this score may differ depending on the quality, type and number of available studies. The following grading was given:

(++): strong presumption: based on the results of a meta-analysis, or several cohort studies or at least one cohort study and two case-control studies, or more than two case-control studies;
(+): moderate presumption: based on the results of a cohort study or a nested case-control study or two case-control studies;
(±): weak presumption: based on the results of one case-control study. This synthesis takes the work beyond the status of a simple mapping exercise.

Toxicological data that were considered in the literature review were mainly those regarding metabolism, mode of action and molecular pathways. When substances were clearly identified in the epidemiological studies, a scoring system was defined to assess the biological plausibility from the study results: coherence with pathophysiological data and occurrence of health outcome.
(++): hypothesis supported by 3 mechanisms of toxicity
(+): hypothesis supported by at least one mechanism of toxicity

Overall, strong presumptions of associations between occupational exposures were found for NHL, prostate cancer, multiple myeloma and Parkinson's disease. The full results of the INSERM report are summarized in table 3.

Health outcome	Population with significant risk excess	Presumption strength	Numbers of analyzed studies
Parkinson's disease	Occupational and non-occupational exposure	++	7 meta-analysis + 1 prospective cohort
NHL	Farmers, operators, manufacturing plant personnel	++	6 meta-analysis + 1 prospective cohort
Multiple myeloma	Farmers, operators	++	6 meta-analysis + 2 prospective cohorts
Prostate cancer	Farmers, operators, manufacturing plant personnel	++	1 meta-analysis (2012, including 46 studies))
Leukemia	Farmers, operators, manufacturing plant personnel	+	7 meta-analysis + 1 prospective cohort
Alzheimer's disease	Farmers	+	3 prospective cohorts
Cognitive disorders	Farmers	+	1 meta-analysis (>40 studies; mainly on OP insecticides)

Health outcome	Population with significant risk excess	Presumption strength	Numbers of analyzed studies
Fertility and fecundability disorders	Occupational exposure	+	Several transversal studies
Hodgkin lymphoma	Agricultural workers	±	4 meta-analysis + 1 prospective cohort
Testicular cancer	Agricultural workers	±	2 meta-analysis + several cohort studies + 1 case-control study
Brain cancer (glioma, meningioma)	Agricultural workers	±	3 meta-analysis + cohort studies + transversal studies
Melanoma	Agricultural workers	±	2 meta-analysis + several cohort studies + 1 case-control study
Amyotrophic lateral sclerosis	Farmers	±	2 meta-analysis
Anxiety, depression	Farmers, farmers with a history of acute poisoning, operators	±	1 case-control study + several transversal studies (mainly on OP insecticides)

Table 3. Statistically significant associations between occupational exposure to pesticides and health outcomes in adults.

In regards to the active substances identified by the report as having a presumed moderate or strong association with health effects, many of them have (fortunately) been prohibited for use in Switzerland, and in the EU (i.e., DDT, paraquat, etc.) This is mainly due to the fact that the majority of the diseases examined are diseases of the elderly; therefore, the studies performed to date are based on persons who were old at the time of the study and exposed many years ago. By definition, it is not yet possible to investigate the potential long term effects of many of the more recent PPPs.

Nevertheless, of the active substances identified to have a moderate or strong association with health effects, six of them are used in Switzerland (table 4). These include: the herbicides 2,4-D, MCPA, mecoprop, glyphosate, the insecticide chlorpyrifos, and the foliar fungicide mancozeb. All of these active substances had a presumed moderate or weak association with hematopoietic cancers. The foliar fungicide mancozeb had a presumed weak association with Parkinson's disease. Two active substances, the insecticide chlorpyrifos and the herbicide glyphosate, had a presumed moderate association with NHL. This indicated that there are more than 337 authorized PPPs currently in use in Switzerland that are associated with adverse clinical health outcomes.

Active substance	EU Classification	Presumption strength	Biological plausibility	Products authorized in Switzerland
Organophosphates Insecticide: Chlorpyrifos	Acute Tox cat 3	Leukemia (+)	yes (++)	15
		Neurodevelopment (+)	yes (++)	
		NHL (±)	yes (++)	
Dithiocarbamates Fungicide: Mancozeb	Repro cat 2	Leukemia (+)	?	84
		Melanoma (+)	?	
		Parksinson's disease (in combination with paraquat)	yes (+)	
Phenoxy herbicides: 2,4-D	Acute Tox cat 4	NHL (+)	?	48
MCPA	Acute Tox cat 4	NHL (±)	?	37
Mecoprop	Acute Tox cat 4	NHL (±)	?	49
Aminophosphonate glycine herbicide: Glyphosate		NHL (+)	?	104

Table 4. Findings related to approved active substances: epidemiological assessment and biological plausibility.

3.3.3 Comparison of the EFSA and INSERM reports

The EFSA and INSERM reports mark two of the most widely accepted scientific reviews of the current state of evidence regarding pesticide exposure and resulting health effects. The EFSA report is a comprehensive systematic review of all available epidemiological 3319 studies that were published during a 5-year window. On the other hand, the INSERM report was limited to predefined outcomes and aimed to investigate the biological plausibility of epidemiological studies by reviewing toxicological data. The reports did not assess the same body of published data and there were different criteria used for grading the evidence, as well as for reporting and summarizing the findings. Overall, the INSERM report identified a greater number of associations with adverse health effects than the EFSA report. However, despite these facts, it is important to highlight that both reports demonstrated a well-documented association between pesticide exposure and Parkinson’s disease and childhood leukaemia. The agreement between the studies on an association between pesticide exposure and Parkinson’s disease warrants a deeper investigation (Stage 5).

3.4 Summary of Agricultural Cohort Studies

Prospective cohort studies have played a major role in understanding the contribution of environmental exposures to the development of many diseases. In particular, studies of agricultural populations have been of great interest due to the large number of people employed in this sector worldwide. Prospective agricultural cohort studies have also contributed to a better understanding of disease risks associated with PPPs for the general population as such exposures may also occur outside agriculture.

Of the 30 cohorts assessed (described in the Methodology), 5 cohorts presented results that were relevant to the investigation of PPP exposures and resulting chronic health effects. It is important to highlight that several cohorts that aim to assess PPP exposures and resulting chronic health effects have not concluded the enrolment phase, or have not yet published their results. These cohorts, in particular, the Prospective Investigation of Pesticide Applicators' Health (PIPAH) study of the United Kingdom (Harding et al. 2017) may offer new findings once the results are published.

A summary of the relevant cohorts investigating PPP exposure and resulting chronic health effects (cancers and neurodegenerative effects) are presented in Table 5. Full descriptions of the cohorts methodology and main findings follow. Cohorts are presented in chronological order, from most recent recruitment period.

Cohort	Country	Years of Recruitment	Men	Women	Health effect studied
Pesticide exposure in emerging farmers	South Africa	2008-2009	210	109	Neurobehavioral/neurodegenerative outcomes
AGRICAN	France	2005-2007	103,135	84,336	Cancers
PHYTONER	France	1997-1998	739	179	Neurobehavioral/neurodegerative outcomes
Agricultural Health Study	USA	1993-1997	55,748 applicators, 219 spouses	32,127 spouses, 1,562 applicators	Broad range of health effects: cancers, neurodegenerative outcomes, respiratory effects, dermal effects.
Cancer in the Norwegian agricultural population	Norway	1969-1989	136 463	109 641	Cancers

Table 5. Summary of agricultural prospective cohorts investigating occupational PPP exposures and chronic health effects in agricultural communities.

3.4.1 Pesticide Exposure in Emerging Farmers study

The population of interest for this study was farmers in the deciduous, citrus fruit and grape industry in the Western Cape of South Africa. In 2009, 319 farmers were enrolled (66% male and 34% female) from the Western Cape. This prospective cohort consisted of 17 months, and included a baseline cross-sectional study, three quarterly follow-ups and a final follow-up. Exposure to pesticides (specifically organophosphates – OP) was derived from three metrics: (i) OP applicator status, (ii) cumulative OP exposure weighted for task/activity, (iii) diagnosed past poisoning. Pesticide bio-monitoring (urine and blood plasma) was also conducted during all the data collection phases to detect OP pesticide exposure. Testing included a questionnaire exploring demographic details, work history, medical history; the Q16 and the Brief Symptom Inventory (BSI). Additionally, neurobehavioral performance was assessed on the following: Digit span forward and backward, Digit Symbol, Santa Ana Pegboard, Pursuit Aiming, Benton Visual Retention and Vibration sense as measured by vibration sense threshold using a 256 Hz frequency tuning fork (Holtman et al. 2016).

What were the main findings?

- In the baseline study, a threefold risk for decreased vibration sense (OR=3.08; 95% CI 1.05 to 9.05) following prolonged cumulative OP exposure was found and an almost six-fold risk for decreased vibration sense following past poisoning events (OR=5.97; 95% CI 2.14 to 16.66).

