A person wearing a blue protective suit and a cap is sitting on a balcony, looking out over a vast yellow field. In the background, there is an industrial city with smokestacks and buildings under a blue sky with white clouds. The person is sitting on a wooden chair, and their legs are crossed. The field is a bright yellow color, and there are some green plants in the foreground. The city in the background has several tall buildings and smokestacks, with smoke rising from them. The sky is a clear blue with some white clouds.

Measured and modelled environmental exposure of residents to pesticides

Daniel Martins Figueiredo

Measured and modelled environmental exposure of residents to pesticides

Meten en modelleren van blootstelling aan bestrijdingsmiddelen bij omwonenden

Measured and modelled environmental exposure of residents to pesticides

**Meten en modelleren van blootstelling aan
bestrijdingsmiddelen bij omwonenden**

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht
op gezag van de
rector magnificus, prof.dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

donderdag 27 oktober 2022 des middags te 12.15 uur

door

Daniel Martins Figueiredo

geboren op 18 juni 1992
te Cascais, Portugal

Promotoren:

Prof. dr. R.C.H. Vermeulen

Prof. dr. D.J.J. Heederik

Copromotor:

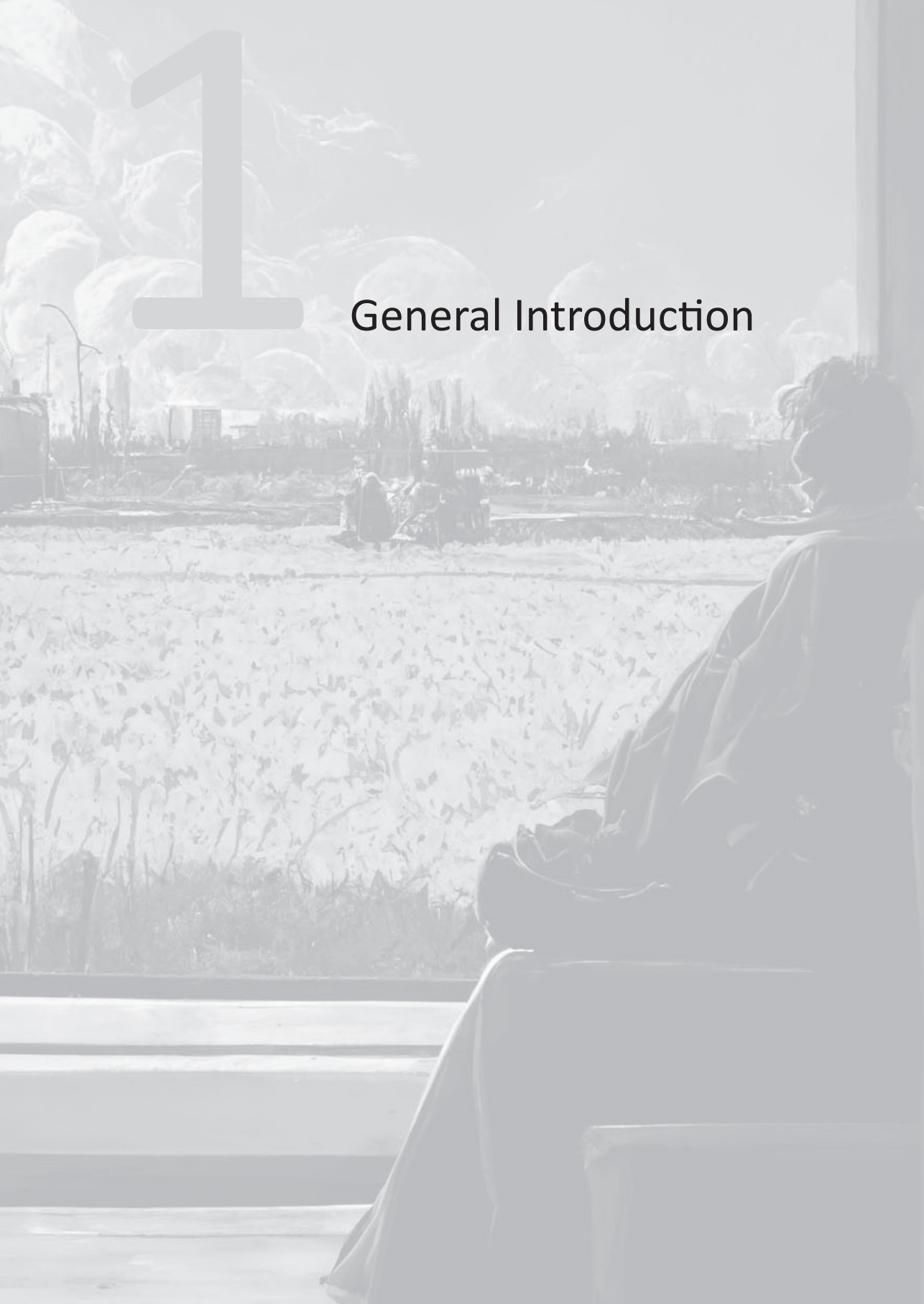
Dr. J.H. Duyzer

inhoud nog niet ontvangen



1

General Introduction



The practice of agriculture first began about 10,000 years ago (Eveleens 1983). With time, it became clear that crops could be affected by diseases and pests. Since this might lead to loss in yield resulting in possible population starvation, many initiatives to find ways of overcoming these problems were initiated. The first recorded use of insecticides was about 3500 years ago (Oberemok et al. 2015). Initially, used products were not chemically fabricated. The rising of synthetic pesticide usage started no more than 85 years ago, in the 1940s, with the discovery of pest control properties of dichloro-diphenyl-trichloroethane, 2,4-dichlorophenoxyacetic acid, amongst others. Since then, many pesticides have been introduced in the market and usage increased even more after the Green revolution in the Global South (between 1950 and late 1960s) (Hurt 2020). The application frequency also increased, depending on crop, from an average of one spray per season in 1960-1961 to eight sprays per season in 1980-1981 (Bakker et al. 2020). From 1990 to 2019, pesticide usage across the globe almost doubled. Although for some developed countries, such as the Netherlands, usage remained more or less constant (FAO 2021) mainly due to investments in alternatives. The Multi-year Plan for Crop Protection is an example of this, with one important objective being to halve the use of pesticides for the year 2000 in comparison to 1984-1986 (RIVM 2015).

In this thesis, the English word ‘pesticide’ is used. The word is used in the context of a product used by farmers to control pests (e.g. weeds, bacteria, moulds or fungi, insects) that affect plant health. In agriculture, pesticides are also referred to as plant protection products. In all other cases, such as measured data and exposure of residents, it refers to the active ingredient(s) present in the plant protection products formulation.

Pesticides can be grouped into different categories depending on their purpose. In this study we focus on three major pesticide categories: herbicides, which are used to control undesired weeds; fungicides, used to kill fungi or their spores; insecticides, used to kill or repel insects. At this moment, almost 300 active ingredients, belonging to these three major classes, are approved for use in the European Union (EU). (EC, 2021). Contrary to legacy pesticides (e.g. chlordane, aldrin), all currently applied pesticides degrade more rapidly in the environment (Hermansonv et al. 2005). Nevertheless, these pesticides; often connotated as “current-use pesticides”, still pollute natural resources such as air, soil, and water (Pérez et al. 2021). Humans can be exposed to pesticides once these are present in different environmental matrixes. Exposure can occur via dietary intake when treated crops are being consumed. It is reported that pesticides may affect respiratory, reproductive, nervous, hormone and endocrine, and circulatory systems and cause various human health-related effects (Ansari et al. 2021).

Traditionally, research has focused on (occupational) pesticide exposure among agricultural workers. However, as pesticides can move from their application sites during and after agricultural application, the general population in surrounding residential areas may be exposed. It has also been hypothesized, that due to spray drift and volatilization of pesticides from nearby agricultural land, residents are likely to be exposed to lower levels but for a longer duration resulting in cumulative lifetime exposures that could be of the same order of magnitude with some occupational exposure (Dereumeaux et al. 2020).

In the Netherlands, approximately 30% of homes are located within 250 meters from fields where spraying occurs. This close proximity has led to concerns among residents, researchers and local and national politicians. This resulted in a request by the Dutch government for advice on the issue. In response, the Health Council of the Netherlands published its advice in 2014. To summarize, the Health Council advice showed and concluded that i) health effects among users have been reported in the (peer review) scientific literature; ii) there also have been indications of effects in the general population; iii) there is a paucity on information on actual exposures levels from pesticides outside the intended sprayed area. Therefore, the conclusion was that there were sufficient reasons to initiate an exposure assessment study among residents living close to agricultural land in The Netherlands. This resulted in a national program on exposure to pesticides of residents near treated crops called the 'OBO-study' that took place between 2015 – 2019.

In a recent literature review, Teyssere et al. highlighted that improvement on understanding residential exposure to pesticides is needed and could be expected from studies combining different methods of exposure assessment to study spatio-temporal variation of concentrations, determinants and routes of exposure (Teyssere et al. 2020). For measuring (human) exposure, biomonitoring is still often the preferred approach (Hardy et al. 2021) since it offers the advantage of integrating all of the possible sources and routes of exposure. These routes of exposure can be multiple as shown in Figure 1 (figure presented in OBO 2019). However, for most compounds, rapid elimination of the pesticides from the body results in short temporal windows of detection (Aylward et al. 2014), creating considerable logistic challenges in studies on pesticide exposure. It is therefore advised to combine biomonitoring with environmental sampling in order to get a better and more comprehensive picture of spatial and temporal exposures (e.g. Raherison et al. 2019).

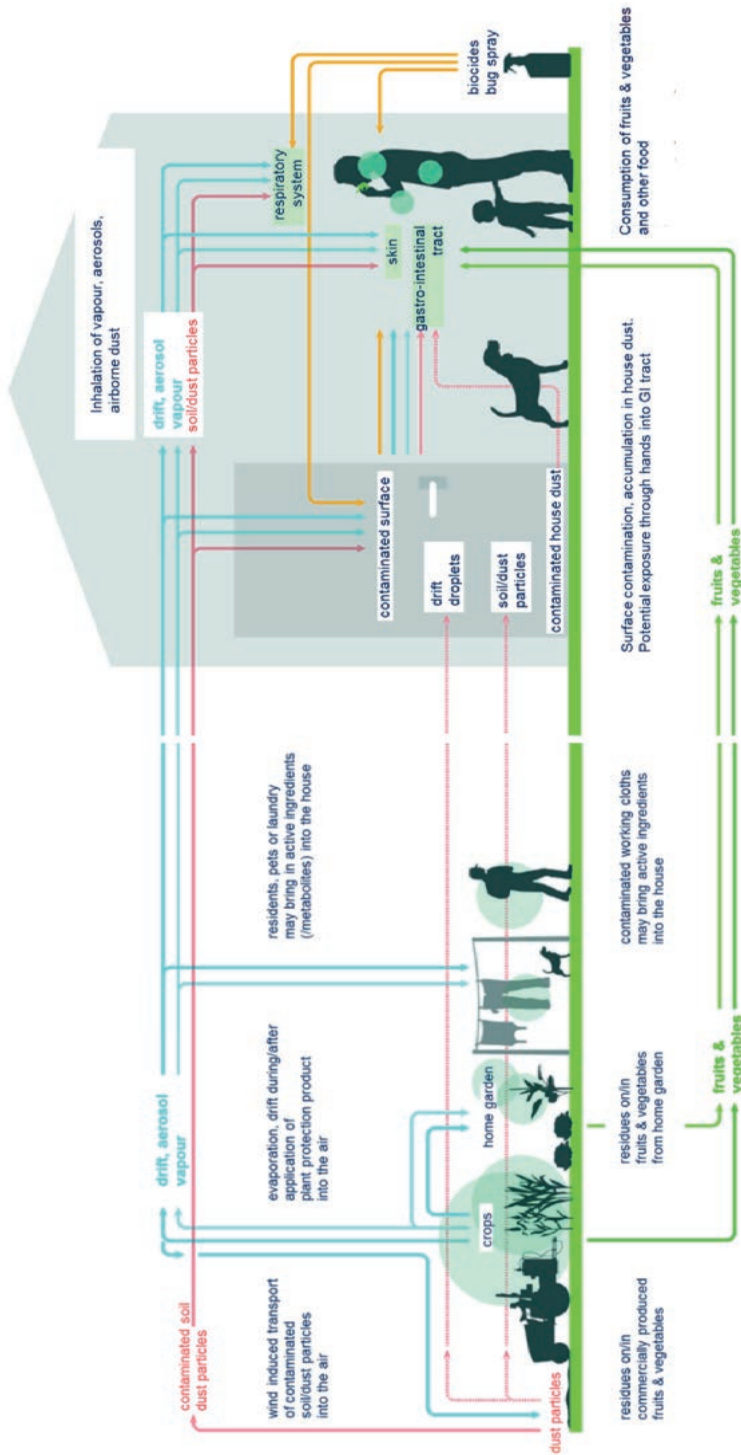


Figure 1. Exposure sources and routes. Different suggested sources and routes for outdoor (left panel) and indoor (right panel) exposure to pesticides. Colored arrows represent different types of routes: blue: direct exposure; red: indirect exposure via food; green: indirect exposure via food; yellow: direct and indirect exposure from products used at home. Reprinted [with permission] from OBO 2019.

While for estimating farmer exposures multiple statistical models exist, far fewer models exist for modeling residential exposures. These modelling approaches range from crude approaches (Chang et al. 2014) such as using home distance to agricultural field or surface area of crops surrounding a home as proxy for environmental exposure (Cecchi et al. 2021, Lombardi et al. 2021, Simões et al. 2022), to more robust approaches, which account for the mass-balances involved from spraying application to exposure of residents (Butler Ellis et al. 2017), but also require more detailed inputs such as the type of nozzles used, organic matter content in the top soil layer, meteorological conditions, amongst others. The use of one over the other is mostly based on availability of data and purpose of the study.

In the OBO-study, field measurements, auxiliary data collection and modelling efforts were combined. For a complete description of the OBO-study we refer to OBO 2019. Box 1 briefly summarizes the OBO-study main findings. This thesis goes into a more in depth analysis and discussion of results using the data collected in the OBO-study. The following chapters in this thesis aim to describe the spatial and temporal variation of different current-used pesticides, as well as environmental routes and potential determinants of exposure.

Box 1: Main findings from the OBO-study

1. Higher concentrations of several pesticides were found in environmental samples collected from inside and outside the homes of people (residents) living in close proximity to bulb fields compared to concentrations in homes further away from the fields (controls).
2. These higher concentrations of pesticides were observed in the homes of people living close to bulb fields both in the use and non-use period.
3. Biomarkers of two out of the five analyzed pesticides were found in more than half of urine samples from both residents and controls, including (young) children. This was observed in, as well as outside, periods of pesticide use. Relationships between the concentrations of these two pesticides in urine and distance to sprayed fields or periods of pesticide use were not consistently observed. However, concentrations found in urine correlated with the concentrations of pesticides inside and outside the homes.
4. Concentrations of pesticides inside and outside the homes of growers were generally higher than those found for residents living near agricultural land.
5. Volatilization of pesticides from the field after spraying and uptake of pesticides in house dust are likely the most important routes for exposure to pesticides of residents living close to bulb fields in our study. Because wind during spraying was often not directed towards the homes of residents, drift was hardly observed in the field study. From experimental studies performed within the OBO-study and involving flower bulb fields, we conclude that drift can reach higher altitudes and larger distances than thought before.
6. The OBO-study has generated tools for a time-resolved predictive model to estimate exposure of residents of bulb fields and other crops with downward spraying, via both air and house dust, for all pesticides, locations and moments. However, important knowledge and information gaps still remain precluding estimates on a national scale.

The OBO-study looked at exposure to pesticides of residents living near agricultural land. The study did not assess possible health effects of such exposures.

Reprinted and adapted [with permission] from OBO 2019

Chapter 2 details the protocol for the OBO-study. Here, the methodology used to study residential exposure to pesticides is presented. The manuscript covers the different modules of the study design, from selection of pesticides to field measurements and the modelling of exposures. It also provides a list of (practical) lessons learned which may be useful when setting up similar future studies.

Chapter 3 describes the spatial and temporal variation of 46 different current-use-pesticide concentrations in air outside and inside homes located close (<250m) and further away from treated fields. This manuscript also covers a study on factors influencing the local fate of pesticides in air.

Chapter 4 is a characterization of the spatial and temporal variation of 46 different current-use-pesticide concentrations in house dust and compares results from two widely applied methods: i) pesticides levels in dust from bespoke doormats and ii) collected through vacuum samples of floors. In addition, determinants of occurrence and concentrations in dust were investigated.

Chapter 5 describes, for five commonly used pesticides in the Netherlands, the association between hand exposure (as a proxy of dermal exposure) to pesticides and the excretion of metabolites from urine collected by residents living close to treated agricultural fields. Hand wipes and urine biomarker levels between participants from farmer and non-farmer families were compared and levels were compared between spraying and non-spraying periods.

Chapter 6 demonstrates the usability of a newly developed deterministic model framework (referred to as OBOmod) to assess exposure of residents living near fields where pesticides are applied. The manuscript covered the different model descriptions, an example simulation and an evaluation of the framework by comparing the computed concentrations with the concentrations measured in outdoor and indoor air, as well as in indoor dust.

Chapter 7 reviews and discusses this thesis' main findings, debates about knowledge gaps and opens a window into future research.

"Unintended, accidental, or unavoidable human exposures may result from pesticide use." – Krieger 1995

References

- Ansari, I., El-Kady, M. M., Arora, C., Sundararajan, M., Maiti, D., & Khan, A. (2021). 16 - A review on the fatal impact of pesticide toxicity on environment and human health (S. Singh, P. Singh, S. Rangabhashiyam, & K. K. B. T-G. C. C. Srivastava (eds.); pp. 361–391). Elsevier. <https://doi.org/10.1016/B978-0-12-822928-6.00017-4>
- Appenzeller, B.M.R., Hardy, E.M., Grova, N. et al. Hair analysis for the biomonitoring of pesticide exposure: comparison with blood and urine in a rat model. *Arch Toxicol* 91, 2813–2825 (2017). <https://doi.org/10.1007/s00204-016-1910-9>
- Bakker, L., W. Van der Werf, P. Tittonell, K. A. G. Wyckhuys, and F. J. J. A. Bianchi. 2020. Neonicotinoids in global agriculture: evidence for a new pesticide treadmill? *Ecology and Society* 25(3):26. <https://doi.org/10.5751/ES-11814-250326>
- Butler Ellis, M. C., van de Zande, J. C., van den Berg, F., Kennedy, M. C., O’Sullivan, C. M., Jacobs, C. M., Fragkouli, G., Spanoghe, P., Gerritsen-Ebben, R., Frewer, L. J., & Charistou, A. (2017). The BROWSE model for predicting exposures of residents and bystanders to agricultural use of plant protection products: An overview. *Biosystems Engineering*, 154, 92–104. <https://doi.org/10.1016/j.biosystemseng.2016.08.017>
- Cecchi, A., Alvarez, G., Quidel, N., Bertone, M. C., Anderle, S., Sabino, G., Magnarelli, G. G., & Rovedatti, M. G. (2021). Residential proximity to pesticide applications in Argentine Patagonia: impact on pregnancy and newborn parameters. *Environmental science and pollution research international*, 28(40), 56565–56579. <https://doi.org/10.1007/s11356-021-14574-2>
- Chang, E.T., Adami, H., Bailey, W.H., Boffetta, P., Krieger, R.I., Moolgavkar, S.H. et al. (2014). Validity of geographically modeled environmental exposure estimates *Crit. Rev. Toxicol.*, 44 (2014), pp. 450–466 <https://doi.org/10.3109/10408444.2014.902029>
- Dereumeaux, C., Fillol, C., Quenel, P., & Denys, S. (2020). Pesticide exposures for residents living close to agricultural lands: A review. *Environment International*, 134 (November 2019), 105210. <https://doi.org/10.1016/j.envint.2019.105210>
- Hardy, E. M., Dereumeaux, C., Guldner, L., Briand, O., Vandentorren, S., Oleko, A., Zaros, C., & Appenzeller, B. M. R. (2021). Hair versus urine for the biomonitoring of pesticide exposure: Results from a pilot cohort study on pregnant women. *Environment International*, 152. <https://doi.org/10.1016/j.envint.2021.106481>
- Hermanson, M. H., Isaksson, E., Teixeira, C., Muir, D. C. G., Compher, K. M., Li, Y. F., Igarashi, M., & Kamiyama, K. (2005). Current-use and legacy pesticide history in the Austfonna ice cap, Svalbard, Norway. *Environmental Science and Technology*, 39(21), 8163–8169. <https://doi.org/10.1021/es051100d>
- Hurt, R, D (2020). *The Green Revolution in the Global South: Science, Politics, and Unintended Consequences*. Nexus Series. Tuscaloosa: University Alabama Press, 2020. ISBN 978-0-8173-2051-5.

- Krieger, R. I. (1995). Pesticide exposure assessment. *Toxicology Letters*, 82–83, 65–72. [https://doi.org/10.1016/0378-4274\(95\)03545-1](https://doi.org/10.1016/0378-4274(95)03545-1)
- Simões, M., Huss, A., Brouwer, M., Krop, E., Janssen, N., & Vermeulen, R. (2022). Residential proximity to crops and agricultural pesticide use and cause-specific mortality: A prospective census-based cohort study in the Netherlands. *Science of The Total Environment*, 817, 152932. <https://doi.org/10.1016/j.scitotenv.2022.152932>
- Oberemok, V. V., Laikova, K. V., Gninenko, Y. I., Zaitsev, A. S., Nyadar, P. M., & Adeyemi, T. A. (2015). A short history of insecticides. *Journal of Plant Protection Research*, 55(3), 221–226. <https://doi.org/10.1515/jppr-2015-0033>
- Pérez, D. J., Iturburu, F. G., Calderon, G., Oyesqui, L. A. E., De Gerónimo, E., & Aparicio, V. C. (2021). Ecological risk assessment of current-use pesticides and biocides in soils, sediments and surface water of a mixed land-use basin of the Pampas region, Argentina. *Chemosphere*, 263. <https://doi.org/10.1016/j.chemosphere.2020.128061>
- Raherison, C., Baldi, I., Pouquet, M., Berteaud, E., Moesch, C., Bouvier, G., & Canal-Raffin, M. (2019). Pesticides Exposure by Air in Vineyard Rural Area and Respiratory Health in Children: A pilot study. *Environmental Research*, 169(November 2018), 189–195. <https://doi.org/10.1016/j.envres.2018.11.002m>
- RIVM (2015). <https://www.rivm.nl/en/chemkap/fruit-and-vegetables/government-policy> [accessed 20-01-2022]
- Teyssie, R., Manangama, G., Baldi, I., Carles, C., Brochard, P., Bedos, C., & Delva, F. (2020). Assessment of residential exposures to agricultural pesticides: A scoping review. *PLoS ONE*, 15(4), 1–19. <https://doi.org/10.1371/journal.pone.0232258>



2

Pesticide Exposure of Residents Living Close to Agricultural Fields in the Netherlands: Protocol for an Observational Study

Figueiredo, D.M.¹, Krop, E.J.M.¹, Duyzer, J.², Gerritsen-Ebben, M.G.², Gooijer, Y.M.³, Holterman, H.J.⁴, Huss, A.¹, Jacobs, C.M.J.⁵, Kivits, C.M.⁶, Kruijne, R.⁵, Mol, J.G.J.⁷, Oerlemans, A.⁸, Sauer, P.J.J.⁹, Scheepers, P.T.J.⁸, van de Zande, J.C.⁴, Van den Berg, F.⁵, Wenneker, M.⁴, Vermeulen, R.C.H.^{1, 10}

¹Institute for Risk Assessment Sciences (IRAS), Division of Environmental Epidemiology, Utrecht University, 3584 CK Utrecht, The Netherlands

²TNO Urban Environment and Safety, P.O. Box 80015, 3508 TA, Utrecht, The Netherlands

³CLM Onderzoek en Advies BV, P.O. Box 62, 4100 AB, Culemborg, The Netherlands

⁴Wageningen Plant Research, Wageningen University & Research, Wageningen, the Netherlands

⁵Wageningen Environmental Research, Wageningen University & Research, Wageningen, the Netherlands

⁶Schuttelaar & Partners, Wageningen, the Netherlands

⁷Wageningen Food Safety Research, Wageningen University and Research, Wageningen, the Netherlands

⁸Department for Health Evidence, Radboud Institute for Health Sciences, Radboud university medical center, Nijmegen, the Netherlands

⁹Department of Pediatrics, University Medical Center Groningen, Groningen, The Netherlands

¹⁰Julius Center for Health Sciences and Primary Care, University Medical Center, University of Utrecht, 3584 CK Utrecht, The Netherlands

Published: JMIR Res Protoc. Vol. 10(4): e27883.

doi: 10.2196/27883

Abstract

Background: Application of pesticides in the vicinity of homes has caused concern regarding possible health effects in residents living close by. However, the high spatiotemporal variation of pesticide levels and lack of knowledge regarding contribution of exposure routes greatly complicates exposure assessment approaches.

Objective: To describe the study protocol of a large exposure survey in The Netherlands assessing pesticide exposure of residents living close (< 250 meters) to agricultural fields, to better understand possible routes of exposure, to develop an integrative exposure model for residential exposure, and to describe lessons learnt.

Methods: We performed an observational study involving residents living in the vicinity of agricultural fields and residents living more than 500 meters away from any agricultural fields (controls). Residential exposures were measured both during pesticide use period (UP) after a specific application, and non-use period (NP), during 7 and 2 days, respectively. We collected environmental samples, outdoor and indoor air, dust, soil (garden, field), and personal samples (urine, hand wipes). We also collected data on spraying applications, as well as on home characteristics, participant's demographics and food habits via questionnaires and diaries. Environmental samples were analyzed for 46 prioritized pesticides. Urine samples were measured for biomarkers of a subset of five pesticides. Alongside the field study, and by taking spray events and environmental data into account, we developed a modelling framework to estimate environmental exposure of residents to pesticides.

Results: Our study was conducted between 2016 and 2019. We assessed 96 homes and 192 participants, including seven farmers and 28 controls. We followed 14 applications, applying 20 active ingredients. We collected ~5000 samples: 1018 air, 445 dust (224 vacuumed floor, 221 doormat), 265 soil (238 garden, 27 fields), 2485 urines samples, 112 handwipes, 91 tank mixtures.

Conclusions: To our knowledge, this is the first study on resident's exposure to pesticides addressing all major non-dietary exposure sources and routes (air, soil, dust). Our protocol provides insights on used sampling techniques, the wealth of data collected, developed methods, modelling framework and lessons learnt. Resources and data are open for future collaborations on this important topic.

Introduction

Background

The application of pesticides in the vicinity of homes has raised questions regarding health concerns from residents living near agricultural land. Occupational pesticide exposure has been associated with different health effects like diseases of the respiratory tract (Hoppin 2014, Lytras et al. 2018), cancer (Weichenthal et al. 2012), and neurodegenerative diseases like Parkinson's disease (Brouwer et al. 2017, van der Mark et al. 2012). Although residents are likely exposed to lower concentrations compared to occupationally exposed individuals, they are continuously exposed, due to spray drift and transport of pesticides volatilizing from nearby agricultural land to their homes (Dereumeaux et al. 2020). In addition, possible accumulation of pesticides in the home environment (Béranger et al. 2019) can contribute to higher and prolonged exposure of those residents (Deziel et al. 2018) compared to urban residents. In comparison to occupationally exposed workers, more vulnerable groups such as children and the elderly, may be exposed in the home environment (Hung et al. 2018).

While few studies found no clear difference between outdoor air concentrations between urban and rural areas (Estellano et al. 2015), several others have shown that pesticide concentrations in air are higher close to agricultural fields (Fang et al. 2017, Climent et al. 2019) and are higher during the spraying seasons (Carratalá et al. 2017, Liu et al. 2018). Both results are also true for air and dust in the indoor environment (Rudel et al. 2003, Wang et al. 2019). Additionally, when looking at internal dose (measured by biomarkers of exposure), some studies observed no significant differences in pesticide exposure levels between urban and rural populations (Kimata et al. 2009, Koureas et al. 2014) whereas others did (Couture et al. 2009, Dereumeaux et al. 2018, Fernández et al. 2020).

Data in The Netherlands on pesticide exposure to residents is limited, while, due to the population density and large agricultural sector, approximately 27% of all homes are located within 250 m of at least one cultivated agricultural field. Given the variable outcomes in the scientific literature and the lack of information on exposure levels of the Dutch (rural) population due to pesticide use on agricultural fields, the Health Council of the Netherlands advised the government to perform research in order to fill the above-mentioned gaps of knowledge. For this, the OBO-study (Dutch acronym for "Research on Exposure of residents to pesticides") was conducted.

Aims

Our study

The OBO-study aimed to assess pesticide exposure for residents living close (< 250 meters) to agricultural fields and to better understand possible routes of environmental exposure. Since most spraying in the Netherlands is done with a downward spraying technique (de Vreede et al. 1998, Zande et al. 2012, Zande et al. 2019, Zande & ter Horst 2019), and bulb cultivation is known to have a large use of pesticides (CBS 2015), the focus was on pesticide exposure among residents living in the vicinity of bulb fields. The emphasis of this study was on the assessment of residential pesticide exposure, not on potential adverse health or toxicological effects.

This protocol

To address the above-mentioned aim, three research questions were formulated:

1. What are the concentrations of pesticides in the environment of residents living close to agricultural cultivation of flower bulbs compared to those living further away?
2. What is the personal exposure to pesticides of residents living close to agricultural cultivation of flower bulbs compared to those living further away?
3. What are the sources and routes of exposure contributing to environmental and personal exposure to pesticides in areas with the cultivation of flower bulbs?

In this paper, we describe the OBO study, providing an outline of the methodology used to answer the above-mentioned questions. We provide relevant information for other researchers planning to setup similar study designs, apply similar methods, and explore collaborations (e.g. make use of the collected data in pooled analysis). We also provide some lessons learnt.

Study contribution

To the best of our knowledge, this is the first time that in the field of residential exposure to pesticides, a study was setup that i) followed various spraying applications, ii) collected both environmental and personal samples, iii) targeted a wide-range of pesticides (i.e. insecticides, herbicides and fungicide), and iv) was performed in different time periods (outside and during spraying periods) allowing the comprehensive study on both spatial and temporal variation in residential pesticide exposure.

Contributions of the study to the knowledge base are:

- Creation of a FAIR dataset which includes concentrations of many different pesticides in relevant matrices such as air, dust, soil and urine. The dataset also contains collected detailed information on spraying applications (i.e. frequency,

mixture applied, quantity, etc). It can be used in future studies for multiple aims, for example to determine the more common pesticide mixtures in the environment or, together with data from other studies, develop robust models to estimate the concentrations of pesticides in certain matrices (e.g. indoor home dust as a result of the take-home route).

- Adding to the growing knowledge of pesticides distribution in the environmental matrices and its main determinants. Not only for sprayed pesticides but also some pesticides that were not reported to have been applied.
- Providing valuable and useful information for other researchers and biological monitoring studies regarding toxicokinetics of some pesticides in the human body.
- Providing insights into associations between different matrices (i.e. relation of pesticides content between air, dust, urine, etc.). These results add to the scientific evidence by bringing to light new knowledge.
- Developing a modelling framework that comprises verified models which explain the most relevant pesticide fate processes (e.g. spray drift and evaporation) as well as exposure routes (e.g. dermal and inhalation). Verification is possible by comparing measured values in the different matrices with modelled values, using all the collected information on spraying applications and meteorological conditions. This framework or parts of it can be used in future studies as an exposure assessment tool.
- Performing spray drift and volatilization experiments to increase the knowledge on the abovementioned processes. These experiments emphasized the drift reducing nozzles as important exposure reduction factor and the importance of volatilization in pesticides release from the fields.
- Tackling some important current knowledge gaps regarding exposure of residents. Examples are the relation between outdoor and indoor concentrations in air and understanding which exposure routes contribute most to personal exposure. In our modelling framework we compared four main exposure routes: contact with surfaces, dust ingestion, dermal contact with the body and inhalation of gas and particle-phase.
- Many of the results can be used not only for policy making in the Netherlands but can also be informative for other countries with similar agricultural practices and topographies. Moreover, this protocol, describing the study design, can serve as a basis for studies in countries with different agricultural practices but with common goals.

Methods

Study design

The OBO study started in January 2016. Enrollment and sample collection was performed during 2016 and 2017. Sample and data analysis were done almost in parallel with each other between mid-2017 to mid-2019. The study focused on flower bulb cultivation and downward spray applications.

An exposure assessment strategy was developed to include personal, environmental sampling, and the collection of contextual information. Additional experimental studies were conducted to generate complementary information on methods of urine collection from non-toilet trained infants (Oerlemans et al. 2018), the toxicokinetics (Oerlemans et al. 2019), as well as experimental applications to understand better pesticide spray drift and volatilization. The study design is shown in Figure 1.

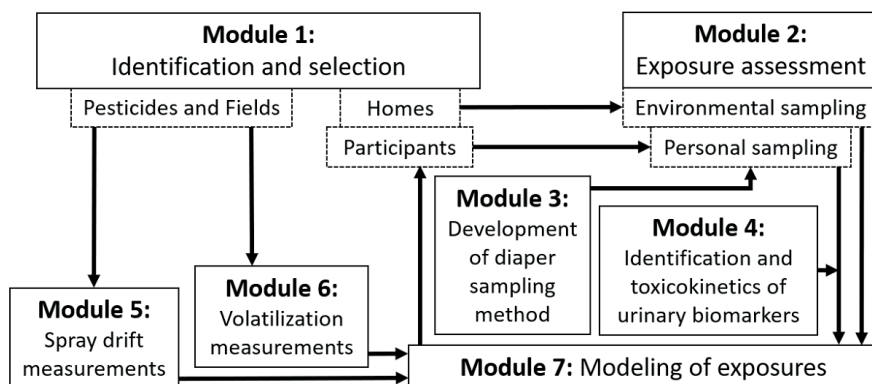


Figure 1. Schematic of study design.

At the start of the OBO-study the focus was on identification and selection of pesticides to be analyzed, of fields, homes and participants (i.e. residents living in selected homes) (Module 1). In Module 2, exposure assessment was conducted in and around the homes after one of the selected pesticides was sprayed on a selected field. Methods for diaper sampling and estimation of personal pesticide exposure were developed in Modules 3 and 4, respectively. On some of the fields, spray drift experiments (Module 5) and volatilization experiments (Module 6) were conducted. Finally, results from Modules 2, 4, 5 and 6 gave input to Module 7, the modelling of exposure for each of the homes (from Module 1). Each module is discussed in more detail below.

Module 1– Identification and selection of pesticides, fields, homes and participants

Pesticides

For the selection of relevant pesticides to target in our chemical analyses the main aspects taken into account were: Information about registration and usage of pesticides on flower bulbs for the year 2015, collected from available data (CBS 2015) and interviews with growers, existing monitoring data for soil/crop from flower bulb fields, amenability to multi-residue analysis methods, estimated deposition and source strength of emissions from plants and from top soil layer, estimated dermal exposure and skin absorption potential, and possible exposure originating from other, non-agricultural pesticide use (e.g. food consumption) (Kruijne et al. 2019). Detailed inclusion and exclusion criteria are provided in Figure 2.

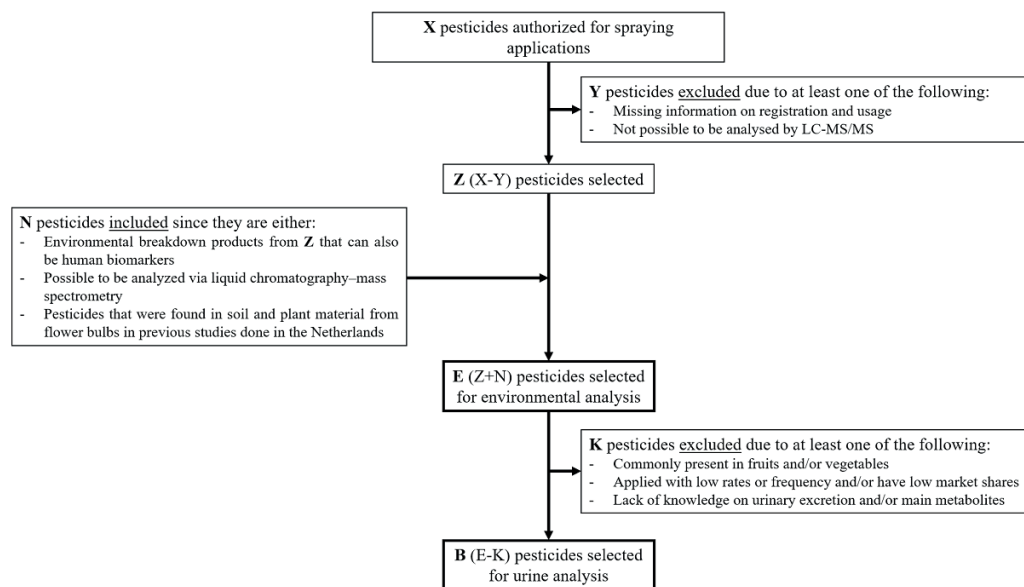


Figure 2. Exclusion and Inclusion criteria used for selection of pesticides to be analyzed in environmental and urine samples.

For the analysis of environmental samples, the aim was to include as many pesticides as possible that are currently applied and/or known to be found in flower bulb fields (see Supplementary Material, S1), while applying a single analytical method. This was done to reduce costs. For this, we considered multi-residue methods based on liquid chromatography with tandem mass spectrometry (LC-MS/MS) and gas chromatography

with tandem mass spectrometry (GC-MS/MS). LC-MS/MS was selected as it covered the largest number of the targeted pesticides. In addition, this method was also more suited to include several relevant degradation products/metabolites. The final selection included 46 prioritized pesticides/metabolites (see Supplementary Material, S2) to be measured in air, dust and soil.

For the analysis of the urine samples (internal exposure assessment at personal level), the target analyte (biomarker of exposure) in almost all cases is not the parent pesticide but a metabolite formed upon uptake. For the 46 pesticides selected for environmental measurements, data on their human biomarkers, analytical standards of the potential biomarkers, and methods for their analysis were not yet available. Consequently, as part of the OBO study, data on biomarkers and excretion profiles had to be generated (see module 4), analytical standards synthesized, and analysis methods developed. This was a substantial effort and obviously could not be done for all 46 pesticides. For this reason, assessment of internal exposure was restricted to a sub-set of five pesticides, which should be representative to facilitate modelling and extrapolation to other pesticides. Ideally, the pesticides selected for biomonitoring represented the three main product types (herbicide, insecticide and fungicide), different physicochemical properties of the pesticide, and actual spray applications on flower bulbs. We made a short list of eight prioritized pesticides that were frequently sprayed in bulb fields and could serve as representatives for the whole set and offered good prospects regarding the biomarker analytical challenges. In short, these criteria pertained to factors such as: representing different physicochemical properties, pesticide market shares, frequency of application, dosage, vapor pressure, half-life in the environment, and dermal absorption rate. To minimize the influence of dietary contributions on the biomarker levels we also considered the likelihood of being present in food items.

The eight selected pesticides were chlorpropham, asulam, flonicamid, acetamiprid, thiacloprid, prochloraz, tebuconazole and trifloxystrobin. All of these substances were expected to be routinely used by the growers, and most of them, with exception for chlorpropham, have low likelihood of dietary exposure in comparison with other pesticides (see Supplemental Material, S3). However, as indicated above, due to feasibility constraints only a maximum of five pesticide biomarkers could be analyzed in urine (i.e. B in Fig 2 must be equal to 5). Finally, the pesticides (biomarkers) that were selected for biomonitoring were: asulam (asulam); carbendazim (5-HBC); chlorpropham (4-HSA); prochloraz (2,4,6-TCP); tebuconazole (TEB-OH).

Fields

Selected fields needed, firstly, to have residents' homes located in the vicinity (within 250 m) of flower bulb fields, secondly, growers with an already defined cultivation plan, and thirdly, growers willing to participate and share their spray plan (mainly: product formulation, amount applied, type of nozzle used, spraying date and hour) with the research team.

Here, we defined location as a place consisting of one or more agricultural fields, with at least one bulb cultivation and surrounded by homes at different distances from those fields. An evaluation by visiting the location and the growers resulted in the final selection of study locations.

It is important to note that there were also other fields besides the selected field within 250 m of participating homes. To account for this, growers of all fields near a home (<250 m) that could potentially influence indoor and outdoor environmental concentrations were asked to share their spraying schemes. In the case of no collaboration (40%), spraying schemes were generated based on type of bulb, weather conditions and standard spray schemes of this crop type reported by local agronomist experts.

Homes

Spray applications on a field may expose residents to pesticides through spray drift and through volatilization. Homes located within 50 m distance at the downwind side of the treated field have been described as directly exposed to spray drift (Coronado et al. 2011). The pesticide deposited on crop and/or soil may volatilize and this process might affect homes in each direction, especially if they are located within a short distance up to 250 m (Butler Ellis et al. 2010). Therefore, residents living in homes located within 250 m from a selected field were invited to join the study, with, ideally, recruited homes situated at different distances around that field (Figure 3). Control homes were also included in the study. These homes were located in semi-urban areas (i.e. <1500 residential addresses/km²), situated within 20 km from a selected field, and which did not have agricultural fields within 500 m distance.

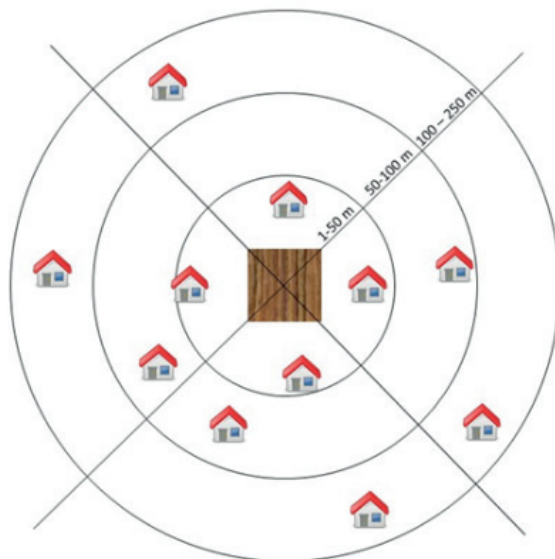


Figure 3. Selection of homes at different distances from selected fields. The figure represents an ideal situation, in which homes are located in different directions and at different distances around one field. However, in reality this was never the case in reality, as several fields are normally joined and homes are found in clusters in a few directions only.

Participants

Before residents were contacted, the study protocol was approved by the Medical Ethical Committee of the University Medical Center Utrecht (Protocol number NL54727.041.15).

Residents were invited via a letter accompanied by a brochure explaining the study. Interested invitees were interviewed by phone to check if they met the following inclusion criteria: having his/her primary place of residence at the pre-selected location; sufficient knowledge of the Dutch language and no cognitive impairment and therefore able to complete the administered questionnaires and communicate with the study assistant; we also asked the participants if they were diagnosed with kidney or liver disease as these could change metabolite formation.

Once enrolled in the study, participants were asked about availability and willingness of further household members (partners and children) to participate.

Module 2 – Exposure assessment

For a comprehensive exposure assessment, environmental and urine samples were collected as well as information regarding daily activities, food consumption, building characteristics and other relevant factors, using field forms, questionnaires and diaries.

These data were gathered at two occasions, here named measuring campaigns, during the pesticide use period (UP) and non-use period (NP).

During UP, environmental samples from homes were collected after a reported spray event on a selected field (Module 1). Here, outdoor air was sampled for 7 consecutive days because this is the time that we expected to see an influence in concentrations due to spray drift (day 1) and evaporation (day 1 to 7) of pesticides. This expectation was based upon detailed model calculations of spraying events (using the models described below in Module 7). During NP, we only expected background concentrations and therefore we sampled for a shorter period (2 days). The same applied for biomonitoring. For almost all other environmental samples, namely vacuumed floor dust (VFD), dust from a newly placed clean doormat (DDM), window still dust, soil from the garden (if one existed) and soil from the selected field, collection took place at the end of the 7-days and 2-days period, for UP and NP, respectively. Additionally, in both UP and NP an Electrostatic Dust Collector (EDC) was placed at the start of the measuring campaign and collected at the end.

Regarding personal sampling, morning urine samples were collected daily for 7 consecutive days and handwipes were taken on the first day of urine collection.

A measurement campaign was set in motion through a system allowing remote initiation of the air pumps once the grower informed the research team that spraying of at least one of the eight short listed pesticides was scheduled to happen. This ensured that our sampling periods were aligned with an actual application.

Module 3 – Development of diaper sampling

Self-collection of urine in toilet-trained children and adults was done using a 1 L measuring cup and 250 ml plastic jars. To determine the best method for urine collection in non-toilet trained infants (age 0-3 years), four commonly applied methods were evaluated in a pilot study (in a non-clinical setting). The four methods were: free catch, a urine collection pad (Hessels+Grob, Apeldoorn, the Netherlands), a urine bag (Urinocol Pediatric, Braun), and a disposable polyacrylate diaper (Pampers Baby Dry size 3, Procter & Gamble). The study examined the success scores of sample collection by parents/caretakers and acceptance scores by infant and parents/caretakers. The most successful and best-accepted method and was also the one that collected a sufficient urine volume (>5 mL) to allow biomarker analyses was the disposable diaper (Oerlemans et al. 2018). This was the method used for urine collection in non-toilet trained infants.

Module 4 – Urinary biomarkers: identification and toxicokinetics

For most pesticides, metabolism in humans is unknown and the only available data is derived from animal studies. For urine biomarker analysis, knowledge about the most suitable (specific and sensitive) human biomarker was needed. In addition, in order to link urinary concentrations (internal exposure) to external exposure, knowledge toxicokinetics and urinary excretion profiles was needed. For this, human volunteer studies were set up for each of the five pesticides selected for biomonitoring. Each study involved two independent administrations of the pesticide, one oral and one dermal (two weeks apart), to a group of three males and three females. Individual urine samples were collected for 48 hours. First, a biomarker screening was performed for composite urine samples using LC-full scan high resolution MS. For the most suited biomarker tentatively identified, the analytical standard and its isotopic analogue were purchased. In most cases this required custom synthesis, especially for the isotopic analogues. Following full conformation, dedicated methods for analysis of each biomarker were developed and validated, and all individual samples from each of the volunteers analyzed. This way, data on toxicokinetics were generated, and conversion factors derived (Oerlemans et al. 2019). The conversion factors were used to estimate pesticide uptake (Module 7) based on measured urinary biomarker concentrations (Module 2).

Module 5 – Spray drift experiments

Spray drift models have been developed previously to estimate the environmental fate (i.e. spray drift deposition at ground surface and airborne) of pesticides near application areas (Holterman et al. 1997). However, since residential exposure was not considered during the development of these models, there were knowledge gaps in predicting residential exposure, especially at larger distances (> 15 m) from the field and at greater heights (> 3 m). To address these gaps, experimental studies were carried out on agricultural fields (N=6) to study spray drift at longer distances (5 to 50 m) and greater heights (up to 10 m), as well as the effect of physical barriers. The application techniques for downward spraying were similar as those used in practice. The types of nozzles used were a TeeJet XR11004 and Agrotop TDXL11004. These are respectively standard and 90% drift reducing flat fan nozzles (TCT, 2020).

For ethical and practical reasons, measurements were performed using a fluorescent tracer instead of pesticides. Experiments were repeated using the aforementioned nozzle types as well as with varying foliage coverage on the field (i.e. bare ground – full crop). The results from these studies helped to calibrate the spray drift model, which provided output for use in modelling exposures (Module 7).

Module 6 – Volatilization measurements

Pesticide volatilization experiments were also conducted. Two experimental sites were selected based on the defined field and crop types (e.g. type of flower bulb) in Module 1. In the selected locations, rates of pesticide volatilization from the treated crops and influencing factors were measured on the day of pesticide application and several times during the first week after application. This was achieved by combining measurements of pesticide concentration gradients and on-site meteorological observations, including measurements of turbulence intensity. In addition, the pesticide residues on leaves were determined. Results of these measurements were used to test the volatilization model (van den Berg et al. 2016), which provides hourly emissions from fields due to volatilization for use in modelling exposures (Module 7).

Module 7 – Modelling of exposures

In order to select models suitable for assessing the exposure of residents living near fields where pesticides are intensively used, a screening of different models was conducted (Figueiredo et al. 2018). The most suitable models were combined into a deterministic modelling framework (Figure 4). Selected models were calibrated with results from measurements and experimental studies (Modules 5 and 6, A in Figure 4). Verification of model estimates was done by comparing predicted concentrations in different media (e.g. air, dust, soil) to concentrations measured in and outside homes (Module 2, B in Figure 4). In a next step, deterministic models were used to estimate pesticide exposure of residents living within 250 m of fields where spraying applications occur (Module 7). In this module, the contributions of different exposure routes to total internal exposure were investigated. In addition, different factors (e.g. personal pesticide use, time spent indoors) that might influence personal exposure, were incorporated via statistical modelling technique.

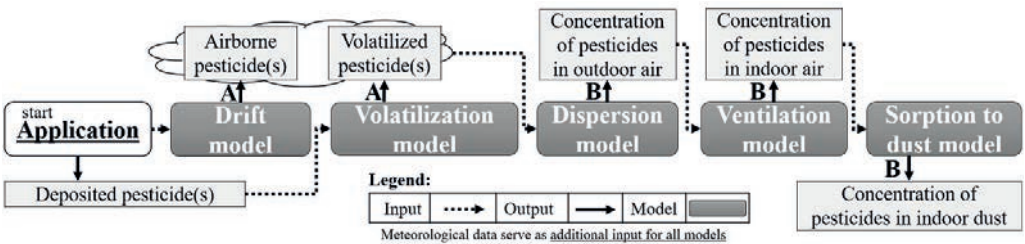


Figure 4. Deterministic modelling framework. A – Models calibrated with results from measurements and experimental studies; B - Verification of modeling steps, by comparing predicted and measured concentrations.

Sample size

A power calculation based on NHANES data (Center of Disease Control, USA), taking urinary 3-Phenoxybenzoic acid (metabolite of pyrethroid pesticides), estimated that with 200 residents we would reach 80% power at an $\alpha = 0.05$ to detect a 40 to 100% difference between background levels (mean 0.292 $\mu\text{g/l}$; SD 0.26) and exposed individuals, assuming an exposure prevalence of 50% and 100%, respectively. Therefore, we aimed to include 200 residents (roughly 100 homes).

Data collection

Measurements

As mentioned in Module 2, different types of environmental and personal samples were collected during this study. All the different sample and collection procedures are summarized in Table 1.

Table 1. Samples and collection methods used in the OBO study ("Research on exposure of residents to pesticides"). ^a

Sample	Collection Method
Outdoor and indoor air	Air was sampled through a standard PM10 inlet and drawn through a glass fibre filter and a tube containing XAD-2 absorbent (Amberlite XAD-2; Sigma-Aldrich, Inc).
Vacuumed floor dust	A dust sampling sock (Allied Filter Fabrics Pty Ltd) was attached to the hose of a vacuum cleaner to sample for 5 minutes on 4 m ² of carpet or 6-8 m ² of smooth floor.
Dust from doormat	A clean doormat was deployed for 1 week and then vacuumed on arrival to lab facilities.
Soil from each field and each residential garden	Five uncovered areas of soil were randomly selected and approximately 150 g to 250 g of topsoil were collected per area and combined into a single aggregate soil sample.
Tank mix sample	Duplicate tank mix samples of the spraying liquid were taken directly before and immediately after the spray event in all selected fields (Module 1). Aliquots of the tank samples were stabilized with methanol.
Window sill dust	Clean wipes were used to collect dust accumulated in window sill surfaces.
Electrostatic Dust Collector (EDC)	EDCs were deployed inside each home at the start of the study and were collected at the end of the sampling period.
Urine b	Spot samples were collected from all participants, except for non-toilet trained toddlers.
Handwipe b	The hand wipe consisted of a facial tissue premoistened with 3 mL of a 50% water/50% ethanol solution.

^a Analyses were performed using targeted liquid chromatography with tandem mass spectrometry for the main biomarkers of 5 preselected pesticides; ^b Personal sampling was performed.

Environmental samples were transported to the laboratory within 48 hours after sampling. Air sampling cartridges and dust were stored at 4°C until analysis, soil and crop samples at -18°C. Analysis of the environmental samples was based on existing methods already available in the consortium laboratories. The methods were slightly adapted to include all 46 selected pesticides and re-validated according to SANTE/11813/2017 (currently SANTE/12682/2019). The latter included establishment of recovery, repeatability, selectivity and LOQ (defined as lowest successfully validated level). For air analysis the glass fiber filter (trapping airborne particles) and the XAD-2 adsorbent (trapping gas-phase pesticides) were combined and extracted by accelerated solvent extraction using acetonitrile/methanol. After evaporative preconcentration, the pesticides were analyzed by LC-MS/MS. LOQs were 0.01 ng/m³ for most pesticides. For analysis of household dust, soil and crops extraction was done by a mixture of water/ acetonitrile, followed by a salt-induced phase partitioning (QuEChERS, for principles and details see Anastassiades et al. 2003 and Perestrelo et al. 2019). The organic phase was analyzed by LC-MS/MS. LOQs were 1 µg/kg for most pesticides.

Urine samples were transported to the laboratory within 24 hours after collection, aliquoted and then stored at -18°C. For each biomarker, a different dedicated method was developed to obtain optimum performance, which was validated and then applied to sample analysis. In all cases, the isotopically labelled analogue of the biomarker was added as internal standard to the urine aliquot to be analyzed (1-5 ml) at the start of the sample preparation. For biomarkers of tebuconazole (TEB-OH), prochloraz (2,4,6-TCP), and thiophanate-methyl/carbendazim (5-HBC) an enzymatic deconjugation step was performed. Biomarkers of chlorpropham (4-HSA) and asulam (parent compound) were analyzed as such. For the other biomarkers extraction/cleanup involved either solid phase extraction (SPE) or a liquid-liquid partitioning step (QuEChERS based), followed by an evaporative concentration step. Analysis of the extracts was done by LC-MS/MS under optimized conditions for the respective biomarkers. LOQs were 0.1 ng/ml for asulam, 4-HAS and TEB-OH, 0.05 ng/ml to 5-HBC and 0.25 ng/ml for 2,4,6-TCP. Not all collected samples were analyzed and the remainder were kept under appropriate storage conditions for future analysis.

