Bestrijdingsmiddelen en omwonenden

Pesticides and residents

Contents

1 General information

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2 Uitgebreide Nederlandse Samenvatting

Zorgen over blootstelling aan bestrijdingsmiddelen

Omwonenden maken zich zorgen over het gebruik van bestrijdingsmiddelen op landbouwgrond dichtbij hun woningen en wat dit betekent voor hun gezondheid. Deze zorgen waren aanleiding voor de Nederlandse overheid om advies te vragen aan de Gezondheidsraad.
In het advies, dat begin 2014 is verschenen, zegt de Gezondheidsraad dat er voldoende redenen zijn om onderzoek te doen naar de blootstelling van omwonenden. Een van de redenen hiervoor is dat bij agrariërs gezondheidseffecten zijn aangetoond. Bovendien zijn in het buitenland aanwijzingen gevonden dat dit ook bij omwonenden mogelijk is. De overheid heeft het advies van de Gezondheidsraad opgevolgd en aan het RIVM opdracht gegeven om een onderzoek naar de blootstelling van omwonenden te coördineren.
Het doel dat de overheid heeft gesteld aan het blootstellingsonderzoek is 'gegevens te verkrijgen over de mogelijke blootstelling van omwonenden van landbouwgrond in gebieden waar veel bestrijdingsmiddelen worden gebruikt'. Met de gegevens kan worden beoordeeld of een gezondheidskundig onderzoek aan de orde is. Ook kunnen methodieken die gebruikt worden bij de toelatingsbeoordeling worden getoetst en mogelijk verbeterd. De resultaten geven mogelijk ook inzicht in de noodzaak voor de overheid om aanvullende maatregelen te nemen om blootstelling te beperken.
Het onderzoek wordt uitgevoerd door een onderzoeksconsortium. Dit is een formele samenwerking van verschillende organisaties in Nederland, die de kennis en expertise voor een blootstellingsonderzoek in huis hebben. Het RIVM coördineert het onderzoeksconsortium.

Aansluiten bij ervaringen van omwonenden

De zorgen van omwonenden over bestrijdingsmiddelen vormden een belangrijke aanleiding om blootstellingsonderzoek uit te voeren. Daarom heeft het consortium bij het ontwerpen van het onderzoek ook de ervaringen van omwonenden meegenomen. Het consortium heeft tijdens huisbezoeken bij een aantal omwonenden kunnen ervaren hoe het is om dichtbij landbouwpercelen te wonen. Dit heeft veel informatie opgeleverd, onder andere over hoe de omwonenden in aanraking komen met bestrijdingsmiddelen.

Naast de zorgen over blootstelling door het wonen naast agrarische percelen, maken omwonenden zich zorgen over situaties waarin mensen 'omstander' of 'voorbijganger' zijn. Denk bijvoorbeeld aan een fietser die langs een perceel rijdt waar op dat moment wordt gespoten. De toelatingsprocedure van bestrijdingsmiddelen op de markt houdt al rekening met blootstelling van omstanders of voorbijgangers. Hier zal het blootstellingsonderzoek zich dan ook niet op richten. Omwonenden worden echter op een andere en mogelijk langduriger manier blootgesteld dan voorbijgangers en omstanders. Hoe hoog deze blootstelling is, is niet bekend. Dit gaan we dan ook onderzoeken.

Vragen om te onderzoeken

Het blootstellingsonderzoek duurt meerdere jaren. Het doel van het onderzoek is om de blootstelling te bepalen van mensen die dichtbij landbouwgrond wonen waar vaak bestrijdingsmiddelen worden gebruikt.

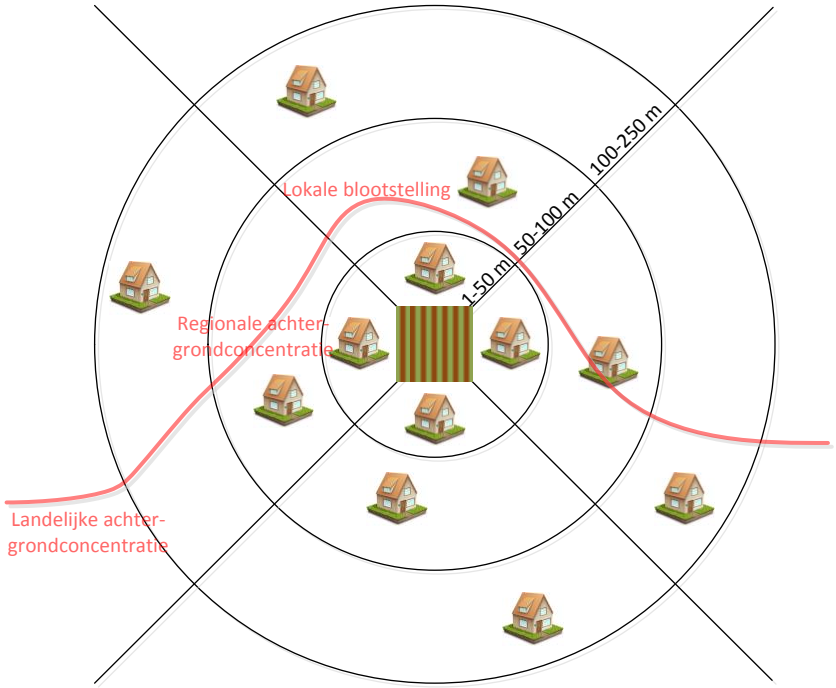
Deze doelstelling leidt tot de volgende onderzoeksvragen:
1. Wat zijn de concentraties bestrijdingsmiddelen in de omgeving van mensen die dichtbij landbouwgrond wonen?
2. Wat is de persoonlijke blootstelling van omwonenden aan bestrijdingsmiddelen?
3. Hoe worden omwonenden blootgesteld? Via welke bronnen en routes komen zij in aanraking met bestrijdingsmiddelen?
4. Wat is de blootstelling van omwonenden aan bestrijdingsmiddelen gedurende een heel jaar en in verschillende gebieden in Nederland?

Het onderzoek

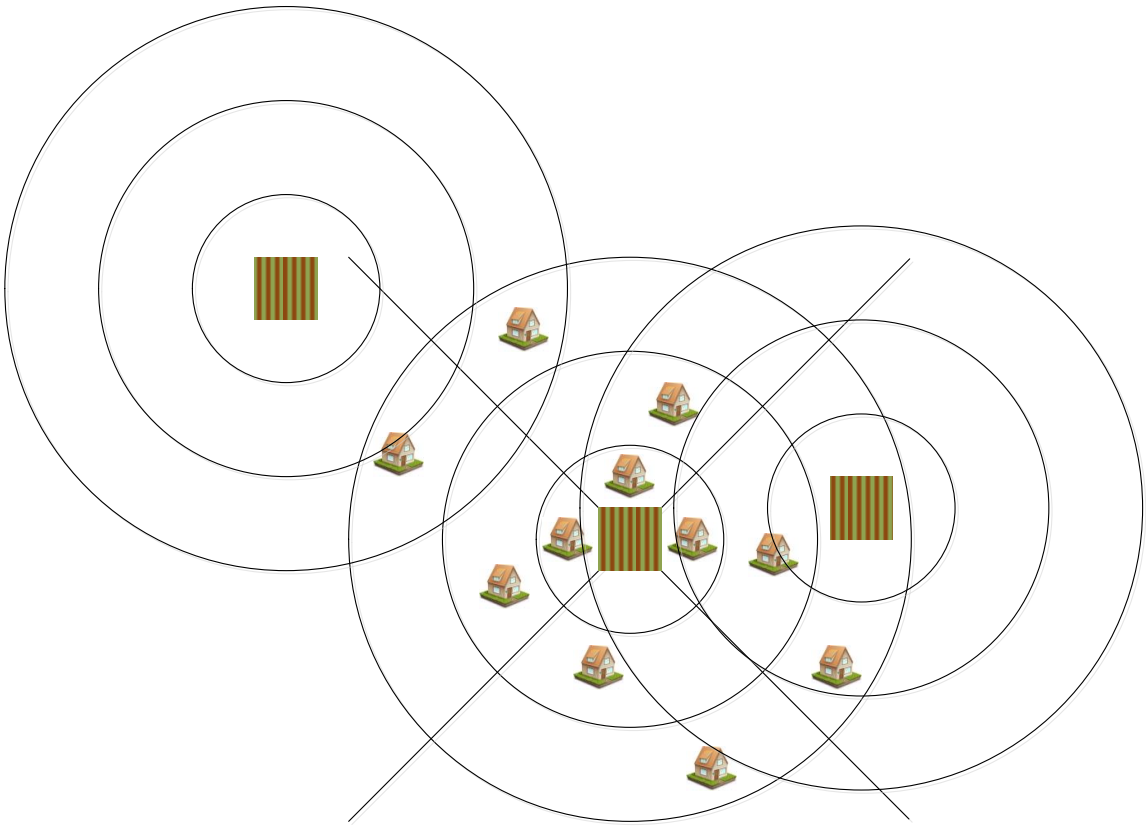
Beoordeling van verschillende situaties
Het consortium gebruikt een combinatie van methodes uit om de blootstelling te kunnen meten. Daarnaast zullen modelberekeningen worden gedaan. De modelberekeningen geven schattingen van de blootstelling voor situaties waarvoor geen metingen gedaan kunnen worden. Bijvoorbeeld om te kijken wat gebeurt als de weersomstandigheden veranderen of als andere bestrijdingsmiddelen worden gebruikt.

Metingen en biomonitoring
Het onderzoek wordt gedaan in gebieden met fruitteelt en gebieden met bollenteelt. Op alle onderzoekslocaties worden metingen in de leefomgeving gedaan, bijvoorbeeld in de tuin en het huis van omwonenden. De blootstelling via de lucht (drift, verdamping) en via insleep (huisstof) staat centraal bij de milieumetingen. Deze milieumetingen in lucht en huisstof worden gecombineerd met enkele metingen aan grond en gewassen uit de tuin.
Met biomonitoring wordt bekeken of omwonenden bestrijdingsmiddelen in hun lichaam hebben opgenomen. Dit wordt gemeten door bijvoorbeeld urinemonsters of veegmonsters van de huid af te nemen.
De combinatie van milieumetingen en biomonitoring laat zien of en hoe bestrijdingsmiddelen vanuit de omgeving in het lichaam van omwonenden terechtkomen. In twee jaar tijd zullen circa 10.000 monsters verzameld worden.

Voor alle locaties wordt ook informatie verzameld over de situatie waarin de metingen gedaan worden, bijvoorbeeld over wanneer bestrijdingsmiddelen zijn gebruikt, wat de afstand is tot de huizen en hoe het weer was op dat moment. Op een deel van de onderzoekslocaties doen we uitgebreidere metingen om de verspreiding van het middel na het spuiten beter te kunnen volgen. Het is niet nodig om dit op alle locaties te doen, omdat deze gegevens algemene informatie opleveren die bruikbaar is voor alle situaties.

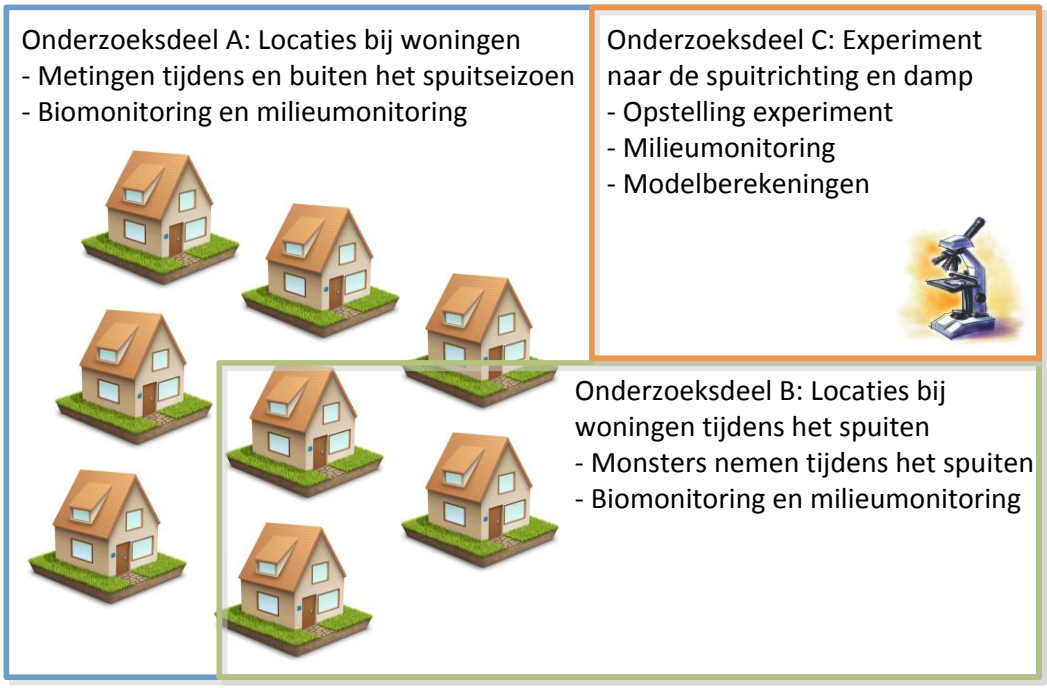


Figuur 1. Bestrijdingsmiddelen zijn altijd en overal aanwezig, dit zijn zogenaamde achtergrondconcentraties. Nabij landbouwgrond zijn de concentraties naar verwachting hoger. Door op verschillende afstanden te meten, krijgen we daar inzicht in.



Figuur 2. Omwonenden kunnen worden blootgesteld vanuit verschillende percelen. Het onderzoek stelt de bewoner centraal en houdt er rekening mee dat de blootstelling vanuit verschillende bronnen kan komen.

Ter aanvulling worden ook experimentele bespuitingen uitgevoerd om uit te vinden hoe de metingen zo goed mogelijk uitgevoerd kunnen worden. Bovendien worden alle gegevens gebruikt om modelberekeningen te maken. Het ontwerp van het onderzoek is weergegeven in figuur 3.



Figuur 3. Ontwerp van het onderzoek.

Onderzoekslocaties en deelnemers

Om de blootstelling van omwonenden te kunnen bepalen, is een groot aantal monsters nodig. Deze moeten verzameld zijn op verschillende onderzoekslocaties en op verschillende momenten. Met een onderzoekslocatie bedoelen we in dit geval een aantal woningen die zich nabij één of meer percelen bevinden waar een bepaald gewas op wordt verbouwd. We streven ernaar om in twee jaar tijd op 15 locaties te meten, met 12-14 woningen per locatie. Dit moet ongeveer 400 deelnemers opleveren: 200 volwassenen en 200 kinderen. Per woning zullen we ongeveer 50 monsters verzamelen.
Per locatie selecteren we huishoudens die zich binnen van tevoren bepaalde afstanden van een perceel bevinden, namelijk 0-50 meter, 50-100 meter en 100-250 meter. We kiezen de meeste woningen binnen een straal van 50 meter, omdat we daar de hoogste blootstelling aan bestrijdingsmiddelen verwachten.

Focus op fruit- en bollenteelt

In het eerste jaar van het onderzoek richten we ons op twee gewassen, namelijk boomgaardfruit en bloembollen, omdat daar veelvuldig bestrijdingsmiddelen worden gebruikt. Ook worden in deze teelten de meest

gebruikte manieren van bespuiting toegepast, namelijk spuiten naar beneden (bollen) of opzij en omhoog (fruit). In het tweede jaar van het onderzoek zullen vooral de locaties met fruitteelt opnieuw worden gekozen om verschillen tussen de jaren te onderzoeken. Eventueel kunnen in het tweede jaar ook andere teelten erbij worden onderzocht. Dit is dan voor vergelijking van de blootstelling aan andere middelen en andere manieren van bespuiting.

Stoffen
In het onderzoek worden tientallen werkzame stoffen onderzocht. We selecteren stoffen die veel gebruikt worden. Ook baseren we de selectie op eigenschappen die beïnvloeden hoe de stoffen zich na gebruik in de omgeving verspreiden.

Mogelijkheden en beperkingen van het onderzoek

Op dit moment weten we bijna niets over de blootstelling van omwonenden. Het onderzoek zal veel nieuwe kennis over die blootstelling leveren. Het onderzoek zal

- een groot aantal metingen uitvoeren en monsters nemen in gebieden waar vaak en veel bestrijdingsmiddelen worden gebruikt. De resultaten geven de inwendige en uitwendige blootstelling van deze omwonenden weer, zowel tijdens als buiten het spuitseizoen.
- deze meetresultaten voor blootstelling, en gegevens over emissie en gedrag, met elkaar verbinden om inzicht te krijgen in bronnen, routes, en blootstelling.
- op basis van de metingen en verklaringen, de mogelijke blootstelling van omwonenden aan bestrijdingsmiddelen gedurende een heel jaar en in verschillende gebieden in Nederland, inzichtelijk maken.

Het moge duidelijk zijn dat na afloop van het onderzoek nog steeds onzekerheden blijven bestaan. Belangrijk is dat we inzicht krijgen in hoe groot de onzekerheden zijn. Dan zijn namelijk toch uitspraken te doen over de mate waarin omwonenden worden blootgesteld aan bestrijdingsmiddelen. In het onderzoek zal daarom expliciet aandacht worden besteed aan de invloed van de belangrijkste onzekerheden.

Deelname aan het onderzoek kan als gevolg hebben dat telers voorzichtiger handelen met bestrijdingsmiddelen, dan zij normaal gesproken zouden doen. Ook omwonenden zouden zich meer bewust kunnen worden van mogelijke blootstelling. Daardoor kunnen zij gedrag gaan vertonen dat leidt tot lagere of juist hogere blootstelling. Aangepast gedrag bij telers en omwonenden is echter niet te voorkomen. Bij omwonenden en telers zal gedrag worden nagevraagd om hier rekening mee te kunnen houden.

Zowel in de monstername als in de chemische analyses zitten beperkingen. Niet alle stoffen zijn even goed waar te nemen. We moeten ook rekening houden met andere bronnen van blootstelling. Via het voedsel krijgen mensen ook restanten van bestrijdingsmiddelen binnen. Of zij zijn zelf werkzaam in de landbouw en komen tijdens hun werk met bestrijdingsmiddelen in aanraking. Ook daarover verzamelen we informatie om de uitkomsten te kunnen begrijpen. Daardoor levert het onderzoek ook waardevolle informatie over telers, loonwerkers en andere mensen die beroepsmatig blootgesteld worden.

Voor de berekeningen wordt een situatie in de praktijk nagebootst in een model. In de modellen wordt rekening gehouden met onder andere het soort gewas, het gebruikte bestrijdingsmiddel, weersomstandigheden en de locatie. Variaties in die factoren kunnen doorgerekend worden, zodat ook robuuste schattingen voor de blootstelling op andere locaties gemaakt kunnen worden. En voor dezelfde locatie onder andere omstandigheden. Echter, niet alle denkbare en door omwonenden genoemde routes van blootstelling zijn in een model beschikbaar. Bijvoorbeeld situaties waarin specifieke weersomstandigheden leiden tot mogelijk hoge blootstelling; zo kan een model dat rekening houdt met dampdrift niet in een cijfer uitdrukken wat er gebeurt bij mist.

Met deze resultaten kan het RIVM aan de overheid adviseren of een verdiepend onderzoek naar de gezondheid van omwonenden nodig is. Door de combinatie van meten en modelberekeningen kan het RIVM uiteindelijk ook aanknopingspunten geven om maatregelen te nemen voor vermindering van de blootstelling.

Maatschappelijke inbedding en transparantie

Informatie over het onderzoek wordt door het RIVM aangeboden via de website www.bestrijdingsmiddelen-omwonenden.nl. Deelnemers aan het consortium, aan de externe beoordelingsronde en aan de begeleidingsgroep tekenen een verklaring van belangen. Deze verklaringen zijn openbaar.

Beoordeling door internationale experts
Het onderzoeksvoorstel is door 16 onafhankelijke buitenlandse experts beoordeeld. Hun algemene oordeel was dat het een zeer goed en relevant onderzoek is. De deskundigen hadden natuurlijk ook kritische opmerkingen. Hun opmerkingen hebben op enkele punten geleid tot aanpassing en verbetering van het onderzoeksvoorstel.
Vervolgens wordt het onderzoeksvoorstel besproken in een landelijke Begeleidingsgroep. In deze Begeleidingsgroep hebben behalve (onafhankelijke) deskundigen, ook ervaringsdeskundigen (omwonenden, telers) zitting.

Advisering door stakeholders
Een Klankbordgroep van maatschappelijke belanghebbenden adviseert het RIVM over alle aspecten van het onderzoek en de coördinatie. De Klankbordgroep adviseert het RIVM over het onderzoeksvoorstel inclusief de beoordelingen van de buitenlandse experts en de Begeleidingsgroep. Tijdens en na het onderzoek adviseert de Klankbordgroep als eerste over de presentatie van (tussen)resultaten.

Onderzoek aan mensen
Er is wetgeving gericht op onderzoek aan mensen (Wmo) en gericht op het omgaan met persoonsgegevens (Wbp). De onderzoeksplannen worden daarom voorgelegd aan een medisch-ethische toetsingscommissie voor goedkeuring, voordat het onderzoek mag beginnen. Het onderzoek is opgenomen in het register van het RIVM voor de Wet bescherming persoonsgegevens (Wbp). Het RIVM zorgt dat wordt voldaan aan alle wetten en regels.