- When cumulative OP exposure was adjusted for past poisoning, the association with vibration sense was attenuated and was of borderline significance (OR=2.34; 95% CI 0.70 – 7.86).
- In the cohort study, there were no significant associations between cumulative OP days weighted by activity and neurobehavioral deficits. However, participants with recent poisoning experiences during the study period had a more than two and-a-half risk of showing a decline neurological test over time (OR 2.67; 95% CI 1.05 to 6.80). When recent poisoning was included in the regression model with cumulative OP exposure, the previously non-significant association for cumulative exposure (high versus no exposure) changed to a significant association showing a decline in performance on the neurological test (OR=3.95; 95% CI 1.03 to 15.08) over time.
- Overall, neurobehavioral outcomes tended to be adversely affected by past pesticide poisoning episode.

What conclusions can be made?

- Evidence to support association of chronic OP pesticide exposure and past poisoning event with neurobehavioral outcomes.
- On-going research is required with this cohort of farmers over a longer period of time to investigate the effects of long-term OP exposure in the absence of acute poisoning.

3.4.2 The AGRICAN (AGRIculture and CANcer) Study

The AGRIculture and CANcer (AGRICAN) cohort study is a French prospective study, and one of the largest cohorts worldwide assessing various tasks related to lifetime occupational history of major agricultural activities, exposure to pesticides, and cancer incidence. This large cohort enables the study of rare cancers or subtypes (for haematological, respiratory or brain cancers) specifically in understudied populations (women, farm workers). To be selected for the cohort, men and women had to be aged at least 18 years, active or retired, have been affiliated with the French agricultural health insurance scheme Mutualité Sociale Agricole (MSA) for ≥3 years during their lifetime, and be living in one of the 11 geographical areas covered by a population-based cancer registry at the time of enrolment from 1 November 2005 to 31 December 2007.

A postal enrollment questionnaire was sent between November 2005 and March 2006. The eight-page self-administered questionnaire concerned (1) demographic characteristics, (2) personal life habits: history of smoking, some information on diet and alcohol consumption, (3) health data: height and weight, self-report of 15 health conditions and reproductive history, (4) a complete job calendar with a lifetime history of agricultural activities including details on 13 crops and 5 livestock. For all crops and livestock, information on dates of beginning and end, minimum and maximum surface areas concerned by the task, history of pesticide treatments and other tasks in contact with crops was sought. If the subject had been involved in pesticide treatment tasks, the history of spraying equipment and practice and the history of using personal protective equipment were also sought.

Place of residence and affiliation to the health insurance scheme were checked annually in the *MSA* files to prevent cohort members being lost to follow-up. Vital status of all eligible individuals was also checked annually by crossing the database with the *MSA* files and, for cohort members only, with the National Death Index (*Répertoire National pour l'Identification des Personnes Physiques*). For each identified death among cohort members, cause of death is subsequently obtained from the national death registry (*Centre d'épidémiologie sur les causes médicales de décès*, CepiDC). Person-year accumulation began in the cohort from the date of enrolment (date of reception of the questionnaire) in the study (November 1, 2005–December 31, 2007) and ended on December 31, 2009, or on the date of death or on the date the study participant was lost to follow-up.

What are the main findings?

- Results have been published in 2016 and 2017. The most up-to-date results were published this year by Lemarchand et al. (2017). It is important to note that these results were not considered in the EFSA nor INSERM reports. As such, this research provides new results on cancer incidence in the agricultural population in France, which could be as the most comparable population to French-speaking cantons of Switzerland.
- Overall, aggregated cancer incidence rates did not differ between the cohort and the general population. However, there were specific disease patterns for farmers.
- Farmers had a lower incidence of tobacco-related cancers, and a significantly higher incidence ratio for prostate cancer and non-Hodgkin lymphoma (table 6).

Health effect	Reference	Results
Central nervous system (CNS) tumours	Piel et al. (2017)	• Overall results: Participants were followed for 5.2 years on average, 18,284 died during follow-up (10.7%) and 1,786 were lost to follow-up (1.0%). 273 incident cases of primary CNS tumours were diagnosed, including 126 gliomas (46.2%), 87 meningiomas (31.9%), 27 neuromas and 17 lymphomas. Several increased risks of CNS tumours in farmers, especially in pesticide users (hazard ratio = 1.96; 95% confidence interval: 1.11–3.47). Associations varied with tumour subtypes and kinds of crop and animal farming. The main increases in risk were observed for meningiomas in pig farmers and in farmers growing sunflowers, beets and potatoes and for gliomas in farmers growing grasslands. In most cases, more pronounced risk excesses were observed among pesticide applicators. • Duration: When considering all tumours together, a significant association with duration was found in farmers growing wheat ($HR_{10years}$ = 1.30; 95% CI: 1.05–1.61), beets ($HR_{10years}$ = 1.47; 95% CI: 1.12–1.92), potatoes ($HR_{10years}$ = 1.21; 95% CI: 1.00–1.45), field-grown vegetables ($HR_{10years}$ = 1.78; 95% CI: 1.19–2.67) and in pig farmers ($HR_{10years}$ = 1.28; 95% CI: 1.01–1.64 • Crops: For all CNS tumours, significant increases in risk were observed among beet growers who used pesticides (HR = 2.68; 95% CI: 1.49–4.80) or treated their seeds (HR = 3.85; 95% CI: 1.94–7.62), but not among those who performed exclusively any other task (HR = 1.48; 95% CI: 0.88–2.47
Prostate cancer	Lemarchand et al. (2017)	Men, especially those who had ever worked on farm, had a significantly increased incidence of prostate cancer (standardized incidence ratio (SIR) = 1.07, 95%CI 1.03–1.12), which was more pronounced among farm workers and in subjects who had ever (SIR = 1.09, 95%CI 1.03–1.15) or never (SIR = 1.27, 95%CI 1.06–1.50) used pesticides The increased risk in pesticide users and in non-users suggests a role of various hazards such as direct or secondary exposure to pesticides applied on crops.
	Lemarchand et al. (2016)	An excess of prostate cancer risk among participants involved in grassland activities, mainly in haymaking (HR 1.18, 95% CI 1.02–1.36). Pesticide use and harvesting among fruit growers were associated with an elevated prostate cancer risk, with a two-fold increased risk for the largest area. For potato and tobacco producers, an elevated prostate cancer risk was observed for almost all tasks, suggesting a link with pesticide exposure since all of them potentially involved pesticide exposure.

Health effect	Reference	Results
Lip cancer	Lemarchand et al. (2017)	An excess of lip cancer was observed in men, almost all cases occurring in men who used pesticides on crops (SIR = 2.05, 95%CI 1.27–3.13). These excesses were more pronounced among farm workers.
Skin melanoma	Lemarchand et al. (2017)	Unlike men, women experienced an increased risk of skin melanoma (SIR = 1.23 95%CI 1.05–1.43), in particular those using pesticides on crops.
Multiple myeloma (MM)	Lemarchand et al. (2017)	Higher risks were observed in men and women for multiple myeloma (SIR = 1.38, 95%CI 1.18–1.62 and SIR = 1.26, 95%CI 1.02–1.54 respectively), more pronounced in male farm owners (SIR = 1.59 95%CI 1.29–1.95) and users of pesticides on crops (SIR = 1.49, 95%CI 1.19–1.84).
Non-Hodgkin's Lymphoma (NHL)	Lemarchand et al. (2017)	Men had an increased incidence of non-Hodgkin lymphoma (NHL) (SIR = 1.09, 95%CI 1.01–1.18)

Table 6. Summary of findings from AGRICAN publications.

What conclusions can be made?

- The AGRICAN study provides the most recent results on cancer incidence in the agricultural population in France. Importantly, these results were not considered in the EFSA and INSERM reports.
- Overall, aggregated cancer incidence rates were not different between the agricultural cohort and the general population.
- Farmers had a lower incidence for tobacco-related and female breast cancers.
- Farmers had a higher incidence of prostate cancer than the general population. Pesticide use and harvesting among fruit growers were associated with an elevated prostate cancer risk, with a two-fold increased risk for the largest farming area.
- Male farmers had an increased incidence of NHL.
- Male and female farmers have a higher risk for MM, with a more pronounced risk in male farm owners and users of pesticides on crops.
- Risk for skin melanoma in women was greater among pesticide users on crops.
- Pesticide use was associated with increased risks of CNS tumours in all farmers.

3.4.3 The PHYTONER Study

The aim of the PHYTONER study is to investigate the role of pesticides on neurobehavioral performances in French vineyard workers. PHYTONER is a study based on the population of workers affiliated with the MSA, the regional branch of the French health and welfare department for agricultural workers. In this cohort, a total of 929 subjects were recruited from February 1997 to December 1998 in south-western France from MSA. Subjects had to have been 40–55 years old in 1995, to have been employed for 1000 h or more in the year 1995 and to have been affiliated to MSA from 1975 to 1995 (so that they had a minimum of 20 years of work in agriculture at enrolment).