A selection of samples to be analyzed was done based on location of the home, to guarantee a good distribution of home distances to the selected field, and on the wind direction during the application. This resulted in groups of homes per different distances (i.e. homes between 0-50 m, 50-150 m and 150-250 m) both down and upwind of the fields where applications took place. From the selected homes, all collected samples were analyzed. For the remaining homes only DDM was analyzed, providing us with an idea of the distribution of indoor dust concentrations on all locations.

Questionnaires & Diaries

Per home, the research assistant filled in a field form on building characteristics (see Supplementary material, S4), with data on the type of flooring, age of the building and materials used to build it, volume and area, number of floors, ventilation system, type of heating and possible air leakages (e.g. cracks). Each participant also completed a questionnaire and diary (see Supplementary material, S4) on personal characteristics, socio-economic position, presence and type of pets, use of medication, educational level, type of work/education, wearing shoes indoors and own use of pesticides. Parents were asked to fill in the questionnaires for their children. Questionnaires were completed before the measurement campaign started. During measurement campaigns (i.e. during both UP and NP), participants filled out a daily diary on food intake, hours spent at home and/or elsewhere, and personal use of chemicals, biocides or pesticides. Via an additional short questionnaire we check if items on the original personal questionnaire had changed during the campaign.

Data management

All data collected from the field study was transferred to the OBO data manager at Utrecht University. Entry of the collected questionnaire data was done using the Castor EDC interface, making our data storage compliant with relevant regulations (e.g. such as GDPR, ISO 27001 and ISO 9001) (Castor EDC. 2019). For diaries, we used a tailor-made data entry program. The entry was done in duplicate and then checked against each other (100% check). A third person looked at the differences and, if errors were found, records were rechecked against the original hard copies. Once completed, pseudomized data was used for analyses.

Ethics

Stakeholder engagement & dissemination

The OBO study was commissioned by Netherlands National Institute for Public Health and the Environment (RIVM). It was conducted by a consortium of Dutch institutes, consisting of: Utrecht University, The Netherlands Organization for Applied Research TNO, Wageningen University & Research, Radboud university medical center, Consultancy and communication agency Schuttelaar & Partners, CLM Advice and Research, and Prof. P.J.J. Sauer. The research proposal has been reviewed by a panel of 16 international experts. During the preparation and execution of the OBO study a stakeholder group advised on all research, communication and ethical aspects. This group consisted of representatives of public sector policy makers, researchers, the private sector, Non-Governmental Organizations, and citizens.

Results

Identification and selection

Of the contacted growers of possible selected fields, 17% participated in the study. Nine fields were included, encompassing spraying at different crop stages, variability for different meteorological parameters (such as temperature and wind speed) and 20 different applied pesticides (the majority being fungicides, 45%). Some fields were sprayed more than once during the UP, so we were able to follow a total of 14 different primary spraying applications at our selected fields. A total of 80 homes and 16 control homes were included in the study, with a total of 192 participants, of which 39 were younger than 18 years old. An overview is provided in Supplementary material S5. Initially, 1778 homes located around the selected fields and 482 control homes were selected and invited to participate. In total, 80 homes responded and were included, corresponding to a response rate of 4.5%, and 16 control homes responded and were included (response rate: 3.3%). We were able to have a good spatial distribution of homes around selected fields: 25% of homes were located within 50 m, 43% between 50-150 m and 32% within 150 m and 250 m from the selected fields. Out of the 192 participants, 164 were residents living within 250 m from a selected field. In this group, slightly more than half of the participants are female (54%) and the average age at participation was 44 yrs. (2-88 yrs.). For the 28 participants living in control homes, slightly more than half of the participants are male (57%) and the average age at participation was 50 yrs. (12-76 yrs.).

We selected 46 active ingredients of pesticides (see Supplementary Material, S2) for environmental analysis (E in Figure 2). For biomonitoring, our five pesticide biomarkers selected were: asulam (asulam); carbendazim (5-HBC); chlorpropham (4-HSA); prochloraz (2,4,6-TCP); tebuconazole (TEB-OH). Carbendazim was not on the initial short list. Analyses of indoor dust in the initial phase of the project led to the choice to include this substance in our selection as it was detected in almost all indoor dust samples, often in co-occurrence with thiophanate-methyl. Both are fungicides. The no-longer registered carbendazim arises from use of thiophanate-methyl that transforms into carbendazim both in the environment and upon uptake by humans. Thiophanate-methyl had no field spray application in bulb fields but is used for bulb disinfection. It might be emitted from the bulb disinfection site, and/or end up in the field upon planting of the bulbs.

Exposure Assessment

In total, we collected 969 outdoor air samples, 49 indoor air samples, 224 VFD samples, 221 DDM samples, 238 soil samples from residents' garden, 27 soil samples from the application fields, 2054 morning urine samples, 431 day urines, 112 handwipes and 91 tank mix samples.

We analyzed $\pm 50\%$ of all collected samples. These consist of 628 outdoor air samples, 43 indoor air samples, 128 VFD samples, 170 DDM samples, 124 soil samples from residents' garden, 20 soil samples from the fields, 791 morning urine samples, 311 day urines. All collected handwipes and tank mix samples were analyzed. The spray events and the respective applied pesticides and tank mixtures are shown in Table 2. The modelling framework was used and verified in all presented locations for several different meteorological conditions (see Supplemental Material, S5).

Table 2. Selected fields and respective applications with reported and measured pesticides concentration in the tank mixture.

Location	Selected field size [ha]	Measurement campaign	Sprayed #	Grower self-reported dosage [kg/ha]	Measured dosage [kg/ha]
A	2.45	UP1	Folpet	0.23	n.d.
			Mancozeb	1.50	n.d.
			Tebuconazole ^a	0.05	0.06
			Thiacloprid ^a	0.12	0.11
B	2.29	UP1	Flonicamid ^a	0.07	0.06
			Fluopyram ^a	0.08	0.07
			Trifloxystrobin ^a	0.08	0.06
C	2.00	UP1	Chlorpropham ^a	0.80	0.76
			Pendimethalin ^a	0.80	n.d.
		UP2	Mancozeb	1.88	n.d.
			Tebuconazole ^a	0.15	0.15
D	1.09	UP1	Chlorpropham ^a	0.80	0.88
			Pendimethalin ^a	0.80	0.69
		UP2	Chlorothalonil	0.50	n.d.
			Esfenvalerate	0.01	n.d.
			Mancozeb ^b	1.24	n.d.
			Prochloraz ^{a, b}	0.16	0.10

E	4.58	UP1	Acetamiprid ^a	0.05	0.07
			Esfenvarelate	0.01	n.d.
			Mancozeb	1.50	n.d.
			Mepanipyrin ^a	0.15	0.20
		UP2	Cyhalotrin-Lambda ^a	0.01	n.d.
			Mancozeb	1.50	n.d.
			Flonicamid ^a	0.07	0.07
			Tebuconazole ^a	0.08	0.07
F	1.83	UP1	Folpet	0.15	n.d.
			Tebuconazole ^a	0.15	0.17
		UP2	Acetamiprid ^a	0.05	0.08
G	3.64	UP1	Asulam	0.20	0.21
			Cyhalotrin-Lambda ^a	0.01	0.05
			Metamitron ^a	0.37	0.53
			Mineral oil	4.80	n.d.
			Quinmerac	0.03	n.d.
		UP2	Asulam	0.20	0.21
			Cyhalotrin-Lambda ^a	0.01	0.05
			Mancozeb	1.28	n.d.
			Metamitron ^a	0.37	0.24
			Paraffin oil	4.80	n.d.
			Pymetrozine ^a	0.10	0.07
			Quinmerac	0.03	n.d.
H	8.40	UP1	Esfenvarelate	0.01	n.d.
			Fluopyram ^a	0.08	0.07
			Trifloxystrobin ^a	0.08	0.07
I	1.47	UP1	Trifloxystrobin ^a	0.13	0.09

UP1: pesticide use period 1.; UP2: pesticide use period 2.; n.d.: not determined.; ^aAnalyzed pesticide.; ^bOnly applied on part of the field.

Discussion

There is ongoing concern in the Netherlands on the use of pesticides and their potential impact on the environment and human health. In the last decade several initiatives and regulations have been implemented to reduce the use of pesticides, and to reduce the emission of pesticides during (spray drift) and after (volatilization) applications. However, there remains a lack of information on exposure of residents to pesticides coming from agricultural fields. The OBO study was designed to provide a comprehensive insight of the exposure of residents and contributing exposure routes.

Strengths

The design of the OBO study has many strengths. We collected multiple sample types from various matrices in both pesticide use and non-use periods. This allowed us to compare i) exposed locations with control locations in both use and non-use periods, ii) to compare environmental concentrations among exposed location by use period and distance to fields, iii) study the interrelationships between concentrations in various matrices (e.g. air and dust), iii) to compare biomonitoring results between exposed and control subjects, iv) to relate biomarker levels to environmental concentrations, and v) to use measurements for model calibration and verification.

In the environmental samples, we managed, using a single LC-MS/MS-method, to determine 46 active substances. This group covered around 60% of the different pesticides registered in the spraying records around the selected fields. The inclusion of 46 different substances allowed us to analyze substances applied in the selected fields, applied in other fields in the vicinity, and pesticides with no recorded use in the area, allowing comparison of patterns between these different use categories.

An emphasis of our study was on modelling of the exposure of residents to pesticides. This resulted in a framework of models that may be useful to also estimate exposure from substances and mixtures that were not included in our study.

Limitations

A limitation of the study is that participating growers were not blinded (i.e. they were informed on the research aim), therefore one could hypothesize that growers sprayed only e.g. if the wind was blowing away from residential homes or very low wind speeds. Of course, in the end, growers will spray when they need so as to avoid cultivation loss. To account for this, we collected information from multiple applications that occurred not just on the selected field but also in surrounding fields.

Another limitation is that our study focused only on exposure as a result from downward spraying. Information regarding the degree of exposure to pesticides of residents living near crops where sideways or upward spraying techniques are used (such as fruit trees) is still lacking in the scientific literature and needs to be assessed in future studies. Here, a study design similar to OBO can be used.

Finally, it is important to add that given the low participation rates, the homes and residents included in our study might not be representative of the population living in the vicinity of agricultural fields.

Lessons from the OBO study

There are several lessons learned from the OBO study. We feel these are relevant for the research community and might help future projects in tackling these *a priori*:

Co-creation

- It was extremely important to have a clear line of communication with the stakeholders and involve them in both the design and the study period. This allowed us to address their concerns upfront. Communication was done via presential meetings and the outcome of these was then transmitted through the whole OBO consortium. We noticed that it was very important to make the aim of the project clear from the start and to check if all stakeholders understood the main goals (i.e. managing expectations).
- The collaboration with the branch organizations was also very important as they assisted with the recruitment of growers.
- Information events proved very helpful for dissemination and discussion of results in both the local communities and the growers.

Practical

a) Participation and selection

- Obtaining participation of selected households (at different distances and directions) around selected fields, with a diverse population (i.e. in age, sex) proved to be a difficult task. Although overall we achieved a good spatial distribution of homes per distance to selected field, in some locations, we had more than 50% of the homes located in one of the distance categories (i.e. <50 m, 50-150 m, 150-250 m). Ideally, we would have for each location 1/3 of the homes per ring. In addition, due

to additional requirements, such as multiple persons within a household and the presence of children made selection of appropriate households challenging.

- The recruitment of growers proved difficult both due to the underlying needs of the project regarding data (e.g. spraying schedule) but also pressure within the agricultural sector (e.g. “is the outcome of the project going to affect me and other farmers?”). However, once farmers were enrolled in the study they continued until the end. As mentioned above, the involvement of key branch organization was very important in this step.
- In the selection of urinary biomarkers, we selected pesticides with a lower exposure background via food intake to make the environmental exposure signal more clear. This was done based on information available in literature, but it was complicated to achieve high specificity.

b) *Periodicity of spraying applications*

- Regarding the active air sampling: logistics were complex as the exact timing of application was often unknown. Our solution was to install all equipment and wait till the application, however this created some downtime periods where there were not enough measuring instruments available. Aside from changes in intended date of application due to changes in meteorological conditions, regular communication with the grower regarding the date of intended application was very useful for the field work planning.

c) *Analytical*

- Synthesis of the analytical standards (and isotope labels) took considerable amount of time and caused a delay in analysis of the urine samples. It is difficult to do this in another way. We had to know what was actually sprayed, and what was found in the environment. Only then we could finalize the selection of the 5 pesticides and only then start volunteer studies, and finally get the biomarkers synthesized. This is important to take into account when setting up a new study.
- In retrospect, the dust samples provided a lot of valuable information regarding presence of various pesticides in the environment. So it would have been useful if we had done a full scan pre-screen of household dust in houses (and fields) of candidate growers/residents homes. For that, no ethics approval is needed, so we

could have done this at a very early stage of the study, during the time we were working on pesticide selection.

d) *Exposure of residents to pesticides and communication of results*

- It is important to take into account that we might have only captured a few different exposure scenarios by doing field work. We were constrained by existing meteorological conditions and by the applications that occurred within that time window. As a solution to this, we used the developed modelling framework to simulate realistic worst-case scenarios, by looking into long-term meteorological ranges and different applications settings.
- In the beginning of the project we promised participants feedback on their results, but given abovementioned time delays, this took a longer time, which resulted in a frustrating process for participants. For future projects we recommend informing a-priori the participants on possible delays that might occur.
- Given the very high sensitivity of the methods, detected exposures may still translate to very low absolute exposures. Therefore, results need to be carefully communicated in order to prevent possible misunderstanding.

Concluding remark

To conclude, the OBO study can shed light on current and future questions through the materials collected, developed methods and wealth of data. These can, for example, be used for testing model improvements, to put results of other exposure experiments into context or to develop new hypothesis, therefore also giving place for future collaborations.

Acknowledgments

This study was funded by the Dutch ministry of Infrastructure and Water Management and the ministry of Economic Affairs and Climate Policy. We would like to thank all participants and growers for their willingness to participate in this study, the stakeholders for continuous feedback given and all the parties involved in the OBO study group.

Collaborations

We cordially invite other researchers to propose non-commercial research based on the available data in OBO or requests for additional chemical analyses with associated funding. Any such requests can be submitted to exposome.office@uu.nl with subject: OBO-research.

Conflicts of Interest

None declared.

References

- Anastassiades, M., Lehotay S. J., Stahnbaier, D., Schenck, F. J. J. (2003) AOAC Int. 86, 412-431. Fast and easy multiresidue method employing acetonitrile extraction/partitioning and “dispersive Solid-Phase Extraction” for the Determination of Pesticide Residues in Produce. PMID: 12723926
- Béranger, R., Billoir, E., Nuckols, J. R., Blain, J., Millet, M., Bayle, M. L., Combourieu, B., Philip, T., Schüz, J., & Fervers, B. (2019). Agricultural and domestic pesticides in house dust from different agricultural areas in France. *Environmental Science and Pollution Research*, 26(19), 19632–19645. <https://doi.org/10.1007/s11356-019-05313-9>
- Brouwer, M., Huss, A., van der Mark, M., Nijssen, P. C. G., Mulleners, W. M., Sas, A. M. G., . . . Vermeulen, R. C. H. (2017). Environmental exposure to pesticides and the risk of parkinson's disease in the Netherlands. *Environment International*, 107, 100-110. [https://doi.org/S0160-4120\(17\)30075-2](https://doi.org/S0160-4120(17)30075-2)
- Butler Ellis, M. C., Lane, A. G., O'Sullivan, C. M., Miller, P. C. H., Glass, C. R. (2010). Bystander exposure to pesticide spray drift: New data for model development and validation. *Biosystems Engineering* 107:162–168. <https://doi.org/10.1016/j.biosystemseng.2010.05.017>
- Carratalá, A., Moreno-González, R., & León, V. M. (2017). Occurrence and seasonal distribution of polycyclic aromatic hydrocarbons and legacy and current-use pesticides in air from a Mediterranean coastal lagoon (Mar Menor, SE Spain). *Chemosphere*, 167, 382–395. <https://doi.org/10.1016/j.chemosphere.2016.09.157>
- Castor EDC. (2019). Castor Electronic Data Capture. [online] Available at: <https://castoredc.com>
- CBS(2015). <https://opendata.cbs.nl/statline/#/CBS/nl/dataset/84007NED/table?ts=1605800063102> [accessed last time 25-11-2020]
- Climent, M. J., Coscollà, C., López, A., Barra, R., & Urrutia, R. (2019). Legacy and current-use pesticides (CUPs) in the atmosphere of a rural area in central Chile, using passive air samplers. *Science of the Total Environment*, 662, 646–654. <https://doi.org/10.1016/j.scitotenv.2019.01.302>
- Couture, C., Fortin, M. C., Carrier, G., Dumas, P., Tremblay, C., & Bouchard, M. (2009). Assessment of exposure to pyrethroids and pyrethrins in a rural population of the monteregie area, quebec, canada. *Journal of Occupational and Environmental Hygiene*, 6(6), 341-352. <https://doi.org/10.1080/15459620902850907>
- de Vreede, J. A. F., Brouwer, D. H., Stevenson, H., van Hemmen, J. J., Exposure and Risk Estimation for Pesticides in High-volume Spraying, *The Annals of Occupational Hygiene*, Volume 42, Issue 3, April 1998, Pages 151–157, <https://doi.org/10.1093/annhyg/42.3.151>
- Dereumeaux, C., Saoudi, A., Gorla, S., Wagner, V., De Crouy-Chanel, P., Pecheux, M., Berat, B., Zaros, C., & Guldner, L. (2018). Urinary levels of pyrethroid pesticides and determinants in pregnant French women from the Elfe cohort. *Environment International*, 119(April), 89–99. <https://doi.org/10.1016/j.envint.2018.04.042>
- Dereumeaux, C., Fillol, C., Quenel, P., & Denys, S. (2020). Pesticide exposures for residents living close

- to agricultural lands: A review. *Environment International*, 134(May 2019), 105210. <https://doi.org/10.1016/j.envint.2019.105210>
- Deziel, N. C., Beane Freeman, L. E., Hoppin, J. A., Thomas, K., Lerro, C. C., Jones, R. R., ... Friesen, M. C. (2018). An algorithm for quantitatively estimating non-occupational pesticide exposure intensity for spouses in the Agricultural Health Study. *Journal of Exposure Science & Environmental Epidemiology*. <https://doi.org/10.1038/s41370-018-0088-z>
- Estellano, V. H., Pozo, K., Efstathiou, C., Pozo, K., Corsolini, S., & Focardi, S. (2015). Assessing levels and seasonal variations of current-use pesticides (CUPs) in the Tuscan atmosphere, Italy, using polyurethane foam disks (PUF) passive air samplers. *Environmental Pollution*, 205, 52–59. <https://doi.org/10.1016/j.envpol.2015.05.002>
- Fang, Y., Nie, Z., Die, Q., Tian, Y., Liu, F., He, J., & Huang, Q. (2017). Organochlorine pesticides in soil, air, and vegetation at and around a contaminated site in southwestern China: Concentration, transmission, and risk evaluation. *Chemosphere*, 178, 340–349. <https://doi.org/10.1016/j.chemosphere.2017.02.151>
- Fernández, S. F., Pardo, O., Adam-Cervera, I., Montesinos, L., Corpas-Burgos, F., Roca, M., Pastor, A., Vento, M., Cernada, M., & Yusà, V. (2020). Biomonitoring of non-persistent pesticides in urine from lactating mothers: Exposure and risk assessment. *Science of the Total Environment*, 699. <https://doi.org/10.1016/j.scitotenv.2019.134385>
- Figueiredo, D. M., Vermeulen, R. C. H, Duyzer, J. (2018). An integrated modelling framework to estimate residents' exposure to pesticides from boom sprayer applications. *Occupational and Environmental Medicine* Mar 2018, 75 (Suppl 1) A34; <https://doi.org/10.1136/oemed-2018-ISEEabstracts.84>
- Holterman, H.J., Van de Zande, J.C., Porskamp, H.A.J., Huijsmans, J.F.M. (1997). Modelling spray drift from boom sprayers. *Computers and Electronics in Agriculture* 19:1-22. [https://doi.org/10.1016/S0168-1699\(97\)00018-5](https://doi.org/10.1016/S0168-1699(97)00018-5)
- Hoppin, J. A. (2014). Pesticides and respiratory health: Where do we go from here? *Occupational and Environmental Medicine*, 71(2), 80-2013. <https://doi.org/10.1136/oemed-2013-101876>
- Hung, C., Huang, F., Yang, Y. et al. Pesticides in indoor and outdoor residential dust: A pilot study in a rural county of Taiwan. *Environ Sci Pollut Res* 25, 23349–23356 (2018). <https://doi.org/10.1007/s11356-018-2413-4>
- Kimata, A., Kondo, T., Ueyama, J., Yamamoto, K., Kamijima, M., Suzuki, K., . . . Hamajima, N. (2009). Relationship between dietary habits and urinary concentrations of 3-phenoxybenzoic acid in a middle-aged and elderly general population in Japan. *Environmental Health and Preventive Medicine*, 14(3), 173-179. <https://doi.org/10.1007/s12199-009-0077-x>
- Koureas, M., Tsakalof, A., Tzatzarakis, M., Vakonaki, E., Tsatsakis, A., & Hadjichristodoulou, C. (2014). Biomonitoring of organophosphate exposure of pesticide sprayers and comparison of exposure levels with other population groups in Thessaly (Greece). *Occupational and Environmental Medicine*, 71(2), 126-133. <https://doi.org/10.1136/oemed-2013-101490>

- Kruijine, R., Mol, H., Jeurissen, L., Wenneker M. & Van de Zande, J. (2019). Pesticides and Local Residents - Selection of Substances, Measuring Locations and Target Population. Wageningen, Wageningen Environmental Research, Report 2924. [75 pp.].
- Liu, L., Tang, J., Zhong, G., Zhen, X., Pan, X., & Tian, C. (2018). Spatial distribution and seasonal variation of four current-use pesticides (CUPs) in air and surface water of the Bohai Sea, China. *Science of the Total Environment*, 621, 516–523. <https://doi.org/10.1016/j.scitotenv.2017.11.282>
- Lytras, T., Kogevinas, M., Kromhout, H., Carsin, A. E., Anto, J. M., Bentouhami, H., . . . Zock, J. P. (2018). Occupational exposures and 20-year incidence of COPD: The european community respiratory health survey. *Thorax*, 73(11), 1008-1015. <https://doi.org/10.1136/thoraxjnl-2017-211158>
- Oerlemans, A., van Dael, M. F. P., Vermeulen, R. C. H., Russel, F. G. M., & Scheepers, P. T. J. (2018). Urine collection methods for non-toilet-trained children in biological monitoring studies: Validation of a disposable diaper for characterization of tebuconazole exposure. *Toxicology Letters*, 298, 201–206. <https://doi.org/10.1016/j.toxlet.2018.09.018>
- Oerlemans, A., Verscheijden, L. F. M., Mol, J. G. J., Vermeulen, R. C. H., Westerhout, J., Roeleveld, N., ... Scheepers, P. T. J. (2019). Toxicokinetics of a urinary metabolite of tebuconazole following controlled oral and dermal administration in human volunteers. *Archives of Toxicology*, 93(9), 2545–2553. <https://doi.org/10.1007/s00204-019-02523-5>
- Perestrelo, R., Silva, P., Porto-Figueira, P., Pereira, J. A. M., Silva, C., Medina, S., Camara, J. S. (2019) *Anal. Chem. Acta* 1070, 1-28. QuEChERS - Fundamentals, relevant improvements, applications and future trends. <https://doi.org/10.1016/j.aca.2019.02.036>
- Rudel, R. A., Camann, D. E., Spengler, J. D., Korn, L. R., & Brody, J. G. (2003). Phthalates, alkylphenols, pesticides, polybrominated diphenyl ethers, and other endocrine-disrupting compounds in indoor air and dust. *Environmental Science and Technology*, 37(20), 4543–4553. <https://doi.org/10.1021/es0264596>
- TCT (2020). Drift Reducing Nozzle list (DRD-lijst). [<https://www.helpdeskwater.nl/onderwerpen/emissiebeheer/agrarisch/open-teelt/driftreducerende/>]
- van de Zande, J.C., H.J. Holterman & J.F.M. Huijsmans (2012). Spray drift assessment of exposure of aquatic organisms to plant protection products in the Netherlands. Part 1: Field crops and downward spraying. Wageningen UR Plant Research International, Plant Research International Report 419, Wageningen. 84p. <https://edepot.wur.nl/243240>
- van de Zande, J. C., & ter Horst, M. M. S. (2019). Crop related aspects of crop canopy spray interception and spray drift from downward directed spray applications in field crops. (Report / Stichting Wageningen Research, Wageningen Plant Research, Business Unit Agrosystems Research; No. WPR-420). Stichting Wageningen Research, Wageningen Plant Research, Business Unit Agrosystems Research. <https://doi.org/10.18174/514310>
- van de Zande, J.C., H.J. Holterman, J.F.M. Huijsmans, M. Wenneker (2019). Spray drift for the assessment of exposure of aquatic organisms to plant protection products in the Netherlands. Part 2: Sideways and upward sprayed fruit and tree crops. Wageningen Plant Research, Report

- WPR-564, Wageningen. 2019. 85 p. <https://doi.org/10.18174/448381>
- van den Berg, F., Jacobs, C. M. J., Butler Ellis, M. C., Spanoghe, P., Doan Ngoc, K., & Fragkoulis, G. (2016). Modelling exposure of workers, residents and bystanders to vapour of plant protection products after application to crops. *Science of the Total Environment*, 573, 1010–1020. <https://doi.org/10.1016/j.scitotenv.2016.08.180>
- van der Mark, M., Brouwer, M., Kromhout, H., Nijssen, P., Huss, A., & Vermeulen, R. (2012). Is pesticide use related to parkinson disease? some clues to heterogeneity in study results. *Environmental Health Perspectives*, 120(3), 340-347. <https://doi.org/10.1289/ehp.1103881>
- Wang, X., Banks, A. P. W., He, C., Drage, D. S., Gallen, C. L., Li, Y., Li, Q., Thai, P. K., & Mueller, J. F. (2019). Polycyclic aromatic hydrocarbons, polychlorinated biphenyls and legacy and current pesticides in indoor environment in Australia – occurrence, sources and exposure risks. *Science of the Total Environment*, 693, 133588. <https://doi.org/10.1016/j.scitotenv.2019.133588>
- Weichenthal, S., Moase, C., & Chan, P. (2012). A review of pesticide exposure and cancer incidence in the agricultural health study cohort. *Ciencia & Saude Coletiva*, 17(1), 255-270. <https://doi.org/S1413-81232012000100028>

Supplementary Material 1 - List of most relevant pesticides in flower bulb cultivation in The Netherlands

Table S1. List of most relevant pesticides in flower bulb cultivation in The Netherlands (emphasis on field application in tulip, lily) [situation 2015]

Pesticides	Amenability ³ to		
	MRM4 LC-MS/MS	MRM4 GC-MS/MS	5 SRM
TIER 1. Applied in flower bulbs			
acetamiprid	+	-	
asulam	+	-	
boscalid	+	+	
chlorpropham	+	+	
chlorothalonil ¹	-	+	
chlorigazon	+	±	
cyprodinil	+	+	
deltamethrin	±	+	
dimethenamide-P	+	+	
diquat ¹	-	-	+
esfenvaleraat ¹	-	+	
flonicamid	+	-	
fludioxonil	+	+	
fluopyram	+	+	
flutolanil ²	+	+	
fosthiazate ²	+	±	
folpet ¹	-	+	
glyfosaatv	-	-	+
iprodion ¹	-	+	
kresoxim - methyl	+	+	
lambda-cyhalothrin	±	+	
mancozeb ¹	-	-	+
mepanipyrim	+	+	
metamitron	+	±	
metolachlor-S	+	+	
paraffin oil ¹	-	-	+
pendimethalin	+	+	
prochloraz	+	±	

prothioconazole	+	±
pymetrozine	+	-
spirotetramat	+	+
tebuconazole	+	+
thiacloprid	+	-
tolclofos-methyl ²	+	+
trifloxystrobin	+	+

TIER 2. Data on pesticides found in bulb fields (existing field monitoring data in The Netherlands, bulb fields, 2014, as far as not already mentioned under TIER 1.)

azoxystrobin	+	+
carbendazim	+	-
difenoconazole	+	+
dimethomorph	+	+
fluopicolide	+	+
imidacloprid	+	-
linuron	+	+
oxamyl	+	-
pirimicarb	+	+
propamocarb	+	±
pyraclostrobin	+	+
sulcotrione	+	-
terbuthylazine	+	+
thiophanate-methyl	+	-

Tier 3. Metabolites from MRM LC-MS/MS amenable pesticides that may also occur as human biomarkers of exposure 5

fluopyram-benzamide	+	-
desaminometamitron	+	-
prothioconazole-desthio	+	-
spirotetramat-enol	+	-
trifloxystrobin acid (CGA 321113)	+	-

¹ not included in environmental measurements

² used for soil treatment

³ + means method well suited; ± means moderately suited/not very sensitive; - means not suited/not sensitive

⁴ MRM = multi-residue method (extraction/instrumental method allowing simultaneous measurement of the indicated pesticides)

⁵ SRM = single residue method (dedicated method needed for analysis of that specific pesticide)

⁶ only metabolites for which analytical standards were readily available in 2015 were included for environmental analysis

Supplementary Material 2 - List of targeted pesticides and chemical properties

Table S2. List of 46 pesticides targeted for analysis of environmental samples

Type	Pesticides	Vap [mPa] ^a	Log K _{oa} [-] ^b	dt50 in soil (days) ^a
Fungicides	Azoxystrobin	1.1E-07	1.4E+01	1.8E+02
	Boscalid	7.2E-04	1.3E+01	4.8E+02
	Cyprodinil	4.9E-01	9.5E+00	4.5E+01
	Difenoconazole	3.3E-05	1.4E+01	8.5E+01
	Dimethomorph	9.9E-01	1.1E+01	4.4E+01
	Fludioxonil	3.9E-04	1.2E+01	2.1E+01
	Fluopicolide	8.0E-04	1.5E+01	1.4E+02
	Fluopyram	4.2E-03	1.4E+01	1.2E+02
	Flutolanil	1.8E+00	1.1E+01	1.1E+02
	Kresoxim-methyl	2.3E-03	1.0E+01	1.0E+00
	Mepanipyrim	2.3E-02	9.5E+00	5.7E+01
	Prochloraz	1.5E-01	1.0E+01	2.0E+01
	Propamocarb	7.3E+03	8.3E+00	2.0E+01
	Prothioconazole	4.5E-09	1.4E+01	7.7E-01
	Pyraclostrobin	2.6E-05	1.7E+01	3.3E+01
	Tebuconazole	1.7E-03	1.2E+01	4.7E+01
	Thiophanate-methyl	9.5E-03	8.7E+00	2.0E+00
	Tolclofos-methyl	5.7E+01	6.8E+00	7.6E+00
	Trifloxystrobin	3.4E-03	9.9E+00	1.7E+00
	Fluopyram-benzamide ^(c)	4.2E-03	6.8E+00	8.6E+00
	Prothioconazole-desthio ^(c)	1.1E-03	1.2E+01	4.2E+01
	Trifloxystrobin-acid ^(c)	5.5E-03	9.9E+00	7.0E+01
	Carbendazim [*]	1.0E-04	1.1E+01	2.2E+01
Herbicides	Asulam	1.9E-01	9.9E+00	9.0E+00
	Chloridazon	6.0E-02	9.0E+00	3.5E+01
	Chlorpropham	2.4E+01	8.1E+00	1.3E+01
	Dimethenamid-P	2.5E+00	7.6E+00	7.0E+00
	Linuron	1.9E-01	9.8E+00	4.8E+01
	Metamitron	8.6E-04	1.1E+01	1.1E+01
	Pendimethalin	1.3E+00	9.6E+00	1.0E+02
	Metolachlor-S	4.2E+00	9.3E+00	2.1E+01
	Sulcotrione	5.0E-03	1.1E+01	3.6E+00
	Terbuthylazine	9.0E-02	9.0E+00	2.2E+01
	Metamitron-desamino ^(c)	4.5E-04	8.7E+00	3.1E+01
Insecticides	Acetamiprid	5.9E+00	8.1E+00	3.0E+00
	Cyhalotrin-lambda	4.5E-04	1.1E+01	2.7E+01
	Deltamethrin	1.2E-05	9.9E+00	2.1E+01
	Flonicamid	9.4E-04	1.3E+01	3.1E+00
	Fosthiazate	5.6E-01	9.8E+00	1.3E+01
	Imidacloprid	2.1E-01	1.4E+01	1.7E+02

Oxamyl	3.1E+01	7.5E+00	6.0E+00
Pirimicarb	9.7E-01	9.2E+00	7.3E+01
Pymetrozine	1.8E-03	1.1E+01	2.3E+01
Spirotetramat	6.0E-06	1.4E+01	7.0E-01
Thiacloprid	8.0E-07	1.0E+01	8.1E+00
Spirotetramat-enol ^(t)	6.0E-06	1.6E+01	1.9E+00

^aVapor pressure and Half-life in soil, from Lewis et al. 2016, ^b US EPA. 2020 KOAWIN v1.10 estimate, ^(t) transformation product, *besides being a fungicide, carbendazim is also a degradation product of thiophanate-methyl.

Supplementary Material 3 - Short list of eight pesticides

To create this short list of pesticides we looked at each group (herbicides, insecticides and fungicides) distinctly to choose the most appropriate ones from each group. Our focus was on pesticides which were authorized for spraying applications. We used the registry of the Ctgb to search for pesticides with an authorized use in one or both flower bulb crops tulip and lily; as at the end of 2015. The selection process is described below for each of these groups.

Herbicides

Indices

Dose rate: Metamitron had the highest recommended dose rate and S-metolachlor the lowest.

Market shares: The highest market shares were reported for chlorpropham and pendimethalin (tulip and lily) and for metamitron (tulip). Also with high shares were asulam and S-metolachlor.

Vapor pressure: Low vapor pressure pesticides were asulam and metamitron. The pesticides pendimethalin, dimethenamide-P, S-metolachlor, and chlorpropham had the highest vapor pressures within the herbicide group.

Dermal absorption rates: Within the above group the highest calculated dermal absorption rates were for chlorpropham, S-metolachlor, and dimethenamide-P.

Exposure to herbicides through food is very unlikely, with the exception being maybe chlorpropham (through potatoes). However, the other selection indices were considered to outweigh a potential issue with background exposure through other routes apart from the environmental route.

Based on these indices for the group of herbicides, **chlorpropham and asulam** were considered the most relevant candidates for inclusion in the biomonitoring. Chlorpropham representing a volatile, low to moderate dose rate pesticide, and asulam representing a non-volatile, high dose rate pesticide.

Insecticides

Indices

Dose rate: Thiacloprid had the highest recommended dose rate and lambda-cyhalothrin the lowest.

Market shares: The market shares of these insecticides were generally lower than the market shares of the investigated herbicides. However, an insecticide with relatively high market share in tulip was spirotetramat.

Vapor pressure: Low vapor pressure pesticides were deltamethrin and spirotetramat. The other pesticides have considerably higher vapor pressures.

Dermal absorption rates: Within the above group the highest calculated dermal absorption rates were for acetamiprid, flonicamid, thiacloprid, and pymetrozine.

All insecticides were applied 2, 3 or 4 times, with the exception of lambda-cyhalothrin which was applied 11 times in tulip and 20 times in lilies.

Based on the above indices for the group of seven insecticides, it was proposed to select either **flonicamid, acetamiprid, or thiacloprid** for biomonitoring in the vicinity of the selected experimental fields used for lily cultivation. The choice depended on the product used by the participating grower.

Fungicides

Indices

Dose rate: Prochloraz had the highest recommended dose rate and Fluopyram the lowest.

Market shares: The market shares of these fungicides were generally lower than the market shares of the herbicides proposed and were comparable with the market shares of the insecticides. The highest market shares were reported for prochloraz, fluopyram, and trifloxystrobin (80%; in lily). The fungicides with the highest market share in tulips were boscalid (55%), and tebuconazole (50%).

Vapor pressure: Low vapor pressure pesticides were prothioconazole and boscalid. The other pesticides have considerably higher vapor pressures.

Dermal absorption rates: Within the above group the highest calculated dermal absorption rates were for tebuconazole, prochloraz, and prothioconazole.

All fungicides were applied 3 to 5 times in tulip, and up to 6 times in lily. The risk of background exposure from food intake was high for boscalid and was also relatively high for tebuconazole, fluopyram, and to a lesser extent for trifloxystrobin and prochloraz.

Based on the above information for the eight identified fungicides, it was proposed to select **prochloraz** for the biomonitoring in the vicinity of the selected experimental fields used for lily cultivation. For tulip, **tebuconazole** was proposed. **Trifloxystrobin** would be a third candidate because it was used both in tulips and lilies. Similar to the insecticides, the choice will depend on the pesticides used by the participating growers.

The final short-list of eight pesticides (active ingredients) is presented in Table 3.

Table S3. Short list of pesticides pre-selected for biomonitoring

Product use	Active ingredient	Product(s)
Herbicide	chlorpropham	Intruder, Certis Chloor IPC 40% Vloeibaar
	asulam	Asulox
Insecticide	flonicamid	Teppeki
	acetamiprid	Gazelle
	thiacloprid	Calypso
Fungicide	prochloraz	Mirage plus 570 SC Allure vloeibaar
	trifloxystrobin	Luna sensation (also contains fluopyram); Flint
	tebuconazole	Spirit (also contains folpet) Luna experience (also contains fluopyram)

Supplementary Material 4 – OBO Questionnaire, diary and field form (translated)

The original documents were written in the dutch language. The material here presented is a translation of the original documents (without formatting).

Questionnaire

About this questionnaire

This questionnaire includes questions regarding your living situation, lifestyle habits and your work/company and/or study. Also, questions are asked about medicine use, ownership of pets, smoking habits and the use of pesticides. This questionnaire is intended for persons of 16 years and older. The total time needed to complete this questionnaire is 15 to 20 minutes. All your answers will be handled with confidentiality and will be processed and reported in coded form.

In this questionnaire you will encounter different types of questions:

Questions where you can tick one or more boxes or where you can write your answer out on a line, or both. Next, there can be questions where you are asked to enter numbers in boxes.

Instructions for completing this questionnaire:

- Please write with a blue or black pen, not with a thick marker.
- Please write all open questions in block letters.
- Note the arrows (=>) which might occur after an answer. An arrow is followed with an explanation.
- If you make a mistake, please check the box with the correct answer and circle the correct box. Do not use correction fluids.
- If you want to make a comment or clarify your answer, you can write next to the question.

If questions are not clear or if you need help with the completion of this questionnaire, you can contact the research assistant through phone or email [contact below].

PART 1 general questions

1. What is your date of birth?

-- -- ----
day month year

2. What is your gender?

Male
Female

3. What is your height?

cm

4. What is your weight?

kg

5. What is the highest level of education you completed?

None
Primary school
etc

Questions 6 and 7 only to be filed in by women

6. Do you currently breast-feed?

Yes
No

7. For how long have you been breast-feeding?

--
months

PART 2 questions about your living environment and lifestyle habits

8. Did you have pets in the past 6 months? (excluding poultry/cattle)

Yes
No => please continue with question 10

9. Which pets did you own in the past 6 months? Please also provide the number of pets per kind of pet. [several answers possible]

Dog	(amount)
Cat	(amount)
Rodent	(amount)
Bird	(amount)
Other	(name and amount)

10. Have you been in direct contact with poultry during the past 6 months?

Yes
No

11. Did you use tobacco products and/or e-cigarettes during the past 6 months?

Yes
No => please continue with question 13

12. Which tobacco products and/or e-cigarettes did you use during the past 6 months?

Cigarettes	(amount/day)
Shag	(amount/day)
Cigars	(amount/day)
e-cigarette	(amount/day)
Other	(amount/day)

13. Did you eat homegrown vegetables, fruit and/or herbs during the past 6 months?

Yes

No => please continue with question 16

14. Indicate per season what proportion of homegrown vegetables, fruit and/or herbs you ate during the past 6 months. [check applicable boxes]

	(Almost) all	About 3/4	About half	About 1/4	(Almost) nothing
Spring					
Summer					
Autumn					
Winter					

15. Did you use groundwater for watering your vegetable garden during the past 6 months?

Yes

No

16. What happens to your footwear [usually] when you come from outside and you enter the house?

I keep my footwear on inside

I leave my footwear in the hallway/kitchen/garage/shed

I leave my footwear outside

Other, namely:

17. What happens with the footwear of other persons living in your household when they come from outside and they enter the house?

They keep their footwear on inside

They leave their footwear in the hallway/kitchen/garage/shed

They leave their footwear outside

Other, namely:

18. Where do you usually dry the laundry during Summer?

Inside

Outside

19. Please indicate on average per day how many hours you did dry your laundry outside during the past 6 months?

0-1 hours a day

1-2 hours a day

2-4 hours a day

4-8 hours a day

8 hours or more/day

20. How often have you smelled pesticides in or around your home during the past 6 months?

Never => please continue with question 22

Less than once a month

1 to 2 times a month

2 to 3 times a month

More than 4 times a month

21. To what extent were you bothered by the smell of pesticides in or around your home during the past 6 months? [please provide a number on a scale from 1 to 10, 1= not bothered, 10=very much bothered]

--

PART 3 questions regarding medicine use

22. Did you use medicine(s) on doctor's prescription during the past 6 months?

Yes

No => please continue with question 24

I do not want to answer this question => please continue with question 24

23. Which medicine(s), only on doctor's prescription, did you use during the past 6 months? (if you do not remember the name of the medicine please indicate what you used the medicine for)

24. Did you use medicine(s) and/or homeopathic substances without prescription during the past 6 months? (e.g. paracetamol, nicotine patches)

Yes

No => please continue with question 26

I do not want to answer this question => please continue with question 26

25. Which medicine(s), without prescription, did you use during the past 6 months? (if you do not remember the name of the medicine please indicate what you used the medicine for)

PART 4 questions about the house

26. What is the year of construction of the house you are currently living in? (give an estimation if you do not know the exact year)

year

27. How long do you live in the house you are currently living in? (1 if you live here less than 12 months)

--
years

28. Please indicate per room and per season if windows were opened usually during the day.

	Spring	Summer	Autumn	Winter
Living room				
Bathroom				
Kitchen				
Your bedroom				
Other rooms				

29. How many people are living in your household without counting yourself?

Amount of people without counting yourself

--

Year of birth person 1 ----

Year of birth person 2 ----

etc

PART 5 questions regarding work, business and/or study

30. Which of the following situations are applicable to you regarding work and study during the past 6 months?

(several answers possible)

Work, 36 hours per week or more, including own business (farm) and self-employed

Work, 35 hours per week or less, including a side job or helping on the farm (or other business)

Fulltime student (high school, university etc)

Part-time student (e.g. evening education)

Volunteer work => please continue with question 49

Retired => please continue with question 49

None of the above => please continue with question 49

31. Please provide the following information regarding your work and/or education of the past 6 months.

Company/education 1

Profession/job description

Activities/tasks

Amount of days/week Amount of hours/week

Zip-code, house number

Company/education 2

etc

32. Which modes of transportation do you [usually] use from and to your work/business and/or education? Please indicate the average amount of time you spend during a weekday

Walking (minutes/day)

Bicycling (minutes/day)

Scooter/Motor/Moped (minutes/day)

Car/Van (minutes/day)

Tractor/Agricultural vehicle (minutes/day)

Public transport (minutes/day)

Other, namely: (minutes/day)

33. On an average weekday do you usually travel between different locations?

Yes

No => please continue with question 35

34. Through which modes of transportation do you [usually] use during a week/workday? Please indicate the average amount of time you spend during a week/workday.

Walking (minutes/day)

Bicycling (minutes/day)

Scooter/Motor/Moped (minutes/day)

Car/Van (minutes/day)

Tractor/Agricultural vehicle (minutes/day)

Public transport (minutes/day)

Other, namely: (minutes/day)

35. What is the total area of your business or the business where you are employed? Inclusive all agricultural plots/ fields/greenhouses.

hectare

I'm not working at an agricultural business => please continue with question 39

36. Please provide the agricultural products of your business or the business where you are employed. Please also indicate from when to when the crops were grown, and whether on open ground or in a greenhouse.

Agricultural product	From	Till	Open ground	Greenhouse
Example: potatoes	February 2018	April 2018	Yes	No

37. Are there poultry and/or cattle present at your business or the business where you are employed?

Yes, namely:

No

38. After which time do you enter the plot [usually] after it has been sprayed by you or other persons?

0-12 hours

12-24 hours

1-2 days

2-7 days

7 days or more

39. Did you use pesticides and/or biocides at your work during the past 6 months?

Yes

No => please continue with question 45

40. Which pesticides have you been using at your work during the past 6 months?
(please provide the name of the substance and the registration number which can be found on the back of the packing)

Name of substance	Registration number

41. Please indicate which protective equipment you used if you have been working with pesticides and/or biocides. Also indicate if the protective equipment is being cleaned, thrown away or reused without cleaning.

Protective equipment	Cleaned	Thrown away	Reused without cleaning
(reusable) overall or other protective clothing			
Boots			
Gloves			
Mouth cap			
Full- or half-face mask			
Eye protection			
Other, namely			
I'm not using any protective products when working with pesticides => continue with question 43			

42. Where and when do you take your protective clothing off usually, when used during spraying activities?
- Inside in a barrack/shed and directly after spraying
- Inside in a barrack/shed, not directly after the spraying activities
- Outside directly after the spraying activities
- Outside, not directly after the spraying activities
- I take off my protective clothing inside the house
- Other, namely:
43. Please indicate how often the clothing used during spraying is washed together with other clothing, of you or other members of the household.
- Always
- Often
- Sometimes
- Almost never
- Never
44. How are pesticides and/or biocides being applied during your spraying activity?
- With a hand sprayer and/or back sprayer
- With an engine grease gun
- With a spraying machine without (closed) cabin
- With a spraying machine with closed cabin
- Other, namely:
45. Do others perform spraying activities with pesticides and/or biocides in your direct working environment?
- Yes
- No => please continue with question 49

46. Which pesticides have others been using at your working environment?
(please provide the name of the substance and the registration number which can be found on the back of the packing)

Name of substance	Registration number

47. Please indicate which protective equipment you used when others are working with pesticides and/or biocides. Also indicate if the protective equipment is being cleaned, thrown away or reused without cleaning.

Protective equipment	Cleaned	Thrown away	Reused without cleaning
(reusable) overall or other protective clothing			
Boots			
Gloves			
Mouth cap			
Full- or half-face mask			
Eye protection			
Other, namely			
I'm not using any protective products when working with pesticides => continue with question 43			

48. Please give a short description of how you and/or others in your direct working environment are handling and using pesticides and/or biocides. (think about filling systems, spraying methods, spraying machines, frequencies, amount of liters, amount of hectares etc)

PART 6 use of pesticides and/or biocides in and around the house

49. Please indicate per category if you used these products in and around the house during the past 6 months. (usage of the products during work are not included)

	Yes	No
Products for example fleas and ticks by pets		
Products for head lice		
Products for insects (lice, ants, caterpillars, mosquitos etc)		
Products for weeds or moss		
Products for mold (for example paint or kit against mold)		
Products for snails		
Products for rats and mice		
Other, namely		

=> if you only said "no" at the last question, please continue with question 53

50. Which pesticides and/or biocides did you use in and around the house during the past 6 months? (name and registration number, which can be found on the packing. If you do not remember the name, please indicate the purpose of the product)

Name of substance	Registration number

51. Did you use any protective equipment or clothing during the use of pesticides/biocides in and around the house during the past 6 months? Yes, only if I used the pesticides/biocides
 Yes, only if others used pesticides/biocides in my direct living environment
 Yes, both if I and others were using pesticides/biocides in my direct living environment
 No => please continue with question 53

52. Which protective equipment or clothing did you use in and around the house during the past 6 months? (reusable) overall or other protective clothing
 Boots
 Gloves
 Mouth cap
 Full- or half-face mask
 Eye protection
 other, namely:

53. If you do have other information which you think might be important for your urine measures, please indicate this below:

Thank you very much for the completion of this questionnaire!

Diary

About this dairy

This dairy includes questions about your food intake, use of pesticides and locations you visited. Also, you are asked to write some numbers and times. For example the time of last toilet visit. Enclosed to this dairy is the protocol for urine collection.

You are asked to fill in this dairy one day before urine collection.

This questionnaire is intended for persons of 16 years and older. The total time needed to complete this dairy is 15 to 20 minutes. All your answers will be handled with confidentiality and will be processed and reported in coded form.

In this diary you will encounter different types of questions:

Questions where you can tick one or more boxes or where you can write your answer out on a line, or both. Next, there can be questions where you are asked to enter numbers in boxes.

Instructions for completing this questionnaire:

- Please write with a blue or black pen, not with a thick marker.
- Please write all open questions in block letters.
- Note the arrows (=>) which might occur after an answer. An arrow is followed with an explanation.
- If you make a mistake, please check the box with the correct answer and circle the correct box. Do not use correction fluids.
- If you want to make a comment or clarify your answer, you can write next to the question.

If questions are not clear or if you need help with the completion of this questionnaire, you can contact the research assistant through phone or email [contact below].

PART 1 before urine collection

1. Please indicate per location how much time you spend today. (in hours and minutes, leave the box empty when you did not spend any time at that location)

Inside

Own house (including sleeping)	[hours/minutes]
Inside at work/company	[hours/minutes]
Inside in a shed, garage etc	[hours/minutes]
Inside somewhere else, namely	[hours/minutes]

Transport

In a vehicle (car/bus etc)	[hours/minutes]
On a tractor or other agricultural vehicle	[hours/minutes]
On a bicycle or walking	[hours/minutes]

Outside

At own garden or street	[hours/minutes]
Outside at work/company	[hours/minutes]
At agricultural field/orchard	[hours/minutes]
Outside somewhere else, namely	[hours/minutes]

2. Have you been in direct (skin)contact with pets, poultry or cattle today?
Yes
No
Not sure
3. Did you enlighten the fireplace inside today?
Yes
No
4. Please indicate per category if you possibly have been in contact or close to these products today. (usage of the products during work are not included)

Yes No

Products for example fleas and ticks by pets
 Products for head lice
 Products for insects (lice, ants, caterpillars, mosquitos etc)
 Products for weeds or moss
 Products for mold (for example paint or kit against mold)
 Products for snails
 Products for rats and mice
 Other, namely

5. In which rooms did you open any windows and/or doors today? Please indicate for how long the doors and/or windows were open.

Up to 1 hour	1 to 2 hours	2 to 4 hours	4 to 8 hours	8 hours or more
Living room				
Your bedroom				
Bedroom child(ren)				
Kitchen				
Toilet				
Bathroom				
Other, namely				

6. Please indicate your food intake per time stamp of the day, including the amount per food type. For vegetables and fruit, it is asked if it is home grown or biological.

Vegetables

	Time of consumption	Total amount in pieces or gram	Homegrown? Y/N	Biological? Y/N
Endive				
Eggplant				
Broccoli				
Celery				
Cauliflower				
Beans (all kinds)				
Champignon				

Others: vegetable mix, cucumber, cabbage, corn, bell pepper, leeks, lettuce, spinach, tomato, onion, chicory, carrot

Fruit

	Time of consumption	Total amount in pieces or gram	Homegrown? Y/N	Biological? Y/N
Strawberries				
Apple				
Banana				
Berries (all kinds)				
Blackberries				
Citrus fruits (lemon, orange etc)				
Grapes				

Others: raspberries, cherries, kiwi, nectarine, pear, peach

Other food

	Time of consumption	Total amount in pieces or gram
Potatoes		
Bread		
Eggs		
Other wheat products (e.g. cereals, muesli)		
Pasta (all kinds)		
Rice (all kinds)		
Superfoods (chia seeds, quinoa, etc)		

Drinks

	Time of consumption	Total amount of glasses
Soda		
Packed juice		
Fresh juice		
Coffee		
Milk (all kinds)		
Tea		
Water		
Wine and beer		

7. Did you barbecue today?
Yes
No
8. Has there been a barbecue or firepit in use at your garden or direct surroundings today?
Yes
No
9. Did you use any medicine today? (including paracetamol, cough drops etc)
Yes
No => please continue with question 11
I do not want to answer this question => please continue with question 11
10. Which medicine did you use today? (if you can not recall the name please indicate for what you used it)

11. If you do have other information which you think might be important for your urine measures, please indicate this below:

This was the dairy for today, please answer the questions on the next page tomorrow morning after the urine collection.

[Instruction for urine collection]

Needed: container, cool box, cup

Tip: place the container on top of the toilet seat to ensure you won't forget it.

Urine Collection

1. What is the date of urine collection?

-- -- ----
day month year

2. At which time did you collect urine?

-- --
hours minutes

3. What is the time of your last toilet visit before urine collection?

-- --
hours minutes

Field form

Dear participant,

Would you be so kind to complete this form before the first house visit? If there are any uncertainties you can leave the question open and the fieldworker will help you during the house visit. During the house visit we would like to sketch a map of your home and garden. If you do have (construction) map we would be very pleased to get a copy. Thanks in advance!