Het onderzoek kan alleen slagen als alle betrokken partijen zich vrij kunnen uitspreken over het doel, de opzet, de uitvoering en de uitkomsten van het onderzoek. Hoe het onderzoek eruit ziet en de manier van communiceren met

alle mensen die het aangaat, spelen hierin een belangrijke rol. Het onderzoek in WP6 heeft daarom als doel doelmatige communicatie met belanghebbenden.

Projectorganisatie

Het onderzoek wordt uitgevoerd door 10 partijen in acht nauw verweven werkpakketten (WP's). De volgende instituten werken samen met het RIVM:

1. Universiteit Utrecht - Institute for Risk Assessment Sciences (IRAS)
2. Radboud Universitair Medisch Centrum Nijmegen (Radboud UMC)
3. Universitair Medisch Centrum Groningen (UMCG)
4. Wageningen Universiteit en Research - ALTERRA
5. Wageningen Universiteit en Research - Plant Research International (PRI)
6. Wageningen Universiteit en Research - Praktijkonderzoek Plant & Omgeving (PPO)
7. RIKILT
8. TNO
9. Centrum Landbouw en Milieu (CLM)
10. Schuttelaar & Partners

Werkpakketten en de planning in de tijd

WP1 zal tijdens het onderzoek coördinerende taken behartigen. Daarnaast regelt dit WP ook dat alle gegevens voor en uit het onderzoek altijd goed toegankelijk zijn. De definitieve selectie van locaties, huishoudens, telers en stoffen wordt vroeg in 2015 vastgesteld (WP2). Het veldwerk vindt plaats in 2015 en 2016 in WP3 en WP7. De chemische analyses (WP4) starten later in 2015 en zullen tot medio 2017 lopen. Interpretatie en analyse van de meetresultaten (WP5) begint in de 2^{e} helft van 2015 en zal doorlopen tot eind 2017. Het deelonderzoek dat is gericht op doelmatige communicatie over het onderzoek (WP6) begint vroeg in 2015 en zal gedurende het project vinger aan de pols houden. De rapportage komt eind 2017 uit.

De taken van het RIVM als coördinator omvatten: projectbeheer, borgen dat de uitvoering in overeenstemming is met wet- en regelgeving, inhoudelijke toetsing, zorgen voor de toetsing op wetenschappelijke en maatschappelijke relevantie en kwaliteit, communicatie, afstemming met vergelijkbaar onderzoek en tussentijdse advisering en ondersteuning. Het RIVM zal ook gedurende het onderzoek de vinger aan de pols houden of de metingen alleen al aanleiding geven om maatregelen te nemen.

3 Summary

Introduction and motivation
The application of plant protection products (PPPs) in the vicinity of homes has raised much public concern and discussion regarding the possible health effects to people living in close vicinity to agricultural land (residents). These concerns have resulted in a request by the Dutch government for advice by the Dutch Health Council on this issue. In 2014 the Health Council published its advice, in which it stated that there is sufficient reason to initiate an exposure study among residents in agricultural areas. Reasons include observed health effects in farmers and growers in combination with some evidence of effects in residents in studies outside the Netherlands, and the lack of reliable exposure data from the Netherlands. Following the advice of the Health Council, the Dutch government commissioned an exposure study with the objective of 'acquiring data on the potential exposure of residents in agricultural areas in which PPPs are used intensively'.

Aim, objectives and research questions
The aim of the proposed multi-year study (2015 – 2017) is to assess the exposure to PPPs of persons living in close vicinity to agricultural land on which PPPs are (intensively) applied. The study aim can be translated into the following main research questions:

- What are concentration levels of PPPs in the outdoor and indoor environment of residents living near agricultural land?
- What is the personal exposure of residents living near agricultural land to PPPs?
- What are the exposure sources and routes contributing to environmental and personal exposure to PPPs?
- What is the exposure to PPPs distributed through the year and across different areas in the Netherlands?

Design and methods
As grown crops and PPPs applied in The Netherlands are manifold, this will inevitably lead to a large variation of environmental conditions and potential exposures to PPPs to be included. To obtain a sound assessment of residents' exposures to PPPs, a large number of samples, collected within a well-designed sampling frame, are needed. The study design therefore foresees collection of data regarding emission strength of PPPs from fields, outdoor and indoor concentrations, and finally biomonitoring of persons living in close vicinity to selected crops. Selected households will be those residing within several pre-defined distance categories to the fields (0 – 50m, 50 – 100m, 100 -250m) with an overrepresentation at close proximity (<50m). Deterministic and statistical models will be used to interpret the monitoring results of the study and extrapolate this research, allowing for the estimation of exposure to PPPs in situations for which no measurements are available.

Expected results
The expected results of the project are:

- Descriptive statistics (means and percentiles) on measured environmental concentrations and personal exposures to PPPs for selected locations.
- An integrative modeling framework, consisting of a chain of models, allowing for extrapolation to other locations, crops and PPPs.
- Descriptive tables and maps of estimated residential exposure to PPPs of priority PPPs in the Netherlands.

Planned products
The project will deliver detailed measurements and an integrative model framework which can be used for estimating population exposures to existing and emerging PPPs.

Analysis of choices made and of remaining uncertainties
An explicit choice has been made to have an integrative work plan combining environmental and biological monitoring with modeling of exposures. Such an integrative approach is deemed necessary as to ensure the project delivers tangible and interpretable results.

4 Introduction and motivation

The application of plant protection products[1] (PPPs) in the vicinity of homes has raised concerns from local residents[2]. These concerns are related to the adverse health effects that may be associated with the potentially increased exposure to these PPPs.

Current authorisation procedures do not include a separate assessment of risks for residents, except for residents living near greenhouses. The safety of residents is assumed to be covered by authorisation procedures that apply to operators, workers and bystanders. However, it is not clear if this assumption is valid, given that residents are likely exposed to lower levels but for a longer duration per application, due to drift and evaporation of PPPs from nearby agricultural land and as other populations are exposed (e.g. children and the elderly which may be more susceptible). Current exposure assessment methods for operators, workers and bystanders using environmental fate models do not take account of this type of exposure and may therefore not be suitable to estimate actual exposure of residents.

The concerns regarding exposure to PPPs of residents and possible associated health effects have resulted in a request by the Dutch government for advice on the issue. This was addressed by a committee of the Health Council of the Netherlands. In 2014 the Council published its advice, in which it stated that there was sufficient reason to initiate an exposure assessment study among residents living close to agricultural land. Reasons include observed health effects in farmers and growers coupled with some evidence of health effects in residents in studies outside the Netherlands, in combination with very limited knowledge about the actual exposure of residents in the Netherlands. In the advice, it was foreseen that an exposure study should cover multiple years, multiple crops and PPPs, and involve both measurements of the environment and of residents to understand the contribution of various sources to personal exposure (Health Council of the Netherlands, 2014).

Following the advice of the Health Council, the Dutch government has commissioned the National Institute for Public Health and the Environment (RIVM) to coordinate an exposure assessment study with the objective of 'acquiring data on the (potential) exposure of residents in agricultural areas in which PPPs are used intensively'. Because of the different fields of expertise that are necessary for the conduct of such a study, it should be designed and performed by a broad consortium of research institutes, and its goals should be guided by input from stakeholder groups such as the residents themselves, but also including the growers and manufacturers of PPPs.

[1] In this text PPP is used to denote any (single) substance, either active substance, metabolite or transformation product, that may potentially affect public health or the environment.
[2] In this document a resident is defined as a person who lives near agricultural land. The definition of a resident is specified in more detail in 6.2.1.

5 Aim, objectives and research questions

The starting point for this research proposal are concerns raised about adverse health effects due to application of PPPs near residents' homes. The Dutch Health Council indicated that, as a first step, it was necessary to collect data about exposure of residents. The preparation of an exposure study provided an opportunity to discuss the exact study aims with stakeholders. Several stakeholders (ranging from residents to health care professionals to the agro-chemical industry) perceive the lack of actual exposure data as a serious problem: In particular, it was made clear that before any health effect could be evaluated, exposure levels in residents should be quantified and compared to background population levels.

It is simply not feasible to measure exposure levels of all residents living close to agricultural land, or to all used PPPs. Therefore, a study design has been selected that combines measurements of persons' exposure levels to PPPs (using biomonitoring) with exposure models in order to be able to achieve reliable exposure estimates to PPPs of the population in the Netherlands.

Measurements will be done in residents living in the vicinity to crops (from very close vicinity to a distance of about 250m). These measurements will provide information regarding actual exposure levels of the residents, but also on factors that influence exposure levels. Such factors include for example distance of the place of residence to the agricultural land, but also chemical characteristics of the PPP, application techniques and meteorological conditions.

Existing models that calculate transport and fate of PPPs and predict how these environmental concentrations lead to personal exposure of residents, will be calibrated and/or validated using the measurement results, and the additional information collected during the measurements (the factors that influence exposure levels) will be integrated. Such *integrated model frameworks* can then be applied to extrapolate exposure assessment to a broader range of PPPs used in agriculture, and to the whole population. Some of the input parameters (for example regarding drift of PPPs for the models will be obtained in *experimental studies*. Thus, only a comprehensive study, in which carefully designed measurements, detailed auxiliary data collection, experimental studies and modelling efforts go hand-in-hand, can clarify the extent to which the agricultural use of PPPs in the vicinity of homes contributes to total exposure of residents in space and time to PPPs.

The study aim can be summarised into the following main research questions:

i) What is the personal exposure of residents living near agricultural land to PPPs?

ii) What are concentrations of PPPs in the environment of residents living near agricultural land?

iii) What are the exposure sources and routes contributing to personal and environmental exposure to PPPs?

iv) What is the exposure to PPPs distributed through the year and across different areas in the Netherlands?

Information about exposure levels and sources as well as routes can ultimately be used to provide input in authorisation procedures for PPPs, epidemiological studies, and if applicable, to estimate the effect of existing and future exposure mitigation strategies on population exposures. However, although their importance is recognised, authorisation procedures and mitigation strategies fall outside the scope of the exposure study.

Finally, for the current study, the characterisation and quantification of human exposure is the central aim. In discussions with residents it became clear that their concerns are not limited to their own exposure and health, but include also general concerns with regard to the impact of PPPs on the direct environment. Although the study will monitor environmental concentrations of PPPs as a means to estimate human exposure, the study does not aim to present a comprehensive overview of environmental concentrations of PPPs as such, or to evaluate the impact of PPPs on the environment. Also, it should be noted that human exposure is the principal endpoint and that health effects will not be investigated in this research.

6 Design and methods

Chapter 6.1 describes the overall design of the study. Chapters 6.2 to 6.8 provide outlines of the different components of the study and chapter 7 gives an overview of expected results. Specific details on methods can be found in the annexes (Annex 1 - 7). An overview over the organisation of the project into work packages is given in Chapter 11 (organisation of the project).

To answer the research questions, we will perform an exposure assessment strategy in which biomonitoring, complemented with easy-to-obtain environmental sampling and the collection of contextual information (e.g. on land and PPP use), in all selected study locations is combined with more extensive concentration measurements in a subset of the study population. This is illustrated in Figure 1.

In order to avoid detailed measurements in various contact media and biological samples in a very large number of residents, an efficient study design has been chosen. It consists of the combination of two measurement protocols that allow the inclusion of a relatively large number of study locations with their respective residents (outlined as protocol A), while also obtaining detailed information about the contribution and routes of exposure (outlined as protocol B). Spraying experiments (see protocol C) will generate complementary information that is necessary for an optimal sampling protocol in A and B and will deliver important data for model development. The overall design is illustrated in Figure 1.

All in all, measurements of PPPs will be performed in about 15 locations in the Netherlands, selected based on their vicinity to several specific crops. Within each location, about 12 households will be included, and if possible, 2 persons per household, resulting in a sample of about 400 persons who will be repeatedly measured with respect to their exposure to PPPs. The monitoring campaign will cover two calendar years.

Since it is impossible to cover all registered PPPs, the focus in the study will be on prioritized PPPs (n=~10). Within protocol A, other commonly used PPPs will be included in the methods if analytically feasible without compromising method performance for the prioritized PPPs. For protocol B and C, analysis will be restricted to specific PPPs applied which in all likelihood are covered under the prioritized 10 PPPs.

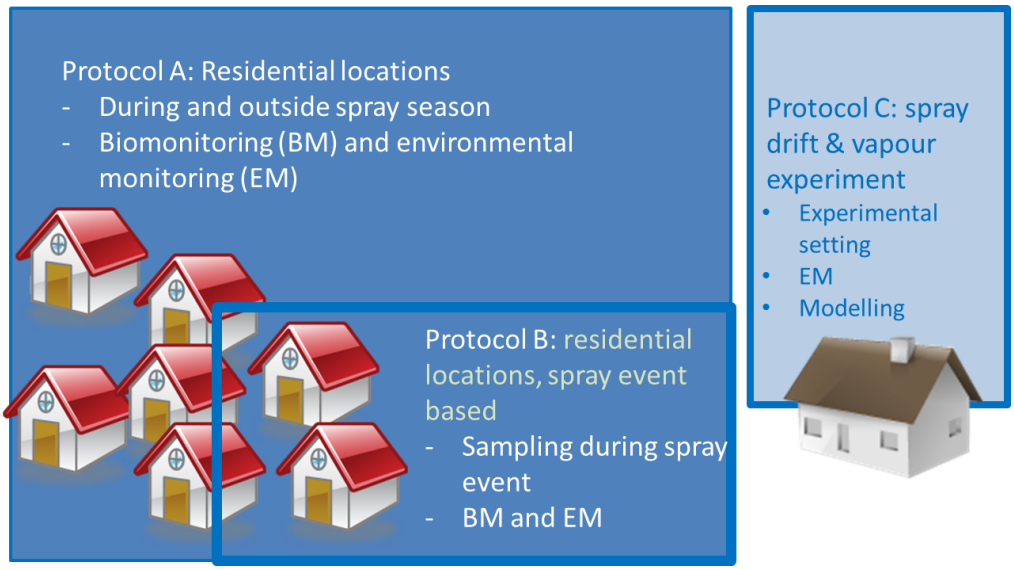


Figure 1. *Graphical presentation of the overall study design.*

6.1 Study protocols

6.1.1 Protocol A

The whole study is centred around a large biomonitoring survey in which a significant number of residents (n=400) living near fields on which PPP's are applied, are repeatedly sampled at multiple locations in the Netherlands (6 in 2015 and 9 in 2016). Participants are recruited at various distances from agricultural fields (see below selection of study participants) so as to measure the direct contribution of drift, evaporation, and transfer to homes, and to establish regional and national background levels. Protocol A is complemented with easy-to-obtain environmental sampling (e.g. dust) and the collection of contextual information (e.g. meteorological conditions, or activities of study participants that may be related to exposure levels) on all selected study locations. This part of the study will provide insight into the levels of exposure of residents living near fields as compared to background levels and the statistical relation between the measured environmental concentrations and personal exposures.

Procedure

The sampling scheme of protocol A follows residents during the spray season and in the off-season. During the spray season we will collect exposure measurements on two occasions during the season for seven consecutive days each. In the off-season this is limited to two days. This design is chosen, as residents in agricultural areas are likely to experience exposure from different agricultural fields, with possibly a variety of crops. Urine collection will take place at fixed times that are not dependent on application events. However, the start of protocol A is initiated by a specific spraying event as described in protocol B.

Data collection

Protocol A includes the collection of urine samples, outdoor air samples, household dust, deposition samples on vegetation, and registration of local meteorological conditions. During a measurement series, we will collect from the

individual's the first morning void on seven consecutive days. In addition, outdoor air sampling will be performed during the study period (covering all days of the urine samples), and house dust will be collected (at the end of the urine sampling period). Contextual information will be collected, amongst others by asking participants to keep a diary on lifestyle factors, activities, and observed spraying events. Records of pesticide application (time and type of a used PPP on a specific field) will be collected from farmers with fields nearby the participating households after the measurement campaign (See tables 1 and 2).

Analysis

Urine and environmental samples that link to known PPPs applications (within 24h prior of collection) will be analysed for the list of pre-selected PPPs (see 6.4). Applications that will qualify for this are known applications reported by a farmer whose field(s) lie(s) within 250m distance of a dwelling (see 6.2.4). A random subset of urine samples that do not link to a specific application (>48/72h after a spray event), to be collected during non-application times or upwind from the application, will be analysed to measure individual background exposure levels and to study potential delayed uptake. Summary statistics on all collected samples will provide information on exposure of residents to selected PPPs within the study locations.

6.1.2 Protocol B

Protocol B is completely nested within protocol A. In order to obtain a more detailed insight into the relationship between actual application events and the routes of exposure, protocol A is extended with a more extensive environmental monitoring program related to a specific PPP application. This will be performed for a subset of the homes included in protocol A. Its goal is to gather detailed information about propagation and exposure pathways. Since this involves more elaborate (environmental) measurements in addition to biomonitoring, protocol B is employed at all locations but only in a subset of the study population (about 4 to 6 homes per location).

Procedure

The measurement campaign of protocol B will be triggered by a specific spray event: Protocol B will start on the day a farmer reports an intended application. Households (about 4 to 6 per location) involved in protocol B will be preferentially selected based on close proximity to the field (<50m) and on their willingness to participate in this more detailed measurement campaign.

Data collection

Study participants will be asked (in addition to the samples already collected under protocol A) to provide additional collection of urine samples from the time the application starts until the next morning void as part of protocol A. In addition, we will perform 24-hr indoor and outdoor air monitoring in which droplets and the gas-phase will be separated, and personal air monitoring (adults only). To measure dermal exposure, hands of study subjects will be wiped at the time that samples will be collected. Also, deposition of PPPs at indoor and outdoor surfaces will be measured. In order to estimate the source strength (and thus the exposure potential) we will measure the drift and evaporation potential at selected locations (see table 1 and 2).

Analysis

For protocol B, a subset of PPPs will be selected based on characteristics that influence how they are dispersed after application, such as physico-chemical properties of the substance. Summary statistics on all samples collected under protocol B will provide in-depth information on potential peak exposures of the study population regarding the prioritised PPPs and provides information on direct droplet drift after application.

6.1.3 Protocol C

Drift and evaporation models have previously been developed to assess droplet and evaporation drift to the environment. These models have been developed to estimate the environmental fate of PPPs near application areas such as droplet deposition onto surface water. They have not been developed to assess exposure to residents. Consequently, there are gaps in knowledge in the description of exposure of residents especially at larger distances from the field. Targeted experimental studies (termed protocol C) will be carried out to fill these knowledge gaps especially for drift at longer distances (>50m to 250m) as well as drift at higher receptor heights than previously evaluated (3 to 6m). This is necessary in order to calibrate the output of environmental fate models regarding drift and evaporation models. In principle, such measurements could be linked to protocol B, which is linked to a spray event reported by a farmer. However, within protocol B there is no control over the spectrum of applied PPPs, and it might additionally be impossible to access exactly those distances from the specific field (or heights above ground) necessary to perform measurements. Therefore, experiments will be performed under controlled conditions at experimental farms.

Procedure: The spray experiments will be performed in a field simulation on national "experimental farms", that are available for such experiments. Spray experiments will be performed using tracers to assess drift. Spray experiments will additionally be performed with PPPs to assess evaporation of the compounds. Spray experiments will be limited to 2-3 PPPs of the prioritized group of 10 PPPs as assessed within protocol A and B. In order to cover different physico-chemical characteristics of the PPPs. Repeated experiments will provide information regarding, meteorological conditions, time points of measurements after a spraying event, distances and height above ground on drift and evaporation.

Data collection: Spray experiments will be performed using standard spraying equipment for a "usual" application of the target PPP and crop. Measurements will be performed at distance intervals of some 10^{th} of meters up to a distance of 250m and will have a high resolution in terms of height above ground in small increments of 0.5m. Measurements will be repeated 10 times.

Analysis: All measurements will be analysed, summarised and additionally be used to calibrate and further develop statistical as well as deterministic models (see WP5, summarised in Annex x). These models will then be used to extrapolate the monitoring results to other PPPs, crops and other exposure situations, as outlined above.

6.2 Selection procedure of locations

6.2.1 General approach

The selection procedure of the measurement locations is aimed at making a justifiable and sensible selection of the sites to be studied. The general approach that will be followed is:

- selection of crops will be done based on (extensive) use of relevant PPPs on these crops;
- study locations will be selected based on existing maps on locations of crops and residences in the vicinity (up to 250m);
- addresses of places of residence within a location will be extracted from cadastral maps, which will subsequently be used to contact potential study participants.

The selection criteria for study locations partly depend on the choices made with respect to the target PPPs and crops. Also the required number of residents and their location with regard to the fields can be an argument to choose a specific site.

6.2.2 Selection of crops

Selection criteria are translated via geo-data and via geographic information system (GIS) calculations into maps. About 5 primary crops will be selected based on the use of PPPs. The initial selection will be done using existing (historical) data to identify crops with an extensive use of PPPs.
For 2015, the study will focus on two main crops, namely orchard fruit and flower/bulb cultivations. These are selected because of the extensive use of PPPs on these crops, and because they reflect the two most important application techniques (downward versus sideward /upward spraying). For these crops, locations with a high exposure potential for residents are selected (see section 6.2.4). In the second year, measurements of PPPs from these crops will be repeated to assess variation over the years, and other crops will be incorporated with the goal to evaluate exposure to additional PPPs with diverse physical and chemical characteristics, application techniques, and area and meteorological characteristics to support the generalizability of the results. In 2015 an inventory will be done for hotspot areas of potential exposure for use of PPPs in other crops. From these results, crop-location combinations may be selected for further investigation in 2016.