Participants were initially categorized into three groups (no pesticide exposure, direct exposure and indirect exposure) following examination of detailed job calendars. All participants were interviewed and completed a battery of nine neurobehavioral tests at baseline. Subjects were informed of the 4-year follow-up by their occupational physicians and were phoned to arrange interviews at home with a psychologist from May 2001 to December 2003. Subjects who could not be contacted were sought at length using phone data bases and by questioning their neighbors at their enrolment address. Enrolment and follow-up questionnaires included detailed information on individual, lifestyle and other factors likely to affect neurobehavioral status, or understanding of the test. Job calendars collected at enrolment included the dates of the start and end of each job, the exact title of the jobs and tasks performed. These data were entered for the period between enrolment and follow-up. After answers were reviewed, subjects were classified according to their entire life history as (i) ‘directly exposed’ if they had mixed or applied pesticides in vineyards, or cleaned or repaired spraying equipment in one or more job, (ii) ‘certainly indirectly exposed’ if they had never been directly exposed but had to perform tasks in contact with treated plants (re-entry tasks such as pruning or harvesting), (iii) ‘possibly indirectly exposed’ if they had worked in a vineyard (in offices, buildings, cellars, etc.) but reported no contact with treated plants, or (iv) ‘non-exposed’ if not classified in one of the above categories.

What are the main findings?

- This French prospective cohort study is the first to present data on the progression of neurological disorders associated with pesticide exposure, specifically among vineyard workers.
- Results have been published from 2001 to 2013 in 3 studies (table 7). Collective results demonstrate long-term cognitive effects related to low-level exposure to pesticides among French vineyard workers.

Health effect	Reference	Results
Cognitive disorders	Blanc-Lapierre et al. (2013)	Exposure (ever vs. never) to organophosphates was associated with low cognitive performance The insecticide mevinphos had the strongest impact on the risk of low cognitive performance.
	Baldi et al. (2011)	Follow-up of the cohort showed lower cognitive performances in pesticide-exposed subjects. The risk of obtaining a low performance on the tests was higher in exposed subjects, with ORs ranging from 1.35 to 5.60. Evolution of performances over the follow-up period demonstrated that exposed subjects had the worst decreases in performance. The risk of having a two-point lower score on the Mini-Mental State Examination was 2.15 (95% CI 1.18 to 3.94) in exposed subjects.
	Baldi (2001)	The risk of scoring a low performance on neuro-cognitive tests was consistently higher in exposed subjects. When taking into account educational level, age, sex, alcohol consumption, smoking, environmental exposures, and depressive symptoms and when restricting analysis to subgroups, results remained significant for most tests, with odds ratios (OR) exceeding 2. These results point to long-term cognitive effects of low-level exposure to pesticides in occupational conditions.

Table 7. Summary of findings from AGRICAN publications.

What conclusions can be made?

- The PHYTONER study is the first to provide prospective data based on a large sample of workers on the natural development of neurological disorders and neuropsychological effects associated with chronic low-level pesticide exposure.
- Follow-up of the PHYTONER cohort (4 year post enrollment) showed lower cognitive performances in pesticide-exposed vineyard workers.
- Evidence of an evolution towards Parkinson's disease or other dementias in vineyard workers chronically exposed to pesticides.
- According to De Baan et al. (2015), fungicides are mainly used in Swiss vineyard while insecticides are barely used. This might not be the case for other countries such as France, therefore the risk for workers in Switzerland might be different compared to workers in France. Other countries' results should be carefully extrapolated to Switzerland.

3.4.4 Agricultural Health Study

The Agricultural Health Study (AHS) is one of the most widely recognized agricultural cohort studies. The AHS is a prospective study of cancer and other health outcomes in a cohort of licensed pesticide applicators and their spouses from Iowa and North Carolina in the United States. The study started in 1993 with the goal of answering questions about how agricultural lifestyle and genetic factors affect the health of farming populations. The study is a collaborative effort involving investigators from National Cancer Institute, the National Institute of

Environmental Health Sciences, the Environmental Protection Agency, and the National Institute for Occupational Safety and Health. Between 1993 and 1997, 52,394 licensed private pesticide applicators (mostly farmers) from Iowa and North Carolina were enrolled in the study, as well as 32,345 of their spouses. In total, more than 89,000 farmers and their spouses in Iowa and North Carolina have participated in the study. The study also included 4,916 commercial pesticide applicators in Iowa in its first two phases (see Figure 4 for phase description). The average ages at enrollment were 47.1 years, 38.0 years, and 46.9 years for private applicators, commercial applicators and spouses, respectively.

The study began by collecting baseline information from participants when they enrolled (1993-1997). Follow-up telephone interviews were conducted in the second (1999-2003) and third phases (2005-2010) of the study. Participants provided updated information on farming practices, lifestyle, and health and were asked to complete a dietary questionnaire and provide a sample of cheek cells as a source of DNA. The Phase 3 interview also updated information on farming practices, lifestyle, and health. All participants who were eligible to participate at Phase 3 were asked to provide information updating health and farming status in Phase 4. Participants completed the questionnaires either by mail, telephone or through the Internet; for the first time, next-of-kin were able to provide general health update information for those who could not complete the questionnaires themselves (Figure 4).

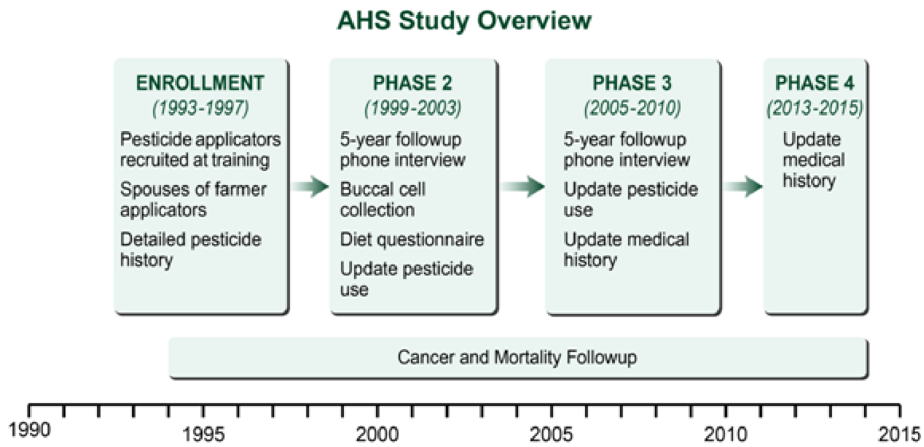

Figure 4. AHS study methodology overview.

What are the main findings?

- Between 1994 and 2017, more than 265 individual peer-reviewed articles have been published on the results of the AHS. The most recent publications (from 2014-2017) have not been assessed in the INSERM and EFSA reports. Unfortunately, there is no comprehensive summary or database of the AHS findings (personal communication, Dr. Laura Beane-Friedman, September 2017).
- Overall, the AHS has found that AHS participants have lower rates of specific diseases compared to the rest of the population, most likely due to lower rates of smoking and higher rates of physical activity. However, participants also demonstrated higher risk for developing certain diseases, such as Parkinson’s Disease, as well as some cancers, including prostate cancer.

Table 8 provides a summary of the cohort results relating to cancers and neurodegenerative diseases.

Health effect	Reference	Results
Thyroid cancer	Lerro et al. (2015)	Malathion, the most commonly reported OP, was associated with increased risk of thyroid cancer (RR = 2.04, 95% CI: 1.14, 3.63)
Breast cancer	Lerro et al. (2015)	Any OP use was associated with an elevated risk of breast cancer (RR = 1.20, 95% CI: 1.01, 1.43).
Ovarian cancer	Lerro et al. (2015)	Diazinon use was associated with ovarian cancer (RR = 1.87, 95% CI: 1.02, 3.43).
Non-Hodgkin's Lymphoma	Alavanja et al. (2014)	NHL, statistically significant positive exposure-response trends were seen with lindane and DDT. Terbufos was associated with total NHL in ever/never comparisons only. In subtype analyses, terbufos and DDT were associated with small cell lymphoma/chronic lymphocytic leukemia/marginal cell lymphoma, lindane and diazinon with follicular lymphoma, and permethrin with multiple myeloma (MM).
Prostate cancer	Koutros et al. (2013)	Three organophosphate insecticides were significantly associated with aggressive prostate cancer: fonofos for the highest quartile of exposure (Q4) vs. nonexposed, RR= 1.63, 95% CI: 1.22, 2.17; $P_{trend} < 0.001$); malathion (RR for Q4 vs. nonexposed = 1.43, 95% CI: 1.08, 1.88; $P_{trend} = 0.04$); and terbufos (RR for Q4 vs. nonexposed = 1.29, 95% CI: 1.02, 1.64; $P_{trend} = 0.03$). The organochlorine insecticide aldrin was also associated with increased risk of aggressive prostate cancer (RR for Q4 vs. nonexposed = 1.49, 95% CI: 1.03, 2.18; $P_{trend} = 0.02$).
	Alavanja et al. (2003)	A prostate cancer standardized incidence ratio of 1.14 (95% confidence interval: 1.05, 1.24) was observed for the Agricultural Health Study cohort. Use of chlorinated pesticides among applicators over 50 years of age and methyl bromide use were significantly associated with prostate cancer risk. Several other pesticides showed a significantly increased risk of prostate cancer among study subjects with a family history of prostate cancer but not among those with no family history. Important family history-pesticide interactions were observed.
Parkinson's Disease (PD)	Kamel et al. (2007)	Incident PD was associated with pesticide use (cumulative days) at enrollment (OR = 2.3, 95% CI: 1.2, 4.5).