1. What is the surface of the house?

< 40 m²
40 – 80 m²
80 – 120 m²
120 – 160 m²
160 - 200 m²
> 200 m²

2. What is the surface of the living room?

_____ m²

3. What is the volume of the house?

< 100 m³
100 – 200 m³
200 – 300 m³
300 - 400 m³
400 - 500 m³
> 500 m³

4. What is the height of the house (building of the house)?

_____m

5. What is the construction year of the house?

6. What is the type of house?
 - Detached house
 - Semidetached house
 - Terraced house
 - Appartment
 - Corner house
7. Does the house have a sloping or flat roof?
 - Sloping
 - Flat
8. What is the construction material of the house?
 - Brick
 - Concrete
 - Wood
 - Metal
 - Plastic
9. How many floors has the building in which the house is located?
 _____ floors (including ground floor and attic, excluding basement)
10. On which floor are the living room, kitchen and bedrooms located? (0 = ground floor)

Floor living room		
Floor kitchen		
Floor bedroom adult 1		
Floor bedroom adult 2		
Floor bedroom child 1		
Floor bedroom child 2		
11. Please specify the kitchen type:
 - Open kitchen (clear open connection between kitchen and living room)
 - Closed kitchen
12. How is the house supplied with hot water?
 - District heating
 - Central heating (gas)
 - Central heating (electric/solar panels)
 - Geyser in the kitchen with no ventilation flap (gas)
 - Geyser in the kitchen with ventilation flap (gas)
 - Other, namely _____
13. What is the heating system of the house?
 - Hot air heating
 - Radiators/underfloor heating
14. How is the house heated?
 - District heating
 - Central heating
 - Separate heating elements on gas
 - Separate heating elements on wood

Separate heating elements on oil

Fire place

Electrical heating

Other, namely _____

15. Do you use gas for cooking?

No

Yes

16. Is there a hood above the cooking area?

No

Yes, exhaust air is recirculated into the kitchen after passing an active coal filter

Yes, exhaust air is ventilated outside the house

17. Please specify the ventilation type in the house (several answers possible):

Air conditioning

Mechanistic ventilation for incoming air

Is always on

Is sometimes turned on by resident

Mechanistic ventilation for discharge of air

Is always on

Is sometimes turned on by resident

Mechanistic ventilation for incoming air and discharge of air

Is always on

Is sometimes turned on by resident

Natural ventilation

Ventilation grille (passive)

Small (<1500cm²) window that can be opened by resident

Large (>1500cm²) window that can be opened by resident

Door to the outside

Other, namely _____

18. Are there visible holes/cracks in the house that might influence ventilation?

No

Yes

19. Is the house airtight (with foam rubber)?

No

Yes

20. What type of flooring is used in the house?

Smooth floor (e.g. vinyl, parquet, laminate flooring, tiles)

Smooth floor with carpet (larger than 1 m²)

Carpeting

21. How old is the floor (give an estimation if you are not certain)?

_____ years

22. Are there any pets present in the house?

Cat amount:

Dog amount:

Bird amount:

Rodent amount:

Other, namely _____

Supplementary Material 5 – Selected fields, followed applications, meteorological conditions, participating homes and residents

Table S5. Performed measurements, meteo conditions in spraying day and total number of participants.

Location	Measurement campaign	Spraying day Mean (Min, Max)			Participating homes	Participating residents	
		T (°C)	Hum (%)	Ws (m/s)		Adults	2-17 yrs
A	UP1	13 (10,16)	80 (61,95)	3 (1,5)	10	21	5
	NP	n.a.			9	21	3
B	UP1	23 (17,32)	72 (37,96)	6 (2,8)	5	10	0
	NP	n.a.			5	10	0
C	UP1	5 (3,6)	87 (79,95)	6 (2,12)	11	17	3
	UP2	9 (7,11)	68 (60,79)	3 (1,5)	10	19	3
	NP	n.a.			11	19	3
D	UP1	4 (4,5)	88 (83,98)	3 (2,6)	10	17	7
	UP2	19 (16,25)	70 (51,83)	5 (3,10)	10	15	5
	NP	n.a.			11	19	7
E	UP1	9 (7,12)	68 (60,79)	3 (1,5)	3	6	9
	UP2	17 (12,24)	73 (38,97)	4 (1,8)	4	7	9
	NP	n.a.			4	7	9
F	UP1	16 (12,22)	62 (46,74)	5 (3,7)	12	16	5
	UP2	24 (18,30)	65 (44,93)	2 (1,6)	4	6	0
	NP	n.a.			9	14	3
G	UP1	18 (15,20)	75 (64,89)	5 (3,7)	7	9	3
	UP2	20 (17,23)	76 (54,91)	3 (2,5)	7	9	3
	NP	n.a.			7	9	3
H	UP1	22 (17,26)	57 (46,74)	5 (4,7)	8	9	2
	NP	n.a.			8	9	2
I	UP1	9 (4,13)	76 (48,94)	5 (2,8)	14	21	4
	NP	n.a.			14	21	4
Control locations	UP	n.a.			11	18	2
					6	8	2
	NP				15	26	2

n.a.: not applicable



3

Spatio-temporal variation of outdoor and indoor pesticide air concentrations in homes near agricultural fields

Daniel M. Figueiredo ^a, Jan Duyzer ^b, Anke Huss ^a, Esmeralda J.M. Krop ^a, M.G. Gerritsen-Ebben ^b, Yvonne Gooijer ^c and Roel C.H. Vermeulen ^{a, d}

^a Institute for Risk Assessment Sciences (IRAS), Division of Environmental Epidemiology, Utrecht University, 3584 CK Utrecht, The Netherlands

^b TNO Circular Economy & Environment, P.O. Box 80015, 3508 TA, Utrecht, The Netherlands

^c CLM Onderzoek en Advies BV, P.O. Box 62, 4100 AB, Culemborg, The Netherlands

^d Julius Center for Health Sciences and Primary Care, University Medical Center, University of Utrecht, 3584 CK Utrecht, The Netherlands

Published: Atmospheric Environment, Vol. 262, ID. 118612.

doi: 10.1016/j.atmosenv.2021.118612

Abstract

Background: Previous research has shown that many current-use pesticides can be detected in air around application areas. Environmental exposure to pesticides may cause adverse health effects, necessitating accurate assessment of outdoor and indoor air concentrations for people living close to spraying sites. We evaluated outdoor and indoor air concentrations of different pesticides, as well as factors influencing spatial and temporal variations.

Methods: We collected outdoor air samples at 58 homes located within 250 m of bulb fields and 15 control homes located further than 500 m from any agricultural field. Outdoor air sampling following a pesticide spray event was performed 24-h a day for 7 consecutive days. Two full day samples were collected at the same locations during a non-use period. In homes located within 50 m from agricultural fields ($N = 18$), indoor air was also sampled for the first 24 h after field spraying. Samples were analysed for a total of 46 pesticides and degradation products. From these, 11 were actively used on nearby fields, 3 were used in bulb disinfection and 6 were degradation products.

Results: Compared to non-use periods, pesticides concentrations were 5–10 times higher in outdoor air during application periods. Similar concentration differences were observed between exposed homes and controls both during pesticide use and non-use period. For 14 pesticides, there were moderate correlations (spearman > 0.4 – 0.7) between outdoor and indoor air concentrations. Wind direction, evapotranspiration and agricultural area surrounding a home were the most important determinants of air concentration of the applied pesticides.

Conclusions: This study provides strong evidence suggesting that environmental exposure to pesticides via air is not limited to the day of application and may occur year-round. The concentrations appeared higher during the use period. Factors influencing the local fate of pesticides in air may differ significantly between compounds.

Introduction

Currently there are almost 500 active ingredients (pesticides) approved for use in the European Union (EU) (EC, 2020). These pesticides differ greatly in environmental persistence, toxicity and other physico-chemical properties. Questions are posed regarding the health effects of acute and long-term exposures of residents to these current-use pesticides (CUPs) (Rull et al. 2009, Galea et al. 2011, Park et al. 2020, Dereumeaux et al. 2020).

CUPs enter the atmosphere via spray drift (Zivan et al. 2016), volatilization from plants and soil (Bedos et al. 2002) or surface water (Liu et al. 2018), and erosion of agricultural soils (Yang et al. 2016). Pesticide degradation occurs, mainly via soil microorganisms (Parte et al. 2017), sunlight (Borrás et al. 2017) and atmospheric oxidants (Socorro et al. 2017). These compounds are redistributed (Tiryaki & Temur 2010) into different environmental compartments (i.e. air, water, and soil) via wind dispersion, as well as via wet (Cindoruk & Ozturk 2016) and dry deposition (Sauret et al. 2009). Some pesticides and degradation products may remain in the environment long after application. Environmental persistence is one of the main factors leading to public concern regarding pesticide use, exposure (Saillenfait & Malard 2020) and possible health risks (Coscollà et al. 2017, Upadhayay et al. 2020).

One of the main environmental compartments where pesticides are present is air (e.g. López et al. 2017, Córdoba Gamboa et al. 2020). Large spatial and temporal differences in CUPs concentrations in the atmosphere have been reported (Désert et al. 2018, Villiot et al. 2018). Distance to the site of pesticide application is an important factor for the exposure level of residents (Brouwer et al. 2017, Teyseire et al. 2020). Several studies have reported possible links between non-occupational exposure via air and respiratory and allergic symptoms such as rhinitis (Mamane et al. 2015, Raherison et al. 2019). Therefore, to assess possible health effects of CUPs it is imperative to understand exposure distributions and drivers of the outdoor and indoor CUPs concentrations.

The specific aims of the study where: i) to investigate differences in air concentrations between different CUPs and to look at seasonal differences covering the *use* and *non-use* period; ii) to study the effect of distance from application site per CUP, by following specific spray applications and measuring the applied pesticides in outdoor and indoor air of surrounding homes; and iii) for the applied CUPs, to evaluate

predicting factors (e.g. meteorological conditions and agricultural area surrounding a home) via statistical models.

Materials and methods

Study design

The observational study was carried out from May 2016 to December 2017. Outdoor air samples were taken during periods of *use* and *non-use* for 73 homes. 58 homes were located within 250m from bulb fields, labelled Location Homes (Loc Homes); 15 were located further than 500m from any agricultural field, labelled Control homes (Controls).

We tried to include Loc Homes situated at different distances from the bulbs fields in order to have a good representation of three different distance categories: homes located within 50m, between 50-150 m and within 150m and 250m from the fields.

In the *use* period, measurements of CUPs in air outside homes were carried out 24-hours a day for seven consecutive days. Sampling began when a selected field was sprayed. In the *non-use* period (i.e. period where the selected CUPs were not used), measurements were carried out 24-hours a day on two consecutive days. Finally, for Loc Homes situated within 50m (N=18) from the selected fields, one 24-hour indoor air sample was collected on the day spraying took place (i.e. the first day).

Pesticides & Fields

A total of 46 CUPs and degradation products with a large range of physicochemical properties (see Supplementary material 2, Figueiredo et al. 2021) were selected for analysis (11 herbicides, 12 insecticides and 23 fungicides). The selection was based on CUPs frequently used in bulb fields (N=37), CUPs used in bulb disinfection (N=3), and degradation products of CUPs in the former groups (N=6). A list of all analysed CUPs and degradation products can be found in Supplementary material A.

Eligible fields needed to have: flower bulbs present at the time of the study, farmers willing to participate, and at least one planned application of the selected CUP. A total of fourteen eligible fields were available and we randomly selected nine for the study (selected fields). Detailed information on the spraying applications in these fields, including CUPs used in the tank mixtures and quantities applied in each field have been previously described (Table 2, Figueiredo et al. 2021).

Loc Homes & Controls

Homes close to fields were selected to study spatial variation of atmospheric concentrations in relation to local spraying applications. Homes further away were selected as controls to assess rural background concentrations.

We initialized a recruitment process which consisted of contacting the farmers of eligible bulb fields to participate in the study and then, in case of acceptance, contacting residents living close to those fields. All residential addresses within 250 m of the perimeter of the field (i.e. potential Loc Homes) were selected using the Dutch Register of Addresses and Buildings (BAG).

Potential Controls were selected using the BAG to identify residential addresses located more than 500 m from any agricultural fields, situated within 20 km from a selected field and located in a not strongly urbanized area (i.e. <1500 addresses/km²). This choice falls upon the fact that we wanted to capture the rural background concentrations. Homes located in fully urbanized areas (e.g. city) were not selected as these would not capture more local background effects (Coscollà et al. 2013, Balmer et al. 2019).

In total, 80 Loc Homes and 16 Controls were included in the study. Not all Loc Homes participated in the collection during both periods. Three homes missed a collection during the *use* period (i.e. seven-day measurements) due to holidays and four homes ended their participation while the study was ongoing.

Due to budget constraints not all samples were analysed. The selection of homes for which samples were analysed was done in a “semi-random” fashion per experiment. To have a good spatial distribution we randomly selected homes from predefined distance categories. In addition, homes both up and down-wind at time of the application were selected in all cases. All samples collected from Control homes were analysed.

In total, we analysed 369 and 134 outdoor air samples in Loc Homes during *use*, and *non-use* period, respectively. We also analysed 89 and 26 outdoor air samples in Controls during *use* and *non-use* period, respectively.

Sampling outdoor and indoor air

Air sampling system was constructed by TNO (OBO 2019). In this system, air is sampled through a standard PM₁₀ inlet (sampling the fraction of particles with an aerodynamic diameter smaller than 10 µm), drawn through a glass fibre filter, and a tube containing

XAD-2 absorbent (Amberlite XAD-2). The filter/XAD-2 combination absorbs both gaseous and particle bound pesticides.

Sampling was started by remotely initiating air pumps using a GSM connection. This was done at the time the farmer notified the study team that the plan was to carry out the application on the selected field. Sampling rate was controlled at 60-70 dm³/min. Sampling started with the first inlet and filter set. After a 24 h period it automatically switched to use the second inlet and filter set, and so on. The same procedure was used for indoor sampling, with the only differences being that a pump with a lower capacity (drawing air at 25 dm³/min) was used.

Outdoor air was collected, either in the front or back garden of the home. The indoor air was collected inside the home on the ground floor.

Chemical analyses

We transferred 30 grams of XAD-2 resin and the 102 mm glass fibre filter from the sampling filter holder into a metal extracting cell. A mix of Deuterium labelled pesticides was added to the samples to act as an internal standard.

The samples were extracted using low temperature Accelerated Solvent Extraction (ASE) and concentrated to a fixed volume of 1000 µl. With each batch of samples, a reagent blank and a quality control sample were included. The quality control consists of 5 ng/pesticides mixture added to 10 g blank XAD-2. The pesticide concentration in the concentrated extracts was determined using liquid chromatograph coupled to a Mass spectrometer (LC-MS/MS). A detailed explanation can be found in OBO 2019. The LOD (lower limit of detection in ng/m³) was determined based on the average sample volume of air used. The lower limit of quantification (LOQ) was estimated as 10 times the standard deviation of the lowest concentration measured. The LOD was derived as three times this standard deviation. Limits of detection (LODs) varied between 0.003 and 0.03 ng/m³. The LOD specific to each pesticide can be found in Supplementary material A.

To test the method and ensure no breakthrough of pesticides, two containers with XAD-2 were mounted one after the other. The first containing 8 grams of XAD-2 and the second containing 4 grams of XAD-2. Pesticide recovery on the XAD in both containers and the percentage of pesticide in the second holder indicates the degree of breakthrough. The results of the breakthrough measurements may be found in Supplemental material F.

Results below the limit of detection

Levels above the LOD but below the LOQ may be more accurate than imputed values (Succop et al. 2004), therefore we used the LOD as cut-off for detection. Imputation of levels below the LOD was performed using methods proposed by Lubin et al. (2004). The imputation consists of imputing the values below LOD based on the maximum likelihood estimation while accounting for both correlation and distribution of all pesticide data. Imputation was only done when the pesticide (or by-product) was detected (>LOD) in at least 40% of the measured samples.

Statistical analysis

During our measuring period, 7 CUPs were applied in the selected fields and 4 on fields within 250 m of location homes. Therefore, our focus was on this group of 11 CUPs. A full list of the 46 targeted pesticides and their detection frequency in both outdoor and indoor air samples can be found in Supplementary Material A and B, respectively. A list of relevant physico-chemical properties of the 11 focused pesticides can be found in Supplementary Material C.

Results of samples were grouped as *use* and *non-use* period separately for each CUP. This grouping was done using the information supplied by the farmers, who provided a list of the CUPs they used in each month.

Different statistical tests were used to analyse the data. All analyses were performed using *R*, version 3.5 (R Core Team 2017). The data was log₁₀ transformed to meet the requirements of inferential statistics. Student's t-Test was used to determine whether CUPs concentrations differed significantly between *use* and *non-use* periods and between Loc Homes and Controls.

In some of the Loc Homes (N=7) one or more residents were farmers (i.e. worked in agricultural sector). Therefore, samples from these homes (Farm Homes) were excluded from the general analysis. It is known that these farmers have a higher pesticide exposure (Curl et al. 2002) compared to other residents. This is not solely related to applications in the direct surroundings but also involves other factors such as the take-home (or para-occupational) pathway (Hyland et al. 2017). This refers to bringing home pesticides via clothing, shoes and other means (Deziel et al. 2017, Pardo et al. 2020). The detection frequency of all CUPs in both outdoor and indoor air samples in farm homes is shown in the supplementary material (A and B, respectively).

Concentration of CUPs in outdoor air applied in the selected fields were plotted as a function of distance. Here, we grouped distance by our a-priori defined distance categories (<50m; 50-150m; 150-250m; >250m; controls). This grouping was based on previous research done on drift effect on air concentrations downwind at different distances from agricultural crops (e.g. Table 5, Siebers et al. 2003). A trend line was added to the graphs using *loess* regression based on polynomial function.

Temporal variation of air concentrations is studied for CUPs sprayed in the selected fields during the *use* period. Plots were created for each applied CUP and respective location where the selected fields are located. A detailed list of the sprayed tank mixtures per location can be found in Figueiredo et al. (2021). Spearman's rank correlation coefficient was used to study the relationship between indoor and outdoor air concentrations. All 46 pesticides were included in this analysis if there were at least 10 pairs of detectable outdoor and indoor concentrations.

Mixed-effect models were built, using the *nlme* R package (Pinheiro et al. 2021), for each CUP to evaluate predicting factors of outdoor air concentrations. This analysis was only done with data collected in the *use* period and for pesticides that were applied during the measurement period (N=11). Controls were excluded since level in these homes were considered mainly representative of background concentrations. We used mixed-effect models for variable selection rather than a fixed-effects structure to account for possible correlations in our outcome data due to the repeated measurements taken over time (7 consecutive days). Here, an autocorrelation structure (AR1) was added to the model making the correlations (r) decay over time with the assumption that concentrations measured shortly after the application are more strongly correlated (i.e. $r(\text{day1}, \text{day2}) = r(\text{day2}, \text{day3})$, but $r(\text{day1}, \text{day2}) > r(\text{day1}, \text{day7})$).

For independent variables, daily average evapotranspiration, humidity, cloud cover, wind speed and wind direction were retrieved from the Royal Netherlands Meteorological Institute (KNMI). Evapotranspiration is calculated based on temperature and solar radiation. Hence, temperature was not included as an independent variable to avoid multicollinearity, given that it is highly correlated (Pearson's correlation coefficient [95%CI] = 0.92 [0.91, 0.93]) with evapotranspiration. Meteorological information is collected continuously and its available from De Kooy and Schiphol meteorological stations, both located near (<20km) the selected fields. In addition, distance to closest agricultural field and total area of agricultural fields within 500 meters from a home (Buffer) were taken from ArcGIS (ArcMap Version 10.4) based on the Netherlands 2017 crops registration ("Basisregistratie Percelen 2017") (Esri Nederland) and on the

Netherlands registration of addresses and buildings (“Basisregistraties adressen en gebouwen”) (Overheid).

A stepwise algorithm was run backward and forward for variable selection. Each model was built using a 5-fold cross validation, meaning that the dataset was split into 5 groups (with the condition that data from homes cannot be split). Four groups were used to build the model and the remaining group to test model fit. This step was repeated until all groups were used as test dataset. To see which variables were repeatedly selected (probability of inclusion > 95%), the 5-fold cross validation was executed 20 times resulting in 100 iterations.

From the collected information on the spraying techniques used, most fields within 250 meters from the included homes reported very similar application settings. These settings are: height of the boom sprayer, distance between nozzles, speed of the boom sprayer and spraying pressure used (see Supplementary material D). Sprayed quantities were also quite similar between different applications (see Table 2, Figueiredo et al. 2021). Hence, difference in application technique was not included in data interpretation.

Finally, household use of pesticides was also not taken into account in the interpretation of results. No home owner reported use of any of the included pesticides. See supplementary material D for a full list of reported used products and/or active ingredients.

Results and discussion

Concentrations in Outdoor air

Figure 1 shows the concentrations in the *use* and *non-use* period for both Loc Homes and Controls. Panel A displays the 7 CUPs that were applied in the selected fields. Panel B displays the 4 CUPs that were applied during the measurement period in other fields located within 250m from Loc Homes. The highest 24-hr air concentrations were found for CUPs that were routinely applied and sprayed in higher dosages (CBS 2020), such as chlorpropham and pendimethalin. These were found in concentrations up to 2754 ng/m³ and 123 ng/m³, respectively.

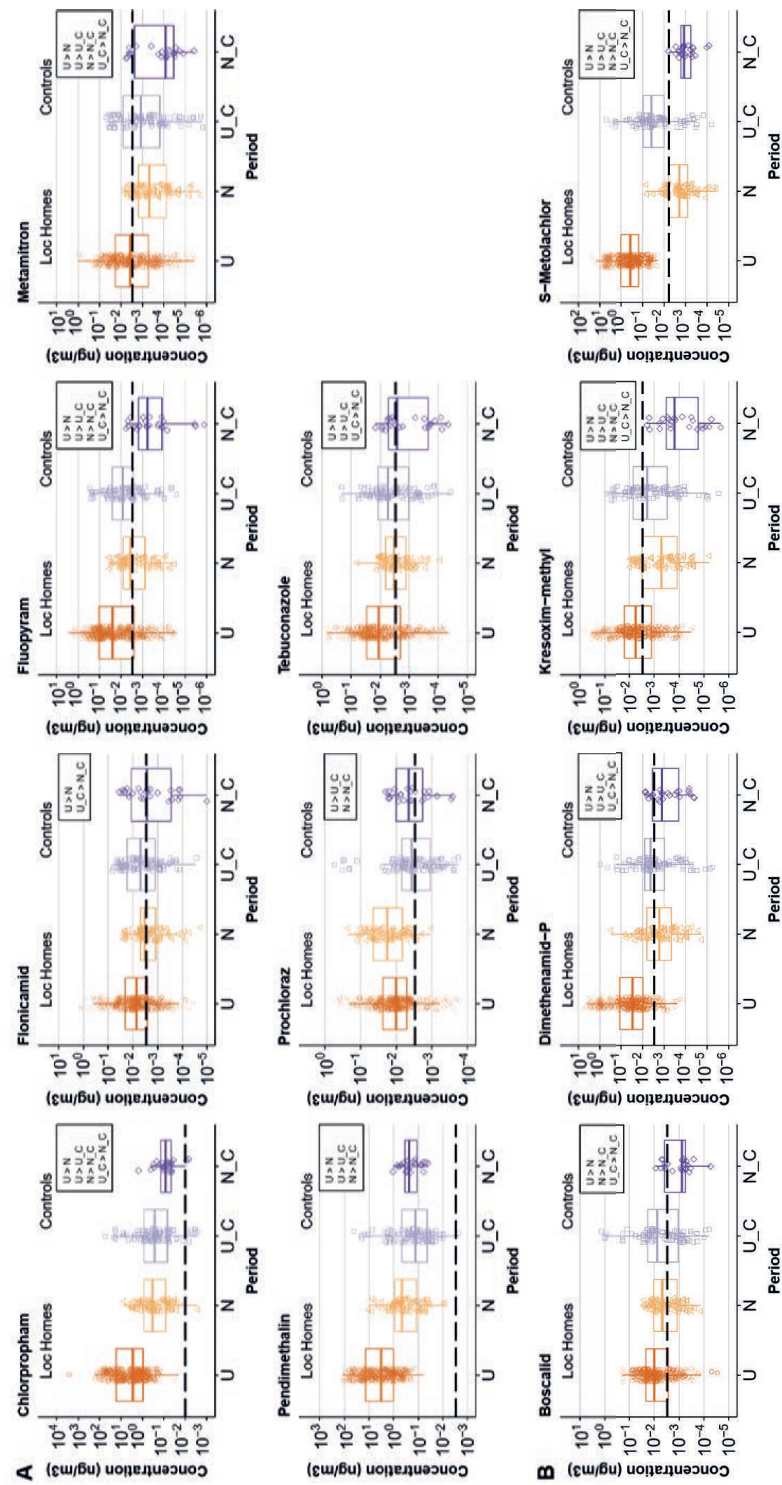


Fig 1. Concentration in outdoor air of applied CUPs, grouped per location and period. Use (U) and Non-Use period (N) for locations and U_C and N_C for Controls. Panel (A) refers to CUPs applied in the main fields and panel (B) to CUPs used in other fields in the vicinity (< 250 m). Summary statistics in boxplots (min, max, 1st and 3rd quartile and median). Black dotted line indicates the detection limit. Each dot above the black dotted line is a measured value and below that line is an imputed value. The average concentrations which are significantly higher ($\alpha = 0.05$) than others are shown in the right top box of each graph.

Use vs Non-use Period

Overall, concentrations were significantly higher (generally factor 5 to 10) in the *use* period than in the *non-use* period. For Loc Homes, concentrations were significantly higher in the *use* period for all CUPs except prochloraz. These results are not surprising, given that active spraying occurs during the *use* period and weather conditions are more favourable for pesticides to volatilise to air (warmer weather and less rainfall). For Controls, the same result was observed, with the exception of prochloraz and pendimethalin. For both these CUPs, concentrations in the *use* period were very similar to those in the *non-use* period. For pendimethalin, we hypothesize that this is a consequence of i) low persistence as a gas in the atmosphere but high persistence in soil (see Supplementary material C) and ii) the potential to be carried significantly through the air (Vighi et al. 2016). This combination of factors indicates that, although pendimethalin can reach Loc Homes and Controls in the gas-phase, it will be rapidly degraded. Therefore, the effect of spraying applications and volatilization during *use* period is less important than the contribution of pendimethalin bound to small particles (i.e. particle-phase) that are carried with the wind. This also would explain the similar concentrations in the *non-use* period.

The reasoning for no difference in prochloraz concentrations between Controls in *use* and *non-use* period is similar to pendimethalin. Prochloraz also shows low atmospheric persistence (< 2 hours, see Supplementary material C) and high persistence in soils (several months, EFSA 2011).

Finally, CUPs in Figure 1 with higher vapour pressures, namely chlorpropham, pendimethalin, dimethenamid-P and s-metolachlor (Lewis et al. 2016), show higher differences in concentrations between *use* and *non-use* period for Loc Homes. This observation is an indication that more volatile compounds will be found in higher concentrations in the *use* period. Whilst for pesticides that have lower vapor pressure and persist longer in agricultural soils, such as boscalid and flonicamid, differences in concentrations between both periods are less pronounced.

Loc Homes vs Controls

Concentrations were, overall, significantly higher (generally factor 5 to 10) at Loc Homes compared to Controls. In the *use* period, concentrations were significantly higher in Loc Homes versus Controls for nearly all CUPs, with the exception of flonicamid and boscalid. For boscalid, the combination of persistence in soil ($dt_{50} > 1$ year) and atmospheric persistence ($dt_{50} < \text{half-day}$) leads to a continuous release (when weather conditions allow) to the atmosphere (Karlsson et al. 2016). These leads to an even

distribution of this compound in a larger area. However, for flonicamid, the story is inverted but the outcome is the same. A low persistence in soil (days, Liu et al. 2014) is accompanied by a higher persistence in the atmosphere, which gives enough time for gas-phase flonicamid to travel over long distances during the *use* period.

For the *non-use* period, concentrations were significantly higher around Loc Homes for 8 out of the 11 sprayed CUPs. Similar to the *use* period, no difference was observed for flonicamid concentrations. In addition, no differences were observed for dimethenamid-P and tebuconazole. Both these CUPs are non-persistent in soil (Kočárek et al. 2018, Matadha et al. 2020) and rapidly degrade in the atmosphere. Therefore, given that it is a period where no sprayings occur, both dimethenamid-P and tebuconazole concentrations in Loc Homes and Controls are likely reflecting just background concentrations.

In sum, the differences shown in air concentrations over the use and non-use period and between location and control homes are largely explained by a combination of three factors. These are: persistence in the soil, medium to long-range transport of pesticides (influenced by atmospheric persistence) and release into the atmosphere via volatilization. The latter is mainly governed by some dominant physicochemical factors, such as vapour pressure (see Houbraiken et al. 2015 for detailed explanation on volatilization) and by meteorological conditions.

Concentrations – Distance from spraying field to home

A decrease in concentrations with distance from the main field is observed for all pesticides (Figure 2). This finding is in line with conclusions drawn in other studies, where concentrations in ambient outdoor air were higher closer to the applying fields than further away (Garron et al. 2009, Coronado et al. 2011, Fang et al. 2017). Moreover, concentrations in controls are predominately governed by long-range (i.e. regional) transport of CUPs (Guida et al. 2018).

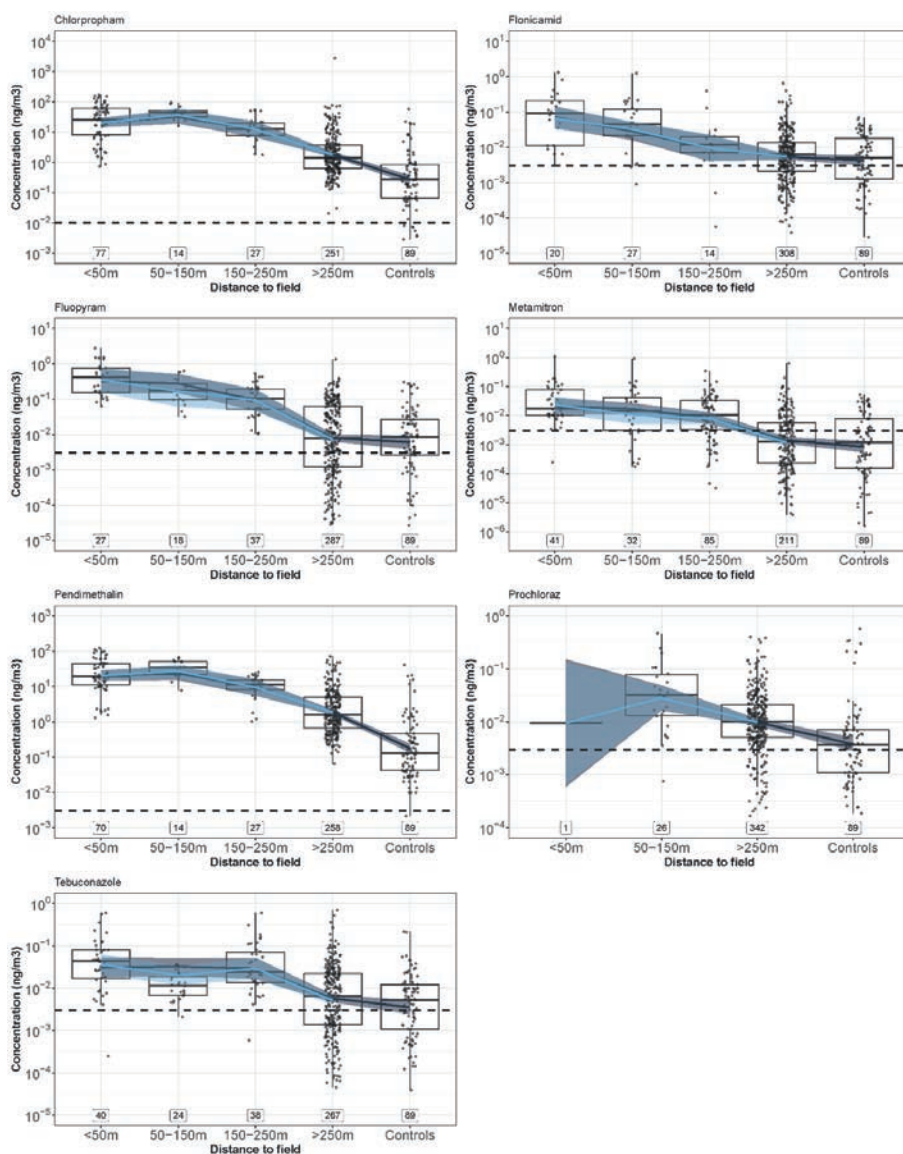


Fig 2. Concentration of CUPs vs distance from home to applying field. Grouped by categories: <50m – less than 50 meters from applying field; 50-150m – within 50 to 150 meters from applying field; 150-250m – within 150 to 250 meters from applying field but still in the vicinity; >250m – more than 250 meters from applying field but still in the vicinity; Controls – more than 500 meters from any field.

Above the x-axis are the number of samples per category. Summary statistics in boxplots (min, max, 1st and 3rd quartile and median). Black dotted line indicates the detection limit (LOD). Each dot above the black dotted line is a measured value and below is an imputed value. The blue line represents the trend (via Loess smoothing) without accounting for Controls, while the black line includes the controls as an additional group.

Temporal variability of outdoor air concentrations during use period

No consistent temporal pattern in outdoor air concentrations during the *use* period (day 1 to 7) was observed (Figure 3). This is likely due to shifting wind directions and the fact that these homes are located in areas where there is an abundance of agricultural fields in addition to the selected field. So, our measurements do not only capture the contribution of the selected field to air concentrations but also pesticide drift and volatilization from other crops that might be sprayed during that week. Also, in many of the sampling days, homes were not downwind from most of the agricultural fields, which indicates that measured concentrations are likely background. This explains the small variability in concentrations seen for some of the CUPs, such as fluopyram and tebuconazole (A-UP1), flonicamid (E-UP2) and prochloraz (D-UP2).

There are however singularities that are worth pointing out. We see that the temporal patterns are similar for CUPs present in the same tank mixture and applied in the same selected fields (pendimethalin and chlorpropham in C-UP1 and D-UP1; flonicamid and tebuconazole in E-UP2). We also see a clear influence of wind direction in some of the temporal trends, especially when most homes are located downwind of the agricultural fields. This is the case on day 3 of C-UP2 and day 5-7 of G-UP1 (displayed in figure 3). Here, we see an increase in air concentrations of tebuconazole (C-UP2) and metamitron (G-UP1), when the wind blows from east (day 3) and blows from south, respectively. These results show that concentration increases when the wind is coming from the source in the direction of the home, even when there was no active spraying at the source.

Our measurements also highlight important relating to temporal variation of CUPs concentrations in air. Increases in 3 to 4 orders of magnitude in concentrations can happen from one day to the other (e.g. Metamitron day 6 to 7 in G-UP2). We hypothesize that, given the sudden shift in concentrations, this is related to spray drift and not volatilization, and is likely to only occur if a home is downwind from an ongoing spraying application.

In summary, the temporal variability of CUPs concentrations near houses located in areas with intensive bulb growing is determined by two processes: 1) low background concentrations related to medium and long range transport of CUPs used in areas further away and 2) high concentrations related to use in the vicinity of a house located downwind. Air concentrations may vary several orders of magnitude.

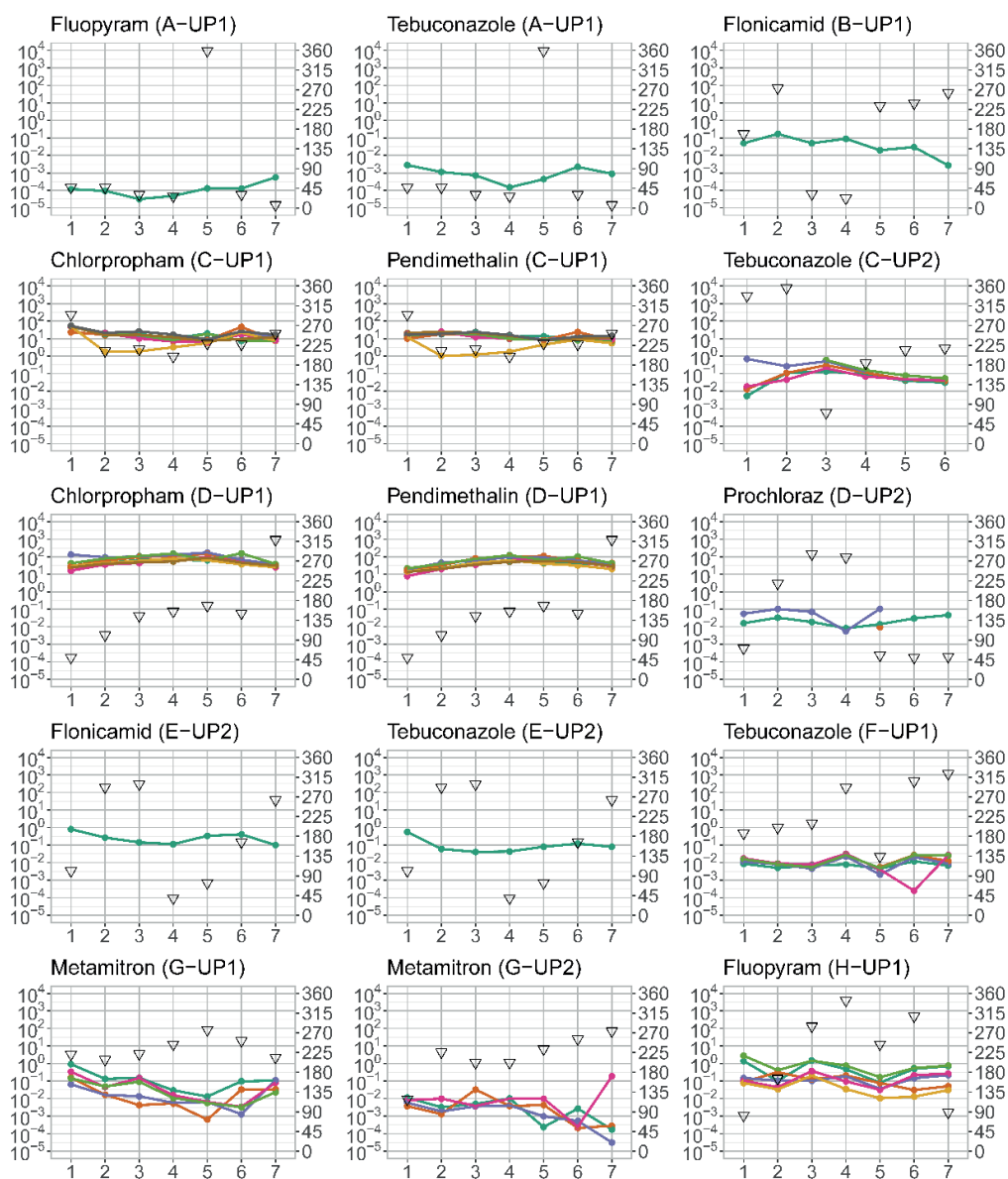


Fig 3. Daily atmospheric concentrations at Loc Homes for CUPs applied in selected fields and wind direction during use period. Each plot represents a measured pesticide in a specific location (see Table 2, Figueiredo et al. 2021). For each plot: Lines represent the different homes where measurements were taken. Dots are measured cumulative 24-hour air concentrations and inverted triangles are daily averaged wind direction. The x axis is days 1 to 7; primary y axis (left) is the concentration in outdoor air (ng/m³), secondary y axis (right) is the wind direction (blowing from).

Concentrations in indoor air

Figure 4 shows the concentrations in indoor air of Loc Homes for both the *use* and *non-use* period. The observed indoor concentrations show patterns similar to the observed outdoor air concentrations. The highest measured 24-hr air concentrations were 25 ng/m³ and 4 ng/m³, from chlorpropham and pendimethalin, respectively.

For most pesticides, concentrations were significantly higher in the *use* period than they were in the *non-use* period, with the exception for flonicamid, prochloraz and kresoxim-methyl. For prochloraz we did not observe a difference in outdoor air concentrations between the *use* and *non-use* period. However, for flonicamid and kresoxim-methyl we did observe a difference in outdoor air concentrations between the *use* and *non-use* period, which is not reflected here in the indoor air concentrations. This is likely due to the fact that during the sampling day homes were not downwind of applications. Therefore measured concentrations in the *use* period are likely reflecting background concentrations.

We hypothesize that resuspended particle bound pesticides may contribute to the observed indoor air concentrations during the non-use. These are transported through air to the homes, settled inside the homes and persist more easily in the indoor environment (see comparison of pesticides in indoor and outdoor dust from Hung et al (2018)). Higher persistence in the indoor environment can be caused by limited ventilation, lower photodegradation (particularly in darker zones), and trapping surfaces (e.g. carpets).

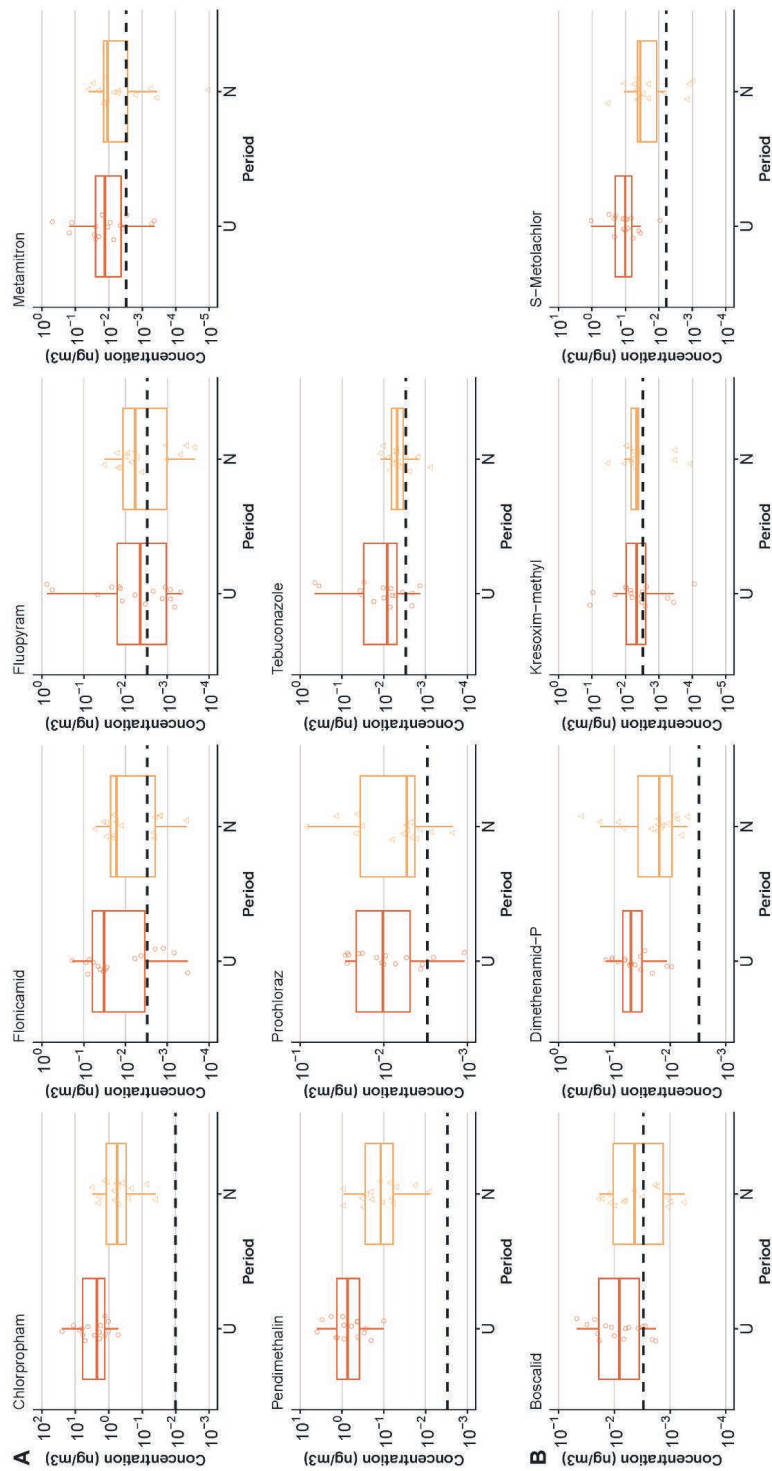


Fig 4. Indoor air concentrations of applied CUPs, grouped per period. Use (U) and Non-Use period (N). Panel (A) refers to pesticides applied in the selected fields and panel (B) to pesticides used in other fields in the vicinity. Summary statistics in boxplots (min, max, 1st and 3rd quartile and median). Black dotted line indicates the detection limit. Each concentration above the level of the black dotted line is a measured value and below is an imputed value.

Comparison between outdoor and indoor air concentrations

Table 1 shows the CUPs ordered by vapour pressure and the respective spearman correlation between paired outdoor and indoor samples (concentrations in Supplementary material C). The median day 1 indoor/outdoor ratio was 1.16, showing that overall, the concentrations were very similar between both environments on day 1. The minimum and maximum I/O ratios, 0.33 and 3.85, are found for Pendimethalin and Carbendazim, respectively.

Table 1. Spearman correlation: Outdoor and Indoor air concentrations.

CUPs ^b	<i>p</i> ^a	95% CI	p-value
Chlorpropham	0.60	[0.26 , 0.81]	0.002
S-Metolachlor	0.68	[0.39 , 0.85]	<0.001
Fluopyram-benzamide	0.41	[0.01 , 0.70]	0.051
Pendimethalin	0.51	[0.13 , 0.76]	0.012
Dimethenamid-P	0.65	[0.33 , 0.83]	0.001
Toclofos-methyl	0.45	[0.06 , 0.72]	0.028
Prochloraz	0.54	[0.18 , 0.78]	0.007
Carbendazim	0.51	[0.14 , 0.76]	0.011
Linuron	0.45	[0.06 , 0.72]	0.028
Kresoxim-methyl	0.57	[0.22 , 0.79]	0.004
Tebuconazole	0.42	[0.02 , 0.70]	0.044
Fluopyram	0.49	[0.11 , 0.75]	0.016
Flonicamid	0.33	[-0.09 , 0.65]	0.118
Metamitron	0.36	[-0.05 , 0.67]	0.081
Boscalid	0.43	[0.03 , 0.71]	0.038
Prothioconazole-desthio	0.40	[-0.01 , 0.69]	0.056
Pyraclostrobin	0.31	[-0.11 , 0.63]	0.140

^a Spearman correlation coefficient

^b Pesticides ordered by decreasing vapour pressure. Vapour pressure reported in Supplementary material A.

The correlation between indoor and outdoor air concentrations was moderate for most pesticides (>0.4 for 76%). As discussed by Bennet & Furtaw, there is a large set of parameters such as type of flooring, dust loading and many more that are involved in the occurrence of pesticides in the indoor environment (Bennet and Furtaw 2004). These parameters can affect individual pesticide concentrations in different ways making it a complex system (see Figure 1, Liang et al. 2018). Important unknowns are the influence of indoor sources (e.g. resuspension) and sinks (e.g. accumulation in different indoor surfaces) on indoor pesticide concentrations (Weschler & Nazaroff 2008, Chandra Yadav et al. 2020). These affect the ratio of outdoor-indoor concentrations. In addition, it should be realized that we are only looking at a small

time window (1 day), so concentrations indoors can be quite different from those outdoors because equilibrium might not have been reached (Kulmala et al. 1999). Even with this complexity we observed that correlations seem to be higher for more volatile compounds, such as chlorpropham and s-metolachlor. We hypothesize that this is because gas-phase pesticides are less affected by indoor sources and sinks than those that are mainly bound to particles and usually present in settled dust (Wei et al. 2019). These indoor sources and sinks may cause quasi random fluctuations in indoor concentrations thereby preventing relationships between indoor and outdoor concentrations from being found.

Variable selection for mixed effect models describing outdoor air concentrations

Results from the variable selection of the mixed-effect models are presented in Table 2. Wind direction was the variable selected most consistently (> 95% of the iterations for 7 CUPs) as an important determinant of air concentrations amongst almost all CUPs. It stands to reason since wind direction determines dispersion. We also see that for some CUPs (Pendimethalin, Prochloraz, Tebuconazole and Metamitron) this variable was selected less often. This means that other parameters that determine concentration are important. In this group we find CUPs that are either frequently applied in the Netherlands (e.g. Pendimethalin) or CUPs with a high persistence in the environment, such as prochloraz and metamitron (Mamy et al. 2005). Both these characteristics can attenuate the variability of concentrations at a local scale (Chiaia-Hernandez et al. 2017, Désert et al. 2018). This brings out variables, such as the total area of agricultural fields within 500 meters from a home (Buffer) and evapotranspiration (EV), as more important predictors for these CUPs.

Table 2. Results of individual mixed effect models describing air concentrations. Percentage of the model runs in which the parameter is dominant.

CUPs ^a	Distance (m) ^b	Wind direction (degrees)	Wind speed (m/s)	Evapo- transpiration (mm)	Buffer ^c	Humidity (%)	Cloud cover
Chlorpropham	40	100	94	0	89	100	29
Metolachlor-S	1	100	35	63	99	46	17
Pendimethalin	63	12	7	39	97	100	100
Dimethenamid-P	3	100	88	90	100	29	0
Prochloraz	93	47	1	18	100	100	55
Kresoxym-methyl	4	96	100	100	100	4	5
Fluopyram	5	100	100	100	64	14	1
Tebuconazole	8	63	73	100	12	0	0
Flonicamid	6	100	47	24	85	1	99
Boscalid	82	98	1	100	97	9	23
Metamitron	8	21	93	100	52	38	26

^a Pesticides ordered by decreasing vapour pressure. Vapour pressure reported in Supplementary material A. Underlined

– Selected in more than 95% of the model runs

^b Distance to closest field (meters)

^c Buffer – Area (radius 500 meters) of agricultural crops surrounding a home (m²)

An interesting finding is that EV was mainly selected for CUPs with lower vapor pressure. This is counterintuitive, since it was expected that this variable would be frequently selected for more volatile CUPs. There are two reasons that might explain this finding. Firstly, EV is calculated based on temperature and global radiation. Therefore, it might be acting as a proxy for sunlight photodegradation, which is one of the “most destructive pathways for pesticides” (cited from Katagi 2004). However, this is unlikely given the short time scale of transport of sprayed pesticides from the fields to the homes. Secondly, we can see that Buffer was selected over EV for the more volatile compounds. It seems that, for this group, buffer acts as a proxy for emission to the atmosphere. Therefore, it is plausible that the area of agricultural crops around homes explains more than local EV for the one-week period.

Relative humidity was also selected in all models as an important explanatory variable for air concentrations of the three more volatile compounds (chlorpropham, pendimethalin and prochloraz). This finding can be partially explained as humidity goes hand in hand with temperature, which largely affects pesticide evaporation. But, it also might be an indicator of pesticide atmospheric degradation. For example, pendimethalin is degraded in the atmosphere by ozone (Mattei et al. 2019) and we

know that, in sites with large leaf area index, there is a stronger ozone-humidity correlation (Kavassalis & Murphy 2017).

Finally, Buffer was frequently selected as an important predictor for the more volatile compounds. Also, it seems that for some pesticides (metolachlor-S, dimethenamid-P and kresoxym-methyl), Buffer was selected over distance to closest field in almost all iterations. All three pesticides were not applied in the selected field but are reported as being applied in other fields in the vicinity (Panel B, Figure 1).

Strengths & Limitations

In our study we incorporated several pesticides with different physico-chemical properties. The collection of samples at different distances and at different periods provided a good indication of both temporal and spatial CUPs air concentration distribution. The inclusion of both sprayed and non-sprayed CUPs is quite unique. This allowed us to see differences between these two and better understand their occurrence in the environment. Moreover, the incorporation of indoor air samples besides the outdoor air samples gave us new insights in the concentration equilibrium between both environments.

The large number of analysed samples allowed us to build a robust variable selection process in the empirical modelling. Also, by measuring for consecutive days we were able to account for the temporal variability.

Knowing the exact time of spraying for selected fields proved to be very important, allowing us to start sampling shortly before application and capture both drift and volatilization for an extended period (7 days). However, this might introduce some bias. Some farmers may change spraying practice when they are aware of our measurement target and strategies.

As a limitation, our targeted pesticide group did not comprise all CUPs and mixtures. Therefore, some of the drawn conclusions may not apply to pesticides outside of this selection. Also, samples were taken around fields where downward spraying occurred, therefore it remains to be seen if our results can be extrapolated to other crops and application technique (e.g. upward spraying).

Finally, when comparing concentrations between the different periods and locations we could only do an assessment based on available data. Some information that might be relevant to understand release of the different CUPs into the atmosphere, such as soil moisture and canopy height, was not available. This inherently leads to a more limited interpretation of our results.

Conclusions

We detected several pesticides and degradation products in air around both homes located close to (<250m) and further away (>500m) from spraying fields, during and outside spraying periods. Outdoor air concentrations were generally 5 to 10 times higher for homes close to fields (<250m) than control homes (>500m) for almost all CUPs. Outdoor and indoor air concentrations during the spraying of CUPs were also a factor of 5 to 10 higher than those outside the spraying periods.

Differences in outdoor air concentrations between location and control homes were also seen outside the spraying periods. This suggests evaporation of earlier used pesticides in or outside the study area. Frequently applied CUPs or CUPs with low persistence in the environment (soil or air) showed the largest contrast in average concentrations for the above comparisons.

We saw a decrease in outdoor air concentrations with distance from the field of application. This indicates that spatial variability in air concentrations around homes located at least 250m of spraying fields is mostly driven by local spraying applications. Temporal variability in air concentrations during the spraying period seems to be mainly driven by local spraying applications and wind direction.

Concentrations in the indoor and outdoor air were moderately correlated for almost all CUPs and the observed correlations seemed to be higher for more volatile CUPs. Given that people spend most of their time in the indoor environment, it stands to reason that the next step in research should be to study the impact of different indoor sources and sinks on pesticide concentrations in indoor air and the temporal variance of indoor air concentrations during longer periods of time. A key source of pesticides inside houses, as suggested in literature, could be indoor dust.

Lastly, the area of agricultural crops surrounding the receptor (at least 250m) seems to act as proxy for pesticide use in past years and persistence (i.e. past applications). This parameter should be taken into account, or at least not be neglected, in future modelling developments, given that it might explain part of the variability in pesticide atmospheric concentrations.

Acknowledgements

Funding: This work was conducted within the OBO Project (Dutch acronym for “Research on Exposure of residents to pesticides”), funded by the Dutch ministry of Infrastructure and Water Management and the ministry of Economic Affairs and Climate Policy. This work was commissioned by the Dutch National Institute for Public Health and the Environment (RIVM).

The authors thank all members of the OBO consortium for the discussions regarding research orientation. We also thank all the field workers that were involved in the collection of the data used in this manuscript, as well as the TNO laboratory personnel that analysed the air samples. We are grateful for the assistance of the National Institute for Public Health and Environment during all phases of the study.

