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Plan **F**édéral de **R**éduction des **P**roduits phytopharmaceutiques

Federaal **R**eductie**P**lan voor **G**ewasbeschermingsmiddelen

Monitoring of the chronic health effects from the use of Plant Protection Products (PPP)

2020

Are there other epidemiology studies ongoing or published, and more scientific papers indicating long-term effects, diseases and cancers in the agricultural community?

Study carried out as part of the Federal Plan for the Reduction of Plant protection products during the 2018-2022 programme.

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Abstract

The Federal Public Service Health, Food Chain Safety and Environment (FPS) monitors on a regular basis newly published peer-reviewed scientific papers worldwide on potential overincidences of long-term effects, associated with plant protection products.

In the current project, it was decided to mainly rely on the outcome of studies from the French AGRIculture and CANcer (AGRICAN) cohort. The reason to rely mainly on the AGRICAN study is that, it may be reasonably presumed that the French agricultural practices are not meaningfully different from the Belgian ones. This study included about 180.000 active or retired farmers, or employees between 2005 and 2007 in 12 metropolitan departments with cancer registries. It provides for a prospective follow-up of affiliates for at least 10 years to analyse the exposures by questionnaires and cross them with health data (cancer, Parkinson disease (PD), chronic obstructive pulmonary disease, asthma,…). It aims to analyse primarily the incidence of cancers and mortality due to cancers linked to agricultural activities, although other long-term findings may also be studied. The study was not launched to examine specifically the effects of the exposure to plant protection products (PPPs) alone, although the latter is of course an important part of it.

A first conclusion of the AGRICAN study, supported by other cohort studies, is that the long-term outcome of life-long exposure to animals, crops and pesticides may be quite diverse. On the basis of cancer incidences in general, or mortalities subsequent to cancer incidences, figures in the agricultural community are not spectacularly worse than those in the general population. On the contrary, there is even a slight but consistently lower overmortality overall, and also the overall cancer incidence may even be indistinguishable from (AGRICAN), or about 10-15% lower (other cohors) than, that of the general population. Incidence ratios in the agricultural workers and PPP applicators may display overincidences of a limited number of tumours, among which lymphopoietic cancers (including multiple myeloma (MM)) and prostate cancer seem to be the most recurring ones. In addition, the weight of evidence also indicates a slight but rather consistent association between exposure to PPP's and PD.

The conclusions of this analysis were based essentially on data in epidemiological prospective cohorts, which are considered superior to case-control studies, which may suffer recall bias, although case-control studies may be more sensitive to identify rare tumours. However, meta-analysis, regrouping all these studies also indicate the same trend, and are re-enforcing confidence in the obtained picture.

In the absence of plausible modes/mechanisms of actions, the likelihood of causality between PPPs and long-term effects remains uncertain, from the risk-assessment point of view. The need for more fundamental research is warranted regarding for instance DNA damage, oxidative stress, metabolic outcomes and endocrine (*e.g.* thyroid) effects.

Especially for the assessment of PD, a break-through to newer approaches focusing on presumed mechanisms of action, possibly coupled (but not restricted) to guideline toxicity studies with repeated administration, seems primordial in this respect.

Following the consultation and reporting of the published peer-reviewed scientific papers worldwide on potential overincidences of long-term effects, associated with plant protection products, following perspectives are proposed by the FPS.

At the bottom line, there are at least 6 main points of focus to evaluate long-term effects of PPPs in the human population, or to mitigate as much as possible PPP exposures in real life:

(i) Focusing on both regulatory long-term guideline studies and published open literature studies, including *in-vitro* alternatives.
Existing evaluations should thus as much as possible be completed by the search of new modes of action, to elucidate possible lacks in current knowledge of endpoints which would remain undiscovered until now.

(ii) Ensuring a maximal follow-up of (mainly prospective) epidemiological studies, associated with techniques to assess to the best extent possible real exposure levels, for instance by using biomonitoring tools. The more efficient exploitation of crop-exposure matrices, in combination with until now underused purchase/use information of professional PPPs offers an additional tool to obtain a better view on real exposure levels in and around-theagricultural entities.

(iii) In Belgium (but also in other EU member states with intensive agriculture), there is an urgent need to evaluate the potential risk of short- or long-term exposure to PPP for instance in regions known to be affected by high PPP exposure like fruit orchards and ornamental plant production, etc. which are sectors well known for their involvement of high levels or substantial diversity of PPP. This is true for farmers and applicators, but more so for residents, for which there are still many data gaps regarding their exposure to PPP's.

(iv) Further resources should be allocated to develop reliable and robust registries of longterm/severe effects. In Belgium (like in other EU countries) cancer registries are installed since about a decade. However, also a proper repository of developmental defects, covering the whole country, is blatantly absent in Belgium. There is an urgent need to put in place a Belgian network, collecting data on a large scale, and supporting in this way the EU database on fertility effects and developmental anomalies (see objectives of EUROCAT).

(v) The establishment of an association between exposure and adverse health outcomes depends heavily on an accurate estimation of exposure, in the absence of which the effect is flattened out. The legal possibility and effective need to impose an on-line registration of actual use of PPP's, the possibility to have law enforcement to monitor and control these inputs, and the potential value crossing these data to location and consequently health data (registries of cancer, developmental anomalies,...) using GIS, makes this approach a very powerful tool in order to explore post-marketing monitoring of long-term threats of PPPs of both professional groups and the general population.

(vi) Finally, exploring ways to avoid as much as possible exposure to PPPs during 'real-life' application, in order to protect operators, workers, bystanders and residents. Possible regulatory actions include the installation of default buffer zones for field application (2m) or high-crop (orchard) application (5m), below which no reliable exposure assessment is possible because of lacking exposure data. In addition to rapidly evolving engineering controls like spot-application (*e.g.* via drone-application), there is an urgent need to install default, clear and easily enforceable buffer zones vis-à-vis residents living in the neighbourhood of agricultural premises, and especially in order to protect vulnerable people (children, aged people, pregnant women, etc…).

It is left to the discretion of risk managers and policy-makers to determine the level of concern and concomitant measures to decide on socio-economic measures in this respect.

Aperçu

Le Service Public Fédéral Santé Publique, Sécurité de la Chaîne Alimentaire et Environnement passe régulièrement en revue les nouvelles publications de la littérature scientifique (validées par des pairs) mondiale portant sur l'apparition d'effets à long terme associés aux PPPs.
Pour le présent projet, il a été décidé de se baser essentiellement sur le résultat d'études menées sur la cohorte française AGRIculture & CANcer (AGRICAN). L'étude AGRICAN a été choisie car on peut raisonnablement supposer que les pratiques agricoles françaises ne sont pas fondamentalement différentes des pratiques belges. Environ 180 000 agriculteurs en activité ou retraités, exploitants ou salariés ont été inclus dans cette étude entre 2005 et 2017. Ils proviennent de 12 départements métropolitains disposant d'un registre de cancers. L'étude prévoit, pendant 10 ans au moins, un suivi prospectif des affiliés à l'aide de questionnaires dont les réponses sont croisées avec des données de santé (cancers, maladie de Parkinson, broncho-pneumopathie chronique obstructive, asthme...) afin d'analyser l'exposition aux PPPSs. L'étude vise avant tout à évaluer **l'incidence des cancers et de la mortalité due aux cancers liés aux activités agricoles**, mais d'autres observations à long terme sont aussi effectuées. L'évaluation des effets de l'exposition aux PPPs constitue bien entendu une partie importante de cette étude bien qu'elle n'ait pas été spécifiquement lancée dans ce but.

Une première conclusion de l'étude AGRICAN, corroborée par d'autres études de cohorte, est qu'être en contact pendant toute une vie avec des animaux, des cultures et des pesticides peut avoir des effets à long terme plutôt divers. Les chiffres relatifs à l'incidence du cancer en général ou à la mortalité due à ces cancers montrent que les résultats dans la communauté agricole ne sont pas notablement plus mauvais que ceux dans la population générale. Au contraire, dans l'ensemble on constate même que la surmortalité est plus faible, légèrement certes mais systématiquement. Par ailleurs, l'incidence générale des cancers est similaire à celle dans la population générale (AGRICAN), voire 10 à 15 % inférieure (autres cohortes). Les taux d'incidence chez les ouvriers agricoles et les opérateurs de PPPs peuvent être plus élevés pour un nombre limité de tumeurs, les plus fréquentes semblant être les **lymphomes** (y compris **le myélome multiple**) et **le cancer de la prostate**. En outre, le poids des preuves indique également une association mince mais plutôt systématique entre l'exposition aux PPPs et la **maladie de Parkinson (MP).**
Les conclusions de cette analyse étaient essentiellement basées sur des données provenant d'études de cohortes prospectives considérées supérieures aux études cas-témoins. En effet, même si ces dernières peuvent être plus sensibles quand il s'agit d'identifier des tumeurs rares, elles peuvent présenter un biais de souvenir. Néanmoins une méta-analyse regroupant toutes ces études révèle la même tendance, ce qui renforce la confiance dans l'image obtenue.

En l'absence de modes/mécanismes d'action plausibles, la probabilité d'un lien de causalité entre les PPPs et les effets à long terme demeure incertaine du point de vue de la gestion des risques. Le besoin de recherche plus fondamentale se justifie, par exemple pour les dommages à l'ADN, le stress oxydatif, les perturbations métaboliques, les effets sur les glandes endocrines

(par ex. la thyroïde).
Pour l'évaluation de la MP en particulier, il semble primordial d'avancer en recourant à des approches plus récentes qui se concentrent sur les modes d'action présumés en les combinant éventuellement - mais pas uniquement - à des études sur la toxicité de l'administration répétée de ces produits, imposées dans les lignes directrices.

Après avoir consulté des articles scientifiques avec relecture par les pairs publiés dans le monde sur la surincidence éventuelle d'effets à long terme de l'utilisation de produits phytopharmaceutiques, le SPF propose les perspectives suivantes.

Fondamentalement, pour évaluer les effets à long terme des PPPs sur la population humaine ou pour réduire autant que possible l'exposition aux PPPs *in vivo*, il faut se concentrer sur au moins 6 points principaux :

(i) Mettre l'accent tant sur les **études à long terme résultant de la science réglementaire imposées dans des lignes directrices** que sur les études publiées dans la littérature en accès libre, y compris les alternatives *in vitro*.
Les évaluations devraient donc être complétées le plus possible par l'exploration de nouveaux modes d'action afin de remédier à d'éventuelles lacunes dans les connaissances actuelles de biomarqueurs encore inconnus à ce jour.

(ii) Assurer un suivi maximal des études **épidémiologiques** (surtout prospectives), associées à des techniques pour évaluer au mieux les taux d'exposition réels, en utilisant des outils de biosurveillance par exemple. L'exploitation plus efficace des matrices cultures-expositions combinées aux données sur l'achat/l'utilisation de PPPs professionnels - données actuellement sous-utilisées - constitue un outil supplémentaire pour se forger une meilleure idée des taux d'exposition réels dans les exploitations agricoles et leurs alentours.

(iii) En Belgique (mais aussi dans d'autres États membres de l'UE pratiquant l'agriculture intensive), il faut évaluer d'urgence les risques potentiels liés à l'exposition à court ou à long terme à des PPPs, par exemple dans les zones connues pour leur exposition élevée aux PPPs comme les cultures fruitières et les cultures de plantes ornementales *etc.*, qui sont des secteurs réputés pour leur recours à des niveaux élevés ou à une grande diversité de PPPs. Ceci vaut pour les agriculteurs et les opérateurs mais plus encore pour les habitants alors que pour ces derniers, il manque encore de nombreuses données sur leur exposition aux PPPS.

(iv) Des moyens supplémentaires devraient être consacrés à la conception de **registres** fiables et solides sur les effets graves/à long terme. En Belgique (tout comme dans d'autres pays de l'UE), les registres du cancer existent depuis une décennie. Néanmoins, en Belgique, le manque de registres fiables des anomalies dévelopementales couvrant l'ensemble du territoire est flagrant. Il est dès lors urgent de constituer un **réseau belge** de collecte de données à grande échelle qui alimenterait la base de données de l'UE sur les troubles de la fertilité et les anomalies dévelopementales (voir les objectifs d'EUROCAT).

(v) L'établissement d'un lien de causalité entre l'exposition aux PPPs et les effets néfastes sur la santé dépend fortement **de la possibilité d'évaluer correctement l'exposition aux PPPs.** En l'absence de telles données, l'effet est lissé. Le besoin effectif d'imposer par une loi un **enregistrement en ligne** de l'utilisation réelle des PPPs, la possibilité juridique de le faire et de prévoir un contrôle officiel de la saisie de ces données, ainsi que la valeur potentielle du croisement de ces données avec celles sur la localisation et subséquemment avec des données sanitaires (registres du cancer, anomalies dévelopementales...) à l'aide d'un système d'information géographique (SIG) font de cette approche un outil très efficace pour étudier la surveillance post marché des menaces à long terme que les PPPs font peser tant sur les catégories professionnelles que sur la population générale.

(vi) Enfin, examiner les manières **d'éviter autant que possible l'exposition** aux PPPs lors de l'application en conditions réelles afin de protéger les opérateurs, les ouvriers, les passants et les résidents. Les mesures réglementaires possibles comprennent l'instauration systématique de zones tampons pour l'épandage en champ (2 m) ou sur arbres à hautes tiges (vergers - 5 m), en-deçà desquelles aucune évaluation fiable de l'exposition n'est possible faute de données d'exposition. En plus de recourir à l'ingénierie de contrôle qui évolue rapidement comme l'épandage ciblé (à l'aide de drones par exemple), il faut d'urgence créer systématiquement des zones tampons bien définies et faciles à faire respecter pour protéger les riverains des parcelles agricoles, en particulier les personnes vulnérables (enfants, personnes âgées, femmes enceintes...).

Il revient aux gestionnaires de risques et aux décideurs politiques de déterminer dans quelle mesure tout ceci est préoccupant et de prendre des mesures socio-économiques en la matière.

Overzicht

De Federale Overheidsdienst (FOD) Volksgezondheid, Veiligheid van de Voedselketen en Leefmilieu volgt op regelmatige basis wereldwijd nieuw gepubliceerde, peer-reviewed wetenschappelijke papers over mogelijke overincidenties van langetermijneffecten in verband met gewasbeschermingsmiddelen (GBMs).

In het huidige project is besloten hoofdzakelijk uit te gaan van de resultaten van studies van het Franse "AGRIculture et CANcer (AGRICAN)"-cohort. De reden om zich hoofdzakelijk op de AGRICAN-studie te baseren, is dat redelijkerwijs mag worden aangenomen dat de Franse landbouwpraktijken niet wezenlijk verschillen van de Belgische. Deze studie omvatte ongeveer 180.000 actieve of gepensioneerde landbouwers, of werknemers tussen 2005 en 2007 in 12 grootstedelijke departementen die kankerregisters bijhouden. De studie voorziet in een prospectieve follow-up van de deelnemers gedurende ten minste 10 jaar om de blootstellingen aan de hand van vragenlijsten te analyseren en deze te kruisen met gezondheidsgegevens (kanker, ziekte van Parkinson, chronische obstructieve longziekte, astma, ...). Het is de bedoeling om in de eerste plaats de **kankerincidentie en de mortaliteit als gevolg van kanker in verband met landbouwactiviteiten** te analyseren, hoewel ook andere bevindingen op lange termijn kunnen worden bestudeerd. De studie werd niet opgezet om specifiek de effecten van de blootstelling aan GBMs alleen te onderzoeken, hoewel dit laatste natuurlijk een belangrijk onderdeel ervan is.

Een eerste conclusie van de AGRICAN-studie, die door andere cohortstudies wordt gesteund, is dat de langetermijneffecten van een levenslange blootstelling aan dieren, gewassen en pesticiden nogal uiteenlopend kunnen zijn. Uitgaande van het aantal kankergevallen in het algemeen of van het aantal sterfgevallen ten gevolge van kanker, zijn de cijfers in de landbouwgemeenschap niet spectaculair slechter dan die in de algemene bevolking. Integendeel, over het geheel genomen is de oversterfte zelfs iets geringer en constant lager. Ook de totale kankerincidentie is mogelijk zelfs niet te onderscheiden van (AGRICAN), of ongeveer 10-15 % lager dan (overige cohortes), die van de algemene bevolking. De incidentieverhoudingen bij werknemers in de landbouw en bij toepassers van GBMs, kunnen een overincidentie van een beperkt aantal tumoren vertonen, waarbij **lymfopoiëtische aandoeningen** (met inbegrip van **multipel myeloom**) en **prostaatkanker** het meest lijken voor te komen. Daarnaast wijst het beschikbare bewijsmateriaal ook op een gering maar vrij consistent verband tussen blootstelling aan GBMs en de **ziekte van Parkinson.**

De conclusies van deze analyse waren hoofdzakelijk gebaseerd op gegevens in epidemiologische prospectieve cohorten, die superieur worden geacht aan patiënt-controleonderzoeken, die beïnvloed kunnen worden door herinneringsbias, hoewel patiënt-controleonderzoeken gevoeliger kunnen zijn voor het identificeren van zeldzame tumoren. Meta-analyses die al deze onderzoeken bundelen, wijzen echter op dezelfde trend en versterken het vertrouwen in het verkregen beeld.

Vanuit het oogpunt van de risicobeoordeling, blijft de waarschijnlijkheid van een causaliteit tussen GBMs en langetermijneffecten bij gebrek aan plausibele werkingswijzen/-mechanismen onzeker. Er is behoefte aan meer fundamenteel onderzoek naar bijvoorbeeld DNA-beschadiging, oxidatieve stress, stofwisselingseffecten en endocriene (*bv.* schildklier) stoornissen.

Vooral voor de beoordeling van de ziekte van Parkinson lijkt een doorbraak naar nieuwere benaderingen, gericht op veronderstelde werkingsmechanismen, eventueel gekoppeld aan (maar niet beperkt tot) richtlijnstudies naar toxiciteit met herhaalde toediening, in dit opzicht primordiaal.

Na raadpleging en rapportering van de wereldwijd gepubliceerde peer-reviewed wetenschappelijke papers over mogelijke overincidenties van langetermijneffecten in verband met GBMs, worden de volgende perspectieven voorgesteld door de FOD.

Uiteindelijk zijn er minstens zes belangrijke aandachtspunten om de langetermijneffecten van GBMs op de menselijke bevolking te evalueren, of om de werkelijke blootstelling aan GBMs zoveel mogelijk te beperken:

(i) Focussen op **regelgevende langetermijn** richtlijnstudies en gepubliceerde literatuurstudies, met inbegrip van *in vitro* alternatieven.

Bestaande evaluaties moeten dus zoveel mogelijk worden aangevuld met het zoeken naar nieuwe werkingsmechanismen, om mogelijke lacunes in de huidige kennis van eindpunten op te helderen die tot nu toe onontdekt zouden zijn gebleven.

(ii) Zorgen voor een maximale opvolging van (hoofdzakelijk prospectieve) **epidemiologische** onderzoeken, in combinatie met technieken om de reële blootstellingsniveaus zo goed mogelijk te beoordelen, bijvoorbeeld door gebruik te maken van biomonitoringinstrumenten. De efficiëntere benutting van gewassen-blootstellingsmatrices, in combinatie met de tot dusver onderbenutte aankoop-/gebruiksinformatie van professionele GBMs, biedt een extra instrument om een beter beeld te krijgen van de reële blootstellingsniveaus in en rond de landbouwentiteiten.

(iii) In België (maar ook in andere EU-lidstaten met intensieve landbouw) is er dringend behoefte aan een evaluatie van het potentiële risico van kortstondige of langdurige blootstelling aan GBMs, bijvoorbeeld in regio's waarvan bekend is dat er een hoge blootstelling aan GBMs is, zoals fruitboomgaarden, sierteelt, enz. - sectoren waarvan bekend is dat er grote hoeveelheden of een grote verscheidenheid aan GBMs in voorkomen. Dit geldt voor landbouwers en toepassers, maar meer nog voor omwonenden, voor wie er nog veel gegevens over hun blootstelling aan GBMs ontbreken.

(iv) Er zouden meer middelen moeten worden uitgetrokken om betrouwbare en degelijke **registers** van langdurige/ernstige effecten te ontwikkelen. In België (net als in andere EU-landen) worden sinds ongeveer een decennium kankerregisters bijgehouden. Maar een behoorlijk register van ontwikkelingsstoornissen, dat het hele land bestrijkt, ontbreekt in België op flagrante wijze. Er is dringend behoefte aan de oprichting van een **Belgisch netwerk** dat op grote schaal gegevens verzamelt en op die manier de EU-databank inzake vruchtbaarheidseffecten en ontwikkelingsanomalieën ondersteunt (zie doelstellingen van EUROCAT).

(v) De vaststelling van een verband tussen blootstelling en gezondheidsproblemen is sterk afhankelijk van een **nauwkeurige schatting van de blootstelling**, bij gebreke waarvan het effect wordt afgevlakt. De wettelijke mogelijkheid en de daadwerkelijke noodzaak om een **online registratie** van het werkelijk gebruik van GBMs op te leggen, de mogelijkheid tot rechtshandhaving om deze input te monitoren en te controleren, en de potentiële waarde van het kruisen van deze gegevens met locatiegegevens en bijgevolg gezondheidsgegevens (register voor kanker, ontwikkelingsanomalieën, ...) via GIS, maken van deze aanpak een zeer krachtig instrument om na te gaan hoe de langetermijnrisico's van GBMs voor zowel beroepsgroepen als de bevolking in het algemeen na het in de handel brengen worden gemonitord.

(vii) Tot slot, zoeken naar manieren om **blootstelling** aan GBMs bij toepassing in het dagelijkse leven zoveel mogelijk te vermijden, teneinde toepassers, werknemers, omstanders en omwonenden te beschermen. Mogelijke regelgevende maatregelen zijn onder meer de aanleg van standaardbufferzones voor veld- (2 m) en boomgaardtoepassingen (5 m). Daaronder is wegens het ontbreken van blootstellingsgegevens geen betrouwbare beoordeling van de blootstelling mogelijk. Naast snel evoluerende technische maatregelen zoals doelgericht toepassen/spot application (*bv.* met behulp van drones) is er dringend behoefte aan de aanleg van duidelijke en gemakkelijk te handhaven standaardbufferzones ten opzichte van omwonenden van landbouwbedrijven, met name ter bescherming van kwetsbare personen (kinderen, bejaarden, zwangere vrouwen, enz.).

Het wordt aan de risicobeheerders en de beleidsmakers overgelaten om de mate van bezorgdheid en de daarmee samenhangende maatregelen vast te stellen teneinde in dit verband sociaal-economische maatregelen te nemen.

Executive summary

The issue of epidemiology of cancer and other severe effects has been studied and is still studied at length. It is not felt that a Federal Public Service Health, Food Chain Safety and Environment (FPS)-initiated monitoring study can add meaningful new information to the campaigns which are actually run.
Instead, critical and objective appraisal of the new scientific literature by the federal authorities is a much more realistic and achievable goal in the perspective of policy-supporting measures.
It was decided to mainly rely on the outcome of studies from the French AGRICAN cohort (in the meanwhile part of an international consortium including 21 other cohorts spread across 9 countries (see http://agricoh.iarc.fr/)).
Therefore, the FPS monitors on a regular basis the newly published peer-reviewed scientific papers worldwide on potential overincidences of long-term effects, associated with plant protection products.

In several systematic reviews including the EFSA report (2013) and the former INSERM report (2013) indications of positive associations were observed for the whole class of pesticides, via different routes of exposure, and several health outcomes. The EFSA study was not restricted to hard clinical findings like cancer, neurodegenerative or developmental diseases, but also other outcomes, including exposure endpoints (biomonitoring), for the period 2006-2012. Two conditions were cited, namely childhood cancer and neurological disorders, like Parkinsonism. Triggered by this and other reviews, EFSA published later an analysis (2017) where it was found that **poor exposure characterisation** primarily defined the major limitation of epidemiological studies. Frequent use of case–control studies as opposed to prospective studies was considered another limitation. Inadequate definition or deficiencies in health outcomes need to be avoided and reporting of findings could be improved in some cases.

Taking into account the higher value of cohort studies, it was found that the outcome of the AGRICAN cohort studies, spanning the publication years of 2013 to 2020, would constitute a reliable starting base for further recommendations regarding the potential long-term effects of plant protection products (PPP).

As per 2020, 10 major peer-reviewed AGRICAN publications and 4 congress abstracts were consulted in order to collate the main conclusions on the associations between some cancers in the agricultural population and either crop/animal exposure and PPP exposure. Overall cancer incidences were compared (as far as possible) to those highlighted in other epidemiological cohort studies, being the Agricultural Health Study (AHS, US); Canadian Census Health and Environment Cohorts (CanCHEC), Pesticides Users Health Study (PUHS, UK) and the Nordic Occupational Cancer (NOCCA, Scandinavia). The most important source of information was the AHS which is, like AGRICAN, a prospective cohort study.

In an early publication, Tual et al. (2013) reported that PPP poisoning and exposure to PPP in potato growing was significantly associated with chronic bronchitis (CB) risk, but that the nature and circumstances of exposure to hazardous agents needs to be further explored. Another study by Baldi *et al.* (2014) dealing with respiratory findings revealed an increased risk of allergic asthma, observed with exposure to certain crops, PPP use and early life on a farm with vine-growing, grassland, beets, fruit and vegetable-growing. It was found that, even if the precise mechanisms (direct airway damage, interactions with irritant receptors, modulation of inflammatory response, etc.) remain unclear, practical measures to reduce the impact of potentially harmful risk factors like PPP should be carefully considered.

In Levêque-Morlais *et al.* (2015), first mortality results obtained in the AGRICAN cohort, showed that farmers indicated **no overmortality** due to farming (and accordingly, to PPP use) above average when compared to the general population.
Lemarchand *et al.* (2017) found that **overall cancer incidence** in the AGRICAN cohort and the general population was not very different. No statistically significant difference was observed for the overall cancer incidence with standardised incidence ratios (SIR) for both ♂ and ♀ around unity. However, specific SIR's were significantly higher for **prostate cancer** (+7%) and **non-Hodgkin lymphoma** (NHL) (+9%) among ♂, skin melanoma among ♀ (+23%), **multiple myeloma** (MM) (+38%,♂- and 26%,♀).

In the following section, the AGRICAN studies where associations between specific cancers and agricultural activities were observed, are summarised:

In Lemarchand *et al.* (2016), AGRICAN investigators found an increased risk for **prostate cancer** in a number of distinct situations, *i.e.* cattle breeder, grassland activities, fruit growers and potato/tobacco producers. It was noted that in some cases stratifying the examined population (tasks, area involved, duration,…) may lead to samples of insufficient number of cases possibly reducing biologically meaningfulness. When the overall figures are analysed, it should be said that for the population "pesticide use on crops" no clear-cut statistically significant increase of the prostate cancer risk could be revealed. Strikingly, in certain (but not all) cases, higher risks were observed among people who never wore protective gloves, highlighting the importance of personal protection in PPP handling and harvesting.

Boulanger *et al.* (2017) reported a possible link between agricultural activity, especially field-grown vegetables (+89%), and greenhouse cultivation (+95%) and **bladder cancer**. It may be highlighted that, while no specific active substance (a.s.) was associated with this increased incidence, the possible contribution of arsenicals, historically massively used in French agriculture, are of no concern at the Belgian level, and are anyway prohibited in the EU as well.

Lung cancer risk (Tual et al., 2007), was inversely related to exposure to cattle (-40%) especially after protracted duration (40 years) of farming, and the effect was of borderline significance in horse farming, while the effect was not seen in case of poultry or pig farming. More pronounced decreased risks were reported among individuals who had cared for animals, undertaken milking, and were

exposed to cattle in infancy. The authors considered the results reflecting strong evidence of an inverse association between lung cancer and cattle and horse farming.
Boulanger *et al.* (2018) reported associations between lung cancer and several crop-related tasks (amongst others winegrowers). However, except for a significant significant effect for PPP users (2× increased risk) and a trend for harvesters, most findings were of borderline statistical significance. In a recent congress communication (Boulanger *et al.*, 2019), which is to be confirmed in a full peer-reviewed study) of this author, an increased risk of lung cancer among women has been observed, especially when arsenates were involved. It was however stated that at this stage, exposure assessment should be refined and it was also recognised that some chance findings due to multiple comparisons could not be excluded. It is also useful to highlight that a.s. on the basis of arsene salts were never authorised in Belgium.

A possible role of PPP in the occurrence of Central Nervous System (CNS) tumours was investigated in a series of publications (Piel *et al.*, 2017-2019), with higher risk observed in PPP users (+96%), however the overall association lost significance when each tumour type (glioma and meningioma) was investigated separately. A significant increase in meningioma risk was also found among pig farmers performing animal care and/or local disinfection (+143%). In follow-up studies, the authors put forward several carbamate insecticides, fungicides and herbicides being potential candidates for the observed brain tumour findings. While a potential mode of action could be proposed (i.e. oxidative stress exerted by many carbamates), it should be noted that most of the cited a.s. are not on the EU-market anymore, or are in a process of phasing-out.

Refining the outcome of MM, Tual *et al.* (2019) found increased incidences in people using PPP's on crops (especially corn) since 1960 onwards (possibly suggesting a driving effect of older, outdated PPP's), and using insecticides on animals or using disinfectants in animal barns. While haematological findings could also be linked to other biological factors (known to play a role in the meat industry), recent cohort studies (like the AGRICOH cohort, including AGRICAN data) failed to find associations between animal farming and lymphohaematopoietic cancers (LHCs). However, taking into account the elevated risks of MM in the agricultural population, especially applicators of PPPs in 4/5 prospective and retrospective cohort studies, it seems important to further focus on this issue.

It was noted that NHL or one of its subtypes were slightly but consistently increased in 2/5 cohort studies. However, recent congress communications (Busson *et al.*, 2019a,b and 2020, full data not available) suggested again a possible link in the AGRICAN cohort as well. The preliminary data would support the role of pesticide exposure (including benzimidazoles) on NHL risk, both in crops and farm animal use.

Other recent (but also preliminary) results of the AGRICAN cohort illustrate a possible association between agricultural activities in some livestock premises (cattle), and full field or greenhouse crops, and elevated sarcoma incidences (Renier *et al.*, 2020). While these data are preliminary, it should be remarked that the absolute numbers were considered very low in some cases, and that this very heterogeneous and complex group of sarcoma is poorly described in the scientific literature.

Therefore the interpretation of these findings, should be considered very cautiously for the time being. The various associations highlighted between animal production activities or cultures (vegetable, greenhouse culture) and the occurrence of sarcomas deserve further investigation before confirmation of a causal relationship to PPP exposure.