	Tanner at al. (2011)	PD was associated with use of a group of pesticides that inhibit mitochondrial complex I (OR = 1.7; 95% CI: 1.0, 2.8) including rotenone (OR = 2.5; 95% CI: 1.3,4.7) and with use of a group of pesticides that cause oxidative stress (OR = 2.0; 95% CI: 1.2, 3.6), including paraquat (OR = 2.5; 95% CI: 1.4, 4.7).

Table 8. Summary of findings from AHS publications.

What conclusions can be made?

- Farmers from the AHS have lower rates of specific diseases compared to the rest of the population, most likely due to lower rates of smoking and higher rates of physical activity.
- Farmers exposed to pesticides have a higher risk for developing PD. Rotenone and paraquat are linked to increased risk of developing PD.
- Farmers have a higher risk for developing prostate cancer, particularly aggressive sub-types. Malathion, terbufos, fonofos and aldrin, associated with an increased risk of aggressive prostate cancer.
- Farmers with OP use have an increased risk for several hormonally-related cancers, including breast, thyroid, and ovary, suggesting potential for hormonally-mediated effects.
- Lindane, DDT terbufos, diazinon and permethrin are associated with an increased risk of developing specific subtypes of NHL.
- Spouses of farmers are often exposed to pesticides, and should be included in cohort studies. About 60% of the spouses of pesticide applicators in the AHS reported using pesticides themselves. Women who reported using OP insecticides were more likely to develop breast cancer than women who never used these insecticides. Malathion, the most commonly used OP insecticide, was associated with an increased risk of thyroid cancer, and diazinon, another common OP insecticide, and was associated with an increased risk of ovarian cancer.
- Accidental high pesticide exposure events may affect health later in life.
- Although none of these active substances are now authorized in Switzerland, they were used in the past. Thus, several workers and farmers were probably exposed to them previously. These workers have thus a higher risk in developing PD or cancer than unexposed individuals.
- In addition, information on health effects regarding all the active substance and the mixtures used as well as the co-formulants added in commercial products are not always known, and might have an impact on the health of users.

3.4.5 Cancer in the Norwegian Agricultural Population

In Norway, multi-register linkage is possible due to the unique identification number assigned to all residents of Norway. Through linkage between data from the agricultural censuses in 1969-1989, the Central Population Register, and the Norwegian cancer register, a cohort of farm holders in Norway and their families was established. The national agricultural censuses held by Statistics Norway have provided computerized file information since 1969, and therefore it was possible to identify the majority of individuals engaged in agricultural work. All persons who were personal holders of agricultural land at the time of censuses and who were born later than 1924 were identified by means of their personal identification number. The resulting file of holders and spouses was linked to the Norwegian cancer register in which incident cancers including the site code of the International Classification of Diseases (seventh revision), morphology, and date of diagnosis were identified. The cancer register receives reports on all new cases of cancer and benign tumors of the central nervous system. Case reporting has been mandatory since 1952 and is considered to be complete.

What are the main findings?

- In 1996, Kristensen et al published the results of the investigation showing that the total cancer incidence among the men in the agricultural sector was considerably lower than for the total rural population. This result has been cited numerous times and provides the basis for the argument that farmers have a generally better health status than other populations.
- However, the differences in tobacco- and alcohol-related cancers and gastrointestinal cancers accounted for most of the total cancer difference between the male farmers and nonfarmers, and can therefore be attributed to lifestyle factors (as shown in other studies). Further, it is also important to note that the socioeconomic status of the families in modern Norwegian farming was relatively high, which may result in better health outcomes than the general population.
- Multiple myeloma was associated with pesticide indicators for both genders, mainly for subjects cultivating potatoes (RR = 2.03, 95% CI: 0.51, 8.14).

What conclusions can be made?

- The total cancer incidence among the men in the agricultural sector was lower than for the total rural population. The female study subjects had a total cancer incidence close to the total rural population.
- The differences in tobacco- and alcohol-related cancers and gastrointestinal cancers account for most of the total cancer difference between the male farmers and nonfarmers. For the women, breast cancer had the largest impact on the difference between the farmers and nonfarmers, but also cancer of the lung and uterine cervix was important. The results indicate that the farmers of both genders had favorable habits with respect to several life-style factors and perhaps higher socio-economic status.
- Evidence of an association between pesticides in potato cultivation and multiple myeloma.

3.4.6 What is the state of the evidence from prospective agricultural cohorts?

To date, a total of 5 agricultural prospective cohorts have published results on PPP exposures and resulting health effects. Several other cohorts are currently underway and publications should be monitored to update the state of the evidence. Of the 5 cohorts identified and reviewed, 2 came from France, 1 from Norway, 1 from the US, and 1 from South Africa. The AHS from the US focused on a broad range of health effects, while 2 focused uniquely on neurodegenerative effects and the remaining 2 uniquely on cancers.

Three of the cohorts demonstrated lower overall cancer incidence among agricultural workers when compared to the general population. However, the Norwegian cohort found that this finding was only true for male agricultural workers, as female study subjects had a total cancer incidence close to the total rural population (Kristensen et al. 1996). Currently, it is accepted that agricultural populations present lower rates of mortality, and for the main causes of death (cancer overall, and cardiovascular diseases) (Blair et al 2009; Acquavella et al. 1998). However, it is imperative that these statistics are not blindly referenced without a comprehensive assessment of confounders and disaggregated mortality data, specifically when it comes to cancer rates. Understanding the causation of chronic disease among this population involves analysis of the relationships of exposures and outcomes, protective actors, and risk factors.

Agricultural workers represent a unique population, and characteristics relative to their work, as well as lifestyle factors, must be properly acknowledged towards a determination of their health status vis à vis other populations. The finding that farmers may have lower mortality than the general population most likely remains the result of two important factors: the healthy worker effect, and the overall healthier lifestyle of farmers. The healthy worker effect describes the self-selection of health workers into physically strenuous occupational such as farming and of unhealthy workers out of such occupations. This hypothesis has been discussed since the 1980s, when epidemiological studies first began to indicate that farmers may be of better health, despite exposure to toxic PPPs (Donahan and Thelin, 2016).

Moreover, the hypothesis that agricultural workers have overall healthier lifestyle characteristics has gathered increasing evidence towards the explanation of why this population exhibits lower overall mortality (Acquavella et al. 1998). These lifestyle factors have been found to include: decreased smoking, less alcohol consumption, more exercise, and healthier diet (Donahan and Thelin, 2016).

It is clear that farmers smoke significantly less (approximately 50% less) compared to the general population (Donahan and Thelin, 2016). Chronic cigarette smokers have over 25 times the risk of a lung cancer diagnosis and five times the risk of having one or more of the other smoking-related cancers compared to non-smokers (Shiels et al., 2014). This risk factor has been cited as the central reason for decreased cancer risk among agricultural populations when compared to the general population (Blair et al., 2005; Kristensen et al., 2000).

An additional lifestyle protective factor is the decreased use of alcohol when compared to the general population (Blair et al., 2005). The combination of alcohol use and smoking marks a known risk factor for head and neck and esophageal cancer

In fact, several studies have identified a decreased use of alcohol among farmers associated with a decrease in overall cancer rates (Pukkala et al., 1997; Kristensen et al., 1996).

Increased exercise might also be a benefit for farmers, primarily from their work, as they expend as much as 30% more calories per day than sedentary workers (Donahan and Thelin, 2016). Lung, mouth and throat, liver, pancreas, bladder, and kidney cancers have a decreased relative risk for those populations who regularly exercise (Blair et al., 2005).

Finally, research suggests that the specific dietary habits of agricultural populations can act as protective factors against cancer, notably, the higher consumption of fresh fruits and vegetables as well as a significantly higher intake of fiber when compared to the general population. Meppelink (2014) found that farmers have overall lower blood pressure, lower cholesterol and lower resting heart rate when compared to the general population.

As shown in the literature, agricultural workers have a lower risk, and lower incidence, of tobacco- and alcohol-related cancers. Importantly, the differences in tobacco- and alcohol-related cancers and gastrointestinal cancers account for most of the total cancer difference between the male farmers and nonfarmers (Blair and Zahm, 1995; Kristensen et al., 1996; Waggoner, 2011). Acquavella et al. 1998 has reported that the lower prevalence of smoking decreases the risk of contracting cardiovascular diseases and some cancers (lung, bladder, pancreas), as their level of physical activity reduces the risk of some other cancers (colon and rectum).
Although the *general* health status of agricultural workers appears to be better than comparison populations, their *occupational* health appears to be one of the worst among all occupations (Donahan and Thelin, 2016). Agriculture in every industrialized country is one of the most hazardous occupations, based on occupational fatality and injury rates, and occupational illness rates (Donahan and Thelin, 2016).