6.2.3 Selection of study locations based on crops

In the context of this study, we denominate with a "study location" a cluster of residential buildings that are placed within short distance of an agricultural field (or cluster of agricultural fields) where the crop of interest is grown. Study locations will be selected using available maps (in particular yearly maps of crops, as well as cadastral data of all places of residence) as a basis. A selection criterion is the presence of a suitable number of potentially participating households within short distances of the selected crop, preferably downwind (using the predominant wind direction) of the respective field(s). Residences will be selected that are located at different distances (see 6.2.4) to a field with the crops of interest.

6.2.4 Selection of addresses based on locations

For the selected locations, addresses will be extracted using geo-data (cadastral data). From these addresses, potential participants will be recruited. Addresses (relating to residential buildings) will be selected that are located at different distance categories to a field with the crops of interest: Selected addresses will

be within distance categories of the fields at 0 – 50m, 50 – 100m, 100 -250m, with an overrepresentation of those dwellings at close proximity (<50m) to the fields. Please note that the Netherlands is a very densely populated country and that selecting places of residence within such short distances of fields will be unproblematic, based on pilot work performed in 2014.

The pre-specified distance categories are based on the assumption that within a maximum of 50m, direct droplet and vapour drift are important. In the buffer of 50 to 100m, evaporation followed by dispersion through the air could play a role, while it is expected that at 100-250m direct exposure is less important (regional background; see graphical representation of exposure levels, figure 2). As we will incorporate different crops with a number of locations each, we will derive national background levels from locations where those specific PPPs are not used.

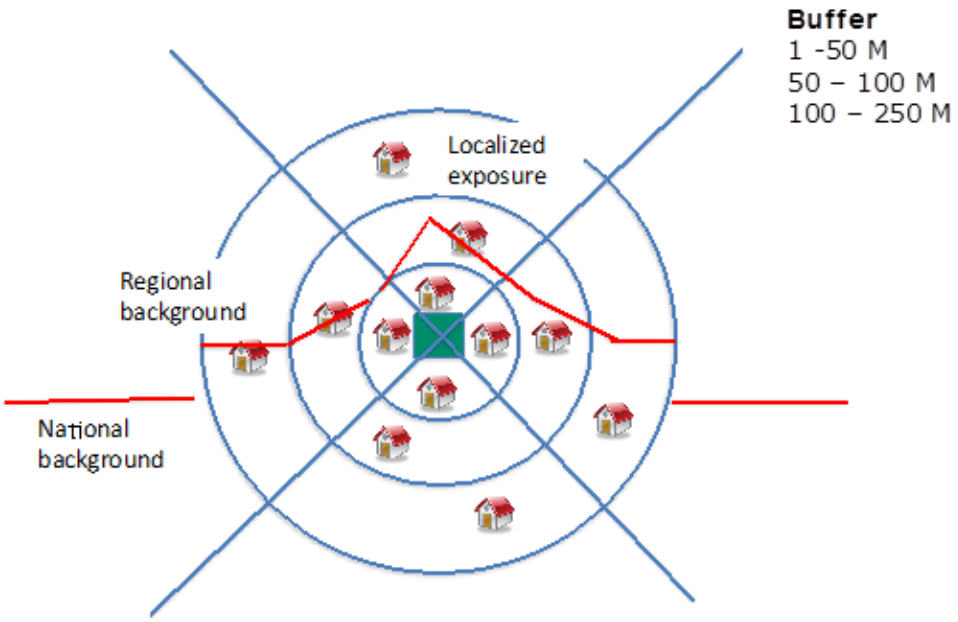


Figure 2. Theoretical location of dwellings within pre-defined buffer zones; single field. Red line indicates a theoretical exposure level to a PPP as compared to national background levels as a function of distance and wind direction.

These zones may be altered in the second year of the project based on results of drift and evaporation experiments (protocol C) and results of year one. Note that a household can have one distance to only one field but one household can also have multiple distances to multiple fields. For example, a household could be within 100-250m of an orchard but also within 50m of a corn field or another orchard (see figure 3). These situations could possibly lead to so called 'hot spots' that will require a specific interpretation. This situation is not uncommon in the Netherlands due to the dense population and close vicinity of residential buildings to agricultural fields.

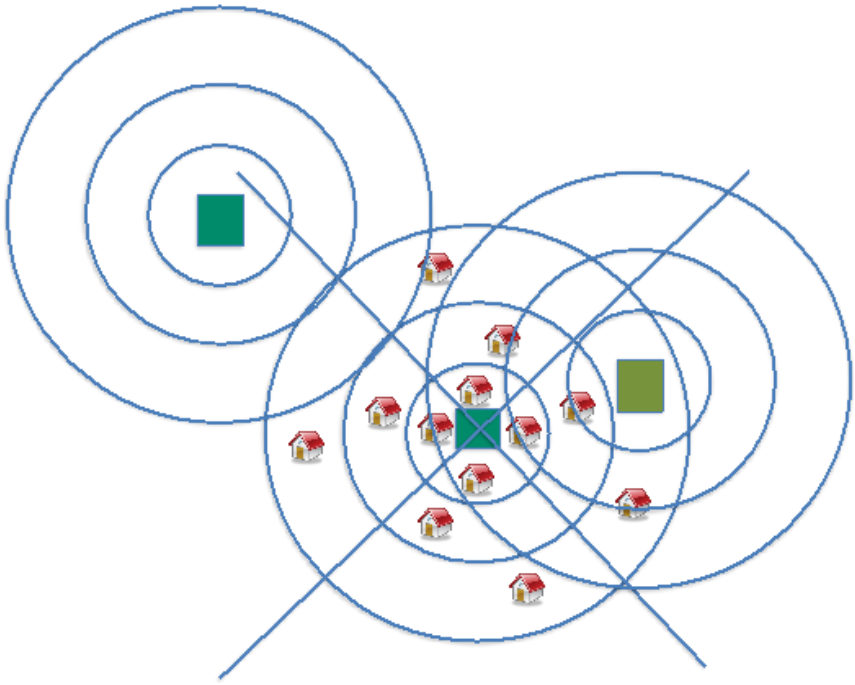


Figure 3. Theoretical location of dwellings within pre-defined buffer zones; multiple fields.

6.2.5 Selection of participants at specific addresses based on locations
Addresses selected in the previous step will be used to contact potential study participants. All necessary geo-data (crops, residential buildings including addresses, farmer registry) are available to the study team to perform the steps described above.

6.3 Selection procedure of participants

6.3.1 Definition of a 'resident'

In this study, a resident is defined as follows:

- a person who lives adjacent to agricultural land on which crops [e.g. flower bulbs, apples] are grown that are treated with PPPs;
- adjacent = within 250 m from the perimeter of a treated field;

For practical reasons, the study focuses on persons whose place of residence is adjacent to agricultural land, although concerns about exposure are broader, e.g. regarding children who attend school adjacent to a treated field. Although, no measurements are collected at schools or other places that could be of heightened interest (e.g. hospitals, nursing homes, kindergartens) the integrated model framework (WP5) will enable modelling of PPPs concentrations in all buildings in The Netherlands independent of their use function.

6.3.2 Target groups
The Health Council identified some population groups of specific interest. These groups were selected based on their potential vulnerability to PPPs and included (very) young children, pregnant women, and the elderly. The selection of subgroups according to gender and age may be relevant to some potential health effects to be studied in future follow-up studies (e.g. related to fertility,

pregnancy, neurodevelopmental disorders, et cetera). From an exposure perspective it is important to select subgroups that, due to different behaviour patterns, may have a different exposure. For instance, toddlers are much more in contact with indoor surfaces than adults. Similarly, young children may get more in contact with outdoor surfaces (e.g. soil) through playing.

In practice, however, there may not be much opportunity to specifically select the study population to include residents from all age groups in equal numbers within the pre-defined distance categories (0 – 50m, 50 – 100m, 100 -250m). If sufficient numbers are available per age group, this study will discriminate the following age groups either in the selection of participants and/or the statistical analysis:

a. infants and toddlers (0-4 y);
b. children (5-11 y)
c. adolescents (12-17 y);
d. adults (18-59 y);
e. elderly (60+ y).

Within these groups we will collect detailed demographic information and time-activity information. This allows for other groupings by for instance gender, time-at-home, etcetera.

6.3.3 Selection of participants

Potential study participants will be contacted based on the extracted addresses: Residents will receive an invitation letter and information about the study by mail. If they are interested in participating, they will be requested to return a completed registration form in a pre-stamped envelope. Those who express their interest will be interviewed by phone using a structured interview script to check if they fulfil the inclusion criteria. Study participants will also be contacted to establish availability and willingness of further household members to participate in the study. Each study participant will sign an informed consent form.
For each selected household, if possible, one adult (aged ≥18 years) and one child (aged <18 years) will be asked to participate. Subjects will be excluded in the case of inability to understand the questionnaires and informed consent procedure. Children of participating residents will be included into the study upon signed consent by the parents.

6.3.4 Farmer families

Farmers' families may be the most exposed group of residents. In addition, other exposure routes may be relevant for this group (e.g. contaminated clothes). This study will neither explicitly select farmers' families, nor exclude them. If the farmer lives on or near the selected fields the dwelling will be deemed suitable (see above selection procedure) and residents are invited to participate. It will be determined if a selected person belongs to a farmer family so that the analysis can take account of this.

6.4 Selection of plant protection products

In 2014, the selection of PPPs will be made based on available usage data according to a survey conducted by Statistics Netherlands in the year 2008. In

this survey, farmers are asked to provide information on crops they grow and pesticide use.
In 2015, the results of the latest survey of the year 2012 will become available. Since the (amounts of) PPPs used on crops in the Netherlands will have undergone changes during this 4-year period, selection of PPPs for the study period of 2016 will be based on the most recent survey. In addition, experts will be consulted regarding the spraying schemes of PPPs on crops of interest. This would allow obtaining the lists of PPPs in the cultivation of a crop that are likely to be used by farmers. This would make sure that efforts to develop analytical methods are focused on compounds that are likely to be used by farmers in practice in residential areas in the vicinity of fields with the selected crop(s).

For the study, approximately 10 PPPs will be selected based on their usage (kg/ha, frequency of application) and characteristics that influence how they are dispersed after application, such as physico-chemical properties of the substance. Because toxicological characteristics do not influence exposure routes, such characteristics would not represent a relevant *a-priori* criterion for selection in this exposure study. However, societal concerns about health effects of specific PPPs may also be a reason to include a specific substance. The unavailability of analytical methods is no reason for excluding PPPs from being selected. If considered relevant with respect to the other aspects/criteria, methods will be developed accordingly. However, limitations with respect to availability of analytical reference standards, uniqueness of urinary metabolites, and cost effectiveness will be taken into account in the selection process.

For the selected PPPs, biomonitoring data and detailed data on dispersion indoors and outdoors (protocol B and C) will be obtained. Within protocol A, data for other commonly applied PPPs will be generated as much as possible (depending on the possibility to include them in the methods used for the selected priority PPPs).

6.5 Data collection

Table 1 summarizes the different matrices, available sampling methods, and their relevance. Table 2 summarizes the contextual data that will be collected. Inclusion in monitoring protocol A, B and C is indicated for each method.

<u>Outdoor concentrations, indoor concentrations and contact surfaces</u>
An outline on the procedure that will be followed to assess outdoor concentrations, indoor concentrations and concentrations of PPPs on contact surfaces is presented in Annex 3 (WP3a). In particular, collecting this information will answer the primary research question 1) What are concentrations of PPPs in the environment of residents living near agricultural land?

<u>Internal concentrations</u>
Annex 4 (WP3b) describes what will be performed to assess personal (internal) exposure levels of PPPs in residents. This will thus answer the primary research question 2) What is the personal exposure of residents living near agricultural land to PPPs?

To extrapolate to other PPPs and other parts of the population, an integrated exposure model framework will be developed. More information on these models is given in WP5, annex 6.

Table 1. *Overview of samples to be collected for protocols A, B and C*

Type of sample	Represents	Relevance	A	B	C
Human material					
Urine	Short term exposure	(Proxy for) internal exposure (in ng/L) (without distinction of exposure routes)	+	+	-
Indoor and personal					
Personal sampler (adsorption tube, filter, other)	Short term (8-24 h)	(proxy for) inhalation exposure (in ng/m³),	-	+	-
High volume sampler (adsorption tube, filter, other)	Mid-term/low concentration in air	proxy for inhalation exposure (in ng/m³);	-	+	-
Skin wipes	Short term (<8 h)	Proxy for dermal exposure (in ng/cm²);	-	+	-
Surface wipes	Deposition (ng/m2)	Proxy for cumulative exposure	-	+	-
Outdoor					
High volume sampler (adsorption tube, filter, other)	Mid-term/low concentration in air	proxy for inhalation exposure (in ng/m³);	-	+	-
Deposition sampling (e.g. passive collection), soil and grass sampling, surface wipes	Short term/long term, e.g. through templates placed outside (related to specific period) or by directly wiping the surfaces (cumulative)	Proxy for dermal exposure (in ng/cm²);	+	+	-
Spray (droplet) and vapour drift sampling on / around field of application Airborne spray concentrations (active or passive) Spray drift deposition Vapour drift	Information about the source of exposure (spray application), concentrations in air at different distances from the crop. Furthermore the emission strength as well as the amount of pesticide remaining on the crop will be measured at regular intervals during several days (or weeks) after application.	Emission strength	-	+	+

Protocol A: Provides insight into the levels of exposure of residents living near fields as compared to background levels and the statistical relation between the measured environmental concentrations and personal exposures and contextual parameters.

Protocol B: Spray event based, optimal set of (environmental and personal) monitoring, necessary for (high quality) extrapolation and exposure modelling

Protocol C: Experimental farms, focus on optimal choice of measurement methods and development of drift and vapour models.

Table 2. *Contextual data collected in the different measurement protocols*

Variable	Method	A	B	C
Professional pesticide use	Diary	+	+	+
Details on application from farmers	Diary and registration forms	+	+	+

Details on urine collection	Diary	+	+	-
Demographic characteristics	Questionnaire	+	+	-
Life style	Diary / Questionnaire	+	+	-
Time activity patterns	Diary	+	+	-
Pesticide use at home	Diary	+	+	-
Awareness of spray events	Diary	+	+	-
Diet, specifically consumption of home-grown produce	Diary	+	+	-
Meteorological conditions	Measurements			

6.6 Sample size calculation

The study aims to investigate, over a two-year period, 15 locations resulting in approximately 200 households (~12-14 per location) with approximately 200 children and 200 adults. Within each household a total of approximately 50 biological and environmental samples will be collected over time. This design will lead to a sound assessment of environmental concentrations and the exposure of residents (including both adults and children). The dataset will have sufficient statistical power, and will provide options for extrapolation and generalization of results. There is a paucity in exposure data for metabolites. Using NHANES data (Center of Disease Control, USA), taking urinary 3-Phenoxybenzoic acid, a metabolite of pyrethroid pesticides, as an example we can calculate that with 400 residents we would have 80% power at an alpha of 0.05 to detect a 20 to 50% difference between exposed subjects and background levels (mean 0.292 ug/l; SD 0.26) assuming an exposure prevalence of a 100% and 50%, respectively. In comparison, the proposed study is about two to three times as large as the recently conducted UK study, which was restricted to biomonitoring.

6.7 Chemical analysis of samples

Actual measurements of PPPs, and where relevant their metabolites, in the direct environment of the study locations (in/outdoor) and at a personal level are of paramount importance in answering the research questions. The study involves the analysis of thousands of samples and the results will provide direct information on local occurrence and personal exposure, and are essential input for modelling purposes. Therefore, the analytical data produced need to be fit-for-purpose, i.e. sufficiently low detection limits, and reliable in terms of PPP identification and quantification in the study samples.

6.7.1 Sample matrices

The study involves analysis of a variety of matrices. From an analytical point of view, the matrices enable us to distinguish between emission strength from fields, outdoor as well as indoor air and surface concentrations as proxies for inhalation and dermal exposure routes, skin wipes as proxies for dermal exposure, personal inhalation exposure measured in air, and urine, for personal exposure. These are also outlined in Table 1.

6.7.2 Analytical methods

Environmental samples and wipes

For the determination of the PPPs, state-of-the-art instrumental methods will be used. Liquid chromatography combined with tandem mass spectrometry (LC-MS/MS) will be the method of choice. For PPPs that are not amenable to LC-MS/MS, gas chromatography with tandem mass spectrometry (GC-MS/MS) will be applied. Samples will be extracted using a suitable extraction solvent and procedure, which may differ depending on the physical/chemical properties of the analyte and the matrix. If required, extracts will be cleaned in order to achieve sufficient selectivity and sensitivity, and to improve robustness of the instrumental analysis.

In many cases, e.g. air, soil, and plant material, analysis methods will allow simultaneous determination of multiple PPPs. This means that, besides

simultaneous determination of the majority of the prioritized 10 PPPs, also other PPPs that are commonly applied in the Netherlands can and will be added to the method. This way, data on occurrence of other (unexpected) PPPs will be generated.

Urine analysis
Since modern PPPs are typically rapidly metabolized in the human body, the target analytes in urine are metabolites rather than the parent PPPs. It is recognized that analytical reference standards of metabolites, which are required for their quantitative determination, may not be commercially available for the prioritized PPPs. In that case efforts will be made to obtain them from the agrochemical industry or through custom synthesis. For the determination of the metabolites, LC-MS/MS is the method of choice. Sample preparation, besides extraction and cleanup, may involve a deconjugation step to convert multiple metabolites into one form for which the analytical reference standard is available. Due to the more extensive sample preparation and the limitations in availability of analytical reference standards, the possibilities for simultaneous quantitative determination of multiple metabolites in urine will be limited.

When no reference standards of the relevant urinary metabolites are available, it is still possible to detect metabolites in urine by non-target qualitative analysis. Here the urine will be analysed with no or minimal sample pre-treatment followed by liquid chromatography with full scan high-resolution mass spectrometry (LC-HRMS). The metabolites known from literature and draft assessment reports available from EFSA, supplemented with theoretically derived phase I/II metabolites are then sought for in the full scan data through their exact mass. The feasibility of this approach has been demonstrated by Jamin et al [2014]. This approach will be used to complement the targeted quantitative analysis.

6.7.3 Validation and quality control
In order to ensure acceptability of analytical results to the different stakeholders, method validation and quality control procedures will be based on internationally accepted guidelines for the determination of PPPs in agricultural and environmental commodities [SANCO/825, OECD 2007, SANCO/ 12571/ 2013].

6.8 Extrapolation of study results

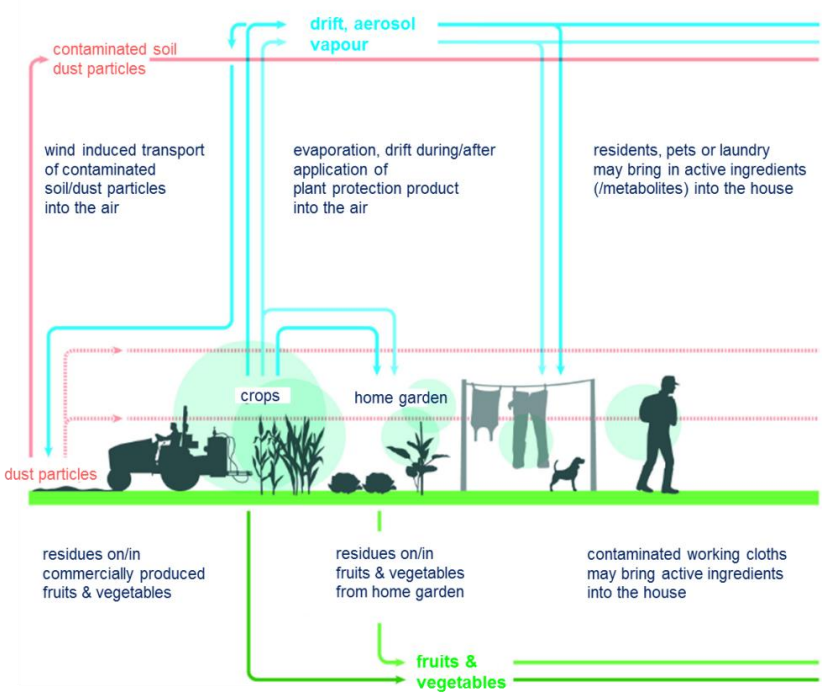
Due to practical considerations, only a limited number of situations will be studied, i.e. a limited number of PPPs, exposure situations, environmental conditions and residents. Consequently, the study results have to be generalised and extrapolated to cover other PPPs, crops and applications, for residents and the population as a whole and by sub-categories of the popualtion according to age, gender, etcetera, if necessary). In other words, is has to be determined how the exposure levels in the studied situation rank with respect to exposure levels of the population (residents, general population). A summary of activities is given below - for a full description of activities see Annex 6.

Measurement data will be used to calibrate and validate both deterministic as well as statistical exposure models. The models will then be used to extrapolate this research to other PPPs and other locations, allowing for the estimation of exposure to PPPs in situations for which no measurements have been carried out. Such models consist of mathematical and empirical descriptions of

processes of emission, dispersion of droplets and gases, and internal and external exposure. They will largely be based upon existing models such as those developed in the BROWSE project, and PEARL/OPS. Information about physico-chemical properties of PPPs, application techniques, and cultivation characteristics on one hand, and meteorological conditions, location of houses and human physiology and activities on the other hand serve as input for these models.