In summary, the outcome of the most important prospective US/EU cohorts was in average comparable for what the overall cancer incidence was concerned. However, for each cohort separately, there was an overincidence of specific tumour types, which was not be observed in the other cohorts. Notable however was the presence of an overincidence for **MM**, **prostate cancer** and **NHL** in 4/5, 3/5 and 2/5 cohorts, respectively.
It should be remarked that a comparison between the outcome of these cohorts, even if impressive number of persons were studied, should be interpreted with caution. The methodologies may be different (prospective/retrospective), the reference populations may differ (general population/non-exposed farmers, etc…), the distinction between type of agricultural activities is not always made (farmers, pesticide applicators, managers, workers,…), the censuses may be limited to farmers having certificates of competences (e.g. PUHS), covering different enrollment time-periods, or being part of larger occupational studies (e.g. NOCCA).

However, for a comparison of overall cancer incidences it has some value.

Remark: the AGRICAN outcome of cancers, as published in a peer-reviewed paper by Lemarchand et al (2017), covered the period 2005-2011, and presented in table 2. The overincidence of tumours in the farmers is compared to that in the general population. Recently (AGRICAN, 2020) a report was published on the internet, citing different incidences. The new incidences were recorded in the period 2005-2015, which may partly explain the difference. Whereas the recent AGRICAN report was certainly peer-reviewed internally, it was not published in a peer-reviewed scientific journal, meaning that the level of detail is less extensive than in a scientific article. However, the published overincidences follow the same trends, and do not meaningfully change the conclusions drawn in the FPS overview.

Table 1: : incidence risk of overall and specific cancers in farmers/applicators as compared to the risk in the general population

<table>
<tr><th>Cancer type</th><th>AGRICAN (FR)</th><th>AHS</th><th></th><th></th><th>NOCCA (Scandinavia)</th><th>PUHS (UK)</th><th>CANCHEC (Canada)</th></tr>
<tr><td>Publication year</td><td>2017</td><td>2005</td><td>2010</td><td>2019</td><td>2009</td><td>2011</td><td>2017</td></tr>
<tr><td>Any cancer</td><td>§[↓5/↓7]</td><td>↓12%</td><td>↓15%</td><td>↓9%</td><td>n.a.</td><td>↓42%|↓29</td><td>↓5%</td></tr>
<tr><td>Colorectal</td><td>-</td><td>-</td><td>-</td><td>([↑6]r)</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>NHL</td><td>↑9 | - §[↑9 |]</td><td>-</td><td>[↑17]r</td><td>(↑12)@ [↑26]r</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>CLL</td><td></td><td>-</td><td></td><td>↑17 [↑30]r</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>DLBCL</td><td>-</td><td>-</td><td>[↑27]r</td><td>(↑16) [↑29]r</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>FL</td><td></td><td></td><td></td><td>[↑27]r</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>MM</td><td>↑38|↑26
§[↑20/↑21]</td><td>(↑34)</td><td>↑42</td><td>(↑18) [↑99]r</td><td>↑7|↑14</td><td>↑49|↑990#</td><td>-</td></tr>
<tr><td>Waldenström £</td><td>§[↑49/↑58]</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Leukaemia</td><td>-</td><td>-</td><td>-</td><td></td><td>-</td><td>-</td><td>-|↑101</td></tr>
<tr><td>AML</td><td>-</td><td>-</td><td>-</td><td>↑29 [↑42]r</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Lip °</td><td>-|- §[↑55 | -]</td><td>-</td><td>↑97</td><td>↑122 [↑146]r</td><td>↑57|-</td><td>-</td><td>↑14|↑125</td></tr>
<tr><td>Melanoma °</td><td>-|↑23 §[-/↑29]</td><td>-</td><td>-</td><td>[↑12]r</td><td>-</td><td>-</td><td>↑15|↑79</td></tr>
<tr><td>Non-melanoma skin</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-|↑73</td><td>-</td></tr>
<tr><td>Ovary</td><td>-</td><td>-</td><td>-</td><td>[↑99]r</td><td>-</td><td>-</td><td>-</td></tr>
</table>

Cancer type	AGRICAN (FR)	AHS			NOCCA (Scandinavia)	PUHS (UK)	CANCHEC (Canada)
Publication year	*2017*	*2005*	*2010*	*2019*	*2009*	*2011*	*2017*
Pancreas	-	-	-	-	-	-	-|↑36
Prostate	↑7 § *[↑3]*	↑24	↑19 [↑66]r	↑15 [↑44]r	-	-	↑11
Testicles	-	-	-	[↑45]r	-	↑26	-
Thyroid	-	-	-	[↑28]r	↑18	-	-

- Percentual differences (↑increase / ↓decrease) in standardised incidence rates (SIR), except hazard rates (HR) in CANCHEC);
- - : no statistically significant difference and (..) borderline (lowest 95%CI value=0.98) statistical difference
- values for ♂ | ♀ (except for AHS); [..]r: relative SIR's; n.a.: not available;° : considered sunlight-related;
- #: estimation highly imprecise, taking into account the extremely wide 95% CI
- @: restricted to B-cell NHL
- §*[..]:* Recent AGRICAN data (2021) in italics, referring to the period 2005-2015, as compared to the published data (2017, referring to the period 2005-2011)
- £: a.k.a. plasmocytic lymphoma, not formerly reported in any cohort.

A first conclusion of the AGRICAN study, supported by other cohort studies, is that the long-term outcome of life-long exposure to animals, crops and pesticides may be quite diverse. On the basis of cancer incidences in general, or mortalities subsequent to cancer incidences, figures in the agricultural community are not spectacularly worse than in those in the general population. On the contrary, there is even a slight but consistently lower overmortality overall, and also the overall cancer incidence may even be indistinguishable from (AGRICAN), or about 10-15% lower than, that of the general population.

Incidence ratios in the agricultural workers and PPP applicators may display overincidences of a limited number of tumours, among which **lymphopoietic cancers** (including **MM**) and **prostate cancer** seem to be the most recurring ones.

In addition, the weight of evidence also indicates a slight but rather consistent association between exposure to PPP's and/or insecticides used on animals and **Parkinson Disease**.

The most convincing association comes from studies which are generally believed to be of major relevance, such as prospective cohorts. It is noted that often, the effect of the duration of exposure on mRR is uncertain. Recent attempts to estimate in a quantitative way the effect of duration on PD incidence revealed only weak associations: a 5 to 10 years exposure duration to PPP was associated with a 5% to 11% increased risk of PD, respectively (Yan *et al.,* 2018). While many studies provide some support for the hypothesis that occupational exposure to PPPs would increase the risk of PD, there is on the other hand a very wide consensus among epidemiologists that there is an urgent need to improve the accuracy of the exposure data, in order to confirm a potential causal relationship between PD and PPP exposure. It is also thought that further high-quality (prospective) cohort studies are required to validate such a causal relationship. In order to reinforce estimates of exposure, there is a high need of rolling out legally binding and verifiable registration tools collating actual uses in the agricultural sector.

Knowing the difficulties and limitations of the assessments on the exposure side, many expectations have risen on the hazard-side, namely in the development of validated *in-vitro* assays and concomitant AOP's. The latter should provide mechanistic plausibility for epidemiological observations on a relationship between pesticide exposure and an elevated risk for PD development.

The conclusions of this analysis were based essentially on data in epidemiological prospective cohorts, which are considered superior to case-control studies, which may suffer recall bias, although case-control studies may be more sensitive to identify rare tumours. However, meta-analysis, regrouping all these studies also indicate the same trend, and are re-enforcing confidence in the obtained picture.

When the largest cohorts worldwide (including AGRICAN Some cohorts and AHS) are considered together, it should be kept in mind that comparisons of the results may be cumbersome, for a number of reasons.

(i) While the AGRICAN studies focus primarily on long-term effects after contact to crops and farm animals, the AHS study relates more to effects subsequent to PPP exposure and less to farm activities *per se*.
(ii) Some cohorts like NOCCA and CANCHEC are part of a bigger epidemiological census and are not designed to specifically examine the fate of the agricultural population.
(iii) The reference populations may be different, and the comparison of the incidence rates may therefore not be straightforward.

It should be clear that even a mere comparison between AGRICAN and AHS, especially as regards a possible association between overincidences and PPP exposure, and in particular specific a.s. or classes thereof, is extremely difficult. However, a general table was made in order to compile the findings (table 2). It is noted that for the time being, the comparison does not generate any meaningful concordance for the a.s. which would be at risk for the observed cancers studied to date. It is in addition also clear, that among the a.s. for which an association was suggested in the AHS cohort, most of them are not used anymore in the EU, and thus in Belgium, as *e.g.* organochlorines are already banned, and few a.s. in the organophosphate and carbamate class remain. The only PPP candidates used in the US which could still be of concern are restricted to glyphosate (association debatable), 2,4-D, (S-) metolachlor, pendimethalin, deltamethrin and dicamba. Also the a.s. studied or cited in the AGRICAN study are not all approved. A limited number of carbamates (IN, FU, HE) are still used as PPP, along with some phenoxy herbicides. No further analysis is done for a.s. which are used as either biocides (e.g. disinfectants) or as veterinary insecticides.

Table 2: concordance between a.s. cited or studies in the prospective cohorts

Cancer type	association with specific a.s. or classes	
	AGRICAN	AHS
PROSTATE	none	methyl bromide
		chlorpyrifos, coumaphos, fonofos, phorate, and permethrin for animal use, and the herbicide butylate
		OP, fonofos, terbufos, aldrin
BLADDER	none	imazethapyr, imazaquin; metolachlor (*), **2,4-D,** 2,4,5-T, OC
LUNG	none	none
	none	
	arsenate salts	**Metolachlor (*)**, **pendimethalin**, chlorpyrifos, diazinon,
		pendimethalin, dieldrin, parathion, chlorimuron-ethyl

Cancer type	association with specific a.s. or classes	
	AGRICAN	AHS
BRAIN	**carbamate insecticides**, carbaryl, **formetanate**, thiofanox	
	carbamate fungicides and herbicides, **mancozeb**, maneb, metiram, chlorpropham, propham, di-allate,	
MULTIPLE MYELOMA	OC, carbaryl, permethrin, dichlorvos, captan, **phenoxy herbicides**, atrazin, dinoterb, **disinfectants**	**glyphosate** (?)
		permethrin
NHL	none	OP, malathion, diazinon
	benzimidazoles (thiophanate-methyl?)	terbofos, **deltamethrin**; **glyphosate**? (DLBCL, CNAP)
		Dicamba (CLL)
SARCOMA	none	

(*: not confirmed in follow-up (FU) study of the AHS, but both liver and follicular cell lymphoma were found in the FU)

At this moment, taking into account the disparity of data (possibly due to different good agricultural practices (GAPs), methodologies, statistical handling, different proxies approximating exposure to PPPs,…), the scientific evidence to infer that the exposure to PPPs in the agricultural population in Belgium leads to severe diseases is subject to considerable scientific debate.

Yet, a limited but somehow consistent association between **lymphopoietic and prostate cancers,** and agriculturally related activities deserves further investigation. Furthermore, an association between exposure to PPPs and **Parkinson Disease** is for the majority of investigators not excluded, and further efforts are warranted both on the exposure side (epidemiology, registration of actual use), as on the hazard side (alternative testing strategies), to solve the problem of causal relationship between PPP exposure and PD.

The existing open scientific literature, including the most powerful observational studies, are indicative of specific increases of incidence of long-term effects, either linked with exposure to crops and/or to PPP's. However, these studies carry also imprecisions and uncertainties, causing some confusion as regard a proper interpretation of the facts. Several elements, potentially subject to improvement, are described below.

(i) By far the largest source of uncertainty in epidemiological studies remains the estimation of the actual exposure. In prospective cohorts, exposure data are recorded at the beginning of enrollment, and may be updated several times thereafter in order to catch potential changes in GAPs. In contrast, case-control studies suffer recall bias, where affected people tend to overestimate occurred exposures to PPP due to their condition. But even in cohort studies, most exposure data rely on declared employment and use calendars, at best supplemented with proxies on the basis of crop-exposure matrices. However, also the latter approach has its limits, as even well-conducted experimental field-trials may generate measured exposures values varying several orders of magnitude.

(ii) Whereas it has often been argued that exposure misclassification is likely to be non-differential and would tend to bias relative risks toward the null hypothesis, and diminish any “real” exposure- response gradients, it has equally been demonstrated that in fact, both under- and overestimation may occur, and it is recognised that in case of sufficiently large cohorts, a non-differential misclassification would be likely.

(iii) In many cases, a substantial number of parameters (crops, farm animals linked or not with PPP use) are tested, and it was often not clear if sufficient effort was paid to rule out the possibility that some of the findings might be due to chance. Regardless of other confounders, the issue of multiple testing remains a serious problem in observational studies.

(iv) While it is evident that epidemiological studies examine by definition health outcomes possibly consecutive to exposure to animals, crops or PPP’s encountered decades before enrollment, one is insufficiently aware that associations inevitably partly reflect uses with completely outdated PPP’s. While these results remain valid for the a.s. under investigation in absolute terms, it is poorly predictive for the a.s. which were marketed in the meanwhile. For example, common a.s. included organochlorines, which are completely banned in the EU. Also neurotoxic organophosphates and carbamates have nowadays almost largely disappeared, and also the number of pyrethroids are declining rapidly. Therefore, it is probable that epidemiological studies alone are an insufficient tool in the context of toxicovigilance of PPP’s.

(v) Whereas exposures are expressed in quantities of a.s. (either individually or grouped by class), it should be stressed that applicators are actually exposed to products containing both a.s. and coformulants. In contrast to a.s., some coformulants are not necessarily inert, and may be introduced on the market with little or no information on their human or environmental health effects (especially if manufactured at low quantities). It is clear that we need a rapid catch up in order to collect and evaluate independently information on the hazards and current levels of human exposure, and take this into account in the interpretation of the “a.s.” effect. Ideally, only coformulants should be used which are sufficiently investigated for their safety.

(vi) In order to overcome the limitation of uncertain actual exposure to PPPs, some recent epidemiological studies include experimental phases encompassing either real environmental measurements and/or biological samples (blood, plasma, urine, hair) enabling elucidation of long-term (neurologic, cancer) risks. Up to now, existing cohorts with this type of markers are scarce, and some examples of biomonitoring of immunological blood parameters reflecting potential precancerous stages (e.g. monoclonal gammopathy of undetermined significance (MGUS) in the case of multiple myeloma or Waldenström disease) are promising.

(vii) Likewise, proxies of exposure may also be derived from more reliable application data in real life. In the EU-context, record-keeping on applied PPP's are mandatory, but are up to now insufficiently implemented. If data on PPP use are kept, these are by no means stored in a portable way, and information remains actually inaccessible to health workers (and moreover restricted to storage ≤3 years). Comparably to the Pesticide Usage Reports (PURs) in California, which have been valorised for research outcomes (crossing actual exposures to GIS and relevant public health register outcomes), such data should be available and used in the EU as well.

Apart from the abovementioned limitations, there is a growing need of mechanistic research, in order to support the interpretation of observed overincidences.

It remains important to remind that while human studies, up to now, have revealed only a number of *associations* between certain long-term effects and agricultural activities (which include, but are not restricted to, PPP exposure), the *causal relationship* remains difficult to establish. Existing regulatory studies on test animals may not necessarily provide a fully reliable indication of the promoting activity, or may be unable to provide mechanistic evidence of severe long-term outcomes (including CMR effects, neurodegenerative or immunologic diseases in animals and/or humans) of certain a.s..

It should also be acknowledged that the impact of PPP exposure on specific live-phases or on specific endpoints, like childhood cancer prevalence during gestation, or neurological conditions like PD are possibly not entirely covered by guideline studies on test animals considered for the PPP toxicity dossiers (in the EU and worldwide). Likewise, the scrutiny of the effect for other vulnerable groups with persons carrying specific genetic traits cannot be fully covered by the classical toxicology studies. As an example, it may be referred to by population studies demonstrating increased effects of environmental exposure to PPP's in people with familial history to prostate cancer. Therefore, risk assessors should acknowledge that further efforts are needed to refine and complement current data requirements and concomitant risk evaluations in order to fill as much as possible knowledge gaps in these domains.

In the case an a.s. has experimentally been identified as a CMR of probable relevance for the human (*e.g.* genotoxic carcinogen, or overt endocrine disruptor), its approval is withdrawn at the EU-level, and is phased out for product authorisation at the zonal/national level, including Belgium. It should in this context be underscored that even if the human relevance is only suspected, the MoA is unfortunately never unequivocally determined.

In the absence of plausible modes/mechanisms of actions, the likelihood of *causality* between PPPs and long-term effects remains uncertain, from the risk-assessment point of view. The need for more fundamental research is warranted regarding for instance DNA damage, oxidative stress, metabolic outcomes and endocrine modulation, is a recurrent issue in risk assessment. Especially for the assessment of PD, a break-through to newer approaches, focusing on presumed mechanisms of action, possibly coupled (but not restricted) to guideline toxicity studies with repeated administration, seems primordial in this respect.

Further perspectives:
At the bottom line, there are 5 main points of focus to evaluate long-term effects of PPPs in the human population, or to mitigate as much as possible PPP exposures in real life:

(i) Focusing on both **regulatory long-term** guideline studies and published open literature studies, including *in-vitro* alternatives.
Existing evaluations should thus as much as possible be driven by the search of new modes of action, to elucidate possible lacks in current knowledge of endpoints which would remain undiscovered until now. One notable example is data gaps on Parkinsonism or certain haematological cancers which would remain undiscovered in animal studies. Especially for the assessment of PD, a break-through to amongst others, newer *in-vitro* approaches seem primordial in this respect.

(ii) Ensuring a maximal follow-up of (mainly prospective) **epidemiological** studies, associated with techniques to assess to the best extent possible real exposure levels, for instance by using biomonitoring tools. The more efficient exploitation of crop-exposure matrices, in combination with until now underused purchase/use information of professional PPPs offers an additional tool to obtain a better view on real on-the-field exposure levels.

(iii) In Belgium (but also in other EU member states with intensive agriculture), there is an urgent need to evaluate the potential risk of short- or long-term exposure to PPP for instance in regions known to be affected by high PPP exposure like fruit orchards and ornamental plant production, etc. which are sectors well known for their involvement of high levels or substantial diversity of PPP. This is true for farmers and applicators, but more so for residents, for which there are still many data gaps regarding their exposure to PPP's.

(iv) Further resources should be allocated to develop reliable and robust **registries** of long-term/severe effects. In Belgium (like in other EU countries) cancer registries are installed since about a decade. However, also a proper repository of developmental defects, covering the whole country, is blatantly absent in Belgium. There is an urgent need to put in place a **Belgian network**, collecting data on a large scale, and supporting in this way the EU database on fertility effects and developmental anomalies (see objectives of EUROCAT).

(v) The establishment of an association between exposure and adverse health outcomes depends heavily on an **accurate estimation of exposure**, in the absence of which the effect is flattened out. The legal possibility and effective need to impose an **on-line registration** of actual use of PPP's, the possibility to have law enforcement to monitor and control these inputs, and the potential value crossing these data to location and consequently health data (registries of cancer, developmental anomalies,...) using GIS, makes this approach a very powerful tool in order to explore post-marketing monitoring of long-term threats of PPPs of both professional groups and the general population.

In addition, the same methodology in order to estimate in a more reliable way environmental PPP levels could also be used to estimate predicted environmental concentrations (PECs) and to monitor a.s. in environmental compartments, amongst others surface and groundwater.

(vi) Finally, we should explore ways to **avoid as much as possible exposure** to PPPs during 'real-life' application, in order to protect operators, workers, bystanders and residents. Possible regulatory actions include the installation of default buffer zones for field application (2m) or high-crop (orchard) application (5m), below which no reliable exposure assessment is possible because of lacking exposure data. In addition to rapidly evolving engineering controls like spot-application (*e.g.* via drone-application), there is an urgent need to install default, clear and easily enforceable buffer zones vis-à-vis residents living in the neighbourhood of agricultural premises, and especially in order to protect vulnerable people (children, aged people, pregnant women, *etc…*).

It is left to the discretion of risk managers and policy-makers to determine the level of concern and concomitant measures to decide on socio-economic measures in this respect.

Résumé détaillé

L'épidémiologie du cancer et d'autres effets graves est étudiée en détail depuis longtemps. Alors qu'on n'a pas le sentiment qu'une étude de surveillance menée à l'initiative du Service public fédéral (SPF) Santé publique, Sécurité de la Chaîne alimentaire et Environnement puisse ajouter de nouvelles informations intéressantes à celles des campagnes en cours actuellement il semble, en revanche, que l'évaluation critique et objective de toute nouvelle littérature scientifique par les autorités fédérales soit un objectif beaucoup plus réaliste et accessible pouvant éclairer les mesures de soutien de la politique.
Il a été décidé de s'appuyer principalement sur les résultats de l'étude de cohorte française AGRICAN (entre-temps devenue membre d'un consortium international regroupant 21 autres études de cohorte réparties sur 9 pays (cf. http://agricoh.iarc.fr/)).
C'est pour cette raison que le SPF passe régulièrement en revue les nouveautés de la littérature scientifiques (validées par des pairs) mondiale portant sur l'apparition d'effets à long terme associés aux PPPs.

Dans plusieurs études systématiques dont le rapport de l'EFSA (2013) et le rapport de l'INSERM (2013 et 2021), des indications d'associations positives ont été observées pour toute la gamme des pesticides, via différentes voies d'exposition, ainsi que plusieurs impacts sur la santé. L'étude de l'EFSA s'est portée sur des observations matérielles comme le cancer, les maladies neurodégénératives ou les troubles du développement, mais aussi à d'autres résultats, dont les biomarqueurs d'exposition (biosurveillance), pour la période 2006-2012. Deux pathologies ont été évoquées, à savoir les cancers pédiatriques et les troubles neurologiques, comme la maladie de Parkinson. Dans l'évaluation de cette étude et d'autres études analogues, l'EFSA (2017) a considéré que la portée de ces études épidémiologiques est avant tout limitée par la **mauvaise caractérisation de l'exposition**. La limitation résulte aussi du recours fréquent aux études cas-témoins plutôt qu'aux études prospectives de cohorte.
Enfin ces études sont appauvries par des définitions inadéquates ou lacunaire des impacts sur la santé et, dans certains cas, par un compte-rendu grossier des observations.

Compte tenu de la valeur supérieure des études prospectives de cohorte, il a été estimé que les résultats de l'étude de cohorte AGRICAN, couvrant les années de publication de 2013 à 2020, constituerait une base de départ fiable pour de nouvelles recommandations sur les effets potentiels à long terme des PPPs.

À l'horizon 2020, les résultats d'AGRICAN ont été consultés au travers de 10 publications majeures relues par les pairs et de 4 résumés de congrès afin de rassembler les principales conclusions sur les associations entre le contact avec des cultures/des animaux et/ou l'exposition à des PPPs et l'occurrence de certains cancers dans la population agricole. Les incidences globales de cancer ont été comparées (autant que possible) à celles mises en lumière dans d'autres études de cohortes épidémiologiques, à savoir l'Agricultural Health Study (AHS, USA), les Canadian Census Health and

Environment Cohorts (CanCHEC), la Pesticides Users Health Study (PUHS, R.-U.) et la Nordic Occupational Cancer Study (NOCCA, Scandinavie). La plus importante source d'informations a été l'AHS qui, comme AGRICAN, est une étude de cohorte prospective.

Dans une première publication, Tual et al. (2013) ont signalé qu'une intoxication aux PPPs et l'exposition à des PPPs dans la culture de pommes de terre était associée de façon significative à un risque de bronchite chronique (BC), mais que la nature et les circonstances de l'exposition aux produits à risque devaient être examinées plus en détail. L'étude de Baldi *et al.* (2014), traitant d'observations au niveau du système respiratoire, a révélé un risque accru d'asthme allergique, constaté dans le cadre de l'exposition à certaines cultures, de l'utilisation de PPP et d'un antécédent de vie sur une exploitation agricole pratiquant la viticulture, le pastoralisme, la culture de betteraves, la culture fruitière et maraîchère. Les auteurs considèrent que, même si les mécanismes précis (dommage direct aux voies respiratoires, interaction avec des récepteurs irritants, variation de la réponse inflammatoire, etc.) restaient flous, des mesures pratiques pour réduire l'impact de facteurs de risque potentiellement nuisibles comme les PPPs devaient être considérés attentivement.

Dans la publication de Levêque-Morlais *et al.* (2015), les premiers résultats en matière de mortalité issus de la cohorte AGRICAN ont montré que les agriculteurs ne présentaient **aucune surmortalité** imputable à l'agriculture (et, subséquemment, à l'utilisation de PPP) supérieure à la moyenne de la population générale.
Lemarchand *et al.* (2017) ont estimé que **l'incidence globale du cancer** dans la cohorte AGRICAN et dans la population générale n'était pas très différente. Aucune différence significative sur le plan statistique n'a été constatée pour l'incidence globale du cancer (les taux d'incidence standardisés (TIS) sont proches de l'unité tant pour les hommes que pour les femmes). Toutefois, les TIS spécifiques se sont révélés significativement plus élevés pour le **cancer de la prostate** (+7%) et le **lymphome non hodgkinien** (LNH) (+9%) chez les hommes, le mélanome cutané chez les femmes (+23%), et le **myélome multiple** (MM) (+38% chez les hommes et +26% chez les femmes).

La section suivante fournit un résumé des études AGRICAN dans lesquelles des associations entre des cancers spécifiques et les activités agricoles ont été observées.

Dans Lemarchand *et al.* (2016), les chercheurs d'AGRICAN ont identifié un risque accru de **cancer de la prostate** dans plusieurs situations distinctes, à savoir l'élevage de bétail, les activités pastorales, la culture fruitière et la production de pommes de terre/de tabac. Il a été relevé que dans certains cas, une stratification de la population examinée (tâches, région concernée, durée...) débouchait un échantillon insuffisant de cas, entrainant probablement une pertinence biologique réduite. En analysant les chiffres globaux, il est permis d'affirmer que pour la population « utilisant des pesticides sur les cultures », aucune augmentation nettement significative sur le plan statistique du risque de cancer de la prostate ne pouvait être établie. Il est frappant de constater que dans certains cas (mais pas dans tous), des risques accrus sont associés aux personnes qui n'ont jamais porté de gants, ce qui met en évidence l'importance des équipements de protection individuelle lors de la manipulation de PPP et lors de la récolte.

Boulanger *et al.* (2017) ont signalé un lien possible entre une activité agricole, en particulier la culture maraîchère en champ (+89%) et la culture en serre (+95%) et le **cancer de la vessie**. Il est à signaler que, même si aucune substance active spécifique n'a été associée à cette incidence accrue, la contribution possible des pesticides arsenicaux (utilisés jadis massivement en France et interdit aujourd'hui dans l'UE) relevée dans l'étude ne constitue pas une préoccupation au niveau de la Belgique.

Dans leur publication Tual *et al.* (2007) ont montré que le risque de **cancer du poumon** était inversement proportionnel à l'exposition à des bovins (-40%), particulièrement après une pratique prolongée (40 ans) de l'élevage ; cet effet étant peu observé (à la limite significatif) dans l'élevage de chevaux et pas observé dans le cas de l'élevage de volailles ou de porcs. Une diminution plus marquée des risques a été notée pour les individus qui avaient pratiqué l'élevage laitier et avaient été exposés à des bovins pendant leur enfance. Les auteurs considèrent ces résultats comme preuves sérieuses d'une association inverse entre le cancer du poumon et l'élevage de bovins et de chevaux.

Boulanger *et al.* (2018) ont signalé des associations entre le **cancer du poumon** et plusieurs tâches liées aux cultures (notamment chez les viticulteurs). Toutefois, hormis un effet significatif pour les utilisateurs de PPP (risque doublé) et une tendance pour les cueilleurs, la plupart des observations étaient d'une signification statistique limite. Dans une communication récente de cet auteur lors d'un congrès (Boulanger *et al.*, 2019, à confirmer dans une étude complète relue par les pairs), un risque accru de cancer du poumon chez les femmes a été observé, en particulier en cas d'utilisation d'arséniates. Il était cependant affirmé qu'à ce stade, l'évaluation de l'exposition devait être affinée et il était également reconnu que certaines observations fortuites dues à de multiples comparaisons n'étaient pas exclues. Il est également utile de souligner que les substances actives à base de sels arsenicaux n'ont jamais été autorisées en Belgique.

Le rôle éventuel des PPPs dans l'occurrence de tumeurs du **système nerveux central** (SNC) a été étudié dans une série de publications (Piel *et al.*, 2017-2019), avec un risque accru observé parmi les utilisateurs de PPP (+96%), mais la signification statistique de cette association globale diminuait en examinant chaque type de tumeur (gliome et méningiome) séparément. Une augmentation significative du risque de méningiome a aussi été rencontrée chez les éleveurs de porcs s'occupant des soins aux animaux ou pratiquant la désinfection locale (+143%). Dans les études de suivi, les auteurs ont mis en évidence plusieurs insecticides, fongicides et herbicides à base de carbamates comme responsables potentiels des tumeurs cérébrales observées. Bien qu'un mode d'action potentiel puisse être suggéré (à savoir un stress oxydatif exercé par de nombreux carbamates), il est à signaler que la plupart des substances actives précitées ne sont plus sur le marché européen aujourd'hui ou sont en voie d'extinction.

En affinant l'effet de **MM**, Tual *et al.* (2019) ont découvert des incidences accrues chez les personnes utilisant des PPPs dans les cultures (en particulier celle du maïs) au cours des années postérieures à 1960 (suggérant l'effet déterminant possible d'anciens PPPs aujourd'hui obsolètes) et utilisant des insecticides sur des animaux ou des désinfectants dans les étables. Dans la mesure où des observations hématologiques pouvaient aussi être liées à d'autres facteurs biologiques (connus pour jouer un rôle dans l'industrie de la viande), les études de cohortes récentes (comme celles d'AGRICOH, incluant les données d'AGRICAN) ne sont pas parvenues à trouver des associations entre l'élevage d'animaux et les cancers du système lymphatique et hématopoïétique (CLH). Toutefois, compte tenu des risques élevés de MM parmi la population agricole, en particulier les opérateurs de PPP dans 4 études de cohortes prospectives et rétrospectives sur 5, il paraît important de continuer à se focaliser sur ce problème.

Il a été relevé que le **LNH** ou l'un de ses sous-types augmentait légèrement mais de façon constante dans 2 études de cohortes sur 5. Cela étant, de récentes communications lors de congrès (Busson *et al.*, 2019 a,b et 2020, données complètes non disponibles) ont à nouveau suggérées un lien possible dans la cohorte AGRICAN également. Les données préliminaires viendraient étayer le rôle de l'exposition à des pesticides (dont les benzimidazoles) dans le risque de LNH, à la fois dans les cultures et l'élevage d'animaux de ferme.