The overall conclusion that from the review of agricultural cohort results is that even if farmers exhibit generally lower mortality rate than the general population, they also demonstrate a distinct pattern of specific disease prevalence, a pattern that has been widely associated with exposures to PPPs (Acquavella et al. 1998 ; Waggoner, 2011). While agricultural populations may have a lower overall cancer mortality rate than the general population, significantly lower lung cancer rates explain about 60% of this difference (Donahan and Thelin, 2016). Given the significantly lower smoking rates and generally healthier lifestyle of agricultural populations, this precision remains imperative to the understanding of epidemiological trends among this population. Evidence from the literature demonstrates distinct chronic disease trends among agricultural workers, including increased risk of neurodegenerative effects such as Parkinson's Disease, and specific cancers including including hematopoietic cancers (leukemia, non-Hodgkin lymphoma, multiple myeloma), skin, soft tissue sarcoma, prostate, testicular, stomach, and brain (Koutros et al. 2013; Alavanja et al. 2014; Donahan and Thelin, 2016; Lemarchand et al. 2017).

3.5 Focus on Parkinson's Disease

3.5.1 Why Parkinson's Disease?

Parkinson's disease (PD) is the most common cause of Parkinsonism and neurodegenerative disorder after Alzheimer's disease (Elbaz et al., 2009). As an idiopathic disease of the nervous system, it is characterized by resting tremor, rigidity, bradykinesia or the presence of a sustained L-dopa response. PD is a slowly progressive neurodegenerative disease with an etiology that is believed to be multifactorial (Riess & Krüger, 1999).

The first hypothesis of a link between pesticide exposure and PD appeared in the 1980s when several cases of parkinsonism and related symptoms appeared after intravenous injection of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a chemical that can cross the blood–brain barrier and is metabolized in glial cells, ultimately leading to the degeneration of nigral dopaminergic neurons (Langston, 1983). MPTP-induced animal models represent one of the main tools for investigations into the mechanisms involved in the death of dopaminergic neurons in PD. Interestingly, MPTP has a chemical structure similar to that of bipyridylium herbicides (e.g. paraquat and diquat) (Elbaz et al., 2009), both non-selective herbicides marketed since the 1960s. Triggered by this accidental observation of the approximate similarity between the pathophysiology of PD and toxicity of pesticides, there has been a large body of epidemiological and experimental evidence produced on pesticide exposures and the development of PD.

Based on the findings from previous research stages, the strongest evidence in regards for a chronic health effect resulting from PPP exposure is for Parkinson's Disease (INSERM, EFSA; Kamel et al.2007; Baldi et al. 2011).

3.5.2 What is the state of the evidence?

State of the evidence comes from four recent meta-analyses that assess the relation of occupational exposures to pesticides and the incidence of PD (table 9). Evidence can be elucidated from the Agricultural Health Study (AHS), as well as the Farming and Movement Evaluation study (FAME), a case–control study focused on neurological health effects, nested within the AHS.

Author and year	Number and type pf studies	Timeframe	Statistical indicator	Association between PPP exposure and PD	Other results
Van der Mark et al. (2012)	46 studies (39 case–control, 4 cohort and 3 cross-sectional studies)	1950 to 2010	summary risk ratio (sRR)	**1.52 (95% CI: 1.23, 1.89).**	Stronger association for herbicides (sRR=1.4, 95% CI: 1.1,1.8) and insecticides (sRR=1.5, 95% CI: 1.5, 2.1).
Van Maele Fabry et al. (2012)	12 cohort studies	1966 and 2011	meta-rate ratio estimate (mRR)	**1.28 (95% CI 1.03–1.59).**	The highest increased risks in studies with strongest exposure assessment: i.e., PD diagnosis confirmed by a neurologist (mRR= 2.56; CI: 1.46–4.48; n= 4). A significant increased risk was for banana, sugarcane and pineapple plantation workers (mRR= 2.05; CI: 1.23–3.42; n= 2).
Allen and Levy (2013)	17 case-control studies and 3 cohort studies	1947 to 2010	summary effect sizes (ES)	**1.49 (95% CI: 1.34, 1.66).**	Summary ES for occupational herbicide exposure showed stronger association with PD compared to that of overall exposure, which may reflect that the risk of PD increases with occupational exposures, due to the intensity, duration and/or frequency of workplace exposures.
Gunnarsson and Bodin (2017)	23 high quality studies, based on GRADE criteria (type not indicated, but the authors found the risk estimate was not influenced by study design).		Relative risk (RR)	**1.67 (95% CI: 1.42–1.97).**	The RR was statistically significantly elevated for exposure to insecticides (RR 5.75) and herbicides (RR 3.22).

Table 9. Summary of studies assessed for occupational PPP exposure and Parkinson’s Disease.

Meta-Analyses

1. Van der Mark et al. (2012) conducted a meta-analysis that included 46 studies (39 case–control, 4 cohort and 3 cross-sectional studies) published from 1950 to 2010. The summary risk ratio (sRR) for occupational exposure to pesticides and PD was **1.52 (95% CI: 1.23, 1.89).** When assessing different groups of pesticides, there was a stronger association for herbicides (sRR=1.4, 95% CI: 1.1,1.8) and insecticides (sRR=1.5, 95% CI: 1.5, 2.1). However, the sRR for exposure to fungicides did not indicate an association with PD (sRR = 0.99; 95% CI: 0.71, 1.4). Within insecticides, several studies in the meta-analysis found a significant association with organochlorine insecticides. This finding builds upon studies on biomarkers in serum (Weisskopf et al. 2010) and in the brains of deceased patients (Corrigan et al. 2000).

2. Van Maele Fabry et al. (2012) conducted a similar systemic review addressing occupational pesticide exposure and PD, but only within cohort studies. A total of 12 cohort studies (published between 1966 and 2011) were combined to derive a meta-rate ratio estimate (mRR) of **1.28 (95% CI 1.03–1.59).** The 28% observed increased risk was statistically significant and did not vary substantially when omitting studies with extreme weight values. The highest increased risks were observed for studies with the strongest design, i.e., the increased risk was higher for cohort studies (mRR= 1.95; CI: 1.29–2.97; n= 3) as well as for prospective cohort studies (mRR= 1.39; CI: 1.09– 1.78; n= 6); as well as for strongest exposure assessment: i.e., PD diagnosis confirmed by a neurologist (mRR= 2.56; CI: 1.46–4.48; n= 4). A significant increased risk was also seen for banana, sugarcane and pineapple plantation workers (mRR= 2.05; CI: 1.23–3.42; n= 2).

3. Allen and Levy (2013) conducted a meta-analysis and pooled 17 case-control studies and 3 cohort studies from 1947 to 2010. The summary effect sizes (ES) for the association between PD and occupational pesticide exposure was **1.49 (95% CI: 1.34, 1.66).** Both occupational herbicide and occupational insecticide exposure showed a significant association with PD. In this meta-analysis, conducted for both occupational and non-occupational exposures, the association between occupational exposures to pesticides were comparable or higher than that for overall pesticide exposure. However, the summary ES for occupational herbicide exposure showed a stronger association with PD compared to that of overall exposure, which may reflect a tendency that the risk of PD increases with occupational exposures, due to the intensity, duration and/or frequency of workplace exposures.

4. Gunnarsson and Bodin (2017) conducted the most recent meta-analysis, as well as the most scientifically reliable, due to their use of GRADE guidelines (Grading of Recommendations Assessment, Development and Evaluation) to assess only those studies fulfilling scientifically high quality standards. Of all occupational exposures, the most extensively studied aspect was the association between Parkinson's disease and exposure to pesticides, which was examined in 25 studies of high quality and 34 studies of lower quality. Of the high quality studies, the weighted relative risk estimate was **1.67 (95% CI: 1.42–1.97).** The study with the highest effect size included 63 patients diagnosed with Parkinson's disease before the age

of 50. The risk ratio (RR) was statistically significantly elevated for exposure to insecticide (RR 5.75) and herbicide (RR 3.22). A major strength of this meta-analysis is that it was based on a systematic literature review including only studies fulfilling scientifically high quality standards. In addition, the authors aimed to eliminate all possible sources of bias, using stratification of data with regard to possible confounders such as study design, gender, and funding. Publication bias was assessed using both funnel plots and a test for publication bias. Through a validated protocol to control for publication bias and study quality, this meta-analysis shows the most recent, and the most scientifically reliable evidence that exposure to any pesticide involves a ≥50% increased risk for developing Parkinson's disease in occupationally exposed populations.