To enable the extrapolation of results we will undertake the following steps

1. Derive deterministic and/or statistical models describing discrete exposure pathways (for an overview of pathways see figure 4).
    a. Emission, evaporation and spray drift from (application on) fields to the environment.
    b. Deposition of residues on contact surfaces in the surrounding of dwellings (e.g. home, garden).
    c. Relationship between outdoor air concentrations of PPPs to indoor air and contaminated surfaces.
    d. Relationship of environmental concentrations to internal exposure levels of residents accounting for oral, dermal and inhalation exposure routes.
2. Link the different exposure pathways to an integral exposure model framework describing the process from application of PPPs on agricultural lands to exposure of residents.
3. Predict exposure distributions based on the integral model framework for measured PPPs in the project and selected other PPPs to estimate variation of the exposure to PPPs throughout the year and across different areas in the Netherlands.



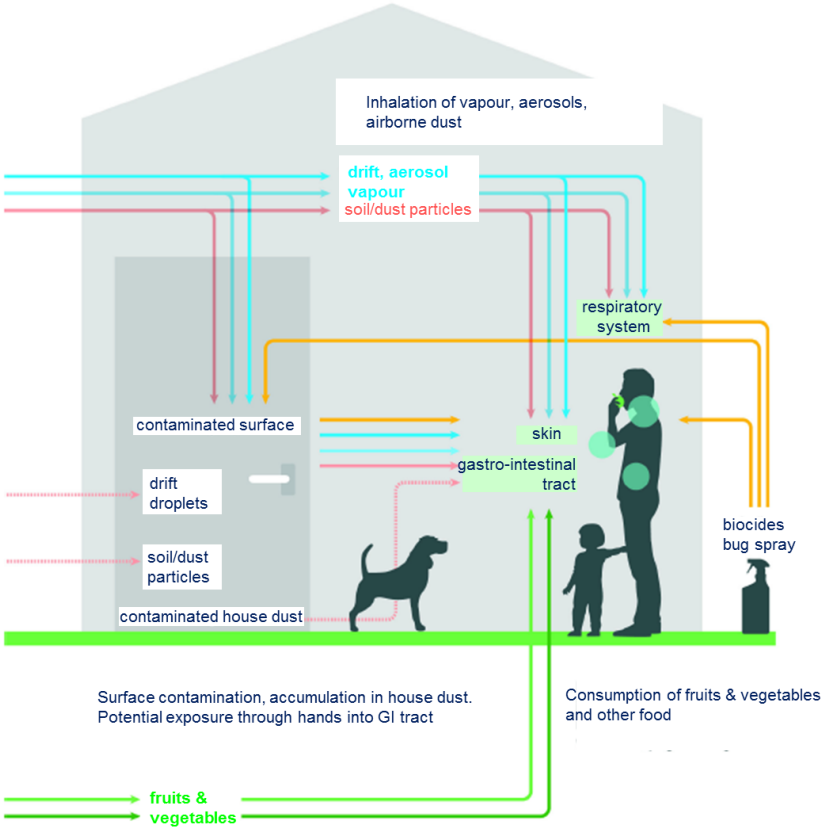


Figure 4. Exposure sources and exposure routes. Adapted from [Health Council of the Netherlands 2014].

6.8.1 Integration of exposure models describing exposure pathways

In first instance we will study discrete processes, e.g. drift and evaporation from fields to the environment, associations between PPPs in outdoor and indoor air, associations between indoor air and settled dust, associations between outdoor and indoor exposure sources and personal exposures to PPPs. Associations will be investigated using both mathematical and empirical/statistical models. These models can in part be based on existing models (for example from the BROWSE project and PEARL/OPS). This step will provide us with an answer to our primary research question number 3) What are the exposure sources and routes contributing to environmental and personal exposure to PPPs?

6.8.2 Derivation of an integral exposure model framework

In a second step we will develop an integral model framework combining the different steps in the exposure process to model the total cascade from emission to personal exposure. The integral model framework will be verified using the existing data either as independent validation sets or by cross-validation. The integral model framework should be able to support calculation of exposure (or another endpoint) by combining use patterns of PPPs with (elementary) PPP properties, environmental conditions, the built environment and human

behaviour patterns. In particular, the final integral model framework will enable us to answer research question number 4) What is the exposure to PPPs distributed through the year and across different areas in the Netherlands?

6.9 Communication

6.8.1 Relevance and motivation

Effective communication is more than a simple one-way transfer of information. Communication needs to address public and stakeholders concerns and facilitate a productive and meaningful interaction between actors from different backgrounds and with diverging interests. Research has demonstrated that effective mutual communication is one of the key challenges in risk governance.

Effective communication is essential from the start till the end of this study: i.e. from recruitment of the study population till the framing of the message on the outcomes of the study. Effective communication means accommodating the communication to the information needs and the attitude of different stakeholders (residents, farmers/growers, civil society and policymakers). It means a key message with the right tone of voice and comprehensible terminology and tools that are used and understood by stakeholders. Managing the expectations on the outcomes of the study (e.g. measuring exposure to PPPs instead of measuring health risks of PPPs) will also be an important area of concern for the communication.

The communication is targeted at three groups of stakeholders:

- Primary stakeholders are residents and farmers/growers who are directly involved in the study;
- Secondary stakeholders are residents and farmers/growers in the Netherlands who are not actively involved in the study;
- Tertiary stakeholders are parties like (local/regional) governments and policy makers, Nefyto, NGOs, scientists, distributors of PPPs (like members of Agrodis) and their specialists advising growers, sector organisations like NFO and KAVB, etc.

To successfully communicate about the research and its results to these stakeholders, specific knowledge is indispensable. We therefore define a twofold aim in our communication strategy:

- The communication on the study and its outcomes is accommodated to the knowledge, attitude and expectations of the primary, secondary and tertiary stakeholders.
- Consensus and clear agreements on the implementation of the communication strategy of all parties in the consortium of this study. All partners need to abide to the agreed key message, use the same terminology and commit themselves to the planning and coordination of the external communication.

For a full description of activities see Annex 7.

6.10 Field implementation

The project described in this proposal involves many different organizations and research elements. This requires a strong overall coordination (WP1) but

importantly requires detailed planning, preparation, organization and execution of the field study. WP7 (See Annex 8) provides the necessary field coordination both towards farmers (partner CLM) and to residents (partner IRAS). To enable the conduct of measurement protocol A and B in the field, a dedicated field team will be established encompassing all required expertise. The field team will be directed by one central coordinator who is responsible for the coordination of the field work, including the recruitment of participants.

7 Expected results

The aim of the proposed multiyear study is to assess the exposure to PPPs of persons living in close vicinity to agricultural land on which PPPs are applied. The study aim can be translated into the following main research questions:

i) What is the personal exposure of residents living near agricultural land to PPPs?
ii) What are concentrations of PPPs in the environment of residents living near agricultural land?
iii) What are the exposure sources and routes contributing to personal and environmental exposure to PPPs?
iv) What is the exposure to PPPs distributed through the year and across different areas in the Netherlands?

This proposed work is an integrative work plan combining environmental and biological monitoring with modeling of exposures. Such an integrative approach is necessary as to ensure the project delivers tangible and interpretable results. Results will allow the extrapolation of exposures to other locations, crops and PPPs.

The expected results of the project are:

1. Descriptive statistics (means and percentiles) on measured environmental concentrations and personal exposures for the selected locations and PPPs.
2. Calibration and/or validation of discrete models describing the fate of PPPs from their use on the field to residences and their inhabitants.
3. An integrative modeling framework allowing for extrapolation to other locations, crops and PPPs.
4. Descriptive tables and maps of residential exposure to PPPs of priority PPPs in the Netherlands.

Expected results per workpackage are:

WP1

- A clear organizational structure fostering efficient conduct of research.
- Process management ensuring that the research aims, deliverables and milestones are met.
- A comprehensive and accessible database of all study data.
- Oversight of the research including quality control monitoring and if needed taking appropriate action to adapt the research protocol.

WP2

- A listing of suitable locations for the conduct of measurements as described in protocol A, B and C.
- A listing of priority PPPs to be measured in the research project, evaluating crops, amount and types of PPPs used in the Netherlands, and physico-chemical characteristics.

WP3

- The conduct of environmental sampling at the selected locations.
- The conduct of personal sampling, including biomonitoring.

- Descriptive statistics on environmental concentrations, personal exposures and biomonitoring of PPPs.

WP4

- Analyses of collected environmental samples for the parent compounds (PPPs).
- Analyses of biological samples for the parent compounds and/or their metabolites.

WP5

- Optimized and validated deterministic and statistical models to predict environmental concentrations.
- Optimized and validated deterministic and statistical models to predict personal exposures and internal concentrations.
- An integrated exposure model that allows for the prediction of PPPs for locations, crops and PPPs not covered under the measurement campaigns.

WP6

- Knowledge on the needs and attitude of stakeholders and participants reagarding pesticides, risk information, and exposure research, feeding into recommendations to communication strategies for effective communication to all stakeholders, before, during and after the study.

WP7

- An effective field-protocol describing all activities to be conducted in the field from recruitment to sample collection, treatment and storage.
- Conduct of the field-work.

There are several potential risks for the different steps in the project. These pertain to:

- **Selection of households**. There is a chance that the participation is lower than expected resulting in lower geographical coverage and loss of power. The risk of this is minimized by extensive pre-work done to select preliminary locations. Due to the dense nature of the Netherlands, sufficient number of households can be found in close proximity to agricultural fields (>400,000 households within 100m) and as such the risk is thought to be minimal.
- **Not obtaining all environmental and personal samples**. The planned field work is complex logistically and requires collaboration of farmers, and residents. Although the partners in the project are experienced in the conduct of complex population-based research, there may be situations where samples are lost. Due to the repeated nature of the sampling protocol the impact of sample loss is mitigated.
- **Analytical challenges**. The concentrations expected in environmental samples is expected to be low. However, current analytical techniques are sensitive and therefore it is not expected that the limit of quantification will be insufficient. We will use state-of-the-art analytical techniques to analyze the environmental samples. Samples below the limit of detection will be furthermore treated statistically by informative imputation techniques. For biological monitoring, metabolite concentrations may be low (same as above) and standards for metabolites may not be available. To minimize the risk we will take the availability of measurable metabolites into account for the selection of PPPs to be assessed in the measurement campaign. Furthermore, we

have reserved budget to be able to synthesize metabolites if needed.

- **Modeling challenges**. Although the model framework is based on existing efforts there is a chance that the resulting models are not sufficiently accurate to estimate population exposures to PPPs. We estimate the risk of this to be low based on previous experience. However, these models have not been validated for predicting personal (internal) levels of exposure to PPPs. There is however ample experience on modeling personal exposures to environmental exposures and on pharmacokinetic modeling in the consortium, thus minimizing this risk.
- **Results cannot be generalized**. The aim of the project is to develop a generalized exposure modeling framework which can be used to estimate the exposure to PPPs, crops and locations not covered in the measurement protocol. There may however be application techniques or physical properties of PPPs which were not covered in the measurement campaign. As such there will be more uncertain model outcomes in these occasions.

8 References cited

Bogers RP, Schram-Nijkerk D, Devilee J, Knol AB, Breugelmans ORP (2014) Verkenning van mogelijkheden voor onderzoek naar blootstelling aan gewasbeschermingsmiddelen bij omwonenden. RIVM Bilthoven, rapport 630030002/2014. Download at: www.rivm.nl/bibliotheek/rapporten/630030002.pdf

Galea KS, MacCalman L, Jones K, Cocker J, Teedon P, Sleeuwenhoek AJ, Cherrie JW, Van Tongeren M (2011) Biological monitoring of pesticide exposures in residents living near agricultural land. BMC Public Health 2011, 11:856

Health Council of the Netherlands. Crop protection and local residents. The Hague: Health Council of the Netherlands, 2014; publication no. 2014/02. http://www.gezondheidsraad.nl/en/publications/environmental-health/crop-protection-and-local-residents

Jamin EL, Bonvallot N, Tremblay-Franco M, Cravedi JP, Chevrier C, Cordier S, Debrauwer L (2014). Untargeted profiling of pesticide metabolites by LC–HRMS: an exposomics tool for human exposure evaluation. Anal Bioanal Chem 406:1149–1161.

OECD (2007) Guidance Document on Pesticide Residue Analytical Methods. OECD Environment, Health and Safety Publications, Series on Testing and Assessment No. 72 and Series on Pesticides No. 39. ENV/JM/MONO (2007) 17. http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2007)17&doclanguage=en

Quirós-Alcalá L, Bradman A, Nishioka M, Harnly ME, Hubbard A, McKone TE, Ferber J, Eskenazi B (2011). Pesticides in house dust from urban and farmworker households in California: an observational measurement study. Environmental Health 10:19

Renn O, Klinke A, Van Asselt M (2011) Coping with Complexity, Uncertainty and Ambiguity in Risk Governance: A Synthesis. Ambio 40:231-246

SANCO/12571/2013. Guidance document on analytical quality control and validation procedures for pesticide residues analysis in food and feed. http://ec.europa.eu/food/plant/plant_protection_products/guidance_documents/docs/qualcontrol_en.pdf

SANCO/825/00 rev. 8.1, 16/11/2010 Guidance document on pesticide residue analytical methods. http://ec.europa.eu/food/plant/protection/resources/guide_doc_825-00_rev7_en.pdf

9 Critical success factors and risks

9.1 Critical success factors

Describe critical success factors (risks) and indicate go/no-go moments.

The following points are considered essential for the success of the project:
- Involvement and motivation of volunteer participants (residents);
- Good cooperation and willingness of farmers that apply the PPPs;
- Strong overall coordination;
- Skilled field work team in place;
- Good analytical methods which are sensitive enough to also measure low exposure levels;
- Use and/or (further) development of suitable dispersion and exposure models to extrapolate the measurement results to various environmental and application conditions, other PPPs, and target groups;
- Good cooperation and coherence among WPs and consortium members;
- Room for adjustments of the work plan. Since the study is complex there need to be options to adapt certain aspects of the project if this is considered the best approach for success of the project;
- Good communication with all relevant stakeholders.

The following points are considered risks inherent to the project:
- Farmers at the selected study locations are aware of the study and as a result may alter their (spraying) behaviour. Although it is quite certain this will happen to some extent, it is uncertain how much bias (compared to the uncontrolled situation) this creates.
- Residents at the selected study location alter their normal behaviour such as time-activity-patterns. Although it is quite certain this will happen to some extent, it is uncertain how much bias (compared to the uncontrolled situation) this creates.
- Either the background levels of exposure, or the absolute levels of exposure, are such that the contribution of (in)direct residential exposure cannot be established. The impact will be that it will not be possible to identify hotspots of exposure outside the study locations.

The following go / no go moments have been defined in the project:
- Selection and inclusion of sufficient sites and volunteers from target populations;
- Timely availability of overall study protocol;
- Availability of measurement method(s) for selected PPPs;
- Availability of analytical method(s) for selected PPPs;

9.2 Statutory regulations and required permits

The work is carried out in accordance with a range of statutory regulations, permits etc. Describe relevant regulations and required permits (e.g. concerning medical-ethical evaluation, protection of personal data, use of unusual hazardous chemicals or unusual quantities of chemicals, public private partnerships).

Research in this proposal will be conducted in accordance with applicable guidelines including, the Nuremberg Code of 1947, the revised Declaration of Helsinki in its last version of 2013, the convention for the protection of human rights and dignity of human beings with regard to the application of biology and medicine: Convention on Human Rights and Biomedicine (Council of Europe,

Oviedo, 1997) and its additional protocol concerning biomedical research (Strasbourg, 2005), the recommendation of the committee of ministers to member states in research on biological materials of human origin (Rec (2006)4), the Universal Declaration of Human Rights and Covenants on Human Rights" (UN General Assembly, December, 1984) and the EU directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

Every partner will comply with all relevant national and EU legislations relating to the conduct of human studies, the study and handling of biological materials and the management of data to protect privacy and maintain confidentiality. Approval of the project plan will be obtained by a medical ethics committee within the framework of the Dutch Medical Research Involving Human Subjects Act (in Dutch: Wet medisch-wetenschappelijk onderzoek met mensen; WMO). Handling of personal data will comply with the Personal Data Protection Act (in Dutch: Wet bescherming persoonsgegevens; Wbp).

Compliance to ethics regulations will be secured by:

- In preparation of the Grant Agreement, each partner will be expected to complete due diligence checklists which require a detailed account of each institutions' procedures for conduct of research on humans.
- All investigators in the studies that involve human samples have extensive experience of conducting or participating in research with and the ethical handling and utilisation of human material for experimental use.

9.3 Conflicts of interest

Any conflicts of interests of partners in the proposal are identified and appropriate checks and balances are formulated.

Declaration of interest forms of all participating researchers will be collected and updated during the study period. Participation in the project will depend on approval of the DoIs by RIVM. DoIs will be made available to the public via the website.

10 Analysis of choices made and remaining uncertainties

In the design of the study, all potentially relevant exposure routes are considered. Protocol B has the aim to gather detailed information about propagation and exposure pathways. This is done by collecting environmental samples, and by gathering contextual information that is necessary to understand the exposure scenario under study. Not all scenarios can be studied, in which case exposure has to be modelled.

In the preparation of this study, the project team has visited residents at their homes to get insight into the perspective of residents, and to get a better understanding of what kind of exposure situations and routes occur in real life. Residents expressed their concerns about various exposure scenarios, some of which were not yet considered by the project team. Below, the residents' concerns and perspectives are summarized, and it is indicated how they will be addressed in the study.

Routes of exposure
The vast majority of the residents' comments concerned routes of exposure. Some examples include deposition on children's toys in the garden; wind erosion transporting contaminated dust from fields, and contamination of eggs of residents' chickens. Some of these potential exposure routes are addressed in the study by taking samples, e.g. indoor deposition and in the garden. Other routes are indirectly covered by modelling, in which contextual information (e.g. time-space information) is combined with modelled environmental concentrations of PPPs; an example is exposure as a result of being a bystander during a spray event. Some potential routes (e.g. contaminated chicken eggs), are neither measured nor modelled.

Incidents
Incidents of intoxication by soil fumigants (in this case metam sodium) have been reported by residents. Also cases of children playing with empty bags (containing residues of PPPs) of coated seeds were mentioned. Residents therefore requested to also study exposure due to these type of incidents. In the exposure study, information about such incidents will be collected as contextual information. In case of an incident, elevated levels may be observed in urine. However, it is impossible to model the impact of incidents and extrapolate incidental situations to more general scenarios. The models will, however, enable to model more extreme scenarios including adverse weather conditions.

Micro environmental situations
Some residents had questions about the effect of specific local situations on their exposure. For example, what is the effect of hedges, what if a field is surrounded by houses, etc. The exposure study will take these situations into account as far as is possible by performing spray experiments and studying the influence of obstacles, which is subsequently used as input in dispersion models. However, very specific situations cannot be modelled and a certain degree of uncertainty about specific living situations will always remain.

In addition, potential effects of exposure on the environment are not evaluated within this study.

Health

Obviously, residents' concerns were mostly health-related. However, the study objective is to investigate residents' exposure, and the study is not aimed at also evaluating health effects.

11 Project organisation

11.1 Structure and partners

Identify collaboration partners: describe the role of the partners. This refers to the scientific and logistic capabilities of the consortium partners. Do its members have experience with carrying out the proposed research? Are they familiar with the specific field? Also consider the benefit of any described collaboration in the proposed consortium.

The project is divided in 8 closely related work packages (WPs). The main tasks of the WPs are given in Figure 1 and the table below.

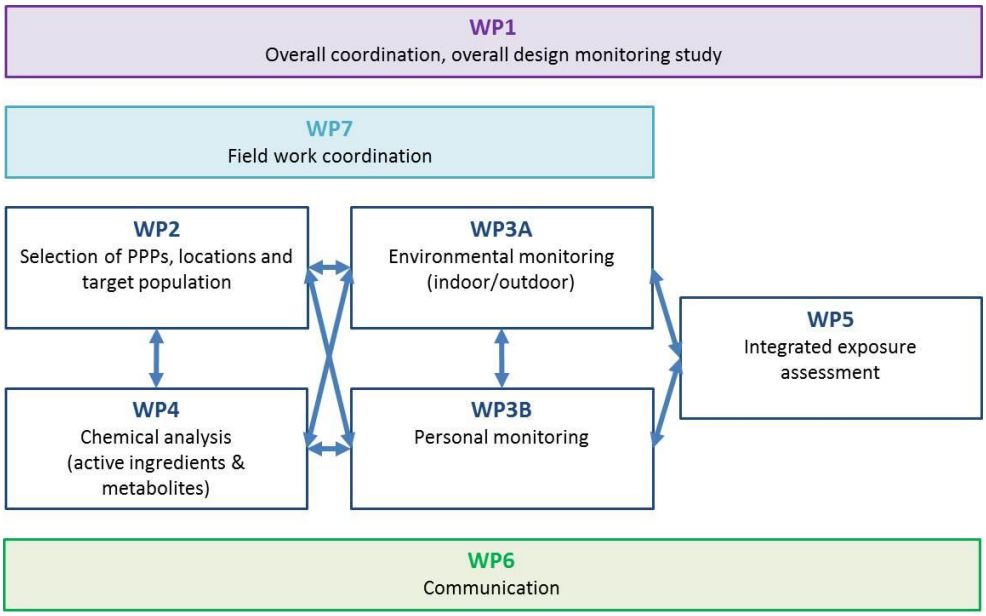


Figure 1. Organisation of the project.

WP	Main tasks	WP leader
1	Overall coordination, study design, project and data management	RIVM IRAS (Roel Vermeulen)
2	Selection of locations, households, PPPs	Alterra (Erik van den Berg)
3a 3b	Collection of biological and environmental samples a. Environmental monitoring b. Personal monitoring	TNO (Rianda Gerritsen) Radboud UMC (Paul Scheepers)
4	Chemical analyses of biological and environmental samples	RIKILT (Hans Mol)
5	Statistical analyses of exposure data and integrated modelling of PPPs	IRAS (Roel Vermeulen)
6	Communication	Schuttelaar and Partners (Jacqueline Vink)
7	Fieldwork logistics	CLM (Erna van der Wal) IRAS (Roel Vermeulen)

12 Outcomes

In the planning of the project it is foreseen that several intermediate reports are produced. These include a progress report after each year of the study, the description of the obtained measurement results, and the model results of selected PPPs.