D'autres résultats récents (mais également préliminaires) de la cohorte AGRICAN montrent une association possible entre les activités agricoles sur certaines exploitations d'élevage de bétail (bovins) et de cultures en plein champ ou en serre, et des incidences élevées de **sarcome** (Renier *et al.*, 2020). Ces données étant préliminaires, il est à signaler que les chiffres absolus ont été considérés comme très faibles dans certains cas, et que ce groupe très hétérogène et complexe de sarcomes est mal défini dans la littérature scientifique. Dès lors, l'interprétation de ces observations est à considérer avec beaucoup de prudence pour l'instant. Les diverses associations mises en lumière entre les activités de production animale ou les cultures (culture maraîchère, culture en serre) et l'occurrence de sarcomes nécessite une investigation plus poussée avant de confirmer un lien de causalité avec l'exposition à des PPP.

En résumé, les résultats des études de cohortes prospectives les plus importantes aux USA/dans l'UE étaient en moyenne comparables pour ce qui est de l'incidence générale du cancer. Toutefois, pour chaque cohorte séparément, on notait une surincidence de certains types spécifiques de tumeurs, non observée dans les autres cohortes. Un élément notable, cependant, était l'existence d'une surincidence pour le **MM**, le **cancer de la prostate** et le **LNH** dans respectivement 4, 3 et 2 cohortes sur 5.

Il est à signaler qu'une comparaison entre les résultats de ces cohortes, même si un nombre impressionnant de personnes a été étudié, est à interpréter avec prudence. Les méthodologies peuvent être différentes (prospective / rétrospective), les populations de référence peuvent différer (population générale, agriculteurs non exposés, etc.), une distinction entre les types d'activités agricoles n'est pas toujours établie (agriculteurs, opérateurs de PPP, chefs d'exploitation, ouvriers, ...), les recensements peuvent se limiter aux agriculteurs porteurs de certificats de compétence (p. ex. PUHS), couvrir des périodes d'inclusion différentes ou faire partie d'études d'un groupe professionnel plus large (p. ex. NOCCA).

Cet exercice présente toutefois une certaine valeur pour une comparaison des incidences du cancer en général.

Remarque : les données AGRICAN, telles que publiées dans l'article scientifique revue par des pairs de Lemarchand *et al* (2017), couvrait la période 2005-2011, et présentée dans le tableau 1. La surincidence des tumeurs chez les fermiers est comparée à celle de la population générale. Récemment (AGRICAN, 2020) un rapport a été publié sur Internet, citant différentes incidences. Les nouvelles incidences portent sur la période 2005-2015, ce qui peut expliquer en partie la différence. Alors que le récent rapport AGRICAN a certainement été évaluée en interne, il n'a pas été publié dans une revue scientifique à comité de lecture, ce qui signifie que le niveau de détail est moins étendu que dans un article scientifique. Cependant, les surincidences publiées suivent les mêmes tendances et ne modifient pas de manière pertinente les conclusions tirées dans l'aperçu du SPF.

Tableau 1 : Risque d'incidence de cancers chez les agriculteurs/opérateurs comparé au risque au sein de la population générale

Type de cancer	AGRICAN (FR)	AHS			NOCCA (Scandinavie)	PUHS (R.-U.)	CANCHEC (Canada)
Publié en	*2017*	*2005*	*2010*	*2019*	*2009*	*2011*	*2017*
Tout cancer	*§[↓5/↓7]*	↓12%	↓15%	↓9%	n.a.	↓42%|↓29	↓5%
Colorectal	-	-	-	([↑6]r)	-	-	-
LNH	↑9 | - *§[↑9 |]*	-	[↑17]r	(↑12)@ [↑26]r	-	-	-
LCC		-		↑17 [↑30]r	-	-	-
LDGC-B	-	-	[↑27]r	(↑16) [↑29]r	-	-	-
LF				[↑27]r	-	-	-
MM	↑38|↑26 *§[↑20/↑21]*	(↑34)	↑42	(↑18) [↑99]r	↑7|↑14	↑49|↑990#	-
Waldenström £	*§[↑49/↑58]*						
Leucémie	-	-	-		-	-	-|↑101
LMA	-	-	-	↑29 [↑42]r	-	-	-
Lèvres °	-|- *§[↑55 | -]*	-	↑97	↑122 [↑146]r	↑57|-	-	↑14|↑125
Mélanome °	-|↑23 *§[-/↑29]*	-	-	[↑12]r	-	-	↑15|↑79
Cutané non mélanome	-	-	-	-	-	-|↑73	-
Ovaires	-	-	-	[↑99]r	-	-	-
Pancréas	-	-	-	-	-	-	-|↑36

Type de cancer	AGRICAN (FR)	AHS			NOCCA (Scandinavie)	PUHS (R.-U.)	CANCHEC (Canada)
Publié en	*2017*	*2005*	*2010*	*2019*	*2009*	*2011*	*2017*
Prostate	↑7 § *[↑3]*	↑24	↑19 [↑66]r	↑15 [↑44]r	-	-	↑11
Testicules	-	-	-	[↑45]r	-	↑26	-
Thyroïde	-	-	-	[↑28]r	↑18	-	-

- Différences en pourcentage (↑augmentation / ↓diminution) dans les taux d'incidence standardisés (TIS), à l'exception du coefficient de risque (HR) dans CANCHEC) ;
- - : Pas de différence statistique significative et (..) différence statistique limite (valeur IC95% la plus faible =0,98)
- Valeurs pour ♂ | ♀ (sauf pour l'AHS); [..]r: TIS relatifs ; n.d.: non disponible ; ° : considéré comme lié au soleil ;
- #: Estimation très imprécise, compte tenu de l'IC95% extrêmement large
- @: Limité au LNH de cellules B
- §*[..]:* données récentes AGRICAN (2020) en italique, référant à la période 2005-2015, comparé aux données publiées (2017, référant à la période 2005-2011)
- £: a.k.a. lymphome plasmocytaire, pas cité préalablement dans les cohortes

Une première conclusion de l'étude AGRICAN, corroborée par d'autres études de cohorte, est qu'être en contact pendant toute une vie avec des animaux, des cultures et des pesticides peut avoir des effets à long terme plutôt divers. Les chiffres relatifs à l'incidence du cancer en général ou à la mortalité due à ces cancers montrent que les résultats dans la communauté agricole ne sont pas notablement plus mauvais que ceux dans la population générale. Au contraire, on constate même dans l'ensemble une surmortalité plus faible, légèrement certes mais systématiquement. Par ailleurs, l'incidence générale des cancers dans la cohorte AGRICAN est similaire à celle dans la population générale, voire 10 à 15 % inférieure.

Les taux d'incidence chez les ouvriers agricoles et les opérateurs de PPP peuvent être plus élevés pour un nombre limité de tumeurs, les plus fréquentes semblant être les **lymphomes** (dont le **myélome multiple (MM)**) et le **cancer de la prostate**.

En outre, le poids des preuves indique également un lien de causalité, mince mais plutôt systématique, entre l'exposition aux PPPs et/ou l'utilisation d'insecticides sur des animaux et la **maladie de Parkinson (MP)**.

L'association la plus convaincante émane d'études considérées généralement comme d'une pertinence majeure, comme les études de cohorte prospectives. Il est constaté que souvent, l'effet de la durée de l'exposition sur une méta-analyse des ratios de taux (mRR) est incertain. Des tentatives récentes d'estimation quantitative de l'effet de la durée sur l'incidence de MP n'a révélé que de faibles associations : une durée d'exposition aux PPPs de 5 à 10 ans était associée, respectivement, à une augmentation de 5 à 11 % du risque de MP (Yan *et al.,* 2018). Alors que nombreuses études tendent à étayer l'hypothèse qu'une exposition professionnelle aux PPPs augmenterait le risque de MP, un très large consensus existe par ailleurs parmi les épidémiologistes quant à la nécessité urgente d'améliorer la précision des données d'exposition, pour confirmer une éventuelle relation de causalité entre la MP et l'exposition aux PPP. On pense également que de nouvelles études de cohorte (prospectives) de grande qualité sont nécessaires pour valider pareille relation de causalité. Pour renforcer les estimations d'exposition, il y a grand besoin de développer des outils d'enregistrement légalement contraignants et vérifiables pour le collationnement des données d'utilisation réelles dans le secteur agricole.

Connaissant les difficultés et les limites des estimations sur le volet « exposition », de grandes attentes sont nées sur le volet « danger », notamment dans le développement d'essais *in-vitro* et des mécanismes d'effets indésirables correspondants. Ces derniers devraient fournir des mécanismes de plausibilité pour les observations épidémiologiques quant à une relation entre l'exposition à des pesticides et un risque accru de développement de la MP.

Les conclusions de cette analyse étaient essentiellement basées sur des données provenant d'études de cohortes prospectives qui sont estimées supérieures aux études cas-témoins. En effet, même si ces dernières peuvent être plus fines quand il s'agit d'identifier des tumeurs rares, elles peuvent présenter un biais de souvenir. Néanmoins une méta-analyse regroupant toutes ces études révèle la même tendance, ce qui renforce la confiance dans l'image obtenue.

Lors de l'examen conjoint des plus vastes études de cohorte dans le monde (dont les études du genre AGRICAN et l'AHS), il faut garder à l'esprit qu'une comparaison des résultats peut s'avérer malaisée, pour toute une série de raisons.

(i) Alors que les études AGRICAN se focalisent avant tout sur les effets à long terme après un contact avec des cultures et des animaux de ferme, l'étude AHS se rapporte davantage aux effets consécutifs à une exposition aux PPPs et moins aux activités agricoles *en soi*.
(ii) Certaines études de cohorte comme NOCCA et CANCHEC s'inscrivent dans le cadre d'un recensement épidémiologique plus large et ne sont pas spécifiquement conçues pour examiner le sort de la population agricole.
(iii) Les populations de référence peuvent être différentes, et c'est pourquoi la comparaison des taux d'incidence pourrait ne pas être linéaire.

Il faut clairement préciser que même une simple comparaison entre les études AGRICAN et AHS, surtout en ce qui concerne une possible association entre des taux d'incidence accrue et une exposition aux PPPs, et en particulier à des substances actives ou classes spécifiques de ces produits, est extrêmement difficile. Néanmoins, un tableau a été créé pour compiler les observations (tableau 2). On constate qu'actuellement, la comparaison ne fournit aucune concordance significative pour les substances actives qui présenteraient un risque pour les cancers observés étudiés à ce jour. En outre, il ressort clairement que parmi les substances actives pour lesquelles l'étude de cohorte AHS suggère une association, la plupart ne sont plus utilisées dans l'UE, et donc en Belgique, attendu que les organochlorés *p. ex.* sont déjà interdits et que peu de substances actives subsistent dans la catégorie des organophosphorés et des carbamates. Les seuls PPPs potentiels utilisés aux É.-U. et qui seraient encore préoccupants se limitent au glyphosate (association discutable), au 2,4-D, au (S)-métolachlore, à la pendiméthaline, la deltaméthrine et le dicamba. De même, les substances actives étudiées ou citées dans l'étude AGRICAN ne sont pas toutes approuvées. Un nombre limité de carbamates (IN, FU, HE) sont toujours utilisés comme PPPs, ainsi que certains herbicides phénoxy. Aucune analyse plus détaillée n'a été réalisée pour les substances actives qui sont utilisées soit comme biocides (désinfectants p. ex.) soit comme insecticides vétérinaires.

Tableau 2 : concordance entre les substances actives citées ou étudiées dans les études de cohorte prospectives

Type de cancer	Association avec des substances actives ou classes de substances actives spécifiques	
	AGRICAN	AHS
PROSTATE	aucune	bromure de méthyle
		chlorpyrifos, coumaphos, fonofos, phorate, perméthrine à usage animal et l'herbicide butylate
		OP, fonofos, terbufos, aldrin
VESSIE	aucune	imazéthapyre, imazaquine ; métolachlore (*), **2,4-D,** 2,4,5-T, OC
POUMON	aucune	aucune
	aucune	
	sels arsenicaux	**métolachlore (*)**, **pendiméthaline**, chlorpyrifos, diazinon,
		pendiméthaline, dieldrine, parathion, chlorimuron-ethyl
CERVEAU	**insecticides carbamates**, carbaryl, **formétanate**, thiofanox	
	fongicides et herbicides carbamates, **mancozèbe**, manèbe, métirame, chlorpropham, propham, di-allate,	
MYÉLOME MULTIPLE	OC, carbaryl, perméthrine, dichlorvos, captan, **herbicides phénoxy**, atrazine, dinoterb, **désinfectants**	**glyphosate** (?)
		perméthrine
LNH	aucune	OP, malathion, diazinon
	benzimidazoles (thiophanate-méthyl?)	terbofos, **deltaméthrine**; **glyphosate**? (LDGC-B, CNAP)
		dicamba (LLC)
SARCOME	aucune	

(*: non confirmé dans l'étude de suivi (FU) de l'AHS, mais des lymphomes du foie et des cellules folliculaires ont tous deux été constatés dans la FU)

Actuellement, compte tenu de la disparité des données (probablement due à des différences de bonnes pratiques agricoles, de méthodologie, de traitement statistique, d'approximation de l'exposition aux PPPs...), les preuves scientifiques pour conclure que l'exposition à des PPPs dans la population agricole en Belgique entraîne des maladies graves est sujette à un débat scientifique considérable.

Toutefois, une association limitée mais plus ou moins systématique entre les **lymphomes et le cancer de la prostate** et des activités liées à l'agriculture mérite une investigation plus poussée. En outre, pour la majorité des chercheurs, une association entre l'exposition aux PPPs et la **maladie de Parkinson** n'est pas exclue, et des travaux supplémentaires se justifient à la fois sur le volet exposition (épidémiologie, enregistrement de l'utilisation réelle) et sur le volet danger (stratégies de test alternatives) pour résoudre le problème d'une relation de causalité entre l'exposition aux PPPs et la MP.

La littérature scientifique accessible actuelle, y compris les études d'observation les plus performantes, indiquent une augmentation d'incidence spécifique de certains effets à long-terme liée à l'exposition aux cultures et/ou aux PPPs. Ces études comportent toutefois des imprécisions et des incertitudes qui sèment la confusion quant à l'interprétation correcte des données. Plusieurs éléments susceptibles d'amélioration sont évoqués ci-dessous.

(i) La plus grande source d'incertitude dans les études épidémiologiques reste, de loin, l'estimation de l'exposition réelle. Dans les études de cohorte prospectives, des données d'exposition sont enregistrées au début de l'inclusion, et sont susceptibles d'être actualisées plusieurs fois par la suite pour déceler des changements potentiels dans les protocoles généraux d'évaluation. Au contraire, les études cas-témoins souffrent d'un biais de souvenir, les personnes touchées ayant tendance, vu leur état de santé, à surestimer les expositions subies. Mais même dans les études de cohorte, la plupart des données d'exposition se fondent l'utilisation déclarée et sur des calendriers d'utilisation, complétées dans le meilleur des cas par des approximations basées sur des matrices cultures-exposition. Néanmoins, cette dernière approche a elle aussi ses limites, car même des essais expérimentaux en champ bien conduits peuvent générer des valeurs d'exposition mesurée variables dans plusieurs ordres de grandeur.

(ii) Bien qu'il ait souvent été avancé qu'une classification incorrecte de l'exposition serait plutôt de nature non-différentielle et aurait tendance à biaiser les risques relatifs vers une hypothèse zéro en réduisant les gradients exposition « réelle »-réponse, il a également été démontré qu'en fait, une sous-estimation et une surestimation sont toutes deux possibles, et il est reconnu que dans le cas de cohortes suffisamment larges, une classification incorrecte non-différentielle est la plus probable.

(iii) Dans de nombreux cas, un nombre substantiel de paramètres (cultures, animaux de ferme en lien ou non avec l'utilisation de PPP) sont testés et souvent il n'est pas clairement précisé si une attention suffisante a été accordée à exclure la possibilité que certaines observations soient dues au hasard. Indépendamment d'autres facteurs confondants, la question du testing multiple reste un problème dans les études d'observation.

(iv) Alors qu'il est évident que les études épidémiologiques examinent par définition les effets sur la santé potentiellement consécutifs à une exposition à des animaux, à des cultures ou à des PPPs remontant à plusieurs dizaines d'années avant l'inclusion, on néglige souvent de voir que les associations, inévitablement, reflètent en partie des utilisations de PPP totalement obsolètes. Bien que ces résultats restent valables pour les substances actives étudiées en termes absolus, leur valeur prédictive est minime pour les substances actives arrivées sur le marché entre-temps. Par exemple, les substances actives courantes incluaient les organochlorés, qui sont totalement interdits dans l'UE. De même, les organophosphorés et carbamates neurotoxiques ont presque totalement disparu aujourd'hui, et le nombre de pyréthroïdes diminue rapidement également. C'est pourquoi il est probable que les études épidémiologiques à elles seules soient un outil insuffisant dans le cadre de la toxicovigilance des PPPs.

(v) Alors que les données d'exposition sont exprimées en quantités de substances actives (soit individuellement, soit groupées par classe), il est à souligner que les agriculteurs et les opérateurs sont en fait exposés à des produits contenant à la fois une substance active et des coformulants. Certains de ceux-ci ne sont pas forcément inertes, et contrairement aux substances actives, ils peuvent être introduits sur le marché avec peu, voire aucune information sur leurs effets sur la santé humaine ou sur l'environnement (surtout s'ils sont fabriqués en petites quantités). Il est évident que nous devons rapidement rattraper le retard pour récolter et évaluer de manière indépendante des informations sur les risques et les niveaux actuels d'exposition humaine, et en tenir compte dans l'interprétation de l'effet « substance active ». Idéalement, il ne faudrait utiliser que des coformulants dont la sécurité a été suffisamment étudiée.

(vi) Pour surmonter la contrainte des incertitudes dans l'exposition réelle aux PPP, certaines études épidémiologiques récentes comprennent des phases expérimentales englobant des mesures réelles dans l'environnement et/ou le prélèvement d'échantillons biologiques (sang, plasma, urine, cheveux) permettant d'élucider les risques à long terme (neurologiques, cancérologiques). À ce jour, les études de cohorte comportant ce type de marqueurs sont rares et certains exemples de biosurveillance de paramètres sanguins immunologiques reflétant d'éventuels stades précancéreux (p. ex. gammapathie monoclonale de signification indéterminée (MGUS) dans le cas du myélome multiple) sont prometteuses.

(vii) De même, des approximations de l'exposition pourraient être dérivées de donnés d'application en champs plus fiables. Dans le contexte de l'UE, un enregistrement des PPPs appliqués est obligatoire, mais a été insuffisamment mis en œuvre jusqu'ici. Lorsque des données d'utilisation de PPP sont récoltées, elles ne sont d'aucune manière stockées de façon exportable et les informations restent en fait inaccessibles aux travailleurs de la santé (et en outre limitées au stockage ≤3 ans). Par analogie avec les « Pesticide Usage Reports (PURs) » en Californie, qui ont été valorisés pour obtenir des résultats de recherche (croisement de données d'exposition réelle avec un système d'information géographique (SIG) et les résultats de registres de santé publique pertinents), des données de ce genre devraient être disponibles et utilisées dans l'UE également.

Indépendamment des limites susmentionnées, il existe un besoin croissant de recherche systématique pour étayer l'interprétation des surincidences observées.

Il demeure important de rappeler qu'alors que les études sur l'être humain n'ont à ce jour révélé qu'un certain nombre d'*associations* entre certains effets à long terme et les activités agricoles (incluant, mais non limitées à l'exposition à des PPPs), le *lien de causalité* reste difficile à établir. Les études réglementaires actuelles sur des animaux pourraient ne pas nécessairement donner une indication totalement fiable du potentiel promoteur des substances actives, ou ne pas être à même de fournir des preuves systématiques d'impacts graves à long terme (dont les effets CMR, les maladies neurodégénératives ou immunologiques chez les animaux et/ou l'être humain).

Il faudrait également admettre que l'impact de l'exposition aux PPPs sur des phases spécifiques la vie ou sur des biomarqueurs spécifiques, comme la prévalence de cancers pédiatriques pendant la grossesse, ou les états neurologiques comme la MP, n'est peut-être pas complètement couvert par les études sur des animaux imposées dans les lignes directrices, prises en compte pour les dossiers de toxicité des PPPs (dans l'UE et dans le monde). De même, le dépistage d'effets pour d'autres groupes vulnérables de personnes présentant des caractéristiques génétiques spécifiques n'est pas possible au moyen des études de toxicologie classique. À titre d'exemple, on peut se référer à des études de population démontrant un impact accru de l'exposition ambiante à des PPPs chez les personnes présentant des antécédents familiaux de cancer de la prostate. C'est pourquoi les évaluateurs de risques devraient reconnaître la nécessité d'efforts supplémentaires pour affiner et compléter les exigences de données actuelles et les évaluations de risques correspondantes afin de combler autant que possible les lacunes dans les connaissances en ces domaines.

Au cas où une substance active a été identifiée expérimentalement comme ayant des effets CMR probablement pertinents pour l'être humain (*p. ex.* génotoxique, carcinogène, ou perturbateur endocrinien manifeste), son approbation est retirée au niveau de l'UE et elle entre en phase d'extinction pour ce qui est de l'autorisation de produits au niveau régional/national, y compris en Belgique. Dans ce contexte, il est à souligner que même si la pertinence pour l'être humain n'est que suspectée, le mode d'action n'est malheureusement jamais déterminé sans équivoque.

En l'absence de modes/mécanismes d'action plausibles, la probabilité d'un *lien de causalité* entre les PPPs et les effets à long terme demeure incertaine du point de vue de la gestion des risques. La nécessité de davantage de recherche fondamentale se justifie en ce qui concerne par exemple les dommages sur l'ADN, le stress oxydatif, les effets sur le métabolisme et la perturbation endocrinienne est un thème récurrent dans l'évaluation des risques. En particulier pour l'évaluation de la MP, une avancée par le recours à des approches plus récentes, axées sur des mécanismes d'action présumés, éventuellement associées (mais non limitées) à des études de toxicité après administration répétée imposées dans les lignes directrices, paraît primordiale à cet égard.

Perspectives futures :
Fondamentalement, pour évaluer les effets à long terme des PPPs sur la population humaine ou pour réduire autant que possible l'exposition aux PPPs en champs,, il faut se concentrer sur 5 points principaux :

(i) Mettre l'accent tant sur les **études à long terme résultant de la science réglementaire** imposées dans des lignes directrices que sur les études publiées dans la littérature en accès libre, y compris les alternatives *in vitro*.
Les évaluations existantes devraient donc être motivées le plus possible par l'exploration de nouveaux modes d'action, afin de combler d'éventuelles lacunes dans les connaissances actuelles de biomarqueurs encore inconnus à ce jour. Un exemple notable est le manque de données sur la maladie de Parkinson ou certains cancers hématologiques que des études sur des animaux ne permettraient pas de combler. En particulier pour l'évaluation de la MP, une avancée par l'utilisation d'approches plus récentes *in vitro*, entre autres, paraît primordiale à cet égard.

(ii) Assurer un suivi maximal des études **épidémiologiques** (surtout prospectives), associées à des techniques pour évaluer au mieux les taux d'exposition réels, en utilisant des outils de biosurveillance par exemple. L'exploitation plus efficace des matrices cultures-expositions combinées aux données sur l'achat/l'utilisation de PPP professionnels - données actuellement sous-utilisées - constitue un outil supplémentaire pour se forger une meilleure idée des taux d'exposition réels sur le terrain.

(iii) En Belgique (mais aussi dans d'autres États membres de l'UE pratiquant l'agriculture intensive), il faut évaluer d'urgence les risques potentiels liés à l'exposition à court ou à long terme à des PPP, par exemple dans des zones connues pour leur exposition élevée à des PPPs comme les cultures fruitières et les cultures de plantes ornementales etc., qui sont des secteurs réputés pour leur recours à des niveaux élevés ou à une grande diversité de PPPs. Ceci vaut pour les agriculteurs et les opérateurs, mais plus encore pour les habitants alors que pour ces derniers, il manque encore de nombreuses données sur leur exposition aux PPP.

(iv) Des moyens supplémentaires devraient être consacrés à la conception de **registres** fiables et solides sur les effets graves/à long terme. En Belgique (comme dans d'autres pays de l'UE), les registres du cancer existent depuis environ une décennie. Néanmoins, en Belgique, le manque de registres fiables des anomalies congénitales couvrant l'ensemble du territoire est flagrant. Il est urgent de constituer un **réseau belge** de collecte de données à grande échelle qui alimenterait la base de données de l'UE sur les troubles de la fertilité et les anomalies congénitales (voir les objectifs d'EUROCAT).

(v) L'établissement d'un lien de causalité entre l'exposition aux PPPs et les effets néfastes sur la santé dépend fortement d'une **évaluation précise** de l'exposition aux PPP. En l'absence de telles données, l'effet est lissé. Le besoin effectif d'imposer par une loi **un enregistrement en ligne** de l'utilisation réelle des PPPs, la possibilité juridique de le faire et de prévoir un contrôle officiel de la saisie de ces données, ainsi que la valeur potentielle du croisement de ces données avec celles sur la localisation et subséquemment avec des données sanitaires (registres du cancer, anomalies congénitales...) à l'aide d'un système d'information géographique (ISG), font de cette approche un outil très efficace pour étudier la surveillance post-marché des risques à long terme que les PPPs font peser tant sur les catégories professionnelles que sur la population générale.
Il est en outre possible d'utiliser la même méthodologie pour estimer de façon plus fiable les niveaux de PPP et en prédire les concentrations dans l'environnement, et pour surveiller les substances actives dans des niches environnementales tels que les eaux de surface et la nappe phréatique.

(vi) Enfin, examiner les manières **d'éviter autant que possible l'exposition** aux PPPs lors de l'application en conditions réelles afin de protéger les opérateurs, les ouvriers, les passants et les résidents. Les mesures réglementaires possibles comprennent l'instauration systématique de zones tampons pour l'application en champ (2 m) ou sur vergers (5 m), en-deçà desquelles aucune évaluation fiable de l'exposition n'est possible faute de données d'exposition. En plus de recourir à l'ingénierie de contrôle qui évolue rapidement comme l'épandage ciblé (à l'aide de drones par exemple), il faut d'urgence créer systématiquement des zones tampons bien définies et faciles à faire respecter pour protéger les riverains des parcelles agricoles, en particulier les personnes vulnérables (enfants, personnes âgées, femmes enceintes...).

Il revient aux gestionnaires de risques et aux décideurs politiques de déterminer dans quelle mesure tout ceci est préoccupant et de prendre des mesures socio-économiques en la matière.

Uitvoerige samenvatting

De kwestie van de epidemiologie van kanker en andere ernstige effecten is en wordt nog steeds uitvoerig bestudeerd. Zoals eerder besproken, is men van mening dat een door de Federale Overheidsdienst (FOD) Volksgezondheid, Veiligheid van de Voedselketen en Leefmilieu opgestarte monitoringstudie geen zinvolle nieuwe informatie zou toevoegen aan de campagnes die tot nog toe worden gevoerd.
In plaats daarvan is een kritische en objectieve beoordeling van de nieuwe wetenschappelijke literatuur door de federale overheid een veel realistischer en haalbaarder doel met het oog op beleidsondersteunende maatregelen.
Er werd besloten om uit te gaan de studieresultaten van de Franse AGRICAN-cohorte (die intussen deel uitmaakt van een internationaal consortium dat 21 andere cohorten, verspreid over 9 landen, omvat (zie http://agricoh.iarc.fr/)).
Daarom volgt de FOD regelmatig de wereldwijd gepubliceerde, intercollegiaal getoetste wetenschappelijke artikelen op die handelen over mogelijke overincidenties van langetermijneffecten verbonden aan het gebruik van gewasbeschermingsmiddelen.

In verschillende systematische studies, waaronder het EFSA-rapport (2013) en het voormalige INSERM-rapport (2013 en 2021), werden aanwijzingen voor positieve associaties gevonden voor de hele klasse van bestrijdingsmiddelen, via verschillende blootstellingsroutes, en voor verschillende gezondheidsuitkomsten. De EFSA-studie was niet beperkt tot harde klinische bevindingen zoals kanker, neurodegeneratieve aandoeningen of ontwikkelingseffecten, maar omvatte ook andere uitkomsten, waaronder eindpunten van blootstelling (biomonitoring), voor de periode 2006-2012. Er werden twee aandoeningen genoemd, namelijk kinderkanker en neurologische aandoeningen, zoals parkinsonisme. Naar aanleiding van deze en andere studies publiceerde de EFSA later een analyse (2017) waarin werd vastgesteld dat voornamelijk een **gebrekkige karakterisering van de blootstelling** de belangrijkste beperking van epidemiologische studies vormde. Het frequente gebruik van case-controlstudies in plaats van prospectieve studies werd als een andere beperking beschouwd. Inadequate definities of tekortkomingen in de gezondheidsresultaten moeten worden vermeden en de rapportage van de bevindingen zou in sommige gevallen kunnen worden verbeterd.

Rekening houdend met de hogere waarde van cohortstudies werd vastgesteld dat de resultaten van de AGRICAN-cohortstudies voor de publicatiejaren 2013 tot 2020 een betrouwbare uitgangsbasis zouden vormen voor verdere aanbevelingen betreffende de mogelijke langetermijneffecten van gewasbeschermingsmiddelen (GBM).

In 2021 werden 10 belangrijke intercollegiaal getoetste AGRICAN-publicaties en 4 samenvattingen van congressen geraadpleegd om de belangrijkste conclusies over de verbanden tussen sommige vormen van kanker bij de landbouwbevolking en hetzij blootstelling aan gewassen/dieren, hetzij blootstelling aan GBM samen te brengen. De totale incidentie van kanker werd (voor zover mogelijk) vergeleken met die welke naar voren kwam in andere epidemiologische cohortstudies, namelijk de Agricultural Health Study (AHS, VS), de Canadian Census Health and Environment Cohorts (CanCHEC), de Pesticides Users Health Study (PUHS, VK) en Nordic Occupational Cancer (NOCCA, Scandinavië). De belangrijkste bron van informatie was de AHS, die net als AGRICAN een prospectieve cohortstudie is.

In een vroege publicatie meldden Tual *et al.* (2013) dat er een significant verband was tussen vergiftiging door GBM en blootstelling aan GBM in de aardappelteelt en het risico op chronische bronchitis, maar dat de aard en omstandigheden van de blootstelling aan gevaarlijke stoffen verder moesten worden onderzocht. Een andere studie van Baldi *et al.* (2014) die betrekking had op de luchtwegen toonde een verhoogd risico op allergische astma aan, dat werd waargenomen bij blootstelling aan bepaalde gewassen, gebruik van GBM en opgroeien op een boerderij met wijnbouw, grasland, bieten, fruit- en groenteteelt. Hieruit bleek dat, ook al blijven de precieze mechanismen (directe schade aan de luchtwegen, interacties met irriterende receptoren, modulatie van de ontstekingsreactie enz.) onduidelijk, praktische maatregelen om de impact van mogelijk schadelijke risicofactoren zoals GBM te beperken, nauwgezet bestudeerd moeten worden.