References

- BAG, Overheid.nl. <https://data.overheid.nl/dataset/basisregistratie-adressen-en-gebouwen--bag->, accessed on 17 July 2020.
- Balmer, J.E., Morris, A.D., Hung, H., Jantunen, L., Vorkamp, K., Rig  t, F., Evans, M., Houde, M., Muir, D.C.G. (2019). Levels and trends of current-use pesticides (CUPs) in the arctic: An updated review, 2010–2018, *Emerging Contaminants*, Volume 5, 2019, Pages 70–88, ISSN 2405–6650, <https://doi.org/10.1016/j.emcon.2019.02.002>
- Bedos, C., Cellier, P., Calvet, R., Barriuso, E., 2002. Occurrence of pesticides in the atmosphere in France. *Agronomie* 22, 35–49. <http://doi.org/10.1051/agro:2001004>
- Bennett, D.H., Furtaw, E.J., 2004. Fugacity-based indoor residential pesticide fate model. *Environ. Sci. Technol.* 38, 2142–52.
- Borr  s, E., R  denas, M., Vera, T., G  mez, T., & Mu  oz, A. (2017). Atmospheric degradation of the organothiophosphate insecticide – Pirimiphos-methyl. *Science of the Total Environment*, 579, 1–9. <https://doi.org/10.1016/j.scitotenv.2016.11.009>
- Brouwer, M., Huss, A., van der Mark, M., Nijssen, P. C. G., Mulleners, W. M., Sas, A. M. G., ... Vermeulen, R. C. H. (2017). Environmental exposure to pesticides and the risk of Parkinson’s disease in the Netherlands. *Environment International*, 107(January), 100–110. <http://doi.org/10.1016/j.envint.2017.07.001>
- CBS (2020). Statistics Netherlands. Use plant protection products in agriculture; active substance, application. <https://opendata.cbs.nl/#/CBS/nl/dataset/84010NED/table?defaultview> (accessed on 2 June 2020)
- Chandra Yadav, I., Devi, N. L., Li, J., & Zhang, G. (2020). Polychlorinated biphenyls and organochlorines pesticides in indoor dust: An exploration of sources and health exposure risk in a rural area (Kopawa) of Nepal. *Ecotoxicology and Environmental Safety*, 195, 110376. <https://doi.org/10.1016/j.ecoenv.2020.110376>
- Chiaia-Hernandez, A. C., Keller, A., W  chter, D., Steinlin, C., Camenzuli, L., Hollender, J., & Krauss, M. (2017). Long-Term Persistence of Pesticides and TPs in Archived Agricultural Soil Samples and Comparison with Pesticide Application. *Environmental Science & Technology*, 51(18), 10642–10651. <https://doi.org/10.1021/acs.est.7b02529>
- Cindoruk, S. S., & Ozturk, E. (2016). Atmospheric deposition of organochlorine pesticides by precipitation in a coastal area. *Environmental Science and Pollution Research*, 23(24), 24504–24513. <https://doi.org/10.1007/s11356-016-6697-y>
- C  rdoba Gamboa, L., Solano D  az, K., Ruepert, C., & van Wendel de Joode, B. (2020). Passive monitoring techniques to evaluate environmental pesticide exposure: Results from the Infant’s Environmental Health study (ISA). *Environmental Research*, 184(September 2019), 109243. <https://doi.org/10.1016/j.envres.2020.109243>
- Coronado, G.D., Holte S., Vigoren E., Griffith, W.C., Barr, D.B., Faustman, E. (2011). Organophosphate

- pesticide exposure and residential proximity to nearby fields: evidence for the drift pathway. *J Occup Environ Med* 53:884–891. <http://doi.org/10.1097/JOM.0b013e318222f03a>
- Coscollà, C., Hart, E., Pastor, A., & Yusà, V. (2013). LC-MS characterization of contemporary pesticides in PM10 of Valencia Region, Spain. *Atmospheric Environment*, 77, 394–403. <https://doi.org/10.1016/j.atmosenv.2013.05.022>
- Coscollà, C., López, A., Yahyaoui, A., Colin, P., Robin, C., Poinsignon, Q., & Yusà, V. (2017). Human exposure and risk assessment to airborne pesticides in a rural French community. *Science of the Total Environment*, 584–585, 856–868. <https://doi.org/10.1016/j.scitotenv.2017.01.132>
- Curl, C. L., Fenske, R. A., Kissel, J. C., Shirai, J. H., Moate, T. F., Griffith, W., Thompson, B. (2002). Evaluation of take-home organophosphorus pesticide exposure among agricultural workers and their children. *Environmental Health Perspectives*, 110(12), 787–792. <http://doi.org/10.1289/ehp.021100787>
- Dereumeaux, C., Fillol, C., Quenel, P., & Denys, S. (2020). Pesticide exposures for residents living close to agricultural lands: A review. *Environment International*, 134(May 2019), 105210. <https://doi.org/10.1016/j.envint.2019.105210>
- Désert, M., Ravier, S., Gille, G., Quinapallo, A., Armengaud, A. et al. (2018). Spatial and temporal distribution of current-use pesticides in ambient air of Provence-Alpes-Côte d'Azur Region and Corsica, France. *Atmospheric Environment*, Elsevier, 2018, 192, pp.241-256. <https://doi.org/10.1016/j.atmosenv.2018.08.054>
- Deziel, N. C., Beane Freeman, L. E., Graubard, B. I., Jones, R. R., Hoppin, J. A., Thomas, K., Friesen, M. C. (2017). Relative contributions of agricultural drift, para-occupational, and residential use exposure pathways to house dust pesticide concentrations: Meta-regression of published data. *Environmental Health Perspectives*, 125(3), 296–305. <http://doi.org/10.1289/EHP426>
- EC (2020). <http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=activesubstance.selection&language=EN>. (Last access March) 2020.
- EFSA. European Food Safety Authority; Conclusion on the peer review of the pesticide risk assessment of the active substance prochloraz. *EFSA Journal* 2011; 9(7):2323. [120 pp.]. Available online: www.efsa.europa.eu/efsajournal.html <https://doi.org/10.2903/j.efsa.2011.2323>
- Fang, Y., Nie, Z., Die, Q., Tian, Y., Liu, F., He, J., & Huang, Q. (2017). Organochlorine pesticides in soil, air, and vegetation at and around a contaminated site in southwestern China: Concentration, transmission, and risk evaluation. *Chemosphere*, 178, 340–349. <https://doi.org/10.1016/j.chemosphere.2017.02.151>
- Figueiredo, D. M., Krop, E. J., Duyzer, J., Gerritsen-Ebben, R. M., Gooijer, Y. M., Holterman, H. J., Huss, A., Jacobs, C. M., Kivits, C. M., Kruijne, R., Mol, H. J., Oerlemans, A., Sauer, P. J., Scheepers, P. T., van de Zande, J. C., van den Berg, E., Wenneker, M., & Vermeulen, R. C. (2021). Research on exposure of residents to pesticides in The Netherlands: Study Protocol. *JMIR Res Protoc* 2021;10(4):e27883 <https://doi.org/10.2196/27883>
- Galea, K. S., Maccalman, L., Jones, K., Cocker, J., Teedon, P., Cherrie, J. W., & Tongeren, M. Van. (2015).

- Comparison of residents pesticide exposure with predictions obtained using the UK regulatory exposure assessment approach. *Regulatory Toxicology and Pharmacology*, 73(2), 634–643. <http://doi.org/10.1016/j.yrtph.2015.09.012>
- Garron, C. A., Davis, K. C., & Ernst, W. R. (2009). Near-field air concentrations of pesticides in potato agriculture in Prince Edward Island. *Pest Management Science*, 65(6), 688–696. <http://doi.org/10.1002/ps.1746>
- Guida, Y. de S., Meire, R. O., Torres, J. P. M., & Malm, O. (2018). Air contamination by legacy and current-use pesticides in Brazilian mountains: An overview of national regulations by monitoring pollutant presence in pristine areas. *Environmental Pollution*, 242, 19–30. <https://doi.org/10.1016/j.envpol.2018.06.061>
- Houbroken, M., van den Berg, F., Butler Ellis, C. M., Dekeyser, D., Nuytens, D., De Schampheleire, M., & Spanoghe, P. (2016). Volatilisation of pesticides under field conditions: Inverse modelling and pesticide fate models. *Pest Management Science*, 72(7), 1309–1321. <https://doi.org/10.1002/ps.4149>
- Hung, C. C., Huang, F. J., Yang, Y. Q., Hsieh, C. J., Tseng, C. C., & Yiin, L. M. (2018). Pesticides in indoor and outdoor residential dust: a pilot study in a rural county of Taiwan. *Environmental Science and Pollution Research*, 25(23), 23349–23356. <https://doi.org/10.1007/s11356-018-2413-4>
- Hyland, C., & Laribi, O. (2017). Review of take-home pesticide exposure pathway in children living in agricultural areas. *Environmental Research*, 156(March), 559–570. <http://doi.org/10.1016/j.envres.2017.04.017>
- Karlsson, A. S., Weihermüller, L., Tappe, W., Mukherjee, S., & Spielvogel, S. (2016). Field scale boscalid residues and dissipation half-life estimation in a sandy soil. *Chemosphere*, 145, 163–173. <https://doi.org/10.1016/j.chemosphere.2015.11.026>
- Katagi T. (2004) Photodegradation of Pesticides on Plant and Soil Surfaces. In: Ware G.W. (eds) *Reviews of Environmental Contamination and Toxicology. Continuation of Residue Reviews*, vol 182. Springer, New York, NY. https://doi-org.proxy.library.uu.nl/10.1007/978-1-4419-9098-3_1
- Kavassalis, S. C., & Murphy, J. G. (2017). Understanding ozone-meteorology correlations: A role for dry deposition. *Geophysical Research Letters*, 44(6), 2922–2931. <https://doi.org/10.1002/2016GL071791>
- Kočárek, M., Kodešová, R., Sharipov, U., Jursík, M (2018). Effect of adjuvant on pendimethalin and dimethenamid-P behaviour in soil, *Journal of Hazardous Materials*, Volume 354, 2018, Pages 266–274, ISSN 0304-3894, <https://doi.org/10.1016/j.jhazmat.2018.04.073>
- Kulmala, M., Asmi, A., & Pirjola, L. (1999). Indoor air aerosol model: the effect of outdoor air, filtration and ventilation on indoor concentrations. *Atmospheric Environment*, 33(14), 2133–2144. [https://doi.org/https://doi.org/10.1016/S1352-2310\(99\)00070-9](https://doi.org/https://doi.org/10.1016/S1352-2310(99)00070-9)
- Lewis, K.A., Tzilivakis, J., Warner, D. and Green, A. (2016) An international database for pesticide risk assessments and management. *Human and Ecological Risk Assessment: An International Journal*, 22(4), 1050–1064. DOI: 10.1080/10807039.2015.1133242

- Liang, Y., Bi, C., Wang, X., & Xu, Y. (2019). A general mechanistic model for predicting the fate and transport of phthalates in indoor environments. *Indoor Air*, 29(1), 55–69. <https://doi.org/10.1111/ina.12514>
- Liu, X., Zhu, Y., Dong, F., Xu, J., & Zheng, Y. (2014). Dissipation and residue of flonicamid in cucumber, apple and soil under field conditions. *International Journal of Environmental Analytical Chemistry*, 94(7), 652–660. <https://doi.org/10.1080/03067319.2013.871714>
- Liu, L., Tang, J., Zhong, G., Zhen, X., Pan, X., & Tian, C. (2018). Spatial distribution and seasonal variation of four current-use pesticides (CUPs) in air and surface water of the Bohai Sea, China. *Science of the Total Environment*, 621, 516–523. <https://doi.org/10.1016/j.scitotenv.2017.11.282>
- López, A., Yusà, V., Muñoz, A., Vera, T., Borràs, E., Ródenas, M., & Coscollà, C. (2017). Risk assessment of airborne pesticides in a Mediterranean region of Spain. *Science of the Total Environment*, 574, 724–734. <https://doi.org/10.1016/j.scitotenv.2016.08.149>
- Lubin, J.H., Colt, J.S., Camann, D., et al. (2004). Epidemiologic evaluation of measurement data in the presence of detection limits. *Environ Health Perspect.* 2004;112(17):1691-1696. . <http://doi.org/10.1289/ehp.7199>
- Mamane, A., Raherison, C., Tessier, J.F., Baldi, I., Bouvier, G., 2015. Environmental exposure to pesticides and respiratory health. *Eur. Respir. Rev.* 24, 462–473. <http://doi.org/10.1183/16000617.00006114>
- Mamy, L., Barriuso, E. and Gabrielle, B. (2005), Environmental fate of herbicides trifluralin, metazachlor, metamitron and sulcotrione compared with that of glyphosate, a substitute broad spectrum herbicide for different glyphosate-resistant crops. *Pest. Manag. Sci.*, 61: 905-916. <https://doi-org.proxy.library.uu.nl/10.1002/ps.1108>
- Mattei, C., Dupont, J., Wortham, H., & Quivet, E. (2019). Influence of pesticide concentration on their heterogeneous atmospheric degradation by ozone. *Chemosphere*, 228, 75–82. <http://doi.org/10.1016/j.chemosphere.2019.04.082>
- Matadha, N.Y., Mohapatra, S., Siddamallaiiah, L., Udupi, V.R., Gadigeppa, S., Raja, D.P., Donagar, S.P. & Hebbar, S.S (2020): Persistence and dissipation of fluopyram and tebuconazole on bell pepper and soil under different environmental conditions, *International Journal of Environmental Analytical Chemistry*, <http://doi.org/10.1080/03067319.2019.1704745>
- OBO (2019). Research on exposure of residents to pesticides in the Netherlands: OBO flower bulbs. Onderzoek Bestrijdingsmiddelen en Omwonenden.
- Pardo, L.A., Beane Freeman, L.E., Lerro, C.C. et al. Pesticide exposure and risk of aggressive prostate cancer among private pesticide applicators. *Environ Health* 19, 30 (2020). <https://doi.org/10.1186/s12940-020-00583-0>
- Park, S., Choi, J. R., Kim, S. K., Lee, S., Lee, K., Kim, J. Y., Oh, S. S., & Koh, S. B. (2020). Increased risk of atherosclerosis associated with pesticide exposure in rural areas in Korea. *PLoS ONE*, 15(5), 1–11. <https://doi.org/10.1371/journal.pone.0232531>
- Pinhoiro J, Bates D, DebRoy S, Sarkar D, R Core Team (2021). nlme: Linear and Nonlinear Mixed Effects Models. R package version 3.1-152, <https://CRAN.R-project.org/package=nlme>.

- R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>.
- Raherison, C., Baldi, I., Pouquet, M., Berteaud, E., Moesch, C., Bouvier, G., & Canal-Raffin, M. (2019). Children: A pilot study. *Environmental Research*, 169 (November 2018), 189–195. <http://doi.org/10.1016/j.envres.2018.11.002>
- Rull, R.P., Gunier, R., Von Behren, J., Hertz, A., Crouse, V., Buffler, P.A. et al. (2009). Residential proximity to agricultural pesticide applications and childhood acute lymphoblastic leukemia *Environ. Res.*, 109, pp. 891–899. <https://doi.org/10.1016/j.envres.2009.07.014>
- Saillenfait AM., Malard S. (2020) Human Risk Associated with Long-Term Exposure to Pyrethroid Insecticides. In: Eljarrat E. (eds) *Pyrethroid Insecticides. The Handbook of Environmental Chemistry*, vol 92. Springer, Cham. http://doi-org-443.webvpn.fjmu.edu.cn/10.1007/698_2019_427
- Sauret, N., Wortham, H., Strekowski, R., Herckès, P., & Nieto, L. I. (2009). Comparison of annual dry and wet deposition fluxes of selected pesticides in Strasbourg, France. *Environmental Pollution*, 157(1), 303–312. <https://doi.org/10.1016/j.envpol.2008.06.034>
- Siebers, J., Binner, R., & Wittich, K. P. (2003). Investigation on downwind short-range transport of pesticides after application in agricultural crops. *Chemosphere*, 51(5), 397–407. [https://doi.org/10.1016/S0045-6535\(02\)00820-2](https://doi.org/10.1016/S0045-6535(02)00820-2)
- Socorro, J., Lakey, P. S. J., Han, L., Berkemeier, T., Lammel, G., Zetzsch, C., Pöschl, U., & Shiraiwa, M. (2017). Heterogeneous OH Oxidation, Shielding Effects, and Implications for the Atmospheric Fate of Terbutylazine and Other Pesticides. *Environmental Science and Technology*, 51(23), 13749–13754. <https://doi.org/10.1021/acs.est.7b04307>
- Succop, P.A., Clark, S., Chen, M. & Galke, W. (2004). Imputation of data values that are less than a detection limit. *J Occup Environ Hyg.* 2004;1:436–441. <http://doi.org/10.1080/15459620490462797>
- Teyssie, R., Manangama, G., Baldi, I., Carles, C., Brochard, P., Bedos, C., & Delva, F. (2020). Assessment of residential exposures to agricultural pesticides: A scoping review. *PLoS ONE*, 15(4), 1–19. <https://doi.org/10.1371/journal.pone.0232258>
- Tiryaki, O., & Temur, C. (2010). The fate of pesticide in the environment. *Journal of Biological and Environmental Sciences*, 4(10), 29–38.
- Upadhyay, J., Rana, M., Juyal, V., Bisht, S. S., & Joshi, R. (2020). Impact of Pesticide Exposure and Associated Health Effects. *Pesticides in Crop Production*, 69–88. <https://doi.org/10.1002/9781119432241.ch5>
- Vighi, M., Matthies, M. & Solomon, K.R. (2017) Critical assessment of pendimethalin in terms of persistence, bioaccumulation, toxicity, and potential for long-range transport, *Journal of Toxicology and Environmental Health, Part B*, 20:1, 1–21, <http://doi.org/10.1080/10937404.2016.1222320>
- Villiot, A., Chrétien, E., Drab-Sommèsous, E., Rivièrè, E., Chakir, A., & Roth, E. (2018). Temporal and seasonal variation of atmospheric concentrations of currently used pesticides in Champagne in the centre of Reims from 2012 to 2015. *Atmospheric Environment*, 174(November 2017), 82–91. <https://doi.org/10.1016/j.atmosenv.2017.11.046>

- Weij, W., Ramalho, O., & Mandin, C. (2019). A long-term dynamic model for predicting the concentration of semi volatile organic compounds in indoor environments: Application to phthalates. *Building and Environment*, 148(October 2018), 11–19. <http://doi.org/10.1016/j.buildenv.2018.10.044>
- Weschler, C. J., & Nazaroff, W. W. (2010). SVOC partitioning between the gas phase and settled dust indoors. *Atmospheric Environment*, 44(30), 3609–3620. <http://doi.org/10.1016/j.atmosenv.2010.06.029>
- Yang, X., Van Der Zee, S. E. A. T. M., Gai, L., Wesseling, J. G., Ritsema, C. J., & Geissen, V. (2016). Integration of transport concepts for risk assessment of pesticide erosion. *Science of the Total Environment*, 551–552, 563–570. <https://doi.org/10.1016/j.scitotenv.2016.02.058>
- Zivan, O., Segal-Rosenheimer, M., Dubowski, Y. (2016). Airborne organophosphate pesticides drift in Mediterranean climate: the importance of secondary drift. *Atmos. Environ.* 127, 155e162. <https://doi.org/10.1016/j.atmosenv.2015.12.003>

Supplementary material A

Table A1. Percentage of outdoor air samples above the LOD.

			Farm Homes		Loc Homes		Controls	
Pesticide	LOD (ng/m3)	Vapor Pressure (mPa at 20°C)*	U	N	U	N	U	N
Reported as being applied in bulb fields								
Chlorpropham	0.010	24.0	100	100	100	99	92	92
S-metolachlor	0.006	3.70	98	44	100	29	80	4
Fluopyram-benzamide*	0.003	3.62	98	100	80	76	82	54
Pendimethalin	0.003	3.34	100	100	100	100	99	100
Dimethenamid-P	0.003	2.51	87	78	89	41	55	29
Tolclofos-methyl	0.003	0.88	100	100	97	95	83	88
Pirimicarb	0.003	0.43	4	11	3	6	10	13
Prochloraz	0.003	0.15	94	100	87	96	57	71
Linuron	0.003	0.05	92	78	98	46	61	42
Mepanipyrim	0.003	0.02	44	0	35	1	17	8
Oxamyl	0.003	0.02	19	0	12	1	1	0
Pymetrozine	0.003	4E-03	2	0	5	0	1	0
Trifloxystrobin	0.003	3E-03	54	44	44	21	33	0
Trifloxystrobin-acid*	0.003	3E-03	44	56	38	58	16	25
Kresoxim-methyl	0.003	2E-03	87	67	64	28	39	0
Tebuconazole	0.003	1E-03	71	78	70	56	60	50
Fluopyram	0.003	1E-03	88	67	74	56	71	17
Flonicamid	0.003	9E-04	98	78	72	53	57	46
Metamitron	0.003	7E-04	62	56	56	13	35	25
Boscalid	0.003	7E-04	92	89	75	60	58	33
Asulam	0.003	5E-04	29	56	9	18	12	4
Metamitron-desamino*	0.003	4E-04	65	11	42	19	25	17
Prothioconazole-desthio*	0.003	4E-04	100	100	94	92	87	67
Flutolanil	0.003	4E-04	15	44	12	29	17	4
Cyhalotrin-lambda	0.030	2E-04	38	22	24	28	11	29
Acetamiprid	0.003	2E-04	25	0	8	0	0	0
Pyraclostrobin	0.003	3E-05	92	89	80	84	49	50
Deltamethrin	0.003	1E-05	35	33	34	51	19	17
Prothioconazole	-	7E-06	0	0	0	0	0	0
Spirotetramat	0.010	6E-06	13	0	15	0	13	0
Chloridazon	0.003	1E-06	67	33	31	11	22	4
Thiacloprid	0.003	3E-07	38	0	17	1	9	0
Spirotetramat-enol*	0.003	1E-07	2	0	0	0	0	0
Azoxystrobin	0.003	1E-07	48	44	38	21	26	8
Not applied in bulb fields but reported as used in bulb disinfection								
Propamocarb	0.003	730	48	56	50	38	48	38
Carbendazim	0.003	0.09	98	100	95	88	49	63
Thiophanate-methyl	0.003	9E-03	0	0	0	0	0	0
Imidacloprid	0.003	4E-07	37	33	30	21	28	17
Not applied in bulb fields and not reported as used in bulb disinfection								
Fosthiazate	0.003	0.56	37	0	28	0	8	0
Cyprodinil	0.003	0.51	25	22	35	15	30	4
Terbutylazine	0.003	0.15	48	11	59	4	60	13
Sulcotrione	0.003	5E-03	0	11	0	0	0	0
Dimethomorph	0.003	1E-03	8	0	5	0	1	0
Fludioxonil	0.010	4E-04	4	0	7	1	7	0
Fluopicolide	0.003	3E-04	25	0	20	0	12	0
Difenoconazole	0.003	3E-05	40	44	31	46	31	17

LOD – Limit of detection; U – Pesticides use period & N – Pesticides non-use period. * Retrieved from Pesticide Properties Database (PPDB) - Lewis et al. 2016

Supplementary material B

Table B1. Percentage of indoor air samples above the LOD.

			Farm Homes		Loc Homes	
Pesticide	LOD (ng/m3)	Vapor Pressure (mPa at 20°C)	U	N	U	N
Reported as being applied in bulb fields						
Chlorpropham	0.010	24.0	100	100	100	100
S-metolachlor	0.006	3.70	100	100	100	80
Fluopyram-benzamide*	0.003	3.62	83	100	88	93
Pendimethalin	0.003	3.34	100	100	100	100
Dimethenamid-P	0.003	2.51	83	100	100	100
Tolclofos-methyl	0.003	0.88	100	100	88	100
Pirimicarb	0.003	0.43	33	67	38	40
Prochloraz	0.003	0.15	100	100	88	87
Linuron	0.003	0.05	83	100	88	73
Mepanipyrim	0.003	0.02	83	67	56	40
Oxamyl	0.003	0.02	50	33	6	13
Pymetrozine	0.003	4E-03	17	50	44	7
Trifloxystrobin	0.003	3E-03	83	33	25	40
Trifloxystrobin-acid*	0.003	3E-03	83	67	63	80
Kresoxim-methyl	0.003	2E-03	100	100	69	80
Tebuconazole	0.003	1E-03	83	100	81	80
Fluopyram	0.003	1E-03	100	83	56	67
Flonicamid	0.003	9E-04	100	67	75	60
Metamitron	0.003	7E-04	83	100	81	73
Boscalid	0.003	7E-04	100	100	81	60
Asulam	0.003	5E-04	33	33	19	0
Metamitron-desamino*	0.003	4E-04	83	67	38	47
Prothioconazole-desthio*	0.003	4E-04	100	100	94	93
Flutolanil	0.003	4E-04	67	100	19	13
Cyhalotrin-lambda	0.030	2E-04	67	50	56	93
Acetamiprid	0.003	2E-04	50	0	19	0
Pyraclostrobin	0.003	3E-05	100	100	100	67
Deltamethrin	0.003	1E-05	67	33	75	60
Prothioconazole	-	7E-06	0	0	0	0
Spirotetramat	0.010	6E-06	50	17	25	0
Chloridazon	0.003	1E-06	100	67	38	33
Thiacloprid	0.003	3E-07	67	50	19	7
Spirotetramat-enol*	0.003	1E-07	50	0	13	7
Azoxystrobin	0.003	1E-07	67	83	50	80
Not applied in bulb fields but reported as used in bulb disinfection						
Propamocarb	0.003	730	67	67	63	73
Carbendazim	0.003	0.09	100	100	100	93
Thiophanate-methyl	0.003	9E-03	0	0	0	0
Imidacloprid	0.003	4E-07	67	67	44	47
Not applied in bulb fields and not reported as used in bulb disinfection						
Fosthiazate	0.003	0.56	67	17	63	7
Cyprodinil	0.003	0.51	67	100	44	40
Terbutylazine	0.003	0.15	67	50	31	60
Sulcotrione	0.003	5E-03	0	0	0	0
Dimethomorph	0.003	1E-03	17	0	19	7
Fludioxonil	0.010	4E-04	17	0	19	13
Fluopicolide	0.003	3E-04	50	33	31	7
Difenoconazole	0.003	3E-05	83	83	63	73

LOD – Limit of detection; U – Pesticides use period & N – Pesticides non-use period. * Retrieved from Pesticide Properties Database (PPDB) - Lewis et al. 2016

Supplementary material C

Table C1. Focused pesticides and physicochemical properties of relevance.

Pesticide	CAS RN	Vap* (mPa)	HC* (Pa m ³ mol ⁻¹)	DT50soil* (days)	DT50air** (hr)
Chlorpropham	101-21-3	24.0	5E-02	13.1	32.2
Flonicamid	158062-67-0	9E-04	4E-08	3.1	329.7
Fluopyram	658066-35-4	1E-03	2.98E-05	309.0	20.8
Metamitron	41394-05-2	7E-04	9E-08	30.0	6.6
Pendimethalin	40487-42-1	3.3	1.27	182.3	4.2
Prochloraz	67747-09-5	0.2	2E-03	120.0	1.7
Tebuconazole	107534-96-3	1E-03	1E-05	63.0	11.2
Boscalid	188425-85-6	7E-04	5E-05	484.4	14.2
Dimethenamid-P	163515-14-8	2.5	5E-04	11.0	2.5
Kresoxim-methyl	143390-89-0	2E-03	4E-04	16.0	3.4
S-Metolachlor	87392-12-9	3.7	2E-03	51.8	2.3

* Retrieved from Pesticide Properties Database (PPDB) - Lewis et al. 2016. Vap Vapour pressure determined at 20°C ;

HC Henry's Law constant determined at 25°C ; DT50soil – Typical aerobic soil degradation

** DT50air – Atmospheric degradation estimated using EPISUITE, AopWIN

Supplementary material D

Table D1. Reported settings of spraying applications that occurred during the use period in the vicinity (within 250 meters) from Loc Homes.

Reported settings of spraying application	MR (%)	OthR (%)
Boom height (cm)	50 (83%)	<50 (14%) ; <40 (3%)
Distance between nozzles (cm)	50 (81%)	25 (7%) ; 30 (2%) ; 45 (10%)
Nozzle pressure (bar)	[2,3] (74%)	<2 (2%) ; >3 (24%)
Boom speed (km/h)	[6,8.5] (74%)	[3,5.5] (26%)

MR – Most reported setting; OthR – Other reported settings; % - Percentage from the total reports; [,] – mathematical notation for closed interval

Supplementary material E

Table E1. Reported products or active ingredient used inside or outside the homes included in the study.

Number of homes	Reported used product or action*	Chemical**
13	Roundup	Glyphosate
7	Againts weed	(Glyphosate)
5	HG Groene Aanslag Reiniger	Didecyldimethylammonium chloride
5	Flea collar for cat or dog	(Diazinon)
4	nr	Iron(II) sulfate
3	Against ants	(Permethin) ; (Tetramethrin); (Deltamethrin)
3	Vapona anti mierenpoeder	Deltamethrin
2	nr	Glyfosaat
2	Baythion KO	Deltamethrin
2	nr	Thiacloprid
2	Against rats	(Brodifacoum)
2	AA Mix	MCPA ; 2,4-D ; dicamba
2	Bayer Natria tegen motten	Cis-9-trans-12-Tetradecadienyl acetate
2	Against fleas and ticks	(Polydimethylsiloxane)
2	Bravecto	Fluralaner
2	LUXAN METAREX M TEGEN SLAKKEN	Metaldehyde
1	Control of worms in birds	Levamisole
1	Agains aphids	(Permethrin)
1	Against bathroom mold	(Sodium hypochlorite)
1	POKON MOS EN ONKRUID WEG 50M2	Iron(II) sulfate
1	nr	Sodium hypochlorite
1	HG Schimmelreiniger	Sodium hypochlorite
1	Against snails	(Iron(II) sulfate)
1	Against fleas and ticks in dogs	Pyriprole
1	Pet star Dimethicon	Polydimethylsiloxane
1	Prioderm Dimeticon Lotion	Polydimethylsiloxane
1	Activyl spot-on	Indoxacarb
1	Spot on (Bob Martin)	Fipronil

* Some residents reported the product while others reported only the action and not the specific product used. Nr – not reported. ** – If neither the product nor the chemical were reported, but only the action, then based on the products available for the Dutch market we indicate the most probable to be used, these chemicals are indicated by the name placed in closed brackets ().

Supplementary material F

Tabel F1 — LC-MSMS In-huis validatie doorslag metingen data op 5000 ng/ml met 10 g XAD-2 herhaalbaarheid (n=4)

	1xLO Q ng/ml	Recovery %	s r ng/ml	RSDr %	Precision %	Uncertainty %	Extended uncertainty %	
acetamiprid	5500	103	235	4,3	-3	7	14	
asulam	62	1	10	15	99	100	200	
azoxystrobin	5073	99	171	3,4	1	6	12	
boscalid	5404	90	173	3,2	10	12	23	
carbendazim	6824	133	312	4,6	-33	34	67	
chloridazon	5102	98	240	4,7	2	7	14	
chlorpropham	13022	79	479	3,7	21	22	44	
cyhalotrin-lambda	50265	84	2679	5,3	16	18	35	
cyprodinil	5474	95	273	5,0	5	9	17	
deltamethrin	18489	113	1882	10	-13	18	35	
difenoconazol	4769	95	197	4,1	5	8	17	
dimethenamid-P	6364	97	181	2,8	3	6	13	
dimethomorph A	2185	92	89	4,1	8	10	20	
dimethomorph B	3216	100	106	3,3	0	6	12	
flonicamid	4459	101	228	5,1	-1	7	14	
floupyram-benzamide	5499	97	225	4,1	3	7	14	
fludioxonil	14129	88	794	5,6	12	14	28	
fluopicolide	5029	98	238	4,7	2	7	14	
fluopyram	4937	101	163	3,3	-1	6	12	
flutolanil	4968	98	195	3,9	2	7	14	
fosthiazate	4809	96	245	5,1	4	8	16	
imidacloprid	5250	103	236	4,5	-3	7	14	
kresoxim-methyl	5425	97	197	3,6	3	7	14	
linuron	5187	101	239	4,6	-1	7	14	
mepanipyrim	5286	94	254	4,8	6	9	18	
metamitron	4233	85	459	11	15	19	39	
metamitron-desamino	2203	40	109	5,0	60	61	121	
metolachlor-S	8200	94	305	3,7	6	8	17	
oxamyl	2599	52	219	8,4	48	49	98	
pendimethalin	5514	96	150	2,7	4	7	14	
primicarb	5186	93	214	4,1	7	10	19	
prochloraz	5072	96	215	4,2	4	8	15	
propamocarb	4212	70	429	10	30	32	64	
prothioconazol	-	-	-	-	-	-	-	
prothioconazole-desthio	6782	125	271	4,0	-25	25	51	
pymetrozine	4740	91	199	4,2	9	11	22	
pyraclostrobin	5847	98	255	4,4	2	7	14	
spirotetramat	5629	95	297	5,3	5	9	17	

spirotratanat-enol	3167	69	2136	67	31	74	149
sulcotrione	107	2	14	13	98	99	198
tebuconazol	4797	95	80	1,7	5	7	15
terbuthylazine	3531	79	179	5,1	21	22	44
thiacloprid	5854	97	224	3,8	3	7	14
thiophanate-methyl	-	-	-	-	-	-	-
toctofos-methyl	15408	96	802	5,2	4	8	17
trifloxystrobin acid	107	2	26	24	98	101	202
trifloxystrobin	5886	99	222	3,8	1	6	13

Exp lanation of symbols:
S r intra-laboratory repeatability standard deviation
RS Dr intra-laboratory repeatability coefficient of variation



4

Pesticides in doormat and floor dust from homes close to treated fields: Spatio-temporal variance and determinants of occurrence and concentrations

Daniel Figueiredo^{1*}, Rosalie Nijssen², Esmeralda Krop ¹, Daan Buijtenhuijs¹, Yvonne Gooijer³, Luuk Lageschaar³, Jan Duyzer⁴, Anke Huss¹, Hans Mol², Roel Vermeulen^{1,5}

¹ Institute for Risk Assessment Sciences, Division of Environmental Epidemiology, Utrecht University, PO Box 80178, 3508, TD, Utrecht, the Netherlands

² Wageningen Food Safety Research, part of Wageningen University & Research, Akkermaalsbos 2, Wageningen, 6708 WB, The Netherlands

³ CLM Onderzoek en Advies BV, P.O. Box 62, 4100 AB, Culemborg, The Netherlands

⁴ TNO Circular Economy and Environment, P.O. Box 80015, 3508 TA, Utrecht, The Netherlands

⁵ Julius Centre for Public Health Sciences and Primary Care, University Medical Centre, PO Box 85500, 3508, GA, Utrecht, the Netherlands

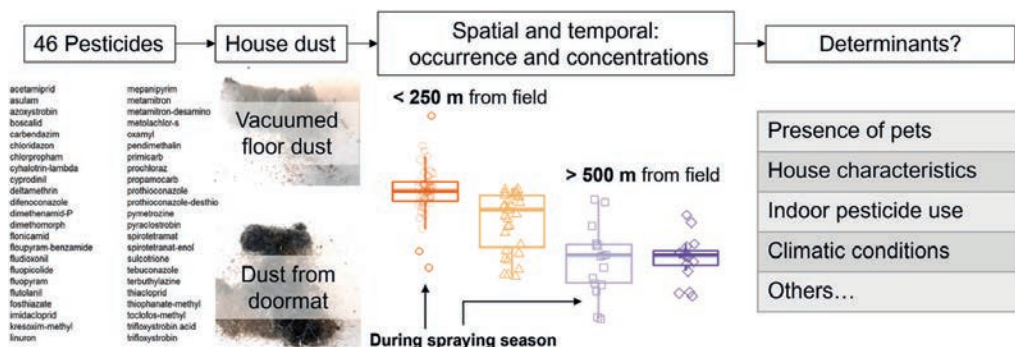
Published: Environmental Pollution, Vol. 301, ID. 119024

doi: 10.1016/j.envpol.2022.119024

Abstract

Indoor dust has been postulated as an important matrix for residential pesticide exposure. However, there is a lack of information on presence, concentrations and determinants of multiple pesticides in dust in residential homes close to treated fields. Our objective was to characterize the spatial and temporal variance of pesticides in house dust, study the use of doormats and floors as proxies for pesticides in indoor dust and identify determinants of occurrence and concentrations. Homes within 250 m from selected bulb fields were invited to participate. Homes within 20 km from these fields but not having agricultural fields within 500 m were selected as controls. House dust was vacuumed in all homes from floors (VFD) and from newly placed clean doormats (DDM). Sampling was done during two periods, when pesticides are used and not-used. For determination of 46 prioritized pesticides, a multi-residue extraction method was used. Most statistical analyses are focused on the 12 and 14 pesticides that were detected in >40% of DDM and VFD samples, respectively. Mixed models were used to evaluate relationships between possible determinants and pesticides occurrence and concentrations in DDM and VFD. 17 pesticides were detected in more than 50% of the homes in both matrixes. Concentrations differed by about a factor five between use and non-use periods among homes within 250 m of fields and between these homes and controls. For 7 pesticides there was a moderate to strong correlation (Spearman rho 0.30-0.75) between concentrations in DDM and VFD. Distance to agricultural fields and air concentrations were among the most relevant predictors for occurrence and levels of a given pesticide in DDM. Concentrations in dust are overall higher during application periods and closer to fields (< 250 m) than further away. The omnipresence of pesticides in dust lead to residents being exposed all year round.

Graphical abstract



Introduction

Pesticides in house dust

Pesticides play an important role in the agricultural production. An average amount of four million tons of pesticides are sprayed every year worldwide, with about 12% being applied in Europe (FAO, 2019). As pesticides may be dispersed outside the intended areas of application (Bueno et al. 2017), this may lead to exposure of the surrounding population (Zivan et al. 2016). Several studies have reported pesticides in house dust (e.g. Audy et al. 2018, Lee et al. 2018, Dong et al. 2019) and, although concentrations in the environment typically reflect annual usage, many of the active ingredients can still be detected after one year in house dust (Smith et al. 2017). Some studies even show that pesticides that were banned or restricted for many years still can be found in the indoor environment (Rudel et al. 2003).

Dust as exposure route to pesticides

The body of evidence regarding routes of human (residential) exposure to pesticides via house dust increased in recent years (Deziel et al. 2017). Dust has moved more into the focus as a possibly relevant contributor to human pesticide exposure (Golla et al. 2012, Bennett et al. 2019). This is due to the following reasons: firstly, dust ingestion, inhalation and contact with house dust have been shown to be primary routes of exposure for residents (Melymuk et al. 2020), especially for small children (Whitemore et al. 1994, Roberts & Dickey 1995); secondly, people usually spend most of their time indoors at home (Brasche & Bischof 2005), making this environment a prime source for exposure to contaminated dust (Dalvie et al. 2014). Thirdly, several studies have found associations between residential pesticide exposure and a wide range of health effects (e.g. Sabarwal et al. 2018, Rappazzo et al. 2018, Raheison et al. 2019), although only very few studies, like the one from Waheed et al. (2017) single out dust exposure from residential exposure.

How do pesticides end up in house dust?

Pesticides can accumulate in indoor dust via different routes. Drift of pesticides usually occurs over short distances (0 - 250 m), with higher concentrations in both air and ground deposits closer to agricultural fields (0 - 50 m) (Garron et al. 2009, Zande et al. 2017) and declining exponentially with distance from the applied field (Carlsen et al. 2006). Pesticides can however be bound to particles and can travel longer distances and penetrate into homes further away and settle as house dust (Coronado et al. 2011). Additionally, the gas-phase fraction of pesticides can be bound to indoor dust particles (Wei et al. 2019). Pesticides can also reach the house dust by the take-home

route (Hyland & Laribi 2017), where contaminated soil is dragged into the residence by contaminated clothing and shoes or by pets (López-Gálvez et al. 2019).

Dust from doormat and vacuuming – current and historical pesticide use

Although pesticides can end up in indoor house dust via several routes, most previous studies assessing pesticide concentrations in dust have used solely vacuumed floor dust (e.g. Colt et al. 2008, Smith et al. 2016, Tamaro et al. 2017) or wipe dust sampling (e.g. Stout et al. 2009, Mercier et al. 2011) to investigate the occurrence. These methods reflect both current and historical pesticide use (Béranger et al. 2018), since it is not known for how long the collected dust has been present. Therefore they fail to capture pesticides exclusively used in the study period. A solution to this, is using a bespoke clean doormat for the study period. By doing so, the sample taken from the doormat reflects solely currently used pesticides (Plascak et al. 2019). Only a limited number of studies have compared different dust matrixes (Lu et al. 2000, Moschet et al. 2018, Rostkowski et al. 2019, Dubocq et al. 2021) and few have looked into determinants of occurrence and concentrations of pesticides in indoor dust (Gunier et al. 2011, Deziel et al. 2019).

Aim of our study

Here we present the results of indoor dust measurements of 46 pesticides across two different dust matrixes, vacuumed floor dust (VFD) and dust from a bespoke study doormat (dust from doormat, DDM). Five aims were a-priori defined: i) Study patterns for different pesticides occurrence in both dust matrixes; ii) Study temporal differences, by comparing concentrations between a period when pesticides are applied and a period when they are not applied; iii) Study spatial differences, by comparing concentrations in homes located close to fields with homes located further away; iv) Study the relation between concentrations of pesticides in VFD and DDM and increase our knowledge on the take-home exposure route; and v) Identify determinants of occurrence and concentration of pesticides in indoor dust samples (VFD and DDM), as an effort to further improve future pesticide exposure models.

Materials and methods

Study design

This research is part of the Dutch OBO study (OBO 2019). The study took place from May 2016 to December 2017 in homes in the vicinity of bulb fields, a cultivation representative of down-ward boom spraying. “Location” was defined as an area

consisting of homes surrounding a selected field, on which information about the applied pesticides was available. All sampling sites were located in the Netherlands, in the North-Holland and South-Holland provinces. Dust samples were taken during pesticide *use* and *non-use* periods in 9 different locations. In the use period, pesticides in dust were sampled per location for one week, with a spray event on the selected field as starting timepoint. In the non-use period (i.e. period when pesticides are not used), sampling was carried out also for one week.

Selection of pesticides for targeted analysis

Pesticides were selected based on registration, usage in tulip and lily cultivation and availability of a single analytical method. A more detailed description of the selection process can be found in Kruijne et al. 2019. In summary, a total of 46 pesticides were selected for analysis, comprising 29 pesticides that are frequently sprayed in bulb fields, 3 pesticides used in bulb disinfection, 6 breakdown products of some of these pesticides and 8 pesticides that were found in a previous study in soil and plant material from flower bulbs (OBO 2019).

The selected pesticides represent a vast range of different physico-chemical properties as well as the three product types. These include 11 herbicides: asulam, chloridazon, chlorpropham, dimethenamid-p, linuron, metamiltron, metamiltron-desamino, pendimethalin, s-metolachlor, sulcotrione and terbuthylazine; 12 insecticides: acetamiprid, cyhalothrin-lambda, deltamethrin, flonicamid, fosthiazate, imidacloprid, oxamyl, primicarb, pymetrozine, spirotetramat, spirotetramat-enol and thiacloprid; and 23 fungicides: azoxystrobin, boscalid, cyprodinil, difenoconazole, dimethomorph, fludioxonil, fluopicolide, fluopyram, fluopyram-benzamide, flutolanil, kresoxim-methyl, mepanipyrim, prochloraz, propamocarb, prothioconazole, prothioconazole-desthio, pyraclostrobin, tebuconazole, thiophanate-methyl, carbendazim, toclofos-methyl, trifloxystrobin, trifloxystrobin-acid. The list of analysed pesticides and relevant physical-chemical properties can be found in supplementary material A. Excluded from selection were chlorothalonil, diquat, esfenvaleraat, folpet, glyfosaat, iprodione and mancozeb. All these pesticides required an analytical method different from the selected one. Detailed information on these selection can be found in Figueiredo et al. 2021a.

Recruitment

With the aim of getting a good spatial distribution of houses around sprayed fields with at least one of those fields being treated with a pesticide listed for analyses, we initialized a recruitment process (Figure 1). First, farmers of bulb fields were contacted to participate in the study and provide information on their fields and then, in case

of acceptance, the residents living in the vicinity of those fields were approached. Here, recruitment and selection are briefly described. More details can be found in Figueiredo et al. 2021a, including the power calculation for minimum samples needed (study size).

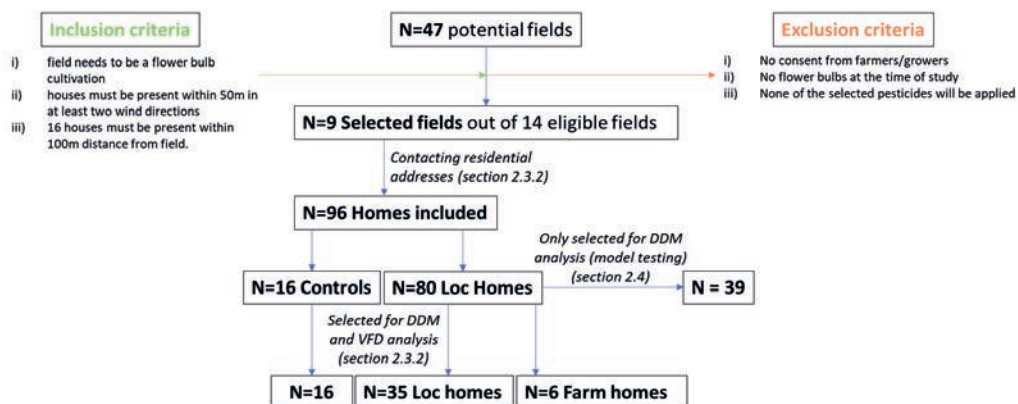


Fig 1. Flowchart of recruitment process for both fields and homes.

Farm Homes – Homes where farmers live; Loc Homes – Homes located within 250 meters from a selected field; Controls – Homes located more than 500 meters from any agricultural field but in the same region as the Loc Homes

Fields

A search for eligible fields resulted in 47 potential fields. This selection was based on 1) field needs to be a flower bulb cultivation and 2) houses must be present within 50 m in at least two wind directions, and at least 16 houses must be present within 100 m distance. Thirty-three locations did not participate because farmers did not give consent (N=26), because there were no flower bulbs present at the time of the study or none of the selected pesticides were going to be applied (N=7). From the 14 eligible fields 9 were randomly selected for the study.

Homes

After inclusion of a field in the study, all residential addresses within 250 m of the perimeter of the field, here called “Location” (Loc) Homes, were selected using the Dutch cadastral data “Basisregistraties adressen en gebouwen (BAG)”. Potential control homes, further called “Controls”, were also selected using BAG to identify homes in medium to low urbanized areas (i.e. <1500 addresses/km²), situated within 20 km from a target field, and not having any agricultural fields within 500 m of the home.

Invitation letters and a brochure were sent to all identified addresses and interested invitees were interviewed by phone using a structured interview script.

In total, 1778 residential addresses and 482 addresses at control locations received an invitation to the study. Eighty potential Loc Homes responded, corresponding to a response rate of 4.5% (range 2.1% to 33.3% by location). Additionally, 16 control homes were included (response rate: 3.3%). Not all homes partook in all measurement campaigns as three homes missed one of the two seven-day measurement campaigns due to holidays and residents from four homes ended their participation before the end of the study.

Due to budgetary reasons dust samples (both DDM and VFD) were only analysed for 41 homes that were selected out of the 80 homes initially included in the study. In short, the aim was to have a good spatial distribution of Loc Homes (i.e. different distances from the field were equally represented). For this, we selected some homes located very close to the fields (<50 m) (N=16), some more further away (50 m – 150 m) (N=14) and some located between 150 m and 250 m (N=11). These buffers are based on previous research done on pesticide concentrations at different distances downwind (Siebers et al. 2003, Figueiredo et al. 2021b) and ensured that homes were located both up and down-wind of the application (all cardinal directions). All controls were included in the sample analyses.

Some of the participants were also growers. These homes (N=6), defined here as “Farm” homes, were treated as a separate group in all analyses, since it is known from previous studies that these homes are more prone to pesticide accumulation and take-home exposures (Curl et al. 2002, Curwin et al. 2005).

Additional homes – Modelling testing purposes

Of the homes initially not selected (N=39) we later analysed the dust doormat sample from the *use* period for each home, using identical protocols and laboratory as the initial analyses. We here use this separate dataset solely for model testing purposes (test dataset). We chose DDM over VFD for additional analyses as DDM has a determined sampling time and surface, increasing comparability and avoids the influence of long-term pesticide accumulation (Harnly et al. 2009).

Sample collection

Vacuumed floor dust (VFD)

In all participating homes, VFD was collected from the living room by a research assistant. In the *use* period, it was collected 7 days after a spray event. The recruited farmers informed us a-priori on which day and time they would spray. This defines the spray event. Spray events were not the first spraying occurring in the selected fields. In the *non-use* period, VFD was collected at the time of doormat retrieval. For this, a sample sock (Allied Filter Fabrics, Hornsby, Australia) was attached to the hose of a vacuum cleaner. Initially, the research assistant vacuumed 2 m² of carpet or 4 m² of smooth floor for 2 min. After analysing the first samples (N=18) this was increased to 4 m² of carpet or 6-8 m² of smooth floor, depending on available free floor space, to increase the amount of dust collected. Sampling duration was increased to 5 min. Sampling duration and sampled area were recorded for each home and the results were standardised per gram of collected dust. In a sensitivity analysis, we saw that the increase in sampling time and surface area vacuumed did not significantly affect pesticide concentration per gram dust and therefore, for the final analysis, results were pooled. The sample amount varied from 0.02 to 28 g, with a median value of 0.37 g. Samples were stored at -18° C until analysis.

Dust Doormat (DDM)

In each participating home, a clean doormat (100% polypropylene) was cut to applicable size and placed indoors at the main entrance by a participant. In the *use* period, the participant placed the doormat on the day of the spray event. In the *non-use* period it was placed during a month where no sprayings occurred. The doormat was collected by the research assistant within 5 days after the end of the measurement campaign and transported in a clean box to the laboratory. We recorded the size of the doormat and start and end date of collection for each home and standardised the result per gram of collected dust. In the laboratory, we used a sample sock (Allied Filter Fabrics, Hornsby, Australia) to vacuum clean all dust material from the doormat. Samples were stored at -18°C until analysis. The amount of dust material retrieved from the doormat varied from 0.55 to 196 g, with a median of 6.0 g.

Analysis method for determination of pesticides in dust samples

For determination of pesticides in the dust samples, a multi-residue extraction method was used. This is based on salt-induced phase partitioning technique (QuEChERS) (Lehotay 2007, Perestrelo et al., 2019) and Liquid Chromatography-tandem Mass Spectrometry (LC-MS/MS). This way, all 46 selected pesticides and relevant metabolites

could be measured simultaneously. We chose not to do fractioning or sieving of the dust sample given that we are interested in total exposure, several other studies also used this approach (Cao et al. 2012).

In brief, the entire dust sample was extracted with water and acetonitrile/1% acetic acid by mechanical shaking. Salts were added to induce phase partitioning. The organic phase containing the pesticides was used for LC-MS/MS analysis. Dust is a complex, variable and heterogenous matrix, resulting in variable and often strong matrix effects (ion suppression) in the LC-MS/MS analysis. Therefore quantification was based on the standard addition method. To this end, for each sample extract, two aliquots were taken. To one aliquot the mix standard of 46 pesticides was added. After 2-fold dilution with water, the extracts with and without standard addition were analysed by LC-MS/MS. For details on sample preparation, LC-MS/MS conditions and quality assurance see supplementary material B.

In-house validation and on-going analytical quality control were done according to EU guidance document SANTE/11945/2015 (currently SANTE/12682/2019). In most cases (83%), recoveries were between 70 and 120%. The precision (RSD) were below 20% at the 50 µg/kg level, and around 20% at lower levels. The limit of quantification (LOQ) was 1 µg/kg for most pesticides (N=33), 3-50 µg/kg for 12 pesticides. The limit of detection (LOD) was estimated in case the LOQ was higher than 1 µg/kg, and in these cases ranged from 1 to 20 µg/kg. See the supplementary material B for details.

Treatment of left-censored data

For left-censored data (<LOD) imputation was performed when at least 40% of the measured samples had levels above the LOD. Concentrations between LOD and LOQ, although semi-quantitative, were used as such since these are likely more accurate than imputed values (Succop et al. 2004). For each pesticide, imputation was performed using the method proposed by Lubin et al. (2004). Here, unbiased estimates are obtained by imputing the values below LOD based on the maximum likelihood estimation, while accounting for the distribution and correlation of all pesticide data. Here, imputation was performed including 100 iterations.

Sampling period and number of analysed samples

Both types of dust samples were grouped according to the period of sampling: during the period the pesticide was used, normally between March and August, or outside the period the pesticide was used, October to December. Periods of application of each pesticide were defined based on reported spraying schedules. Samples were therefore

grouped by use and *non-use* for each pesticide separately. The reported spraying periods of each pesticide can be found in supplementary material C.

In total 292 dust samples were analysed, with 125 being DDM samples and 128 being VFD samples. From the DDM samples there were 14 from Farm Homes (N=7 in both periods), 79 from Loc Homes (N=48 *use* period and N=31 *non-use* period) and 32 from Controls (N=16 in both periods). From the VFD samples there were 14 from Farm Homes (N=7 in both periods), 82 from Loc Homes (N=48 *use* period and N=34 *non-use* period) and 32 from Controls (N=16 in both periods). As indicated before, additional samples (n=39; 3 from Farm Homes and 36 from Loc Homes) were analysed for validation of the pesticide occurrence model in DDM.

Questionnaires and variables used for modelling purposes

Per home, a questionnaire on home characteristics was collected as well as lifestyle information and demographics for all participants within a home. Detailed information on the filling of questionnaires and list of all questions asked can be found in Figueiredo et al. 2021a. These questions pertained to *a priori* identified variables that might be related to occurrence and variance in concentrations of pesticides in indoor dust. In short, this information consists of variables that i) are related to house characteristics and can affect the dynamics of pesticides in indoor dust, such as having a smooth vs carpeted flooring, forced vs natural ventilation, sealed against draught or having visible leakages, amongst others; ii) are related to house dynamics, such as leaving shoes outside or inside, number of inhabitants, number of pets and type of pets, use of pesticides, amongst others.

In addition to the above, we also use meteorological variables, such as humidity, precipitation, wind speed and direction. Distance from home to closest agricultural field is used as a spatial variable. See Figueiredo et al. for details on collection of both meteorological and spatial variables (section 2.7, Figueiredo et al. 2021b)

Finally, as an additional variable, we also predicted concentrations in dust (Dustpred) based on the deterministic equation by (Weschler and Nazaroff, 2010). Here, air concentrations sampled via active air samplers parallel to the dust collection are used as input. Detailed methods and results regarding air measurements can be found in Figueiredo et al. 2021b. The full list of variables and type (i.e. discrete or continuous) as well as information on the equation used to calculate Dustpred can be consulted in Supplementary material D. All variables were included as independent variables in the undermentioned modelling steps.