A final report will be produced at the end of the project describing all procedures and results. Reports and communications to the different stakeholders will be overseen by WP6 on communication as to ensure that the language in the reports are targeted to the intended readers.

Scientific publications have not been budgeted within the framework of this project but it can be anticipated that several scientific publications will be generated based on work conducted in this project.

Annexes: Detailed description of Work Packages and CVs of the research team

Annex 1: (WP1) Overall coordination, overall design monitoring study
Annex 2: (WP2) Selection of plant protection products (PPPs), locations and target population
Annex 3: (WP3a) personal monitoring;
Annex 4: (WP3b) environmental monitoring
Annex 5: (WP4) Chemical analysis
Annex 6: (WP5) Integrated exposure modeling framework
Annex 7: (WP6) Communication
Annex 8: (WP7) Preparation, organization and execution of the field study
Annex 9: CVs of the research team

Annex 1. (WP1) Overall coordination, overall design monitoring study

1.1 Design and Methods

1.1.1 Aim and objectives

The aim of WP1 is to develop the overall study protocol (see description of study in main document) and to provide scientific oversight of the project.

Specifically, the aims are:

- Development of an overall study protocol and adjustment of this protocol based on newly acquired knowledge and insights.
- Scientific oversight of work conducted in the different WPs regarding:
    - Timelines
    - Concurrence with work description
    - Quality control on generated data
- Provide effective communication within the consortium
- Provide data management support to the consortium so that data from all measurement protocols are retained in a common database.

1.1.2 Expected results and deliverables

WP1 is expected to deliver:

- A common study protocol
- A report on the quality control aspects of obtained data
- A centralised database with all pertinent information on obtained samples within the different measurement protocols, the contextual information and laboratory results.

1.2 WP1 organisation

RIVM is leading WP1 together with UU-IRAS. The RIVM is tasked with the overall coordination of the project, which includes administrative tasks, contact with stakeholders, and process management. UU-IRAS will focus on the scientific coordination of the project. This requires frequent contact between IRAS and RIVM, which will be fostered by having an employee of UU-IRAS who will be placed at the RIVM for one day biweekly.

Data usage agreements will be set up between all partners to allow transfer of data between institutions.

1.3 Planning

The study takes place between 2015 and 2017. During this period the management structure will be in place. After the project, the central database will be maintained and transferred to the RIVM.

Annex 2: (WP2) Selection of plant protection products (PPPs), locations and target population

In Work package 2, the methodologies are developed for the selection of locations and PPPs for the three measurement protocols A, B and C (See Section 6.1).

The aspects that need to be considered are:

- The area of cultivation of crop(s) in the Netherlands.
- The use of plant protection products on crops grown in the Netherlands.
- The application techniques that are being used in a target crop in the Netherlands and the extent of their use in practice.
- The physico-chemical properties of the substance, in particular the vapour pressure.
- The potential of air-borne drift during the application.
- The number of fields around the home of a resident at various distances.
- The number of homes and residents in the vicinity (less than 250 m) of treated fields.
- The chemical analysis of the substance (active ingredient) and its relevant environmental and human metabolites.
- The toxicological characteristics of crop protection products, in particular in relation to vulnerable groups in the population, such as children.

The selection procedure is aimed at making a justifiable and sensible selection of the sites and PPPs to be studied, in order to obtain measurements of exposure in so-called hotspots or large areas with intensive use. The general approach that will be followed is:

- selection of crops based on (extensive) use of relevant PPPs;
- mapping of the selected crops, including residential locations;
- selection of PPPs;
- selection of study locations.

The methodology to be developed will result in the identification of potential hotspot areas for exposure of residents to PPPs. The type of data needed to identify these hotspots, as well as the data sources are described in more detail in the next sections.

1. Area of cultivation of crops

There are large differences in the areas used for cultivation of different crops in the Netherlands. For instance, maize is grown on sandy soils, whereas potato growing areas can be found in the south-west of the Netherlands and in the reclaimed polders of Flevoland. Some crops are limited to a few areas, others are more evenly distributed over the agricultural area of the Netherlands. Further, the areas of orchards do not change from year to year, but for flower-bulb growing there are differences. Flower bulbs in the traditional flower bulb region (i.e. primarily in the north-west of the country) grow on the same fields for most of the time, although the types of flowers are rotated (tulip, lily, daffodil, crocus, dahlia, etc.). In the rest of the Netherlands, the fields with

flower bulb crop move to different locations from year to year. Crop rotation occurs for potatoes: once every 4-5 years potatoes are grown on the same field.

The BRP (Basis Registratie Percelen) is a high-resolution crop map (basis 1:10,000 scale), which is yearly updated and available since 2009. The BRP is a vector data set of parcels which contains major agricultural crops grown in the Netherlands (>100 crops). Crops with intensive PPP use are present in aggregated form (e.g. categorized as flower bulbs, but not as lilies, tulips, etc), greenhouses, or categorized as fruit, but not as apples, pears, etc). The BRP is available to the study team.

2 Use of plant protection products
The use of plant protection products depends on the crop. Pests or plant diseases differ from crop to crop, so the PPPs that are used on a crop will be different as well. However, not all PPPs that are permitted to be used on a specific crop will be used in the growing season. Whether or not a specific PPP will be used depends on the pest type, the availability of alternatives for pest control and the perspective of the farmer of whether or not there is a serious risk of occurrence of a specific pest. Therefore, for the selection of PPPs in this study there is a need to collect data on the spraying schemes that a farmer has at his disposal and the extent of use the various spraying schemes. Some PPPs may be applied only once, whereas others may be used at regular intervals. Experts will be consulted to provide input on actually used PPPs and spraying schemes for crops of interest. This will help us to develop a lists of PPPs that are not only allowed to be used on a specific crop, but those that are actually likely applied by farmers. This would make sure that efforts to develop analytical methods are focused on compounds that are likely to be used by farmers in practice in residential areas in the vicinity of fields with the selected crop(s).

Data on the agricultural use of PPPs by farmers in the Netherlands are available from surveys conducted by Statistics Netherlands (early ’90, 1998, 2004 and 2008). For the evaluation of Dutch policies on the sustainable use of PPPs, these farm-based data were converted into national average applications and combined with information on application methods, equipment/technique, and restrictions to the authorized use (Kruijne et al. 2012). Usage of PPPs continuously changes as a result of registration decisions. Information generated in the most recent survey from 2012 will be taken into account in WP2.

3 Application techniques and practices
Data are needed on the various application methods and techniques used in agriculture, the extent of their use as well as data on the use of these methods in various regions or areas in the Netherlands.
Spraying is the most common application method. Bystander and resident exposure to spray drift requires knowledge of both airborne spray (to determine potential dermal and inhalation exposure) and ground deposits (to determine post application exposure to contaminated ground).
In order to mitigate spray drift and protect sensitive areas (e.g. water bodies, residents, housing) from contamination with PPPs the application parameters, such as droplet size and airflow need to be adjusted according to variable environmental circumstances. Application strategies including use of drift reducing nozzles and reduced airflow applications on the fruit tree rows at the edge of orchard will reduce spray drift and spray deposition significantly,

compared to standard/traditional practices. Resident exposures should be assessed for different types of application techniques.

An inventory of the regional distribution of most often used application techniques is done (PPO/PRI) to show the occurrence of use and availability standard and drift reducing spray technologies (DRT50-DRT95; following ISO22369) in arable and flower bulb crops (Zande et al 2012) and fruit crops (Zande et al., 2014).

Irrespective of their contribution to the total volume of PPPs applied to agricultural crops, other application methods may be relevant and need to be considered as well. E.g. soil injection in lilies, fumigation.

4 The physico-chemical properties of the substance
The properties of the substances show a large variety. Not only the vapor pressure is an important property, also the coefficient of sorption on organic matter and persistence / dissipation rates. These properties have a large influence on the rate of volatilization of these compounds from soil and crop surfaces.

For the PPPs in protocol C, the selection of PPPs will be primarily based on their physico-chemical properties. This more simple approach is due to the fact that the goal of these experiments is to verify the emission and dispersion models for the emission pathways during and after application. Such models are needed within the integrative part of the study as described in WP5.

5 Methods for sampling and analysis
During the main study, in the frame of WP3A and WP3B (indoor/outdoor measurement and personal monitoring of active ingredients and metabolites, respectively), large numbers of samples of contact materials (air, surfaces/wipes, dust, vegetation) and samples for biomonitoring (urine) will be collected and analysed. It is essential that the relevant target analytes can be detected, i.e. that limits of detection are fit-for-purpose, and that reliable quantitative data can be obtained because this will have a high impact on the ability to assess exposure and exposure routes, and subsequent interpretation and modelling. The analytical requirements will be described in detail in WP4 ('Chemical analysis of active ingredients and metabolites'). From that WP, input will be provided on analytical possibilities and limitations with respect to the chemical analysis in the different sample matrices and, where relevant, also the associated sampling protocols. This will include:

- availability of analytical reference standards (may apply to metabolites)
- uniqueness of metabolites for exposure to the active ingredient
- availability of validated methods
- success rate of method development if needed
- stability issues of target analytes in the sample matrices after sampling
- cost and throughput of analysis

For each of the candidate PPPs selected, these aspects will be evaluated and taken into account in the final selection of PPPs in the exposure study.

6 Location selection
To specify the locations for study, first selection criteria are identified, that are subsequently translated via available geo-data and via geographic information system (GIS) calculations into maps.

a. *Selection of target crops*

In the advice of the Health Council, orchards and flower bulbs were identified as crops with a high amount of use of PPPs. These crops will be the first to be investigated in the current exposure study. Other crops will be investigated in a later stage. These maps can be used to generate distributions of the distance between residents and crops with intensive use of PPPs in the Netherlands.

b. Identify the criteria for selection of sites

The criteria for selection of sites needs to be elaborated. The following criteria are important:

- The number of fields in the neighbourhood of the residents at different distances
- The number of residents in all wind-directions at different distances (<50 m, 50-100 m, 100-250 m) format potentially eligible locations .
- Area of crops cultivated in the neighbourhood of the residents including the present and historical situation (former years because of rotation of bulb growing)

c. Identify the sites based on the criteria and translated into GIS data

Once the list of criteria is known, the databases have to be identified where the required data are found, and selections have to be made.

- Location of crops and type of crop can be identified by the BRP (BasisRegistratie Percelen) database. The BRP is a polygon (vector) database. Fruit or bulb fields are not specified per type of fruit/bulb. Therefore, the BRP will have to be linked with the Landbouwtelling (agricultural census data), which contains detailed information regarding the specific crops that were grown by farmers.
- Resident locations can be identified by the BAG (Basisregistratie Adressen en Gebouwen). The BAG is a polygon database. A division can be made between houses, commercial buildings, hotels, etc.
- Location and type of landscape elements can be obtained from the Top10 Vector.

d. Select the sites

Selection depends on the delineation of the study/choices made: which crops, which PPPs. Also, the required number of residents to include to measure exposure can be an argument to choose a site.

The selection of sites for protocol C is made from the available experimental farms in the Netherlands.

Annex 3: (WP3a) Environmental monitoring

The overall measurement campaign aims at including 15 locations (6 in 2015 and 9 in 2016) with 12 households each. For each household preferably 2 persons (adult and child) are included. These will all be part of protocol A. For protocol B a subset of about 4 households per location will be selected and protocol C will be performed on experimental fields (orchard and flower/bulb). In the paragraphs below details on samples per measurement technique for the environmental monitoring part are provided for each protocol separately.

Protocol A
This sampling scheme follows residents during the spray season and in the off-season. In the spray season environmental measurements will be performed at two occasions for seven consecutive days and in the off season for two consecutive days. The environmental measurements in protocol A include outdoor air sampling, settled house dust sampling and outdoor and indoor surface wiping. Next to this, local (micro)meteorological measurements (one meteorological station per 12 households) are taken.

In Table A3-1 the number of samples per sampling technique and per year are presented.

Table A3-1: Number of samples per sampling technique and per year as part of protocol A

	Spray season 1 (7 days)		**Spray season 2 (7 days)**		**Off season (2 days)**		**Total**
Year	**2015**	**2016**	**2015**	**2016**	**2015**	**2016**	
Outdoor air sampling	588	672	588	672	168	192	2880
Settled house dust	84	96	84	96	84	96	540
Surface wipes indoor (floor, window seal)	168	192	168	192	168	192	1080
Deposition samples outdoor (grass, soil, fruit-bearing plant)	252	288	252	288	252	288	1620
Local meteorological measurements	*Real time digital data*	*Real time digital data*	*Real time digital data*	*Real time digital data*	*Real time digital data*	*Real time digital data*	*n.a.*
Urine sampling (WP3B)	1176	1344	1176	1344	1176	1344	5760

Protocol B
Sampling protocol B will start at the time a farm reports an intended use (= application). In this protocol, indoor air sampling, personal air sampling (adult only) and dermal skin wiping (hands and face) will be performed in a subset of about 4 households in close proximity of the field as an addition to protocol A. In addition, for 8 locations spray drift measurement and vapour drift measurements will be performed. Since this protocol is spray event based, no measurements will be performed during the off season.

In Table A3-2 the number of additional[3] samples per sampling technique and per year are presented.

Table A3-2: Number of additional samples per sampling technique and per year as part of protocol B

	Spray season 1 or 2 (7 days)		**Total**
Year	2015	2016	
Indoor air sampling	56	64	120
Personal air sampling (WP3B) (adult only)	70	78	148
Skin wipes (hands and face, adult and child) (WP3B)	112	128	240
Deposition sampling of garden	28	32	60
Spray drift sampling at various distances (8 locations)*	520-528	520-528	1040-1056
Vapour drift at various distances (8 locations)	36	36	72

*total nr of samples differ slightly for flower bulb or orchard

Protocol C
In protocol C spray experiments will be performed with the purpose of filling gaps in existing drift and evaporation models. Notably, at larger distances and higher receptor heights. The measurements will be performed in field simulations on orchard and flower/bulb locations. The spray drift experiments will be performed during a simulated spray application in dormant and full leaf orchard (side/upwards spray application) and either in bare soil or during the growing season of flowers/bulbs. Measurements will be done in 10 replications each. Next to this air sampling indoor and outdoor, deposition sampling, tracer sampling and will be performed Simultaneously mannequins (adult and child) will be equipped with personal air samplers and patches (proxy for dermal exposure) at various distances (3) downwind from the field. The vapor drift experiment will be performed following the second spray drift experiment for both locations.

In Table A3-3 the number of samples per sampling technique and per experiment are presented.

Table A3-3: number of samples per sampling technique and per experiment as part of Protocol C

	Orchard dormant	**Orchard full leaf**	**Flower/Bulb**
Year	**2015**	**2015**	**2015**
Spray drift sampling at various distances	2080	2080	2360
Air sampling indoor	14	14	14
Tracer sampling	On site analysis	On site analysis	
Personal air sampling pumps attached on mannequins*	240	240	240
Patches** placed on mannequins	240	240	240
Vapour drift at various distances	56	56	112

*4 adult and 4 child mannequins placed at 3 distances for 10 replicates = 240 samples
** 8 patches per mannequin which are analysed together per mannequin = 240 samples

[3] Additional to protocol A

Short description environmental measurement methods for Protocol A and B

Active air sampling methods

In general exposure to PPPs via inhalation is considered to be an important route of exposure. Depending on for instance the circumstances and the expected concentrations, either high volume samplers (flow 100-1000 L/min, ng/m^3 range or less, sampling over 1 to 24 hours or more), medium-to-low volume samplers (flow 10-30 L/min, ng/m^3 to µg/m^3 range, sampling less than one hour to 12 hours or more) or low volume personal (flow 0.1-5 L/min, µg/m^3 to mg/m^3 range, sampling few minutes to 8 hours or more) will be used. Depending on the type of PPP one is interested in, and thus the active substance that is measured, particles, aerosols and gases phase are trapped onto (combinations of) filters (cellulose filter, glass fibre, Teflon, etc.), a polyurethane foam (PUF) plug, and/or adsorbent tubes (see for instance Armstrong et al., 2013). The type of PPP also determines the choice of the sampling head, for instance cyclones for respirable dust particles, IOM or GSP samplers for aerosols and inhalable dust, or GGPU samplers for measuring a combination of aerosols and gas.

Although little is known about the concentrations of active substances in various media (including air) after the application, these could be rather low (Duyzer et al., 2004A, Duyzer et al., 2004B). When monitoring personal exposure of residents, in general the use of personal air sampling devices is preferred, because this includes the optimal combination of the concentration in air (varying in space and time) and the location of a person. However, these are small devices with relatively small sampling volumes to limit the burden on the person wearing them. These may not be sufficient to sample a volume large enough to measure the expected (low) concentrations of the active ingredients outside and inside houses. To reach the expected necessary high sampling volume, stationary (static) sampling devices may be used, to measure PPP concentrations in the ng/m^3 range using filters or absorbents like XAD or Tenax (Duyzer and Vonk, 2004). In 2014 estimates of the expected outdoor and indoor (based on outdoor concentration and ventilation rate) concentrations will be made. The necessary sampling rates may vary from 1 l/min to 1 m^3/min, and this will influence the choice of sampling equipment. Currently it is expected that the following equipment will be necessary:

- Outdoor sampling: Personal samplers or medium-volume samplers (on the first day)
- Indoor sampling: Medium-volume or high-volume sampling

Especially the high sampling rates need rather bulky and noisy equipment and special care should be taken to avoid a large burden to the residents. A solution could be placement of noisy pumps outside the house or room or strong acoustic isolation. This has been done with success in classrooms (Duyzer et al, 2014).

Deposition sampling - outdoor

a. Related to spray event

The most commonly used monitors for deposition monitoring are α-cellulose filters and cotton gauzes, typically 10X10 cm in size, which are often referred to as deposition 'coupons'. These paper or cloth monitors are generally backed with backed with aluminium foil or placed in a petri dish to prevent 'break-through' or contamination from the surface. Inside homes also denim or other types or cotton cloth, filter paper, aluminium foil, gauze pads, carpet swatches, formica sheets, mylar sheets, petri dishes, metal, glass or porcelain dishes, and other collectors have been used, which may also be applicable for the outdoor environment (Lewis et al., 2005). Furthermore, the passive dust collectors as proposed to be used for indoor monitoring (see below) may be useful for

outdoor monitoring). Evaporative losses may be significant, especially in case of coupons made of non-adsorbent materials, even for PPPs with low vapour pressures. Therefore, coupons should be removed relatively short after the application, to prevent losses from evaporation. To prevent losses in transit to the laboratory, the coupons should if possible be places in a sealed vessel containing an appropriate solvent (e.g. the one used for extraction). Another option, but less effective, is to place the coupons in sealed containers and freeze them as soon as possible. Rigid, non-adsorbent deposition monitors should be wiped or rinsed in the field at the time of collection to recover the residues.

b. Related to long(er)-term deposition
Apart from the event-related deposition, a general idea of the contamination of the soil (turf) and vegetation in the gardens of homes is a valuable source of information with regard to residential exposure to PPPs. However, due to possible home use of PPPs and possible contamination due to previous agricultural spray events in the neighbourhood of the house (from either the same field or other fields) as well as the fact that it is not (practically) possible to clean for instance the grass before application, measures taken from soil and plants/grass are considered to be related to longer-term exposure, and thus not necessary directly related to an individual spray event. The lifetimes of PPP residues on soil/plants (turf) are generally short to those on indoor surfaces, since rainfall, sunlight, volatilization, erosion, microbial degradation and removal of grass clippings reduce or eliminate most residues in a matter of days or a week (Lewis et al., 2005). The determination of turf dislodgeable PPPs is important for both the assessment of potential chronic exposure, which may occur within a few hours or days after application, and for the estimation of the degree of transfer from lawn to home by 'track-in'. Several methods are available for measuring dislodgeable residues (PUF roller, drag sled, California roller, washing, wiping, vacuum techniques) are available (Lewis et al., 2005). Furthermore, at TNO considerable experience with measuring dislodgeable residue from leaves by washing is available, which is also applicable for instance grass clippings. During the preparation of the field study, the technique considered to be most practical and most useful with regard to the substances to be measured will be chosen.
Furthermore, soil samples could be taken. US EPA described two sampling techniques for the conduct of a soil residue dissipation study, namely 1) surface soil sampling where the top layer of the soil (i.e., 1 cm thick) is removed and retained for analysis, and 2) soil core sampling where samples are collected in 6-inch layers to depths that represent the exposure activity of concern (US EPA, 1998b). For most human activity patterns that are of concern, surface soil sampling is the recommended technique.
Furthermore, these dislodgeable residue and soil samples may also be used as a way for screening which PPPs occur around the house if these samples are to be screened for a broader range/spectrum of active substances from PPPs. Together with indoor surface wipe samples, this may give an idea of the overall exposure to PPPs of residents.