In Levêque-Morlais *et al.* (2015) bleek uit de eerste sterfteresultaten verkregen in de AGRICAN-cohorte dat landbouwers **geen bovengemiddelde oversterfte** als gevolg van de landbouw (en dus ook van het gebruik van GBM) aangaven in vergelijking met de algemene bevolking.
Lemarchand *et al.* (2017) vonden dat de **totale incidentie van kanker** in de AGRICAN-cohorte en de algemene bevolking niet veel verschilde. Er werd geen statistisch significant verschil waargenomen voor de totale kankerincidentie, met ongeveer gelijke gestandaardiseerde incidentiecijfers voor ♂ en ♀. De specifieke gestandaardiseerde incidentiecijfers waren echter significant hoger voor **prostaatkanker** (+7%) en **non-Hodgkin lymfoom** (NHL) (+9%) bij ♂, huidmelanoom bij ♀ (+23%) en **multipel myeloom** (MM) (+38% ♂ en +26% ♀).

In het volgende deel worden de AGRICAN-studies waarbij verbanden tussen specifieke vormen van kanker en landbouwactiviteiten werden waargenomen, samengevat:

In Lemarchand *et al.* (2016) vonden de AGRICAN-onderzoekers een verhoogd risico op **prostaatkanker** in een aantal verschillende situaties, namelijk bij veehouders, graslandactiviteiten, fruittelers en aardappel-/tabaksproducenten. Er werd opgemerkt dat in sommige gevallen de onderverdeling van de onderzochte populatie (taken, betrokken gebied, duur ...) kan leiden tot steekproeven met een onvoldoende aantal gevallen, waardoor de biologische zinvolheid kan verminderen. Wanneer de totale cijfers worden geanalyseerd, moet worden gezegd dat voor de populatie "gebruik van bestrijdingsmiddelen op gewassen" geen duidelijke, statistisch significante toename van het risico op prostaatkanker kon worden aangetoond. Opvallend was dat in bepaalde (maar niet alle) gevallen hogere risico's werden vastgesteld bij mensen die nooit beschermende handschoenen droegen, wat het belang van persoonlijke bescherming bij het hanteren van GBM en het oogsten onderstreept.

Boulanger *et al.* (2017) meldden een mogelijk verband tussen landbouwactiviteit, in het bijzonder vollegrondsgroenten (+89%) en glastuinbouw (+95%), en blaaskanker. Er kan op gewezen worden dat, hoewel geen enkele specifieke werkzame stof in verband werd gebracht met deze verhoogde incidentie, de mogelijke bijdrage van arseenverbindingen, die in het verleden massaal werden gebruikt in de Franse landbouw, op Belgisch niveau geen reden tot bezorgdheid vormt en hoe dan ook in de EU verboden is.

Het risico op longkanker (Tual et al., 2007) was omgekeerd evenredig met de blootstelling aan runderen (-40%), vooral na een lange periode van landbouw (40 jaar), en het effect was van geringe betekenis in de paardenhouderij, terwijl het niet werd waargenomen in de pluimvee- of varkenshouderij. Sterkere verlaagde risico's werden gemeld bij personen die dieren hadden verzorgd, deelgenomen hadden aan het melken en als kind aan runderen waren blootgesteld. De auteurs beschouwden de resultaten als een sterk bewijs van een omgekeerd verband tussen longkanker en vee- en paardenhouderij.

Boulanger *et al.* (2018) rapporteerden over verbanden tussen longkanker en verschillende gewasgerelateerde taken (onder andere wijnbouw). Met uitzondering van een significant effect bij gebruikers van GBM (2× verhoogd risico) en een tendens bij oogsters waren de meeste bevindingen echter van gering statistisch belang. In een recente congresmededeling (Boulanger *et al.*, 2019), die moet worden bevestigd in een volledige, intercollegiaal getoetste studie) van deze auteur, is een verhoogd risico op longkanker bij vrouwen vastgesteld, vooral wanneer het gaat om arseenverbindingen. Er werd echter gesteld dat in dit stadium de beoordeling van de blootstelling moet worden verfijnd en ook werd erkend dat enkele toevallige bevindingen als gevolg van meervoudige vergelijkingen niet konden worden uitgesloten. Het is ook nuttig erop te wijzen dat werkzame stoffen op basis van arseenzouten nooit zijn toegestaan in België.

Een mogelijke rol van GBM bij het ontstaan van tumoren van het centrale zenuwstelsel (CZS) is onderzocht in een reeks publicaties (Piel *et al.*, 2017-2019), waarbij een hoger risico werd waargenomen bij GBM-gebruikers (+96%), maar het algemene verband werd minder significant wanneer elk tumortype (glioom en meningeoom) afzonderlijk werd onderzocht. Er werd ook een aanzienlijke toename van het risico op meningeomen gevonden bij varkenshouders die dieren verzorgden en/of plaatselijk ontsmetten (+143%). In vervolgstudies stelden de auteurs verschillende insecticiden, fungiciden en herbiciden op basis van carbamaat voor als mogelijke kandidaten voor de waargenomen bevindingen op het vlak van hersentumoren. Hoewel een mogelijke werkingswijze zou kunnen worden voorgesteld (namelijk oxidatieve stress die door veel carbamaten wordt veroorzaakt), moet worden opgemerkt dat de meeste van de genoemde werkzame stoffen niet meer in de EU in de handel zijn of geleidelijk uit de handel worden genomen.

Bij de verfijning van het resultaat voor MM vonden Tual *et al.* (2019) verhoogde incidenties bij mensen die sinds 1960 GBM gebruiken op gewassen (vooral maïs), wat mogelijk wijst op een stuwend effect van oudere, verouderde GBM, en bij mensen die insecticiden gebruiken bij dieren of ontsmettingsmiddelen in dierenstallen. Hoewel hematologische bevindingen ook in verband kunnen worden gebracht met andere biologische factoren (waarvan bekend is dat ze een rol spelen in de vleesindustrie), hebben recente cohortstudies (zoals de AGRICOH-cohorte, met inbegrip van de gegevens van AGRICAN) geen verbanden aangetoond tussen veehouderij en lymfohematopoëtische kankers (LHC's). Rekening houdend met het verhoogde risico van MM bij de landbouwbevolking, met name bij gebruikers van GBM in 4 op 5 prospectieve en retrospectieve cohortstudies, lijkt het echter van belang dat aan deze kwestie meer aandacht wordt besteed.

Er werd opgemerkt dat NHL of een van de subtypes ervan in 2 op 5 cohortstudies licht maar consistent verhoogd waren. Recente congresmededelingen (Busson *et al.*, 2019a,b en 2020, volledige gegevens niet beschikbaar) suggereerden echter opnieuw een mogelijk verband, ook in de AGRICAN-cohorte. De voorlopige gegevens zouden de rol van de blootstelling aan bestrijdingsmiddelen (met inbegrip van benzimidazolen) in het risico van NHL ondersteunen, zowel bij gebruik bij gewassen als bij landbouwhuisdieren.

Andere recente (maar ook voorlopige) resultaten van de AGRICAN-cohorte illustreren een mogelijk verband tussen landbouwactiviteiten in sommige veeteeltbedrijven (runderen) en vollegronds- of kasgewassen, en verhoogde incidenties van sarcoom (Renier *et al.*, 2020). Hoewel deze gegevens voorlopig zijn, moet worden opgemerkt dat de absolute aantallen in sommige gevallen als zeer laag werden beschouwd, en dat deze zeer heterogene en complexe groep sarcomen slecht beschreven is in de wetenschappelijke literatuur. Daarom moet de interpretatie van deze bevindingen voorlopig met de grootste omzichtigheid worden benaderd. De verschillende verbanden die naar voren zijn gebracht tussen dierlijke productieactiviteiten of teelten (groente, kasteelt) en het vóórkomen van sarcomen verdienen nader onderzoek alvorens een oorzakelijk verband met de blootstelling aan GBM kan worden bevestigd.

Samenvattend kan worden gesteld dat de resultaten van de belangrijkste prospectieve cohorten in de VS en de EU over het algemeen vergelijkbaar waren wat de totale kankerincidentie betrof. Voor elke cohorte afzonderlijk was er echter een overincidentie van specifieke tumortypes, die niet werd waargenomen in de andere cohorten. Opmerkelijk was echter de aanwezigheid van een overincidentie voor MM, prostaatkanker en NHL in respectievelijk 4/5, 3/5 en 2/5 van de cohorten.
Er dient op gewezen te worden dat een vergelijking tussen de resultaten van deze cohorten, zelfs indien een indrukwekkend aantal personen werd onderzocht, met de nodige voorzichtigheid moet worden geïnterpreteerd. De methodologieën kunnen verschillen (prospectief/retrospectief), de referentiepopulaties kunnen verschillen (algemene bevolking/niet-blootgestelde landbouwers enz.), er wordt niet altijd een onderscheid gemaakt tussen de verschillende soorten landbouwactiviteiten (landbouwers, gebruikers van pesticiden, bedrijfsleiders, arbeiders enz.), de tellingen kunnen beperkt zijn tot landbouwers met getuigschriften van vakbekwaamheid (bv. PUHS), verschillende inschrijvingsperioden bestrijken of deel uitmaken van grotere beroepsstudies (bv. NOCCA).

Voor een vergelijking van de totale kankerincidentie heeft ze echter wel enige waarde.

Opmerking: de AGRICAN-uitkomst voor kanker, zoals gepubliceerd in een peer-reviewed artikel van Lemarchand *et al* (2017), besloeg de periode 2005-2011 en is weergegeven in tabel 1. De overincidentie van tumoren bij de boeren wordt vergeleken met die in de bevolking. Onlangs (AGRICAN, 2020) is op internet een rapport gepubliceerd waarin verschillende incidenten worden genoemd. De nieuwe incidenties zijn geregistreerd in de periode 2005-2015, wat het verschil gedeeltelijk kan verklaren. Waar het recente AGRICAN-rapport zeker intern nagekeken is, is het niet gepubliceerd in een peer-reviewed wetenschappelijk tijdschrift, waardoor de graad van detail lager dan in een wetenschappelijk artikel. De gepubliceerde overincidenties volgen echter dezelfde trends en veranderen de conclusies in het FOD-overzicht niet wezenlijk.

Tabel 1: Incidentierisico van algemene en specifieke kankers bij landbouwers/gebruikers in vergelijking met het risico in de algemene bevolking

Type kanker	AGRICAN (FR)	AHS			NOCCA (Scandinavië)	PUHS (VK)	CANCHEC (Canada)
Publicatiejaar	*2017*	*2005*	*2010*	*2019*	*2009*	*2011*	*2017*
Alle kankers	*§[↓5/↓7]*	↓12%	↓15%	↓9%	n.a.	↓42%|↓29	↓5%
Dikke darm	-	-	-	([↑6]ʳ)	-	-	-
NHL	↑9 | - *§[↑9 |]*	-	[↑17]ʳ	(↑12)@ [↑26]ʳ	-	-	-
CLL		-		↑17 [↑30]ʳ	-	-	-
DLBCL	-	-	[↑27]ʳ	(↑16) [↑29]ʳ	-	-	-
FL				[↑27]ʳ	-	-	-
MM	↑38|↑26 *§[↑20/↑21]*	(↑34)	↑42	(↑18) [↑99]ʳ	↑7|↑14	↑49|↑990#	-
Waldenström £	*§[↑49/↑58]*						
Leukemie	-	-	-		-	-	-|↑101
AML	-	-	-	↑29 [↑42]ʳ	-	-	-
Lip °	-|- *§[↑55 | -]*	-	↑97	↑122 [↑146]ʳ	↑57|-	-	↑14|↑125
Melanoom °	-|↑23 *§[-/↑29]*	-	-	[↑12]ʳ	-	-	↑15|↑79
Niet-melanoom huid	-	-	-	-	-	-|↑73	-
Eierstok	-	-	-	[↑99]ʳ	-	-	-
Pancreas	-	-	-	-	-	-	-|↑36

Type kanker Publicatiejaar	AGRICAN (FR)	AHS			NOCCA (Scandinavië)	PUHS (VK)	CANCHEC (Canada)
	2017	*2005*	*2010*	*2019*	*2009*	*2011*	*2017*
Prostaat	↑7 § *[↑3]*	↑24	↑19 [↑66]r	↑15 [↑44]r	-	-	↑11
Teelballen	-	-	-	[↑45]r	-	↑26	-
Schildklier	-	-	-	[↑28]r	↑18	-	-

- Procentuele verschillen (↑toename/↓afname) in gestandaardiseerde incidentiecijfers, behalve sterftekans in CANCHEC;
- - : geen statistisch significant verschil en (..): gering (laagste 95% BI-waarde = 0,98) statistisch verschil
- waarden voor ♂ | ♀ (behalve voor AHS); [..]r: relatieve gestandaardiseerde incidentiecijfers; n.b.: niet beschikbaar; °: beschouwd als verband houdend met zonlicht;
- #: schatting zeer onnauwkeurig, rekening houdend met het zeer grote betrouwbaarheidsinterval van 95%
- @: beperkt tot B-cel NHL
- §*[..]:* Recente AGRICAN data (2020) in italics, refererend naar periode 2005-2015, vergeleken met de gepubliceerde data (2017, refererend naar de periode 2005-2011)
- £: a.k.a. plasmocytisch lymfoom, voorheen niet geciteerd in de cohortes

Een eerste conclusie van de AGRICAN-studie, die door andere cohortstudies wordt ondersteund, is dat de langetermijngevolgen van een levenslange blootstelling aan dieren, gewassen en pesticiden nogal uiteenlopend kunnen zijn. Uitgaande van het aantal gevallen van kanker in het algemeen of van het aantal sterfgevallen ten gevolge van kanker, zijn de cijfers in de landbouwgemeenschap niet spectaculair slechter dan die van de bevolking in het algemeen. Integendeel, er is over het geheel genomen zelfs een kleine, maar consistent lagere oversterfte, en ook de totale incidentie van kanker kan zelfs niet te onderscheiden zijn van (AGRICAN), d.w.z. ongeveer 10-15% lager dan die van de algemene bevolking.

De incidentiecijfers bij werknemers in de landbouw en bij personen die GBM gebruiken, vertonen wellicht een overincidentie van een beperkt aantal tumoren, waaronder **lymfopoiëtische kankers** (met inbegrip van **MM**) en **prostaatkanker** de meest voorkomende lijken te zijn.

Bovendien wijst het bewijsmateriaal ook op een gering maar vrij consistent verband tussen de blootstelling aan GBM en/of insecticiden die bij dieren worden gebruikt en de **ziekte van Parkinson**.

Het meest overtuigende verband komt uit studies waarvan algemeen wordt aangenomen dat ze van groot belang zijn, zoals prospectieve cohortstudies. Er wordt opgemerkt dat het effect van de duur van de blootstelling op mRR vaak onzeker is. Recente pogingen om op een kwantitatieve manier het effect van de duur op de incidentie van de ziekte van Parkinson te schatten, brachten slechts zwakke verbanden aan het licht: een blootstellingsduur van 5 tot 10 jaar aan GBM werd geassocieerd met een tussen 5 en 11% verhoogd risico op de ziekte van Parkinson, respectievelijk (Yan *et al.,* 2018). Hoewel veel studies de hypothese dat een beroepsmatige blootstelling aan GBM het risico op de ziekte van Parkinson zou verhogen enigszins ondersteunen, bestaat er anderzijds een zeer brede consensus onder epidemiologen dat de nauwkeurigheid van de blootstellingsgegevens dringend moet worden verbeterd om een potentieel oorzakelijk verband tussen de ziekte van Parkinson en blootstelling aan GBM te kunnen bevestigen. Er wordt ook aangenomen dat verdere (prospectieve) cohortstudies van hoge kwaliteit nodig zijn om een dergelijk oorzakelijk verband te valideren. Om de ramingen van de blootstelling te verbeteren is er een grote behoefte aan de invoering van juridisch bindende en controleerbare registratie-instrumenten die het feitelijke gebruik in de landbouwsector inventariseren.

De moeilijkheden en beperkingen van de beoordelingen aan de blootstellingszijde kennende, zijn aan de gevarenzijde veel verwachtingen gewekt, namelijk bij de ontwikkeling van gevalideerde *in-vitro*-analyses en daarmee samenhangende AOP's. Deze laatste moeten een mechanistische plausibiliteit bieden voor epidemiologische waarnemingen betreffende een verband tussen de blootstelling aan pesticiden en een verhoogd risico op de ontwikkeling van de ziekte van Parkinson.

De conclusies van deze analyse waren hoofdzakelijk gebaseerd op gegevens in epidemiologische prospectieve cohorten, die superieur worden geacht aan case-controlstudies, die last kunnen hebben van recall bias, hoewel case-controlstudies gevoeliger kunnen zijn voor het identificeren van zeldzame tumoren. De meta-analyse, waarin al deze studies worden samengebracht, wijst echter ook op dezelfde tendens en versterkt het vertrouwen in het verkregen beeld.

Wanneer de grootste cohorten wereldwijd (met inbegrip van AGRICAN, sommige cohorten, en AHS) samen worden bekeken, mag niet uit het oog worden verloren dat vergelijkingen van de resultaten om een aantal redenen moeizaam kunnen zijn.

(iv) Terwijl de AGRICAN-studies vooral gericht zijn op langetermijneffecten na contact met gewassen en landbouwhuisdieren, heeft de AHS-studie meer betrekking op effecten na blootstelling aan GBM en minder op landbouwactiviteiten op zich.
(v) Sommige cohorten, zoals NOCCA en CANCHEC, maken deel uit van een grotere epidemiologische telling en zijn niet opgezet om specifiek het lot van de landbouwbevolking te onderzoeken.
(vi) De referentiepopulaties kunnen verschillend zijn, en de vergelijking van de incidentiecijfers is dan ook niet zonder meer mogelijk.

Het moge duidelijk zijn dat zelfs alleen al een vergelijking tussen AGRICAN en AHS, vooral wat betreft een mogelijk verband tussen overincidenties en blootstelling aan GBM, en met name specifieke werkzame stoffen of klassen daarvan, uiterst moeilijk is. Er werd echter een algemene tabel opgesteld om de bevindingen samen te vatten (tabel 2). Er wordt opgemerkt dat de vergelijking vooralsnog geen zinvolle concordantie oplevert voor de werkzame stoffen waarvoor er een risico zou bestaan voor de tot op heden bestudeerde waargenomen kankers. Bovendien is het ook duidelijk dat de meeste van de werkzame stoffen waarvoor een verband werd gesuggereerd in de AHS-cohorte niet meer worden gebruikt in de EU, en dus ook niet in België, aangezien bv. organochloorverbindingen al verboden zijn en er nog maar weinig werkzame stoffen overblijven in de klasse organofosfaten en carbamaten. De enige kandidaat-GBM die in de VS worden gebruikt en nog steeds een probleem zouden kunnen vormen, zijn beperkt tot glyfosaat (verband betwistbaar), 2,4-D, (S-)metolachloor, pendimethalin, deltamethrin en dicamba. Ook zijn de werkzame stoffen die in de AGRICAN-studie zijn bestudeerd of geciteerd, niet allemaal goedgekeurd. Een beperkt aantal carbamaten (IN, FU, HE) wordt nog als GBM gebruikt, samen met enkele fenoxyherbiciden. Er wordt geen verdere analyse verricht voor werkzame stoffen die worden gebruikt als biociden (bv. ontsmettingsmiddelen) of als diergeneeskundige insecticiden.

Tabel 2: Concordantie tussen geciteerde werkzame stoffen of studies in de prospectieve cohorten

Type kanker	Verband met specifieke werkzame stoffen of klassen	
	AGRICAN	AHS
PROSTAAT	geen	methylbromide
		chloorpyrifos, coumafos, fonofos, foraat en permetrine voor dierlijk gebruik, en het herbicide butylaat
		organofosfaatverbindingen, fonofos, terbufos, aldrin
BLAAS	geen	imazethapyr, imazaquin; metolachloor (*), **2,4-D,** 2,4,5-T, organochloorverbindingen
LONG	geen	geen
	geen	
	arsenaatzouten	**metolachloor (*), pendimethalin**, chlorpyrifos, diazinon,
		pendimethalin, dieldrin, parathion, chlorimuron-ethyl
HERSENEN	**insecticiden op basis van carbamaat**, carbaryl, **formetanaat**, thiofanox	
	fungiciden en herbiciden op basis van carbamaat, mancozeb, maneb, metiram, chloorprofam, propham, di-allaat,	
MULTIPEL MYELOOM	organochloorverbindingen, carbaryl, permethrin, dichloorvos, captan, **fenoxyherbiciden**, atrazin, dinoterb, **ontsmettingsmiddelen**	**glyfosaat** (?)
		permethrin
NHL	geen	organofosfaatverbindingen, malathion, diazinon
	benzimidazolen (thiofanaat-methyl?)	terbofos, **deltamethrin**; **glyfosaat**? (DLBCL, CNAP)
		dicamba (CLL)
SARCOOM	geen	

(*: niet bevestigd in vervolgonderzoek (FU) van de AHS, maar zowel lever- als folliculair cellymfoom werden gevonden in FU)

Rekening houdend met de uiteenlopende gegevens (mogelijk als gevolg van verschillende goede landbouwpraktijken (GLP), methodologieën, statistische behandeling, verschillende modellen die de blootstelling aan GBM benaderen ...) is het wetenschappelijk bewijs dat de blootstelling aan GBM bij de landbouwbevolking in België tot ernstige ziekten leidt, op dit ogenblik onderwerp van een aanzienlijke wetenschappelijke discussie.

Toch verdient een beperkt, maar enigszins consistent verband tussen **lymfopoëtische en prostaatkankers** en landbouwactiviteiten nader onderzoek. Voorts is een verband tussen blootstelling aan GBM en de **ziekte van Parkinson** voor de meeste onderzoekers niet uitgesloten en zijn verdere inspanningen zowel aan de blootstellingskant (epidemiologie, registratie van feitelijk gebruik) als aan de risicokant (alternatieve teststrategieën) gerechtvaardigd om het probleem van het oorzakelijk verband tussen blootstelling aan GBM en de ziekte van Parkinson op te lossen.

De bestaande open wetenschappelijke literatuur, met inbegrip van de krachtigste observationele studies, wijst op een specifieke incidentieverhoging van langetermijneffecten die verband houdt met de blootstelling aan gewassen en/of aan GBM. Deze studies gaan echter ook gepaard met onnauwkeurigheden en onzekerheden, waardoor enige verwarring is ontstaan over een juiste interpretatie van de feiten. Verscheidene elementen die mogelijk voor verbetering vatbaar zijn, worden hieronder beschreven.

(i) Verreweg de grootste bron van onzekerheid in epidemiologisch onderzoek blijft de schatting van de feitelijke blootstelling. In prospectieve cohorten worden de blootstellingsgegevens bij het begin van de inschrijving geregistreerd en kunnen ze daarna verschillende keren worden bijgewerkt om mogelijke veranderingen in goede landbouwpraktijken op te sporen. Bij case-controlstudies daarentegen is er sprake van recall bias, waarbij zieke mensen geneigd zijn de blootstelling aan GBM die zij als gevolg van hun aandoening hebben ondervonden, te overschatten. Maar zelfs bij cohortstudies berusten de meeste blootstellingsgegevens op opgegeven werkschema's en gebruikskalenders, in het beste geval aangevuld met modellen op basis van 'gewassen-blootstelling matrices'. Ook deze laatste aanpak heeft echter zijn beperkingen, aangezien zelfs goed uitgevoerde experimentele veldproeven gemeten blootstellingswaarden kunnen opleveren die verscheidene orden van grootte variëren.

(ii) Vaak is betoogd dat een verkeerde classificatie van de blootstelling waarschijnlijk niet-differentieel zal zijn, en de relatieve risico's in de richting van de nulhypothese zal vertekenen en eventuele "echte" blootstellings-responsgradiënten zal doen afnemen, maar evenzeer is aangetoond dat in feite zowel een te lage als een te hoge schatting kan voorkomen, hoewel wordt erkend dat in het geval van voldoende grote cohorten een niet-differentiële verkeerde classificatie waarschijnlijk zou zijn.

(iii) In veel gevallen wordt een aanzienlijk aantal parameters (gewassen, landbouwhuisdieren al dan niet in verband met GBM-gebruik) getest, en het was vaak niet duidelijk of voldoende moeite is gedaan om uit te sluiten dat sommige bevindingen aan het toeval te wijten zouden kunnen zijn. Ongeacht andere verwarrende factoren blijft de kwestie van meervoudige tests een ernstig probleem in observationele studies.

(iv) Hoewel het duidelijk is dat in epidemiologische studies per definitie wordt gekeken naar gezondheidsuitkomsten die mogelijk het gevolg zijn van blootstelling aan dieren, gewassen of GBM die tientallen jaren vóór de inschrijving in de epidemiologische studie plaatsvond, is men zich er onvoldoende van bewust dat verbanden onvermijdelijk voor een stuk het gevolg zijn van toepassingen met GBM die in de EU niet meer toegelaten zijn. Hoewel deze resultaten in absolute zin geldig blijven voor de onderzochte werkzame stoffen hebben ze weinig voorspellende waarde voor de werkzame stoffen die intussen op de markt zijn gebracht. Zo omvatten vaak onderzochte werkzame stoffen onder meer organochloorverbindingen, die in de EU thans totaal verboden zijn. Ook de neurotoxische organofosfaten en carbamaten zijn tegenwoordig vrijwel geheel verdwenen, en ook het aantal pyrethroïden neemt snel af. Daarom is het waarschijnlijk dat epidemiologisch onderzoek alleen een ontoereikend instrument is in het kader van de toxicovigilantie van GBM.

(v) Hoewel de blootstelling wordt uitgedrukt in hoeveelheden werkzame stof (hetzij individueel, hetzij gegroepeerd per klasse), moet worden benadrukt dat toepassers in feite worden blootgesteld aan producten die zowel werkzame stoffen als coformulanten bevatten. In tegenstelling tot werkzame stoffen zijn sommige van die hulpstoffen niet noodzakelijk inert, en kunnen ze op de markt worden gebracht met weinig of geen informatie over hun effecten op de gezondheid van mens of milieu (vooral als ze in kleine hoeveelheden worden geproduceerd). Het is duidelijk dat er een snelle inhaalslag nodig is om onafhankelijk informatie over de gevaren en de huidige niveaus van menselijke blootstelling te verzamelen en te evalueren, en daarmee rekening te houden bij de interpretatie van het effect van de "werkzame stof". Idealiter zouden alleen coformulanten mogen worden gebruikt waarvan de veiligheid voldoende is onderzocht.

(vi) Teneinde de beperking van de onzekere feitelijke blootstelling aan GBM te ondervangen, omvatten sommige recente epidemiologische studies experimentele fasen waarin reële milieumetingen en/of metingen in biologische stalen (bloed, plasma, urine, haar) opnemen, waardoor de lange termijn risico's (neurologisch, kanker) beter kunnen worden opgehelderd. Tot dusver zijn bestaande cohorten met dit soort merkers schaars, en zijn er slechts enkele veelbelovende voorbeelden van biomonitoring van immunologische bloedparameters die mogelijke voorstadia van kanker weerspiegelen (bv. monoklonale gammopathie van onbepaalde betekenis (MGUS) in het geval van multipel myeloom of ziekte van Waldenström).

(vii) Evenzo kunnen er ook modellen van blootstelling worden afgeleid uit betrouwbaardere toepassingsgegevens in het echte leven. In de EU-context is het bijhouden van een register van de gebruikte GBM verplicht, maar dit wordt tot dusverre onvoldoende benut. Als er gegevens over het gebruik van GBM worden bijgehouden, worden deze geenszins in draagbare vorm opgeslagen en blijft de informatie feitelijk ontoegankelijk voor gezondheidswerkers (en bovendien beperkt tot opslag ≤ 3 jaar). Op vergelijkbare wijze als de Pesticide Usage Reports (rapporten over pesticidegebruik) in Californië, die zijn gevaloriseerd voor onderzoeksresultaten (kruising van feitelijke blootstelling met het GIS en relevante uitkomsten van volksgezondheidsregisters), moeten dergelijke gegevens ook in de EU beschikbaar zijn en worden gebruikt.

Afgezien van bovengenoemde beperkingen is er een groeiende behoefte aan mechanistisch onderzoek ter ondersteuning van de interpretatie van de waargenomen overincidenties.

Het blijft belangrijk eraan te herinneren dat, hoewel uit studies bij mensen tot dusver slechts een aantal *verbanden* naar voren zijn gekomen tussen bepaalde langetermijneffecten en landbouwactiviteiten (waaronder, maar niet uitsluitend, blootstelling aan GBM), het *oorzakelijk verband* moeilijk vast te stellen blijft. Het is mogelijk dat de bestaande wettelijk voorgeschreven onderzoeken bij proefdieren niet noodzakelijk een volledig betrouwbare indicatie geven van het bevorderend vermogen, of niet in staat zijn mechanistisch bewijs te leveren van ernstige langetermijnresultaten (waaronder CMR-effecten, neurodegeneratieve of immunologische ziekten bij dieren en/of mensen) mogelijks veroorzaakt door bepaalde werkzame stoffen.

Ook moet worden erkend dat de gevolgen van de blootstelling aan GBM voor specifieke levensfasen of voor specifieke eindpunten, zoals de prevalentie van kanker bij kinderen tijdens de zwangerschap, of neurologische aandoeningen zoals de ziekte van Parkinson, mogelijk onvoldoende worden bestreken door de voor de toxiciteitsdossiers voor GBM in aanmerking genomen studies in verband met richtlijnen voor dieren (in de EU en wereldwijd). Evenzo kan het onderzoek naar het effect op andere kwetsbare groepen met personen die drager zijn van specifieke genetische eigenschappen niet volledig worden gedekt door de klassieke toxicologische studies. Als voorbeeld kan worden verwezen naar bevolkingsonderzoeken die aantonen dat blootstelling aan GBM in het milieu een groter effect heeft bij mensen met een familiale voorgeschiedenis van prostaatkanker. Daarom moeten risicobeoordelaars erkennen dat verdere inspanningen nodig zijn om de huidige gegevensvereisten en de daarmee samenhangende risico-evaluaties te verfijnen en aan te vullen, teneinde de leemten in de kennis op deze gebieden zoveel mogelijk op te vullen.