AHS and FAME

Kamel et al. (2007) used data from the AHS cohort to evaluate the association of PD with occupational pesticide exposure. Detailed pesticide exposure data was collected in a prospective manner using two-tiered self-administered exposure assessments at the study enrolment and a follow-up telephone interview. Pesticide use has been reported reliably by these applicators (Blair et al. 2002; Hoppin et al. 2002). Cases were defined as participants who reported physician-diagnosed PD at enrolment (prevalent cases, n = 83) or follow-up (incident cases, n = 78). Cases were compared with cohort members who did not report PD (n = 79,557 at enrolment and n = 55,931 at follow-up

Tanner at al. (2011) in a follow up study, assessed PD incidence and occupational lifetime use of pesticides in the FAME case–control study nested in within the AHS. PD was diagnosed by movement disorder specialists. Controls were a stratified random sample of all AHS participants frequency-matched to cases by age, sex, and state at approximately three controls to one case. In 110 PD cases and 358 controls, PD was associated with use of a group of pesticides that inhibit mitochondrial complex I (OR = 1.7; 95% CI: 1.0, 2.8) including rotenone **(OR = 2.5; 95% CI: 1.3,4.7)** and with use of a group of pesticides that cause oxidative stress (OR = 2.0; 95% CI: 1.2, 3.6), including paraquat **(OR = 2.5; 95% CI: 1.4, 4.7).**

This study represented the most robust analysis of pesticides classified by presumed mechanism, rather than by functional categories or chemical class. The authors found significant associations of PD with use of groups of pesticides classified as complex I inhibitors or as oxidative stressors, providing for the first time, support in humans for findings from decades of experimental work. In particular, PD was strongly associated with rotenone and paraquat, two individual pesticides used extensively to model PD in animals. This study provides strong evidence of an association between rotenone use and PD in humans: PD developed 2.5 times as often in those who reported use of rotenone compared with nonusers, and an association of similar magnitude was observed even when exposure was truncated up to 15 years before PD diagnosis. In addition, the results suggest that paraquat exposure may also play a role in human PD. Because paraquat remains one of the most widely used herbicides worldwide (despite recent bans within the EU) this finding potentially has great public health significance.

3.5.3 What considerations must be taken into account?

Heterogeneity between studies

There was substantial heterogeneity in risk estimates between studies investigated in the meta-analyses (e.g.,, van der Mark, 2012 reported an I^2=63.5%, p=0.001). Heterogeneity was not related to study design, source of control population, adjustment for potential confounders, or geographical area. Van der Mark (2012) reported that differences in exposure assessment methods were the only study characteristic that explained some of this heterogeneity: the OR was of 1.5 (95% CI: 1.3, 1.8) for ever being exposed based on self-report, 1.7 (95% CI: 1.3, 2.3) for regular self-reported exposure questionnaire, and 2.5 (95% CI 1.5 to 4.1) for three studies based on job titles and whose results do not depend on self-report. Allen and Levy (2013) also found a large difference in the magnitude of association amongst the occupational studies, ranging from 0.60 to 6.00, due mainly to the method of exposure assessment. However, it is important to highlight that Gunnarsson and Bodin (2017) when assessing only studies fulfilling good scientific standards resulted in less heterogeneity, and also higher risk estimates.
Most studies used a summary indicator of exposure (ever/never self-report) that did not allow assessing dose–effect relations, and very few used detailed exposure assessment methods such as exposure questionnaires, job-exposure matrices or the involvement of industrial hygienists. In regards to self-reporting or questionnaires, it is important to note that given the advanced age of most PD patients, inaccurate memory recall or impairment of cognitive function is possible. Van Maele-Fabry et al. (2012) found that the strongest evidence of an increased risk came from studies that relied on PD diagnosis confirmed by a neurologist. Gunnarsson and Bodin (2017) used strict exposure criteria and found that the most desirable aspect was quantification of exposure by experts (occupational hygienists) blinded to the health status of the participants.

Study design

Owing to the relatively low frequency of PD, epidemiological data on the relationship between pesticide exposure and PD were most often reported through case–control studies. Neuro-epidemiologists often resort to case-control studies that are practical and, despite their retrospective nature, may have the advantage of more detailed exposure assessment. However, to investigate an etiologic relationship, the use of cohort studies is preferable. Prospective exposure assessments with temporal and cumulative exposure estimates are the most appropriate approach to investigate PD incidence consequent to occupational pesticide exposure.

Some meta-analyses showed differences in the ORs based on the type of study design utilized. Van der Mark (2012) reported an OR of 1.7 (95% CI: 1.4, 2.0) for 33 case–control studies versus 1.4, 95% CI: 0.9, 2.1) among four cohort studies. Though it should be noted that the small number of cohort studies available may have impacted this difference. Furthermore, as PD is a late-onset disease, the retrospective collection of detailed data over a long period of time for a highly complex exposure, such as pesticides, remains difficult. Interestingly, a stronger association between PD and pesticide exposure was suggested in the prospective cohort studies (mRR= 1.39; 95% CI 1.09–1.78; n = 6) than in the retrospective cohort studies (mRR= 1.18; 95% CI 0.71–1.95; n = 6) (Van Maele-Fabry et al., 2012).

3.5.4 What conclusions can be made?

- There is strong evidence in favour of a generic link between occupational exposure to pesticides and PD. The most recent, and scientifically reliable meta-analysis found that exposure to *any* pesticide involves a ≥50% increased risk for developing Parkinson's disease in occupationally exposed populations.
- There is strong evidence in favour of a link between occupational exposure to herbicides and insecticides and PD.
- More evidence is needed for occupational exposure to specific classes of pesticides and for active ingredients. However, there is strong evidence in favour of occupational exposure to organochlorines and PD; and moderate evidence in favour for occupational exposure to paraquat and rotenone and PD.

Presumption of a link between exposure to pesticides and Parkinson's disease

Exposure	Concerned populations affected by a significant excess of risk	Presumption of a link
Pesticides (without distinction)	Professionals	++
Herbicides	Professionals	++
Insecticides	Professionals	++

++ based on results of the meta-analyses

Family and active substances involved in the risk of Parkinson's disease

Exposure	Concerned populations affected by a significant excess of risk	Presumption of a link
Organochlorines	Professionals	++
Paraquat	Farmers	+
Rotenone	Farmers	+

++ based on the results of several cohort studies

+ based on cohort and two case-control studies

INSERM (2013) concluded that there was strong evidence in favour of a generic link between pesticides and PD, but that more detailed data was needed for pesticide classes. EFSA reached a similar conclusion for PD in their literature review and meta-analysis (Evangelia et al., 2013).

Conclusions and Recommendations

The aim of this investigation was to provide a comprehensive summary of existing epidemiological data on health effects related to occupational PPP use among agricultural workers. Overall, it was revealed that there is a significant lack of data on the situation in Switzerland for occupational PPP exposures and resulting health effects. For this reason, international studies were analysed and summarized to more concretely understand how to apply findings to the local setting towards more effective, evidence-based policy making.

Nevertheless, evidence from a plethora of international and European studies provide a foundation of knowledge that can be applied for future investigations. Extrapolations of results to Switzerland should be carefully done, especially when active substances are no longer authorized and the choice of active substances are different in a specific crop. However, in regards to exposures, this investigation found that there are at least five active substances currently authorized and used in Switzerland (i.e., the herbicides 2,4-D, MCPA, mecoprop, glyphosate, the insecticide chlorpyrifos, and the foliar fungicide mancozeb)that have a demonstrated moderate or strong association with chronic health effects.

Furthermore, results from international systematic reviews and prospective agricultural cohorts provide evidence of distinct disease prevalence patterns in agricultural workers occupationally exposed to PPPs. While agricultural workers may have a lower risk of tobacco- and alcohol-related cancers due to lifestyle factors, they have an increased risk for prostate, Non-Hodgkin lymphoma, and multiple myeloma.

Finally, there is strong evidence in favour of a generic link between occupational exposure to PPPs and Parkinson's Disease (PD). The most recent, and scientifically reliable meta-analysis found that exposure to *any* PPP involves a ≥50% increased risk for developing Parkinson's disease in occupationally exposed populations. There is strong evidence in favour of a link between occupational exposure to herbicides and insecticides and PD. More evidence is needed for occupational exposure to specific classes of PPPs and for active ingredients. However, there is strong evidence in favour of occupational exposure to organochlorines and PD; and moderate evidence in favour for occupational exposure to paraquat and rotenone and PD.

One of the key successes of this investigation was the ability to reduce the scope of the research question to more precise exposures (i.e., active substances), and to specific clinical health outpoints. These findings provide a focused starting point for future investigations in Switzerland. Appropriate recommendations should be considered to address this occupational health problem and are elaborated below.

Conclusion 1: General lack of data and evidence of PPP exposures and resulting health effects in Switzerland

Overall, it was determined that there is a general lack of data on the situation in Switzerland for occupational PPP exposures and resulting health effects. Due to increasing evidence of a potential link between PPP exposure and health effects from international literature, it is imperative that increased research is conducted on this topic in Switzerland. Increased research efforts would assist in evidence based policy making and would promote a safer and healthier agriculture workforce in Switzerland, as well as the population at large.