Indoor deposition sampling
a. Wipe sampling
Isopropanol is often used for wiping of pesticides (Deziel et al., 2011; Cohen Hubai et al., 2006) but the recovery can vary per substance. The choice of the wipe material can be based on prior experience with different types of commercially available materials or products (Deziel et al., 2011). Recovery testing could be studies in a laboratory setting by repeated testing of different solvents as wetting agents on standard surfaces spiked with the substance of interest (Deziel et al., 2011). For practical reasons hard surfaces are more likely providing reproducible results and often the standard surfaces consist e.g. of glass, metal, wood, and plastic. The technique of taking a wipe sample is often standardized to include moving a wetted tissue over a standard size surface in

two directions following an S-shaped wipe pattern. In the pre-study the possibility of taking the wipe samples by the study participants themselves (self-assessment) could be evaluated (Bradman and Wyatt, 2005). A kit and instructions for 'self-wiping' could be prepared and tested and compare to wipe sampling performed by research staff for collection efficiency, accuracy and precision. Collection of wipe samples will lead to recovery of deposits that may have accumulated over a long period of time (Bradman and Hyatt, 2006). If the primary interest is to recover surface contamination that recently occurred (e.g. related to a particulate spray event) it is useful to take repeated standardized wipe samples at two (or more) moments in time. A first wipe is likely to reflect long-term (historic) contamination, whereas the second wipe sample is more likely to reflect (recent) deposition that occurred in the period between de two wipe samples.

b. Settled dust plate collector
Two different kind of settled dust plates can be used:
1) an aluminium dust plate that can be wiped after a period of time and
2) a static dust sampler where the wipe can be directly analyzed.
Both deposition samplers can be left for 30 to 60 days in the home at a place where the surface will not be disturbed (e.g. the top of a shelf, top of a refrigerator, top of a dresser). The settled dust and static dust collector will be placed on a spot where it can stay for an undisturbed period of time and not in direct sunlight. Sampling time is variable but given the expected low concentrations a period of 3 months would be advisable. After the sampling period the wipes in the static dust sampler are removed and put into a pre-labelled amber jar and stored at -20C till analyses. The settled dust plate is wiped using both a dry wipe and 6ml of isopropanol. After wiping the artificial surface the wipe is stored in a pre-labelled amber jar and stored at -20C till analyses.

Protocol C
In protocol C spray experiments will be performed with the purpose of filling gaps in existing drift and evaporation models. The measurements will be performed in field simulations on orchard and flower/bulb locations.
In a separate series of spray drift field measurements spray drift deposition on soil surface and airborne spray drift is measured up to 250 m distance from the edge of the field. A comparison is made with exposure measurements of mannequins during application and vapour during and after treatment and volatilisation from the treated area after application. For comparative reasons measurements are done using a tracer.

Spray drift exposure during field applications using a boom sprayer (flower bulbs)
Spray drift measurements are performed in the field using a standard boom sprayer equipped with standard flat fan nozzles (XR11004 at 3 bar spray pressure; reference), and a 75% Drift Reducing Nozzle (nozzle to be determined e.g. ID12002 at 3 bar; new minimal requirements when spraying alongside a waterway) and a spray boom height of 50 cm spraying a bare soil surface and o cropped field (e.g. potato). The spray solution is tap water with a tracer added (Brilliant Sulpho Flavine, BSF) and standard surfactant to mimic a formulated product.
Collectors (Technofil TF-270) are placed on ground surface in double arrays to measure spray drift fallout on soil surface. Following ISO22866 and the CIW spray drift protocol collectors of 0.50 m length are placed on the first 10 m from the field edge and of 1 m length at 5 m intervals up to 250 m from the field edge (total 54 collectors). Airborne spray drift and the dilution with distance from the field edge are measured at vertical measuring poles placed at 5m, 10m, 15m, 25m, 35, 50, 100, 250m using passive collectors. At each measuring pole a double row of collectors (Siebauer Abtrifft Kollektoren) are positioned at

0,5 m intervals up till 6 m height (total 156 collectors). Airborne spray drift is also sampled using active sampling techniques by sucking air through a filter at 9 heights up to 6 m height placed at 3 distances: 5m, 15m en 50m (total 54 collectors). A comparison will be made with passive line collectors placed vertically at 0-1m and 1-2m height as used in UK spray drift experiments quantifying airborne bystander and resident exposure. Measurements will be done in 10 replications and can be done on throughout the year at bare soil surface and in during the growing season spraying a crop (June-September).

Spray drift exposure spraying an orchard
Spray drift measurements will be performed in the dormant (before 1st May) and the full leaf season using a stand cross-flow fan orchard sprayer equipped with standard hollow cone nozzles (Albuz ATR lila at 7 bar spray pressure; reference), and a 90% Drift Reducing Nozzle (e.g. TVI8001 at 7 bar; minimal requirement when spraying alongside a waterway). The spray solution is tap water with a tracer added (Brilliant Sulpho Flavine, BSF) and standard surfactant to mimic a formulated product. Collectors (Technofil TF-270) are placed on ground surface in double arrays to measure spray drift fallout on soil surface. Following ISO22866 and the CIW spray drift protocol collectors of 0.50 m length are placed at 1.5 m from the last tree row and at 3m – 15m from the last tree row and of 1 m length at 5 m intervals from 20 m up to 250 m (total 64 collectors). Airborne spray drift and the dilution with distance from the last tree row are measured at vertical measuring poles placed at 7,5m, 15m, 25m, 35, 50, 100, 250m using passive collectors. At each measuring pole a double row of collectors (Siebauer Abtrifft Kollektoren) are positioned at 0,5 m intervals up till 10 m height (total 210 collectors). Airborne spray drift is also sampled using active sampling techniques by sucking air through a filter at 9 heights up to 6 m height placed at 3 distances: 5m, 15m, 50, 100, 250m (total 54 collectors). A comparison will be made with passive line collectors placed vertically at 0-1m and 1-2m height as used in UK spray drift experiments quantifying airborne bystander and resident exposure. Measurements will be done in 10 replications and can be done during the year in the period march – November (dormant tree March-April/November and full leaf May-October)

Annex 4: (WP3b) Personal monitoring

This annex describes technical details related to personal monitoring of exposure to pesticides. Number of to be collected samples is given in Table A3.1 and A3.2 above.

Choice of biological medium
Urine is the preferred medium because most pesticides are readily excreted as metabolites. For some pesticides it may be possible to analyse the parent substance as well. Urine reflects recent exposure due to the relative short elimination half-lives of most pesticides. Blood will not be used as an alternative because it would require venipuncture which is considered too invasive as method of collection.
Collection of urine samples
In protocol A small aliquots of first morning void urine samples will be collected according to standard procedures. Urine from young children will be collected using a sample bag or an absorption plug that can be placed in the diaper. All collection materials will be tested for potential contaminants or other factors that may interfere with the method of analysis. Depending on the chemical stability of the biomarker of interest a preservative may be added.
In protocol B participants will be asked to collect an uninterrupted sequence of urine samples from the start of the spay event until and including the following morning void. In young children only a limited number of spot urine samples will be collected in the same period (depending on the method of collection in the diaper).
Potential contribution from diet
For some pesticides it is likely that residues of active ingredients and their degradation products on certain food items may contribute to overall exposure. Such cases can be identified by combining preliminary exposure modelling with calculations of dietary uptake using measured residues in The Netherlands. Based on these preliminary calculations scenarios may be identified where oral uptake from diet may potentially mask uptake from other sources and routes relevant to pesticide applications near homes. In such identified scenarios some additional laboratory-based experimental work and modelling may be required to determine relationships between oral uptake from diet and quantities of urinary eliminated metabolites over time in humans or can be extrapolated from published animal data. This includes an assessment of the contribution of the first pass effect in oral uptake compared to potential uptake of the same substance following inhalation and dermal exposure. In this first pass effect the parent substance is absorbed from the gastrointestinal tract and is metabolized in the liver before entering blood circulation or being eliminated in feces/urine. If a pesticide is taken up by inhalation or dermal absorption the parent substance may reach target organs, before being metabolized in liver or other organs. So, uptake route may influence both parent to metabolite ratios and also the pattern of time-resolved elimination of urinary biomarkers.
In the field phase of the study detailed information on food-intake is collected. This allows broad correction of urinary PPPs measurements for food items.
Personal air sampling
Pesticides and their degradation products can appear in the gas-phase, semi volatile and solid phase. For targeted gas phase sampling a single adsorbent material such as activated coal, TENAX, XAD or silica gel can be selected to capture the substance of interest. Font and back-up sections can be applied to monitor potential losses. If collection of multiple substances is required different adsorbent materials can be combined in multi-bed tubes. If substances of interest would appear in both gas and solid phase (e.g. semi-volatile substances) different media may have to be combined (e.g. filter and adsorbent

materials combined). Proven solutions for environmental sampling will be adapted for use in those small probes that can be worn in the breathing zone. If possible methods will be kept similar to the indoor and outdoor measurements as to aid in the comparison of measurements.

Skin wipes

The preferred liquid for collection of skin wipes is aqua pure. If the water solubility would be insufficient isopropyl alcohol or another low-toxicity alternative solvent will be considered. The liquids and the wipe materials will be tested for contamination and/or potential interference with the method of analysis.

Annex 4. (WP4) Chemical analysis of active ingredients and metabolites

This annex provides more detailed information on the chemical analysis of PPPs active ingredients and, where relevant, their degradation products and metabolites.
The study involves analysis of thousands of samples of various matrices. The analysis results will provide direct information on local occurrence and personal exposure, and are essential input for modelling purposes (WP5). The data should be reliable in terms of PPP/metabolite identification and quantification. The method limits of detection/quantification (LOD/LOQ) should be sufficiently low to either detect background PPPs levels, or such that levels below the LOD would be insignificant compared to intake through food, or toxicologically irrelevant.
In the majority of the samples, multiple PPPs need to be measured. For the study, at least 10 prioritized PPPs have to be covered and the simultaneous determination of additional PPPs commonly used in the Netherlands is considered an asset. In case environmental degradation products are the same as urinary metabolites, they need to be included in the scope of the methods for the environmental samples. The use of multi-PPP methods wherever possible is essential because the need for multiple methods for analysis of the same sample to cover the required PPPs will result in unacceptably high workload and costs.

To meet the analytical demands, the use of state-of-the-art instrumentation is essential. This means we will use latest-generation liquid chromatography with tandem mass spectrometry (LC-MS/MS) and gas chromatography with tandem mass spectrometry (GC-MS/MS) for targeted measurement and ultimate sensitivity, and full scan high resolution mass spectrometry for non-targeted measurements. Within the consortium, such equipment is available in several laboratories, and includes 5500/6500 Qtrap (AB Sciex), Xevo TQ-S (Waters), Q-Orbitrap (Q-Exactive), and GC-MS/MS with EI, CI and APCI ionisation. The laboratories of the consortium partners together have extensive experience in PPP residue analysis and the various matrices.
For many PPP/matrix combinations, e.g. a range of PPPs in air, soil, plant materials, methods are already available. However, it is foreseen that, depending on the finally selected set of prioritized PPPs, method development will be required in certain cases and in particular for urine analysis. In other cases, method modifications will be required to fulfill the specific requirements of the main field study. In general, to improve analytical performance, suitable internal standards, preferably isotopically labelled analogues of the target analytes, will be used and added to the sample (or in case of air analysis to the filter/tube before sampling) or extract. In LC-MS/MS and GC-MS/MS, matrix induced response suppression or enhancement will be addressed by using the appropriate calibration procedures if no isotopic label is available (matrix-matched calibration, standard addition).
Once the final methods have been established, they will be (re)validated for each PPP/matrix combination in case of modified or newly developed methods to demonstrate adequate performance. Validation will be done using guidance documents that have been established specifically for the determination of PPPs [SANCO/825, OECD 2007, SANCO/12571/2013] because these documents are being used and accepted by regulatory bodies and the agrochemical industry in their studies in the frame of registration of PPPs. An initial full validation of a method covering a certain PPP/matrix typically involves the analysis of two control samples, five replicates at the anticipated LOQ, and five replicates at a second (higher) level. The requirements for trueness, measured as recoveries of

spikes to control samples, and precision (relative standard deviation of the recovery at each spike level) should fall in the range 70-120% and ≤20%, respectively. Reproducibility, robustness and measurement uncertainty will be derived from QC samples included in each batch of study samples.

Sample analysis: air and contact materials

Air analysis

Air will be actively sampled using filters/adsorption tubes on which PPPs are trapped. For outdoor-, indoor- and personal samplers, different types of devices will be used, which differ in sampling speed (0.2 to 100 L/min) and total air volume sampled (ranging from 1-1000 m3). Depending on the device, particles and aerosols are trapped on a glass or quartz filter and analytes in gas phase are trapped on a suitable adsorption material (typically a polyurethane foam (PUF) and/or a styrene/divinylbenzene polymeric adsorbent (XAD)). Filter and adsorption materials are separately desorbed by a suitable extraction solvent using either hot soxhlet or pressurized liquid extraction, or cold ultrasonic extraction, depending on the target analyte. Extracts are concentrated and analysed by LC-MS/MS and/or GC-MS/MS. The LOQs of the analytes in the final extract are typically in the 1-20 ng/mL range which corresponds to 0.001 ng – 20 ng/m3 depending on the volume sampled.
Since sampling is an inherent part of the air analysis, it is included in the validation. To this end, the analytes are spiked to the sampler and air is sampled under realistic worse case conditions. The different sections of the tube are then desorbed and the total recovery and its repeatability determined. This procedure covers breakthrough, stability during sampling, desorption and instrumental analyses.

Plant material and soil

To preserve sample integrity, samples will be either transported to the analytical laboratory within 24 hours, or otherwise stored at -18°C. For soil, combined top-layer samples will be thoroughly mixed. For plant material (leaves, grass, home-grown fruits/vegetables), an aggregate sample of at least 0.5 kg (preferably 1 kg) of fresh material will be homogenised. Sub portions of the homogenized samples will be stored at -18°C until analysis. Under these conditions the majority of the active ingredients are known to be stable. Most active ingredients can be efficiently extracted using acetonitrile-based extraction ('QuEChERS'). Cleanup is by salt-induced phase partitioning and optional dispersive solid phase extraction after which the extract is analysed by chromatography with tandem mass spectrometry. With these methods, LOQs of 10 µg/kg are typically obtained. For most active ingredients validated methods are already available, but if not, or if lower LOQs are required, a (re)validation has to be performed by spiking the active ingredient to the homogenised sample material.

Dust

Household dust is a complex mixture of a.o. textile fibres, paper fibres, minerals from outdoor soil, plant pollen, human and animal hairs, human skin cells. Extraction will be done using a suitable extraction solvent by either hot soxhlet or pressurized liquid extraction, or ultrasonic extraction/shaking. The appropriate extraction method as well as the need for cleanup still needs to be established. During the validation, also the sampling procedure has to be addressed. This will be done by spiking of dust and sampling according to the protocol (either passive for a long time, e.g. three months, or active for a shorter time). Then the dust will be analysed and the recovery and repeatability will be determined. This way, the procedure assesses any losses/degradation during sampling, extraction efficiency from dust and instrumental analysis.

Surface and skin wipes

Here PPPs deposited on a surface, either plastic/metal/wood/glass or skin, are quantitatively removed by a suitable tissue (wipe). Either the surface or the wipe is wetted with a suitable solvent and then the surface is wiped repeatedly according to a described procedure to transfer the PPP from the surface onto/into the wipe. For skin wipes, the freedom in selection of wetting agents is limited given the toxicity of many organic solvents. Water modified with ethanol or isopropylalcohol have to be used in this case which may be less effective for removal of the active ingredients from the skin. After sampling, the wipe material is extracted using a suitable solvent by either ultrasonication or mechanical shaking. Following concentration and optional cleanup, the extract will be analysed by chromatography with tandem mass spectrometry. The method(s) will be validated by spiking the surface with the anticipated relevant amount of PPP, distributed on the surface area to be sampled. In case of skin, a surrogate surface may have to be used, depending on acceptability of application of active ingredient to skin of human volunteers. Since there may be a considerable time between sampling and extraction/analysis, the storage stability of the active ingredients in the wetted wipe material needs to be examined.

Sample analysis, biomonitoring

Analysis of urinary biomarkers

The proposed analytical approach for biomonitoring analysis is schematically shown in Figure 1. For biomonitoring, urine will be the default matrix to be analysed. Assuming that analytical reference standards of the relevant urinary marker metabolites are available, the preferred method(s) for urine analysis are dedicated targeted determinations of the metabolite(s) and, if meaningful, also the unmetabolised (parent) PPP, based on LC-MS/MS. Depending on substance properties, multiple urinary metabolites could be detected in a single run, but given the limited availability of PPP metabolites, wide-scope quantitative methods will not be possible in case of urine analysis. When for a certain PPP no analytical reference standard is available for any of the expected metabolites, and they cannot be obtained from the agrochemical industry nor synthesized at reasonable expense, it is not possible to perform a quantitative targeted analysis. In such cases a non-targeted measurement (LC-full scan HRMS) will be used as an alternative approach to obtain information on exposure. This would support qualitative interpretation (the metabolite is detected or not) and also a semi-quantitative outcome that can be used to compare urinary metabolite levels on an individual or group level (as long as the same method is used). Non-target measurement could also be used to complement the targeted measurement in case the marker metabolite was not detected but other metabolites (for which no reference standard is available) might be present at higher levels.

For logistical reasons, it will be inevitable that residents store urine samples under cool/dark conditions for several days. After collection, samples will homogenized and subdivided in multiple portions (for target/non-target measurements, creatinine/specific gravity, archive sample). For each purpose appropriate additives are present in the tube or will be added to the tube to stabilize the target analytes (e.g. acidification). In addition, suitable internal standards, preferably isotopically labeled internal standards if available, will be added to the tube allowing to assess artifacts during storage, transport to the analytical laboratories and sample preparation/analysis.

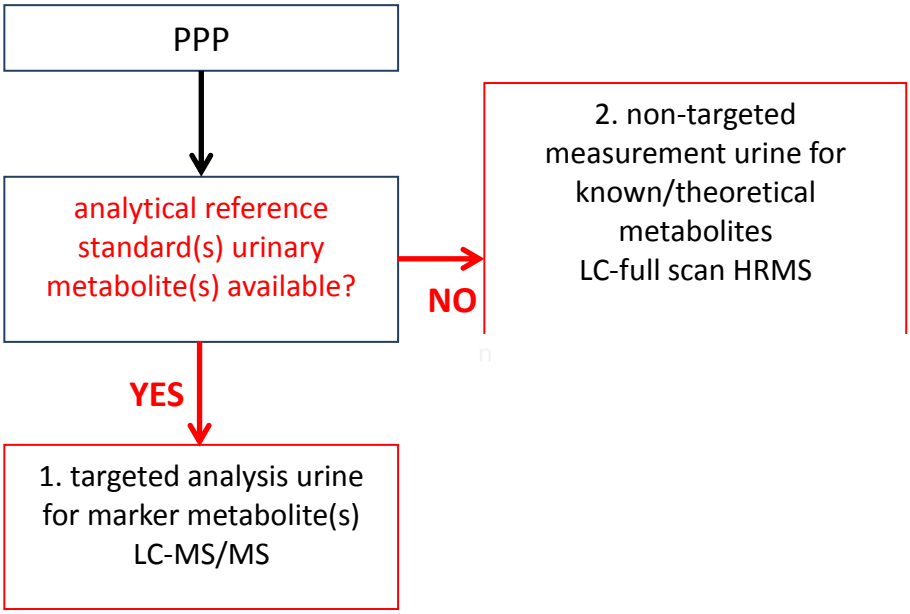


Figure 3. Analytical approach for biomonitoring in main exposure study.

Targeted analysis

Targeted analyses will include the relevant available metabolites and if meaningful the parent substance. The LOQs aimed for are in the sub/low µg/L range. Volumes of typically 1-5 mL will be analysed. In case urine is need to be retrieved from absorbent materials (e.g. in case of infants) the extraction of urine/target analytes from this material is part of the method. The analysis may involve an enzymatic or chemical deconjugation step. The sample is then typically cleaned using solid phase extraction (SPE) and subsequently analysed by chromatography with tandem mass spectrometry. It is anticipated that for a number of the 10 selected PPPs, existing methods need to be tested for applicability or need to be developed, and that in all cases validation will be required. For validation, urine samples will be spiked and analysed. Storage stability is an important aspect of the validation and will be examined under simulated field conditions.

Non-targeted urine analysis (PPP-metabolite profiling)

The effectiveness of a non-target approach to distinguish between exposed and non-exposed populations has recently been demonstrated by Jamin et al [2014]. Here, the urine is analyzed with no or minimal sample pre-treatment by liquid chromatography with full scan high resolution mass spectrometry (LC-HRMS). The metabolites known from literature and draft assessment reports available from EFSA, supplemented with theoretically derived phase I/II metabolites are then sought for in the full scan data through their exact mass.

References:

Appenzeller BMR, Tsatsakis AM (2012). Hair analysis for biomonitoring of environmental and occupational exposure to organic pollutants: State of the art, critical review and future needs. Toxicology Letters 210:119–140.

Clifton MS, Wargo JP, Weathers WS, Colón M, Bennett DH, Tulve NS. Quantitative analysis of organophosphate and pyrethroid insecticides, pyrethroid transformation products, polybrominated diphenyl ethers and bisphenol A in residential surface wipe samples. J Chromatogr A. 2013 Jan 18;1273:1-11. doi: 10.1016/j.chroma.2012.11.003. Epub 2012.

Cooper GAA, Kronstrand R, Kintz P (2012). Society of Hair Testing guidelines for drug testing in hair. Forensic Science International 218:20–24.

Deziel NC, Viet SM, Rogers JW, Camann DE, Marker DA, Heikkinen MS, Yau AY, Stout DM 2nd, Dellarco M. Comparison of wipe materials and wetting agents for pesticide residue collection from hard surfaces. Sci Total Environ. 2011 Sep 15;409(20):4442-8. doi: 10.1016/j.scitotenv.2011.07.002. Epub 2011 Aug 3.