Indien een werkzame stof experimenteel is geïdentificeerd als CMR die waarschijnlijk relevant is voor de mens (bv. genotoxisch carcinogeen of duidelijk hormoonontregelend), wordt de goedkeuring ervan op EU-niveau ingetrokken en wordt de toelating van het product geleidelijk ingetrokken op zonaal/nationaal niveau, inclusief in België. In dit verband dient te worden onderstreept dat zelfs indien de menselijke relevantie slechts wordt vermoed, het werkingsmechanisme helaas nooit ondubbelzinnig wordt vastgesteld.

Bij gebrek aan plausibele werkingsmechanismen blijft de waarschijnlijkheid van *causaliteit* tussen GBM en langetermijneffecten vanuit het oogpunt van de risicobeoordeling onzeker. Er is een gerechtvaardigde nood aan meer fundamenteel onderzoek met betrekking tot bijvoorbeeld DNA-schade, oxidatieve stress, metabolische afwijkingen en endocriene modulatie, is een steeds terugkerend probleem bij de risicobeoordeling. Vooral voor de beoordeling van de ziekte van Parkinson lijkt een doorbraak naar nieuwere benaderingen, gericht op veronderstelde werkingsmechanismen, eventueel gekoppeld aan (maar niet beperkt tot) op richtlijnen gericht toxiciteitsonderzoek met herhaalde toediening, in dit verband van primordiaal belang.

Verdere perspectieven:
Uiteindelijk zijn er vijf belangrijke aandachtspunten om de langetermijneffecten van GBM op de menselijke bevolking te evalueren, of om de blootstelling aan GBM in het echte leven zo veel mogelijk te beperken:

(vii) De nadruk leggen op zowel **wettelijk voorgeschreven langetermijnonderzoek** gericht op richtlijnen als gepubliceerd open literatuuronderzoek, met inbegrip van *in-vitro*-alternatieven.
Bestaande evaluaties moeten dus zoveel mogelijk worden aangestuurd door het zoeken naar nieuwe werkingsmechanismen, om mogelijke lacunes in de huidige kennis van eindpunten op te helderen die tot nu toe onontdekt zouden zijn gebleven. Een opmerkelijk voorbeeld is het ontbreken van gegevens over parkinsonisme of bepaalde hematologische kankers die in dierstudies onontdekt zouden blijven. Vooral voor de beoordeling van de ziekte van Parkinson lijkt een doorbraak naar onder meer nieuwere *in-vitro*-benaderingen in dit verband van primordiaal belang.

(viii) Zorgen voor een maximale opvolging van (hoofdzakelijk prospectieve) **epidemiologische** studies, in combinatie met technieken om de reële blootstellingsniveaus zo goed mogelijk te beoordelen, bijvoorbeeld door gebruik te maken van biomonitoringinstrumenten. De efficiëntere exploitatie van ‘gewassen-blootstelling matrices’, in combinatie met de tot dusver onderbenutte aankoop-/gebruiksinformatie van professionele GBM, biedt een extra instrument om een beter zicht te krijgen op de reële blootstellingsniveaus in het veld.

(ix) In België (maar ook in andere EU-lidstaten met intensieve landbouw) is er dringend behoefte aan een evaluatie van het potentiële risico van blootstelling aan GBM op korte of lange termijn, bijvoorbeeld in regio's waarvan bekend is dat ze in hoge mate aan GBM worden blootgesteld, zoals door de aanwezigheid van fruitboomgaarden of de productie van sierplanten enz., sectoren die bekend staan om hun gebruik van grote hoeveelheden of een grote verscheidenheid aan GBM. Dit geldt voor de landbouwers en de gebruikers, maar meer nog voor de omwonenden, voor wie er nog veel gegevens over hun blootstelling aan GBM ontbreken.

(x) Er moeten meer middelen worden uitgetrokken om betrouwbare en degelijke **registers** van langdurige/ernstige effecten te ontwikkelen. In België worden (net als in andere EU-landen) sinds ongeveer een decennium kankerregisters bijgehouden. In België ontbreekt het echter ook op flagrante wijze aan een robuust gegevensbestand van ontwikkelingsstoornissen dat het hele land bestrijkt. Er is dringend behoefte aan een **Belgisch netwerk** dat op grote schaal gegevens verzamelt en op die manier de EU-databank inzake vruchtbaarheidseffecten en ontwikkelingsanomalieën ondersteunt (zie doelstellingen van EUROCAT).

(xi) De vaststelling van een verband tussen blootstelling en schadelijke gezondheidseffecten is sterk afhankelijk van een **nauwkeurige schatting van de blootstelling**, bij gebreke waarvan het effect wordt afgevlakt. De wettelijke mogelijkheid en de daadwerkelijke noodzaak om een **on-line registratie** van het feitelijke gebruik van GBM op te leggen, de mogelijkheid om deze inputs via rechtshandhaving te bewaken en te controleren, en de potentiële waarde van het kruisen van deze gegevens met locatiegegevens en bijgevolg gezondheidsgegevens (registers voor kanker, ontwikkelingsanomalieën ...) met behulp van GIS maken van deze aanpak een zeer krachtig instrument om het toezicht op de bedreigingen van GBM op lange termijn na het in de handel brengen ervan bij zowel beroepsgroepen als de bevolking in het algemeen te onderzoeken.
Bovendien zou dezelfde methodologie om GBM-niveaus in het milieu op een meer betrouwbare manier te schatten ook kunnen worden gebruikt om de verwachte milieuconcentraties te schatten en om werkzame stoffen te monitoren in milieucompartimenten, onder andere oppervlakte- en grondwater.

(xii) Tot slot moet worden gezocht naar manieren om **blootstelling aan GBM tijdens het gebruik "in het echte leven" zoveel mogelijk te vermijden**, teneinde exploitanten, werknemers, omstanders en omwonenden te beschermen. Mogelijke regelgevende maatregelen zijn onder meer de instelling van standaard bufferzones voor gebruik op het veld (2 m) of in boomgaarden (5 m), onder welke grens geen betrouwbare beoordeling van de blootstelling mogelijk is wegens het ontbreken van blootstellingsgegevens. Naast snel evoluerende technische mogelijkheden zoals het gericht aanbrengen (bv. via drones), is er dringend behoefte aan de instelling van standaard, duidelijke en gemakkelijk te handhaven bufferzones ten opzichte van omwonenden van landbouwbedrijven, en in het bijzonder ter bescherming van kwetsbare personen (kinderen, bejaarden, zwangere vrouwen enz.).

Het wordt aan de risicomanagers en de beleidsmakers overgelaten om de mate van bezorgdheid en de daarmee samenhangende maatregelen vast te stellen om in dit verband sociaal-economische maatregelen te nemen.

1 Introduction

1.1 Legal context

Since 2012, in the frame of the 2009/128 Directive, EU-Member States have to develop and implement a National Action Plan in order to reduce the risk due to the use of plant protection products (PPPs).

In their National Action plans, … "Member States shall put in place systems for gathering information on pesticide acute poisoning incidents, as well as chronic poisoning developments where available, among groups that may be exposed regularly to pesticides such as operators, agricultural workers or persons living close to pesticide application areas." (art. 7 (2) of 2009/128 Directive)

1.2 EU-member states' approaches

1.2.1 Outside Belgium

A review in 2016 of the National Action Plans (NAPs) in EU as published on CIRCABC shows two different approaches to get a view of the chronic effects of PPP.

1. Collection of chronical intoxication cases (Bulgaria, Cyprus, Czech Republic, France, Latvia, Luxemburg)
2. Investigations for an appropriate monitoring methodology (Finland, France, Italy)

Member State	**Monitoring measure (art.7.2)**
Bulgaria	Measure 11 : collection of info at Pirogov Hospital (from June '15) for professional users and residents. These result into indicators.
Cyprus	Collection of chronic incidents by authorities
Czech Republic	Monitoring of the sale of PPP with potential chronic damages. Collection of cases of chronic poisoning of people.
Finland	Investigation of means of gathering information on acute poisoning incidents and, as far as possible, chronic poisoning incidents related to PPPs.
France	Action 114 : coordination of toxicovigilance; development of monitoring tools
Italy	Coordination of the research to assess pesticide exposure and its acute and chronic impacts on the general public.
Latvia	Procedures for the establishment, updating and maintenance of a register of patients suffering from certain illnesses
Luxemburg	Development of a monitoring scheme.

In general, it is observed that the issue of monitoring of chronic intoxications, is difficult and EU Member States are not very successful in implementing this.

While Member States generally have systems to gather information on pesticide acute poisoning, the accuracy of these data and their use was questioned. Systems for gathering such information on chronic poisoning are not widely implemented. According to information gathered by the EU Council, ten Member States (The Czech Republic, Estonia, Lithuania, the Netherlands, Slovakia, Hungary, Poland, Germany, France and Bulgaria) have a "*dedicated system for gathering data on chronic poisoning*". In the remaining 17 Member States, chronic poisoning is not systematically monitored. Member States emphasised that it is particularly challenging to gather information on chronic poisoning developments, as it is very difficult to link clinical symptoms to pesticide exposure, which may have taken place many years previously. It is of note that from the ten MS cited, no MS published easily accessible data yet, generated by these purported dedicated systems.

https://www.consilium.europa.eu/media/31443/st13138en17.pdf

1.2.2 Belgian approach

In the Belgian National Action Plan (NAPAN), many projects[1] were dedicated to implement the obligations of the SUD-art. 7.2. These projects aim : to include biomarkers for pesticides in an existing biomonitoring programme; to collect information about population exposure; to review the scientific literature related to the effects of a chronic exposures to PPPs on professional users.

This report results from the last of the above projects.

[1] See projects Vla.4.1, Vla.4.2, Wal. 4.1, Wal. 4.2 and Fed.4.4 in the first programme. See also projects Fed.2.34 and Wal.2.3.3 in the second programme.

2 Available pertinent scientific information for Belgium

The issue of epidemiology and cancer and other severe effects has been studied and is still studied at length. It is not felt that a Federal Public Service Health, Food Chain Safety and Environment (FPS)-initiated monitoring study can add meaningful new information to the campaigns which are actually run.

Instead, critical and objective appraisal of the open scientific literature by the federal authorities, reflecting agricultural practices thought to be not too distant from the Belgian ones, is a much more realistic and achievable goal in the perspective of policy-supporting recommendations and measures.

In view of the paucity of data currently available in the EU on the potential effects of agricultural occupational exposures on the health of farmers and agricultural workers, particularly in terms of cancer, a French cohort study was launched at the end of 2005 among affiliates of the «Mutualité Sociale Agricole», the AGRICAN cohort (AGRIculture and CANcer). This study included about 180000 active or retired farmers, or employees between 2005 and 2007 in 12 metropolitan departments with cancer registries. It provides for a prospective follow-up of affiliates for at least 10 years to analyse the exposures by questionnaires and cross them with health data (cancer, Parkinson's disease, chronic obstructive pulmonary disease, asthma,…). The AGRICAN study aims to analyse primarily the incidence of cancers and mortality due to cancers linked to agricultural activities, although other long-term findings may also be studied.

It is useful to stress that the AGRICAN-campaign seeks to assess associations between long-term effects and agricultural activities (it is in truth not launched to examine specifically the effects of the exposure to PPPs alone, although the latter is of course an important part of it).

The reason to rely mainly on the AGRICAN study is that, whilst it is widely acknowledged that France is one of the major consumers of PPPs in terms of sold active substances (a.s.) in the EU context (actually, the Netherlands, Belgium, Italy, Portugal, Spain, Germany, France and Slovenia all had amounts of PPPs sold per hectare above 2 kg/ha), it may be reasonably presumed that the French agricultural practices are not meaningfully different from the Belgian ones.

In the meanwhile, the AGRICAN cohort, is part of an international consortium of agricultural cohorts that includes 21 other cohorts spread across 9 countries (see http://agricoh.iarc.fr/).

Thanks to the very large number of participants and the prospective design, the AGRICAN/AGRICOH cohort offered a unique opportunity to study rare diseases, which otherwise could remain undetected.

Therefore, the FPS monitors on a regular basis the newly published peer-reviewed scientific papers relevant for the Belgian situation on potential overincidences of long-term effects, associated with PPP use.

Following table gives an overview of the most important cohort studies on agricultural long-term effects and puts the AGRICAN cohort into perspective. It is considered that only prospective or retrospective cohorts should be withheld, as these seem the most relevant for this purpose. Please note that not all cohorts are uniquely specifically set up to cover only the agricultural population.

Table 1: overview of the most important cohort studies on agricultural long-term effects

Cohort	Country	Enrollment	♂	♀	total	Studied health effect
AGRICAN	France	2005-2007	103135	84336	187471	Cancer/ Respiratory effects/ Neurobehavioural/ neurodegenerative disorders
Agricultural Health Study (AHS)	USA	1993-1997	55748 ♂/♀	32127♂/♀ (spouses)	87875	Broad range of health effects
Canadian Census Health and Environment Cohorts (CanCHEC)	Canada	1991-2010	49965	20605	70570	Broad range of health effects (specific cancer incidences in agricultural population)
Pesticides Users Health Study (PUHS)	UK	1987-2004	59085	3875	62960	Cancers
Cancer in the Norwegian Agricultural Population (CNAP)	Norway	1969-1989	136463	109641	246104	Cancers
Nordic Occupational Cancer (NOCCA) Study*	Scandinavia	1961-2005	622440	158515	780242	Cancers
AGRICOH**	France-USA-Norway					Multicenter cohort of AGRICAN, AHS, CNAP

*occupational study for different sectors (farmers subpopulation), limited to people 30-64yr, census 1971-2003 (DK), 1971-2005 (FI), 1982-2004 (IC), 1961-2003 (NO), 1961-2005 (SE).

**: includes prospective cohorts AGRICAN, AHS and CNAP.

3 General screening of diseases and long-term PPP exposure – relevant published reports

We have restricted our analysis to a limited number of cases.

3.1 EFSA review report, 2013 : very wide outcomes, although the extent of real exposure is uncertain

In 2013, EFSA (Ntzani *et al.*, 2013) published a quite important and very robust external scientific report summarising the association between any PPP and 23 major categories of human health outcomes based on a systematic literature review, together with an on-line database of all the epidemiological studies analysed in the report.

In both the EFSA report and a former INSERM report (2013) indications of positive associations were observed for the whole class of PPPs, via different routes of exposure, and several health outcomes. The study was not restricted to hard clinical findings like cancer, neurodegenerative or developmental diseases, but also other outcomes, including exposure endpoints (biomonitoring), for the period 2006-2012.

In the EFSA review, genuine association was observed for childhood leukaemia, neurological diseases (Parkinson Disease (PD)) and type I and II diabetes, especially type II could be involved as well.

In a follow-up review at INSERM (2021), the experts confirmed the «strong presumption» of a link between pesticide exposure and 6 pathologies: non-Hodgkin's lymphoma (NHL), multiple myeloma, prostate cancer, Parkinson's disease, cognitive disorders, as well as certain respiratory system disorders (chronic obstructive pulmonary disease and chronic bronchitis). These experts claimed that «moderate links» would have been identified between occupational exposure to pesticides and Alzheimer's disease, anxiety-depression disorders, certain cancers (leukaemia, central nervous system, bladder, kidney, and soft tissue sarcomas), asthma and wheezing, and thyroid disorders. Finally, according to INSERM (2021), epidemiological studies of pediatric cancers would reveal a «strong presumption» of a link between pesticide exposure during childhood as well as maternal exposure to pesticides during pregnancy (due to occupational or residential use) and the risk of certain pediatric cancers, in particular leukaemia and tumours of the central nervous system.

At this moment, neither childhood cancer due to potential exposure to PPP of the parents or residential exposure nor diabetes have been highlighted in the AGRICAN study. Prospective studies were given more weight than retrospective ones, since recall bias seems to be quite important. Multiple testing is huge, which can in some instances call into question the statistically relevant findings. A lot of outcomes suffer also from severe heterogeneity (large I^2 values >70%).

The conclusion was, shortly, that very wide outcomes were reported, and a more reliable estimation of the extent of exposure is necessary. In addition, the impact of a purported low dose chronic exposure was perceived as uncertain. Data of new techniques like metabolomics should be included in future epidemiology studies. Endocrine disorders, such as obesity should be better investigated as well.

The authors recognise that negative associations which remain unpublished will surely be missed. Publication bias was tested by funnelling analysis, and a big publication bias was not observed. In short, a number of methodological limitations of the epidemiological studies were highlighted in the EFSA report making it difficult to draw firm conclusions. It is of note that the prospective AGRICAN cohort was not part of this analysis.

Triggered by this and other reviews, EFSA published later an analysis where it was found that poor exposure characterisation primarily defined the major limitation of epidemiological studies (Ockleford *et al.,* 2017). Frequent use of case–control studies as opposed to prospective studies was considered another limitation. Inadequate definition or deficiencies in health outcomes need to be avoided and reporting of findings could be improved in some cases.

3.2 AGRICAN outcomes

At the moment of finalisation of this limited literature overview, it was noted that there was no overarching publication, assembling all the AGRICAN studies conducted during the period 2013-2020. One "mid-way" publication existed (Tual *et al*., 2016), recapitulating the published studies until 2016, and its weight should be considered in the light of the many reports published thereafter. Yet, the paper contained the starting hypothesis for the AGRICAN investigators. It was clarified that the occupational cancer incidence in the French agricultural population has been poorly studied until the beginning of the enrollment, while it concerned more than one million people, and France is one of the most important countries using PPPs in the world. The authors were of the opinion that certain cancers (malignant haemopathies, skin cancers, prostate cancer, brain tumours, gastric cancers, etc.) are recognised being in excess in this population. They stated that this was particularly the case in PPP users although no one is in a position to attribute potentially elevated cancer risks to any particular a.s. or even chemical classes of PPP's so far.

In the current context, it may be anticipated that the situation is likely to be similar in the Belgian agricultural population.

In the following subchapters, a short overview is given on the different epidemiological studies published by the AGRICAN group in the field of long-term effects and farming, including the possible exposure to PPPs during these farming activities.

3.2.1 Tual *et al.* (2013): chronic bronchitis in the AGRICAN cohort

In this publication, the authors reported that agricultural settings not previously reported, such as potato production, may be a risk factor for chronic bronchitis (CB). CB was reported by 1207 farmers (8.4%). Two farming activities were associated with CB: cattle raising, odds ratio, (OR)=1.24, 95%CI: 1.03-1.48), and potato production (OR=1.33, 95%CI: 1.13-1.57). Associations were more pronounced in small-scale cattle raising and in large-scale potato production, in particular among the longest exposed workers (>20 years). PPP poisoning and exposure to PPP in potato farmers were significantly associated with CB risk (OR=1.64 and OR=1.63, respectively). It was noted that, if no poisonings were reported, the association between pesticide use and CB incidence was not significant.

The authors concluded that the nature and circumstances of exposure to hazardous agents need to be further explored.

3.2.2 Baldi *et al.* (2014): asthma risk in the AGRICAN cohort

The study pertained to self-reported, doctor-diagnosed asthma, in relation with history of life-time exposure to 13 crops and 5 livestock premises, PPP exposure and early life on a farm. Among the 1246 asthmatics (8.0%), 505 were allergic (3.3%) and 719 non-allergic (4.6%). A significant elevation of risk was observed, for allergic asthma, in 5/13 crops and 1/5 livestock premises investigated. Statistical significance was noted in vine- (OR=1.43, 95%CI: 1.15-1.77) and fruit-growing (OR=1.58, 95%CI: 1.20-2.09), greenhouses (OR=1.66, 95%CI: 1.10-2.51), grasslands (OR=1.35, 95%CI: 1.08-1.68), beets (OR=1.52, 95%CI: 1.16-2.00) and horses (OR=1.35, 95%CI: 1.02-1.80). No significant finding was noted for other crops or livestock growing, and associations for non-allergic asthma were unremarkable, either.

Associations between allergic asthma and both PPP use on crops or PPP poisoning history were significant in grassland, vineyards and fruit-growing (3/11 crops studied) and with non-allergic asthma only in beets. Living on a farm in the first year of life tended to be protective for childhood allergic asthma in farms with livestock (OR=0.72, p=0.07) but not in farms with vineyards, fruit or vegetables (OR=1.44, p=0.07). The authors concluded on an increased risk of allergic asthma and exposure to certain crops, PPP use and early life on a farm with vine-growing, grassland, beets, fruit and vegetable-growing. They also found that, even if the precise mechanisms (direct airway damage, interactions with irritant receptors, modulation of inflammatory response, *etc.*) remain unclear, practical measures to reduce the impact of potentially harmful risk factors like PPP should be carefully considered.

3.2.3 Levêque-Morlais *et al.* (2015): General health and mortality in the AGRICAN cohort

A first key publication *(Levêque-Morlais et al., 2015)* in the AGRICAN campaign indicates no overmortality due to farming (and accordingly, PPP use) above average.

Mortality was studied until 12.2009 (605956 person-years) with standardised mortality ratio (SMR) by comparison with the general population of the areas (area-specific rates were stratified by gender and 5-year age). Over this period, 11450 deaths (6741 in ♂and 4709 in ♀) were observed, including 3405 cancer-related deaths.

Overall, SMRs were significantly reduced for global mortality (SMR = 0.68, 95 % CI 0.67–0.70 in ♂ and SMR = 0.71, 95 % CI 0.69–0.73 in ♀) **and** for death by cancer (SMR = 0.67, 95 % CI 0.65, 0.70 in ♂ and SMR = 0.76, 95 % CI: 0.71, 0.80 in ♀). These results were mainly explained by less frequent smoking-related causes of death (lung cancer, cardiovascular diseases). Non-significant excesses of death were observed only for rheumatoid arthritis and arthrosis, suicides (♀), death for event of undetermined intent (♂) and breast cancer in ♂ agricultural workers.

It is observed that for ♂ breast cancers, the observed incidence is 9/2218 *vs.* expected incidence of 7/3287 , *i.e.* an increase of about 0.19%. Given the low number of cases, no conclusion can be drawn from these figures, but further research is certainly warranted.

In conclusion for this study, these first mortality results obtained in France based on a large prospective agricultural cohort, show that farmers would be in healthier condition than the general population.

As a comparison, the mortality rates in the AHS was examined (Waggoner *et al*, 2011). The AHS cohort of pesticide applicators (N=57310) and their spouses (N=32346) in North Carolina and Iowa, the authors computed standardised mortality ratios (SMRs) comparing deaths from time of the enrollment (1993-1997) through 2007 to state-specific rates. To compensate for the cohort's overall healthiness, relative SMRs were estimated by calculating the SMR for each cause relative to the SMR for all other causes. In the follow-up, 6419 deaths were observed. The all-cause mortality rate was less than expected in both applicators (SMR=0.54, 95%CI: 0.52-0.55) and spouses (SMR= 0.52, 95%CI: 0.50-0.55). SMRs for all cancers, heart disease, and diabetes were significantly below 1.0.

However, after adjusting for the lower overall mortality rate of the cohort, performing a "relative SMR analysis" for applicators, the relative mortality ratio was elevated for all cancers (rSMR= 1.20, 95%CI: 1.13-1.27), more specifically melanoma, and digestive system, **prostate** (rSMR= 1.53, 95%CI: 1.31-1.78), kidney, and brain cancers. Lymphohaematopoietic cancer mortality was also elevated, with notable elevated relative rates in leukaemia (rSMR= 1.59, 95%CI: 1.44-2.48), **non-Hodgkin lymphoma (NHL)** (rSMR= 1.57, 95%CI: 1.27-1.93) and **multiple myeloma (MM)** (rSMR= 1.89, 95%CI: 1.29-1.96).

Among their spouses, relative SMRs exceeded 1.0 for lymphohaematopoietic cancers and malignancies of the digestive system, brain, breast, and ovary.

In the British PUHS restrospective cohort (Frost *et al,* 2011), "all-cause" mortality was lower for both ♂ (SMR=0.58, 95%CI: 0.55-0.60) and ♀ (SMR=0.71, 95%CI: 0.52-0.98) compared to the general population. Mortality was below that expected for all cancers combined among ♂(SMR=0.71, 95% CI: 0.66-0.77).

3.2.4 Lemarchand *et al.* (2017): Overall cancer incidence in the AGRICAN cohort

In a more general article, Lemarchand *et al.* (2017) concluded that overall cancer incidence in the AGRICAN cohort and the general population was not very different. On the basis of the standardised incidence rates (SIRs) no statistically significant difference could be concluded on the overall cancer incidence for both ♂ (SIR=0.99, 95%CI: 0.97-1.01) and ♀ (SIR=0.98, 95%CI: 0.95-1.02). Over the examined period, 11067 incident cancer cases were identified (7304 ♂, 3763 ♀). However, the risks were significantly higher for **prostate cancer** (SIR=1.07, 95% CI: 1.03-1.11) , **NHL** (SIR= 1.09, 95% CI: 1.01-1.18) and lip cancer (SIR=2.05, 95%CI: 1.27–3.13) among ♂, skin melanoma among ♀ (SIR= 1.23, 95% CI: 1.05-1.43) and **MM/plasmocytoma** (♂: SIR= 1.38, 95% CI: 1.18-1.62; ♀: SIR= 1.26, 95% CI: 1.02-1.54). It was noted that Diffuse large

B-cell lymphoma (DLBCL), the most common type of NHL in the general population, was not significantly increased, while MM, another NHL-subtype, showed a significant increase.

The systematic increased incidence of MM/plasmocytoma in people who work on the farm (♂♀), ♂ farm owners, and ♂ applicators of PPP on crops is somehow remarkable, and deserves further corroboration.

As a comparison, a recent (retrospective) Canadian cohort analysis (Kachuri *et al.,* 2017, CANCHECK cohort) in an occupational subpopulation of 70570 agricultural workers (25-75 years of age) was performed. The overall cancer incidence in agricultural workers was lower than among the general population (hazard ratio (HR)=0.95, 95%CI: 0.93–0.98). Among ♂, increased risks were observed for **NHL** (HR=1.10, 95% CI:1.00–1.21), **prostate** (HR=1.11, 95% CI: 1.06–1. 16), melanoma (HR=1.15, 95% CI: 1.02–1.31), and lip cancer (HR = 2.14, 95% CI: 1.70–2.70). Among ♀ there was an increased risk of **pancreatic cancer** (HR = 1.36, 95% CI: 1.07–1.72). Increased risks of melanoma (HR = 1.79, 95% CI: 1.17–2.73), **leukaemia** (HR = 2.01, 95% CI : 1.24–3.25) and **MM** (HR = 2.25, 95% CI : 1.16–4.37) were observed in a subset of ♀ crop farmers. The Canadian study indicated that exposure to PPPs may have contributed to increased risks of **haematopoietic cancers**, while increased risks of lip cancer and melanoma is related to sun exposure. Decreased risks suggests reduced smoking and alcohol consumption in this occupational group compared to the general population. While differences with the EU cohort were seen, there were also some concordances, like for prostate cancer and NHL, including MM. Both cohorts did not indicate that agriculturally occupied people would display elevated “any” cancer incidence compared to the general population.

In the AHS (Alavanja *et al.,* 2005) the overall cancer incidence among PPP applicators (N=57311, comprising ~90% private farmers) and their spouses (N=32347) were significantly lower than expected, particularly for respiratory and urinary cancers (possibly associated to lower smoking prevalence). Commercial PPP applicators had an overall cancer incidence comparable with the expected (SIR=1.01, 95%CI: 0.84–1.20). **Prostate** cancer was elevated among private applicators (SIR=1.24, 95%CI: 1.18–1.33) and commercial applicators (SIR 1.37, 95%CI: 0.98–1.86). Excess **ovarian** cancer (N=8) was observed for ♀ applicators (SIR 2.97, 95% CI:1.28–5.85), but not for ♀ spouses (SIR 0.55, 95% CI 0.38–0.78). The ♀ spouses had a significant excess of melanoma (SIR 1.64, 95% CI 1.24–2.09), which was not observed among PPP applicators. The **NHL** incidence was not significantly increased (SIR 1.02, 95% CI: 0.84–1.22), while **MM** could be considered slighltly elevated (SIR 1.34, 95% CI: 0.97–1.81) among the private applicators.

In a further update of the AHS cohort, Koutros *et al.* (2010) re-evaluated the cancer incidence among applicators (N=4535) and their spouses (N=1896). Overall cancer rates in private applicators were significantly less elevated than those in the general population (SIR= 0.85, 95%CI: 0.83–0.88). A significant excess of **prostate cancer** was seen for both private and commercial applicators (SIR=1.19, 95%CI: 1.14–1.25) and (SIR=1.28, 95%CI: 1.00–1.61), respectively. When calculated for the entire group of applicators over the different US states, no elevated risk was observed for cancers like NHL or MM. However, in a subpopulation of the AHS elevated risk was observed for lip cancer, (SIR=1.97, 95%CI: 1.02–3.44) and **MM** (SIR=1.42, 95%CI: 1.00–1.95) among private applicators from North Carolina and for marginal zone lymphoma (**MZL**, a subtype of NHL) among Iowa spouses, SIR = 2.34 (95%CI:1.21, 4.09).

In order to correct for the overall cancer deficit, the authors evaluated whether there was an excess or deficit of cancer cases for each specific cause, relative to the overall deficit of cancers in AHS subjects, and re-calculated a ratio of the SIR for each site to the SIR for all cancer sites overall minus that site of interest, expressed as the *relative* standardised incidence ratio (rSIR). The authors further clarify that the interpretability of the rSIR is predicated on the assumption that those factors responsible for the observed deficit for all cancers apply across the individual cancer sites in the absence of applicator-related factors. It is of note that, in view of the uncertainty surrounding such assumption, use of the this kind of relative ratios seems controversial (Wen *et al.,* 1983).

Private applicators showed an increased risk for **NHL** (rSIR= 1.17, 95% CI: 1.01–1.35) including **DLBCL** (rSIR= 1.27, 95% CI: 1.01–1.60), CLL/SLL/MCL (rSIR= 1.51, 95% CI: 1.08–2.12). Also **MM** showed an over-incidence (rSIR= 1.41, 95% CI: 1.11–1.78). An excess of **prostate** cancer was observed (rSIR= 1.66, 95% CI: 1.57–1.77). **Ovary cancer** incidence was also elevated (rSIR= 2.88, 95% CI: 1.50–5.54), although it should be remarked that the number of people affected was quite low (N=8). The authors concluded that despite to the lower overall cancer incidence, agricultural exposures including PPP's, microorganisms, sunlight, and other chemicals may increase risks for specific cancer sites.

In the most recent update of the AHS (Lerro *et al.*, 2019), more or less the same trend in the cancer excesses was observed as before. Overall AHS cancer incidence in private applicators was lower than in the general population (SIR=0.91, 95%CI: 0.89–0.93). Overincidences were observed in prostate, lip, thyroid, testicular cancers, as well as certain B-cell lymphomas (*e.g.* **MM**), and acute myeloid leukaemia (AML). Peritoneal cancers were elevated only among spouses of private applicators. The authors concluded that the cancer incidence patterns in the AHS suggest farm exposures' relevance to cancer aetiology.