Statistical analysis

All data analyses were performed using R, version 4.0.0 (R Core Team 2017). The pesticide concentration data was log₁₀ transformed to meet the assumptions of inferential statistics.

Samples categorization and focus of analysis

Not all of the 46 targeted pesticides were applied during the course of the study, therefore, for data analysis and interpretation purposes, pesticides were categorized into three groups: i) pesticides that were reported as being applied in the selected field and/or on fields located in the vicinity of the included homes (< 250 m) during the course of the study; ii) pesticides that were not reported as being applied but were used for bulb disinfection purposes; and iii) pesticides that were neither reported as being applied or used for bulb disinfection. The results are presented separately for these three groups given that bulb disinfection is not bound to a fixed period of usage and might be used inside facilities that are not located close to agricultural fields.

The field participating in our study was often not the only field applying pesticides in the proximity of the participating Loc Homes. Information regarding spraying applications and applied mixtures was a posteriori collected or estimated (based on expert decision) for all fields within 250 m of location homes. Information on the different spraying applications is reported in OBO 2019. Data on pesticides used for bulb disinfection in 2017 was retrieved from local farmers and data available from Ten Brinke 2017, an agricultural advisory company.

We first summarized the detection frequency for all 46 targeted pesticides. In subsequent statistical analysis, however, the focus was solely on pesticides that were quantified in at least 40% of the measured samples. This comprises some of the pesticides applied in bulb fields (N = 9 for DDM and N=10 for VFD) and almost all pesticides used in bulb disinfection (N=3 for DDM and N=4 for VFD). No quantitative assessment can be performed for the remaining pesticides given that more than 60% data is missing (Jakobsen et al. 2017).

Spatial and temporal differences in concentrations

In order to study spatial differences we compared concentrations in Loc Homes vs Controls. For temporal differences we compared concentrations in the *use* period vs *non-use* period. Concentrations were plotted for easy visualization of the aforementioned comparison. Student's t-Test were used to determine whether the means of different groups (i.e. samples taken during the *use* and *non-use* period and Loc Homes vs

Controls) were equal to each other. For this comparisons data was analysed from 41 Loc Homes and from 16 Controls, both during use and non-use period, respectively.

Correlations between the two matrixes

Spearman's rank correlation coefficient was used to study the relationship between pesticide concentrations in the two types of dust samples (DDM and VDF). Here, Spearman correlation coefficients for Loc Homes and Controls were calculated separately, instead of grouping all samples together (i.e. Loc Homes + Controls). We chose to look at correlations per group given that concentrations in Loc Homes were generally much higher than in Controls in both periods. This would drive the correlations if all samples were taken together and would likely hide any pattern between DDM and VFD that solely occurs in Loc Homes or Controls. All analyses were performed with concentrations in nanograms per collected amount of dust (ng/g). As a sensitivity analysis, correlations were additionally calculated using concentrations in nanograms per surface area (ng/m²).

Identifying possible determinants of occurrence and concentrations of different pesticides in indoor dust

To assess possible determinants of occurrence and concentrations of pesticides in indoor dust, mixed models were built using the *lme4* package for R. Two correlated random effects (intercept and slope) were estimated for each level of the HouseID factor (i.e. in *lme4* Period | HouseID). Analyses were carried out for both the occurrence (binary – logistic regression) and log-transformed concentrations of pesticides (continuous - linear regression) in dust.

A multivariate logistic regression model was built using a backward stepwise algorithm for variable selection in combination with the *glmer* function to identify the best model to predict occurrence of pesticides in indoor dust. Here, percentage of values above LOD was used as dependent variable.

To predict concentrations in dust the *lmer* function as implemented in R was used. Here, each pesticide concentrations was used as dependent variable. The obtained models were tested using the independent dataset of 39 DDM samples.

Finally, for the logistic model, the AUC (area under the curve) was calculated as performance measurement using the *pROC* library for R. For the linear regression model, we calculated the R² and RMSE.

Results

Table 1 shows the percentage of samples above LOD for the three groups: Farm Homes, Loc Homes and Controls. The results are ordered by decreasing half-life in soil and clustered by type of dust sample (DDM, VFD) and by period (*use* and *non-use*). All pesticides were detected at least once in both types of dust with the exceptions of cyhalothrin-Lambda, terbutylazine and sulcotrione, detected only in VFD.

Detection of pesticides in DDM and VFD

DDM – Pesticides detection frequency

Regarding pesticides applied in bulb fields (group I, Table 1), these were, on average, detected in 64% and 54% of the samples collected in Farm homes during the *use* and *non-use* periods, respectively. For Loc Homes, these were detected in 32% and 23% of the samples collected during the *use* and *non-use* periods, respectively. For Controls, these were detected in 12% and 8% of the samples collected during the *use* and *non-use* periods, respectively. Regarding pesticides used in bulb disinfection (group II, Table 1), these were, on average, detected in 94% and 92% of the samples collected in Farm homes during the *use* and *non-use* periods, respectively. For Loc Homes, these were detected in 49% and 58% of the samples collected during the *use* and *non-use* periods, respectively. For Controls, these were detected in 45% and 30% of the samples collected during the *use* and *non-use* periods, respectively. For pesticides that were not used in either of the above-mentioned situations (Group III, Table 1) detection was very low (overall average of 6%).

VFD – Pesticides detection frequency

Regarding pesticides applied in bulb fields (Group I, Table 1), these were, on average, detected in 59% and 50% of the samples collected in Farm homes during the *use* and *non-use* periods, respectively. For Loc Homes, these were detected in 32% and 21% of the samples collected during the *use* and *non-use* periods, respectively. For Controls, these were detected in 11% and 13% of the samples collected during the *use* and *non-use* periods, respectively. Regarding pesticides used in bulb disinfection (Group II, Table 1), these were, on average, detected in 75% and 88% of the samples collected in Farm homes during the *use* and *non-use* periods, respectively. For Loc Homes, these were detected in 70% and 67% of the samples collected during the *use* and *non-use* periods, respectively. For Controls, these were detected in 63% and 59% of the samples collected during the *use* and *non-use* periods, respectively. For pesticides that were not used in either of the above-mentioned situations (Group III, Table 1) detection was very low (overall average of 14%).

Table 1. Percentage of detectable pesticide concentrations by exposure group, type of dust sample and use period.

	Farm Homes				Loc Homes				Controls			
	Use period		Non-use period		Use period		Non-use period		Use period		Non-use period	
Active ingredient (pesticide group)	VFD	DDM	VFD	DDM	VFD	DDM	VFD	DDM	VFD	DDM	VFD	DDM
Group I - Reported as being applied in bulb fields during the study period												
boscalid (F)	88	100	100	100	92	98	88	84	43	88	63	63
azoxystrobin (F)	88	88	83	83	66	65	59	52	50	19	50	25
fluopyram (F)	88	88	67	100	54	56	38	61	14	13	13	13
flutolanil (F)	88	100	83	83	34	42	26	39	14	13	0	0
pendimethalin (H)	75	100	67	100	68	96	41	71	29	19	31	13
mepanipyrim (F)	50	50	0	17	6	19	0	6	0	0	0	0
linuron (H)	75	100	17	100	36	52	9	19	0	6	0	0
tebuconazole (F)	75	100	83	83	84	81	79	61	64	75	69	44
prothioconazole-desthio (F)	63	63	83	50	58	67	41	45	21	19	19	13
chloridazon (H)	88	75	83	83	24	10	6	6	7	0	0	0
pyraclostrobin (F) ^a	100	100	100	100	92	96	79	84	21	75	38	50
metamitron-desamino (H)	50	63	67	33	34	21	9	3	0	0	13	0
tolclofos-methyl (F)	88	100	83	83	24	17	18	29	0	0	6	0
chlorpropham (H)	38	50	0	0	26	48	18	13	14	19	6	0
cyhalotrin-lambda (I)	13	0	0	0	2	0	0	0	0	0	0	0
pymetrozine (I)	13	38	33	17	14	17	3	19	0	0	0	0
S-metolachlor (H)	100	100	50	83	46	69	6	13	14	6	0	0
deltamethrin (I) ^a	13	0	17	0	0	4	12	6	7	6	13	0
prochloraz (F) ^a	100	100	100	100	82	90	79	94	14	38	63	50
metamitron (H)	63	75	67	83	38	23	12	10	0	0	0	0
asulam (H)	75	88	50	67	30	31	3	19	7	0	0	0
pirimicarb (I)	13	38	50	17	12	8	9	6	7	0	6	0
fluopyram-benzamide (F)	13	25	17	33	2	0	0	0	0	0	0	0
thiacloprid (I)	50	38	67	33	30	2	21	3	0	6	0	6
dimethenamid-P (H)	50	38	33	17	14	6	0	3	0	0	0	0
oxamyl (I)	38	25	33	17	10	6	9	0	0	6	0	0
flonicamid (I)	63	75	50	83	56	19	24	16	21	0	19	6
acetamiprid (I)	75	75	50	67	18	6	9	0	14	0	13	0
trifloxystrobin (F)	50	50	17	67	12	8	6	10	7	6	0	6
trifloxystrobin-acid (F)	13	38	0	0	0	0	0	0	0	0	0	0
kresoxim-methyl (F)	50	63	33	50	16	2	21	6	0	0	13	0
prothioconazole (F) ^a	50	38	50	50	6	15	0	10	0	0	0	0
spirotetramat (I)	63	63	33	33	4	4	0	3	0	0	13	0
spirotetramat-enol (I)	50	50	33	17	2	2	3	3	0	0	6	0
Group II - Not applied in bulb fields but reported as used in bulb disinfection in 2017												
imidacloprid (I)	63	100	83	83	82	25	65	35	93	75	88	44
propamocarb (F)	75	75	67	83	62	29	41	29	57	6	44	25
thiophanate-methyl (F)	75	100	100	100	46	71	71	84	36	19	56	13
carbendazim (F)	88	100	100	100	90	73	91	84	64	81	50	38
Group III - Not applied in bulb fields and not reported as used in bulb disinfection												
fluopicolide (F)	13	0	33	0	10	2	9	3	7	0	6	0
difenoconazole (F)	25	0	33	0	28	6	18	13	7	6	13	6
cyprodinil (F)	13	13	0	0	20	17	18	13	0	13	13	0
dimethomorph (F)	13	13	33	17	28	19	21	10	7	6	13	19
fludioxonil (F)	38	13	17	0	50	33	50	16	14	25	31	6
terbuthylazine (H)	0	0	17	0	4	0	0	0	7	0	0	0
fosthiazate (I)	25	25	17	17	0	0	0	0	0	0	0	0
sulcotrione (H)	0	0	0	0	0	0	0	0	7	0	0	0

Farm Homes – Homes where farmers live; Loc Homes – Homes located within 250 meters from a selected field; Controls – Homes located more than 500 meters from any agricultural field but in the same region as the Loc Homes. Use – Period when pesticides are sprayed; Non-use – Period when pesticides are not sprayed. VFD – Vacuumed floor dust; DDM – Dust from doormat. F – Fungicide; H – Herbicide; I – Insecticide. Pesticides that are not used but are transformation products are in italic. All values are in percentage (%) of samples where a given pesticide was detected above the limit of detection. The colour scheme is used to highlight detection frequency, darkest colour = 100% detection and lightest colour = 0% detection. Colour scheme is divided into the following 8 detection (%) range intervals (from lighter to darker): 0 -> (0,11] -> (11,25] -> (25,50] -> (50,75] -> (75,90] -> (90,100) -> 100. a Can also be used for bulb disinfection (Ten Brinke 2017)

Concentrations in DDM and VFD

Imputation of values below LOD was performed for pesticides with more than 40% of the samples having levels above the LOD, resulting in 12 pesticides with imputed values for DDM and 14 for VFD. Most of these pesticides had at least 50% of measured samples above LOD, with exception of fluopyram and prothioconazole-desthio.

In Figure 2 we present the results of the comparison between group means for these pesticides for DDM, by comparing Loc Homes vs Controls, during *use* and *non-use periods*. Figure 3 shows the same comparison for pesticides in VFD. All Student's t-Test results from the spatial and temporal comparisons can be found in supplementary material E.

DDM – Concentrations in space (Loc Homes vs Controls) and time (Use vs Non-use)

Differences between Loc Homes and Controls in the *use* period were statistically significant for 9 out of the 12 pesticides for DDM. For 8 of these 9 pesticides, Loc Homes had higher concentrations and imidacloprid was the only pesticide with higher concentrations in Controls compared with Loc Homes. In the *non-use* period, significant differences between Loc Homes and Controls were as pronounced, with 10 out of 12 pesticides having higher concentrations in Loc Homes.

For Loc Homes, we only observed significantly higher concentrations for 3 pesticides applied in bulb fields in the *use* when comparing with the *non-use* period (panel A, Figure 2). For Controls, significant differences were only observed for tebuconazole, imidacloprid and carbendazim, with the last two belonging to the bulb disinfection group (panel B, Figure 2).

VFD – Concentrations in space (Loc Homes vs Controls) and time (Use vs Non-use)

Differences between Loc Homes and Controls in the *use* period were statistically significant for 9 out of the 14 pesticides for VFD. In the *non-use* period, significant

differences between Loc Homes and Controls were less pronounced, with 6 out of 14 pesticides having higher concentrations in Loc Homes. Similar to DDM, imidacloprid was found in higher concentrations in Controls than in Loc Homes.

We observed for both VFD samples collected in Loc Homes higher concentrations in the *use* as compared to *non-use* period, for 6 pesticides applied in bulb fields (panel A, Figure 3). For Controls, no clear differences were observed except for prochloraz, where concentrations were significantly higher in the *non-use* period as compared to the *use* period. Although reported as being sprayed during the measuring period, prochloraz can also be used in bulb disinfection.

Correlation between pesticides in DDM and VFD

Correlations between concentrations in DDM and VFD were calculated for each pesticide that had >40% detects in both dust matrixes. These were 11 pesticides out of the 14 initially imputed. Each correlation comprised 111 paired observations. All calculated Spearman correlation coefficients can be consulted in Supplementary material F.

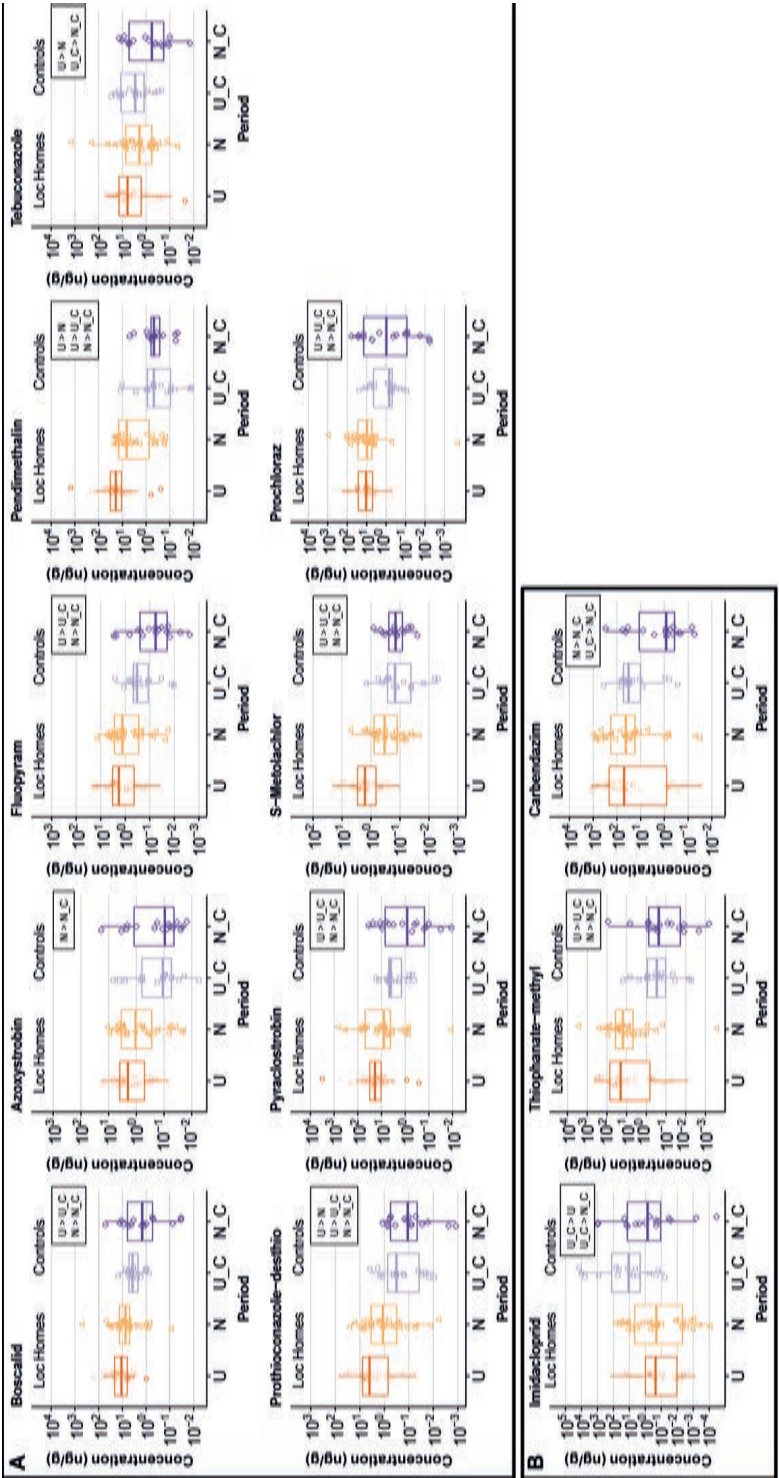


Fig 2. Pesticide concentrations in house doormat grouped by Use (U) and Non-Use period (N) for locations and U_C and N_C for Controls. Panel (A) refers to pesticides applied in bulb fields and panel (B) to pesticides used in bulb disinfection. Summary statistics in boxplots (min, max, 1st and 3rd quartile and median). The box in the upper right corner of each graph is a comparison between the different groups and indicates which differences between group means is statistically significant at the 0.05 level.

The average correlation between concentrations in both types of dust is, for Loc Homes, 0.24 [-0.01, 0.55] and 0.27 [-0.06, 0.40], in the *use* and *non-use* period, respectively. For Controls, 0.23 [-0.18, 0.74] and 0.25 [-0.36, 0.60], in the *use* and *non-use* period, respectively.

In Loc Homes, correlations were absent (-0.01) to moderate (0.55) in the *use* period. Three pesticides showed statistically significant ($\alpha < 0.05$) correlations between both matrixes. Prothiconazole-destio and pyraclostrobin showed moderate correlation coefficients, 0.38 and 0.55, respectively. Whist imidacloprid showed a weak correlation coefficient of 0.14. There were no statistically significant correlations for Loc Homes in the *non-use* period.

In Controls, correlations were very weak (0.06) to moderately-strong (0.74) in the *use* period. Three pesticides showed statistically significant correlations between both matrixes. Fluopyram and tebuconazole showed moderate correlation coefficients, 0.57 and 0.55, respectively. Imidacloprid displays a moderately-strong correlation coefficient of 0.74. In the *non-use* period, two different pesticides showed strong statistically significant correlations, pendimethalin and prochloraz, both 0.60.

From the sensitivity analysis (see supplementary material G), where the correlation between concentrations in nanograms per surface area (ng/m^2) were calculated, no significant correlation between pesticides in Loc Homes was observed. Whilst, for Controls, concentrations of imidacloprid, pendimethalin and prochloraz were moderate to strongly correlated between both dust matrixes.

Pesticides occurrence in dust – Multivariate mixed-effect logistic models

In the multivariate analysis, for DDM, and after selection via a stepwise approach, the resulting model encompasses 5 variables, namely half-life in soil, vapour pressure, average kg applied per year, distance to field and predicted dust concentration. Predicted performance (calculated AUC) of the DDM model was 75% using the independent DDM dataset.

In the multivariate analysis, for VFD, and after selection via a stepwise approach, the resulting model encompasses the same variables as the DDM multivariate model, except for distance to nearest agricultural field, which was only selected for the DDM model. The odds ratio for each predictor variable can be found in supplementary material H.

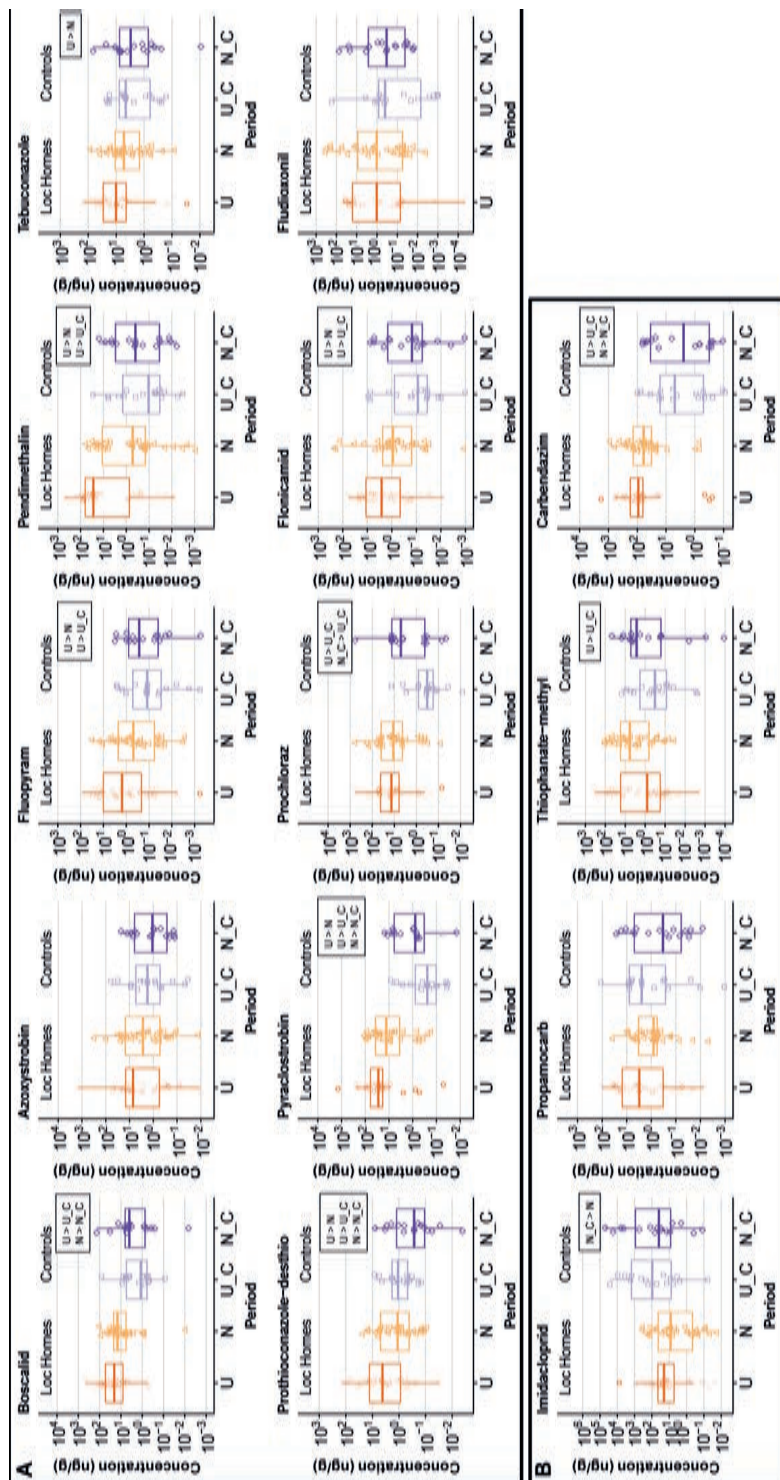


Fig 3. Pesticide concentrations in vacuumed house dust grouped by Use (U) and Non-Use period (N) for locations and U_C and N_C for Controls. Panel (A) refers to pesticides applied in bulb fields and panel (B) to pesticides used in bulb disinfection. Summary statistics in boxplots (min, max, 1st and 3rd quartile and median). The box in the upper right corner of each graph is a comparison between the different groups and indicates which differences between group means is statistically significant at the 0.05 level. No box = no statistically significant difference between groups.

Pesticides concentration in dust – Multivariate mixed-effect linear models

Multivariate models for pesticide concentration in dust varied significantly per pesticide for both DDM and VFD. However, for DDM, distance to field and predicted concentration in dust were the most selected variables between models (Table 2). Models were only built for imputed pesticides. Results from univariate linear models for each pesticide can be consulted in Supplementary material I. Specifically, five pesticides, namely fluopyram, pendimethalin, prothioconazole-desithio, pyraclostrobin and s-metolachlor, have predicted concentration in dust and distance in common as predictive variables with similar beta coefficient (β) signs.

For three pesticides, namely azoxystrobin, prochloraz and imidacloprid, the presence of dogs in the household was a predictive variable, but with a positive β for imidacloprid. The self-reported use of snail or slug bait products (Pest vs Snails) showed to be an important predictor in models for prochloraz, thiophanate-methyl and carbendazim, all fungicides. Meaning that concentrations for these pesticides were higher in homes where residents reported using products against snails.

For VFD, five pesticides, namely pendimethalin, tebuconazole, pyraclostrobin, prochloraz and imidacloprid, have predicted concentration in dust (Dustpred) in common with similar positive effect estimates (positive β). For five pesticides, namely azoxystrobin, fluopyram, tebuconazole, flonicamid and fludioxonil, presence of dogs in the home is correlated with lower concentrations (negative β) in house dust. Distance to closest field showed to be an important variable in models for boscalid, pyraclostrobin, prochloraz and carbendazim, all with a similar negative β , meaning a decrease in indoor concentrations when living further away from the fields.

Reported pesticide smell was associated with increase (positive β) in boscalid and prothioconazole-desithio concentrations in VFD. Increase in evaporation from crops was associated with increase (positive β) in indoor concentrations for four different pesticides.

Finally, predicted performance of the DDM models is low (R^2 0.004 – 0.460), with the explained variance being higher for pesticides that were applied in bulb fields. For example, 0.46 for the pyraclostrobin, and 0.26 for the tebuconazole model. All β values, as well as calculated R^2 and RMSE for the DDM model can be consulted in Supplementary material J.

Table 2. Determinants of pesticide concentration in doormat (DDM) and vacuumed floor dust (VFD) sample

Grouping		DDM Multivariate model ** per pesticide												VFD Multivariate model ** per pesticide													
	Variables	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	9	10	11	12	13	14	
Presence of pets	Dog = Y			-						-	+				-			-							-	-	
	Cat = Y										+																
	Rodent = Y													-													
House information	Living room size										+																
	Sealed against draught										-																
	Leakage								+																		
	Natural ventilation								-																		
Pesticide smell or usage	Roof = Flat																	+								-	
	Number of persons																										
	Distance*													-													
																	+			+							
Climatic conditions	Pesticide Smell																										
	Pest vs Snails = N												-														
	Pest vs Fungi = N																										
	Pest vs Fleas & Ticks = N																										
Climatic conditions	Wind Speed																										
	Humidity																										
	Cloudness					-							-													+	
	Evaporation*																										
Other	Precipitation Duration																										
	Duspred*			+		+				+								+		+							

* This variables were log10 transformed; ** Beta coefficients sign (+ or -) presented solely for statistically significant variables with p-value < 0.05. Pesticides: (1) Boscalid, (2) Azoxystrobin, (3) Fluopyram, (4) Pendimethalin, (5) Tebuconazole, (6) Prothioconazole-deshio, (7) Pyraclostrobin, (8) S-Metolachlor, (9) Prochloraz, (10) Imidacloprid, (11) Thiophanate-methyl, (12) Carbendazim, (13) Flonicamid, (14) Fludioxonil.

Discussion

Detection of pesticides in house dust

All 46 targeted pesticides were present in at least one dust sample, with most of them being detected in both VFD and DDM. This is in line with previous studies that also detected several pesticides in indoor dust (Blanchard et al. 2013, Bennet et al. 2019), not just sprayed pesticides but even others that are no longer allowed (Béranger et al. 2019).

When comparing with Béranger et al, where settled dust was analyzed from homes located in different agricultural areas in France (Béranger et al. 2019), some pesticides were found with similar detection rates, like lambda-cyhalothrin, cyprodinil and s-metolachlor (1-15%), whereas others, like tebuconazole, chlorpropham and imidacloprid (used in bulb disinfection), were detected much more frequently in our study. A recent study done in China (Wang et al. 2019), had similar detection rates as our study for carbendazim and imidacloprid in indoor floor dust, both being detected in more than 70% of all samples.

It is difficult to ascertain why some pesticides used in the study period are detected at low rates in comparison with others. This is because many variables influence occurrence, such as application frequency, applied dosage (Degrendele et al. 2016), persistence in the environment (Richards et al. 2016), amongst others. For most pesticides we don't have enough information to infer on the reason(s) for low detection. We do see that lambda-cyhalothrin and deltamethrin, although persistent in the environment, are rarely detected in VFD and DDM. This is likely because i) they are both are pyrethroids, which usually have rather low application rates and ii) their LOD/LOQ are a higher compared to most other pesticides.

Closer to agricultural fields the detection frequency increased for pesticides in both DDM and VFD, as also reported in other studies (e.g. Lemley et al. 2002, Colt et al. 2004, Bennet et al. 2020). However, the above was not found for pesticides that were not applied in the bulb fields and not reported in bulb disinfection. For this group, detection frequency was, as could be expected, independent of the proximity to the fields.

Our results show a less pronounced contrast in detection frequency for pesticides that are used solely in bulb disinfection. This was expected, given that this group is not bound to a fixed period of usage and might be used inside facilities that are not located

close to agricultural fields. This information is new and adds to the body of evidence regarding spatio-temporal exposure to pesticides, since exposure to this specific group is more continuous and not bound to a certain time-interval.

The presence of multiple pesticides in both types of dust in the non-use period makes evident that exposure to dust containing pesticides continues outside the actual spraying season. Also, high detection rates might be an indication of slower degradation times (i.e. higher half-life) in the indoor environment. This can be due to a combined indoor accumulation, recirculation and absence of photodegradation in shaded areas inside the household.

Concentrations and spatio-temporal distribution

Our results indicate that, overall, concentrations in indoor dust are higher in farm homes and in location homes closer to fields, and are higher in the period of pesticide usage. These findings match previous reports. Quirós-Alcalá et al. reported that pesticide concentrations were higher in indoor dust of farmer homes compared to non-famer-homes (Quirós-Alcalá et al. 2011). Also, a study done in farm, rural, and urban houses in the New York State (Obendorf et al. 2006) concluded the same, here, samples were taken in different seasons and pesticide concentrations were also higher in summer (i.e. during spraying time) in rural farm homes. Smith et al. also measured higher pesticide levels in indoor dust in the spraying season as compared to the non-spraying season (Smith et al. 2017).

However, the above conclusions do not apply to all pesticides. An interesting finding is that for imidacloprid, an insecticide used in bulb disinfection, concentrations were significantly higher in DDM and VFD of Controls, in the *use* and *non-use* period, respectively. We suspect that these levels are likely driven by either household use (as seen in a study by Deziel et al. 2015) or presence of bulb disinfection sites closer to Controls than Loc Homes. The first being more likely, given that, although the sale of products for agricultural use that contain this insecticide was prohibited in the EU starting from December 2018 (EU 2018), imidacloprid can still be used against ticks/fleas and also as biocide (against ants, flies, etc) in households. A recent study also found similar imidacloprid concentrations in indoor dust (Shin et al. 2020).

In a recent study, azoxystrobin, pyraclostrobin and trifloxystrobin were also observed in indoor dust from 188 North Carolina homes with similar detection frequencies. However, average azoxystrobin concentrations in Loc Homes were factor 5 to 10 higher than the concentrations observed in that study (Cooper et al. 2019).

Another important finding was the high concentrations of carbendazim measured at both Loc Homes and Controls. These high concentrations are in the same order of magnitude as those found in household dust from homes in California (Shin et al. 2020). Although no longer approved for usage, this fungicide is a degradation product of thiophanate-methyl, which was still allowed for spraying in several different crops until late 2020 (EU 2019). Thiophanate-methyl is a fungicide with known endocrine disruptive effects (Lu et al. 2003), and other potential adverse health effects (Götte et al. 2020). Exposure to thiophanate-methyl is likely more local given its rapid degradation (see dt_{50} in Table 1), whilst for carbendazim, a more persistent fungicide in bare soils (6 to 12 months) (Singh et al. 2016), exposure can be spread across larger areas due to medium and long-range transport and be long-lasting. Concerns regarding the possible long-term risk associated to carbendazim and thiophanate-methyl were also recently reported in a peer-review performed by the European Food Safety Authority (Arena et al. 2018). These concerns were strengthened by the finding of carbendazim in several handwipes (taken from participants in OBO) and strong correlation with urine samples from participants of the OBO study (Oerlemans et al. 2021).

Pesticides in VFD and DDM: How do they correlate?

To the best of our knowledge, this is the first study to measure, simultaneously, pesticides in dust from doormats and from vacuum floor dust samples. Overall, correlations were low to moderate between the two matrixes with some exceptions. Statistically significant correlations were found between VFD and DDM for seven different pesticides, which is likely a reflection of the take-home route. We also noticed that these seven pesticides share one commonality: persistence in the soil. Both pyraclostrobin and prothioconazole-desthio are moderately persistent (Zhang et al. 2012 and EPA 2007, respectively), whilst the remaining five are persistent (Chopade et al. 2010, Matadha et al. 2019, Lewis et al. 2016). Therefore, it seems likely that solely more persistent pesticides are taken home via clothes, skin, vehicles, pets and shoes (i.e. take-home route).

Finally, the poor correlation between VFD and DDM for several pesticides shows that results can be variable depending on the method used. Though, a recent study comparing pesticides in vacuumed outdoor and indoor dust also reported similar correlation ranges (overall moderate) (Simaremare et al. 2021). Correlations between the two matrixes can also be influenced by cleaning habits and other parameters (such as leaving windows open). As previously discussed, DDM captures only a snapshot of the spraying season (a single week in our case), while VFD captures an accumulation over a longer period, therefore also capturing pesticides susceptible to medium to

long-range transport. So, it might be that for health assessment studies VFD becomes more relevant, while for exposure assessment DDM has advantages due to the more defined surface and time period of measurements.

Take-home route

It is evident, from our results, that the take-home route is relevant for Farm Homes, given that occurrence of almost all pesticides in Farm Homes doormats was higher than Loc Homes and Controls. This is also indicated in several publications (Bradman et al. 2009, Marwanis et al. 2019). By extension, the take-home route might also be relevant in homes located further away from agricultural areas, given that several pesticides were detected in the doormats from these homes in both spraying and non-spraying seasons. Moreover, it's not just an important factor in the spraying season but throughout all year, as also concluded by Gunier et al (Gunier et al 2016). Given that humans spend most of their lifetime indoors (Farrow et al. 1997, Baker et al. 2007), the take-home route might be a relevant source for higher indoor exposure to pesticides.

Determinants and prediction of different pesticides occurrence in dust

With the developed logistic regression model we were able to accurately predict occurrence of a given pesticide in dust in 75% of the samples. This is similar to a study done in the central valley of California, where the occurrence-model had an accuracy around this percentage (ROC C-statistics 70-74%) (Nuckols et al. 2008). The selected explanatory variables, being vapor pressure, half-life in soil, distance to agricultural fields and air concentrations (used to predict concentration in dust) are known parameters in deterministic models for pesticide concentrations and remain the most important determinants of pesticide occurrence in dust.

Determinants and prediction of different pesticides concentration in dust

Concentrations were more difficult to estimate than occurrence. The linear regression models explained only a small part of the variance in concentrations of different pesticides in dust. Similar results were described by Gunier et al reporting predictive performance of their models between R^2 0.04-0.28 (Gunier et al. 2011).

Selected explanatory variables vary a lot between each model and it is important to stress that correlation is not necessarily causation. For example, we do not find a rationale for dogs being a factor influencing azoxystrobin and prochloraz concentrations in dust, whilst for imidacloprid it could make sense since it can be used against ticks/fleas on dogs. We also did not find a rational behind the influence in concentrations of three fungicides by reported use of snail or slug bait products. Overall, only the

predicted concentration in dust based on air concentrations and distance appear more often as important determinants across all models for pesticide in DDM.

In summary, it is easier to predict which pesticides will be present in dust, but quantitative estimation remains challenging especially for pesticides not directly used in the vicinity of the homes. For quantitative estimates more information about the actual source strengths are needed, but difficult to obtain.

Strengths and limitations

To our knowledge, this is the first study employing a combination of DDM and VFD sampling techniques. This is one of the main strengths of our study since it allowed us to, first, study what drives pesticide concentrations in dust, second, to understand if patterns between homes and periods are the same for both types of dust, and finally, to better assess the take-home route and infer on possible predictors of exposure to pesticides in dust. Moreover, this is the first study to look at possible determinants of occurrence and concentrations for some current-used pesticides, such as fluopyram, s-metolachlor, flonicamid and thiophanate-methyl.

Our approach allowed us to analyze two different types of dust samples, which is the recommended procedure to ensure complete characterization of contaminants in indoor dust (Schultz et al. 2018). We succeeded in having a good spatial distribution of homes around bulb fields in different locations. Adding to this, collected samples were representative of both use and non-use periods. Lastly, the targeted pesticides are a good representation of varying physico-chemical properties, and the results show the capacity of our approach to detect very low concentrations in dust.

Our study also has some limitations. Not all collected samples were analyzed, but we tried to ensure good spatial distribution and analyze samples from homes located in all four main cardinal directions. Dust samples were quite heterogeneous with various types of materials (e.g. pet hair, fibers, dirt) (see Figure B1, supplementary material B) adding to the total mass. These materials differ in physico-chemical properties which will affect pesticide sorption (different for each material) (Mattei et al. 2019). This limitation is however not restricted to our study but to every study that looks into home dust.

Some of the low detection rates might be due to collection of dust before a certain pesticide was applied. Although sampling of VFD and DDM was performed in the middle of the use period, it is still possible that certain pesticides were only sprayed after dust collection. We chose not to collect at the end of the use period to avoid loss of information due to the environmental degradation of the sprayed pesticides.

Although the sampling of VFD was done in the living room to ensure comparability between homes, it might not represent average concentration in indoor dust for each home. The presence of different sources and major activities associated with each type of room are the main drivers of dust composition, therefore it is highly probable that concentrations within the same home vary per room (Lioy et al. 2002). In future studies it is recommended to vacuum more rooms to also have an idea about intra-home variations in pesticide in dust. Especially in attics, chemical burden might be higher than in the rest of the home, as suggested by Cizdziel & Hodge 2000.

Finally, there is also possible variation in DDM due to the placement of the mat. The doormats might not capture everything during the measuring period, as they were covering the main entrance but not all entrances to the home.

Conclusion

We found pesticides in indoor dust of all homes included in our study. There is clear evidence that exposure to contaminated dust occurs for longer periods and is not solely bound to homes close to agricultural fields. There is also a clear spatial pattern for both the probability of detection and measured concentrations. Pesticide concentrations in dust from homes closer to fields was in general a factor five higher than controls, as well as factor five higher in the spraying season compared to the non-spraying season. A statistical model to estimate occurrence of different pesticides in dust was developed. The main determinants were similar to the ones included in current deterministic models. As long as the input data is available, this model can be used in studies to predict what pesticides might be present in the homes.

Lastly, DDM might be a better proxy for pesticides in indoor dust for exposure assessment studies, given that it can be deployed for a certain period and capture exposure in a clearly defined time-frame, whilst VFD might be more appropriate for health assessment, given that it captures both past and current exposures, result of a continuous indoor accumulation and degradation of sprayed pesticides.

Acknowledgements

Funding: This work was conducted within the OBO Project (Dutch acronym for “Research on Exposure of residents to pesticides”), funded by the Dutch ministry of Infrastructure and Water Management and the ministry of Economic Affairs and Climate Policy. The work was commissioned by the Dutch National Institute for Public Health and the Environment (RIVM).

The authors thank all members of the OBO consortium for the discussions regarding research orientation. We also thank all the field workers that were involved in the collection of the data used in this manuscript, as well as the laboratory personnel that analysed the dust samples. We are grateful for the assistance of the RIVM during all phases of the study.

References

- Arena, M., Auteri, D., Barmaz, S., Bellisai, G., Brancato, A., Brocca, D., Bura, L., Byers, H., Chiusolo, A., Court Marques, D., Crivellente, F., De Lentdecker, C., Egsmose, M., Erdos, Z., Fait, G., Ferreira, L., Goumenou, M., Greco, L., Ippolito, A., ... Villamar-Bouza, L. (2018). Peer review of the pesticide risk assessment of the active substance thiophanate-methyl. *EFSA Journal*, 16(1), 1–31. <https://doi.org/10.2903/j.efsa.2018.5133>
- Audy, O., Melymuk, L., Venier, M., Vojta, S., Becanova, J., Romanak, K., Vykoukalova, M., Prokes, R., Kukucka, P., Diamond, M.L., Klanova, J., 2018. PCBs and organochlorine pesticides in indoor environments - A comparison of indoor contamination in Canada and Czech Republic. *Chemosphere* 206, 622–631. <https://doi.org/10.1016/j.chemosphere.2018.05.016>
- Baker, M., Keall, M., Au, E.L., Howden-Chapman, P. (2007). Home is where the heart is--most of the time. *The New Zealand medical journal*, Volume:120, Issue:1264 Published: 2007-10-26. ISSN: 1175-8716. PMID: 17972978
- Bennett, B., Workman, T., Smith, M. N., Griffith, W. C., Thompson, B., & Faustman, E. M. (2019). Longitudinal, Seasonal, and Occupational Trends of Multiple Pesticides in House Dust. *Environmental Health Perspectives*, 127(1), 17003. <http://doi.org/10.1289/EHP3644>
- Bennett, B., Workman, T., Smith, M. N., Griffith, W. C., Thompson, B., & Faustman, E. M. (2020). Characterizing the neurodevelopmental pesticide exposome in a children's agricultural cohort. *International Journal of Environmental Research and Public Health*, 17(5), 1–15. <https://doi.org/10.3390/ijerph17051479>
- Béranger, R., Billoir, E., Nuckols, J. R., Blain, J., Millet, M., Bayle, M. L., Fervers, B. (2019). Agricultural and domestic pesticides in house dust from different agricultural areas in France. *Environmental Science and Pollution Research*, 26(19), 19632–19645. <http://doi.org/10.1007/s11356-019-05313-9>
- Blanchard, O., Mercier, F., Ramalho, O., Mandin, C., Le Bot, B., & Glorennec, P. (2014). Measurements of semi-volatile organic compounds in settled dust: Influence of storage temperature and duration. *Indoor Air*, 24(2), 125–135. <https://doi.org/10.1111/ina.12066>
- Bradman, A., Salvatore, A. L., Boeniger, M., Castorina, R., Snyder, J., Barr, D. B., Jewell, N. P., Kavanagh-Baird, G., Striley, C., & Eskenazi, B. (2009). Community-based intervention to reduce pesticide exposure to farmworkers and potential take-home exposure to their families. *Journal of Exposure Science and Environmental Epidemiology*, 19(1), 79–89. <https://doi.org/10.1038/jes.2008.18>
- Brasche, S., & Bischof, W. (2005). Daily time spent indoors in German homes - Baseline data for the assessment of indoor exposure of German occupants. *International Journal of Hygiene and Environmental Health*, 208(4), 247–253. <http://doi.org/10.1016/j.ijheh.2005.03.003>
- Bueno, M.R., da Cunha, J.P.A.R., de Santana, D.G., 2017. Assessment of spray drift from pesticide applications in soybean crops. *Biosyst. Eng.* 154, 35–45. <http://doi.org/10.1016/j.biosystemseng.2016.10.017>

- Cao, Z. G., Yu, G., Chen, Y. S., Cao, Q. M., Fiedler, H., Deng, S. B., Huang, J., & Wang, B. (2012). Particle size: A missing factor in risk assessment of human exposure to toxic chemicals in settled indoor dust. *Environment International*, 49, 24–30. <https://doi.org/10.1016/j.envint.2012.08.0>
- Carlsen, S. C. K., Spliid, N. H., & Svensmark, B. (2006). Drift of 10 herbicides after tractor spray application. 2. Primary drift (droplet drift). *Chemosphere*, 64(5), 778–786. <http://doi.org/10.1016/j.chemosphere.2005.10.060>
- Cizdziel, J. V. & Hodge, V. F. (2000). Attics as archives for house infiltrating pollutants: trace elements and pesticides in attic dust and soil from southern Nevada and Utah. *Microchemical Journal*, 64(1), 85–92. [https://doi.org/10.1016/S0026-265X\(99\)00018-1](https://doi.org/10.1016/S0026-265X(99)00018-1)
- Colt JS, Lubin J, Camann D, Davis S, Cerhan J, Severson RK, Cozen W, Hartge P (2004) Comparison of pesticide levels in carpet dust and self-reported pest treatment practices in four US sites. *J Expo Anal Env Epid* 14:74–83 <https://doi.org/10.1038/sj.jea.7500307>
- Colt, J. S., Gunier, R. B., Metayer, C., Nishioka, M. G., Bell, E. M., Reynolds, P., Buffler, P. A., & Ward, M. H. (2008). Household vacuum cleaners vs. the high-volume surface sampler for collection of carpet dust samples in epidemiologic studies of children. *Environmental health : a global access science source*, 7, 6. <https://doi.org/10.1186/1476-069X-7-6>
- Cooper, E. M., Rushing, R., Hoffman, K., Phillips, A. L., Hammel, S. C., Zylka, M. J., & Stapleton, H. M. (2020). Strobilurin fungicides in house dust: is wallboard a source? *Journal of Exposure Science and Environmental Epidemiology*, 30(2), 247–252. <https://doi.org/10.1038/s41370-019-0180-z>
- Coronado GD, Holte S, Vigoren E, Griffith WC, Barr DB, Faustman E. (2011). Organophosphate pesticide exposure and residential proximity to nearby fields: evidence for the drift pathway. *J Occup Environ Med* 53:884–891. <http://doi.org/10.1097/JOM.0b013e318222f03a>
- Curl, C. L., Fenske, R. A., Kissel, J. C., Shirai, J. H., Moate, T. F., Griffith, W., Thompson, B. (2002). Evaluation of take-home organophosphorus pesticide exposure among agricultural workers and their children. *Environmental Health Perspectives*, 110(12), 787–792. <http://doi.org/10.1289/ehp.021100787>
- Curwin, B. D., Hein, M. J., Sanderson, W. T., Nishioka, M. G., Reynolds, S. J., Ward, E. M., & Alavanja, M. C. (2005). Pesticide contamination inside farm and nonfarm homes. *Journal of Occupational and Environmental Hygiene*, 2(7), 357–367. <https://doi.org/10.1080/15459620591001606>
- Dalvie, M. A., Sosan, M. B., Africa, A., Cairncross, E., & London, L. (2014). Environmental monitoring of pesticide residues from farms at a neighbouring primary and pre-school in the Western Cape in South Africa. *Science of The Total Environment*, 466–467, 1078–1084. <https://doi.org/https://doi.org/10.1016/j.scitotenv.2013.07.099>
- Degrendele, C., Okonski, K., Melymuk, L., Landlová, L., Kukučka, P., Audy, O., Kohoutek, J., Čupr, P., & Klánová, J. (2016). Pesticides in the atmosphere: A comparison of gas-particle partitioning and particle size distribution of legacy and current-use pesticides. *Atmospheric Chemistry and Physics*, 16(3), 1531–1544. <https://doi.org/10.5194/acp-16-1531-2016>
- Deziel, N. C., Beane Freeman, L. E., Graubard, B. I., Jones, R. R., Hoppin, J. A., Thomas, K., Friesen,

- M. C. (2017). Relative contributions of agricultural drift, para-occupational, and residential use exposure pathways to house dust pesticide concentrations: Meta-regression of published data. *Environmental Health Perspectives*, 125(3), 296–305. <https://doi.org/10.1289/EHP426>
- Deziel, N.C., Freeman, L.B., Hoppin, J., Thomas, K., Lerro, C., Jones, R., Hines, C., Blair, A., Graubard, B., Lubin, J., Sandler, D., Chen, H., Andreotti, G., Alavanja, M., Friesen, M., 2019. An algorithm for quantitatively estimating non-occupational pesticide exposure intensity for spouses in the agricultural health study. *J. Expo. Sci. Environ. Epidemiol.* <https://doi.org/10.1038/s41370-018-0088-z>
- Dong, T., Zhang, Y., Jia, S., Shang, H., Fang, W., Chen, D., Fang, M., 2019. Human Indoor Exposome of Chemicals in Dust and Risk Prioritization Using EPA's ToxCast Database. *Environ. Sci. Technol.* 53 (12), 7045–7054. <https://doi.org/10.1021/acs.est.9b00280>
- Dubocq, F., Kärrman, A., Gustavsson, J., & Wang, T. (2021). Comprehensive chemical characterization of indoor dust by target, suspect screening and nontarget analysis using LC-HRMS and GC-HRMS. *Environmental Pollution*, 276. <https://doi.org/10.1016/j.envpol.2021.116701>
- EPA (2007). US EPA - Pesticides - Fact Sheet for Prothioconazole. https://www3.epa.gov/pesticides/chem_search/reg_actions/registration/fs_PC-113961_14-Mar-07.pdf (last accessed January 2022)
- EU (2018). Amending Implementing Regulation (EU) No 540/2011 as regards the conditions of approval of the active substance imidacloprid. <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32018R0783&from=DA> (last accessed January 2022)
- EU (2019). Reg. (EU) 2019/1589. Document 32019R1589. ELI: http://data.europa.eu/eli/reg_impl/2019/1589/oj (last accessed January 2022)
- FAO (2019). FAOSTAT - Inputs/Pesticides Use <https://www.fao.org/documents/card/en/c/cb3411en/> (last accessed January 2022)
- Farrow, A., Taylor H., Golding, J. (1997) Time Spent in the Home by Different Family Members, *Environmental Technology*, 18:6, 605-613, <https://doi.org/10.1080/09593331808616578>
- Figueiredo, D.M., Krop E.J., Duyzer J., Gerritsen-Ebben, R.M., Gooijer, Y.M., Holterman, H.J., Huss, A., Jacobs, C.M., Kivits, C.M., Kruijne, R., Mol, H.J., Oerlemans, A., Sauer, P.J., Scheepers, P.T., van de Zande, J.C., van den Berg, E., Wenneker, M., Vermeulen, R.C. (2021a). Research on exposure of residents to pesticides in The Netherlands: Protocol for an Observational Study. *JMIR Res Protoc* 2021;10(4):e27883. <https://doi.org/10.2196/27883>
- Figueiredo, D. M., Duyzer, J., Huss, A., Krop, E. J. M., Gooijer, Y., & Vermeulen, R. C. H. (2021b). Spatio-temporal variation of outdoor and indoor pesticide air concentrations in homes near agricultural fields. *Atmospheric Environment*, 262(June), 118612. <https://doi.org/10.1016/j.atmosenv.2021.118612>
- Galea, K. S., Maccalman, L., Jones, K., Cocker, J., Teedon, P., Cherrie, J. W., & Tongeren, M. Van. (2015). Comparison of residents pesticide exposure with predictions obtained using the UK regulatory exposure assessment approach. *Regulatory Toxicology and Pharmacology*, 73(2), 634–643. <http://doi.org/10.1016/j.yrtph.2015.09.012>
- Garron, C. A., Davis, K. C., & Ernst, W. R. (2009). Near-field air concentrations of pesticides in potato

- agriculture in Prince Edward Island. *Pest Management Science*, 65(6), 688–696. <http://doi.org/10.1002/ps.1746>
- Golla, V., Curwin, B., Sanderson, W., & Nishioka, M. (2012). Pesticide Concentrations in Vacuum Dust from Farm Homes: Variation between Planting and Nonplanting Seasons. *ISRN Public Health*, 2012, 1–10. <https://doi.org/10.5402/2012/539397>
- Götte, J. Y., Carrizo, J. C., Panzeri, A. M., Amé, M. V., & Menone, M. L. (2020). Sublethal effects of carbendazim in *Jenynsia multidentata* detected by a battery of molecular, biochemical and genetic biomarkers. *Ecotoxicology and Environmental Safety*, 205(May). <https://doi.org/10.1016/j.ecoenv.2020.111157>
- Gunier, R. B., Ward, M. H., Airola, M., Bell, E. M., Colt, J., Nishioka, M., Buffler, P. A., Reynolds, P., Rull, R. P., Hertz, A., Metayer, C., & Nuckols, J. R. (2011). Determinants of agricultural pesticide concentrations in carpet dust. *Environmental Health Perspectives*, 119(7), 970–976. <https://doi.org/10.1289/ehp.1002532>
- Gunier, R. B., Nuckols, J. R., Whitehead, T. P., Colt, J. S., Deziel, N. C., Metayer, C., Reynolds, P., & Ward, M. H. (2016). Temporal trends of insecticide concentrations in carpet dust in California from 2001 to 2006. *Environmental Science and Technology*, 50(14), 7761–7769. <https://doi.org/10.1021/acs.est.6b00252>
- Harnly, M. E., Bradman, A., Nishioka, M., Mckone, T. E., Smith, D., Mclaughlin, R., Kavanagh-Baird, G., Castorina, R., & Eskenazi, B. (2009). Pesticides in dust from homes in an agricultural area. *Environmental Science and Technology*, 43(23), 8767–8774. <https://doi.org/10.1021/es9020958>
- Hyland, C., & Laribi, O. (2017). Review of take-home pesticide exposure pathway in children living in agricultural areas. *Environmental Research*, 156(March), 559–570. <http://doi.org/10.1016/j.envres.2017.04.017>
- Jakobsen, J. C., Gluud, C., Wetterslev, J., & Winkel, P. (2017). When and how should multiple imputation be used for handling missing data in randomized clinical trials - A practical guide with flowcharts. *BMC Medical Research Methodology*, 17(1), 1–10. <https://doi.org/10.1186/s12874-017-0442-1>
- Kruijne, R., Mol, H., Jeurissen, L., Wenneker M. & Van de Zande, J. (2019). Pesticides and Local Residents - Selection of Substances, Measuring Locations and Target Population. Wageningen, Wageningen Environmental Research, Report 2924. [75 pp.].
- Lee, Y.-H., Kim, H.-H., Lee, J.-I., Lee, J.-H., Kang, H., Lee, J.-Y., 2018. Indoor contamination from pesticides used for outdoor insect control. *Sci. Total Environ.* 625, 994–1002. <https://doi.org/10.1016/j.scitotenv.2018.01.010>
- Lehotay, S.J. (2007). Determination of pesticide residues in foods by acetonitrile extraction and partitioning with magnesium sulfate: collaborative Study. *J. AOAC Int.* 2007;90:485-520. PMID: 17474521
- Lemley, A. T., Hedge, A., Obendorf, S. K., Hong, S., Kim, J., Muss, T. M., & Varner, C. J. (2002). Selected pesticide residues in house dust from farmers' homes in central New York State, USA. *Bulletin of*

- Environmental Contamination and Toxicology, 69(2), 155–163. <https://doi.org/10.1007/s00128-002-0042-5>
- Lewis, K.A., Tzilivakis, J., Warner, D. and Green, A. (2016) An international database for pesticide risk assessments and management. *Human and Ecological Risk Assessment: An International Journal*, 22(4), 1050-1064. <http://doi.org/10.1080/10807039.2015.1133242>
- Lioy, P. J., Freeman, N. C. G., & Millette, J. R. (2002). Dust: A metric for use in residential and building exposure assessment and source characterization. *Environmental Health Perspectives*, 110(10), 969–983. <http://doi.org/10.1289/ehp.02110969>
- López-Gálvez, N., Wagoner, R., Quirós-Alcalá, L., Van Horne, Y. O., Furlong, M., Avila, E., & Beamer, P. (2019). Systematic literature review of the take-home route of pesticide exposure via biomonitoring and environmental monitoring. *International Journal of Environmental Research and Public Health*, 16(12), 1–24. <http://doi.org/10.3390/ijerph16122177>
- Lu, C., Fenske, R. A., Simcox, N. J., & Kalman, D. (2000). Pesticide exposure of children in an agricultural community: Evidence of household proximity to farmland and take home exposure pathways. *Environmental Research*, 84(3), 290–302. <http://doi.org/10.1006/enrs.2000.4076>
- Lu, S. Y., Liao, J. W., Kuo, M. L., Wang, S. C., Hwang, J. S., & Ueng, T. H. (2004). Endocrine-disrupting activity in carbendazim-induced reproductive and developmental toxicity in rats. *Journal of Toxicology and Environmental Health - Part A*, 67(19), 1501–1515. <https://doi.org/10.1080/15287390490486833>
- Lubin, J.H., Colt, J.S., Camann, D., et al. (2004). Epidemiologic evaluation of measurement data in the presence of detection limits. *Environ Health Perspect.* 2004;112(17):1691-1696. . <http://doi.org/10.1289/ehp.7199>
- Marwanis, A.S., Sean, S., Farhanah, S.S., Sabreena,, S., Nurzafirah, M., Mohamad, A.A.A (2019). A review of the take-home exposure pathway of workplace hazards. *International Journal of Medical Toxicology & Legal Medicine*. Year : 2019, Volume : 22, Issue : 3&4. <http://doi.org/10.5958/0974-4614.2019.00052.4>
- Matadha, N. Y., Mohapatra, S., Siddamallaiiah, L., Udupi, V. R., Gadigeppa, S., & Raja, D. P. (2019). Uptake and distribution of fluopyram and tebuconazole residues in tomato and bell pepper plant tissues. *Environmental Science and Pollution Research*, 26(6), 6077–6086. <https://doi.org/10.1007/s11356-018-04071-4>
- Mattei, C., Dupont, J., Wortham, H., & Quivet, E. (2019). Influence of pesticide concentration on their heterogeneous atmospheric degradation by ozone. *Chemosphere*, 228, 75–82. <https://doi.org/10.1016/j.chemosphere.2019.04.082>
- Melymuk, L., Demirtepe, H., & Jílková, S. R. (2020). Indoor dust and associated chemical exposures. *Current Opinion in Environmental Science and Health*, 15, 1–6. <https://doi.org/10.1016/j.coesh.2020.01.005>
- Mercier, F., Glorennec, P., Thomas, O., Le Bot, B., 2011. Organic Contamination of Settled House Dust, A Review for Exposure Assessment Purposes. *Environ. Sci. Technol.* 45 (16), 6716–6727. <https://doi.org/10.1021/es200925h>

- Moschet, C., Anumol, T., Lew, B. M., Bennett, D. H., & Young, T. M. (2018). Household Dust as a Repository of Chemical Accumulation: New Insights from a Comprehensive High-Resolution Mass Spectrometric Study. *Environmental Science and Technology*, 52(5), 2878–2887. <https://doi.org/10.1021/acs.est.7b05767>
- Nuckols, J. R., Riggs, P. D., Gunier, R. B., Rull, R. P., Bell, E. M., Nishioka, M., Hertz, A., Reynolds, P., Buffler, P. A., Ward, M. H. (2008). Geographic-Based Prediction of Agricultural Pesticides in Household Carpet Dust in the Central Valley of California, *Epidemiology*: November 2008 - Volume 19 - Issue 6 - p S320 <https://doi.org/10.1097/01.ede.0000340499.92825.58>
- Obendorf, S. K., Lemley, A. T., Hedge, A., Kline, A. A., Tan, K., & Dokuchayeva, T. (2006). Distribution of pesticide residues within homes in central New York State. *Archives of Environmental Contamination and Toxicology*, 50(1), 31–44. <https://doi.org/10.1007/s00244-004-0185-y>
- OBO (2019). Research on exposure of residents to pesticides in the Netherlands: OBO flower bulbs. *Onderzoek Bestrijdingsmiddelen en Omwonenden*. <https://www.rijksoverheid.nl/binaries/rijksoverheid/documenten/rapporten/2019/04/10/bijlage-1-onderzoeksrapport-obo/bijlage-1-onderzoeksrapport-obo.pdf>
- Oerlemans, A., Figueiredo, D. M., Mol, J. G. J., Nijssen, R., Anzion, R. B. M., van Dael, M. F. P., Duyzer, J., Roeleveld, N., Russel, F. G. M., Vermeulen, R. C. H., & Scheepers, P. T. J. (2021). Personal exposure assessment of pesticides in residents: The association between hand wipes and urinary biomarkers. *Environmental Research*, 199, 111282. <https://doi.org/https://doi.org/10.1016/j.envres.2021.111282>
- Perestrelo, R., Silva, P., Porto-Figueira, P., Pereira, J.A.M., Silva, C., Medina, S., Câmara, J.S. (2019). QuEChERS – Fundamentals, relevant improvements, applications and future trends. *Analytica Chem. Acta* 1070 (2019) 1-28. <https://doi.org/10.1016/j.aca.2019.02.036>
- Plascak, J. J., Griffith, W. C., Workman, T., Smith, M. N., Vigoren, E., Faustman, E. M., & Thompson, B. (2019). Evaluation of the relationship between residential orchard density and dimethyl organophosphate pesticide residues in house dust. *Journal of Exposure Science and Environmental Epidemiology*, 29(3), 379–388. <http://doi.org/10.1038/s41370-018-0074-5>
- Quirós-Alcalá, L., Bradman, A., Nishioka, M., Harnly, M. E., Hubbard, A., McKone, T. E., Ferber, J., & Eskenazi, B. (2011). Pesticides in house dust from urban and farmworker households in California: An observational measurement study. *Environmental Health: A Global Access Science Source*, 10(1). <https://doi.org/10.1186/1476-069X-10-19>
- R Core Team (2017) R: A Language and Environment for Statistical Computing.
- Raherison, C., Baldi, I., Pouquet, M., Berteaud, E., Moesch, C., Bouvier, G., & Canal-Raffin, M. (2019). Children: A pilot study. *Environmental Research*, 169 (November 2018), 189–195. <http://doi.org/10.1016/j.envres.2018.11.002>
- Rappazzo, K. M., Warren, J. L., Davalos, A. D., Meyer, R. E., Sanders, A. P., Brownstein, N. C., & Luben, T. J. (2019). Maternal residential exposure to specific agricultural pesticide active ingredients and birth defects in a 2003–2005 North Carolina birth cohort. *Birth Defects Research*, 111(6), 312–323.