Duca RC, Hardy E, Salquèbre G, Appenzeller BMR (2014). Hair decontamination procedure prior to multi-class pesticide analysis. Drug Test. Analysis 6:55–66.

Egeghy PP, Cohen Hubal EA, Tulve NS, Melnyk LJ, Morgan MK, Fortmann RC, Sheldon LS (2011). Review of Pesticide Urinary Biomarker Measurements from Selected US EPA Children's Observational Exposure Studies. Int. J. Environ. Res. Public Health 8:1727-1754.

Fenske RA, Bradman A, Whyatt RM, Wolff MS, Barr DB. Lessons learned for the assessment of children's pesticide exposure: critical sampling and analytical issues for future studies. Environ Health Perspect. 2005 Oct;113(10):1455-62.

Garcia-Jaresa C, Regueiroa J, Barrob R, Dagnacc T, Llomparta M (2009). Analysis of industrial contaminants in indoor air. Part 2. Emergent contaminants and pesticides. Journal of Chromatography A, 1216:567–597.

Sobus JR, Morgan MK, Pleil JD, Barr DB (2010). Biomonitoring: uses and considerations for assessing non-occupational human exposure to pesticides. Hayes' Handbook of pesticide toxicology, Krieger R (Ed.), Elsevier Ltd., Oxford, UK, Chapter 45:1021-1036.

Van Emona JM, Chuang JC (2012). Development of a simultaneous extraction and cleanup method for pyrethroid pesticides from indoor house dust samples. Analytica Chimica Acta 745:38–44.

Annex 5 (WP5) Integrated exposure modeling framework

5.1. Design and Methods

5.1.1. Aim and objectives

Work Package 5 (WP5), 'integrated exposure assessment', is called "integrated", because it is intended to combine and connect the exposure information collected within WP3 (see Figure 1; main proposal) with existing exposure models. Only a limited number of PPPs and their exposure levels in the environment and in humans can be included in the main monitoring study. Therefore it is important to be able to extrapolate the results from the main study to other areas with similar PPPs use, and to the use of other PPPs to ultimately estimate the exposure of residents to PPPs in the Netherlands. For this purpose, currently available exposure models will be updated, tested and integrated into a model framework consisting out of a chain of optimized models.

The aims of work package 5 (WP5) are to:

- Combine information on existing models of dispersion of PPPs, with data collected in WP3 regarding outdoor and indoor air concentrations, contact surfaces, personal exposure (dermal, air, biological) as well as contextual information, in order to
- Develop an integrated exposure framework that allows the estimation of population exposure to PPPs.

As a preparation of the work in WP5, within 2014, three steps will be performed:

1. Screening of existing deterministic exposure models regarding their utility in the planned study.
2. Assess what input information, to be collected in WP3, is required for the selected models.
3. Assess which output is needed from the different models especially with regard to the temporal resolution (hourly, yearly), spatial resolution, and exposure distributions (median, percentiles).

The specific work steps of WP5 within the actual project (2015 – 2017) include:

4. Apply (selected) deterministic exposure models to estimate spray drift, evaporation and deposition of PPPs.
5. Test existing deterministic exposure models using the measured outdoor concentrations, indoor concentrations and PPP concentration on contact surfaces.
6. Estimate personal exposure from outdoor and indoor concentrations and from contact surfaces, allowing for contextual information such as behavioural and time-allocation information of the participants.
7. Develop and validate statistical land use regression models to estimate personal exposure using application information on PPPs and contextual information.
8. Optimize the developed model by integrating statistical and deterministic models.

9. Estimate population exposure levels to PPPs using the integral model framework.

The sections below explain all of these work steps in more detail.

Preparation work for WP5:

5.1.2. Screening of existing deterministic exposure models regarding their utility in the planned study

Several deterministic models exist and these have to be reviewed regarding their utility for the planned study. For example, models include, among others:

a) Gaussian plume models. "Pluim plus", is a model based on the Gaussian plume principle and equivalent to the "Nieuw Nationaal Model". The model can be used to calculate hourly outdoor PPP concentrations and the related distribution of PPPs.

b) Ventilation models. Two ventilation models are available that calculate exchange between outdoor and indoor concentrations of PPPs: COMIS and gComis. The ventilation model gComis is a so-called zone model that uses air flow based on building characteristics to estimate indoor concentrations of PPPs based on outdoor concentrations.

c) For complex outdoor situations with, for example, hedges or other obstacles, modelling environments such as the CFD package FLUENT are available. Fluent can take the influence of such obstacles into account to calculate dispersion of PPPs. This model will likely be applicable for the development of experiments (protocol C) as well as for the correct interpretation of observations in complex environments.

d) Regional-scale weather models coupled to a dispersion module. An example is RAMS-HYPACT, which uses the output from large-scale weather models to derive regional dispersion patterns at the scale of cities to countries. The RAMS-HYPACT system can be connected to a detailed land-use map of the Netherlands, allowing a realistic estimate of PPP source distributions over the country. Such a system may therefore provide an internally consistent extrapolation tool.

e) Larger-area based models exist, for example EUROS LOTOS, which can calculate European background levels of PPPs. This can be important, given that in many areas, longer-duration exposure is driven primarily by background concentrations.

f) IDEFICS is a mixed 2-3-dimensional physical model for spray applications with boom sprayers that describes the trajectories of drops successively by combining deterministic models for the motions of droplets combined with statistical variations of air turbulence. The basic results of the model consist of deposits on the crop, on the ground downwind to the crop, and the vertical distribution of airborne spray and vapour at a fixed position downwind

g) BREAM model is a computational model for spray applications with boom sprayers, developed for the UK, to predict the potential exposure to pesticides for bystanders and residents in the countryside that can be used as a tool in risk assessments. It models three main routes of exposure for residents and bystanders being droplets and vapors released at the time of a pesticide application; vapors emitted from a treated area post a pesticide application; and
dusts contaminated with pesticide that may be emitted from treated cropped areas particularly during harvesting operations.

h) PEARL-OPS. OPS is a dispersion model used in national reports on air quality and resembling the "Nieuw Nationaal Model" in its original version. A special version, OPS-St, has been developed to compute dispersion and deposition at relatively short distances, and for emission from surface sources, like fields treated with PPP. Recently, OPS-St has been extended with special modules to compute deposition of pesticides and exposure of bystanders, workers and residents. It has been coupled to the PEARL model, that describes, amongst many other things, emission of PPPs to air after application. The PEARL emission estimates are based upon a description of processes taking place in soil and vegetation, using information on soil, the properties of crops, and physico-chemical properties of the PPPs. PEARL-OPS is part of the BROWSE-model, as described below.

i) BROWSE-model. BROWSE is an abbreviation for Bystanders, Residents, Operators and Workers Exposure models for plant protection products. The main project goal of BROWSE is to develop a (set of) model(s) to predict inhalation as well as dermal and ingestion exposure of Bystanders, Residents, Operators and Workers to plant protection products, and to incorporate these models into a software tool that can be used to contribute to the implementation of Regulation.

j) For fruit crops spray applications not deterministic models are available. Some empirical models and calculators are available for spray drift deposition on soil surface and airborne spray drift with distance downwind of the treated orchard.

During the preparation phase an inventory will be made of the availability of the models, their strength and weakness and for the respective selected model, the input and output characteristics of the models, and the feasibility to collect all necessary data in the planned field study.

Results of this work step will be an inventory of applicable and available deterministic and empirical models, their data needs and outputs, that can be used to model drift, evaporation and deposition of PPPs. In addition, gaps in the model framework from field application to personal exposure of residents will be identified.

5.1.3. Assess what input information is needed for selected models, which need to be collected in WP3.

In order for contextual and other pertinent information to be collected in WP3, a complete list of what is necessary will have to be developed beforehand. This list

will include information on the PPPs chemical characteristics, spraying techniques, meteorological conditions, building characteristics, behavioural information as well as time-activity information of the study participants.

Results of this work step will be a list of contextual information that needs to be collected during the field phase in WP3.

Work to be performed in WP5 during the main phase of the project:

5.1.4. Use (selected) deterministic exposure models to estimate drift, evaporation and deposition of PPPs.

The existing (and selected, see work step above) deterministic and empirical models exposure models will be applied. In particular, this means that for all PPPs that are included in WP3 and for all places of residence that are included in the measurement campaign, the models will be used to calculate drift, evaporation and deposition of these particular PPPs in these particular places. Observations at the sites, notably from protocol B and C, will be used to test the models. The model exercises support interpretation of the exposure measurements.

Results of this work step will be the output of the deterministic exposure models – i.e. modelled exposure for the selected PPPs included in WP3 for the places of residence included in the measurement study.

5.1.5. Validate existing deterministic exposure models using the measurement data of outdoor concentrations, indoor concentrations and surfaces.

During the measurement campaign, it is planned to collect data on about 400 participants (protocol A) and, additionally, on a subset of the participants during spray-event-related extended measurements (protocol B). This data set will be rich in terms of size and variation of expected exposures towards PPPs that will allow us to explore factors that influence exposure levels. However, it is expected that many of the measurements will be below the limit of detection (LOD). For this case, we will need to use statistical methods that can handle left-truncation of measurement data. In particular, we will explore several statistical techniques, such as Robust regression on Ordered Statistics, Maximum Likelihood based conditional imputation, and in the case of regression analyses, Tobit regression to allow for mixtures of exposure distributions and dependence between certain sets of measurements.

The measurement data set will be used to validate the output of the deterministic models (i.e. compared with 'truth'). Deterministic models are based on physical laws. These models may need calibration (i.e. adapted based on measurements), but should be generalizable to other situations. Subsequently, performance indicators such as spearman rank correlation and kappa coefficients between modelled and observed exposures can be calculated to estimate the models' ability to correctly estimate exposure of participants. Next, to also evaluate the quantitative (absolute) ability of the models' exposure level predictions, we will calculate indicators such as Bland-Altman plots, and

percentage correctly modelled within a factor of 2 and 4. These performance indicators will be calculated for outdoor and indoor concentration models, as well as for models predicting surface concentrations of PPPs. Identification of situations where the model does not perform will facilitate further development on these models.

Results of this work step will be a set of data that does take account of the result of measurements below the limit of detection, validation of the pre-selected deterministic exposure models in combination with performance indicators in how far the models are able to predict absolute or relative levels of exposure as measured in WP3A (external environmental monitoring). Identification of situations where the models do not predict well will facilitate further optimizations of the models.

5.1.6. Calculate personal exposure from indoor and outdoor exposures in combination with contextual information such as behavioural and time-allocation information of the participants.

Transfer functions will be developed that allow calculation of personal (internal) exposure levels as measured in WP3B (internal monitoring) from external exposure levels (outdoor, indoor and contact surface concentrations). From the excretion of metabolites the integrated uptake over time and over different routes of uptake will be estimated. The use of full parameterized physiology-based pharmacokinetic (PBPK) models is preferred. In the (likely) case these models are not available a simpler generic PBPK or toxicokinetic (TK) model will be used. For the derivation of transfer functions, contextual information such as distance to a field, meteorological conditions, behavioural information and time-allocation information will be taken into account. Since the transfer functions will be based on statistical calculations, we will use *k*-fold cross validation (n=5 or 10) to estimate model performance. In *k*-fold cross-validation, the original sample is randomly partitioned into *k* equal size subsamples. Of the *k* subsamples, a single subsample is retained as the validation data for testing the model, and the remaining $k - 1$ subsamples are used as training data.

Results of this work step will be a set of validated transfer functions to derive internal exposure values from external concentration values.

5.1.7. Develop and validate statistical models of personal exposure using application information on PPPs and contextual information.

In addition to applying deterministic exposure models as a step to calculate external exposures (see steps outlined above), we will additionally apply statistical modelling of personal exposure. Statistical (empirical) models have shown for other environmental exposures to have complementary properties to deterministic models especially for smaller geographical areas. Similar approaches have been used for a long time in air pollution research, where both deterministic dispersion modelling, as well as land-use-regression modelling as a statistical means to derive exposure estimates have been applied. For air pollution, land-use regression utilizes the monitored levels of the pollutant of interest as the dependent variable and variables such as traffic, topography, and other geographic variables as the independent variables in a multivariate

regression model (Ryan et al 2007). In a similar way, multivariate regression models could also be used to model the exposure to PPPs. As outlined above, we will split the data set into a development and a validation data set in order to be able to obtain valid exposure models. We will again calculate performance indicators.
Both types of models, deterministic or statistical will be evaluated and their performance assessed and compared. Strengths of both models will be combined with the aim to develop an exposure assessment framework with the possibility to estimate exposure under current conditions as well as extrapolation to other (unmeasured) conditions (see 1.1.8).

This work step will result in performance indicators of statistical models to predict internal exposure values from external concentration values.

5.1.8. Development of an Integral model framework.

In recent work on air pollution, the integration of deterministic and statistical models has been found to considerably improve models especially at the more local scale. We will employ a Bayesian Maximum Entropy (BME) model to formally combine results from the empirical and statistical models to predict exposure of residents to PPPs. The BME method provides a mathematically rigorous framework that integrates a variety of available knowledge bases (e.g., spatial dependency model, empirical relationships, scientific model, physical laws, and so forth) with data having varying levels of epistemic uncertainty. In the BME method, the data are categorized into two groups: (i) measurement data with relatively low uncertainties (Hard data); and (ii) soft data, having an uncertainty characterized by a probability density function (PDF) of any type (e.g., Gaussian, Uniform).

The result of this work step will be a "best integral model framework" to predict exposure to PPPs. This will be paramount to predict general population levels to PPPs as such (1.1.9).

5.1.9. Estimate population exposure levels to PPPs using the integral model.

Using the measurements, we will be able to summarise exposures to a list of selected PPPs of persons living in close proximity to agricultural land at selected locations. The derived models will enable us to extrapolate these results to:

a) Other locations with similar land use (e.g. crops) and PPPs use as covered under the measurement campaign.
b) To other PPPs and application methods which are not covered under the measurement campaign.

We will first extrapolate the obtained results on selected PPPs to other locations with similar crops and PPPs use to estimate the exposure to PPPs of the Dutch population. This is important, as the measured locations do not reflect the complete exposure distribution. Based on the derived models we will estimate exposures at different time-resolution (hourly, daily, yearly) and will estimate the median and percentiles (5, 25, 75, 95th) of the exposure distributions.

In a second step we will extend the modelling framework to estimate exposure levels to other PPPs (and crops) that were not covered explicitly under the

monitoring program. This will be done for the top 50 used PPPs in the Netherlands. This enables us to 'layer' the exposure distributions, which may indicate hotspots of PPPs exposures that are not evident from single PPPs modelling.

Results of this work step will be an estimation of population exposure levels to PPPs.

In summary, results of the WP5 activities include a selection of the best performing exposure model(s), which will be validated against measurements. Another expected result are validated transfer functions to calculate personal (internal) exposure from outdoor, indoor and surface (external) exposures, and an estimation on the influence of contextual information on exposure levels. Finally, WP5 will result in estimations of population exposure levels of PPPs.

5.2. Expected results and deliverables

As a preparation of WP5, expected results are to obtain:

- A list of applicable deterministic models for estimation of drift, evaporation and deposition of PPPs.
- A list of input information that is necessary for modelling and that needs to be fed into WP3 to be collected during the field work.
- A list of output parameters and metrics from the different models.

Within WP5, the expected results are to obtain:

- Validated deterministic as well as statistical models, validation will be performed with the measurement data collected in WP3.
- Performance indicators on which models are best suited to estimate exposure levels correctly.
- Estimation of PPPs' outdoor, indoor and surface concentrations using exposure models.
- Estimation of personal PPP exposure levels using the integrated exposure model framework.
- Extrapolation of population exposure levels to other areas and PPPs.

The following products will be delivered:

- A verified model framework (consisting out of a chain of models) that evaluates personal exposure to PPPs given a list of contextual information
- Tables and/or maps of exposure to PPPs in the Netherlands.
    - Maps will show the geographical distribution of exposure metrics across the country.
    - The tables and maps will show statistical numbers (means, percentiles) of exposure metrics. Results will be shown for relevant time scales (annual, peak etc.) and different spatial scales (distance to fields etc.)

The presentation and dissemination of the results will be discussed with WP6 members to ensure a balanced approach.

5.3. WP5 organisation

UU-IRAS has the lead on WP5. UU-IRAS will focus on the validation of the models, and the translation of the model outputs to personal exposure. Several research institutes play an important role in WP5. These are in particular the leaders of the other work packages: Radboud-umc, WUR-Alterra, WUR-PPO, WUR-PRI and TNO, and CML.

IRAS
- WP management
- Modeling outdoor to indoor concentrations of PPPs (collaboration with TNO)
- Modeling personal exposure from outdoor and indoor concentrations of PPPs (collaboration with TNO)
- Modeling personal external-internal exposures (collaboration with RU)
- Interpolation of results for measured compounds (collaboration all)
- Extrapolation of results to other cultivations / PPPs (collaboration all)

TNO
- Modeling outdoor to indoor concentrations of PPPs (collaboration with IRAS)
- Modeling personal exposure from outdoor and indoor concentrations of PPPs (collaboration with IRAS)
- Interpolation of results for measured compounds (collaboration all)
- Extrapolation of results to other cultivations / ppps (collaboration all)

WUR-Alterra
- Vapour, and evaporation modeling (WUR / Alterra)
- Interpolation of results for measured compounds (collaboration all)
- Extrapolation of results to other cultivations / PPPs (collaboration all)

WUR-PRI
- Spray drift modeling (WUR / PRI)
- Interpolation of results for measured compounds (collaboration all)
- Extrapolation of results to other cultivations / PPPs (collaboration all)

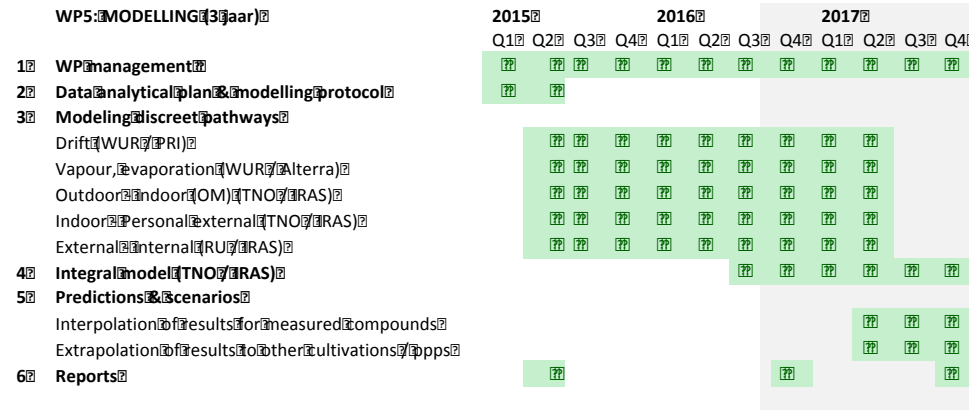
WUR-PPO
- Providing information on PPPs use and application techniques
- Interpolation of results for measured compounds (collaboration all)
- Extrapolation of results to other cultivations / PPPs (collaboration all)

CLM
- Providing information on PPPs use and application techniques
- Interpolation of results for measured compounds (collaboration all)
- Extrapolation of results to other cultivations / PPPs (collaboration all)

Radboud-UMC
- Modeling personal external-internal exposures (PBPK modeling; collaboration with IRAS)
- Interpolation of results for measured compounds (collaboration all)
- Extrapolation of results to other cultivations / PPPs (collaboration all)

5.4. Planning

The field study takes place in 2015 and 2016 with the majority of modelling activities taking place in 2017. In the table below a planning of activities is given.



5.5. Critical success factors and risks

5.5.1. Critical success factors

Deterministic and statistical exposure models

a) Availability

Risk:

- Risk are low as the research group is actively involved in the development of several of these models.

Approach:

- Consultation in- and outside the working group of experts

b) Validation

Risk:

- Measurement dataset is too limited to provide robust validation

Approach:

- Based on year 1 of the project we will have a better impression of the exposure distributions measured. Measurement protocol in year 2 will be adapted based on these results to render the most informative measurement set possible.

c) Performance of models

Risk:

- Model performance is inadequate for accurate estimation of PPPs exposures of residents

Approach:

- Existing models have shown utility in previous work to estimate environmental concentrations. As such the risk is deemed low. By establishing a suite of models and approaches the project is put in the best situation to avoid failure of models.

Integration of deterministic and statistical models

a) No "best model" selection possible

Risk:

- The joined models do not lead to significant improvements in predictive ability

Approach:

- Inter- and extrapolation of results will be done using the best available models

Extrapolation to other areas and PPPs

a) Models are not generalizable enough

Risk:

- Models may not cover all situations limiting extrapolation

Approach:

- Situations where the models perform outside their operational characteristics will be noted and reported as such.

5.5.2. Organizational and technological challenges

For WP5, a strong and large group of researchers from different organizations work together. This has the advantage that there is a lot of expertise available which can be combined. It also requires a clear and structured coordination and organization.

Risk:

- Several partners are responsible for discrete parts of the model development and for collecting the measurement data. This may lead to disjoint project deliverables.

Approach:

- An effective management structure and communication has been developed for the overall project. Frequent telephone conferences will be held to ensure that all partners are fully informed about each others' activities.

5.5.3. Expectations and communication

Risk:

- Maps may raise anxiety or concern in the population, e.g. if a person checks his or her place of residence regarding exposures and detects levels higher than background levels. This may be misunderstood as a potential risk to health, which is not what is evaluated in this project.