In a review of 28 AHS studies, Weichental *et al.* (2010) reported that overall cancer incidence was increased among applicators in the highest exposure categories for diazinon and EPTC. Elevated incidences of specific cancers, like lymphohaematopoietic cancers, including leukaemia, **NHL** (lindane) and **MM** (permethrin). **Prostate cancers** were associated with exposure to fonofos and methyl bromide. Other cancers which were significantly increased included lung, pancreas, colon, rectum, bladder, brain cancer and melanoma. The authors concluded that most of the 32 PPPs examined were not strongly associated with cancer incidence in PPP applicators. Increased rate ratios (or odds ratios) and positive exposure–response patterns were reported for 12 PPPs registered in Canada and/or the United States at that time (for which only 2 of them would be relevant in the EU-context, *i.e.* dicamba (colon and lung cancer) and pendimethalin (lung, rectum, pancreas cancer), as the others are not approved anymore.

In the British PUHS restrospective cohort (Frost *et al.,* 2011), cancer incidence was below that expected for all cancers combined among ♂(SIR=0.85, 95%CI: 0.81-0.90), particularly for cancers of the lip, oral cavity and pharynx, digestive organs and respiratory system. The incidence of **testicular** cancer (SIR=1.26, 95%CI 1.04-1.53), ♀ **non-melanoma** skin cancer (SIR=1.73, 95%CI 1.06-2.82) and **MM** (♂SIR=1.49, 95%CI 1.05-2.13; ♀SIR=10.9, 95%CI 4.10-29.1) were significantly above expected.

In a Scandinavian restrospective (occupational) cohort NOCCA (Pukkala *et al.*, 2009), increased risks (the entire national study population used as reference) were observed in farmers for lip cancer (♂SIR=1.57; 95%CI: 1.51-1.62) and **thyroid** cancers (♀SIR=1.18, 95%CI: 1.07-1.30). **MM** incidence was slightly high with ♂SIR=1.07; 95%CI: 1.03-1.11 and ♀SIR=1.14; 95%CI: 1.05-1.24. Other cancers were unremarkable, including prostate cancers (SIR=0.99; 95%CI: 0.98-1.00) and NHL (♂SIR=0.99; 95%CI: 0.96-1.02 and ♀SIR=0.92; 95%CI: 0.86-0.99)

Overall, the outcome of the most important prospective US/EU cohorts was comparable for what the overall cancer incidence was concerned. However, for each cohort separately, there was an overincidence of specific tumour types, which would not be observed in the other cohorts. Notable however was the presence of an overincidence for **MM**, **prostate cancer** and **NHL** in 4/5, 3/5 and 2/5 cohorts, respectively.

It should be remarked that a comparison between the outcome of these cohorts, even if impressive number of persons were followed, should be interpreted with caution. The methodologies may be different (prospective/retrospective), the reference populations may differ (general population/non-exposed farmers, etc…), the distinction between type of agricultural activities is not always made (farmers, pesticide applicators, managers, workers,…), the censuses may be limited to farmers having certificates of competences (e.g. PUHS), covering different enrollment time-periods, or being part of larger occupational studies (e.g. NOCCA). In addition, study goals may be different.

However, for a comparison of overall cancer incidences it has some value.

Remark: the AGRICAN outcome of cancers, as published in a peer-reviewed paper by Lemarchand et al (2017), covered the period 2005-2011, and presented in table 2. The overincidence of tumours in the farmers is compared to that in the general population. Recently (AGRICAN, 2020) a report was published on the internet, citing different incidences. The new incidences were recorded in the period 2005-2015, which may partly explain the difference. Whereas the recent AGRICAN report was certainly peer-reviewed internally, it was not published in a peer-reviewed scientific journal, meaning that the level of detail is less extensive than in a scientific article. However, the published overincidences follow the same trends, and do not meaningfully change the conclusions drawn in the FPS overview.

Table 2: incidence risk of overall and specific cancers in farmers/applicators as compared to the risk in the general population

Cancers	AGRICAN (FR)	AHS			NOCCA (Scandinavia)	PUHS (UK)	CANCHEC (Canada)
Publication year	2017	2005	2010	2019	2009	2011	2017
Any cancer	§[↓5|↓7]	↓12%	↓15%	↓9%	n.a.	↓42%|↓29	↓5%
Colorectal	-	-	-	([↑6]r)	-	-	-
NHL	↑9 | - §[↑9 |]	-	[↑17]r	(↑12)@ [↑26]r	-	-	-
CLL		-		↑17 [↑30]r	-	-	-
DLBCL	-	-	[↑27]r	(↑16) [↑29]r	-	-	-
FL				[↑27]r	-	-	-
MM	↑38|↑26 §[↑20|↑21]	(↑34)	↑42	(↑18) [↑99]r	↑7|↑14	↑49|↑990#	-
Waldenström £	§[↑49|↑58]						
Leukaemia	-	-	-		-	-	-|↑101
AML	-	-	-	↑29 [↑42]r	-	-	-
Lip °	-|- §[↑55 | -]	-	↑97	↑122 [↑146]r	↑57|-	-	↑14|↑125
Melanoma °	-|↑23 §[- |↑29]	-	-	[↑12]r	-	-	↑15|↑79

Cancers **Publication year**	**AGRICAN (FR)** **2017**	**AHS** **2005**	 **2010**	 **2019**	**NOCCA (Scandinavia)** **2009**	**PUHS (UK)** **2011**	**CANCHEC (Canada)** **2017**
Non-melanoma skin	-	-	-	-	-	-|↑73	-
Ovary	-	-	-	[↑99]r	-	-	-
Pancreas	-	-	-	-	-	-	-|↑36
Prostate	↑7 § [↑3]	↑24	↑19 [↑66]r	↑15 [↑44]r	-	-	↑11
Testicles	-	-	-	[↑45]r	-	↑26	-
Thyroid	-	-	-	[↑28]r	↑18	-	-

- Percentual differences (↑increase / ↓decrease) in standardised incidence rates (SIR), except hazard rates (HR) in CANCHEC);
- - : no statistically significant difference and (..) borderline (lowest 95%CI value=0.98) statistical difference

- values for ♂ | ♀ (except for AHS); [..]r: relative SIR's; n.a.: not available;° : considered sunlight-related;
- #: estimation highly imprecise, taking into account the extremely wide 95% CI
- @: restricted to B-cell NHL
- §*[..]:* Recent AGRICAN data (2021) in italics, referring to the period 2005-2015, as compared to the published data (2017, referring to the period 2005-2011)
- £: a.k.a. plasmocytic lymphoma, not formerly reported in any cohort

3.2.5 Lemarchand *et al.* (2016) : Prostate cancer in the AGRICAN cohort

In a follow-up publication (Lemarchand *et al.*, 2016), AGRICAN investigators found an increased risk for prostate cancer in a number of distinct situations, *i.e*. among:

(i) cattle breeders 'ever' using insecticides (veterinarian and/or barn disinfection), *ca.*+20%, without further details.

(ii) people involved in grassland activities, mainly in "haymaking" (+18%), however no association with herbicide use was noted. Likewise, tobacco harvesting also exhibited an increased risk (+26%), again without clear link with PPP use. Authors didn't demonstrate the potential causative agent in such tasks.

(iii) fruit growers ('ever' PPP use and harvesting), with about a 2×-increased risk (the 95% CI was broader, though: 1.08-4.80, indicating higher uncertainty because of small number of individuals involved) for the largest area (>25 ha).

(iv) potato and tobacco producers (sowing and harvesting), where the authors *suggest* a link with PPPs, which is however debatable, as the absence of time-dependent response remains without explanation. It is true that the non-significant increases of cases associated with PPP use is at the limit of significance (tobacco: +24%, CI: 0.99-1.54; potato: +19%, CI: 1.00-1.41).

The authors conclude that the risk of prostate cancer is increased in several farming activities (cattle especially hog breeding, grassland and fruit-growing) and for some tasks including PPP use.

It is also remarkable that in **vineyard**, one of the most important French crops, and probably the most risky in terms of exposure to PPPs, no increase of prostate cancer hazard on average was observed, in none of the tasks (PPP use, re-entry, grape harvesting, green space maintenance, wine-cellar activities). The slight increase in the sub-stratified group of PPP users (10-19 years use), contrarily to the absence of significant findings in the other groups (0-9 years, 20-29 years, 30-39 years, >40 years), as well as the absence of any finding in the sub-stratified groups regarding treated areas, may have been a reason to consider the effect as a chance event, as there seem to be neither a time-dependent, nor an area-dependent modification of the risks.

The authors however highlight that factors of ethnicity or familiar factors, possibly explaining prostate cancer antecedents, were not investigated. Alternatively, it should be remarked that the spurious statistically significant findings in a limited number of crops, activities or exposure situations, could equally well be explained by the multiple statistical tests undertaken.

When the overall figures are analysed, it should be said that for the population "pesticide use on crops" no clear-cut statistically significant increase of the prostate cancer risk could be revealed (N= 789, HR=1.10; 95% CI: 0.97–1.25).

It is however worth noting that in certain cases higher risks were observed among people who never wore protective gloves. HR's amounted to 1.23 (95% CI 0.98–1.54) for potatoes to 1.44 (95% CI 1.10–1.88) for fruit-growing, which highlights the importance of personal protection in PPP handling and harvesting. On the other hand, the authors recognised that no potential responsible a.s. was identified to explain the greater prostate cancer risk related to, amongst others, full-field activities like hay making and wheat/barley harvesting.

In the other large prospective cohort from the US (AHS), farmers and commercial pesticide applicators have a small but significantly higher rate SIR=1.14 (95%CI 1.05–1.24) of prostate cancer than the general population of Iowa and North Carolina (Alavanja *et al.,* 2003). These figures compared well with the SIRs estimated in later updates among private applicators in Alavanja *et al.* (2005): SIR=1.24 and Koutros *et al.* (2010): SIR=1.19.

Alavanja *et al.,* 2003 also reported that occupational use of a widely used halogenated fumigant, methyl bromide, was significantly associated with a higher risk among applicators suffering the highest exposures OR=3.47 (95%CI: 1.37–8.76, but N=5, p_{trend}=0.004) . A pattern of chlorinated pesticide use (especially among applicators > 50 years of age, p_{trend}=0.005 for exposure level) may also be related to prostate cancer risk. A family history of prostate cancer appeared to significantly increase the prostate cancer risks among those using several widely used insecticides, including chlorpyrifos, coumaphos, fonofos, phorate, and permethrin for animal use, and the herbicide butylate.

Koutros *et al.* (2013) examined the implication of PPPs as risk factors for aggressiveness of prostate cancer in 1962 incident cases (including 919 aggressive prostate cancers) among 54412 applicators. Rate ratios (RRs) were calculated to evaluate lifetime use of 48 PPPs and prostate cancer incidence in applicators, as compared to non-exposed people from the same profession. Organophosphate insecticide highest quartile exposure was significantly associated with aggressive prostate cancer, and amounted to: RR=1.63, 95%CI: 1.22-2.17; P_{trend}<0.001 (fonofos), RR=1.43, 95%CI: 1.08-1.88; P_{trend}=0.04 (malathion) and RR=1.29, 95%CI: 1.02-1.64; P_{trend}=0.03 (terbufos). The organochlorine insecticide aldrin was also associated with an increased risk (RR=1.49, 95%CI: 1.03-2.18; P_{trend}= 0.02). In addition, significant increases in risk of total prostate cancer with increasing use of fonofos and aldrin were observed among those with a family history of prostate cancer.

There is a vast quantity of meta-analyses dealing with the issue of prostate cancer overincidence in farmers, PPP applicators or workers in manufactories of PPPs. In a comprehensive meta-analysis of Van Maele-Fabry and Willems (2003) an increased meta-rate ratio (mRR) estimate for prostate cancer based on 25 estimators of relative risk from 22 studies, (mRR=1.13, 95%CI: 1.04-1.22), in various PPP-related occupations, including farmers, was very similar to 3 previously published mRRs for prostate cancer in farmers before 1995. Follow-up studies encompassing broader time-spans, and focussing on a mRR for prostate cancer in either PPP applicators (Van Maele-Fabry and Willems, 2004) or manufacturing workers (Van Maele-Fabry *et al.*, 2006) resulted into estimates of mRR=1.24, 95%CI: 1.06-1.45 and mRR=1.28, 95%CI: 1.05-1.58, respectively. Strikingly, in a meta-analysis focussing on pesticide applicators, the authors observed that “substantial heterogeneity of rate ratios existed”, with U.S. studies suggesting a larger risk than those conducted in Europe. The authors argue that this may be associated with the higher underlying risk of prostate cancer among U.S. versus European men. One or more of the factors causing this excess propensity to develop prostate cancer might also influence the carcinogenicity of PPPs.

It was remarked that the underlying data did not identify PPP exposure as an independent cause for prostate cancer, but was indicative of a trend where agricultural activities and/or PPP production could be suspected being a potential causative factor. A recurring conclusion was that future epidemiological studies should focus on reliable methods to estimate actual exposures.

It is noted that in the EFSA review of Ntzani (2013), the association between prostate cancer and PPP exposure was not confirmed. The authors highlighted that the studies reviewed contained insufficient qualitative and quantitative information on exposure in order to distinguish the influence of PPPs from other occupational, environmental, and lifestyle factors and that overall, there was no evidence supporting an association between PPP exposure and prostate cancer. A possible explanation could be that the effect is too weak to be seen in a wider context.

It should be remarked that in the latest AGRICAN publication, the effects are restricted to 20-30% higher risks when compared to the control population. Other reviewers (*e.g.* Alavanja and Bonner, 2012) are of the opinion that "*epidemiologic evidence from a number of different studies now more convincingly shows that prostate cancer is related to pesticide use*", with however disparities among races and between those with and those without a family history of prostate cancer which may be explained by either chance, differences in pesticide use patterns, or differences in genetic susceptibility (as reflected by interaction by family history prostate cancer prevalence). The possibility of certain a.s. showing preliminary gene-environment analyses should be completed, and (epi)genetic biomarkers may be necessary in aetiological studies of pesticides and prostate cancer risk.

According to the authors of the AGRICAN cohort, various other publications indicated the potentiality of increased hazard of prostate cancer. Although the increased risks were relatively slight (+13% to +28%), it was suggested that the presence of a general trend should be a signal to further elucidate the problem.

As highlighted under 3.2.4, prostate cancer incidence in farmers/applicators was significantly above the reference population incidence in 3 of the 5 consulted cohort studies, including the AHS prospective cohort.

A further follow-up of relevant published data during the next decade could possibly confirm the first findings obtained in the first phase of the AGRICAN study.

The larger AGRICOH cohort (Togawa *et al,* 2021) dealt with a.o. the prostate cancer issue. The analysis included 8 cohorts that were linked to their respective cancer registries: France (AGRICAN: n = 128101), the US (AHS: n = 51165, MESA: n = 2177), Norway (CNAP: n = 43834), Australia (2 cohorts combined, Australian Pesticide Exposed Workers: n = 12215 and Victorian Grain Farmers: n = 919), Republic of Korea (KMCC: n = 8432), and Denmark (SUS: n = 1899). For various cancer sites and all cancers combined, standardised incidence ratios (SIR) and 95% confidence intervals (CIs) were calculated for each cohort using national or regional rates as reference rates and were combined by random-effects meta-analysis.

During nearly 2800000 person-years, a total of 23188 cancers were observed. Elevated risks were observed for prostate cancer (n° of cohorts = 6, meta-SIR = 1.06, 95%CI: 1.01-1.12), compared to the general population. In contrast, a deficit was observed for the incidence of several other cancers.

3.2.6 Boulanger *et al.* (2017): Bladder cancer in the AGRICAN cohort.

Among 148051 farm owners and workers included in AGRICAN, the incidence of bladder cancers was analysed. The authors observed an elevated risk among field-grown vegetable workers (HR=1.89, 95%CI: 1.20-2.99), with an exposure-response relationship with duration of work [≥30 years: HR=2.54, 95%CI: 1.11-5.83, p_{trend}=0.02), and higher risk among ♀ (HR=3.82, 95%CI: 1.58-9.25, $p_{interaction}$=0.05). Non-significantly increased risks were also observed in greenhouse farmers (HR = 1.95), pea sowing (HR = 1.84), rape sowing (HR=1.64); several tasks involving PPP use, especially seed treatment (HR = 1.24); and in activities and tasks potentially exposing to a.s. on the basis of arsenic (HR=1.49) or re-entry tasks (HR = 1.63).

The authors therefore raised the question of a possible link between agricultural activity, especially field-grown vegetables, and greenhouse cultivation and bladder cancer. It may be highlighted that, while no specific a.s. was associated with this increased incidence, the purported contribution of arsenicals, historically massively used in French agriculture, are of no concern at the Belgian level, and are anyway prohibited in the EU as well.

In the US cohort (AHS) occupational exposure to pesticides and bladder cancer risk was investigated (Koutros *et al.*, 2016). Associations with bladder cancer risk were observed for two imidazolinone herbicides, imazethapyr and imazaquin, apparently selected among 8/65 a.s. investigated as plausible carcinogenic on the ground of being “aromatic amines” (which are generally known as bladder carcinogens). Ever use of imazaquin (RR=1.54, 95%CI: 1.05-2.26) was associated with increased overall risk (but imazethapyr not) whereas the excess risk among users of imazethapyr was evident among never smokers (highest quartile *vs* non-exposed RR=3.03, 95%CI: 1.46-6.29, $P_{interaction}$=0.005). This is in contrast to imazaquin, for which no data on smoker/no smoker interaction were reported. Likewise, increased risks overall and among never smokers for use of several chlorinated pesticides (metolachlor) including chlorophenoxy herbicides (2,4,5-T and 2,4-D) and some organochlorine insecticides were observed. The authors concluded on several associations between specific PPPs and bladder cancer risk, many of which were stronger among never smokers, suggesting that possible risk factors for bladder cancer may be more readily detectable in those unexposed to potent risk factors like tobacco smoke.

3.2.7 Tual *et al.* (2017): Lung cancer in the AGRICAN cohort.

The authors assessed the relationship between animal farming and lung cancer by investigating the types of animals, tasks, and timing of exposure. Analyses included 170834 participants from the AGRICAN cohort in France. Incident lung cancers were identified through linkage with cancer registries from enrolment (2005–2007) to 2011. A Cox model was used to calculate HRs and 95% CIs. Lung cancer risk was inversely related to duration of exposure to cattle (≥40 years: HR=0.60, 95%CI: 0.41-0.89; p_{trend}<0.01) and (borderline) to horse farming (≥20 years: HR=0.64, 95%CI: 0.35-1.17; p_{trend}=0.09), especially for adenocarcinomas, but not with poultry or pig farming. More pronounced decreased risks were reported among individuals who had cared for animals, undertaken milking, and who had been exposed to cattle in infancy. In contrast, lung cancer risk was higher with use of insecticides on cattle among those not performing care for animals or milking, overall (HR=2.71, 95% CI: 1.19-6.18) and was slightly higher with use of insecticides on pigs (HR=1.85, 95% CI: 1.01-3.39). The authors considered the results reflecting strong evidence of an inverse association between lung cancer and cattle and horse farming and considered further research necessary to identify possible aetiologic protective agents and biological mechanisms, which are unknown until now.

As a comparison, Beane Freeman *et al.* (2012) found comparable decreased lung cancer risks but not with cattle and horses, but only with poultry farming (RR=0.6; 95%CI: 0.40-0.97). Raising poultry was associated with an increased risk of colon cancer (RR = 1.4; 95%CI: 0.99-2.0) with further increased risk with larger flocks (p_{trend}=0.02). Risk of NHL was also elevated in those who raised poultry (RR=1.6; 95%CI: 1.0-2.4), but there was no evidence of increased risk with larger flocks (p_{trend}=0.5). Raising sheep was associated with a significantly increased risk of MM (RR=4.9; 95%CI: 2.4-12.0). Performing veterinary services increased the risk of Hodgkin lymphoma (RR=12.2; 95%CI: 1.6-96.3), although it is noted that the precision of the last 2 estimates with high CI's renders the biological significance debatable. Overall, there was a weak trend (p_{trend} =0.04) for the association between lower lung cancer risk and increasing number of livestock on the farm. The authors concluded on an inverse association between raising poultry and livestock overall, and lung cancer risk and some evidence of increased risk of specific lymphohaematopoietic malignancies with specific types of animals and performing veterinary services.

3.2.8 Boulanger *et al.* (2018) : Lung cancer incidence in the AGRICAN cohort.

In this study, authors asserted that winegrowers could have been at higher risk of adenocarcinoma (HR=1.27, 95%CI: 0.94-1.72). They also found an association between pea growing and small cell lung cancer: significant effect of duration (p_{trend}=0.04) and the suggestion of a surface-effect relationship (p_{trend}=0.06); increased risk (HR=2.38; 95% CI: 1.07-5.28) for PPP users; and significant effect of duration (p_{trend}=0.01) for harvesters. The risk of squamous cell carcinoma was increased for sunflower growing (HR=1.59; 95%CI: 0.97-2.62), fruit-tree pruning (HR=1.44; 95%CI: 0.92-2.27) and PPP use on beets (HR=1.47; 95%CI: 0.92-2.34). Corn and/or wheat/barley growers were at lower risk of lung cancer. It is of note that in a more general comparison (see Lemarchand *et al.*, 2017) SIRs were lower for upper aero-digestive tract and respiratory cancers. Therefore, It was concluded that associations between lung cancer and several crop-related tasks existed, but it was also recognised that some chance findings due to multiple comparisons could not be excluded.

The studies under 3.2.7 and 3.2.8 were not designed to highlight any relationship of PPP use and lung cancer risk.

Therefore, in a further but yet preliminary analysis (Boulanger, 2019, meeting notules), linking the AGRICAN data with the crop-exposure matrix PESTIMAT, the cancer risk due to exposure to inorganic arsenicals, was investigated. In the EU, arsenic acid and its salts are well-known pulmonary carcinogens for the human (Carc. Cat 1A, H350). Since epidemiological data are scarce for agricultural exposures, this work assessed lung cancer risk, including duration-effect relationships, associated to arsenicals use in farming, by gender and histology.

It appeared that among about 10% (N=14359) of the AGRICAN cohort, potentially exposed to arsenicals, in vineyard growing (before 2001) or in fruit-tree or potato growing (before 1973), 98 incidents of lung cancer were registered. Only ♀ exhibited a higher risk of lung cancer (HR=3.14; 95% CI: 1.42–6.96), for exposure to any a.s. (n=7 exposed cases, all adenocarcinomas), but with no duration-effect relationship. Risks were significantly elevated for lead, copper and sodium arsenate. The authors concluded on an increased risk of lung cancer, especially adenocarcinomas, among women. They however stated that at this stage, exposure assessment was broad: the use of an exposure index, based on probability, frequency and intensity of use, should help refining the analyses in future research in this field.

While this finding is notable, it is also useful to highlight that a.s. on the basis of arsene salts were never authorised in Belgium.

As a comparison, AHS cohort studies were consulted. In a first publication (Alavanja *et al.*, 2004) a SIR=0.44; 95%CI: 0.39-0.49 for lung cancer was observed overall, due in large part to a low cigarette smoking prevalence. Two herbicides, metolachlor and pendimethalin (for low-exposed groups to 4 higher exposure categories: OR’s of 1.0, 1.6, 1.2, 5.0; p_{trend} = 0.0002; and OR = 1.0, 1.6, 2.1, 4.4; p_{trend} = 0.003, respectively), and two insecticides, chlorpyrifos and diazinon (OR=1.0, 1.1, 1.7, 1.9; p_{trend} = 0.03; and OR = 1.0, 1.6, 2.7, 3.7; p_{trend} = 0.04, respectively), showed some evidence of exposure response for lung cancer in applicators. In a second follow-up publication (Bonner *et al,* 2017), hazard ratios were elevated in the highest exposure category of lifetime days of use for pendimethalin (1.50; 95%CI: 0.98-2.31), dieldrin (1.93; 95%CI: 0.70-5.30), and chlorimuron-ethyl (1.74; 95%CI: 1.02-2.96), although monotonic exposure–response gradients were not evident. The HR’s for intensity-weighted lifetime days of use of these pesticides were similar. For parathion, the trend was statistically significant for intensity-weighted lifetime days (p_{trend}=0.049) and borderline for lifetime days (p_{trend}=0.073). None of the remaining pesticides evaluated was associated with lung cancer incidence. The authors concluded on an association between chlorimuron-ethyl, pendimethalin, dieldrin, and parathion use and lung cancer risk, indicating that follow-up is warranted.

Regarding the relevance for the current PPP regulatory decisions, it is of note that only pendimethalin and S-metolachlor (an enriched stereoisomer of the metolachlor racemate) are still approved on the EU-market.

It is of note that in a follow-up study, investigating (S-) metolachlor in the AHS, elevated incidences of overall cancer, bladder cancer and lung cancer was not confirmed (Silver *et al*, 2015). On the other hand, the latter study revealed an elevated trend in liver and follicular cell lymphoma, while this was not found in earlier AHS studies. They evaluated cancer incidence for 49616 applicators, 53% of whom reported «ever using» metolachlor. No association between metolachlor use and incidence of all cancers combined, or most site-specific cancers was recorded.

On the contrary, for liver cancer, in analyses *restricted to exposed workers*, elevations observed at higher categories of use were not statistically significant. However, trends for both lifetime and intensity-weighted lifetime days of metolachor use were positive and statistically significant *with an unexposed reference group (Q4 RR amounted to 3.99 (95%CI: 1.43–11.1,* *N=10, P_{trend}=0.01, in «lifetime days» and 3.18 (95% CI: 1.10–9.22, N=9, P_{trend}=0.03), in «Intensity-weighted lifetime days»* analysis.

A similar, but somewhat weaker pattern was observed for **follicular cell lymphoma**, but no other lymphoma subtypes (Q4 RR amounted to 2.89 (95%CI: 1.13–7.38, N=9, P_{trend}=0.03, in «lifetime days» and 2.57 (95% CI: 0.95–6.95, N=8, P_{trend}=0.04), in «Intensity-weighted lifetime days» analysis. It is appropriate to highlight that an association between metolachlor and liver cancer in humans, not observed before though, is in line with observation of increased liver neoplasms in guideline animal studies (and could thus have an impact on CLP classification). However, the authors warned that findings of both liver cancer and follicular cell lymphoma warrant follow-up to better differentiate effects of metolachlor use from other factors.

3.2.9 Piel *et al.* (2017-2019): Central nervous system tumours in the AGRICAN cohort.

In the same AGRICAN cohort (Piel *et al.,* 2017), a possible role of PPPs in the occurrence of Central Nervous System (CNS) tumours was suggested, but the authors stressed that scientific evidence is still insufficient. During a ~5.2 years average follow-up (2005-2011), 273 incident cases of CNS tumours occurred, including 126 gliomas and 87 meningiomas. Statistically significant increases in meningioma risks were found in farmers growing beets (HR=2.54; 95% CI: 1.31–4.90) and sunflowers (HR=3.56; 95% CI: 1.44–8.82) and in PPP applicators on potatoes (HR=3.09; 95% CI: 1.06–9.03). The authors noted that beet and potato growing were at the top of a 14 field crop ranking concerning the frequency of PPP use in France with treatments per year rates of respectively 18.8 for potatoes (mainly fungicides) and 16.5 for beets (mainly herbicides). A significant increase in meningioma risk was also found among pig farmers performing animal care and/or local disinfection (HR=2.43; 95% CI: 1.16–5.09) and no significant association was found on the other crops and animals. It is of note that authors indicated an increased risks of CNS tumours in farmers, especially in PPP users (HR=1.96; 95% CI: 1.11-3.47), however the association lost significance for each tumour type separately (i.e. glioma and meningioma).

The authors concluded that, even if they cannot completely rule out the contribution of other factors, PPP exposures could be of primary concern to explain these findings.

In regard of the very important pig growing industry in Belgium (Flanders), the outcome may be used to investigate further a potential association between pig growing industry and brain cancer.

In follow-up studies (Piel *et al.,* 2019a,b) of ~6.9 years, 381 incident cases of CNS tumours were reported, including 164 gliomas and 134 meningiomas. Considering tumour subtypes more specific associations were found between brain tumour appearance and carbamate <u>insecticides</u> (Piel *et al,* 2019a). The authors considered the hazard ratios for gliomas increased with thiofanox (HR = 1.18; 95% CI: 0.43-3.22) and formetanate (HR=4.60; 95% CI 1.67-12.70), and for meningiomas again with thiofanox (HR= 3.67 ; 95% CI 1.16-11.56) and with carbaryl (HR= 1.51; 95% CI 0.82-2.79). The authors highlighted that carbamates are obviously able to reach the CNS, and that many carbamates could exert oxidative stress, for which the brain is considered to be very sensitive. However, it is of note that from these 3 a.s., only formetanate is yet approved at the EU-level as a PPP (the latter being most probably a candidate for substitution given its very low reference doses ≤0.005 mg/kg b.w./d). In their conclusion, the authors assert that some other carbamate insecticides, with strong similarities in chemical structures (as carbaryl), were also associated with an increased risk of CNS tumours and would deserve further attention (formetanate, dioxacarb, promecarb, isolan, thiofanox and methomyl). However, except formetanate, all of them remain unapproved in the EU and therefore have no relevance in terms of non-consumer exposure in agriculture.

Further analyses (Piel *et al,* 2019b) showed also increased risks of CNS tumours with overall exposure to carbamate fungicides (HR = 1.88; 95% CI: 1.27-2.79) and, to a lesser extent (only a trend), to carbamate herbicides (HR = 1.44; 95% CI: 0.94-2.22). Positive associations were observed with specific carbamates, including some fungicides (mancozeb(†?), maneb†, metiram) and herbicides (chlorpropham†, propham†, di-allate†). The strongest associations, corresponding to risks 2-3× times higher, were observed with the (dithio/thio)-carbamates used by farmers growing vineyards, fruits, potatoes and beets. The authors concluded that, although some associations need to be corroborated in further studies and should be interpreted cautiously, these findings provide additional carcinogenicity evidence for several carbamate fungicides and herbicides. It is of note that several of the cited a.s. are not approved anymore† , are likely (†) or possibly (†?) in phasing out in the EU and thus also in the Belgian context.

To date, none of the other cohort studies identified increased brain cancer incidences being associated to agricultural activities overall (see 3.2.4). According to Alavanja and Bonner (2012), major limitation of the studies published is the lack of details regarding exposure. Analyses by job title alone often result in misclassification of exposure, resulting in an underestimation of brain cancer risk by occupation. No firm, specific pesticide link to brain cancer has been made but additional studies are warranted.