Recommendation 1: Promote the development/amelioration of a vigilance system through increased stakeholder collaboration

Epidemiological studies, the focus of this investigation, represent only one tool towards data collection and enhanced human risk assessment. Data from clinical case reports, poison control centres, and population level censuses and databases can contribute to data collection and monitoring in order to assess the potential PPP risks for agricultural populations and the general population. The ongoing collection, reporting and evaluation of adverse occupational health effects has the potential to improve the health and safety of PPP users by reducing the likelihood of the reoccurrence of adverse events, as well as to mitigate the consequences of such events (EFSA, 2017). The European Food Safety Authority (EFSA) defines this continuous process as *vigilance*, which is distinct from monitoring and surveillance, in that it implies a process of paying close and constant attention, specifically to post-marketing events related to the use of a PPP. The term *phytopharmacovigilance* is considered the most appropriate term for a vigilance system for PPP use, exposure and health effects in agriculture (EFSA, 2017). Phytopharmacovigilance data can be used to identify emerging PPP risks, estimate the magnitude of PPP related health effects, and evaluate the need for intervention and prevention efforts. While PPPs in Switzerland go through authorization procedures before they are marketed and include recommendations for worker protection measures (Swiss Federal Council, 2017), such protocols do not address all environmental conditions, PPP mixtures, chronic exposure patterns, and other parameters that can be encountered. As such, vigilance serves as a warning system of any effects not detected during the risk assessment process. Moreover, a well-documented vigilance system can establish a routine medical follow-up of people at risk, and document interventions and/or treatments administered as well as their efficacy. In turn, this information is critically important towards the design of preventive campaigns to improve the health of agricultural workers, to guide policy decisions, and to improve the quality of the public health system and its performance. Improving the health of agricultural workers through targeted prevention also makes economic sense by reducing the need for costly medical interventions often necessary for the treatment of chronic disease.

A central obstacle remains the lack of coordination between institutional stakeholders when it comes to data sharing and collaborative vigilance efforts. Indeed this barrier is not limited to Switzerland but rather represents a trend of sectoral specialization characteristic of modern governments, in which organizations are governed by their own priorities, agenda and operating mode (OECD, 2002). Such situations often lead to departmentalism and the production of stand-alone data that remain within a department's or organization's respective policy silos (Russel and Jordan, 2004). The incidence of health outcomes due to PPP exposures represents a highly complex condition for public health and occupational health vigilance. In fact, the US Centers for Disease Control and Prevention (CDC) recommends that vigilance programs for PPP-related illnesses require experts from a broad range of backgrounds, including toxicology, epidemiology, medicine, data management, occupational and environmental health, occupational hygiene, integrated pest management and health education (NIOSH, 2005). Occupational health issues, particularly those that involve chronic PPP exposure require a shift from traditional sectoral specialization to a collaborative government approach in order to be effectively addressed, and to ensure that evidence-based decisions are made in order to protect worker populations.

Conclusion 2: Active substances in use have a moderate or strong association with specific health effects.

This investigation revealed the top active substances that have a moderate or strong association with chronic health effects, including the herbicides 2,4-D, MCPA, mecoprop, glyphosate, the insecticide chlorpyrifos, and the foliar fungicide mancozeb (INSERM, 2013). All of these active substances had a presumed moderate or weak association with hematopoietic cancers. The foliar fungicide mancozeb had a presumed weak association with Parkinson's disease. Two active substances, the insecticide chlorpyrifos and the herbicide glyphosate, had a presumed moderate association with NHL. These six active substances are currently registered and used in Switzerland. Due to the complexity in accessing PPP use data in Switzerland, the first logical step would be to investigate the use of these six active substances to deduce potential exposure levels in different regions.

Recommendation 2: Conduct enhanced exposure assessments of selected active substances

Several knowledge gaps exist in regards to PPP exposure assessment among agricultural workers in Switzerland; however, existing modalities such as the PPP diaries can be easily ameliorated without developing a new and costly system. PPP diaries can be collected systemically and analyzed to better understand the level of various PPPs used in each region and crop type. This can be used to develop more accurate occupational risk models. Such data could allow a more comprehensive overview of occupational exposure to PPPs, a better understanding of what factors drive PPP exposures, and more targeted prevention models. Given that six specific active substances of concern have been identified by the INSERM report, a clear starting point now exists for follow up investigations. Limiting data collection for only these active substances will allow for a targeted research plan.

To overcome the current limitations of PPP diaries, the objective of the diaries should be enlarged to gather epidemiological exposure data. PPP diaries should also be digitalized and anonymized in order to ease the centralization of data, as well as to reduce the paperwork of farmers. Increased data on exposure indicators could provide the first steps towards a more accurate assessment of potential health effects at the population level. In particular, with regional information on PPP exposures from PPP diaries, new linkages could be made with local medical centers to better account for health effects potentially related to PPPs. Such strategies, which adopt geographical information systems (GIS) methodologies, could provide novel and specific data on PPP exposures and subsequent disease – not only for human health but also for environmental issues

Conclusion 3: There are distinct disease prevalence patterns in agricultural workers occupationally exposed to PPPs.

Although the *general* health status of agricultural workers appears to be better than comparison populations, their *occupational* health appears to be one of the worst among all occupations. Even if agricultural workers may have generally lower mortality rates than the general population, they also demonstrate a distinct pattern of specific disease prevalence, a pattern that has been widely associated with exposures to PPPs. Evidence from the literature demonstrates the distinct trends among agricultural workers, including increased risk of neurodegenerative effects, Parkinson's Disease, and specific cancers including prostate cancer, NHL, and multiple myeloma.

Recommendation 3: Develop epidemiological research studies on PPP-related health effects

One way to increase knowledge on PPP exposure and related health effects is to conduct targeted surveys on a specific exposure and to investigate the general health status and specific health problems among agricultural workers. A central barrier previously encountered was the large range of potential health effects that would have to be investigated to better understand association with PPP use and exposure. The results of this investigation provide a starting point for disease endpoints of interest.

Data from the Swiss Health Survey and the Swiss Labour Force Survey could be linked to better assess health at the population level by occupational activity and job tasks. In addition, data from the Swiss General Population Census could be used to construct the first-ever Swiss cohort of agricultural workers. Setting up such a prospective cohort would enable occupational epidemiologists to conduct cause-specific morbidity and mortality studies and to launch nested case-control studies on specific diseases identified in this investigation. With further improvement of data linkages, it should also be possible to investigate specific sub-populations of this cohort, such as the spouses and children of workers. Linkage of this cohort with data from cancer registries would provide an additional valuable parameter for epidemiological cancer research. As shown in stage 4 of this investigation, agricultural cohorts have existed for decades in several countries and have provided significant evidence of epidemiological trends among agricultural populations.

Conclusion 4: Evidence of link between occupational exposure to PPPs and PD

Results showed strong evidence in favour of a generic link between occupational exposure to PPPs and Parkinson's Disease (PD). The most recent, and scientifically reliable meta-analysis found that exposure to *any* PPP involves a ≥50% increased risk for developing Parkinson's disease in occupationally exposed populations. In addition, there is strong evidence in favour of a link between occupational exposure to herbicides and insecticides and PD. More evidence is needed for occupational exposure to specific classes of PPPs and for active ingredients. However, there is strong evidence in favour of occupational exposure to organochlorines and PD; and moderate evidence in favour for occupational exposure to paraquat and rotenone and PD.

Recommendation 4: Develop targeted investigations assessing exposure to PPPs and PD among agricultural workers in Switzerland.

Results from this investigation show strong evidence of a link between occupational PPP exposure and PD. Currently, a lack of data exists on the prevalence of PD among agricultural workers in Switzerland. However, it is known that the disease affects more than 5% to 10% of the adult population in Switzerland (Association PD, 2016). By focusing specifically on PD, data could be extracted from the Swiss Health Survey and linked with the Swiss Labor Force Survey better assess PD incidence at the population level by occupational activity and job tasks. In addition, research investigations could be conducted in collaboration with Parkinson's Disease associations (i.e., Parkinson Suisse - Parkinson Schweiz) to better understand occupational profiles of affected individuals.

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Annex 1
Search String Sampling Methodology developed for Stage 2

The following search strings have been tested based on examples from the literature and consultations IST librarian, A. Sager. Search string is provided and results are highlighted in blue. The search string highlighted in yellow has yielded the most promising results (as a percentage of relevant articles out of total results).

1.1 Specific for agricultural workers' disease (Mattioli)

Adapted from: Mattioli, S., Gori, D., Di Gregori, V., Ricotta, L., Baldasseroni, A., Farioli, A., Zanardi, F., Galletti, S., Colosio, C., Curti, S. and Violante, F. S. (2013), PubMed search strings for the study of agricultural workers' diseases. Am. J. Ind. Med., 56: 1473–1481. doi:10.1002/ajim.22252

(agricultural workers' diseases [MH] OR agricultural exposure* OR "agricultural health" OR "agricultural medicine" OR agricultural work* OR (farm NOT farm[AD]) OR farm work* OR farming OR forestry work* OR tractor*) OR ((agriculture [MH] OR agricult*) OR (farmer* NOT farmer* [AU]) OR fungicid* OR herbicid* OR insecticid* OR ((pesticide* OR pesticides [MH]) NOT pesticides[pharmacological action]) AND (occupational diseases [MH] OR occupational exposure [MH] OR occupational medicine [MH] OR occupational risk [TW] OR occupational hazard [TW] OR (industry [MH] AND mortality [SH]) OR occupational group* [TW] OR work-related OR occupational air pollutants [MH] OR working environment [TW])) NOT (animals [MH] NOT humans [MH])

Number of results: 155,864

1.2 Specific for occupational illness (Mattioli) AND pesticides

Adapted from: Mattioli S, Zanardi F, Baldasseroni A, et al Search strings for the study of putative occupational determinants of disease. Occupational and Environmental Medicine 2010;67:436-443.