- <http://doi.org/10.1002/bdr2.1448>
- Richards, J., Reif, R., Luo, Y., & Gan, J. (2016). Distribution of pesticides in dust particles in urban environments. *Environmental Pollution*, 214, 290–298. <http://doi.org/10.1016/j.envpol.2016.04.025>
- Roberts J.W., Dickey P. (1995) Exposure of Children to Pollutants in House Dust and Indoor Air. In: Ware G.W. (eds) *Reviews of Environmental Contamination and Toxicology. Reviews of Environmental Contamination and Toxicology*, vol 143. Springer, New York, NY.http://doi.org/10.1007/978-1-4612-2542-3_3
- Rostkowski, P., Haglund, P., Aalizadeh, R., Alygizakis, N., Thomaidis, N., Arandes, J. B., Nizzetto, P. B., Booij, P., Budzinski, H., Brunswick, P., Covaci, A., Gallampois, C., Grosse, S., Hindle, R., Ipolyi, I., Jobst, K., Kaserzon, S. L., Leonards, P., Lestremau, F., ... Yang, C. (2019). The strength in numbers: comprehensive characterization of house dust using complementary mass spectrometric techniques. *Analytical and Bioanalytical Chemistry*, 411(10), 1957–1977. <https://doi.org/10.1007/s00216-019-01615-6>
- Rudel, R.A., Camann, D.E., Spengler, J.D., Korn, L.R., Brody, J.G., 2003. Phthalates, alkylphenols, pesticides, polybrominated diphenyl ethers, and other endocrine-disrupting compounds in indoor air and dust. *Environ. Health* 7. <https://doi.org/10.1186/1476-069X-7-2>
- Sabarwal, A., Kumar, K., & Singh, R. P. (2018). Hazardous effects of chemical pesticides on human health—Cancer and other associated disorders. *Environmental Toxicology and Pharmacology*, 63(August), 103–114. <https://doi.org/10.1016/j.etap.2018.08.018>
- Salis, S., Testa, C., Roncada, P., Armorini, S., Rubattu, N., Ferrari, A., Miniero, R., & Brambilla, G. (2017). Occurrence of imidacloprid, carbendazim, and other biocides in Italian house dust: Potential relevance for intakes in children and pets. *Journal of Environmental Science and Health - Part B Pesticides, Food Contaminants, and Agricultural Wastes*, 52(9), 699–709. <https://doi.org/10.1080/03601234.2017.1331675>
- Schultz, I. R., Cade, S., & Kuo, L. J. (2019). The Dust Exposome BT - Unravelling the Exposome: A Practical View. In S. Dagnino & A. Macherone (Eds.), (pp. 247–254). Cham: Springer International Publishing. http://doi.org/10.1007/978-3-319-89321-1_9
- Shin, H. M., Moschet, C., Young, T. M., & Bennett, D. H. (2020). Measured concentrations of consumer product chemicals in California house dust: Implications for sources, exposure, and toxicity potential. *Indoor Air*, 30(1), 60–75. <https://doi.org/10.1111/ina.12607>
- Siebers, J., Binner, R. Wittich, K.P. (2003). Investigation on downwind short-range transport of pesticides after application in agricultural crops. *Chemosphere*, 51 (5) (2003), pp. 397-407, [https://doi.org/10.1016/S0045-6535\(02\)00820-2](https://doi.org/10.1016/S0045-6535(02)00820-2)
- Simaremare, S.R.S., Hung, C.-C., Yu, T.-H., Hsieh, C.-J., Yiin, L.-M. (2021). Association between Pesticides in House Dust and Residential Proximity to Farmland in a Rural Region of Taiwan. *Toxics* 2021, 9, 180. <https://doi.org/10.3390/toxics9080180>
- Singh, S., Singh, N., Kumar, V., Datta, S., Wani, A. B., Singh, D., Singh, K., & Singh, J. (2016). Toxicity,

- monitoring and biodegradation of the fungicide carbendazim. *Environmental Chemistry Letters*, 14(3), 317–329. <https://doi.org/10.1007/s10311-016-0566-2>
- Smith MN, Workman T, McDonald KM, Vredevoogd MA, Vigoren EM, Griffith WC, et al. 2017. Seasonal and occupational trends of five organophosphate pesticides in house dust. *J Expo Sci Environ Epidemiol* 27(4):372–378, PMID: 27553992, <http://doi.org/10.1038/jes.2016.45>
- Succop, P.A., Clark, S., Chen, M. & Galke, W. (2004). Imputation of data values that are less than a detection limit. *J Occup Environ Hyg.* 2004;1:436–441. <http://doi.org/10.1080/15459620490462797>
- Ten Brinke b.v. <https://tenbrinkebv.nl/> (last accessed January 2022).
- Wang, A., Mahai, G., Wan, Y., Jiang, Y., Meng, Q., Xia, W., He, Z., & Xu, S. (2019). Neonicotinoids and carbendazim in indoor dust from three cities in China: Spatial and temporal variations. *Science of the Total Environment*, 695, 133790. <https://doi.org/10.1016/j.scitotenv.2019.133790>
- Wei, W., Ramalho, O., & Mandin, C. (2019). A long-term dynamic model for predicting the concentration of semi volatile organic compounds in indoor environments: Application to phthalates. *Building and Environment*, 148(October 2018), 11–19. <http://doi.org/10.1016/j.buildenv.2018.10.044>
- Weschler, C. J., & Nazaroff, W. W. (2010). SVOC partitioning between the gas phase and settled dust indoors. *Atmospheric Environment*, 44(30), 3609–3620. <http://doi.org/10.1016/j.atmosenv.2010.06.029>
- Whitemore, R. W., Immerman, F. W., Camann, D. E., Bond, A. E., Lewis, R. G., & Schaum, J. L. (1994). Non-occupational exposures to pesticides for residents of two U.S. cities. *Archives of environmental contamination and toxicology*, 26(1), 47–59. <https://doi.org/10.1007/BF00212793>
- Wickerham, E. L., Lozoff, B., Shao, J., Kaciroti, N., Xia, Y., & Meeker, J. D. (2012). Reduced birth weight in relation to pesticide mixtures detected in cord blood of full-term infants. *Environment International*, 47, 80–85. <http://doi.org/10.1016/j.envint.2012.06.007>
- Zande, J.C. van de, Michielsen, J.M.G.P. & Stallinga, H. (2017). Spray drift exposure of bystanders and residents when spraying field crops. Wageningen UR, Wageningen Plant Research Report 722. Wageningen. [29 pp.]. <https://research.wur.nl/en/publications/spray-drift-exposure-of-bystanders-and-residents-when-spraying-fi> (last accessed January 2022)
- Zhang, F., Wang, L., Zhou, L., Wu, D., Pan, H., & Pan, C. (2012). Residue dynamics of pyraclostrobin in peanut and field soil by QuEChERS and LC-MS/MS. *Ecotoxicology and Environmental Safety*, 78, 116–122. <https://doi.org/10.1016/j.ecoenv.2011.11.003>
- Zivan, O., Segal-Rosenheimer, M., Dubowski, Y. (2016). Airborne organophosphate pesticides drift in Mediterranean climate: the importance of secondary drift. *Atmos. Environ.* 127, 155e162. <http://doi.org/10.1016/j.atmosenv.2015.12.003>

Supplementary material A: Analysed pesticides and relevant physical-chemical properties

Table A1. List of analysed pesticides and relevant physical-chemical properties.

	Pesticides	LOD	DT50 Soil (days)	CAS RN	Log koa (-)*	Vapor Pressure (mPa 20-25°C)#
Herbicides	Asulam	1	9	3337-71-1	9.885	1.9E-01
	Chloridazon	1	35	1698-60-8	9.006	6.0E-02
	Chlorpropham	20	30¥	101-21-3	8.143	2.4E+01
	Dimethenamid-P	1	7	163515-14-8	7.625	2.5E+00
	Linuron	1	48	330-55-2	9.793	1.9E-01
	Metamitron	3	11	41394-05-2	11.239	8.6E-04
	<i>Metamitron-desamino</i>	1	31	36993-94-9	8.670	4.5E-04*
	Pendimethalin	1	101	40487-42-1	9.636	1.3E+00
	S-metolachlor	1	21	51218-45-2	9.334	4.2E+00
	Sulcotrione	3	4	99105-77-8	10.706	5.0E-03
Insecticides	Terbutylazine	1	22	5915-41-3	9.028	9.0E-02
	Acetamiprid	1	3	135410-20-7	8.098	5.9E+00
	Cyhalothrin-lambda	10	27	91465-08-6	11.218	4.5E-04
	Deltamethrin	10	21	52918-63-5	9.890	1.2E-05
	Flonicamid	3	3	158062-67-0	12.529	9.4E-04
	Fosthiazate	1	13	98886-44-3	9.828	5.6E-01
	Imidacloprid	1	174	105827-78-9	13.741	2.1E-01
	Oxamyl	1	6	23135-22-0	7.544	3.1E+01
	Pirimicarb	1	9	23103-98-2	9.162	9.7E-01
	Pymetrozine	1	23	123312-89-0	10.659	1.8E-03*
	Spirotetramat	1	<1	203313-25-1	14.220	6.0E-06*
	<i>Spirotetramat-enol</i>	1	<1	203312-38-3	15.862	ND
	Thiacloprid	1	8	111988-49-9	10.329	8.0E-07
Fungicides	Azoxystrobin	1	181	131860-33-8	14.025	1.1E-07
	Boscalid	1	254	188425-85-6	12.720	7.2E-04
	Cyprodinil	1	45	121552-61-2	9.465	4.9E-01
	Difenoconazole	1	85	119446-68-3	13.739	3.3E-05
	Dimethomorph	1	44	110488-70-5	10.765	9.9E-01
	Fludioxonil	1	22	131341-86-1	11.783	3.9E-04
	Fluopicolide	1	139	239110-15-7	14.748	8.0E-04
	Fluopyram	1	119	658066-35-4	13.586	4.2E-03
	<i>Fluopyram-benzamide</i>	1	9	000360-64-5	6.785	ND
	Flutolanil	1	105	66332-96-5	10.586	1.8E+00
	Kresoxim-methyl	3	<2	143390-89-0	10.238	2.3E-03
	Mepanipyrim	1	57	110235-47-7	9.451	2.3E-02
	Prochloraz	1	17	67747-09-5	10.274	1.5E-01
	Propamocarb	1	20	24579-73-5	8.338	7.3E+03
	Prothioconazole	-	<1	178928-70-6	14.022	4.5E-09*

Prothioconazole-desthio	1	42	120983-64-4	11.780	1.1E-03*
Pyraclostrobin	1	33	175013-18-0	17.318	2.6E-05
Tebuconazole	1	47	107534-96-3	11.927	1.7E-03
Thiophanate-methyl	1	2	23564-05-8	8.706	9.5E-03
Carbendazim	1	22	10605-21-7	10.582	1.0E-04
Toclofos-methyl	10	30	57018-04-9	6.761	5.7E+01
Trifloxystrobin	1	2	141517-21-7	9.859	3.4E-03
Trifloxystrobin-acid		nd	252913-85-2	9.859	5.5E-03**

*Estimated using EPI Suite™ system (US EPA 2007)

**IUPAC Ref: CGA 321113

#Pubchem (<https://pubchem.ncbi.nlm.nih.gov>)

ND (Not determined); LOD – Limit of detection; DT50 soil - # Environmental half-life of a pesticide, determined in the field (Source: IUPAC-PPDB), except ¥ determined by <https://toxnet.nlm.nih.gov>.

Supplementary material B: Analysis method for determination of pesticides in dust samples

Dust samples

Household dust, both vacuumed floor dust (VFD) and dust material from doormats (DDM), is a complex sample material. It is highly heterogeneous, and may contain sand/clay particles, dead skin cells, human/animal hair, textile/paper fibers, pollen etc. Examples of dust samples are shown in Figure C1. For the purpose of the study, the entire dust sample was extracted, i.e. no fractionation or sieving was applied. The amount of dust sample varied. For VFD samples the mass collected ranged from VFD 0.02 – 28 g, with a median of 0.37 g. DDM typically contained more sand and ranged from 0.55-196 g, with a median of 6 g.

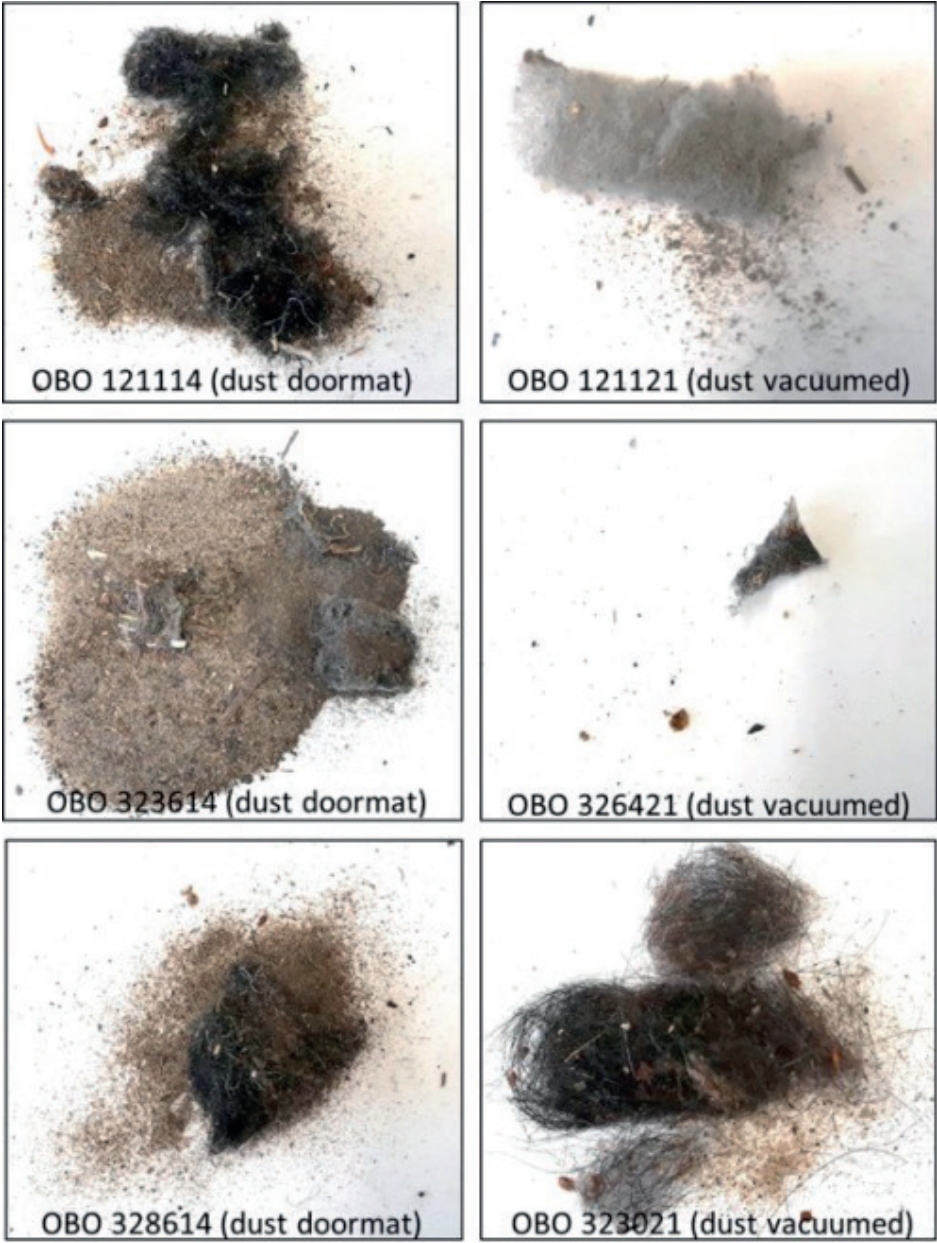


Figure B1. Examples of dust samples.

For determination of the pesticides and certain metabolites in the dust samples, a multi-residue method was used based on QuEChERS extraction and liquid chromatography with tandem mass spectrometry. This is a generic method suitable for extraction of a wide range of pesticides from various matrices. It involves extraction using water and acidified acetonitrile. Besides the salt-induced phase partitioning, no cleanup (dSPE) was performed in order not to compromise scope. In all cases, the entire dust sample was extracted, using a fixed ratio of g dust : mL extraction solvent.

The analytical method was designed for 1 gram dust. In case less material was available, down to an amount of 0.5 gram dust, the volume of extraction solvent/amount of salts were proportionally scaled down. If less than 0.5 dust was available, the reagents as used for 0.5 gram were used.

Analytical reference standards

Analytical reference standards were purchased from LGC or Sigma. Stock solutions were prepared in methanol or acetonitrile at concentrations of 2 mg/mL. A pesticide mix solution of 1 µg/mL was prepared in methanol. Intermediate dilutions for spiking of the samples, extracts, and preparation of working standards were made in methanol. A series of calibration standards for assessment of linearity of response was prepared by dilutions of the intermediate solutions in water: acetonitrile/1% acetic acid (50:50), concentrations 0, 0.125, 0.25, 0.50, 0.75, 2.5, 6.25, 12.5 ng/mL, corresponding to 0.5–50 µg/kg dust).

Extraction procedure

For analysis, all dust material from the sample sock (mounted in the hose of the vacuum cleaner to collect dust from the floor or doormat) was transferred into an extraction tube. For extraction, 2 mL water/g dust and 4 mL of acetonitrile/1% acetic acid/g dust were added. In case of samples >7 g, larger flasks were used for extraction. The pesticides were extracted from the dust by mechanical shaking for 30 min. Then 0.8 g magnesium sulfate and 0.2 g sodium acetate per g dust material were added and the mixture thoroughly shaken to induce phase partitioning. Next, an aliquot of two mL of the upper acetonitrile layer was taken and concentrated to 1.0 mL under a nitrogen flow at 40°C. From this extract, 0.25 mL aliquots were transferred into two filter vials. To the second vial a mix-standard solution of the 46 pesticides was added such that a concentration in final extract corresponding to 50 µg/kg was obtained (initially this was 10 µg/kg, later increased to 50 µg/kg to avoid frequent repeat analysis when samples contained higher levels of pesticides). To both vials water was added to reach a total extract volume of 0.50 mL.

LC-MS/MS analysis

LC-MS/MS analysis was performed on a Waters Acquity UPLC system coupled to a Sciex API6500 Qtrap tandem mass spectrometer by injection of 5 µl onto a 100 x 2.1 mm ID 1.8 µm HSS T3 column (Waters), maintained at 40°C. Gradient elution was performed at a flow rate of 0.4 mL/min, using a water/methanol gradient, containing 5 mM ammonium formate/0.1% formic acid. MS/MS measurement was done using electrospray ionisation (ESI) in positive mode (except fludioxonil, negative mode), acquiring two transitions for each pesticide/metabolite (details see below in Table B1). Quantification was performed using the standard addition method (1-point calibration against the spiked extract of each individual sample, at the level corresponding to 10 or 50 µg/kg) in order to compensate for matrix effects (ion suppression). So, analysis of each sample involved two injections, one of the extract without, and one of the extract with pesticide addition. In case the level of the pesticide in the sample extract exceeded the standard-addition spike level (i.e., the response of the pesticide in the extract with addition was less than 2x response of the pesticide in extract without addition), or exceeded the linear range of detector response, dilutions of the remaining concentrated extract were made, again in two vials, one without and one with standard addition.

Validation and analytical quality control

In-house validation and on-going analytical quality control was done according to EU guidance document SANTE/11945/2015 (currently SANTE/11682/2019).

For the validation, sample material had been collected multiple times at one control household, from a doormat as was used in the field study. The material collected was combined, mixed and then spread out and divided into portions that were as similar as possible. The validation set consisted of a reagent blank, two blank dust portions (1 g), and three sets of five portions (1 g each) that were spiked with the pesticide mix at 1, 3 and 10 µg/kg, respectively. The samples were analysed as described above. Solvent standards were included to verify the linearity of response, and to determine matrix effects (ion suppression/enhancement).

For analytical quality control during sample analysis (on-going validation), with each batch of samples, a reagent blank and a quality control were included. The positive control was prepared by spiking a 1 g subsample from a batch of control dust at 10 or 50 µg/kg.

The linearity was assessed through the back-calculated concentrations (BCC) (concentration calculated using the response of the individual calibration solution and

the equation obtained after linear regression). The criterion was that the BCC should be within $\pm 20\%$ of the true concentration. This was the case except for chlorpropham, lambda-cyhalothrin, metamitron, prothioconazole, and pymetrozine where the sensitivity was insufficient at the lowest level(s).

Matrix effects were determined by comparison of the response obtained for a standard in blank extract with that of a solvent standard, both at 12.5 ng/mL. Strong matrix effects (signal suppression) occurred for most compounds, especially for those eluting between 4 and 5 minutes (signal suppression down to 10% of that in solvent standards in some cases). For other compounds, reduction of signal was observed for most compounds, down to 40-60% of the solvent standard signal (i.e. 60-40% suppression). For quantification this was accounted for by using calibration based on standard addition as described above.

In Table B2 the individual data obtained for trueness (determined through recovery experiments), repeatability (RSD_r), and within-laboratory reproducibility (RSD_{wr} , generated concurrently with sample analysis) are provided. In most cases, average recoveries were between 70-120%. The precision (RSD) were below 20% at the 50 $\mu\text{g/kg}$ level, and around 20% at lower levels. The limit of quantification (LOQ) was defined as the lowest level tested for which the performance criteria as laid down in SANTE/11682/2019 were met. The LOQ was 1 $\mu\text{g/kg}$ for most pesticides ($N=33$), 3-50 $\mu\text{g/kg}$ for 12 pesticides. The limit of detection (LOD) was only estimated in case the LOQ was higher than 1 $\mu\text{g/kg}$, and in these cases ranged from 1 to 20 $\mu\text{g/kg}$.

Table B1. LC-MS/MS conditions

UHPLC conditions		
Eluent	A: 5 mM ammonium formate in MilliQ water + 0.1% formic acid	
	B: 5 mM ammonium formate in methanol/MilliQ water (95/5 v/v) + 0.1% formic acid	
Gradient	Time (min)	Composition
	0	0% B
	1	0% B
	2.5	45% B
	8.5	100% B
	11.5	100% B
	12	0% B
	14	0%B
Flow rate	0.40 mL/min	
Column	Waters HSS T3 (1.7 µm particles, 100 × 2.1 mm)	
Column temperature	40 °C	
Injection volume	5 µl	
MS conditions		
Instrument	Sciex 6500 Qtrap	
Source parameters		
Ion Source gas 1 (GS1)	60	
Ion Source gas 2 (GS2)	60	
Curtain gas (CUR)	35	
Ionspray voltage (IS)	4000	
Source temperature (TEM)	500	

Table B1. LC-MS/MS conditions (continued)**MS/MS settings**

Pesticide name	tr (min)	Precursor	Product	DP	EP	CE	CXP
Acetamiprid (qn)	4.3	223	126	51	10	29	10
Acetamiprid (ql)	4.3	223	73	51	10	79	12
Asulam (qn)	3.0	231	156	60	10	15	12
Asulam (ql)	3.0	231	92	60	10	34	12
Azoxystrobin (qn)	6.2	404.2	372.3	66	10	21	10
Azoxystrobin (ql)	6.2	404.2	344.1	66	10	35	20
Boscalid (qn)	6.4	343.1	306.8	96	10	29	18
Boscalid (ql)	6.4	343.1	139.9	96	10	29	12
Carbendazim (qn)	3.8	192	160	106	10	25	16
Carbendazim (ql)	3.8	192	132	106	10	45	18
Chloridazon (qn)	4.4	222	65	116	10	53	14
Chloridazon (ql)	4.4	222	51	116	10	93	20
Chlorpropham (qn)	6.5	214	171.9	25	10	13	6
Chlorpropham (ql)	6.5	214	153.9	25	10	25	14
Cyhalothrin-lambda (qn)	7.7	467.1	225	36	10	23	12
Cyhalothrin-lambda (ql)	7.7	469.1	227	36	10	23	12
Cyprodinil (qn)	7.0	226.2	77	96	10	67	12
Cyprodinil (ql)	7.0	226.2	93	96	10	47	36
Deltamethrin (qn)	7.8	522.9	280.7	36	10	23	25
Deltamethrin (ql)	7.8	524.9	282.7	36	10	23	25
Difenoconazole (qn)	7.2	406	251	136	10	39	26
Difenoconazole (ql)	7.2	406	337	136	10	25	26
Dimethenamid (qn)	6.4	276.1	168.1	66	10	35	10
Dimethenamid (ql)	6.4	276.1	244	66	10	41	34
Dimethomorph (qn)	6.4	388	301	60	10	37	12
Dimethomorph (ql)	6.4	388	165	60	10	37	12
Flonicamid (qn)	3.5	230.1	203.1	55	10	35	4
Flonicamid (ql)	3.5	230.1	174	55	10	35	4
Fludioxonil (qn)	6.3	247	179.9	-60	-10	-40	-9
Fludioxonil (ql)	6.3	247	169	-60	-10	-42	-12
Fluopicolide (qn)	6.5	383	173	60	10	60	37
Fluopicolide (ql)	6.5	383	145	60	10	75	12
Fluopyram (qn)	6.6	396.9	207.9	56	10	29	14
Fluopyram (ql)	6.6	396.9	172.9	56	10	37	12
Fluopyram benzamide (qn)	4.0	190	129.8	60	10	27	8
Fluopyram benzamide (ql)	4.0	190	169.9	60	10	15	10
Flutolanil (qn)	6.4	324.2	242.1	60	10	37	12
Flutolanil (ql)	6.4	324.2	262.1	60	10	26	12
Fosthiazate (qn)	5.7	284	104.1	61	10	27	13
Fosthiazate (ql)	5.7	284	227.8	61	10	27	15

Imidacloprid (qn)	4.0	256.1	209	41	10	21	14
Imidacloprid (ql)	4.0	256.1	175.1	41	10	25	12
Kresoxim-methyl (qn)	6.9	314.1	115.9	36	10	21	25
Kresoxim-methyl (ql)	6.9	314.1	206.1	36	10	13	25
Linuron (qn)	6.3	249	160	101	10	27	16
Linuron (ql)	6.3	249	182	101	10	23	18
Mepanipyrim (qn)	6.7	224	106.3	60	10	37	12
Mepanipyrim (ql)	6.7	224.1	77.3	60	10	37	12
Metamitron (qn)	4.3	203	175	60	10	30	12
Metamitron (ql)	4.3	203	104	60	10	30	12
Metamitron-desamino (qn)	4.3	188	160	41	10	25	12
Metamitron-desamino (ql)	4.3	188	103.9	41	10	31	8
Metolachlor-S (qn)	6.8	284	252	60	10	26	12
Metolachlor-S (ql)	6.8	284	176	60	10	37	20
Oxamyl (qn)	3.3	237	72	21	10	25	30
Oxamyl (ql)	3.3	237	90	21	10	13	16
Pendimethalin (qn)	7.7	282.2	212.1	61	10	17	12
Pendimethalin (ql)	7.7	282.2	194.1	61	10	27	12
Pirimicarb (qn)	5.4	239.2	72	71	10	37	12
Pirimicarb (ql)	5.4	239.2	182.1	71	10	23	12
Prochloraz (qn)	7.1	376	308	36	10	17	25
Prochloraz (ql)	7.1	376	265.9	36	10	23	25
Propamocarb (qn)	3.0	189.3	102	76	10	25	18
Propamocarb (ql)	3.0	189.3	144	76	10	19	14
Prothioconazole (qn)	6.9	344	125	66	10	39	12
Prothioconazole (ql)	6.9	344	189.1	66	10	27	12
Prothioconazole-desthio (qn)	6.8	311.9	125	36	10	57	10
Prothioconazole-desthio (ql)	6.8	311.9	70	36	10	83	55
Pymetrozine (qn)	3.0	218	105	80	10	27	12
Pymetrozine (ql)	3.0	218	79	80	10	47	12
Pyraclostrobin (qn)	7.1	388	194	81	10	19	10
Pyraclostrobin (ql)	7.1	388	163	81	10	33	16
Spirotetramat (qn)	6.7	374	216	60	10	49	12
Spirotetramat (ql)	6.7	374.2	330	60	10	22	12
Spirotetramat-enol (qn)	5.8	302.1	216	71	10	39	13
Spirotetramat-enol (ql)	5.8	302.1	270.1	71	10	29	13
Sulcotrione (qn)	5.0	331	139	60	10	33	12
Sulcotrione (ql)	5.0	329	139	60	10	45	12
Tebuconazole (qn)	6.9	308.1	70	41	10	39	14
Tebuconazole (ql)	6.9	308.1	124.9	41	10	47	25
Terbutylazine (qn)	6.4	230	174	60	10	23	12
Terbutylazine (ql)	6.4	232	176	60	10	23	12
Thiacloprid (qn)	4.6	253	126	90	10	29	15
Thiacloprid (ql)	4.6	253	90	90	10	49	12
Thiophanate-methyl (qn)	5.3	343	151	96	10	30	14
Thiophanate-methyl (ql)	5.3	343	268	60	10	15	12
Tolclofos-methyl (qn)	7.1	301	125	60	10	27	12

Tolclofos-methyl (ql)	7.1	301	175	60	10	42	12
Trifloxystrobin (qn)	7.2	409.1	186.1	31	10	23	25
Trifloxystrobin (ql)	7.2	409.1	206.1	31	10	21	25
Trifloxystrobin acid (qn)	6.8	394.9	185.9	60	10	23	4
Trifloxystrobin acid (ql)	6.8	394.9	144.9	60	10	61	4

qn = quantifier, ql = qualifier transition.

Table B2. Method performance characteristics for determination of pesticides in dust.

	Initial validation						On-going validation						LOD	LOQ
	1 µg/kg		3 µg/kg		10 µg/kg		10 µg/kg			50 µg/kg				
Pesticide	av REC	RSD _r	av REC	RSD _r	av REC	RSD _r	av REC	RSD _{WR}	n	av REC	RSD _{WR}	n	µg/kg	
Acetamiprid	115%	15%	113%	8%	115%	16%	92%	13%	7	89%	5%	3	1	1
Asulam	99%	15%	100%	10%	118%	23%	92%	17%	6	91%	21%	3	1	1
Azoxystrobin	114%	10%	116%	18%	118%	6%	97%	19%	7	73%	2%	3	1	1
Boscalid	pos (~1.5)		105%	19%	117%	27%	97%	33%	6	77%	4%	3	1	1
Carbendazim	pos (~3.2)		98%	16%	99%	12%	109%	31%	5	106%	28%	3	1	1
Chloridazon	165%	11%	120%	10%	121%	14%	98%	12%	7	88%	10%	3	1	3
Chlorpropham	n.d.		n.d.		n.d.		n.d.			96%	24%	3	20	50
Cyhalothrin-Lambda	n.d.		n.d.		146%	18%	n.d.			38%	16%	3	10	20
Cyprodinil	174%	8%	135%	10%	124%	18%	83%	29%	6	64%	4%	3	1	3
Deltamethrin	-		-		-		-			35%	10%	3	10	50
Difenoconazole	118%	16%	111%	13%	110%	21%	87%	24%	7	68%	1%	3	1	1
Dimethenamid (P)	128%	14%	108%	10%	132%	11%	96%	16%	7	83%	4%	3	1	1
Dimethomorph	108%	18%	122%	12%	121%	22%	94%	19%	7	73%	3%	3	1	1
Flonicamid	139%	30%	114%	17%	152%	19%	95%	18%	7	87%	6%	3	1	3
Fludioxonil	108%	6%	111%	4%	115%	4%	90%	29%	6	73%	4%	3	1	1
Fluopicolide	139%	8%	133%	26%	115%	10%	102%	21%	7	73%	6%	3	1	1
Fluopyram	115%	11%	128%	15%	109%	33%	94%	17%	7	78%	5%	3	1	1
Fluopyram benzamide	141%	6%	101%	10%	88%	12%	101%	14%	6	85%	12%	3	1	1
Flutolanil	115%	13%	121%	7%	135%	14%	94%	17%	7	78%	1%	3	1	1
Fosfiazate	114%	5%	112%	8%	122%	21%	96%	12%	7	84%	6%	3	1	1
Imidacloprid	pos (~2.9)		99%	12%	92%	9%	88%	47%	7	83%	10%	3	1	1
Kresoxim-Methyl	186%	32%	157%	26%	128%	20%	95%	20%	5	82%	14%	3	3	10
Linuron	135%	12%	139%	5%	129%	22%	96%	21%	7	81%	2%	3	1	1
Mepanipyrim	131%	23%	112%	27%	112%	16%	83%	15%	6	73%	4%	3	1	1
Metamitron	n.d.		188%	68%	130%	9%	109%	23%	6	94%	6%	3	3	10
Metamitron-desamino	109%	12%	113%	8%	107%	11%	113%	14%	7	89%	12%	3	1	1
Metolachlor (S)	106%	3%	116%	6%	114%	18%	94%	17%	7	77%	4%	3	1	1
Oxamyl	124%	7%	111%	4%	122%	9%	99%	22%	7	89%	13%	3	1	1
Pendimethalin	pos (~2.8)		85%	8%	103%	13%	104%	32%	7	68%	1%	3	1	1
Pirimicarb	103%	8%	106%	5%	120%	13%	93%	14%	7	88%	2%	3	1	1
Prochloraz	116%	13%	110%	5%	124%	19%	79%	11%	7	69%	1%	3	1	1
Propamocarb	pos (~2.3)		77%	13%	89%	16%	100%	33%	7	78%	17%	3	1	1
Prothioconazole	method not suited												not suited	
Prothioconazole-desthio	151%	16%	121%	29%	129%	28%	86%	15%	7	77%	6%	3	1	3
Pymetrozine	122%	22%	112%	15%	90%	17%	101%	29%	7	84%	17%	3	1	1
Pyraclostrobin	109%	4%	123%	7%	125%	21%	90%	20%	7	69%	3%	3	1	1
Spirotetramat	121%	10%	114%	10%	106%	22%	91%	22%	7	75%	6%	3	1	1
Spirotetramat-enol	105%	7%	106%	7%	107%	28%	93%	12%	7	78%	4%	3	1	1
Sulcotrione	n.d.		84%	71%	112%	9%	79%	12%	7	61%	2%	3	3	10
Tebuconazole	143%	42%	113%	4%	107%	23%	94%	25%	6	75%	6%	3	1	1
Terbutylazine	108%	6%	109%	6%	116%	14%	93%	21%	7	80%	1%	3	1	1
Thiacloprid	113%	11%	119%	7%	117%	11%	93%	14%	7	84%	4%	3	1	1
Thiophanate-methyl	155%	14%	130%	11%	135%	19%	76%	20%	7	72%	6%	3	1	3
Tolclofos-methyl	n.d.		n.d.		110%	15%	94%	36%	7	67%	7%	3	10	10
Trifloxystrobin	121%	5%	117%	6%	124%	20%	88%	22%	7	70%	2%	3	1	1
Trifloxystrobin acid	114%	4%	117%	15%	124%	20%	83%	20%	7	74%	5%	3	1	1
Average	125%	13%	115%	14%	117%	17%	94%	21%		77%	7%			
Median	117%	11%	113%	10%	117%	17%	94%	20%		78%	5%			

Av REC = average recovery; Initial validation: n=4 for 1 and 3 µg/kg, n=5 for 10 µg/kg. RSD_r = repeatability, RSD_{WR} = within laboratory reproducibility (from QC samples concurrently analysed with the sample batches. Pos = dust material used for validation contained the pesticide at indicated level.

Supplementary material C: Pesticide usage periods per pesticide

Table C1. Pesticide usage periods per pesticide

Type	Active ingredient	Spraying months (X) - highlighted											
		Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Herbicides	Asulam			x	x	x	x	x	x				
	Chloridazon		x	x	x	x	x	x	x				
	Chlorpropham	x	x	x	x	x							x
	Dimethenamid-P		x	x	x	x							x
	Linuron		x	x	x							x	
	Metamitron			x	x	x	x	x	x	x			
	Metamitron-desamino	<i>by-product of metamitron</i>											
	Pendimethalin	x	x	x	x	x							x
	S-metolachlor		x	x	x	x							
Insecticides	Acetamiprid				x	x	x	x	x	x	x		
	Cyhalotrin-lambda			x	x	x	x	x	x	x			
	Deltamethrin					x	x	x					
	Flonicamid			x	x	x							
	Oxamyl			x	x	x							
	Primicarb					x							
	Pymetrozine				x	x	x	x	x				
	Spirotetramat					x	x						
	Spirotetramat-enol	<i>by-product of spirotetramat</i>											
	Thiacloprid				x	x	x	x	x	x			
Fungicides	Azoxystrobin	x	x	x	x	x							
	Boscalid			x	x	x	x	x	x				
	Fluopyram				x	x	x	x					
	Fluopyram-benzamide	<i>by-product of fluopyram</i>											
	Flutolanil				x								
	Kresoxim-methyl			x	x	x	x	x					
	Mepanipyrim				x	x	x	x	x	x			
	Prochloraz			x	x	x	x	x	x				
	Prothioconazole					x	x	x	x				
	Prothioconazole-desthio	<i>by-product of prothioconazole</i>											
	Pyraclostrobin					x	x	x	x				
	Tebuconazole			x	x	x	x	x	x	x			
	Toclofos-methyl	x											
	Trifloxystrobin				x	x	x	x	x				
	Trifloxystrobin-acid	<i>by-product of trifloxystrobin</i>											

Supplementary material D: List of variables used in logistic and linear regression model selection

Table D1. List of variables used in logistic and linear regression model selection.

Variable	Type	Definition
Koa	Continuous	Octanol-air partition coefficient
Vap	Continuous	Vapor pressure
FreqApp	Continuous	Frequency of application (number of reported applications)
WatershedDt50	Continuous	Half-life in the water-sediment phase
EnviDT50	Continuous	Environmental half-life (determined in the field)
GUS	Continuous	Groundwater Ubiquity Score - potential to move towards groundwater
HenryCt	Continuous	A measure that represents the concentration of a chemical in air over its concentration in water.
surfacetent	Continuous	Surface tension represents the cohesive forces between liquid molecules
kfoc	Continuous	Soil Adsorption Coefficient (Affinity of the pesticide to absorb to organic carbon)
kgapp16	Continuous	Average amount of pesticide used in the year of 2016 (retrieved from CBS - https://www.cbs.nl/)
Number of pets	Discrete	Number of pets
Dog = Y	Binary	Dog(s) - Y/N
Cat = Y	Binary	Cat(s) - Y/N
Rodent = Y	Binary	Rodent(s) - Y/N
Bird = Y	Binary	Bird(s) - Y/N
Shoes Outside = Y	Binary	Shoes are left outside
DryClothesOut = Y	Binary	Dry your clothes outside
Pest Smell = Y	Binary	Can you smell pesticides?
Number of persons	Discrete	Number of person living in the home
Pest vs Fleas & Ticks = N	Binary	Use pesticides against fleas and/or ticks
Pest vs Headlice = N	Binary	Use pesticides against head Lice
Pest vs Insects = N	Binary	Use pesticides against other insects
Pest vs Herbs = N	Binary	Use pesticides against weeds
Pest vs Fungi = N	Binary	Use pesticides against fungi
Pest vs Snails = N	Binary	Use pesticides against snails
Pest vs Rats = N	Binary	Use pesticides against rats and/or mice
Living room size	Continuous	Area of the living room (where VFD was collected)
Flowrate	Continuous	Average flow rate determined by the blowerdoor value
HouseType	Categorical	What type of house is it? (Det/Duplex/Row)
Roof	Binary	Roof type - Flat or angled
Natural ventilation	Categorical	Natural ventilation only or natural + forced
Leakage	Binary	Is there visible leakage? (eg. Holes or cracks)
Sealed_Draught	Binary	Is the house sealed against draught (with foam/rubber strips)?
Smooth	Binary	Smooth flooring
Floor age	Continuous	Age of the flooring
Distance	Continuous	Distance from home to closest agricultural field (meters)
Sample Weight	Continuous	Weight of the sample (grams)
Vacuumed area	Discrete	Pre-defined vacuumed area (m2)
Wind speed	Continuous	Wind speed registered at the closest KNMI station (m/s at 10 m height)
Wind direction	Discrete	Wind direction registered at the closest KNMI station (Degrees)
Precipitation Duration	Continuous	Duration of rainfall events registered at the closest KNMI station
Precipitation Quantity	Continuous	Amount of rainfall registered at the closest KNMI station (mm)
Cloudness	Discrete	Cloud cover registered at the closest KNMI station (1 to 9 / 9 = upper air invisible)
Humidity	Discrete	Percentage of water vapour present in air
Evaporation	Continuous	Reference crop evaporation (Makkink) (in 0.1 mm)
Dustpred	Continuous	Concentration in dust using equations from Welscher & Nazaroff et al. 2010

Dustpred - (Equation 1).

$$Dustpred = \frac{\rho_{part} \times (f_{om_dust} \times C_{air})}{\rho_{dust} \times (f_{om_part} \times TSP \times K_{oa}^{-1})} \quad (1)$$

Where: ρ_{part} - density of airborne particles (mg/m³); f_{om_dust} - volume fraction of organic matter associated with settled dust (-); C_{air} - total airborne concentration (ng/m³); ρ_{dust} - density of settled dust (mg/m³); f_{om_part} - volume fraction of organic matter associated with airborne particles (-); TSP - mass concentration of airborne particles (μg/m³); K_{oa} - octanol-air partition coefficient (-).

In equation (1), all parameters are fixed, with exception of K_{oa} and C_{air} . We calculated K_{oa} for each pesticide using the EPI Suite KOAWIN model (US EPA 2020). For C_{air} we use measured concentrations in outdoor air as input. These were sampled via active air samplers parallel to the dust collection. Detailed methods and results regarding air measurements can be found in Figueiredo et al. 2021b.

Supplementary material E: Comparison between group means dust concentrations in doormat (DDM) and vacuumed floor dust (VFD) samples

Table E1. Comparison between group means dust concentrations in doormat (DDM) and vacuumed floor dust (VFD) samples.

Pesticides	VFD				DDM			
	U	U	N	U_C	U	U	N	U_C
	vs N	vs U_C	vs N_C	vs N_C	vs N	vs U_C	vs N_C	vs N_C
flonicamid	0.034	<0.001	0.130	0.225				
fluopyram	0.045	0.001	0.175	0.555	0.164	0.002	<0.001	0.082
pendimethalin	<0.001	<0.001	0.078	0.600	<0.001	0.006	<0.001	0.230
prochloraz	0.747	<0.001	0.043	0.003	0.641	<0.001	0.006	0.679
<i>prothioconazole-desthio</i>	<0.001	0.004	0.009	0.081	0.005	<0.001	<0.001	0.965
tebuconazol	0.014	0.062	0.172	0.335	0.006	0.451	0.165	0.009
boscalid	0.104	<0.001	0.008	0.946	0.024	<0.001	0.004	0.123
S-metolachlor					0.188	0.020	<0.001	0.884
azoxystrobin	0.417	0.765	0.071	0.081	0.734	0.118	<0.001	0.551
fludioxonil	0.785	0.062	0.399	0.218				
pyraclostrobin	0.002	<0.001	<0.001	0.202	0.108	0.001	<0.001	0.262
imidacloprid*	0.069	0.061	0.015	0.855	0.867	<0.001	0.296	0.030
propamocarb*	0.170	0.452	0.413	0.547				
thiophanate-methyl*	0.173	0.032	0.072	0.603	0.854	<0.001	<0.001	0.480
<i>carbendazim</i>	0.329	<0.001	<0.001	0.921	0.752	0.620	0.001	0.007

Legend	
colour	α
	< 0.001
	< 0.05

U – Use period; N – Non-use period; U_C - Use period in Controls; N_C – Non-use period in Controls. - p-value

Supplementary material F: Spearman Correlations

Table F1. Spearman Correlation between pesticides concentration in VFD and DDM. Correlations are only reported for pesticides detected in more than 40% of the samples for each dust matrix

Active ingredient (pesticide group)	Loc Homes		Controls	
	Use	Non-use	Use	Non-use
Reported as being applied in bulb fields during the study period				
<u>boscalid (F)</u>	0.11	0.01	-0.14	0.34
<u>azoxystrobin (F)</u>	0.22	0.36	0.29	-0.03
<u>fluopyram (F)</u>	-0.01	0.25	0.57	0.06
<u>pendimethalin (H)</u>	0.16	0.16	0.06	0.60
<u>tebuconazole (F)</u>	0.40	0.38	0.55	0.36
<i>prothioconazole-desthio (F)</i>	0.38	0.36	-0.16	-0.15
<u>pyraclostrobin (F)</u>	0.55	0.26	-0.18	0.39
<u>prochloraz (F)</u>	0.23	0.51	0.25	0.60
Not applied in bulb fields but reported as used in bulb disinfection in 2017				
<u>imidacloprid (I)</u>	0.14	-0.06	0.74	0.27
<u>thiophanate-methyl (F)</u>	0.17	0.38	0.13	0.62
<u>carbendazim (F)</u>	0.29	0.40	0.43	-0.36

Legend: Underlined – correlations that were statistically significant at < 0.05 . In italic – transformation products. Use – Period when pesticides are sprayed; Non-use – Period when pesticides are not sprayed. *F* – Fungicide; *H* – Herbicide; *I* – Insecticide.

Supplementary material G: Spearman Correlation between pesticides concentration in ng/surface area in VFD and DDM

Table G1. Spearman Correlation between pesticides concentration in ng/surface area in VFD and DDM.

	Loc Homes		Controls	
Active ingredient (pesticide group)	U	N	U	N
Reported as being applied in bulb fields during the study period				
boscalid (F)	-0.06	-0.09	-0.21	0.53
azoxystrobin (F)	0.03	0.13	-0.12	0.11
fluopyram (F)	-0.17	0.19	0.42	-0.29
pendimethalin (H)	0.10	0.19	0.28	0.75
tebuconazole (F)	-0.02	0.15	0.04	0.15
prothioconazole-desthio (F)	0.12	0.12	0.17	0.18
pyraclostrobin (F)	0.10	0.16	0.34	0.67
prochloraz (F)	-0.07	0.08	0.38	0.71
Not applied in bulb fields but reported as used in bulb disinfection in 2017				
imidacloprid (I)	-0.05	-0.11	0.88	0.35
thiophanate-methyl (F)	0.15	0.40	0.31	0.61
carbendazim (F)	-0.05	0.21	0.41	-0.12

Legend: Underlined – correlations that were statistically significant at < 0.05 . In italic – transformation products.