3.2.10 Tual *et al.* (2019): Multiple myeloma in the AGRICAN cohort.

Subsequent to the observed trend for increased MM (see under 3.2.4), Tual *et al.* (2019) analysed the fate of 155192 participants of the AGRICAN cohort, including 269 incident MM identified from enrollment (2005–2007) to 2013. The risk was increased in farmers (i) who started using PPPs on crops in the 1960s, especially among those applying PPPs on corn (≥20 years: HR=1.73, 95%CI: 1.08–2.78, p_{trend} <0.01) and (ii) using insecticides on animals (HR=1.48, 95%CI: 1.11–1.98), especially among horse farmers (≥10 years: HR=2.77, 95%CI: 1.22–6.27, p_{trend} =0.01). They also observed significant elevated risks with disinfectant use in animal barns (HR=1.40, 95%CI 1.05–1.86). Some other HR were situated > 1, however without statistical significance at 5% level. The results support the role of PPP use on crops and pesticides on animals in the occurrence of MM risk in farmers. It should be noted that some findings might be due to chance or correlations between exposures. While multiple exposures were frequent, specific correlations between insecticide use on animals and PPP use on corn or between insecticide use on animals and disinfectant use were moderate. In the Tual *et al.* publication, no specific pesticide was studied, but based upon data from other studies, including AHS, a.s. like organochlorines (*e.g.* DDT, chlordane, lindane), carbaryl, permethrin, dichlorvos, captan, phenoxy herbicides, atrazine, dinoterb, and disinfectants like quaternary ammonium, phenol derivatives, and aldehydes were cited as being possibly related to MM risk. In the EU, and consequently Belgium, only captan and some phenoxy herbicides are still approved as PPP.

The authors declared that future studies are planned to include robust exposure data, like those generated by the PESTIMAT crop-exposure matrix (Baldi *et al.*, 2017), to investigate the associations between PPPs like the triazine herbicides and organochlorine insecticides and the risk of MM. One could question on the relevance of this intention in the EU context, as organochlorine insecticides basically fail in the current approval criteria and cannot be used again, and from the dozens of triazine herbicides once applied, only one (terbuthylazine) is still approved in the EU. However, other more contemporary PPP classes could be investigated with this methodology as well.

Tual *et al.* also noted that it was not possible to rule out the impact of biological exposure in farming, which is thought to be a possible risk factor for some haematological cancers in the meat industry. While in a recent meta-analysis on the multicentre AGRICOH study (including the AGRICAN cohort), no clear association was shown between animal farming and lymphohaematopoietic cancers (LHCs) risk, few associations between specific animal species and LHC subtypes were observed yet (El-Zaemey *et al.*, 2019). It was concluded that the observed differences warrant further investigations.

In the PUHS cohort (Frost *et al,* 2011), a clear increase of MM incidence (compared to the general population) was observed both in the ♂ (N=31, SIR=1.49; 95%CI: 1.05-2.13) and in the ♀ (N=4, SIR=10.9; 95%CI: 4.10-29.1). The observation was also linked to an overmortality for this cancer, but only in the ♀. The authors were of the opinion that, at least in the ♀, low numbers, made the estimations imprecise, such that they should be interpreted with care. Generally, scientific literature about the incidence of MM and agricultural activities displayed various outcomes, with both positive and negative findings.

In the AHS cohort, De Roos *et al.* (2005) reported a suggested association of MM incidence and glyphosate (although overall an effect on NHL incidence was unremarkable). The association was considered plausible given the higher RR as a function of cumulative and intensity-weighted exposure days. Compared to the reference, RRs were 1.2 and 2.1, with 95CIs of 0.4-3.8 and 0.6-7.0, for the 2 upper tertiles, respectively. Yet, in the follow-up (Andreotti *et al*, 2018) it was remarked that the non-statistically significant increase in MM noted in the previous AHS analysis was based on 19 exposed cases with a median follow-up of 6.7 years, and this association was not evident in the latest update, with an extended follow-up of 17.5 years and 88 exposed cases. Given the widespread use of glyphosate (certainly in the U.S.), future analyses of the AHS should allow further examination of long-term health effects, including less common cancers. It is of note that in the IARC review of glyphosate (2005), the excesses for MM in 3 case-control studies were noted, but they did "*not weigh this evidence as strongly as that of the NHL since chance events could not be excluded*".

In the pooled case-control study of the U.S. and Canada (Presutti *et al.*, 2016), increased MM risk was observed for ever use of carbaryl (OR=2.02, 95%CI=1.28–3.21), captan (OR=1.98, 95%CI=1.04–3.77) and DDT (OR=1.44, 95%CI=1.05–1.97). The captan finding in the pooled case-control study was however not confirmed in the AHS (Greenburg *et al.*, 2009). In contrast, AHS enrolled applicators experienced a significantly increased risks for MM in the highest tertiles of both lifetime exposure-days (RR = 5.72; 95% CI, 2.76-11.87) and intensity-weighted lifetime exposure-days (RR = 5.01; 95% CI, 2.41-10.42) to permethrin, compared with applicators reporting they never use this a.s. (Rudiecki *et al,* 2009).

In the already cited AGRICOH cohort, including AGRICAN (Togawa *et al,* 2021), it is confirmed that agricultural workers have an elevated risk of multiple myeloma (♀) compared to the general population (n° of cohorts = 4, meta-SIR = 1.27, 95%CI: 1.04-1.54). The differences and the between-cohort variations may be due to underlying differences in risk factors and warrant further investigation of agricultural exposures.

Overall, since MM was quite systematically present in 4/5 of the prospective and retrospective cohorts, further investigation would be highly recommended.

In this respect, the search for the association between PPP exposure and MM could be supported by an interesting and possibly promising biomonitoring study. A unique feature of MM is that it is almost always preceded by a largely asymptomatic condition called **monoclonal gammopathy of undetermined significance** (**MGUS**). People with MGUS have about a 1%/year likelihood of progressing to MM (Kyle *et al.*, 2002). In a small-scale study within the AHS cohort, Landgren *et al.* (2009) observed a 2-fold excess risk of MGUS compared to a demographically similar population (age-adjusted prevalence of MGUS 1.9; 95%CI: 1.3- 2.7), and a full study was launched (Hofmann *et al.*, 2015).

In a recent paper (Hofmann *et al,* 2021), the prevalence of MGUS and the association with a wide range of PPP's in a large sample of ♂ farmers of the AHS cohort was published. The age-standardised MGUS prevalence was significantly elevated among AHS farmers (+7.7%) compared with demographically similar men in the National Health and Nutrition Examination Survey (+2.8%) or Olmsted County, Minnesota (+3.8%; p<0.001). Recent use of permethrin was associated with MGUS [recent use *vs.* no recent use, OR=1.82 (95%CI: 1.06–3.13)], especially among those who had also used it in the past [recent and past use *vs.* never use, OR=2.49 (95%CI:1.32–4.69)]. High intensity-weighted lifetime use of the organochlorine insecticides aldrin and dieldrin was associated with MGUS relative to those who never used either of these pesticides [OR=2.42 (95% CI:1.29–4.54); p_{trend}=0.006]. They also observed a positive association with high lifetime use of petroleum oil/distillates as an herbicide. They concluded that, given the continued widespread use of permethrin in various residential and commercial settings, their findings may have important implications for exposed individuals in the general population.

It should be noted that neither the insecticide permethrin (as PPP) nor the herbicide based on petroleum oils are approved *c.q.* authorised in the EU and Belgium, respectively. However, since the MM incidence is associated with agricultural activities, and possibly PPP exposure, the MGUS incidence in the AGRICAN/AGRICOH cohort, as a probable precursor of MM, should be further investigated.

In addition to the assessment of MGUS, future investigations in this epidemiological study will also focus on leukocyte telomere length as an intermediate biomarker linking pesticide exposures and cancer risk.

3.2.11 Other intermittent (recent) AGRICAN epidemiological studies (not fully peer-reviewed) on sarcoma incidences.

In a recent congress meeting notule, Renier *et al.* (2020) reported investigations on the incidence of sarcoma in the AGRICAN cohort.

This study would have revealed increased risk of sarcoma incidence in cattle growers active ≥10 years ago (HR = 2,43; 95%CI: 1.25—4.75) and running cattle farms having ≥50 animals (HR = 3.85; 95% CI: 1.40—10.61). In crops, significantly elevated risks were observed with vegetable growers in full-field (HR = 1.62; 95%CI: 1.01—2.60) and in greenhouses (HR = 2.32; 95%CI: 1.22—4.07). The authors also highlighted possible elevated risks for subtypes like myosarcoma and fibrosarcoma and some agricultural activities, like vegetable cropping in full field (HR = 8.75; 95% CI: 1.95—39.3). In addition, some other trends have been noted (such as in poultry farms), although all these were not statistically significant, and any association with PPP use was therefore uncertain (as mainly general farming was highlighted). The authors could not find any association between farming and the incidence of gastrointestinal stromal tumoural subtypes (GIST). While these data are not definitive, it could be remarked that on top, the absolute numbers were considered very low in some cases (reflected by an extremely wide 95% CI), that this very heterogeneous and complex group of sarcoma is poorly described in the scientific literature, and therefore the interpretation of these preliminary findings, pending validation, should be considered cautiously for the time being.

Former investigation of association between PPP use and soft-tissue sarcoma (STS) is scarce, but four early case-control studies demonstrating a potential association between STS and exposure to phenoxy herbicides, chlorophenols and contaminating dioxins, were reviewed by Hardell (2008). Hoar *et al.* (1986) found no association between herbicide exposure and STS, but increased risk was revealed in cases of exposure to insecticides and farm animal protection (Zahm and Blair, 2008). Imputation to any current a.s. used is not evident. Outdated a.s. like arsenicals are well-established risk factors for liver angiosarcoma but not soft-tissue sarcoma, and as already mentioned they are not in use anymore.

Whether the preliminary AGRICAN findings would reflect former exposures to tetrachlorodibenzodioxin (TCDD)-like impurities in phenoxy herbicides is unknown, but it should be highlighted that in any case, the presence of and exposure to dioxin impurities is extremely unlikely, as the latter are systematically traced in any a.s. eligible to be formed it in the manufactory process under current EU-law, but cases due to historic exposure are still possible, and mechanisms other than TCDD-related ones may exist.

In conclusion, the various associations highlighted between certain farms (cattle, poultry) and cultures (vegetable, greenhouse culture) and the occurrence of sarcomas deserve further investigation before confirmation of a causal relationship with PPP exposure.

As stated in point, AGRICAN published not peer-reviewed «intermediate results» on its internet page in November 2020. The cited figures (calculated on the period 2005-2015) are sometimes slightly different from those published in the various peer-reviewed papers (mostly 2005-2011), but the trends and concomitantly, the conclusions are not meaningfully different.

4 Special focus on Non-Hodgkin Lymphoma (NHL) in the frame of PPP long-term exposure

4.1 NHL is possibly associated with chronic exposure to certain PPPs' active substances

As discussed under 3.2.4 (Lemarchand et al. (2017), elevated risks were observed in the AGRICAN cohort for **non-Hodgkin lymphoma**, by about 9% in ♂.

This outcome was compared with that of the other prospective AHS cohort. Koutros *et al.* (2014) found a 17% increased risk for NHL. Alavanja *et al.*, (2014) reported that for total NHL, significant positive exposure-response trends in AHS 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 (SCL/CLL), marginal cell lymphoma (MCL), lindane and diazinon with follicular lymphoma (FL), and permethrin with MM. However, no exposure-response among NHL-subtypes for any pesticide was demonstrated. Because 26 pesticides were evaluated for their association with NHL and its subtypes, some chance finding could have occurred. It was concluded that PPPs from different chemical and functional classes were associated with an excess risk of NHL and NHL subtypes, but not all members of any single class of pesticides were associated with an elevated risk of NHL or NHL subtypes.

From the retrospective cohorts cited in 3.2.4, only the CANCHEC cohort reported an elevated risk for NHL with 10% in ♂.

An important, robust and recent systematic review and meta-analysis between PPPs and NHL was published by Schinasi and Leon (2014).

Estimates of associations of NHL with 21 PPP chemical groups and 80 active ingredients were extracted from 44 papers. Meta-analyses suggested that phenoxy herbicides, carbamate insecticides, organophosphorus insecticides and the active ingredient lindane were positively associated with NHL.

In the meta-analysis study of Schinasi and Leon (2014), phenoxy herbicide exposures were associated with B cell lymphoma (1.8, 95%CI: 1.2–2.8, CLR: 2.4), lymphocytic lymphoma (1.8, 95%CI: 0.9–3.5, CLR: 3.8), and diffuse large B-cell lymphoma (DLBCL; 2.0, 95%CI: 1.1–3.7, CLR: 3.3).

The authors concluded that, despite compelling evidence that NHL is associated with certain chemicals, this review indicates the need for investigations of a larger variety of pesticides in more geographic areas, which is potentially missing in the existing scientific literature.

The outcome of this review was in line with earlier publications (Zahm and Blair, 1992; Dreiher and Kordysh, 2006).

In the study investigating the carcinogenic effects of PPP exposure in the AGRICOH cohort (Leon *et al.*, 2019), the authors have identified elevated risk for few other PPPs including the pyrethroid deltamethrin and chronic lymphocytic leukaemia/small lymphocytic lymphoma; and terbufos and NHL overall.

A major scientific dispute erupted on the interpretation of a positive association between the herbicide glyphosate and NHL (IARC, 2015).

In two other Canadian systematic reviews of PPP human health effects (Sanborn et al., 2004 and Bassil, 2007), the authors highlight a possible association between NHL and PPP use. Twentyseven population studies are cited: 11 cohort studies, 14 case-controls and 2 ecological studies, indicating 9, 12 and 2 positive associations, respectively. Amongst them, a quite impressive cohort of 155000 farmers is cited (Morrison et al., 1994). For farm operators who lived on the same farm in both 1971 and 1981, according to 1980 farming practices with mortality follow-up from 1981 to 1987, an increased risk of NHL mortality associated with acreage sprayed with herbicides was observed and for the highest quartile of ≥939 or more ha sprayed, the RR was 2.11 (95% CI 1.13-3.93). The authors noted that "any exposure-disease relationship in the present study between 2,4-D and NHL must be inferred and must, at best, be considered tenuous", while they also stressed that there is only limited evidence suggesting that phenoxy herbicides (likely used in prairies) may be carcinogenic in animals. No reference to possible phenoxy acid contaminants (dioxins, as well-known carcinogenic former impurities) was made, and the cause for the observed overincidence remains unexplained.

4.2 In agriculture, NHL could be associated to exposure to other factors

It has been suggested that the levelling off of NHL incidence rates in several countries in recent years could be related to the ban of various organochlorine substances during the 1970s and 1980s in these countries (see Nelson, 2005 and Ekström-Smedby, 2006).

In an attempt to explain potential associations between agricultural activities and NHL, Chiu and Blair (2006) suggested that 'benzene and solvents' may be related to the development of NHL through pathways involving a t(14;18) chromosomal translocation, frequently found in NHL.

Future epidemiologic studies evaluating the association of PPP, solvents, and farming activities with NHL risk might benefit from defining subgroups of NHL according to t(14;18) status.

From a mechanistic point of view, the hypothesis of the involvement of genotoxic solvents, potentially responsible for elevated chromosomal rearrangements, including t(14;18) is not excluded. However, the Belgian authorities are since about 2000 involved in the complete ban of PPPs containing potentially carcinogenic aromatic solvents, and the presence of such substances as impurities in existing actives (if analytically significant) is restricted to levels 'as low as reasonably achievable'.

Alternatively, the exposure to diesel exhausts (containing notoriously genotoxic polycyclic aromatic hydrocarbons (PAHs)) during agricultural activities is not excluded.

Important reviews, spanning huge amounts on literature regarding alternative explanations for the occurrence of NHL worldwide, were consulted (Fisher and Fisher, 2004). UV radiation, demonstrated to have an immunosuppressive effect could well be a possible risk factor for NHL. Several pathogens have been linked to an elevated risk, including Epstein-Barr virus, HIV, human T-cell lymphotropic virus-1, Helicobacter pylori, hepatitis C, and simian virus 40. Whether these organisms are responsible for specific mutations that initiate tumour growth, antigenic stimulation leading to B-cell proliferation implying increased potential of DNA replication errors, or immunosuppression, which promotes tumour growth, has not been elucidated. While exogenous factors which have been implicated in lymphomagenesis also could include PPP exposures, the reviews also mention exposure to other xenobiotics. It should be noted that the level of detail of epidemiological studies is often insufficient to discriminate against all these potential confounders.

4.3 High heterogeneity of NHL may obscure the association in epidemiological studies

One important remark is worth noting: NHL is a very heterogeneous group of malignancies including a large number of subtypes with different characteristics and most probably diverse aetiologies. The EUCAN database (IARC, 2018) mentions a Belgian incidence rate of about 10 ♀-15♂/100000, making it the 8th-highest ranked tumour (in terms of new cases) after 7 solid-tumours (breast, lung, prostate, colon, bladder, melanoma, rectum) in 2018. However, with as much as 60 subtypes described ((with DLBCL, 85-95%) and (FL, 22%) being the most frequent) (see also general reference in Swerdlow *et al.,* 2016)), the significance of any environmental or endogenous component needs to be elucidated in more detail.

It is of note that although MM traditionally was not considered a subset of NHL, WHO revised the classification of lymphoid neoplasms and suggested that at least some types of MM would be related more closely to lymphomas, including NHL, than to myelomas (Swerdlow et al., 2016).

Until recently, no specific data were available regarding the possible association between NHL and PPP exposure in the AGRICAN cohort.

However, recent advanced congress communications (full data not available however) suggest again a possible link (Busson et *al.*, 2019a and 2020).

In these succinct meeting abstracts, increased risks were reported for NHL overall and MM (SIR=1.05, and SIR=1.23, respectively, however CI not mentioned). Positive associations (possibly not statistically significant) with exposure to PPPs were observed:

i) on crops: DLBCL in grassland and tobacco, MM in corn, wheat/barley and potato, CLL-SLL in corn, wheat/barley and vineyard,
ii) in seed treatment: CLL-SLL, in sunflower, wheat/barley) and MM in wheat/barley, corn,
iii) for use on animals (MM).

According to the authors, the data would support the role of pesticide exposure on NHL risk, not only on crops. Specific associations according to NHL subtypes were observed, but more detailed peer-reviewed data need to be published first in order to appreciate the exact relevance of the observed trends in apparently very extensively stratified populations of the AGRICAN cohort, before concluding on this issue.In a subsequent succinct communication, an attempt was made to assess the role of the use of benzimidazole class of fungicides on NHL risk, overall and for MM, CLL-SLL and DLBCL (Busson *et al.*, 2019b). After exclusion of prevalent cases, *i.e.* individuals with incomplete agricultural profession history data or a zero tracking period, 1133 NHL incident cases were identified from cancer registries (269 MM, 244 CLL-SLL, 190 DLBCL). Nearly 20% of participants were considered exposed to the a.s. (median duration: 7-20 years). A trend (non-statistically significant) for increased NHL risk was observed with exposure to benzimidazole, overall, on any crops (HR=1.13, 95%CI: 0.94–1.37, 150 cases, no duration relationship). Borderline positive associations were reported on specific crops: wheat/barley (NHL: HR=1.23, CLL-SLL: HR=1.42), beets (DLBCL, HR=2.19) and rape (DLBCL, HR=2.32).

Increased risks were reported with MM for use of thiophanate-methyl on wheat/barley (HR=3.46, 23 exposed cases, no duration relationship) and with DLBCL for all 4 benzimidazole fungicides used on beets (HR from 2.34 to 2.57 and for 2 a.s. used on rape (HR=2.39 and 2.46). Which a.s. were used on rape was not exactly reported at this point, and also CI's were not mentioned, thus purported significance remains uncertain. It should also be stressed that the association was based on respectively 7 and 6 cases. Nevertheless, the authors concluded on positive associations between incidence of specific NHL subtypes, and exposure to benzimidazole as a chemical class or a.s. (thiophanate-methyl). As for other observations in these recent intermittent AGRICAN findings, full evidence is needed before confirming such association, let alone causal relationship.

In the AHS, no similar observations for benzimidazoles and NHL were made. However, a recent investigation (Lerro *et al.*, 2020) highlighted that compared to applicators reporting no use, those in the highest quartile of exposure to dicamba had elevated risk of NHL subtype CLL (RRQ4 = 1.20, CI: 0.96-1.50, Ptrend = 0.01) and borderline decreased risk of myeloid leukaemia (RRQ4 = 0.73, 95%CI: 0.51-1.03, P_{trend}=0.01). Increased risk of liver and intrahepatic bile duct cancer was also noted (RRQ4 = 1.80, 95%CI: 1.26-2.56, $P_{trend} < 0.001$). The associations for liver cancer and MM but not CLL remained after lagging exposure of up to 20 years.

Since previous studies suggested associations of NHL with some of these chemicals, and many studies have been limited in their ability to evaluate associations with lymphoma subtypes, Koutros et al. (2019) recently evaluated the use of 11 organophosphate and 2 carbamate insecticides in association with NHL in the North American Pooled Project (NAPP), which includes data from case-control studies in the US and Canada (1690 cases/5131 controls). They estimated the odds for associations between these chemicals and NHL overall, and NHL subtypes, i.e., FL, DLBCL, SLL and others. "Ever use" of malathion was associated with increased risk of NHL overall (OR=1.43, 95%CI: 1.14-1.81) and the observation showed a significant exposure-response for increasing years of use of malathion. In addition there was an increased risk of NHL-subtypes FL (OR=1.58, 95%CI: 1.11-2.27) and DLBCL (OR=1.61; 95%CI: 1.16-2.22), but no apparent associations with SLL or other subtypes. Similar results were obtained for other organophosphate diazinon (no association between use duration and NHL risk). The authors concluded on an association between organophoshate insecticide use and NHL overall, and provided new information on associations with NHL subtypes.

4.4 Epidemiological studies do not lead to consistent conclusions

It is remarkable that while 'positive' associations are observed in ecological or retrospective case-control studies, more robust epidemiological prospective cohort-studies are less conclusive. A notorious example is found in the studies investigating glyphosate-based herbicides, giving slight overincidences of non-Hodgkin lymphomas (NHL) in case-control studies, whereas cohort-studies resulted mostly in no association. In an impressive pooled international prospective cohort of about 316000 people, no such association was found for NHL either (Agricoh cohort of Leon *et al.*, 2019).

However, it should well be noted that the most common NHL subtype DLBCL seems to be somewhat associated (unadjusted for other a.s.) in one case-control study (Pahwa *et al.*, 2019). In most case-control studies, there is no indication of DLBCL (see IARC report of 2015 where this subtype was analysed). Other cohort studies, including the latest update of the AHS (Andreotti *et al.*, 2018) did not find any association between glyphosate exposure, even in the top exposure quartile, for neither NHL (HR=0.87; 95%CI: 0.64–1.20) nor DLBCL (HR=0.97; 95%CI: 0.51–1.85).

Overall, while the association of NHL with glyphosate remains somewhat obscure, the AGRICOH cohort study (Leon *et al.*, 2019) regrouping AHS, AGRICAN and CNAP in a meta-analysis, still indicates a moderately elevated meta HR for DLBCL and use of glyphosate formulations (mHR=1.36, 95%CI: 1.00–1.85).

It is however to be noted that, while the meta HR was slightly high in de Leon AGRICOH meta-analysis, the cohort-specific HRs for ever use of glyphosate and DLBCL were **HR=1.06 (95%CI: 0.51–2.19) in AGRICAN** (French cohort), HR=1.67 (95%CI: 1.05–2.65) in CNAP (Norwegian cohort) and HR=1.20 (95% CI: 0.72–1.98) in AHS (US cohort), meaning a statistically significant finding only in the CNAP, which possibly drove the elevated meta HR of DLBCL.

Therefore, in the presence of a statistically significant result in the meta-analysis, the implication of glyphosate exposure to the DLBCL incidence, albeit weak, cannot be entirely excluded.

A common feature of all of the cited studies consists of self-reported information regarding the use of PPPs, which is prone to exposure misclassification, and thus is a key limitation. In the AGRICOH study, it was recognised that "*non-differential exposure misclassification was an important limitation, showing the need for refinement of exposure estimates and exposure-response analyses*", although these authors suggested that exposure misclassification is probably non-differential, because pesticide exposure was reported or assessed based on information available before the occurrence of the health outcome, introducing bias towards the null hypothesis and possibly giving rise to false-negative results.

With regard to the herbicide glyphosate, the latest INSERM expert review (2021) found a «moderate presumption» of a link to an increased risk of NHL. An excess of risk was suggested for MM and leukaemia, but the results are less solid (weak presumption of a link). They noted that *mutagenicity* tests on glyphosate are generally negative, whereas *genotoxicity tests* are generally positive, findings consistent with an induction of oxidative stress. Interestingly, they recognised an excess of cases in experimental carcinogenesis studies in rodents, but noted they are not convergent. They report different types of tumours, arising in either ♂ or ♀, and only at very high doses or in certain strains.

Other mechanisms of toxicity (intergenerational effects, disruption of microbiota) are reported in the scientific literature, INSERM experts stressed the need to take these into consideration during regulatory assessment procedures. At publication time of this review (2021), the EU-glyphosate DRAR was available (EFSA, 2021). In this assessment, the RMS's took into account abovementioned concerns. They agreed that these published studies, reporting rather biochemical and/or molecular events on DNA and protein level after glyphosate exposure, did not provide sufficiently conclusive evidence on genotoxicity, and therefore not taken into account for classification of glyphosate for genotoxicity/mutagenicity. Some of the *in vitro* and *in vivo* studies suggested, but not reliably demonstrated, that glyphosate may induce oxidative stress. Overall, the alleged carcinogenicity of glyphosate remains controversial, in the absence of demonstrated MoA's.

In conclusion, associations of PPPs with NHL appear to be subtype- and chemical-specific. Non-differential exposure misclassification was an important limitation, showing the need for refinement of exposure estimates and exposure-response analyses.

FPS is of the opinion that, while a causal relationship between haematopoietic cancers and agricultural activities (including exposure to PPPs) is not definitively proven (both for professional people and for bystanders/residents) and there is a **residual doubt of some association,**a policy should be developed in order to further reduce such exposures as much as possible.

4.5 Mechanistic considerations on PPP-induced haematopoietic diseases

Whereas some suspicion has been risen on the association between haematopoietic cancers in general and NHL in particular, robust experimental data to underpin a causal relationship are scarce. An overview of the possible implication of not only agricultural occupation but also other factors was recently discussed by Busson *et al.* (2020).

In their systematic review, the French INSERM (2013) also refers to the Agricultural Health Study (AHS) in order to highlight a "*strong presumption*" of association between the exposure to PPP's and NHL. The specific culprits for such a presumption are lindane, DDT and organophosphates (and more specifically malathion). Slighter associations were observed in professionally exposed people with antecedents of haemotopoietic cancers, t(14;18) translocations and/or asthmatics, although it was remarked that the numbers were quite small. In a recent small-scale French epidemiology study (Agopian *et al.*, 2009), it was demonstrated that the normal time-dependent increase of t(14;18) chromosomal translocations in blood samples during a 9-year follow-up was exacerbated in persons exposed to PPPs. While the study demonstrated no direct connection between agricultural PPP use and malignant progression, the findings suggest that classical epidemiology studies should be extended with relevant exposure or effect biomarkers, in order to reveal causal relationships and modes of action.

In the INSERM review (2013), the authors have suggested possible modes of actions, including genotoxicity (like for thiophanate-methyl, as suggested by Busson *et al.,* 2019b), modulation of haematopoiesis and oxidative stress and have cited a list of several actives which could be associated with NHL such as organochlorines, and some others including chlorpyrifos, atrazine, permethrine, alachlor and glyphosate. From these, only glyphosate is still approved at the EU-level.

In their follow-up review (INSERM, 2021), the experts confirmed the «strong presumption» of a link between pesticide exposure and six pathologies including non-Hodgkin's lymphoma (NHL).

It should be acknowledged that, notwithstanding extensive experimental models (both *in-vitro* and *in-vivo*) to assess carcinogenicity for regulatory purposes, the discrepancy between some epidemiological findings and pre-marketing assays illustrates the need to refine the regulatory strategies to forecast long-term effects of PPPs.

4.6 Provisional conclusions regarding chronic exposure to PPP and NHL

Taken together, the many reviews on this issue seem to converge to one scientific consensus, *i.e.* the aetiology of non-Hodgkin lymphoma, as well as its rise in incidence during the past decades, remains largely unexplained.

One should remain aware of existing publications highlighting the influence of agricultural activities and/or PPP exposure on the NHL incidence; it has become increasingly clear that the NHL heterogeneity may be a seriously confounding element to establish a causal connection between *e.g.* PPP exposure and lymphomagenesis.

Overall, it is acknowledged that as with the other sub-types, consistent patterns of association between glyphosate and NHL across different metrics remain unclear, but since the most powerful cohort study of Leon *et al.* (2019) still highlights an **association between glyphosate exposure and a subset of NHL (DLBCL)**, there is a reason to justify further investigation and risk management should focus in better strategies of exposure reduction in general.

5 Special focus on Parkinson Disease (PD) in the frame of PPP long-term exposure

Many publications suggested an association between exposure to PPP and Pakinsonism or PD. In the already cited INSERM review (2021) it was reported that ecological and case-control studies with geolocalisation, based on characterisation of *agricultural activity* in the vicinity of addresses of residence would suggest a link between exposure of residents living near agricultural land and PD and also between residential proximity to pesticide application zones (radius <1.5 km) and behavioural traits related to autism spectrum disorders in children. Since these studies have important limitations related to fine assessment of exposure and the absence of individual data, the strength of this presumption was considered weak, which again highlights the need for studies and databases making exposure assessment more robust.

5.1 Van der Mark *et al.*, 2012

In an extensive systematic review (Van der Mark *et al.*, 2012) the authors compiled and analysed existing epidemiological studies, both in an occupational or a non-occupational context. The major outcome was that PD was associated with agricultural activities in an occupational context, resulting in relative risks (expressed as summary Risk Ratios, sRR) up to 62% on average (sRR=1.62; 95% CI: 1.40-1.88). The major finding of this review is that, like for most systematic reviews on this topic, there may be a general trend, but most studies are retrospective case-control studies.

Taking into account the latter, 8/16 occupational exposure studies are not statistically significant. From the 4 cohort studies (on 39, both occupational and non-occupational), only one (Ascherio *et al.*, 2006) is statistically significant (RR=1.80, 95%CI: 1.30-2.50).

The major importance of cohort studies resides in the characteristic of their prospectivity, allowing higher confidence in the estimation of exposure overall, even if both case-control and cohort studies often fail to pinpoint an exposure to specific active substances related to a given outcome.