(occupational diseases [MH] OR occupational exposure [MH] OR occupational medicine [MH] OR occupational risk [TW] OR occupational hazard [TW] OR (industry [MeSH Terms] mortality [SH]) OR occupational group* [TW] OR work-related OR occupational air pollutants [MH] OR working environment [TW]) AND fungicid* OR herbicid* OR insecticid* OR ((pesticide* OR pesticides [MH])

Number of results: 137,505

2. Examples of experimented search strings by HG

2.1 Most specific

("pesticides"[Pharmacological Action] OR "pesticides"[MeSH Terms] OR "pesticides"[All Fields] OR "pesticide"[All Fields]) OR fungicid* OR herbicid* OR insecticid* AND occupational[TW] AND worker[TW]

Number of results: 344 results

2.2 More sensitive (broader search)
("pesticides"[Pharmacological Action] OR "pesticides"[MeSH Terms] OR "pesticides"[All Fields] OR "pesticide"[All Fields]) OR fungicid* OR herbicid* OR insecticid* AND (agricultural workers' diseases [MH] OR agricultural exposure* OR "agricultural health" OR "agricultural medicine" OR agricultural work* OR vineyard*) AND (occupational diseases [MH] OR occupational exposure [MH] OR occupational medicine [MH] OR occupational risk [TW] OR occupational hazard [TW] OR (industry [MH] AND mortality [SH]) OR occupational group* [TW] OR work-related OR working environment [TW])
Number of results: 1,815*

2.2.1*This search string can be made more precise by adding specific health endpoints, if so desired, for example:
("pesticides"[Pharmacological Action] OR "pesticides"[MeSH Terms] OR "pesticides"[All Fields] OR "pesticide"[All Fields]) OR fungicid* OR herbicid* OR insecticid* AND (agricultural workers' diseases [MH] OR agricultural exposure* OR "agricultural health" OR "agricultural medicine" OR agricultural work* OR vineyard*) AND (occupational diseases [MH] OR occupational exposure [MH] OR occupational medicine [MH] OR occupational risk [TW] OR occupational hazard [TW] OR (industry [MH] AND mortality [SH]) OR occupational group* [TW] OR work-related OR working environment [TW]) AND cancer
Number of results: 349

2.3 Most sensitive (broader search)
("pesticides"[Pharmacological Action] OR "pesticides"[MeSH Terms] OR "pesticides"[All Fields] OR "pesticide"[All Fields]) OR fungicid* OR herbicid* OR insecticid* AND occupation [TW] OR worker [TW] OR occupational diseases [MH] OR occupational exposure [MH] OR occupational medicine [MH] OR occupational risk [TW] OR occupational hazard [TW] OR (industry [MeSH Terms] mortality [SH]) OR occupational group* [TW] OR work-related OR working environment [TW])
Number of results: 211,734

Annex 2
Search String Sampling Methodology developed for Stage 2

Part a. Variable description for study classification

Category	Variable	Description
Bibliographic	Study No.	First three letters of health endpoint and study number in order of entry. E.g., CAN_1; RES_3
	Author	First author's last name
	Year	Year of publication
	Country	Country where the study was conducted
	Cohort	The name of the epidemiological study
	Study type	The epidemiological study design: cohort, nested case-control, case-control, cross-sectional
Exposure determinants	Job title	Title of occupation of subjects
	Job tasks	Tasks that workers participated in
	Crop or agricultural subsector	Crop or agricultural subsector workers engaged in
	Exposure assessment	Means of measuring pesticide exposure: direct exposure questionnaire (interview or self-administered); measurement of biomarker in biological fluids; residential history; occupational history; Job Exposure Matrix (JEM)
	Exposure route	Type of exposure, if specified: dermal, inhalation.
Active substance	No. of active substances	Number of active substances assessed or implied in health effects

Category	Variable	Description
	Active substance(s)	Pesticide assessed in the study as defined/named in the study
	PPP group	Group of PPPs: herbicide, insecticide, fungicide
	PPP class	Chemical or functional pesticide category in which the pesticide is classified
	Approved in CH	Whether the active substance is approved for use in Switzerland, determined by OFAG PPP index
	Link to OFAG index	Link to the active substance OFAG index page (if approved only, as non approved substance do not have a page)
Health endpoint	Health endpoint (type)	Type of health endpoint: cancer, respiratory, etc.
	Health endpoint (specific)	Specific health endpoint assessed in the study: prostate cancer, asthma, etc.
	Diagnosis	How health endpoint was ascertained: cancer registry, self-reported, etc.
Association	Statistical methods	Statistical method used to calculate the effect estimate
	Association	Association found between "Active substance" and "heath endpoint (Specific)": Yes/No. With comments provided as necessary.
	Description of association	Details of association as relevant for interpretation
	Full result	Results in detail of the association
	Conclusion	Summarizing remarks based on results of the study
	Web link to the study	Retrievable web link

Part b. Database created to classify studies related to occupational PPP exposures and health effects

1	Study No.	Author	Year	Title	Country	Cohort	Study type	Recruitmen	Follow-up pe	Occupation	Job ta	Crop/agricul	Age	Gender	Exposure assessment
2	CAN_1	Silver et al	2015	Cancer incidence and metolachlor use in	USA	Agricultural Health Study (AH	Prospective cohc	1993-1997	2011	Pesticide applicators		NS		male (97%)	take-home survey, and updated use inforr
3	CAN_2	Jones et al	2015	Incidence of solid tumours among pestici	USA	Agricultural Health Study (AH	Prospective cohc	1993-1997	2011	Pesticide applicators		NS		Male (100%)	take-home survey, and updated use inforr
4	CAN_3	Koutros et al	2016	Occupational exposure to pesticides and	USA	Agricultural Health Study (AH	Prospective cohc	1993-1997	2012	Pesticide applicators		NS		Male (100%)	Information on use of individual pesticides
5	"	Koutros et al	"	Occupational exposure to pesticides and	"	"	"			"	"	"	"	"	"
6	CAN_4	Koutros et al	2009	Heterocyclic aromatic amine pesticide us	USA	Agricultural Health Study (AH	Prospective cohc	1993-1997	2004	Pesticide applicators		NS		Male (96%)	information from a self-administered quest
7	CAN_5	Lerro et al	2015	Use of acetochlor and cancer incidence ir	USA	Agricultural Health Study (AH	Prospective cohc	1993-1997	2005	Pesticide applicators		NS		Male (100%)	Computer-assisted telephone interviews a
8	RES_1	Henneberger et	2003	Exacerbation of symptoms in agricultural	USA	Agricultural Health Study (AH	Prospective cohc	1993-1997	2005	Pesticide applicators		NS	16 to 83	Male (96%)	information from a self-administered quest
9	"	Henneberger et	"	Exacerbation of symptoms in agricultural	"	"	"			"	"	"	"	"	"
10	RES_2	Hoppin et al	2008	Pesticides and Atopic and Nonatopic Asth	USA	Agricultural Health Study (AH	Prospective cohc	1993-1997	2005	Pesticide applicators		NS	20 to 88	Female (100%)	self-administered questionnaire (81%) or a
11		Hoppin et al	2008	Pesticides and Atopic and Nonatopic Asth	"	"	"	"	"	"	"	"	"	"	"
12		Hoppin et al	2008	Pesticides and Atopic and Nonatopic Asth	"	"	"	"	"	"	"	"	"	"	
13		Hoppin et al	2008	Pesticides and Atopic and Nonatopic Asth	"	"	"	"	"	"	"	"	"	"	
14		Hoppin et al	2008	Pesticides and Atopic and Nonatopic Asth	"	"	"	"	"	"	"	"	"	"	
15		Hoppin et al	2008	Pesticides and Atopic and Nonatopic Asth	"	"	"	"	"	"	"	"	"	"	
16		Hoppin et al	2008	Pesticides and Atopic and Nonatopic Asth	"	"	"	"	"	"	"	"	"	"	
17		Hoppin et al	2008	Pesticides and Atopic and Nonatopic Asth	"	"	"	"	"	"	"	"	"	"	
18		Hoppin et al	2008	Pesticides and Atopic and Nonatopic Asth	"	"	"	"	"	"	"	"	"	"	
19		Hoppin et al	2008	Pesticides and Atopic and Nonatopic Asth	"	"	"	"	"	"	"	"	"	"	
20	NEU_1			Comparison of neurological health outcomes between two adolescent cohorts											