Approach:

- Results of this project require careful communication. As such a close collaboration with WP6 will be held to ensure effective communication of results to the different stakeholders.

Annex 6: (WP6) Communication

Effective communication is more than a simple one-way transfer of information. Communication needs to address public and stakeholders concerns and facilitate a productive and meaningful interaction between actors from different backgrounds and with diverging interests. Research has demonstrated that effective mutual communication is one of the key challenges in risk governance.

Effective communication is essential from the start till the end of this study: i.e. from recruitment of the study population till the framing of the message on the outcomes of the study. Effective communication means accommodating the communication to the information needs and the attitude of different stakeholders (residents, farmers/growers, civil society and policymakers). Managing the expectations on the outcomes of the study (e.g. measuring exposure to PPPs instead of measuring health risks of PPPs) will also be an important area of concern for the communication.

The communication is targeted at three groups of stakeholders:

- Primary stakeholders are residents and farmers/growers who are directly involved in the study;
- Secondary stakeholders are residents and farmers/growers in the Netherlands who are not actively involved in the study;
- Tertiary stakeholders are parties like (local/regional) governments and policy makers, Nefyto, NGOs, scientists, distributors of PPPs (like members of Agrodis) and their specialists advising growers, sector organisations like NFO and KAVB, etc.

To successfully communicate about the research and its results to these stakeholders, specific knowledge is indispensable. We therefore define a twofold aim in our communication strategy:

- The communication on the study and its outcomes is accommodated to the knowledge, attitude and expectations of the primary, secondary and tertiary stakeholders.
- Consensus and clear agreements on the implementation of the communication strategy of all parties in the consortium of this study. All partners need to abide to the agreed key message, use the same terminology and commit themselves to the planning and coordination of the external communication.

The activities in WP6 and methods used are indicated below:

Activity
1. Stakeholder analysis Quick scan among RIVM advisory group (klankbordgroep) based on which we make a first global overview of stakeholders relevant for this theme, leading to recommendations for a communication strategy to approach stakeholders. **Method** In-depth interviews with a selection of tertiary stakeholders (n = 6)
2. Field research Research on knowledge, attitude, behaviour, information needs, risk perception, used terminology by primary and secondary stakeholders. **Method** In-depth interviews with 15 primary stakeholders (6 farmers and 9 residents) and 9 secondary stakeholders. 24 interviews in total Internet / social media scan focusing on residents to see with whom they get into contact and what terminology they use.
3. Recommendations for communication strategy and commitment of consortium parties Review of the results from part 1 and 2, to develop recommendations for an effective communication strategy, focused on primary, secondary and tertiary stakeholders.
Research phase of the exposure study (2015-2016)
4. Monitoring the implementation of the communication strategy Monitoring the implementation of the communication During the entire research phase: • Editing of general information to particpants and farmers • Three monthly strategic analysis of media monitoring (monitoring data delivered by RIVM). • Half yearly monitoring communication strategy
Analysis and results phase (2017)
5. Quick scan among stakeholders Short research focusing on experiences with communication about the research project among 12 stakeholders (primary, secondary and tertiary stakeholders)
6. Recommendations for communication strategy analysis and results phase Bundling the results from part 5 to come to recommendations for an effective communication strategy on *results of the research project*, focused on primary, secondary and tertiary stakeholders.
7. Mediamonitoring results research project Three monthly strategic analysis of media monitoring (monitoring data delivered by RIVM) on results of the research project, during 2017.

Annex 7: (WP7) Preparation, organization and execution of the field study

7.1. Design and Methods

7.1.1. Aim and objectives

Aim of this project work package is to provide efficient coordination of all the practical fieldwork of the project as summarised in protocol A and B in the full proposal, well-tuned field activities and logistics and ethically acceptable involvement (psychological and physical load) of participants (local residents and farmers). This must lead to motivation and consent of participants during the whole study, feasible research and trustworthy results.

The objectives of WP7 are to:
- Prepare the review of the fieldwork protocol by the Medical Research Ethics Committee (METC)
- Prepare and execute the recruitment of participants (local residents and farmers)
- Coordinate and organize the fieldwork.

A distinction is made between the following components:
10. Preparation of the recruitment
11. Monitoring protocol and establishment of the fieldwork research team
12. Review by the METC
13. Recruitment of participants
14. Coordination and execution of the fieldwork
15. Evaluation
16. Completion of measurement process

The paragraphs below explain these components in more detail.

7.1.2. Preparation of the recruitment

Most of the preparations of the recruitment of participants take place in 2014. In this paragraph a complete overview of preparation activities is given, in order to make the actions for 2015 understandable and logic.

Participants of the field study will be local residents, growers/contractors and their family members. Growers are often the users of PPPs. However, in some cases, they and their family members can be classified as local residents.

a. Selection of potential participants

The target group for the study and desired characteristics will be defined in other parts of the research (WP3). Based on the selection of crops, active substances and locations (described in WP2) the potential participants will be determined. The final choice of locations depends on whether suitable participants can be found at the locations.

This activity takes place in 2014 and will be repeated in the end of 2015, to prepare the recruitment of additional participants for the field research of 2016.

Result is a list of addresses of farmers and residents that can be recruited.

b. Alignment and design of screening questionnaire, draft agreements and informed consent

Screening questionnaire
The questionnaire will be prepared jointly by the WPs and includes questions concerning the personal details of participants. The questions regarding residents are about e.g. age, gender, weight, lifestyle (e.g. leisure activities), occupational and para-occupational exposure to PPPs (exposure via, for example, family members, who work with PPPs and live in the same home) and PPP usage within the home. Farmers will be asked about e.g. landownership and possible relation with (sub)tenants, who applies the PPPs (grower himself, contractor, employee, temporary employee), how availability and quality of data about PPP application is, crops and application techniques.
The questionnaire also contains questions about contact and type of communication between grower and local residents, history (media attention, politics), stakeholders involved (such as the district health service (GGD), Netherlands Food and Consumer Product Safety Authority (NVWA), Agricultural-Horticultural Organisations (LTO), residents' groups, NGOs and political parties) and the way in which residents are organised (possibly affiliated with a group that represents them). This information will be used in WP6, in order to develop an effective communication strategy.

Draft agreements with participants
It is necessary that participants have a clear understanding of:
- The aim of the research
- Methodology
- Everything that we will ask of the participants. This follows from the monitoring protocol.
- Feedback of results, including method and frequency of feedback
- Financial reimbursement
- Confidentiality
- Communication
- Contact persons

The agreements will be formulated in a language the different participants (young and adult residents, farmers/contractors) can understand. This is also an important element in the METC protocol. For each target group, it is important to determine how they can be motivated to participate in the study and how it can be ensured that they remain motivated to continue participating according to the protocol. In cadre 1 an example is given of the way compensation took place in the UK research.

Draft agreements will be formulated in 2014. These will be determined definitive after the final decisions on the monitoring protocol.

Informed consent
Important elements of the informed consent are that the participants have had the possibility to ask questions and they received an explanation about situations of withdrawal from the research without notifying the reason. It should also refer to the representation of young participants by their parents or guardians and children upward of 12 years old should also give accordance of participation themself.

In the form, farmers will be asked to confirm that they are willing to provide the study team with information concerning their PPP usage.

In 2014 a draft version will be made, to be determined definitive in 2015.

Results of these activities are three documents (screening questionnaire, draft agreements and informed consent). Where needed these are tailored per target and age group. Draft versions made in 2014, will be determined definitive in 2015, after the review by the METC and after being checked by the communication experts (on language, recognisability, use of logo, etc).

Cadre 1
Example of **compensation of participants** as used in the UK research (Galea et al, 2011)

Each individual resident participating in the study was compensated for their time incurred in completing the questionnaire and providing urine samples by offering them a gift voucher of their choice. A voucher of similar amount will be made available to the parents of the participating children. The value of the voucher is based on a rate of £5 for each questionnaire and urine sample provided

Farmers were compensated on a similar weekly rate for providing information about spraying events.

Participants were asked to sign a form acknowledging receipt of the compensation.

c. Develop recruitment text, materials and information for participants

Directly at the first contact, management of expectations is important. Besides the specific agreements about how the study will be conducted and the personal contact during visits of researchers, more general information can be used to explain about the background of the study. To this end, we will develop the following:

Material for the purpose of recruitment
- Recruitment letter for residents
- Telephone script for calling residents and farmers.

Information for participants
Contact person for participants is a researcher from the fieldwork research team. This person is in any case the first person to contact in case the participant has questions, concerns or remarks about the research.
Additionally, participants will be informed by:
- Participant's leaflet with information about the research (different versions for adults and children) and contact information
- Information desk where people can ask their questions about the research or report special circumstances by telephone
- Confidential and independent medical adviser (required by WMO / METC), not involved with the research, who can give information about the reliability of the researchers and the (human) safety of the research.

A point of attention here is not only to formulate the communicated message carefully, but also to consider who the messenger should be. Each member of the project team can elicit a different image from the various target groups. Here we will use the advice that results from the activities in the Communication work package.

Results of these activities are several recruitment and information texts and materials (recruitment letter, phone script, tailor made participant's leaflet, prepared confidential medical advisor and an information telephone desk standby as soon as the field work starts. Draft versions will be prepared in 2014 and determined definitive in early in 2015, after the review by the METC and advice from communication experts.

For the general public, including people in the immediate surroundings of participants information material will be developed by RIVM.

7.1.3. Monitoring protocol and establishment of the field work team

In the monitoring protocols of the different work packages (see chapters before) the following elements will be described in detail:

- What will be measured and where:
  - Monitoring of individuals, including biomonitoring
  - Indoor monitoring
  - Environmental monitoring (lawns, plants, public spaces, etc.)
- How will it be sampled: required apparatus, sample labelling, storage by the participants
- Numbers and frequencies (locations, individuals, measurements, etc.)
- Planning: time and duration of the measurement, in particular in relation to the spraying events
- Specific requirements for the measurement, prevention of cross-contamination
- Logistic apparatus and samples: transport, maximum time to pre-treatment and analysis
- Qualifications of those conducting the measurements
- Required mutual communication regarding coordination and particulars.

The measurements and samplings will mainly be carried out on the same time. This could cause some problems, e.g. in required personnel, psychological and physical load of the participants, logistics, etc. This project step will lead to alignment of sub-monitoring protocols and development of one overall and realistic monitoring scheme, a logistic plan and establishment of a field work team.

a. Monitoring protocol

An overall draft monitoring scheme for the fieldwork will be prepared during 2014. After final decisions on monitoring protocols and the review by the METC, the overall field study monitoring protocol will be determined definitive in 2015. Part of the overall protocol are also tools for collection of information on the behaviour, experiences and findings of the participants, like a diary.
At the end of 2015 it will be decided if changes are needed in the monitoring protocol of 2016. If required, the protocol will be adjusted.

b. Logistic plan

Based on the draft research protocols from the various work packages, a logistic plan for the field activities will be prepared in detail. Together with the WP-leaders we will define how the activities can be efficiently organized, who is responsible for what and what de costs are. The plan contains a.o.:

- When, where and what technical devices should be placed
- When samples and monitoring data should be collected.
- How and when transport is organized
- What the maximum time is, between sampling/monitoring and analysis.

The draft plan will be designed in 2014. Before we make the final version in 2015, it will be submitted for review to the WP-leaders and the resulting comments will be processed.

c. Fieldwork team

The fieldwork during the spraying season will be determined by the activities of the grower. During the spray season, the fieldwork team should be stand-by 7 days a week, to be able to quickly respond to spray events that are usually announced at short notice. In this way, a notification can be dealt with quickly and adequately, in cases where immediate measurements are required.

A notification can be for example that a farmer reports (phone, sms, email): "I planned to spray tomorrow morning at 6 o'clock" or "I checked my decision support system (e.g. prediction infection periods fungi related to weather information) and I have to spray within one hour".

The team should contain experts (medical trained people, agronomists) who should have experience in working with people who are concerned about their health, how they can deal with questions about the research and how to carry out the sampling following the protocol.
These researchers will frequently have contact with the participants, visit them to collect samples and to respond to questions. They also are attainable by email and phone.

Before the study begins the team will be trained in communication and all the measurement techniques that will be used. Quality monitoring will take place by means of frequent feedback to the WP-leaders and by oversight of WP1.
At the end of 2015 the approach and organization of the team will be evaluated. In the beginning of 2016 all the (eventually also new) activities will be aligned again conform the (adjusted) monitoring protocol and the requirements of new locations and/or crops.

Result of these activities is a broadly accepted and detailed monitoring protocol and a well elaborated logistic plan.

7.1.4. Review by the METC

Not just the details of the monitoring protocol, but also the recruitment method should beforehand be reviewed by the Medical Research Ethics Committee (METC). The METC reviews and judges if the medical-ethical scientific research involving human suspects is in line with the Medical Research Act (WMO).

The request for approval will be submitted in 2014. The expectation is that the review will not be finished until early February 2015.

At the start of the research a monitor will be appointed to safeguard the procedures during the whole project in accordance to the WMO and the Personal Data Protection Act (Wbp).

Result of this activity is approval by the METC.

7.1.5. Recruitment of participants

During recruitment of participants it is crucial that they clearly understand what the research will (not) bring them. It must be clear that the study will not answer the question of whether or not there is a health risk for the participating individuals. For example, certain substances (PPPs or the corresponding metabolites) could be detected in urine, while it is unknown whether this has health consequences for the participant. From the first contact, expectation management will be an important focus.

<u>How</u>
Potential participants from the various target groups will be approached as follows:
- Letter:

  - Residents: the first contact will take place via a letter in which people are invited to participate in the study. A participation form and a postage-free reply envelope accompany the letter.
  - Farmers: will not be approached by a letter first, because telephone numbers will be collected through existing stakeholder organisations and personal contacts.
- Phone contact:
  - Residents: people who returned the participation form will be called by telephone.
  - Farmers: based on the consultation of regional/agricultural experts a selection is made of farmers on appropriate locations who might be positive about participation in the research and meet the selection criteria. They will be contacted by telephone.

  Following a beforehand-composed telephone script, potential participants will receive an explanation about the research, they will be asked to participate and (if reaction is positive) the screening questionnaire is filled in. Also a date and time for a visit is planned..
- Personal visit (intake interview) to explain the details of the study and personal significance of the measurements, to discuss expectations and conditions for participation. This results in signing *informed consent* form.

Planning
The recruitment of participants starts in February/March 2015. The exact moment depends on the timing of the approval by the METC. It is not allowed to recruit participants in medical research before approval of the METC.

In 2016 an expansion of the amount of locations, possibly crops and participants will take place. The recruitment of these new participants will start from November. No extra review of the METC is required, as long as there are no significant changes in the monitoring protocol.

By whom
The fieldwork team will carry out the recruitment. Eventually an exception can be made in the first telephone call with the farmers, when (in consultation of regional/agricultural experts) it is evident that recruitment will be more successful when the farmer is approached by a warm contact first. It is very important that recruitment is executed by people who know what occupies the participants and how they should deal with that in a good way (van der Wal et al. 2011).

These activities result in sufficient and motivated participants, who comply with the selection criteria.

7.1.6. Coordination and execution of the fieldwork

These activities take place in 2015 and 2016. The coordination of the fieldwork will be guided by the overall fieldwork monitoring protocol. The field team will be directed by one central coordinator who is responsible for the coordination of the field work, including the recruitment of participants. A distinction is made between the coordination and alignment of the research in the field and the management of the contact with the participants.

Coordination of fieldwork
This component is closely related to the coordination of the complete research (WP1) (broader than the fieldwork) and consists of the following:
- Determining whether the monitoring protocol is being followed

- Identifying possible constraints and reporting particularities
- Mutual coordination (research team, WP-leaders) possible realignment (consider the effects of weather conditions or deviating behaviour of growers/local residents)
- Mutual communication and feedback.

Management of the contact with the participants
It is important to build a trusting relationship with the participants. Following the intake interview, supervision and support of the participants will consist of the following:

- Announcing the start of the study
- Announcing measurements, times, duration and person or persons who conduct the measurements
- Communication and explanation during the measurement and during the period between the measurements
- Feedback/evaluation following completion of the measurements
- Feedback of results.

The field researcher will visit participants regularly, not only to collect information but also to maintain good relationships and to provide regular feedback on the progress of the study. Such engagement is very important to keep participants motivated, to collect reliable samples and information and because it helps to minimize attrition of study participants.

At the visit of the residents, the field researcher will collect the samples and diaries. Before taking the sample package, he/she will check that it contains the expected number of completed study packs and that in each study pack, the sample label on the diary matches that on the (urine) sample receptacle. The field researcher will check that the diaries have been fully and correctly completed and that the date and time of collection has been written on the (urine) sample receptacle.
It is not intended to provide participants with details of their individual results, but they will however, upon request, be forwarded a summary of the overall results and the study report.

A field researcher will also contact participating farmers on a regular basis to ensure continued participation, collect PPP usage records and obtain updated information on their planned PPP usage. At the last visit to the farm during a spraying season, the researcher will recheck the farmers spray records to ensure that details of all relevant spray periods have been recorded.

De frequency of visiting participants and the way of having contact (visit, phone calls) depends on sampling methods, sampling frequency, the demands on the period in which samples should be processed – to be defined in the monitoring protocol

These activities result in an efficiently coordinated and organized field study, well supported participating residents and farmers, and a well followed monitoring protocol.

7.1.7. Evaluation

At the end of the monitoring period in 2015 we will evaluate the approach and methodologies with participants and fieldwork team. How did they experience the sampling? Was it feasible? Is there anything to improve? Etc.

The evaluation results in identification of points for improvement to benefit the study in the next year (2016).

7.1.8. Completion of the measurement process

Careful completion is important for the participants of the research. The field study will end in 2016. The year after will be needed for analysis and interpretation of the sampling and monitoring data and reporting. This means that participants will not receive any results of the research until the end of 2017.

This activity results in realistic expectations of the participants with regard to the publications of the results of the study and their involvement in it.

7.2. Expected results and deliverables

In short, the expected results of this work package (WP7) are:
- A well prepared and efficiently coordinated and organized field research
- Sufficient and well supported participating residents and farmers
- A well followed monitoring protocol and monitoring scheme.

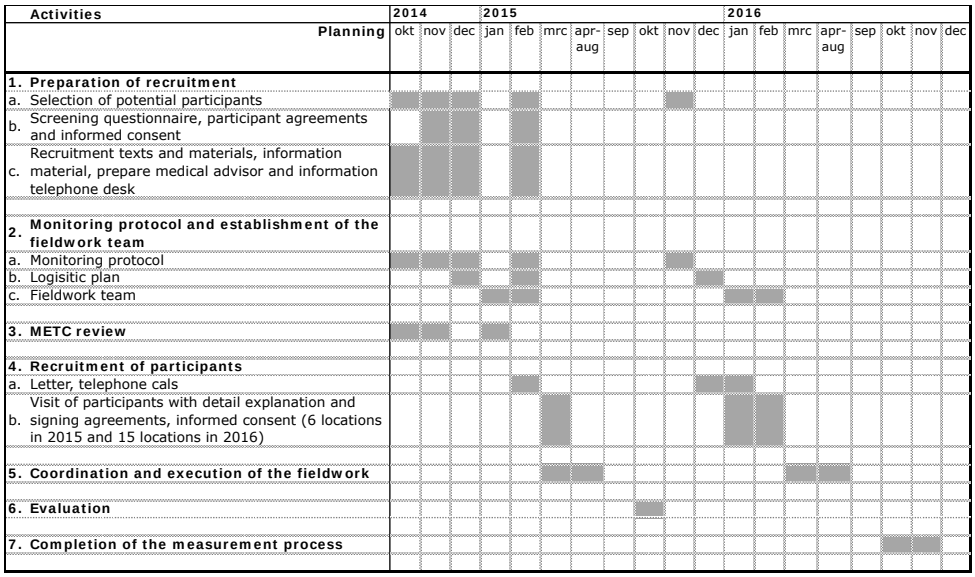
The following products will be delivered:
- A plan for recruitment of participants and cooperation in the fieldwork team, containing the following documents:
  - List of locations and potential participants
  - Screening questionnaire
  - Participant agreements
  - Informed consent
- A monitoring protocol including a logistic plan, that integrates the research protocols of the different WP's
- Complete documentation of the request to the METC and associated approval.
- Lessons learned in the fieldwork of 2015, with points for improvement to benefit the study in 2016.

7.3. Project organisation and budget

CLM and UU-IRAS are the project leaders of WP. They will coordinate the fieldwork. UU-IRAS will focus on everything that concerns the residents and CLM on everything regarding the recruitment and collection of information from farmers.
Several research institutes play an important role in WP7. These are in particular the leaders of the other work packages: Radboud-umc, UMCG, WUR-Alterra and WUR-PPO, TNO, RIKILT and Schuttelaar & Partners.

7.4. Planning

The field study takes place in 2015 and 2016. In the table below a planning of activities is given.



7.5. References

Galea, K., L. MacCalman, K. Jones, J. Cocker, P. Teedon, A.J. Sleeuwenhoek, J.W. Cherrie & M. van Tongeren. 2011. Biological monitoring of pesticide exposures in residents living near agricultural land. BMC Public Health 2011, 11:856.

Wal, A.J. van der, A. Velenturf, J. Spruijt, H. Mulder & J.A. Metselaar, 2011. Evaluatie van de nota Duurzame gewasbescherming – Deelrapport Kennisontwikkeling en -verspreiding. [*Evaluation of the Dutch policy on Sustainable Crop Protection - Knowledge development and dissemination*]. CLM, Culemborg (NL).

Annex 8: CVs of the research team

CVs of all team members and descriptions of the research units are provided in a separate document.