Notwithstanding this, the authors conclude that their overall summary risk estimates strongly suggest that exposure to PPPs, and to herbicides and/or insecticides in particular, increases the risk of developing PD. Heterogeneity among study-specific RRs could not easily be explained by methodological differences, except for a suggestive effect of exposure assessment characteristics. Future studies should therefore focus on using more objective semiquantitative methods for exposure assessment such as job- or crop-exposure matrices, rather than relying solely on self-reporting. Although classes of PPPs have been linked to PD, it remains important to identify the specific chemicals responsible for this association. Therefore, in new, preferably prospective studies, attention should be given to collecting detailed information on specific PPP use.

5.2 Van Maele Fabry *et al.*, 2012

In contrast to the former meta-analysis, Van Maele *et al.* included 12 cohort studies, from which half of them were (the most valuable) prospective cohorts. Especially the prospective cohorts indicated a meta-rate ratio (mRR) of 1.39, 95% CI:1.09-7.78, again indicating a weak to moderate association between PPP exposure and PD. The highest increased risks were observed for studies with the best design, *i.e.* reporting PD diagnosis confirmed by a neurologist (mRR=2.56; CI: 1.46–4.48; n=4) or for cohort studies reporting incidence (in contrast to prevalence) of PD (mRR=1.95; CI: 1.29–2.97; n=3).

When all studies were combined the mRR remained significant : 1.28; 95% CI: 1.03–1.59 but there was a high heterogeneity and inconsistency among the different studies.

The authors highlighted that overall, the consistency of the mRRs between meta-analyses combining case–control studies (majority of studies in Van der Mark *et al*., 2012) and the combination of cohort studies (particularly prospective cohorts) strengthens the hypothesis that exposure to PPPs may be an aetiologic factor of PD. However, the heterogeneity among individual study results is a confounding and could not be easily explained, although the uncertainty on actual exposure levels was most probably the most contributing factor overall.

5.3 Van der Mark *et al.,* 2014

In a more specific retrospective case-control study (Van der Mark *et al.,* 2014), no evidence for a clear causal relationship between PD and exposure to PPPs in the Netherlands was found. However, statistically *non-significant* elevated odds ratios (ORs) observed in the “higher exposure categories” are, according to the authors, in line with earlier evidence that exposure to PPPs might increase PD risk. From all active substance-specific analyses (paraquat[†], maneb, atrazine[†], benomyl[†], dinoseb[†], dichlorvos[†], lindane[†], parathion[†]) a possible association with PD risk was only observed for benomyl ([†]: non-approved a.s.). It is of note that, while this benzimidazole fungicide has previously been associated with PD risk, the authors did not mention that paraquat and maneb were potential even worse culprits for this neurodegenerative condition. In this study, statistically elevated ORs remained absent for these actives, though.

5.4 Brouwer *et al.*, 2017

In another more recent case-control study (Brouwer *et al*., 2017) , of a total of 352 PD cases and 607 hospital-based controls, no significant associations with PD were found for the PPPs paraquat, maneb, lindane, benomyl. Extending the assessment for another 153 PPPs, increased risk of PD was found for 21/153 PPPs, mainly used on cereals and potatoes. Results were suggestive for an association between bulb cultivation and PD. The authors concluded that for paraquat, risk estimates for the highest cumulative exposure tertile were in line with previously reported elevated risks. High correlations limited their ability to identify individual PPPs responsible for this association. While this study provided limited evidence for an association between environmental exposure to specific PPPs and the risk of PD, due to limited biological plausibility and the potential for multiple testing issues, chance findings could not be excluded.

5.5 Pouchieu *et al.,* 2018a (AGRICAN data)

Further results of a possible association between PD and agricultural/PPP activities in the AGRICAN cohort were published by Pouchieu *et al.* (2018a).

The authors reported PD in 1732 subjects (1.2%) at enrollment in the AGRICAN cohort. Lifelong PPP use was associated with an increased risk of PD in all types of activities [odds ratio (OR)=1.31 (cattle) to 1.79 (peas), P<0.05]. Rotenone†, diquat†, paraquat† and several dithiocarbamates were associated with an increased risk of PD [OR=1.31 (cuprobam†) to 1.57 (rotenone)], especially in farmers with the longest exposure. It was concluded that the risk of PD is increased in farmers exposed to PPPs on several French crops and livestock, and supports additional evidence of an association of PD with dithiocarbamate fungicides, rotenone and the herbicides diquat and paraquat. It is noted however that statistical significance disappeared (except for zineb† and ziram) when the ORs were adjusted for co-exposures between active ingredients (ever *vs* never exposed to another a.s.). Furthermore, many of these a.s. are outdated (rotenone) or already non-approved† at the EU (and thus Belgian) level. As a matter of fact, from the 14 investigated a.s., only metiram and ziram are still approved (as per march 2021). A point of critic to the Pouchieu study was that exposure after the (self-reported) PD onset was part of the exposure measures, and that the conduct of a nested case-control within the cohort would be useful (Wendt, 2018). However, the authors retorted (Pouchieu *et al.*, 2018b) that they used a crop exposure matrix to verify PPP exposure, and conducted numerous sensitivity analyses to ensure the robustness of the results, especially regarding exposure assessment. They clarified that exposure to agricultural activities after the PD diagnosis was reported in <1% of cases. Regarding future analyses, Pouchieu *et al.* plan to conduct prospective analyses of the relationship between PPP exposures and PD, crossing different data sources to collect incident cases (Pouchieu *et al.*, 2018b).

Potential culprits like rotenone or paraquat and others, either never authorised or banned since decades, or in their way of phasing-out, will only or mainly be included in epidemiological studies in a frame of historical exposure (i.e. not representative for current and future uses), which remains increasingly cumbersome as time evolves.

In addition, while the abovementioned studies mainly focus on the possible effect of PPP on PD incidence in handlers and agricultural workers, the scientific literature dealing with the effects on bystanders and residents is relatively scarce. In a study, designed to examine the relationship between estimated residential exposure to PPP application and premature mortality from Parkinson's disease, Caballero *et al.* (2018), used mortality records for 2011–2015, which were geocoded using residential addresses, and classified as having exposure to agricultural land-use within 1 km. Generalised linear models were used to explore the association between land-use associated with PPP application and premature mortality from PD. Individuals exposed to land-use associated with a number of a.s. (including glyphosate and paraquat) were shown to have higher odds of premature mortality than the non-exposed individuals.

Nevertheless, the authors considered this study unique in multiple ways, with many innovative strengths and some implicit limitations. It is correctly stressed that studies relating agricultural PPP and PD often implement a temporal model, in which researchers use the participants' memory to recount the exposure of the study population, making them highly subject to recall bias. By analysing data that are retrieved from PD-related deaths and by employing the advanced spatial methodologies, much more detailed understanding of the individual exposure may be developed, avoiding the issues of participant recall bias. Further, agricultural PPP exposure assessments are greatly constricted by the historic pesticide records that are made available to researchers by federal institutions. A great deal of quantitative research on pesticide exposure and PD in the US has been made possible by California's (quite unique) independent Pesticide Usage Report (PUR), which offers extensive information of *actual* PPP application. In the EU (and also in Belgium), it is anticipated that by cross-matching actual PPP use (still to be organised in most if not all EU-member states, by means of on-line registration) and actual health outcomes (including cancer but also neurodegenerative diseases like PD) in a cohort-driven epidemiological context, a much better understanding of aetiology of these long-term effects would be possible.

However, it should be acknowledged that even extremely useful approaches aiming refinements from the exposure side, will be hampered by the uncertainty regarding causality between exposure and disease.

While the plausibility of effect for some of the abovementioned a.s. may appear obvious, the potential MoA in the case of others, like glyphosate (as an a.s., cited above) remains elusive, and needs to be assessed in the course of the next-coming renewal at EU-level. In general, purported effects of an a.s. like glyphosate are possibly confounded by the presence of potentially suspect co-formulants in the mixture (to which people in an agricultural context are exposed in the end), like tallow amine ethoxylates, for which a particular one is banned by law, but for which closely related structures of the banned one should be further investigated. The same may be true for other formulations, less in focus but potentially concerning.

Except for few a.s., it is recognised that, like in the evaluation of cancer incidences, evidence for a one-to-one (let alone causal) the association between particular PPP's (a.s. and or coformulants) and PD is disappointedly poor.

From the <u>regulatory</u> point of view, an additional complication consist in a lack of validated studies, both *in-vitro* and *in-vivo,* precluding the early discovery of potential hazardous a.s. in the PD perspective.

Finally, in a <u>mechanistic</u> perspective, a plausible link between the inherent MoA of certain a.s. like potential mitochondrial toxicants and PD could be established. A.s. such as tebufenpyrad, bixafen, or fenpyroximate) are related to impairment of the mitochondrial electron transport chain and subsequent oxidative stress (cited in Choi *et al,* 2016). Other a.s. were directly or indirectly associated to potential mitochondrial disturbance such as ziram, chlorpyrifos, atrazine or trichlorfon, all currently banned from the EU approved list of PPP's.

In the absence of regulatory toxicity assays, it is assumed that potential leads could be found by developing *in-vitro* assays and the concomitant establishment of AOP's, as a first tier approach. Terron *et al* (2018) proposed an AOP demonstrating mechanistic plausibility for epidemiological observations on a relationship between pesticide exposure and an elevated risk for Parkinson's disease development. Specifically, the AOP would cover the toxicological pathways that link the binding of an inhibitor to mitochondrial complex I with the onset of parkinsonian motor deficits, elucidating causality for the epidemiological association between PPP exposure and the development of PD.

On the other hand, even if there are few *in-vivo* assays, the existing ones could be useful to explore, although currently, the development of these seem to be hampered by the complexity of their protocol (and the concomitant impact on validation), or the general reluctance by animal welfare considerations, or both.

5.6 Conclusion about Parkison disease

Overall, the existing meta-analyses seem to indicate a weak to moderate significant association between exposure to PPPs and PD. The most convincing association comes from studies which are generally believed to be of major relevance, such as prospective cohorts. It is noted that often, the effect of the duration of exposure on mRR is uncertain. Recent attempts to estimate in a quantitative way the effect of duration on PD incidence revealed only weak associations: a 5 to 10 years exposure duration to PPP was associated with a 5% to 11% increased risk of PD, respectively (Yan *et al.,* 2018). While many studies provide some support for the hypothesis that occupational exposure to PPPs would increase the risk of PD, there is on the other hand a very wide consensus among epidemiologists that there is an urgent need to improve the accuracy of the exposure data, in order to confirm a potential causal relationship between PD and PPP exposure. It is also thought that further high-quality (prospective) cohort studies are required to validate such a causal relationship. In order to reinforce estimates of exposure, there is a high need of rolling out legally binding and verifiable registration tools collating actual uses in the agricultural sector.

Knowing the difficulties and limitations of the assessments on the exposure side, much expectations have risen on the hazard-side, namely in the development of validated *in-vitro* assays and concomitant AOP's. The latter should provide mechanistic plausibility for epidemiological observations on a relationship between pesticide exposure and an elevated risk for PD development.

6 Conclusions

6.1 About the achievement of the NAPAN objectives

In the framework of NAPAN the achieved goals are reached for now. There is a continuous effort in the follow-up of existing prospective cohorts of the agricultural community in a setting quite comparable to that of the Belgian situation.

Importantly, in the frame of the NAPAN projects (see 1) considerable efforts are also made to perform a follow-up of the possible CMR-substances in the frame of a.s. evaluation under Reg. (EC) no 1107/2009. For example, a lot of efforts are undertaken to closely be in pace with evaluations of frequently used substances like glyphosate. Contrarily to the IARC evaluation, EU working groups did not consider the substance carcinogenic, and a considerable database was screened to underpin this conclusion. The case has been followed very closely, and since there were suspicions as regards to the role of one particular co-formulant in certain glyphosate-based formulations (GBF) (the so-called polyethoxylated tallowamines), the latter were banned in products authorised in Belgium, in line with the specific provision of the approval regulation of this a.s.

6.2 About epidemiological studies

Important systematic reviews, meta-analyses and epidemiological study reports have been published worldwide, and span a period of more than 50 years. In short, the outcome of these assessments shows sometimes that the incidence of certain cancers or diseases is increased, but not in all cases. Importantly, notwithstanding the fact that most of these studies, taken together, concern a quite important number of cases, no clear **consistency** is observed in the pattern of most diseases.

It would not be useful to go into further detail as regards these publications at this stage, as this has been extensively described in previous chapters of this report.

It is of note that the quite comprehensive systematic review of INSERM (2013) also highlights the occurrence of childhood cancer (notably leukaemia and brain cancer) possibly consecutive to the exposure of adults to PPPs.

In the INSERM review (2013), the possible associations between PPP exposure and adult cancer (perceived as “strong”) included NHL, MM, and prostate cancer. PPP’s recognised as possible culprits included lindane, DDT, PO’s, malathion (NHL) and chlordecone (prostate). The latter was reiterated in the latest expert opinion (INSERM, 2021), confirming a causal link between exposure to chlordecone in the general population and the risk of prostate cancer is confirmed, but is should be remarked that this specific case of a persistent OC insecticide used in the French West Indies on banana crop in the past, is of poor relevance for Belgium (and the EU) nowadays.

In addition, also non-cancer adverse long-term effects are brought under the attention, including the association between either congenital malformations, neurodevelopmental defects, male infertility (related to spermatological deficiencies), and PPP exposure (more specifically in the latter example to the outdated soil disinfectant dibromochloropropane). It is expected that more or less consistent epidemiological findings, such as prostate cancer, NLH, some **leukaemias, MM, Parkinsonism**, etc… revealed in worldwide trials or tentatively in AGRICAN itself, could be the subject of a focussed research. Although it should be recognised that epidemiological studies display a limited resolution power in detecting long-term conditions, further follow-up is of utmost importance, in order to verify the robustness and consistency of these long-term effects.

For now, we may reasonably assume that the same conclusions are probably of application for the Belgian agricultural community. The agricultural practice is probably not so different in Belgium than in France, given the wide use of fungicides in orchards/vineyards in the latter, known to constitute a worse-case in terms of plant protection exposure.

In any case, a further refinement of the database, and concomitant follow-up is necessary, in order to identify possible increased incidences of specific cancers or other long-term severe conditions which do not affect mortality (*i.e.* morbidity analysis).

It should be acknowledged that, in the light of the sometimes contradictory outcome of all epidemiological studies, the latter have inherent limitations. It was well noted by Hart (2018) that epidemiological studies generally detect elevated cancer incidence and mortality cancer hazard decades after carcinogen exposure begins. The timeline for identifying cancer hazards in prospective cohort studies may be accelerated by incorporating biomarkers that may reflect carcinogenic hazards earlier than cancer incidence or mortality outcomes. Expansion of current efforts to collect biological samples from cohort participants would increase the potential to provide timely evidence to evaluate the potential PPPs to cause cancer in humans.

6.3 About the risks of long-term exposure to PPPs

A first conclusion of the AGRICAN study, supported by other cohort studies, is that the long-term outcome of life-long exposure to animals, crops and pesticides may be quite diverse. On the basis of cancer incidences in general, or mortalities subsequent to cancer incidences, figures in the agricultural community are not spectacularly worse than those in the general population. On the contrary, there is even a slight but consistently lower overmortality overall, and also the overall cancer incidence may even be indistinguishable from (AGRICAN), or about 10-15% lower than, that of the general population.

Incidence ratios in the agricultural workers and PPP applicators may display overincidences of a limited number of tumours, among which **lymphopoietic cancers** (including **MM**) and **prostate cancer** seem to be the most recurring ones. In addition, the weight of evidence also indicates a slight but rather consistent association between exposure to PPP's and **Parkinson Disease**.

The conclusions of this analysis were based essentially on data in epidemiological prospective cohorts, which are considered superior to case-control studies, which may suffer recall bias, although case-control studies may be more sensitive to identify rare tumours. However, meta-analysis, regrouping all these studies also indicate the same trend, and are re--enforcing confidence in the obtained picture.

When the largest cohorts worldwide (including AGRICAN cohorts and AHS) are considered together, it should be kept in mind that comparisons of the results may be cumbersome, for a number of reasons.

(vii) While the AGRICAN studies focus primarily on long-term effects after contact to crops and farm animals, the AHS study relates more to effects subsequent to PPP exposure and less to farm activities *per se*.
(viii) Some cohorts like NOCCA and CANCHEC are part of a bigger epidemiological census and are not designed to specifically examine the fate of the agricultural population.
(ix) The reference populations may be different, and the comparison of the incidence rates may therefore not be straightforward.

It should be clear that even a mere comparison between AGRICAN and AHS, especially as regards a possible association between overincidences and PPP exposure, and in particular specific a.s. or classes thereof, is extremely difficult. However, a general table was made in order to compile the findings (table 2). It is noted that for the time being, the comparison does not generate any meaningful concordance for the a.s. which would be at risk for the observed cancers studied to date. It is in addition also clear, that from the a.s. for which an association was suggested in the AHS cohort, most of them are not used anymore in the EU, and thus in Belgium, as organochlorines are already banned, and few a.s. in the organophosate and carbamate class remain. The only PPP candidates used in the US which could still be of concern are restricted to glyphosate (association debatable), 2,4-D, (S-) metolachlor, pendimethalin, deltamethrin and dicamba, although in certain cases (e.g. metolachlor) not the same pattern was observed. Also the a.s. studied or cited in the AGRICAN study are not all approved. A limited number of carbamates (IN, FU, HE) are still used as PPP, along with some phenoxy herbicides. No further analysis is done for a.s. which are used as either biocides (e.g. disinfectants) or as veterinary insecticides.

Table 2: concordance between a.s. cited or studies in the prospective cohorts

Cancer type	**Association with specific active substance or classes**	
	AGRICAN	**AHS**
PROSTATE	none	methyl bromide
		chlorpyrifos, coumaphos, fonofos, phorate, and permethrin for animal use, and the herbicide butylate
		OP, fonofos, terbufos, aldrin
BLADDER	none	imazethapyr, imazaquin; metolachlor (*), **2,4-D,** 2,4,5-T, OC
LUNG	none	none

Cancer type	Association with specific active substance or classes	
	AGRICAN	AHS
	none	
	arsenate salts	**Metolachlor (*)**, **pendimethalin**, chlorpyrifos, diazinon,
		pendimethalin, dieldrin, parathion, chlorimuron-ethyl
BRAIN	carbamate insecticides, carbaryl, formetanate, thiofanox	
	carbamate fungicides and herbicides, **mancozeb**, maneb, metiram, chlorpropham, propham, di-allate,	
MULTIPLE MYELOMA	OC, carbaryl, permethrin, dichlorvos, captan, **phenoxy herbicides**, atrazin, dinoterb, **disinfectants**	glyphosate (?)
		permethrin
NHL	none	OP, malathion, diazinon
	benzimidazoles (thiophanate-methyl?)	terbofos, **deltamethrin**; **glyphosate**? (DLBCL, CNAP)
		Dicamba (CLL)
SARCOMA	none	

(*: not confirmed in follow-up (FU) study of the AHS, but both liver and follicular cell lymphoma were found in the FU)

At this moment, taking into account the disparity of data (possibly due to different good agricultural practices (GAPs), methodologies, statistical handling, different proxies approximating exposure to PPPs,…), the scientific evidence to infer that the exposure to PPPs in the agricultural population in Belgium leads to severe diseases is subject to considerable scientific debate.

Yet, a limited but somehow consistent association between **lymphopoietic and prostate cancers,** and agriculturally related activities deserves further investigation. Furthermore, an association between exposure to PPPs and **PD** is for the majority of investigators not excluded.

However, as stated above, a mere bold statement that “pesticides cause cancer” or “pesticides are endocrine disruptors” in a general way is unwarranted. The existing open scientific literature, including the most powerful observational studies, are indicative of specific cancer incidence, either linked with exposure to crops ans/or to PPP’s. However, these studies carry also imprecisions and uncertainties, causing some confusion as regard a proper interpretation of the facts. Several elements, potentially subject to improvement, are described below.

(viii) By far the largest source of uncertainty in epidemiological studies remains the estimation of the actual exposure. In prospective cohorts, exposure data are recorded at the beginning of enrollment, and may be updated several times thereafter in order to catch potential changes in GAPs. In contrast, case-control studies suffer recall bias, where affected people tend to overestimate occurred exposures to PPP due to their condition. But even in cohort studies, most exposure data rely on stated employment and use calendars, at best supplemented with proxies on the basis of crop-exposure matrices. However, also this approach has its limits, as even well-conducted experimental field-trials may generate measured exposures values varying several orders of magnitude.

(ix) Whereas it has often been argued that exposure misclassification is likely to be non-differential and would tend to bias relative risks toward the null hypothesis, and diminish any "real" exposure-response gradients, it has equally been demonstrated that in fact, both under- and overestimation may occur, although it is recognised that in case of sufficiently large cohorts, the non-differential misclassification would be likely.

(x) In many cases, a substantial number of parameters (crops or PPP's) are tested, and it was often insufficiently clear if sufficiently effort was paid to rule out the possibility that some of the findings might be due to chance. Regardless of other confounders, the issue of multiple testing remains a serious problem in observational studies.

(xi) While it is evident that epidemiological studies examine by definition health outcomes possibly consecutive to exposure to animals, crops or PPP's encountered decades before enrollment, one is insufficiently aware that associations inevitably partly reflect uses with completely outdated PPP's. While these results remain valid for the a.s. under investigation, it is poorly predictive for the a.s. which were marketed in the meanwhile. For example, common a.s. included organochlores, which are completely banned in the EU. Also neurotoxic organophosphates and carbamates have nowadays almost completely disappeared, and also the number of pyrethroids are declining rapidly. Therefore, it is probable that epidemiological studies alone are an insufficient tool in the context of toxicovigilance of PPP's.

(xii) Whereas exposures are expressed in quantities of a.s. (either individually or grouped by class), it should be stressed that farmers and applicators are actually exposed to products containing both a.s. and coformulants. In contrast to a.s., some coformulants (especially if manufactured at low quantities) are not inert, and may be introduced on the market with little or no information on their human or environmental health effects. It is clear that we need a rapid catch up in order to collect and evaluate independently information on the hazards and current levels of human exposure, and take this into account in the interpretation of the "a.s." effect. Ideally, only coformulants should be used which are sufficiently investigated for their safety.

(xiii) In order to overcome the limitation of uncertain actual exposure to PPPs, some recent epidemiological studies include experimental phases encompassing either real environmental measurements and/or biological samples (plasma, urine, hair) enabling elucidation of long-term (neurologic, cancer) risks. Up to now, existing cohorts with this type of markers are scarce, and some examples of biomonitoring of immunological blood parameters reflecting potential precancerous stages (MGUS in the case of multiple myeloma) are promising.

(xiv) Likewise, proxies of exposure may also be derived from more reliable application data in real life. In the EU-context, record-keeping on applied PPP's are mandatory, but are up to now insufficiently implemented. If data on PPP use are kept, these are by no means stored in a portable way, and information remains actually inaccessible to health workers (and moreover restricted to storage ≤3 years). Comparable to the Pesticide Usage Reports (PURs) in California, which has been valorised with relevant research outcomes (crossing actual exposures to GIS and relevant public health register outcomes), such data should be available and used in the EU as well.

Apart from the abovementioned limitations, there is a growing need for mechanistic research, in order to support the interpretation of observed overincidences.

It remains important to remind that while human studies, up to now, have revealed only a number of ***associations*** between certain long-term effects and agricultural activities (which include, but are not restricted to, PPP exposure), the causal relationship remains difficult to establish. Existing regulatory studies on animals sometimes provide a limited indication of the promoting power or may be unable to explain mechanistic evidence of severe long-term outcomes (including CMR effects, neurodegenerative or immunologic diseases in animals and/or humans).

It should also be acknowledged that the impact of PPP exposure on specific live-phases or specific endpoints, like childhood cancer prevalence during gestation, or neurological conditions like PD are probably insufficiently covered by the animal guideline studies considered for the PPP toxicity dossiers (in the EU and worldwide). Likewise, the scrutiny of the effect for other vulnerable groups with persons carrying specific genetic traits (*e.g.* illustrated by population studies demonstrating increased effects of environmental exposure to PPP's in people with familial history to prostate cancer) cannot be covered by the classical toxicology studies. Therefore, risk assessors should acknowledge that further efforts are needed to refine and complement current data requirements and concomitant risk evaluations in order to fill as much as possible knowledge gaps in these domains.

In the case an a.s. has experimentally been identified as a CMR of probable relevance for the human (*e.g.* genotoxic carcinogen, or overt endocrine disruptor), its approval is withdrawn at the EU-level, and is phased out for product authorisation at the zonal/national level, including Belgium. It should in this context be underscored that even if the human relevance is only suspected, the MoA is unfortunately seldomly unequivocally determined.

In the absence of plausible modes/mechanisms of actions, the likelihood of ***causality*** between PPPs and long-term effects remains uncertain, from the risk-assessment point of view. The need for more fundamental research is warranted regarding for instance DNA damage, oxidative stress, metabolic outcomes and endocrine (*e.g.* thyroid) effects and was illustrated in a recent review (Curl *et al.,* 2020). Especially for the assessment of PD, a break-through to newer approaches (Cannon *et al.*, 2009, Jagmag *et al.,* 2016, Charli *et al.*, 2016, Zeng *et al.*, 2018, Bal-Price *et al*., 2018) focusing on presumed mechanisms of action, possibly coupled (but not restricted) to guideline toxicity studies with repeated administration, seems primordial in this respect.

A very specific MoA was mentioned in the latest INSERM review (2021), among succinate dehydrogenase inhibitor (SDHi) fungicides. The mitochondrial function is disrupted by inhibition of the activity of an enzyme complex involved in cellular respiration, and their potential impact on human health was claimed (see also Bénit *et al,* 2019). The INSERM experts asserted that data currently available are insufficient to conclude that SDHi would be specific to fungi SDH and the harmlessness to non-target species would be guaranteed.

The INSERM reviewers were of the opinion that both toxicological and mechanistic studies on SDHi fungicides revealed endocrine disruption, at least in the animal models tested (zebrafish, not necessarily very representative for the human, though). While these substances are non-genotoxic, some show carcinogenic effects in rodents, but it was stated that the findings could be disputed on the basis of a MoA that cannot be extrapolated to humans. They also concluded that additional research is needed to improve the assessment of the carcinogenic potential of SDHi fungicides (and more generally that of non-genotoxic compounds), and to fill significant gaps in the human data through reinforcement of biomonitoring and exploitation of existing cohorts.

Existing reviews (see *e.g.* Berends *et al,* 2018), indicate that, while incidence rates of PCC / sPGL have increased over the past 20 years in the general population, this trend coincides with a higher age and a smaller tumour size at diagnosis. The authors think that these observations are most likely at least in part the result of changes in clinical practice during the study period, with a more intensified use of both imaging studies and biochemical tests for detecting PCC / sPGL. In the meanwhile, robust epidemiological data regarding potential overincidences of neuroendocrine tumours like pheochromocytoma (PCC) and sympathetic paraganglioma (sPGL), linked to SDH modifications, are lacking in specific populations exposed to SDHi PPP's. Potential group-specific effects could be highlighted by stratifying cancer register data by occupational / residential characteristics.

It is noted that ANSES (2019), after expert consultation on the abovementioned SDHI issue, considered that to date, no new element has confirmed the existence of a health alert that would lead to the withdrawal of the authorisations in force, in accordance with the EU PPP regulations, a position which is agreed upon.

7 Further perspectives

At the bottom line, there are 6 main points of focus to evaluate long-term effects of PPPs in the human population, or to mitigate as much as possible PPP exposures in real life:

(xiii) Focusing on both **regulatory long-term** guideline studies and published open literature studies, including *in-vitro* alternatives.
Existing evaluations should thus as much as possible be driven by the search of new modes of action, to elucidate possible lacks in current knowledge of endpoints which would remain undiscovered until now. One notable example is datagaps on Parkinsonism or certain haematological cancers which would remain undiscovered in animal studies. Especially for the assessment of PD, a break-through to amongst others, newer *in-vitro* approaches seem primordial in this respect.

(xiv) Ensuring a maximal follow-up of (mainly prospective) **epidemiological** studies, associated with techniques to assess to the best extent possible real exposure levels, for instance by using biomonitoring tools. The more efficient exploitation of crop-exposure matrices, in combination with until now underused purchase/use information of professional PPPs offers an additional tool to obtain a better view on real on-the-field exposure levels.

(xv) In Belgium (but also in other EU member states with intensive agriculture), there is an urgent need to evaluate the potential risk of short- or long-term exposure to PPP for instance in **regions known to be affected by high PPP exposure** like fruit orchards and ornamental plant production, etc. which are sectors well known for their involvement of high levels or substantial diversity of PPP. This is true for farmers and applicators, but more so for residents, for which there are still many data gaps regarding their exposure to PPP's.

(xvi) Further resources should be allocated to develop reliable and robust **registries** of long-term/severe effects. In Belgium (like in other EU countries) cancer registries are installed since about a decade. However, also a proper repository of developmental defects, covering the whole country, is blatantly absent in Belgium. There is an urgent need to put in place a **Belgian network**, collecting data on a large scale, and supporting in this way the EU database on fertility effects and developmental anomalies (see objectives of EUROCAT).

(xvii) The establishment of an association between exposure and adverse health outcomes depends heavily on an **accurate estimation of exposure**, in the absence of which the effect is flattened out. The legal possibility and effective need to impose an **on-line registration** of actual use of PPP's, the possibility to have law enforcement to monitor and control these inputs, and the potential value crossing these data to location and consequently health data (registries of cancer, developmental anomalies,...) using GIS,

makes this approach a very powerful tool in order to explore post-marketing monitoring of long-term threats of PPPs of both professional groups and the general population.
In addition, the same methodology in order to estimate in a more reliable way environmental PPP levels could also be used to estimate predicted environmental concentrations (PECs) and to monitor a.s. in environmental compartments, amongst others surface and groundwater.

(xviii) Finally, exploring ways to **avoid as much as possible exposure** to PPPs during 'real-life' application, in order to protect operators, workers, bystanders and residents. Possible regulatory actions include the installation of default buffer zones for field application (2m) or high-crop (orchard) application (5m), below which no reliable exposure assessment is possible because of lacking exposure data. In addition to rapidly evolving engineering controls like spot-application (*e.g.* via drone-application), there is an urgent need to install default, clear and easily enforceable buffer zones vis-à-vis residents living in the neighbourhood of agricultural premises, and especially in order to protect vulnerable people (children, aged people, pregnant women, etc…).

It is left to the discretion of risk managers and policy-makers to determine the level of concern and concomitant measures to decide on socio-economic measures in this respect.

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