U: Use Period, N: Non-use Period. F – Fungicide; H – Herbicide; I – Insecticide

Supplementary material H: Results of the multivariate logistic regression for DDM and VFD

Table H1. Determinants of pesticide occurrence in doormat (DDM) and vacuumed floor dust (VFD) samples.

Variable*	Multivariate Logistic Regression			
	DDM		VFD	
	OR (95% CI)	P - value	OR (95% CI)	P - value
Vap	1.11 (1.07-1.16)	< 0.001	1.08 (1.04-1.13)	< 0.001
EnviDT50	1.90 (1.64-2.21)	< 0.001	1.80 (1.57-2.06)	< 0.001
kgapp16	1.76 (1.53-2.03)	< 0.001	1.57 (1.39-1.78)	< 0.001
Distance (m)	0.69 (0.48-0.98)	< 0.05		
Dustpred	2.42 (2.22-2.66)	< 0.001	1.98 (1.83-2.15)	< 0.001

OR - Odds Ratio, CI – Confidence interval, * These variables were log10 transformed.

Therefore the Odds ratio relates to a 10-fold increase in the fixed effect variable.

Vap – Vapor pressure in mPa reported at 20°C

EnviDT50 – Environmental half-life

Kgapp16 – Average amount of pesticide used in the year of 2016 (retrieved from CBS, www.cbs.nl)

Distance – Distance from a home to the closest agricultural field (m)

Dustpred – Concentration in dust, predicted using equations for Welscher & Nazaroff et al. 2010

Supplementary material I: Results of the univariate linear regression for DDM and VFD

Table I1. Univariate linear models of pesticide concentrations in doormat samples (DDM)

DDM Univariate models	Pesticides																							
	1		2		3		4		5		6		7		8		9		10		11		12	
Variables	β	α	β	α	β	α	β	α	β	α	β	α	β	α	β	α	β	α	β	α	β	α	β	α
Number of pets	0.10	0.46	0.32		0.16		-0.26		0.11		-0.03		-0.03		0.15		-1.23		0.13		-0.05			
Dog = Y	-0.10		-0.79		-0.57		-0.17		0.05		-0.27		-0.25		-0.15		-0.39		1.60		-0.24		0.02	
Cat = Y	-0.14		-0.37		-0.19		-0.42		0.27		-0.27		0.08		0.00		-0.34		2.17		-0.93		-0.25	
Rodent = Y	0.17		0.17		0.12		0.09		0.55		0.34		0.06		0.03		0.18		-0.91		0.43		0.73	
Bird = Y	-0.08		-0.45		-0.43		-0.11		0.39		0.04		-0.15		0.20		-0.25		0.50		0.08		0.30	
ShoesOut	-0.17		-0.17		-0.37		0.04		-0.04		-0.18		-0.13		0.05		-0.09		-0.29		-0.35		-0.04	
DryClothesOut = Y	-0.17		-0.16		-0.26		-0.33		0.10		-0.35		-0.34		-0.19		-0.15		0.13		-0.19		-0.11	
Pest Smell = Y	0.09		0.11		0.13		0.08		0.04		0.10		-0.03		0.00		-0.03		-0.08		0.10		-0.16	
Number of persons	0.09		0.07		0.09		0.15		0.18		0.13		0.01		0.09		-0.12		-0.15		0.09		0.17	
Pest vs Fleas & Ticks = N	0.12		0.66		0.50		0.00		-0.01		-0.06		0.14		0.15		0.31		-1.75		0.01		-0.35	
Pest vs Headlice = N	-0.19		-0.63		-0.54		-0.79		0.06		-0.87		-0.35		-0.44		0.55		0.25		0.90		0.26	
Pest vs Insects = N	-0.30		-0.13		-0.33		-0.05		-0.09		-0.45		-0.43		0.06		-0.42		0.36		-0.94		-0.83	
Pest vs Herbs = N	-0.23		-0.29		-0.49		0.12		-0.28		-0.59		-0.42		-0.23		-0.30		-0.09		-0.24		-0.42	
Pest vs Fungi = N	-0.21		-0.33		-0.12		-0.28		-0.36		-0.40		-0.10		-0.24		-0.02		0.58		-0.47		-0.92	
Pest vs Snails = N	-0.19		0.04		0.22		0.00		0.11		-0.05		-0.27		0.29		-0.63		-0.12		-1.42		-1.17	
Pest vs Rats = N	0.10		0.22		0.36		-0.29		-0.13		0.08		0.08		0.09		0.03		0.31		-0.71		-0.87	
Living room size	0.33		0.07		0.54		-0.50		1.16		0.33		0.10		-0.57		0.06		2.80		-1.39		1.85	
Flowrate*	-0.38		-0.15		-0.58		0.11		-0.64		-0.09		0.10		0.05		0.41		-0.19		0.16		-0.42	
House Type																								
Detached	-0.08		-0.06		-0.02		-0.18		0.19		-0.07		-0.44		-0.09		-0.07		-0.22		-0.47		-0.20	
Duplex	-0.22		-0.19		0.04		0.07		-0.18		0.18		-0.41		0.06		-0.05		-0.50		0.09		-0.48	
Row	-0.19		-0.22		-0.10		-0.31		-0.20		-0.27		-0.53		-0.18		-0.01		-0.11		-0.34		-0.61	
Roof																								
Angled	0.18		0.07		0.35		0.41		0.64		0.64		0.06		0.32		-0.13		0.03		0.37		0.50	
Flat	-0.41		-0.51		-1.13		-0.99		-0.27		0.09		-0.11		-0.44		0.38		0.29		-1.03		-0.47	
Natural ventilation	-0.13		-0.17		-0.48		-0.06		0.06		-0.37		-0.18		-0.26		-0.11		0.16		-0.13		0.16	
Leakage	0.06		0.30		0.39		0.61		0.45		0.46		0.14		0.36		-0.04		-0.55		0.09		0.50	
Sealed Draught	0.13		0.50		0.21		0.24		0.43		0.33		0.06		0.30		0.07		-1.18		0.20		0.28	
Smooth	0.23		0.32		0.20		-0.05		0.38		0.41		0.42		0.13		0.26		-0.13		0.32		0.54	
Floor age*	0.17		0.01		0.05		0.02		0.16		0.02		0.05		-0.17		0.33		0.06		0.44		0.14	
Distance*	-0.26		-0.34		-0.65		-0.73		-0.11		-0.48		-0.44		-0.27		-0.19		1.00		-0.64		-0.33	
Sample Weight*	-0.32		-0.42		-0.56		-0.18		-0.42		-0.21		-0.21		-0.17		-0.30		0.54		-0.42		-0.41	
Wind speed*	-0.67		-0.10		-0.89		0.24		-1.40		-0.29		-0.44		-0.03		-0.67		-1.04		-0.08		0.18	
Wind direction	0.08		-0.08		0.00		0.21		-0.12		0.15		0.04		-0.07		0.14		-0.37		0.37		0.32	
Precipitation Duration*	-0.13		-0.05		-0.12		0.01		-0.30		-0.08		-0.10		-0.08		-0.04		-0.06		0.05		-0.03	
Precipitation Quantity*	-0.09		-0.03		-0.07		0.00		-0.17		-0.05		-0.05		-0.06		-0.02		-0.05		0.02		-0.01	
Cloudness	-0.52		0.00		-0.30		-0.47		-1.63		-0.76		-1.06		-0.87		-0.21		-0.88		0.53		0.53	
Humidity*	-1.98		-1.06		-1.17		-3.05		-8.61		-3.96		-1.39		-2.80		-0.20		-0.92		-3.00		-6.42	
Evaporation*	0.34		0.24		0.21		0.18		0.76		0.32		0.26		0.34		0.06		0.02		0.14		0.31	
Dustpred*	0.27		0.28		0.19		0.42		0.56		0.29		0.46		0.22		0.56		-0.46		NA		0.25	

* This variables were log10 transformed

Legend: (1) Boscalid, (2) Azoxystrobin, (3) Fluopyram, (4) Pendimethalin, (5) Tebuconazole, (6) Prothioconazole-desthio, (7) Pyraclostrobin, (8) S-Metolachlor, (9) Prochloraz, (10) Imidacloprid, (11) Thiophanate-methyl, (12) Carbendazim,

Table 12. Univariate linear models of pesticide concentrations in vacuumed floor dust samples (VFD)

VFD Univariate models	Pesticides																											
	1		2		3		4		5		6		7		8		9		10		11		12		13		14	
Variables	β	α	β	α	β	α	β	α	β	α	β	α	β	α	β	α	β	α	β	α	β	α	β	α	β	α	β	α
Number of pets	0.45	0.58	0.43	0.40	0.30	0.05	0.21	0.39	0.59	0.88	-0.87	0.94	-0.25	0.43														
Dog = Y	-0.41	-0.68	-0.94	-0.46	-0.56	-0.17	-0.39	-0.59	-0.82	-1.02	1.37	-0.53	0.20	-0.50														
Cat = Y	-0.19	-0.67	-0.58	-0.73	-0.17	0.06	-0.17	-0.59	-0.39	-0.52	1.35	-0.35	0.23	-0.26														
Rodent = Y	-0.94	-0.01	0.02	-0.72	0.43	0.25	-0.25	-0.56	0.19	-0.68	-1.31	-0.79	-0.58	-0.16														
Bird = Y	-0.03	0.41	0.72	-1.24	-0.17	0.05	-0.74	-0.51	-0.54	-1.00	2.02	-0.14	0.59	-0.56														
ShoesOut	-0.37	-0.49	0.01	-0.11	-0.29	-0.08	-0.09	-5E-03	0.06	-0.05	-0.40	-0.55	-0.35	-0.21														
DryClothesOut = Y	0.21	0.21	0.30	0.36	0.11	-0.03	-0.20	0.11	0.05	-0.27	0.40	0.47	0.10	-0.03														
Pest Smell = Y	0.20	0.40	0.24	0.39	0.26	0.34	0.11	-0.05	0.16	0.24	-0.01	0.06	0.12	0.08														
Number of persons	-0.04	0.09	0.06	0.01	0.25	0.21	-0.06	-0.11	0.24	-0.42	-0.07	-0.16	0.27	0.13														
Pest vs Fleas & Ticks = N	0.30	0.50	0.93	0.83	0.60	0.25	0.47	0.53	0.51	0.62	-1.49	0.62	-0.30	0.32														
Pest vs Headlice = N	-0.35	-1.15	0.40	-0.12	0.05	-0.73	-1.10	-0.87	-0.06	-0.28	-0.44	-0.53	0.84	-0.73														
Pest vs Insects = N	-0.16	0.34	0.20	-0.42	-0.03	-0.12	-0.63	-0.17	-0.18	0.37	0.08	-0.08	-0.24	-0.20														
Pest vs Herbs = N	-0.10	0.28	-0.15	-0.38	-0.05	-0.32	-0.47	-0.27	0.35	0.86	-0.40	-0.04	-0.37	-0.09														
Pest vs Fungi = N	-0.23	-0.46	-0.30	0.49	-0.36	-0.43	-0.19	-0.24	-0.19	0.89	-0.35	-0.40	-0.87	-0.18														
Pest vs Snails = N	-0.15	0.45	0.64	-0.01	0.26	0.38	-0.01	-0.26	0.06	0.37	0.12	-0.03	-0.38	0.17														
Pest vs Rats = N	-0.40	-0.13	-0.25	0.45	-0.11	0.10	0.01	-0.21	-0.41	0.52	-0.30	0.09	-0.68	-0.21														
Living room size	-1.03	-0.91	-1.26	-2.67	0.20	0.11	0.03	0.15	0.08	-1.51	-1.47	0.10	-0.54	0.75														
Flowrate*	0.12	-0.01	-0.25	0.29	-0.53	-0.33	-0.17	0.27	-0.23	-0.04	-0.10	-0.50	-0.49	-0.20														
House Type																												
Detached	0.20	0.45	0.40	-0.08	-0.06	0.27	-0.05	-0.14	-0.05	0.02	-0.31	0.74	-0.48	0.03														
Duplex	0.42	0.58	0.67	0.51	-0.24	0.43	0.29	0.48	-0.28	0.21	-0.16	0.46	-0.01	0.23														
Row	0.32	0.01	0.15	0.06	-0.58	-0.13	0.26	0.39	-0.51	-0.37	-0.47	0.39	-0.03	-0.14														
Roof																												
Angled	0.55	0.60	0.90	0.77	0.71	1.04	0.82	0.41	1.21	0.24	0.15	0.11	0.69	0.76														
Flat	-1.28	0.01	-0.05	-2.61	0.04	-0.85	-1.75	-0.57	-2.08	-0.37	-2.30	0.76	-3.03	-2.32														
Natural ventilation	0.19	0.13	0.01	0.15	0.23	-0.03	-0.21	-0.12	0.39	0.15	-0.16	0.26	-0.33	0.17														
Leakage	0.42	-0.08	0.31	1.11	0.19	0.37	0.73	0.46	0.86	-0.15	-0.01	-0.32	-0.04	0.84														
Sealed Draught	0.24	0.75	0.70	-0.14	0.69	0.22	0.14	0.22	0.87	0.45	-0.71	0.38	0.18	0.39														
Smooth	0.03	-0.22	-0.01	0.26	0.30	0.37	0.10	0.15	0.35	0.04	-0.41	-0.19	0.11	0.50														
Floor age*	-0.17	0.18	0.18	-0.57	-0.28	-0.20	-0.13	0.06	-0.56	-0.24	-0.46	0.06	-0.35	-0.46														
Distance*	-0.42	-0.21	-0.28	-0.50	-0.24	-0.19	-0.71	-0.55	-0.54	-0.41	0.32	-5E-03	-0.09	-0.83														
Sample Weight*	-0.19	0.44	0.17	-0.09	0.04	0.04	-0.61	-0.52	-0.16	0.21	-0.33	0.15	-0.42	-0.51														
Wind speed*	-0.08	-0.11	-1.07	-0.39	-0.81	-0.42	0.16	-0.68	0.87	-0.74	1.37	-1.04	0.14	1.32														
Wind direction	0.34	-0.14	0.28	0.40	0.17	0.05	0.51	0.47	0.32	0.03	0.17	-0.09	0.71	0.26														
Precipitation Duration*	0.01	-0.05	-0.10	0.06	-0.24	-0.16	0.06	0.02	0.01	-0.04	-0.03	-0.20	0.05	0.07														
Precipitation Quantity*	-0.01	-0.04	-0.09	-0.01	-0.15	-0.11	0.01	0.02	-0.03	-0.01	-0.04	-0.11	0.00	0.04														
Cloudness	-0.03	-0.73	-1.15	-1.17	-2.28	-1.34	-0.14	-0.37	0.05	0.12	-1.52	-1.35	0.56	-0.11														
Humidity*	-0.44	-2.93	-1.82	-1.51	-5.85	-2.89	-0.37	2.49	-6.14	1.93	-2.65	-2.14	-1.12	-3.44														
Evaporation*	0.11	0.06	0.20	0.29	0.53	0.54	0.20	-0.01	0.33	0.05	0.26	0.44	-0.10	0.09														
Dustpred*	0.11	-0.07	0.17	0.74	0.43	0.36	0.28	0.71	0.09	1.13	0.77	0.06	-	0.13														

* This variables were log10 transformed

Legend: (1) Boscalid, (2) Azoxystrobin, (3) Fluopyram, (4) Pendimethalin, (5) Tebuconazole, (6) Prothioconazole-desthio, (7) Pyraclostrobin, (8) Prochloraz, (9) Flonicamid, (10) Fludioxonil, (11) Imidacloprid, (12) Propamocarb, (13) Thiophanate-methyl, (14) Carbenazim

Supplementary material J: Results of the multivariate mixed-effect linear models for DDM and VFD

Table J1. Determinants of pesticide concentration in doormat (DDM) and vacuumed floor dust (VFD) samples and calculated R2 and RMSE for DDM models.

DDM Multivariate Model	Pesticides																							
	1		2		3		4		5		6		7		8		9		10		11		12	
Variables	β	α	β	α	β	α	β	α	β	α	β	α	β	α	β	α	β	α	β	α	β	α	β	α
Dog = Y			-0.8														-0.4		1.2					
Cat = Y																			1.5					
Living room size																			3.1					
Sealed against draught																			-0.7					
Pest vs Snails = N																	-0.6				-1.4		-1.2	
Leakage															0.5									
Duspred*					0.2		0.5		0.4		0.5		0.5		0.2		0.7							
Humidity									-6.9														-8.4	
Cloudness																							2.1	
Natural ventilation															-0.4									
Evaporation*	0.3							0.5																
Precipitation Duration								0.3																
Distance*					-0.6		-0.6				-0.5		-0.4		-0.3									
R2	0.004		0.061		0.102		0.116		0.259		0.048		0.460		0.108		0.207		0.005		0.157		0.013	
RMSE (ng/g)	171.8		6.167		1.441		32.49		6.622		20.59		116.8		2.251		53.41		98.18		29.46		236.1	

VFD Multivariate Model	Pesticides																									
	1		2		3		4		5		6		7		9		10		11		12		13		14	
Variables	β	α	β	α	β	α	β	α	β	α	β	α	β	α	β	α	β	α	β	α	β	α	β	α	β	α
Rodent = Y	-0.9																									
Dog = Y			-0.7		-0.9				-0.5														-0.8		-1.0	
Cat = Y																										
Pesticide Smell			0.4								0.3															
Number of persons									0.3																	
Pest vs Fungi = N																										
Pest vs Fleas & Ticks = N																			-0.9							
Duspred*							0.7		0.2				0.4		0.7		1.0									
Wind Speed																	1.9				1.2					
Cloudness								-1.7																		
Roof = Flat																			-2.5							
Evaporation*											0.5		0.9													
Precipitation Duration													0.4													
Distance*	-0.4												-0.6		-0.5						-0.80					

* This variables were log10 transformed; α = p-value, grey color = p-value < 0.05, black color = p-value < 0.001. Pesticides: (1) Boscalid, (2) Azoxytrobin, (3) Flupyram, (4) Pendimethalin, (5) Tebuconazole, (6) Prothioconazole-desthio, (7) Pyraclostrobin, (8) S-Metolachlor, (9) Prochloraz, (10) Imidacloprid, (11) Thiophanate-methyl, (12) Carbendazim, (13) Flonicamid, (14) Fludioxonil.



5

Personal exposure assessment of pesticides in residents: The association between hand wipes and urinary biomarkers

A.Oerlemans^{a1}, D.M.Figueiredo^{b1}, J.G.J.Mol^c, R.Nijssen^c, R.B.M.Anzion^a, M.F.P.van Dael^a, J. Duyzer^e, N. Roeleveld^a, F.G.M. Russel^d, R.C.H.Vermeulen^b, P.T.J.Scheepers^a

^a Department for Health Evidence, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, the Netherlands

^b Institute for Risk Assessment Sciences, University Utrecht, Utrecht, the Netherlands

^c Wageningen Food Safety Research, Wageningen University and Research, Wageningen, the Netherlands

^d Department of Pharmacology and Toxicology, Radboud Institute for Molecular Life Sciences, Radboud University Medical Center, Nijmegen, the Netherlands

^e TNO Urban Environment and Safety, Utrecht, the Netherlands

¹ These authors contributed equally

Published: Environmental Research, Vol. 199, ID. 111282

doi: 10.1016/j.envres.2021.111282

Abstract

Background: Residential exposure to pesticides may occur via inhalation of airborne pesticides, direct skin contacts with pesticide-contaminated surfaces, and consumption of food containing pesticide residues. The aim was to study the association of dermal exposure to pesticides between the use and non-use periods, between farmer and non-farmer families and between dermal exposure and the excretion of metabolites from urine in residents living close to treated agricultural fields.

Methods: In total, 112 hand wipes and 206 spot urine samples were collected from 16 farmer and 38 non-farmer participants living within 50 m from an agricultural field in the Netherlands. The study took place from May 2016 to December 2017 during the use as well as the non-use periods of pesticides. Hand wipes were analysed for the parent compound and urines samples for the corresponding urinary metabolite of five applied pesticides: asulam, carbendazim (applied as thiophanate-methyl), chlorpropham, prochloraz and tebuconazole. Questionnaire data was used to study potential determinants of occurrence and levels of pesticides in hand wipes according to univariate and multivariate analysis.

Results: Carbendazim and tebuconazole concentrations in hand wipes were statistically significantly higher in the pesticide-use period compared to the non-use period. In addition, especially during the use periods, concentrations were statistically significantly higher in farmer families compared to non-farmer families. For asulam, chlorpropham and prochloraz, the frequency of non-detects was too high (57–85%) to be included in this analysis. The carbendazim contents in urine samples and hand wipes were correlated on the first and second day after taking the hand wipe, whereas chlorpropham was only observed to be related on the second day following the spray event.

Conclusions: Concentrations in hand wipes were overall higher in pesticide use periods compared to non-use periods and higher in farmer families compared to non-farmer families. Only for carbendazim a strong correlation between concentrations in hand wipes and its main metabolite in urine was observed, indicating dermal exposure via contaminated indoor surfaces. We expect this to be related to the lower vapour pressure and longer environmental lifetime of carbendazim compared to the other pesticides studies.

Introduction

People living in close vicinity of agricultural activities can become exposed to pesticides through non-occupational pathways. Residential exposure can occur via different routes and from different sources, for example by consumption of food containing pesticide residues, inhalation of airborne pesticides originating from volatilisation or spray drift, and skin contact to surfaces contaminated with drift droplets, soil particles or indoor dust (Bradman et al. 1997; Quiros-Alcala et al. 2011; Hogenkamp, Vaal, and Heederik 2004; Health Council of the Netherlands 2014).

The potential for adverse health effects associated with the application of pesticides has been an important issue for almost 100 years in Europe, the concerns about residential exposure to pesticides originate from the early '80s in the Netherlands (Mulder, Drijver, and Kreis 1993). A literature review by The European Food and Safety Authority (EFSA) showed statistically significant associations between pesticide exposure in children and childhood leukaemia and the development of Parkinson's disease at old age (Ntzani et al. 2013). A more recent systematic review by Van Maele-Fabry et al. supported the association between residential exposure to pesticides and childhood brain tumors (Van Maele-Fabry, Gamet-Payrastre, and Lison 2017). More specifically, Brouwer et al. suggested an association between working in flower bulb cultivation and an increased risk of Parkinson's disease in the Netherlands (Brouwer et al. 2017). Overall, many studies suggest that pesticide exposure could be associated with adverse birth outcomes, neurological diseases, several types of cancer, immune disorders, renal diseases, and endocrine disruption (Gonzalez-Alzaga et al. 2015; Chen et al. 2015; VoPham et al. 2015; Thrasher, Madison, and Broughton 1993; Cosselman, Navas-Acien, and Kaufman 2015; Lebov et al. 2015; Piccoli et al. 2016; Larsen, Gaines, and Deschenes 2017; Brouwers et al. 2011).

A few studies focused on the difference in residential exposure between use and non-use periods of pesticides. It is suggested that seasonal peak pesticide exposure can decrease acetylcholinesterase activity of people who are living near plantations resulting from post-harvesting exposures (Suarez-Lopez et al. 2018; Ramirez-Santana et al. 2020). Furthermore, people living in agricultural areas have a higher risk of exposure during spray periods. This was indicated by increased levels of urinary biomarkers of pesticide exposure (Galea et al. 2015; Crane et al. 2013).

We did not find studies reporting on differences in hand wipes concentrations or dermal exposure in residents between use and non-use periods. A previous study

regarding six commonly applied pesticides in Iowa, US reported that the majority of the hand wipe samples were nondetectable (Curwin et al. 2005). Nevertheless, it can be important to collect hand wipe samples as they might reflect a stronger relation to internal exposure compared to dust measures and to reveal the importance of different routes of exposure (e.g. hand-mouth contact and dermal absorption) (Hoffman, EHS, 2015). Moreover, hand wipes samples are non-invasive and easy to collect. For the determination of external personal exposure, pesticide levels in hand wipe samples can give an indication of dermal exposure, in addition to urinary metabolite levels (Curwin et al. 2005).

Biological monitoring of pesticides and their metabolites in urine is a preferred method for assessing integrated exposure, as pesticides are usually excreted rapidly. Therefore, biological monitoring usually reflects short-term exposures. Urine provides an integrated dose estimate reflecting recent exposure from all sources across different routes of exposure due to the relatively short biological half-lives of most pesticides (Budnik and Baur 2009; Armon and Hänninen 2015). Furthermore, collection of urine samples is often preferred over blood samples because it is less invasive, easy to collect at home by study participants, and available in sufficient quantity, while ethics permission for blood sampling is less accessible for young children (e.g. more difficult to collect blood samples of sufficient volume) (Barr et al. 2006).

In this study, hand wipe samples were collected and analysed for five commonly used pesticides in the Netherlands, i.e. asulam, thiophanate-methyl (degrades into carbendazim), chlorpropham, prochloraz, and tebuconazole. In addition, urine samples from the participants were collected in the same time-frame as the hand wipes and analysed for the corresponding primary urinary metabolites. The aims were to study the association between hand exposure (as a proxy of dermal exposure) to pesticides and the excretion of metabolites from urine collected by residents living close to treated agricultural fields. Additionally, hand wipes and urine biomarker levels were compared between participants from farm and non-farm families and between the use and non-use periods of the corresponding pesticide.

Material and methods

Study design

The current study was nested within the study population of the research project on residential exposure to pesticides in the Netherlands named 'Onderzoek Bestrijdingsmiddelen en Omwonenden' (OBO), which aimed to assess the exposure to pesticides among residents living close to agricultural land. Selection of agricultural fields, pesticides chosen, and participant recruitment were described previously (Vermeulen RCH 2019). The study protocol was approved by the Medical Ethical Committee of the University Medical Center Utrecht (no. NL54727.041.15).

Asulam, carbendazim, chlorpropham, prochloraz, and tebuconazole were the pesticides selected based on authorised use in tulip and lily cultivation in The Netherlands, frequency of application, dose per hectare, physicochemical properties, estimated dermal absorption rate, and contribution from non-agricultural sources, like diet. Carbendazim itself was not sprayed but was measured as an environmental metabolite from applications of thiophanate-methyl used in postharvest treatment and storage.

Non-farmer families (NF) and farmer families (FF) living within 50 m from the perimeter of an agricultural field from a farmer participating in the study were recruited by door-by-door distribution of information leaflets and was the only inclusion criteria. A farmer family was defined as a participating residence where at least one person reported to work in agriculture. We chose a distance of 50 m from the residence to the agricultural field since that is when the highest pesticide burden is expected due to spray drift and volatilization. Potential participants expressed their interest in participation by returning a response card. In total, 54 participants were included of which 16 were members of a FF. All participants collected at least one urine sample during the study period from May 2016 to December 2017. However, not all urine samples from all participants were analysed.

Participants were asked to collect urine samples and hand wipes during two measurement series. The first series of spot urine sample collection was during a pesticide use period between March and September of a selected pesticide and the second series of sample collection during a pesticide non-use period between October and December.

Sample and data collection

Sample and data collection took place in the horticulture regions in the North-West part of the Netherlands. Each participant was visited on two occasions per measurement

campaign. During each visit, the urine samples and hand wipes samples were picked up within three days after completion. The start of the spraying event was announced by a text message (on day 0) and the first morning void was collected on the following day (day 1). The first-morning urine was also collected by the participant on each of six subsequent days (days 2 – 7). Each urine void was collected in a 500 mL polyethene container and immediately stored in a refrigerator until shipment to the laboratory, where it was aliquoted in portions of 15 mL and kept at -18°C until analysis. This measurement series was repeated for the collection of samples in the non-use period. In total, 206 first-morning voids of urine were analysed. Certain urine samples were analysed for multiple pesticide biomarkers as participants could be residents among different agricultural fields, therefore 458 urine results were available

Participants collected a hand wipe sample by themselves (according to a detailed written instruction) in the evening of day 0 (i.e. after a spray application was announced and executed). For 11 participants hand wipes were collected a second time during use period given the occurrence of another spray application and possibility of collecting a second hand wipe. The same procedure was followed in a non-use period. An overview of the total number of analysed urine samples and hand wipes for NF and FF, as well as for each pesticide and for the use and non-use period are presented in supplemental material A. The summarizing numbers are given in Table 1.

Table 1. Number of analysed urine samples and hand wipes.

	Non-farmer families		Farmer families	
	Use period	Non-use period	Use period	Non-use period
Asulam	18	8	21	2
Carbendazim	74	39	14	6
Chlorpropham	52	25	16	8
Prochloraz	16	8	15	8
Tebuconazole	64	28	28	8
Hand wipes	49	31	16	16

The protocol of the self-performed hand wipe by the participants was based on the procedures described previously (Gorce and Roff 2015). Participants were provided with written instructions and a labelled 175 mL Nalgene container with the wipe consisting of a 10 x 10 cm paper tissue (Kimtech Science, Irving, Texas, USA) moistened with 3 mL of 50% of Milli-Q water and 50% of ethanol. Participants were instructed to not wash or rinse their hands in the two hours before sampling and to avoid contact

with wet surfaces (e.g. laundry, hand cloths or kitchen towels). The procedure involved wiping both sides of both hands and fingers, starting at the wrist and wiping in the distal direction. The tissue was placed in the labelled Nalgene container, closed with the cap and stored in a refrigerator until shipment to the laboratory where it was kept at -18°C until analysis. In total, 112 hand wipes were collected and analysed for the assessment of dermal exposure.

A questionnaire was provided to all participants for each occasion of sample collection. The questions included concerned age, sex, body weight, lifestyle, exact times of urine and hand wipe collection, occupation, pesticide use, and home characteristics.

Sample analysis

Urinary biomarkers were only analysed for the pesticide that was allocated to one or multiple selected fields, whereas hand wipes were analysed for all five pesticides in one multi-method (Vermeulen RCH, 2019). The total number of urine samples analysed per biomarker ranged from 48 to 133 and can be found in supplemental material B.

The urinary metabolites were analysed separately as the method of analysis was optimized to achieve the highest sensitivity for each metabolite. Therefore, sample preparation and LC-MS/MS conditions were different for all metabolites. The methods are explained briefly below and a more detailed description of the procedure of sample analysis can be found in supplemental material C.

As asulam is mainly excreted unmetabolized, no deconjugation is required (Vermeulen RCH 2019). An aliquot of thawed urine was spiked with the isotope-labelled analogue as internal standard (ILIS) and homogenised. The extraction was performed by using the Quick Easy Cheap Effective Rugged Safe (QuEChERS) method through the addition of acetonitrile and acetic acid. After shaking, it was followed by the addition of magnesium sulphate and sodium acetate to induce phase separation (Lehotay 2007). The upper acetonitrile layer was subsequently analysed by LC-MS/MS.

The metabolite of carbendazim, methyl 5-hydroxy-2-benzimidazole carbamate (5-HBC), is partly excreted in urine as conjugates (Leenheers et al. 1993). An aliquot of thawed and homogenized urine was spiked with ILIS, acetate buffer, and 15 µL of β -glucuronidase/arylsulfatase. After overnight incubation at 37°C, the extraction was carried out by addition of acetonitrile and acetic acid and shaking. Magnesium sulphate and sodium acetate were added for phase separation. An aliquot of the upper acetonitrile layer was transferred to a clean test tube and evaporated under a gentle

flow of nitrogen. The residue was reconstituted in Milli-Q water and subsequently analysed by LC-MS/MS.

The metabolite of chlorpropham, 4-hydroxychlorpropham-O-sulphonic acid (4-HSA), is excreted in urine as a sulphate conjugate. Deconjugation was not needed as the reference standards for 4-HSA were available. An aliquot of the pre-treated sample was thawed, spiked with ILIS and homogenized. Thereafter, the aliquot was filtered using a 30 kDa ultracentrifuge cartridge. The filtrate was transferred into a vial for LS-MS/MS analysis.

The metabolite of prochloraz, 2,4,6-trichlorophenoxyacetic acid (2,4,6-TCP), is excreted in urine as a conjugate (Vermeulen RCH 2019). An aliquot of thawed and homogenized urine was spiked with ILIS, acetate buffer, and β -glucuronidase/arylsulfatase. After overnight incubation at 37°C a solid-phase extraction (SPE) was performed. The SPE column was loaded with 5 mL of deconjugated urine, washed with 10% of acetonitrile in aqua pure, and eluted with 50% acetonitrile in aqua pure. The eluate was dried under nitrogen and reconstituted in acetonitrile and Milli-Q water and subsequently analysed by LC-MS/MS.

As the human metabolite of tebuconazole, 1-hydroxytebuconazole (TEB-OH), is excreted in urine as a conjugate, deconjugation during sample treatment is required (Oerlemans et al. 2018). An aliquot of thawed and homogenized urine was spiked with ILIS, acetate buffer, and β -glucuronidase/arylsulfatase. After overnight incubation at 37°C, a sub-zero temperature liquid-liquid extraction was performed to induce phase separation (Yoshida and Akane 1999). According to the method of Yoshida and Akane, 3 mL of acetonitrile was added to an aliquot of 1 mL of deconjugated urine and placed at -20 °C for 20 min. The upper acetonitrile layer was subsequently analysed by LC-MS/MS.

All methods included matrix-matched calibration standards, quality control samples, and blanks and were analysed simultaneously with the samples. In-house method validation was done according to SANTE/11945/2015 (European Commission 2015). All methods included normalisation to the response of the ILIS. Limits of quantification (LOQ) for hand wipe and urine sample analysis are given in Table 2. Creatinine was analysed after centrifuging the sample but prior to further pre-treatment of the samples by the laboratory for clinical chemistry of the Radboud university medical center according to the modified Jaffe method (Slot 1965). Relative metabolite concentrations were expressed in $\mu\text{g/g}$ creatinine.

Table 2. Limits of quantification (LOQ) for hand wipe and urine sample analysis using LC-MS/MS.

Pesticide (urinary metabolite)	LOQ hand wipe (ng/wipe)	LOQ urine (ng/mL)
Asulam (asulam)	0.50	0.1
Carbendazim (5-HBC)	0.50	0.05
Chlorpropham (4-HSA)	2.5	0.1
Prochloraz (2,4,6-TCP)	1.0	0.3
Tebuconazole (TEB-OH)	0.25	0.05

5-HBC: methyl 5-hydroxy-2-benzimidazole carbamate, 4-HSA: 4-hydroxychlorpropham-O-sulphonic acid, 2,4,6-TCP: 2,4,6-trichlorophenoxyacetic acid, TEB-OH: 1-hydroxytebuconazole.

The hand wipes were analysed in a multi-method for the five pesticides using liquid chromatography tandem mass spectrometry (LC-MS/MS). Sample extraction was performed in the Nalgene container in which the wipe was stored to reduce extraction losses. The wipe material was cut in small pieces and desorbed with methanol, after which the container was placed in an ultrasonic bath and on a mechanical shaker. An aliquot of methanol was transferred into a test tube and dried under a gentle flow of nitrogen. The residue was reconstituted and was centrifuged to remove remaining solids. The supernatant was transferred to a vial for LC-MS/MS analysis. A more detailed description of the procedure for the hand wipe analysis can be found in supplemental material D.

Data analysis

The LC-MS/MS technique has pesticide-specific LOQs as shown in Table 2. In this study, the LOQ was set as cut-off level for detection. For levels below the LOQ, imputation was done when the analyte was quantified ($>LOQ$) in at least 60% of the samples measured for that analyte (Succop et al. 2004). The values below LOQ were imputed based on the maximum likelihood estimation, while accounting for the distribution of the data and correlation between different compounds across the same medium (Lubin et al. 2004). For urine, imputations were only possible for the biomarkers of tebuconazole and chlorpropham. For hand wipes, imputation was only possible for tebuconazole and carbendazim. We compared FF vs NF to study any significant change between farmers and the remaining rural population (NF).

We used the Wilcoxon non-parametric test to determine if the concentration mean ranks in the use and confirmed non-use period were different from each other, as well as FF vs NF. Spearman's Rho correlation coefficients were calculated between concentrations of three different pesticides in hand wipes on day 0 compared to

the levels of excreted metabolites in morning urine samples on day 1 and 2. As the Spearman method gives a rank correlation coefficient, imputed data can be included in the analysis. Here, the requirement of a minimum of 10 paired samples was used, given that applying this correlation with a smaller sample size reduces statistical power and increases the likelihood for type I or type II errors (see Knudson & Lindsey 2014 for details).

Univariate and Multivariate models

A univariable analysis was applied for the evaluation of the questionnaire data with the aim of understanding the relationship between each different variable and the concentration of pesticides in hand wipes. We also performed a multivariable analysis taking into account all variables in a forward stepwise regression to identify which were associated with the hand wipe concentrations. The inclusion of all variables was based on i) many of these variables have been indicated as possible determinants of pesticide levels in the home environment, such as pets (González-Alzaga et al. 2020), flooring type (Harley et al. 2019), shoes and clothes (Coronado et al. 2011), ii) expert decision. In these analysis we constructed separate models for each pesticide, with the different questionnaire data as independent variables (see supplementary material I for the complete list) and the concentrations in handwipe as dependent variable. The house identification number was added as fixed parameter in every model to account for participants living in the same residence.

FF were excluded from the univariate and multivariate analysis since these homes are known to have different determinants of pesticide burden than the general population compared to NF homes (Curl et al. 2002). The participants aged ≤ 17 (N=13) were also excluded, since a different questionnaire was given to this age group and various questions in this questionnaire were not answered.

All statistical analyses were performed using R version 3.5.3 (R Development Core Team 2010).

Results

Study population

In total, 54 residents enrolled in the hand wipe collection, 28 (52 %) of them were males and the median (SD) age of the population was 40.2 ± 24.4 y. The median (SD) BMI was 22.8 ± 4.5 kg/m². Moreover, the median (\pm SD) reported time spent at home

(i.e. indoors) was 15.6 ± 2.6 h per day. Eighteen (34 %) residents reported application of a pesticide at least once within 6 months before the start of the study.

Urine biomarkers

For the different analysed biomarkers in urine, imputation was only possible for chlorpropham (Fig. 1A) and tebuconazole (Fig. 1B). Supplemental material B summarizes the measured concentrations and the percentage of detects for all five analysed biomarkers. For chlorpropham (4-HSA) in FF, the median concentrations were 0.79 and 0.26 $\mu\text{g/g}$ creatinine for the use and non-use period, respectively. While for NF, the median concentrations were 0.62 and 0.26 $\mu\text{g/g}$ creatinine for the use period and non-use period, respectively. The median concentrations were significantly higher for FF in the use period compared to the non-use period ($p=0.03$). The same being true when comparing NF groups ($p=0.03$). Additionally, when comparing FF with NF for both periods, the median concentrations were close to each other, thus no statistical difference ($p > 0.05$).

In FF the median concentrations of the urinary metabolite of tebuconazole (TEB-OH) were 0.47 and 0.03 $\mu\text{g/g}$ creatinine for the use and non-use period, respectively. In NF, the median concentrations were 0.16 and 0.07 $\mu\text{g/g}$ creatinine for the use and non-use period, respectively. The median concentrations in FF were significantly higher in the use period when compared with the non-use period ($p = 0.006$). The same conclusion is valid for NF ($p = 0.031$). Moreover, concentrations were significantly higher for FF in the use period when comparing with NF ($p = 0.026$). There were no statistically significant differences in urine concentrations between FF vs NF in the non-use period.

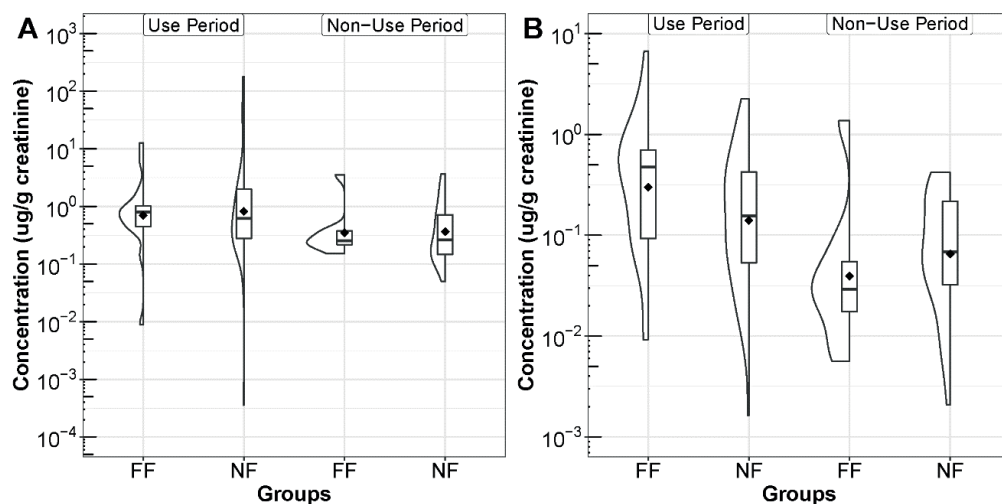


Fig 1. Concentrations of chlorpropham (A) and tebuconazole (B) in the morning urine of residents during the use and non-use period.

The x-axis represents the groups (FF = farmer families, NF = Non-farmer families). The y-axis represents the concentration in urine in $\mu\text{g/g}$ creatinine on a $^{10}\log$ scale. The box plots are representing summary statistics (min, max, 1st and 3rd quartile and median) and on the left side the distribution is presented. The black diamond represents the arithmetic mean.

Hand wipes

A total of 65 hand wipe samples were collected from different residents during the use period of a pesticide; 47 samples were collected in the non-use period. Supplemental material E summarizes the concentrations measured and the percentage of detects for the five pesticides analysed. Imputation of the data was only applicable to two of these, i.e. tebuconazole (Fig. 2A) and carbendazim (Fig. 2B), the percentages of non-detects (<LOQ) were too high to perform imputation for the other compounds.

Regarding residential exposure in FF, the median concentrations of tebuconazole were 1.82 and 0.02 ng/hand wipe for the use and non-use period, respectively. Whereas for NF, the median concentrations were 0.17 and 0.03 ng/hand wipe, for the use and non-use period, respectively. For carbendazim, the median concentrations were 1190 and 295 ng/hand wipe, for the use and non-use period in FF, respectively. Whereas for NF, the mean concentrations were 64.2 and 1.04 ng/hand wipe, for the use and non-use period, respectively.

When comparing the hand wipe results of the FF between periods, the concentrations were significantly higher for tebuconazole in the use period ($p = 0.007$). However, this result is not statistically significant when comparing NF groups ($p = 0.103$). In addition, during the use period, concentrations were significantly higher in FF when comparing with NF ($p < 0.001$).

For carbendazim, we can see that concentrations in FF are significantly higher than NF ($p < 0.001$), for both use and non-use periods. The concentrations were also significantly higher in the use period vs. non-use period when comparing between NF ($p = 0.001$).

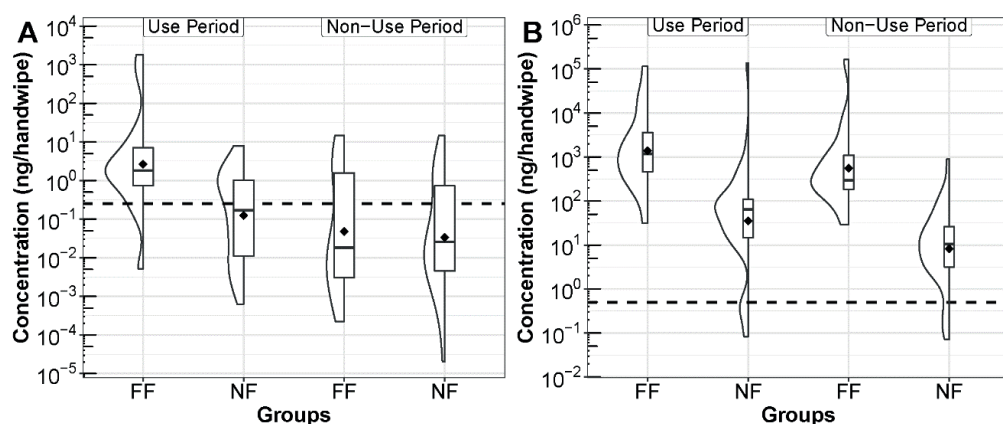


Fig 2. Concentrations of tebuconazole (A) and carbendazim (B) in hand wipes collected from residents during the use and non-use period.

The x-axis represents the groups (FF = farmer families, NF = Non-farmer families). The y-axis represents the concentration in ng/hand wipe on a $^{10}\log$ scale. The box plots are representing summary statistics (min, max, 1st and 3rd quartile and median) and on the left side the distribution is presented. The black diamond represents the arithmetic mean of the logged data. The dotted line indicates the LOQ.

Association between hand wipes and urine samples

A study into the association between hand wipe concentrations and corresponding urine concentrations was possible for three of the five studied pesticides (i.e. tebuconazole, chlorpropham and carbendazim). The hand wipes from day 0 and the morning urine samples of day 1 and 2 were included based on the time the metabolites are expected to be excreted from the body (Oerlemans et al. 2019). Comparisons were performed, including the imputed data (NF+FF) and solely for the use period. For asulam and prochloraz this was not possible since nearly all results were below the LOQ in both the hand wipe and in the urine sample.

Table 3. Spearman correlations between concentrations of three different pesticides in hand wipes on day 0 compared to the levels of excreted metabolites in morning urine samples of day 1 and 2.

Pesticides	Day	Spearman Rho	P-value	N-paired
Carbendazim	1	0.909	< 0.001	11
	2	0.731	0.006	13
Chlorpropham	1	0.309	0.387	10
	2	0.627	0.043	11
Tebuconazole	1	0.340	0.060	32
	2	-0.133	0.480	30

N-paired: Number of paired samples between hand wipe and measured urine biomarker.

A strong Spearman correlation was observed between the concentrations of carbendazim in hand wipes and carbendazim metabolite in urine on day 1 and 2, with a higher correlation on day 1. For chlorpropham results of pesticides found in hand wipes and urine samples correlated on day 2, but not on day 1. For tebuconazole no statistically significant correlations were found, see Table 3.

In addition, a sensitivity analysis was performed with only the paired observations that were > LOQ (i.e. not imputed). These results can be found in supplemental material F. Overall, similar associations were obtained, except for chlorpropham since there were not enough paired observations to perform a rank correlation.

Univariable and multivariable analysis

To test the relationship between different variables and the concentrations found in hand wipes, but also to study changes in coefficient (β) direction when adding multiple variables, both univariable and multivariable analyses were performed. In Table 4, the signs of β for each paired independent variable and outcome, as well as the regression p-values are presented. The results of the multivariable analysis were added in Table 4, indicating the selected variables.

Three reported characteristics of the residence appeared to be significantly associated with changes of carbendazim concentrations in hand wipes. Associated with an increase in concentration (positive β) were: use of pesticides at least once in the home, presence of pets in the home, and specifically, owning a cat. However, in the forward multivariable stepwise regression, only owning a cat remained in the model and continued to be statistically significant without a change in β direction. Additionally,

four variables that were not statistically significant in the univariable analysis were selected in the model: two variables with a p-value < 0.05 and two with a p-value < 0.001. The latter two are 'the age of the floor' and 'the ventilation rate (expressed as exchanges per hour)'. The first variable indicates that the older the floor in the residence, the higher the hand wipe concentration. The second variable indicated that an increase in the number of air changes per hour calculated using the gComis model (Vermeulen RCH 2019), is associated with a decrease in the hand wipe concentrations.

When hand wipes were collected during the tebuconazole use period the concentrations of tebuconazole were significantly increased. In the multivariable stepwise regression, this variable continued to be statistically significant, the β sign did not change and was maintained in the model. Moreover, many other variables were also selected in this step (all $p < 0.05$). Associated with an increase in β were: the average time a person spent indoors, the age of the floor, owning a pet and drying laundry outdoors. In contrast, the reported conditions associated with a decrease in β were: the use of pesticides at least once, average ventilation rate, owning a dog, and reporting the smell of pesticides.

Table 4. Regression coefficients and p-values: results from a univariable and multivariable analysis for carbendazim and tebuconazole concentrations in hand wipes.

Independent variables	Carbendazim				Tebuconazole			
	Univariable		Multivariable		Univariable		Multivariable	
	β	α	β	α	β	α	β	α
Use period = Yes	–	> 0.05			+	< 0.001	+	< 0.001
Age (y)	–	> 0.05	+	> 0.05	–	> 0.05		
Gender = Male	+	> 0.05	+	> 0.05	+	> 0.05	+	> 0.05
BMI (kg/m ²)	–	> 0.05			–	> 0.05	+	> 0.05
Average time spent indoors (h)	–	> 0.05			+	> 0.05	+	< 0.05
Use pesticides at least once	+	< 0.001			+	> 0.05	–	< 0.05
Number of persons in home	–	> 0.05			–	> 0.05	+	> 0.05
Living room size (m ²)	–	> 0.05			+	> 0.05	–	> 0.05
Air changes per hour of the home (1/h)	–	< 0.05	–	< 0.001	–	> 0.05	–	< 0.05
Type of floor = Smooth	+	> 0.05	+	> 0.05	–	> 0.05	+	> 0.05
Age of the flooring (y)	–	> 0.05	+	< 0.001	–	> 0.05	+	< 0.05
Distance from a field (m)	+	> 0.05	+	> 0.05	+	> 0.05		
Owning pets	+	< 0.001			+	> 0.05	+	< 0.05
Own a dog	+	> 0.05			–	> 0.05	–	< 0.05
Own a cat	+	< 0.001	+	< 0.001	+	> 0.05		
Eat vegetables from garden	+	> 0.05			+	> 0.05	+	> 0.05
Bring shoes inside	–	> 0.05			–	> 0.05	+	> 0.05
Dry clothes outside	+	> 0.05	+	< 0.05	–	> 0.05	+	< 0.05
Can smell pesticides	+	> 0.05	–	< 0.05	–	> 0.05	–	< 0.0

β – Effect estimate signal. For an numerical independent variable: an increase in 1 unit will lead to an increase (+) or decrease (–) in concentrations. For a categorical variable: It is a binary option (e.g. Yes/No leads to an increase (+) or decrease (–) in concentrations).

α - Significance level.

Discussion

In this study, we found higher concentrations of tebuconazole in hand wipes in the pesticide use period compared to the non-use period. This was expected since tebuconazole is commonly applied in vegetables, cereals, seeds, and ornamentals, including flower bulbs. Furthermore, this substance is not highly persistent resulting in relatively low environmental background (Dong et al. 2018). For carbendazim the difference of hand wipe concentrations between the use and the non-use period were only significant for NF, with higher concentrations in the use period of its precursor thiophanate-methyl. It is most likely that higher hand wipe concentrations reflected increased background concentrations, which are expected to be higher in the use period both for FF and NF. Carbendazim occurs in the Netherlands mainly as environmental

degradation product of benomyl and thiophanate-methyl and it can persist for more than one year in the environment (Leistra and Matser 2004). These results agree with previous findings that populations are usually exposed to multiple pesticide mixtures, and also to higher concentrations in the use period compared to the non-use period (Smith et al. 2017).

Regarding the measurement results in the morning urine samples and period of sample collection, a similar pattern could be observed for pesticide residues retrieved from hand wipes. However, we only observed statistically significant differences in concentrations between the use and non-use periods for chlorpropham, with higher concentrations in the use period. This outcome matches the results described in a recent review on biomonitoring studies, in which all studies demonstrated higher chlorpropham concentrations for residents in the use period (Dereumeaux et al. 2020). We hypothesize that diet plays a major role in pesticide intake, making it more difficult to detect a contribution from environmental exposure on the total amount of pesticide excreted in urine as a metabolite. Another challenge is the contribution from local or non-professional use of pesticides to the total amount of pesticide exposure. A recent systematic review concluded that there is a lack of consensus regarding differences in urinary metabolite concentrations between exposed and control groups (Lopez-Galvez et al. 2019). In addition, the contribution of pesticide exposure from environmental background levels and indoor sources to the excretion of corresponding metabolites is unknown.

Previous studies described that FF are exposed to higher concentrations of pesticides than residents (Curwin et al. 2007). In our study, we observed a similar pattern, especially for hand wipes. Both tebuconazole and carbendazim concentrations are, overall, higher in FF. However, when looking at urinary biomarkers, the difference between FF and NF is less pronounced, indicating that other routes, such as dietary intake, might play a bigger role in exposure than the dermal pathway.

A statistically significant correlation was found between hand wipe and urine concentrations for carbendazim on both day 1 and 2. This could be an indication of a contribution from the dermal exposure pathway because skin absorption is a comparatively slow absorption process (Atabila et al. 2017). The small decrease in Spearman Rho from day 1 to day 2 could reflect variability in excretion rate after dermal exposure, since it is expected that the concentrations will decrease continuously over time, depending mainly on the toxicokinetics of the pesticide (Oerlemans et al. 2019). We also observed a moderate correlation between urine from day 2 and hand wipe

concentrations for chlorpropham, but we cannot draw any conclusions from this, given that many of the paired values were below LOD. These results are similar to a previous study that showed moderate to strong correlations between exposure via hands and excreted concentrations in urine among pesticide applicators (Tuomainen et al. 2002). Therefore, the hand wipe could likely be used as a proxy for environmental exposure.

To the best of our knowledge no previous studies have looked at possible determinants that drive the concentrations of pesticides in hand wipes from residents. The univariable analysis in this study indicated that for tebuconazole primarily the time of sample collection explains observed variability. However, when adding multiple variables together, other variables become also potential determinants ($p < 0.05$), such as average time spent indoors, indoor applications of pesticides, ventilation rate, owning a dog and reported smells attributed to pesticides.

Regarding carbendazim, our results showed that ventilation rate, age of the flooring and owning a cat are associated with the hand wipe concentrations. A higher airflow rate in a house is associated with lower pesticide concentrations in the indoor environment. We suggest that the age of the floor reflects the function of the floor as a depot for contaminants potentially leading to secondary exposure, which is especially relevant to carbendazim because of the long environmental half-life. And finally, owning a cat increases the hand wipe concentration, which corresponds to previous findings where it was described that pets could carry pesticides from outdoor to the indoor environment as part of the take-home pathway (Deziel et al. 2015). This might be an important indirect exposure route especially for pesticides with a longer environmental half-life.

Prochloraz and asulam were detected in relatively low number of hand wipe and urine samples. Therefore, no statistical analysis were possible for these two pesticides. A probable reason for the low number of detects for asulam is that this pesticide had only a temporary authorization for use in 2016. Background concentrations in homes might therefore be low as well as the contribution from diet. Additionally, in indoor and outdoor air samples collected in the OBO study, asulam was also detected in low number of samples (up to 10%). For prochloraz, we were not able to find an explanation for the low number of detects in urines and hand wipes. In the environmental samples it was detected in high numbers (up to 89% in the use period). In combination with the physicochemical properties, market share and applied amounts on the field it was expected to find sufficient urine and hand wipe samples above the LOD. Regarding human environmental exposure, prochloraz remains an important fungicide to monitor

as it was detected in high numbers, both in indoor and outdoor air, as well as in house dust (Vermeulen RCH 2019).

Although the sample size was small, the composition of the population studied reflects the situation of many rural residents in the Netherlands, i.e. residents of FF and NF with a comparable gender distribution. Furthermore, the methodology used for sample analysis allowed us to detect very low concentrations, which is usually not the case in population studies (Huen et al. 2012). In addition, the data collected via questionnaires proved to be a valuable tool to identify the determinants of dermal exposure. Finally, only few studies combined urine sampling and hand wipe collection in a non-occupational setting. This study adds value to the body of evidence that the dermal pathway is an important route of exposure in a residential setting, since we detected pesticides in many of the hand wipes and we observed, a strong correlation for carbendazim between the observed pesticide concentrations in hand wipes and urine samples.

One of the limitations of the study is that babies and toddlers were not included. This group is considered more susceptible to pesticides and the relative exposure per kg body weight is expected to be higher due to their behaviour (e.g. crawling and playing on the ground, frequent hand-mouth contact) they have more frequent contact with contaminated surfaces. Therefore, the exposure levels found in the studied population cannot be used to make a judgment on the exposure situation for young children.

Although the self-assessment wipe test had a better sampling efficacy compared to wiping by a scientist, the protocol was previously tested for metals and not for pesticides. Additionally, the self-assessment wipe test was previously done by employees and not by residents. The sampling efficacy of the described wipe-method was estimated to be between 70 and 88% (Gorce and Roff 2015). The efficacy of the sampling procedure used in this study was not tested which is a limitation.

The relation between hand wipe concentrations and urine levels would have been better studied if also hand wipes were available on follow-up days. Now the hand wipes were only available on the day of spraying (day 0). Finally, a relatively high number of residents reported that they applied at least one pesticide within 6 months prior to the start of the study, and although this variable was included in the multivariable analysis for both compounds, it only was statistically significant as a determinant of the tebuconazole concentration in hand wipes. This is likely due to the fact that the environmental half-life of tebuconazole (49-610 days) is much longer compared to

chlorpropham (35-65 days) and tebuconazole occurs mainly in the particle-phase, whereas chlorpropham is mainly present in the vapour phase due to its higher vapour pressure (Wang et al. 2017; Rokbani et al. 2019).

Conclusion

In this study we observed that the levels of carbendazim and tebuconazole in hand wipes from residents, as surrogate for dermal exposure, were statistically different between the use and the non-use period of these pesticides in the Netherlands. The concentrations in urine of tebuconazole were also significantly higher in the use periods compared to the non-use periods. We observed large differences in concentrations in hand wipes between FF and NF, but not for urine. Correlations in pesticide concentrations between hand wipes and urine samples were found for carbendazim on the first two days after taking the hand wipe, whereas for chlorpropham a correlation was only detected on day 2. Ventilation rate of the home, age of flooring and owning a cat were observed to be associated with higher carbendazim concentrations in hand wipes and the time of sample collection was the main variable determining dermal tebuconazole concentrations.

Acknowledgements

All farmers and non-farmers families are gratefully acknowledged by the authors for their willingness to participate in this study. We would also thank all the members of the OBO consortium: CLM research and advice, Schuttelaar & Partners, Radboudumc, TNO, Utrecht University, Wageningen University and Research and prof. dr. Pieter Sauer in a personal capacity.

Funding

This work was commissioned by the Dutch National Institute for Public Health and the Environment (RIVM) under contract number M250017-3910052958.

Compliance with ethical standards

Conflict of interest: The authors declare no potential conflict of interest.

Ethical approval: The study protocol with one amendment was approved by the Medical Ethical Committee of the University Medical Center Utrecht in accordance with the 1964 Helsinki declaration and its later amendments. Written informed consent was obtained from all individual participants included in the study.

References

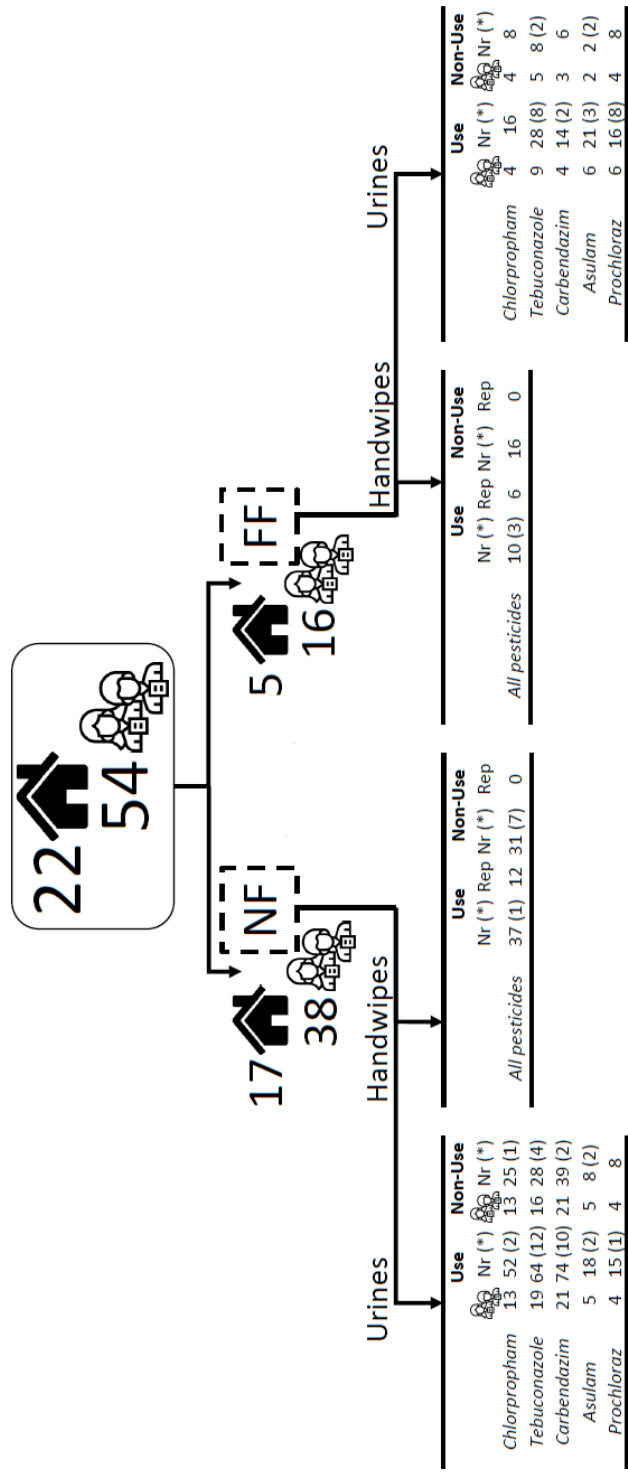
- Armon, Robert H., and Osmo Hänninen. 2015. *Environmental Indicators* (Springer Science+Business Media: Dordrecht).
- Atabila, A., D. T. Phung, J. N. Hogarh, P. Osei-Fosu, R. Sadler, D. Connell, and C. Chu. 2017. 'Dermal exposure of applicators to chlorpyrifos on rice farms in Ghana', *Chemosphere*, 178: 350-58.
- Barr, D. B., K. Thomas, B. Curwin, D. Landsittel, J. Raymer, C. Lu, K. C. Donnelly, and J. Acquavella. 2006. 'Biomonitoring of exposure in farmworker studies', *Environ Health Perspect*, 114: 936-42.
- Bradman, M. A., M. E. Harnly, W. Draper, S. Seidel, S. Teran, D. Wakeham, and R. Neutra. 1997. 'Pesticide exposures to children from California's Central Valley: results of a pilot study', *J Expo Anal Environ Epidemiol*, 7: 217-34.
- Brouwer, M., A. Huss, M. van der Mark, P. C. G. Nijssen, W. M. Mulleners, A. M. G. Sas, T. van Laar, G. R. de Snoo, H. Kromhout, and R. C. H. Vermeulen. 2017. 'Environmental exposure to pesticides and the risk of Parkinson's disease in the Netherlands', *Environ Int*, 107: 100-10.
- Brouwers, M. M., H. Besselink, R. W. Bretveld, R. Anzion, P. T. Scheepers, A. Brouwer, and N. Roeleveld. 2011. 'Estrogenic and androgenic activities in total plasma measured with reporter-gene bioassays: relevant exposure measures for endocrine disruptors in epidemiologic studies?', *Environ Int*, 37: 557-64.
- Budnik, L. T., and X. Baur. 2009. 'The assessment of environmental and occupational exposure to hazardous substances by biomonitoring', *Dtsch Arztebl Int*, 106: 91-7.
- Chen, M., C. H. Chang, L. Tao, and C. Lu. 2015. 'Residential Exposure to Pesticide During Childhood and Childhood Cancers: A Meta-Analysis', *Pediatrics*, 136: 719-29.
- Coronado, G.D.; Livaudais, J.; Hanisch, R.; Tekeste, T. Take-Home Route of Pesticide Exposure. In *Encyclopeida of Environemntal Health*, 1st ed.; Elsevier: Amsterdam, The Netherlands, 2011; pp. 312-324.
- Cosselman, K. E., A. Navas-Acien, and J. D. Kaufman. 2015. 'Environmental factors in cardiovascular disease', *Nat Rev Cardiol*, 12: 627-42.
- Crane, A. L., G. Abdel Rasoul, A. A. Ismail, O. Hendy, M. R. Bonner, M. R. Lasarev, M. Al-Batanony, S. T. Singleton, K. Khan, J. R. Olson, and D. S. Rohlman. 2013. 'Longitudinal assessment of chlorpyrifos exposure and effect biomarkers in adolescent Egyptian agricultural workers', *J Expo Sci Environ Epidemiol*, 23: 356-62.
- Curl, C. L., R. A. Fenske, J. C. Kissel, J. H. Shirai, T. F. Moate, W. Griffith, G. Coronado, and B. Thompson. 2002. 'Evaluation of take-home organophosphorus pesticide exposure among agricultural workers and their children', *Environ Health Perspect*, 110: A787-92.
- Curwin, B. D., M. J. Hein, W. T. Sanderson, D. B. Barr, D. Heederik, S. J. Reynolds, E. M. Ward, and M. C. Alavanja. 2005. 'Urinary and hand wipe pesticide levels among farmers and nonfarmers in Iowa', *J Expo Anal Environ Epidemiol*, 15: 500-08.
- Curwin, B. D., M. J. Hein, W. T. Sanderson, C. Striley, D. Heederik, H. Kromhout, S. J. Reynolds, and M.

- C. Alavanja. 2007. 'Urinary pesticide concentrations among children, mothers and fathers living in farm and non-farm households in Iowa', *Ann Occup Hyg*, 51: 53-65.
- Dereumeaux, C., C. Fillol, P. Quenel, and S. Denys. 2020. 'Pesticide exposures for residents living close to agricultural lands: A review', *Environ Int*, 134: 105210.
- Deziel, N. C., M. C. Friesen, J. A. Hoppin, C. J. Hines, K. Thomas, and L. E. Freeman. 2015. 'A review of nonoccupational pathways for pesticide exposure in women living in agricultural areas', *Environ Health Perspect*, 123: 515-24.
- Dong, B., Y. Yang, N. Pang, and J. Hu. 2018. 'Residue dissipation and risk assessment of tebuconazole, thiophanate-methyl and its metabolite in table grape by liquid chromatography-tandem mass spectrometry', *Food Chem*, 260: 66-72.
- European Commission. 2015. "Guidance document on analytical quality control and method validation procedures for pesticide residues and analysis in food and feed."
- Galea, K. S., L. MacCalman, K. Jones, J. Cocker, P. Teedon, J. W. Cherrie, and M. van Tongeren. 2015. 'Urinary biomarker concentrations of captan, chlormequat, chlorpyrifos and cypermethrin in UK adults and children living near agricultural land', *J Expo Sci Environ Epidemiol*, 25: 623-31.
- Gonzalez-Alzaga, B., A. F. Hernandez, M. Rodriguez-Barranco, I. Gomez, C. Aguilar-Garduno, I. Lopez-Flores, T. Parron, and M. Lacasana. 2015. 'Pre- and postnatal exposures to pesticides and neurodevelopmental effects in children living in agricultural communities from South-Eastern Spain', *Environ Int*, 85: 229-37.
- González-Alzaga, B., Romero-molina, D., López-flores, I., & Giménez-asensio, M. J. (2020). Urinary levels of organophosphate pesticides and predictors of exposure in pre-school and school children living in agricultural and urban communities from south Spain. *Environmental Research*, 186(March), 109459.
- Gorce, J. P., and M. Roff. 2015. 'Hand Self-Wiping Protocol for the Investigation of Lead Exposure in the Workplace', *J Occup Environ Hyg*, 12: 699-707.
- Harley, K. G., Parra, K. L., Camacho, J., Bradman, A., Nolan, J. E. S., Lessard, C., ... Gunier, R. B. (2019). Science of the Total Environment Determinants of pesticide concentrations in silicone wristbands worn by Latina adolescent girls in a California farmworker community : The COSECHA youth participatory action study. *Science of the Total Environment*, 652, 1022–1029.
- Health Council of the Netherlands. 2014. "Crop protection and local residents." In. The Hague: Health Council of the Netherlands. Health Council of the Netherlands, 2014; publication no. 2014/02E.
- Hogenkamp, A., M. Vaal, and D. Heederik. 2004. 'Pesticide exposure in dwellings near bulb growing fields in The Netherlands: an explorative study', *Ann Agric Environ Med*, 11: 149-53.
- Huen, K., A. Bradman, K. Harley, P. Yousefi, D. Boyd Barr, B. Eskenazi, and N. Holland. 2012. 'Organophosphate pesticide levels in blood and urine of women and newborns living in an agricultural community', *Environ Res*, 117: 8-16.
- Knudson, D. V., & Lindsey, C. (2014). Type I and Type II Errors in Correlations of Various Sample Sizes. *Comprehensive Psychology*, 3, 03.CP.3.1. <https://doi.org/10.2466/03.cp.3.1>

- Larsen, A. E., S. D. Gaines, and O. Deschenes. 2017. 'Agricultural pesticide use and adverse birth outcomes in the San Joaquin Valley of California', *Nat Commun*, 8: 302.
- Lebov, J. F., L. S. Engel, D. Richardson, S. L. Hogan, D. P. Sandler, and J. A. Hoppin. 2015. 'Pesticide exposure and end-stage renal disease risk among wives of pesticide applicators in the Agricultural Health Study', *Environ Res*, 143: 198-210.
- Leenheers, L. H., R. Engel, W. E. Spruit, W. J. Meuling, and M. J. Jongen. 1993. 'Determination of methyl 5-hydroxy-2-benzimidazole carbamate in urine by high-performance liquid chromatography with electrochemical detection', *J Chromatogr*, 613: 89-94.
- Lehotay, S. J. 2007. 'Determination of pesticide residues in foods by acetonitrile extraction and partitioning with magnesium sulfate: collaborative study', *J AOAC Int*, 90: 485-520.
- Leistra, M., and A. M. Matser. 2004. 'Adsorption, transformation, and bioavailability of the fungicides carbendazim and iprodione in soil, alone and in combination', *J Environ Sci Health B*, 39: 1-17.
- Lopez-Galvez, N., R. Wagoner, L. Quiros-Alcala, Y. Ornelas Van Horne, M. Furlong, E. Avila, and P. Beamer. 2019. 'Systematic Literature Review of the Take-Home Route of Pesticide Exposure via Biomonitoring and Environmental Monitoring', *Int J Environ Res Public Health*, 16.
- Lubin, J. H., J. S. Colt, D. Camann, S. Davis, J. R. Cerhan, R. K. Severson, L. Bernstein, and P. Hartge. 2004. 'Epidemiologic evaluation of measurement data in the presence of detection limits', *Environ Health Perspect*, 112: 1691-6.
- Mulder, Y. M., M. Drijver, and I. A. Kreis. 1993. '[Case control study of the relationship between local environmental factors and hematopoietic malignancies in young subjects in Aalsmeer]', *Ned Tijdschr Geneesk*, 137: 663-7.
- Ntzani, E.E., M. Chondrogiorgi, G. Ntritsos, E. Evangelou, and I. Tzoulaki. 2013. "Literature review on epidemiological studies linking exposure to pesticides and health effects." European Food and Safety Authority.
- Oerlemans, A., M. F. P. van Dael, R. C. H. Vermeulen, F. G. M. Russel, and P. T. J. Scheepers. 2018. 'Urine collection methods for non-toilet-trained children in biological monitoring studies: Validation of a disposable diaper for characterization of tebuconazole exposure', *Toxicol Lett*, 298: 201-06.
- Oerlemans, A., L. F. M. Verscheijden, J. G. J. Mol, R. C. H. Vermeulen, J. Westerhout, N. Roeleveld, F. G. M. Russel, and P. T. J. Scheepers. 2019. 'Toxicokinetics of a urinary metabolite of tebuconazole following controlled oral and dermal administration in human volunteers', *Arch Toxicol*, 93: 2545-53.
- Piccoli, C., C. Cremonese, R. J. Koifman, S. Koifman, and C. Freire. 2016. 'Pesticide exposure and thyroid function in an agricultural population in Brazil', *Environ Res*, 151: 389-98.
- Quiros-Alcala, L., A. Bradman, M. Nishioka, M. E. Harnly, A. Hubbard, T. E. McKone, J. Ferber, and B. Eskenazi. 2011. 'Pesticides in house dust from urban and farmworker households in California: an observational measurement study', *Environ Health*, 10: 19.
- R Development Core Team. 2010. "R: A language and environment for statistical computing." In. Vienna, Austria: R Foundation for Statistical Computing.

- Ramirez-Santana, M., L. Zuniga-Venegas, S. Corral, N. Roeleveld, H. Groenewoud, K. van der Velden, P. T. J. Scheepers, and F. Pancetti. 2020. 'Association between cholinesterase's inhibition and cognitive impairment: A basis for prevention policies of environmental pollution by organophosphate and carbamate pesticides in Chile', *Environ Res*, 186: 109539.
- Rokbani, O., S. Fattouch, A. Chakir, and E. Roth. 2019. 'Heterogeneous oxidation of two triazole pesticides (diniconazole and tebuconazole) by OH-radicals and ozone', *Sci Total Environ*, 694: 133745.
- Slot, C. 1965. 'Plasma creatinine determination. A new and specific Jaffe reaction method', *Scand J Clin Lab Invest*, 17: 381-7.
- Smith, M. N., T. Workman, K. M. McDonald, M. A. Vredevoogd, E. M. Vigoren, W. C. Griffith, B. Thompson, G. D. Coronado, D. Barr, and E. M. Faustman. 2017. 'Seasonal and occupational trends of five organophosphate pesticides in house dust', *J Expo Sci Environ Epidemiol*, 27: 372-78.
- Suarez-Lopez, J. R., C. R. Butcher, S. Gahagan, H. Checkoway, B. H. Alexander, and W. K. Al-Delaimy. 2018. 'Acetylcholinesterase activity and time after a peak pesticide-use period among Ecuadorian children', *Int Arch Occup Environ Health*, 91: 175-84.
- Succop, P. A., S. Clark, M. Chen, and W. Galke. 2004. 'Imputation of data values that are less than a detection limit', *Journal of Occupational and Environmental Hygiene*, 1: 436-41.
- Thrasher, J. D., R. Madison, and A. Broughton. 1993. 'Immunologic abnormalities in humans exposed to chlorpyrifos: preliminary observations', *Arch Environ Health*, 48: 89-93.
- Tuomainen, A., J. A. Kangas, W. J. Meuling, and R. C. Glass. 2002. 'Monitoring of pesticide applicators for potential dermal exposure to malathion and biomarkers in urine', *Toxicol Lett*, 134: 125-32.
- Van Maele-Fabry, G., L. Gamet-Payastre, and D. Lison. 2017. 'Residential exposure to pesticides as risk factor for childhood and young adult brain tumors: A systematic review and meta-analysis', *Environ Int*, 106: 69-90.
- Vermeulen RCH, Duyzer J, Figueiredo DM, Gerritsen-Ebben MG, Gooijer YM, Hoftijser GW, Holterman HJ, Huss A, Jacobs CJM, Kivits CM, Krop EJM, Kruijne R, Lageschaar LCC, Mol JGJ, Oerlemans A, Sauer PJJ, Scheepers PTJ, Van de Zande JC, Van den Berg F, Wenneker M. 2019. "Research on exposure of residents to pesticides in the Netherlands (Onderzoek Bestrijdingsmiddelen en Omwonenden).", Universiteit Utrecht.
- VoPham, T., M. M. Brooks, J. M. Yuan, E. O. Talbott, D. Ruddell, J. E. Hart, C. C. Chang, and J. L. Weissfeld. 2015. 'Pesticide exposure and hepatocellular carcinoma risk: A case-control study using a geographic information system (GIS) to link SEER-Medicare and California pesticide data', *Environ Res*, 143: 68-82.
- Wang, F. F., Z. Wang, B. H. Zhang, and Q. M. Zhang. 2017. 'Degradation and adsorption of tebuconazole and tribenuron-methyl in wheat soil, alone and in combination', *Chilean Journal of Agricultural Research*, 77: 281-86.
- Yoshida, M., and A. Akane. 1999. 'Subzero-temperature liquid-liquid extraction of benzodiazepines for high-performance liquid chromatography', *Anal Chem*, 71: 1918-21.

Supplemental material A – Infographic study design and collected samples



(*): the number of missing samples.
Rep: the number of repeated measurements.

Supplemental material B – Descriptive results for the urine measurements

Table S1. Biomarker concentrations for the five targeted pesticides

Group	Use Period		Non-Use Period	
	FF	NF	FF	NF
4-HSA µg/g creatinine (i)				
Nr. obs	16	52	8	25
% < LOD	6%	4%	0%	4%
Mean	7.00E-01	8.20E-01	3.50E-01	3.60E-01
SD	4.82E+00	8.11E+00	2.67E+00	3.23E+00
Min	8.90E-03	3.60E-04	1.51E-01	5.00E-02
Max	1.27E+01	1.78E+02	3.54E+00	3.65E+00
Median	7.94E-01	6.19E-01	2.55E-01	2.61E-01
TEB-OH µg/g creatinine (i)				
Nr. obs	28	64	8	28
% < LOD	14%	34%	88%	54%
Mean	2.99E-01	1.40E-01	4.00E-02	6.00E-02
SD	4.74E+00	4.74E+00	5.36E+00	4.07E+00
Min	9.00E-03	2.00E-03	5.00E-03	2.00E-03
Max	6.71E+00	2.25E+00	1.36E+00	4.19E-01
Median	4.73E-01	1.55E-01	2.90E-02	6.90E-02
Asulam µg/g creatinine (ii)				
Nr. obs	21	18	2	7
% < LOD	95%	95%	100%	100%
Min*	5.32E-02	5.44E-01	< LOD	< LOD
Max	5.32E-02	5.44E-01	< LOD	< LOD
Median	< LOD	< LOD	< LOD	< LOD
2,4,6-TCP µg/g creatinine (ii)				
Nr. obs	15	16	8	8
% < LOD	14%	100%	25%	100%
Min*	6.92E-02	< LOD	3.05E-02	< LOD
Max	3.85E+00	< LOD	5.77E-01	< LOD
Median	> LOD	< LOD	> LOD	< LOD
5-HBC µg/g creatinine (ii)				
Nr. obs	14	74	6	39
% < LOD	50%	73%	33%	79%
Min*	5.64E-01	8.74E-02	4.53E+00	1.47E-01
Max	1.26E+01	4.58E+00	1.23E+01	8.38E-01
Median	LOD	< LOD	> LOD	< LOD

FF = Farmer Families; NF = Non-farmer families.

(i) = Samples below LOD were imputed for this pesticide.

(ii) = Due to the low number of detects, mean and standard deviation cannot be calculated for this pesticide.

5-HBC: methyl 5-hydroxy-2-benzimidazole carbamate, 4-HSA: 4-hydroxychlorpropham-O-sulphonic acid, 2,4,6-TCP: 2,4,6-trichlorophenoxyacetic acid, TEB-OH: 1-hydroxytebuconazole.

* = Minimum value observed (above the LOD)

Supplemental material C – Urine sample preparation and analysis using LC-MS/MS analysis

Methods introduced below are described in more detail in Mol et al., (in preparation).

Determination of tebuconazole-1-hydroxy (TEB-OH) - biomarker for tebuconazole

Stock solutions of TEB-OH and the internal standard (D6-TEB-OH) (Alsachim, Illkirch Graffenstaden, France) were prepared in methanol at concentrations of 2 mg/mL. Working solutions of 1000 ng/mL and 100 ng/mL were prepared in 95% of water and 5% of methanol (% v/v). All standards were stored at -20 °C in the dark. A calibration curve of TEB-OH, ranging from 0.05 to 25 ng/mL, including a blank urine, was prepared in a mixture of three randomly provided urine samples, by adding suitable amounts of the working solutions to aliquots of the urine. Each calibration standard was prepared equally as samples were, including addition of the internal standard. With each batch of samples, the calibration curves, and blank acetonitrile and milliQ were freshly prepared and measured three times during the batch analysis to conform the stability of the system.

All specimens were thawed at room temperature prior to sample preparation. An aliquot of 5 mL of urine was transferred to an Erlenmeyer, and 50 µL of the internal standard working solution was added, resulting in a 1 ng/mL concentration of D6-TEB-OH in urine. For deconjugation purposes, 5 µL of *Helix pomatia* β-glucuronidase/arylsulfatase was dissolved per 2.5 mL acetic acid solution in MilliQ water (0.25 M, pH 4.75), and 2.5 mL of this mixture was added to each sample. The samples were incubated overnight for at least 16 h at 37 °C under gentle agitation, and then a subzero-temperature liquid-liquid extraction was performed as previously described by Yoshida and Akane (1999). Briefly, the samples were first centrifuged at 1800 RCF, and 1 mL of the supernatant was transferred to a test tube. An aliquot of three mL of acetonitrile was added, mixed and placed at -20 °C for 20 min to separate the organic layer from the aqueous layer. One mL of the organic layer was transferred to a vial for subsequent LC-MS/MS analysis.

For the quantification of TEB-OH, an aliquot of 2.5 µL of each sample was analyzed on a Waters Acquity LC-MS/MS system via positive electrospray ionization. The chromatographic separation was performed on a Waters BEH C18 column. The MS was operated in multiple reaction monitoring (MRM) mode. The mass transition selected for quantification of TEB-OH was 325.02 → 69.96 (collision energy (CE) 20 eV), and for identification 325.02 → 124.97 (CE 40 eV). The LOQ for TEB-OH was 0.05 ng/mL.

In-house validation and on-going analytical quality control were done according to SANTE/11945/2015 (currently SANTE/12682-2019). The LOQ for TEB-OH was 0.05 ng/ml in urine.

Determination of 4-hydroxychlorpropham-O-sulphonic acid (4-HSA) - biomarker for chlorpropham

4-HSA is a sulfate-conjugate of chlorpropham and most sensitively detected as such, so without deconjugation. The analytical standard (4-HSA potassium salt) is an existing standard available at RIKILT (previously obtained through TNO, Zeist, originally synthesised by Mercachem, Nijmegen, the Netherlands). The internal standard was D7-4-HSA sodium salt purchased from Toronto Research Chemicals (Toronto, Canada). Stock solutions were prepared in methanol at concentrations of 2 mg/ml. A pesticide solution of 10 µg/ml was prepared in milliQ water. An internal standard solution of 0.1 µg/ml isotope label of 4-HSA was prepared in milliQ water. Working standards were prepared by further dilution in water. Procedural calibration standards, undergoing the same procedures as the samples, were prepared in blank urine, by addition of 5-100 µl of (intermediate) mix standard and isotope standard to 0.8-0.9 ml of urine (0, 0.05, 0.1, 0.5, 1, 2, 5, and 10 ng/ml urine; isotope labels at 10 ng/ml).

With each batch of samples, a reagent blank (milliQ water) and a positive control were included. The positive control was prepared by spiking one of the samples from the batch with the pesticide at 2 ng/ml urine.

For sample analysis, urine was thawed and re-homogenised by vortex mixing. A 0.9 ml aliquot was mixed with 0.1 ml of internal standard solution and transferred into an Amicon 30kDa Ultra-centrifuge filter (10 min, 3500xg). The filtrate was transferred into an autosampler filter vial for LC-MS/MS analysis.

LC-MS/MS analysis was performed on a Waters Acquity UPLC system coupled to a Waters Xevo TQS tandem mass spectrometer by injection of 20 µl onto a 100 x 2.1 mm ID 1.7 µm HSS T3 column (Waters), maintained at 45°C. Gradient elution was performed at a flow rate of 0.4 ml/min, using a water/methanol gradient, containing 2 mM ammonium formate, 1 mM ammonium fluoride, and 20 µl/l formic acid. MS/MS measurement was done using ESI in negative, acquiring two transitions. 4-HSA was measured as $[M-H]^-$ using transitions m/z 308>141 and 310>143 (for D7-4-HSA 315>141 and 317>143). The response of 4-HSA in samples and calibrants in blank urine was normalised to the response of the D7-4-HSA internal standard. Quantification was then done using 1-point (2 ng/ml) bracketing matrix-matched calibration. Concentrations

outside the linear range, as established with each batch of analysis through the procedural calibration standards, were diluted and re-analysed.

In-house validation and on-going analytical quality control were done according to SANTE/11945/2015 (currently SANTE/12682-2019). The LOQ for 4-HSA was 0.1 ng/ml urine.

Determination of 2,4,6-trichlorophenoxyacetic acid (2,4,6-TCP) - biomarker for prochloraz

Stock solutions of 2,4,6-TCP and the internal standard ($^{13}\text{C}_6$ -2,4,6-TCP, obtained from Toronto Research Chemicals (Toronto, Canada) were prepared in acetonitrile at concentrations of 2 mg/mL. Working solutions of 1000 ng/mL and 100 ng/mL were prepared in pure acetonitrile. All standards were stored at -20 °C in the dark. A calibration curve of 2,4,6-TCP, ranging from 0.25 to 25 ng/mL, including a blank urine, was prepared in a mixture of three randomly provided urine samples, by adding suitable amounts of the working solutions to aliquots of the urine. Each calibration standard was prepared equally as samples were, including addition of the internal standard. With each batch of samples, the calibration curves, and blank acetonitrile and MilliQ were freshly prepared and measured three times during the batch analysis to conform the stability of the system.

All specimens were thawed at room temperature prior to sample preparation. An aliquot of 5 mL of urine was transferred to an Erlenmeyer, and 5 μL of the internal standard working solution was added, resulting in a 1 ng/mL concentration of $^{13}\text{C}_6$ -2,4,6-TCP in urine. For deconjugation purposes, 5 μL of *Helix pomatia* β -glucuronidase/arylsulfatase was dissolved per 2.5 mL acetic acid solution in MilliQ water (0.25 M, pH 4.75), and 2.5 mL of this mixture was added to each sample. The samples were incubated overnight for at least 16 h at 37 °C under gentle agitation, and then a solid phase extraction (SPE) was performed. Briefly, the SPE column was prepared by washing with 10 mL of 0.1% formic acid in acetonitrile (eluent B) and subsequent with 10 mL of 5% acetonitrile, 0.1% formic acid in water (eluent A). The column was loaded with the deconjugated urine, and the column was washed, in two steps, first with 10 mL of eluent A followed by a solution of 10% eluent B in A. The column was eluted with 5 mL of eluent B. The eluted sample was dried and dissolved in 1 mL of 50% eluent A and 50% eluent B and transferred to a vial for subsequent LC-MS/MS analysis.

For the quantification of 2,4,6-TCP, an aliquot of 2.5 μL of each sample was analyzed on a Waters Acquity LC-MS/MS system via negative electrospray ionization. The

chromatographic separation was performed on a Waters BEH C18 column. The MS was operated in MRM mode. The mass transition selected for quantification of 2,4,6-TCP was 252.84 → 194.81 (CE 10 eV), and for qualification 254.84 → 196.81 (CE 40 eV). The LOQ for 2,4,6-TCP was 0.25 ng/mL.

In-house validation and on-going analytical quality control were done according to SANTE/11945/2015 (currently SANTE/12682-2019). The LOQ for 2,4,6-TCP was 0.5 ng/ml in urine.

Determination of asulam (biomarker for asulam)

Asulam is mainly excreted through urine unmetabolised (Draft Assessment Report, EFSA 2006). A stock solution of asulam (LGC Standards, Wesel, Germany) was prepared in methanol at 2 mg/ml. A solution of 10 µg/ml was prepared in milliQ water. An internal standard solution of 0.1 µg/ml isotope label of D3-asulam (CDN isotopes, Quebec, Canada) was prepared in milliQ water. Working standards were prepared by further dilution in water. Calibration standards were prepared in acetonitrile/1% acetic acid, by addition of 5–100 µl of (intermediate) standard and isotope standard to 0.8–0.9 ml to this solvent (0, 0.05, 0.1, 0.5, 1, 2, 5, and 10 ng/ml solvent; isotope label at 10 ng/ml).

With each batch of samples, two reagent blanks (milliQ water) and two positive controls were included. The positive control was prepared by spiking two samples from the batch with the pesticide at 2 ng/ml urine.

For sample analysis, urine was thawed and re-homogenised by vortex mixing. The extraction method was based on the QuEChERS approach (Lehotay 2007). An aliquot of 1.8 ml of urine was transferred into a polypropylene extraction tube, 0.2 ml of internal standard solution and 2 ml acetonitrile/1% acetic acid were added. After vortex mixing for 2 min, 1 g magnesium sulfate and 0.25 g of sodium acetate were added and the tube shaken for phase separation. An aliquot of 0.5 ml of the upper acetonitrile layer was transferred into an autosampler filter vial for LC-MS/MS analysis.

LC-MS/MS analysis was performed on a Waters Acquity UPLC system coupled to a Waters Xevo TQS tandem mass spectrometer by injection of 5 µl onto a 100 x 2.1 mm ID 1.7 µm HSS T3 column (Waters), maintained at 45°C. Gradient elution was performed at a flow rate of 0.4 ml/min, using a water/methanol gradient, containing 5 mM ammonium formate/0.1% formic acid. MS/MS measurement was done using ESI in positive, acquiring two transitions. Asulam was measured as [M+H]⁺ using transitions m/z 231>156 and 231>92 (for D3-asulam: m/z 234>156, 234>92). The response of

asulam in samples and calibrants in solvent was normalised to the response of the D3-asulam internal standard. Quantification was then done using 1-point (2 ng/ml) bracketing calibration.

In-house validation and on-going analytical quality control were done according to SANTE/11945/2015 (currently SANTE/12682-2019). The LOQ for asulam was 0.1 ng/ml urine.

Determination of methyl 5-hydroxy-2-benzimidazole carbamate (5-HBC) - biomarker for carbendazim and thiophanate-methyl

Thiophanate-methyl is used for bulb disinfection and degrades into carbendazim in the environment. 5-HBC is a urinary biomarker for both thiophanate-methyl and carbendazim. Hence, 5-HBC found in urine may come from either thiophanate-methyl or carbendazim exposure. In urine, 5-HBC is (partially) excreted as conjugates. For the determination of total 5-HBC, a method involving an enzymatic deconjugation step was developed.

5-HBC was purchased as custom synthesized compound through Akos (Steinen, Germany). A stock solution was prepared in methanol at concentrations of 2 mg/ml. A solution of 10 µg/ml was prepared in methanol. Further intermediate dilutions were prepared in milliQ water. An internal standard solution of 1 µg/ml isotope label was prepared in water and contains: ^{13}C - ^{15}N -5-HBC purchased as custom synthesized compound through Akos, Steinen, Germany). Procedural calibration standards, undergoing the same procedures as the samples, were prepared in blank urine, by addition of 6-600 µl of intermediate standard standards and isotope standard to 3 ml of urine (0, 0.01, 0.05, 0.1, 0.5, 2, 5, and 10 ng/ml urine; isotope label at 5 ng/ml).

With each batch of samples, one reagent blank (milliQ water) and two positive controls were included. The positive control was prepared by spiking two samples from the batch with the pesticide/biomarker mix at 2 ng/ml urine.

For sample analysis, urine was thawed and re-homogenised by vortex mixing. The extraction method was based on the QuEChERS approach (Lehotay 2007). An aliquot of 3 ml of urine was transferred into a polypropylene extraction tube, 15 µl of internal standard, 1.5 ml of a 0.2 M acetate buffer (pH 4.5), and 15 µl β-glucuronidase/aryl sulfatase Helix Pomatia (Merck, 2 ml solution, 30 U/ml / 60 U/ml, respectively). The mixture was incubated overnight (at least 16 h) in a water bath at 37°C for deconjugation. After cooling to room temperature, the biomarkers were extracted

with 6 ml acetonitrile/1% acetic acid by shaking end-over-end for 10 min. Then 4 g magnesium sulfate and 1 g sodium acetate were added for phase partitioning, the tube was shaken immediately, and centrifuged 5 minutes at 3500xg.

A 5 ml aliquot of the acetonitrile phase was transferred to a clean tube and evaporated to dryness at 40°C under a flow of nitrogen gas. The residue was reconstituted by subsequent addition of 100 µl of methanol and 400 µl of milliQ water (vortex after each addition). The concentrated extract was transferred into an autosampler filter vial for LC-MS/MS analysis.

LC-MS/MS analysis was performed on a Waters Acquity UPLC system coupled to a Waters Xevo TQS tandem mass spectrometer by injection of 20 µl onto a 100 x 2.1 mm ID 1.7 µm HSS T3 column (Waters), maintained at 45°C. Gradient elution was performed at a flow rate of 0.4 ml/min, using a water/methanol gradient, containing 5 mM ammonium formate/0.1% formic acid. MS/MS measurement was done using ESI in positive mode, acquiring two transitions. 5-HBC was measured as [M+H]⁺ using transitions m/z 208>176 and 208>148 (for ¹³C-¹⁵N-5-HBC: m/z 210>178, 210>150). The response of 5-HBC in samples and calibrants in blank urine was normalized to the response of the ¹³C-¹⁵N-5-HBC as internal standard. Quantification was then done using 1-point (2 ng/ml) bracketing matrix-matched calibration.

In-house validation and on-going analytical quality control were done according to EU guidance document SANTE/11945/2015 (currently SANTE/12682-2019). The LOQ for 5-HBC was 0.05 ng/ml urine.

Summary sample preparation and measurement of urinary metabolites.

Table S2. Summary for sample preparation and measurement of urinary metabolites using LC-MS/MS.

Metabolite ¹	Deconjugation	Extraction method ²	LC column ³	m/z transitions	ESI ⁴
Asulam	No	QuEChERS	HSS-T3	231 > 156 231 > 92	+
5-HBC	Yes	QuEChERS	HSS-T3	208 > 176 208 > 148	+
4-HSA	No	Ultrafiltration	HSS-T3	308 > 141 310 > 143	-
2,4,6-TCP	Yes	Solid Phase Extraction	BEH C18	253 > 195 255 > 197	-
TEB-OH ⁵	Yes	Sub-zero liquid-liquid extraction	BEH C18	325 > 70 325 > 125	+

¹5-HBC: methyl 5-hydroxy-2-benzimidazole carbamate, 4-HSA: 4-hydroxychlorpropham-O-sulphonic acid, 2,4,6-TCP: 2,4,6-trichlorophenoxyacetic acid, TEB-OH: tebuconazole-1-hydroxy.

²QuEChERS: Quick Easy Cheap Effective Rugged and Safe method for pesticide analysis.

³HSS-T3: High Strength Silica, BEH: Ethylene Bridged Hybrid.

⁴ESI: Electrospray ionization.

⁵The method of TEB-OH analysis was previously described by Oerlemans et al. 2019.

Summary for method performance characteristics for determination of pesticide biomarkers in urine using LC-MS/MS.

Table S3. Summary for method performance characteristics of pesticide biomarkers in urine using LC-MS/MS.

Pesticide		Asulam	Carbendazim	Chlorpropham	Prochloraz	Tebuconazole
Biomarker		Asulam	4-HBC	4-HSA	2,4,6-TCP	TEB-OH
Initial Validation	LOD	0.01-0.05	0.01-0.025	0.01-0.05	0.1-0.25	0.01-0.025
	LOQ	0.1 ng/ml	0.05 ng/ml	0.1 ng/ml	0.5 ng/ml	0.05 ng/ml
	Concentration	0.1 ng/ml	0.05 ng/ml	0.1 ng/ml	0.5 ng/ml	0.05 ng/ml
	Recovery (av)	103%	114%	117%	110%	80%
	RSDr (n=5)	15%	8%	19%	5%	1%
	Concentration	1 ng/ml	0.5 ng/ml	1 ng/ml	10 ng/ml	1 ng/ml
	Recovery (av)	118%	105%	95%	92%	86%
	RSDr (n=5)	6%	8%	19%	6%	10%
	Concentration	10 ng/ml	5 ng/ml	10 ng/ml	25 ng/ml	10 ng/ml
	Recovery (av)	106%	98%	90%	97%	88%
	RSDr (n=5)	10%	1%	15%	3%	7%
On-going validation (batch QCs)	Concentration	2 ng/ml	2 ng/ml	2 ng/ml	5 ng/ml	1 ng/ml
	Recovery (av)	104%	102%	92%	93%	90%
	RSDwR	13%	11%	17%	7%	9%

Supplemental material D – Hand wipe sample preparation and LC-MS/MS analysis

The hand wipes were analyzed in a multi-method for the five target substances, i.e. tebuconazole, chlorpropham, prochloraz, asulam and carbendazim. The sample extraction was performed in the plastic container in which the wipe was stored. This reduces the extraction losses.

Stock solutions of the five target substances were prepared in methanol at concentrations of 1 mg/mL, except for carbendazim which was dissolved in DMSO. Additional working solutions of 1000 ng/mL and 100 ng/mL were prepared in 50% methanol and 50% water. Next, a combination calibration curve of tebuconazole, prochloraz, asulam and carbendazim in the range of 0.1 to 10 ng/mL, including a blank, was constituted in 50% methanol and 50% water. For chlorpropham a separate calibration curve was prepared in the range of 1 to 20 ng/mL, including a blank. In addition, blank wipes were added to the measurement protocol to check if the wipes were free from the analytes of interest.

All specimens were thawed at room temperature prior to sample preparation. The wipes were cut in 64 small pieces and these were put back in the same container. 80 mL of methanol was added, and the container was placed in an ultrasonic bath for 1 h, followed by 10 min on a mechanical shaker. 8 mL of methanol extracted was transferred to a test tube and dried at 40°C under a gentle flow of nitrogen. The dried extract was dissolved in 1 mL of 50% methanol and 50% water and was centrifuged at 2000 RCF to remove remaining fibers. The supernatant was transferred to a vial for subsequent LC-MS/MS analysis.

For the quantification of tebuconazole, chlorpropham, prochloraz, asulam and carbendazim, an aliquot of 1.0 μ L of each sample was analyzed on a Waters Acquity LC-MS/MS system via positive electrospray ionization. The chromatographic separation was performed on a Waters CSH C18 column. The MS was operated in MRM mode. The mass transitions selected for quantification are provided in Table S1 below. Chlorpropham was analyzed with the same conditions, but with a lower desolvation temperature of 300°C instead of 600°C.

Table S4. Mass transitions and LOQs of the five pesticides selected for hand wipe analyses.

Pesticide	Quantification	Qualification	LOQ (ng/wipe)
Tebuconazole	308.03 -> 69.94	308.03 -> 124.87	0.25
Chlorpropham	214.1 -> 171.9	214.1 -> 154.1	2.5
Prochloraz	375.97 -> 307.88	375.97 -> 69.94	1.0
Asulam	231.09 -> 155.96	231.09 -> 91.98	0.5
Carbendazim	192.09 -> 160.01	192.09 -> 132.04	0.5

Summary for method performance characteristics for determination of pesticides in hand wipes using LC-MS/MS.

Table S4. Summary for method performance characteristics of pesticides in hand wipes using LC-MS/MS.

Pesticide		Asulam	Carbendazim	Chlorpropham	Prochloraz	Tebuconazole
Initial Validation	LOD	0.01 ng/ml	0.01 ng/ml	0.1 ng/ml	0.05 ng/ml	0.01 ng/ml
	LOQ	0.05 ng/ml	0.05 ng/ml	0.25 ng/ml	0.1 ng/ml	0.025 ng/ml
	Concentration	0.05 ng/ml	0.05 ng/ml	0.25 ng/ml	0.1 ng/ml	0.025 ng/ml
	Recovery (av)	103%	109%	106%	106%	94%
	RSDr (n=5)	17%	16%	11%	19%	18%
	Concentration	1 ng/ml	1 ng/ml	1 ng/ml	1 ng/ml	1 ng/ml
	Recovery (av)	106%	99%	102%	94%	93%
	RSDr (n=5)	15%	11%	7%	14%	14%
	Concentration	10 ng/ml	10 ng/ml	10 ng/ml	10 ng/ml	10 ng/ml
On-going validation (batch QCs)	Recovery (av)	103%	105%	104%	91%	92%
	RSDwR	8%	9%	9%	17%	12%
	Concentration	5 ng/ml	5 ng/ml	5 ng/ml	5 ng/ml	5 ng/ml
	Recovery (av)	103%	99%	101%	102%	98%
	RSDwR	11%	11%	8%	13%	10%

Supplemental material E – Descriptive results for the hand wipe measurements

Table S5. Concentrations in hand wipes of the five targeted pesticides

	Use Period		Non-Use Period	
Group	FF	NF	FF	NF
Nr. obs	16	49	16	31
Carbendazim ng/wipe (i)				
% < LOD	0%	16%	0%	10%
Mean	1.39E+03	3.53E+01	5.57E+02	8.19E+00
SD	7.82E+00	1.35E+01	7.36E+00	7.85E+00
Min	3.11E+01	8.00E-02	2.89E+01	7.00E-02
Max	1.15E+05	1.36E+05	1.63E+05	8.92E+02
Median	1.19E+03	6.42E+01	2.95E+02	1.04E+01
Tebuconazole ng/wipe (i)				
% < LOD	19%	53%	65%	70%
Mean	2.64E+00	1.24E-01	4.80E-02	3.40E-02
SD	1.99E+01	1.43E+01	3.63E+01	2.65E+01
Min	5.20E-03	6.25E-04	2.00E-04	2.04E-05
Max	1.79E+03	7.92E+00	1.48E+01	1.46E+01
Median	1.82E+00	1.70E-01	1.90E-02	2.60E-02
Asulam ng/wipe (ii)				
% < LOD	50%	90%	65%	97%
Min*	2.97E+00	5.00E-01	1.12E+00	8.87E+02
Max	8.13E+02	5.18E+00	8.63E+00	8.87E+02
Median	LOD	< LOD	< LOD	< LOD
Prochloraz ng/wipe (ii)				
% < LOD	31%	82%	18%	80%
Min*	2.02E+00	4.42E+00	2.02E+00	6.20E-01
Max	1.03E+03	7.61E+02	5.39E+04	4.81E+01
Median	> LOD	< LOD	> LOD	< LOD
Chlorpropham ng/wipe (ii)				
% < LOD	75%	82%	59%	67%
Min*	5.65E+00	4.37E+00	3.14E+00	2.68E+00
Max	6.42E+02	1.72E+03	4.55E+01	1.49E+02
Median	< LOD	< LOD	< LOD	< LOD

FF = Farmer Families; NF = Non-farmer families.

(i) = Samples below LOD were imputed for this pesticide.

(ii) = Due to the low number of detects, mean and standard deviation cannot be calculated for this pesticide.

* = Minimum value observed (above the LOD)

Supplemental material F – Spearman correlations between concentrations of two pesticides in hand wipes (Day 0) compared to morning urines on day 1 and 2. Excluding samples below the limit of detection.

Table S6. Correlation between concentrations in handwipes and urine for carbendazim and tebuconazole, when excluding samples below the limit of detection

Pesticides	Day	Spearman Rho	P-value	N-paired
Carbendazim	1	0.909	< 0.001	11
	2	0.731	0.006	13
Tebuconazole	1	-0.461	0.130	12
	2	-0.476	0.240	8

Supplemental material G – Boxplots for unadjusted urine concentrations (µg/L)

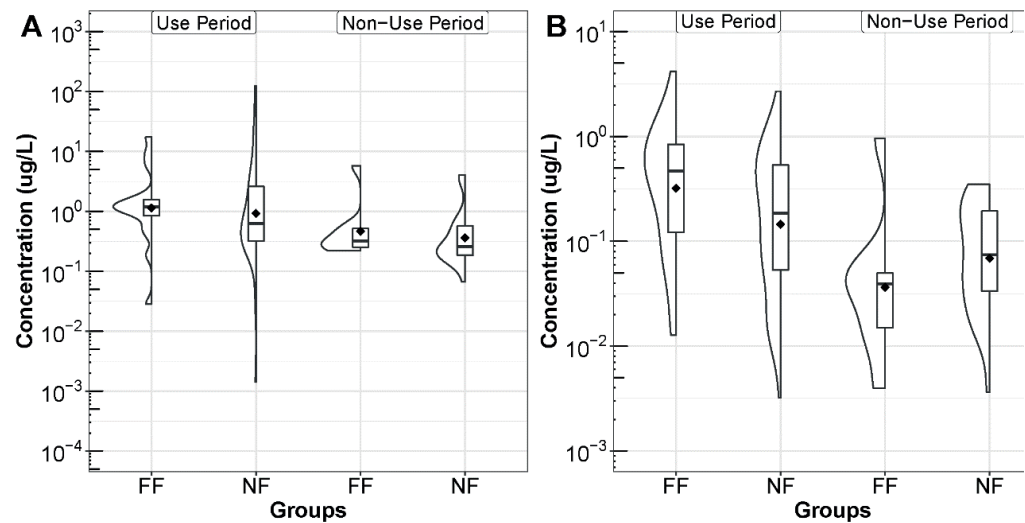


Fig.S1 Concentrations of tebuconazole (A) and chlorpropham (B) in the morning urine of residents during the use and non-use period. The x-axis represents the groups (FF = farmer families, NF = Non-farmer families). The y-axis represents the concentration in urine in µg/Liter on a 10log scale. The box plots are representing summary statistics (min, max, 1st and 3rd quartile and median) and on the left side the distribution is presented. The black diamond represents the arithmetic mean.

Supplemental material H – Urine time series and within-subject correlation for both Use and Non-use periods

Chlorpropham – Non-farmer families

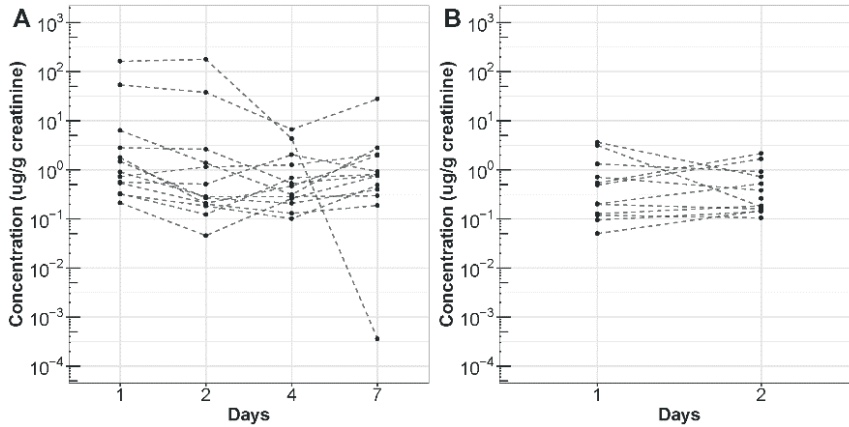


Fig.S2 Chlorpropham (biomarker) concentrations in Use period (A) and Non-use period (B) in the morning urine of residents from Non-farmer families. The x-axis represents the days the morning urine was collected. The y-axis represents the concentration in urine in µg/g creatinine on a 10log scale. Each dotted line represents a subject and each dot is 1 measurement point.

Results from repeated measures correlation:

Use period -> Rho: -0.224 / p-value: 0.166 / 95% confidence interval: [-0.507, 0.104]

Non-use period -> Rho: -0.029 / p-value: 0.925 / 95% confidence interval: [-0.618, 0.581]

Chlorpropham – Farmer families

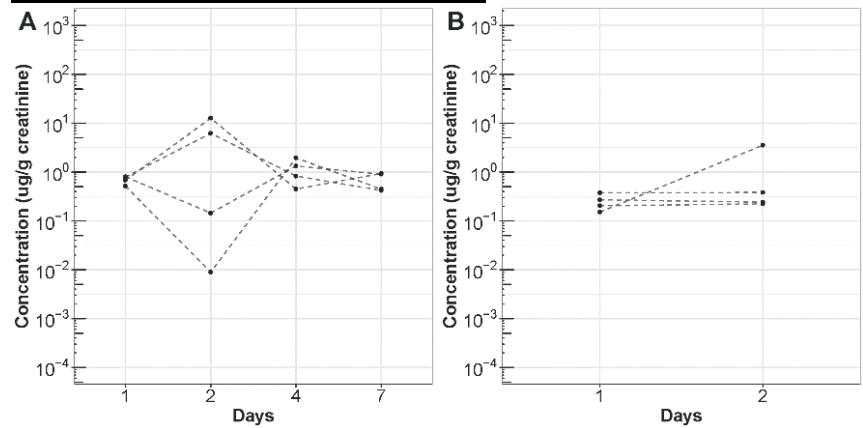


Fig.S3 Chlorpropham (biomarker) concentrations in Use period (A) and Non-use period (B) in the morning urine of residents farmer families. The x-axis represents the days the morning urine was collected. The y-axis represents the concentration in urine in $\mu\text{g/g creatinine}$ on a 10log scale. Each dotted line represents one single individual and each dot is 1 measurement point.

Results from repeated measures correlation:

Use period -> Rho: 0.014/ p-value: 0.964 / 95% confidence interval: [-0.591, 0.609]

Non-use period -> Insufficient pairs

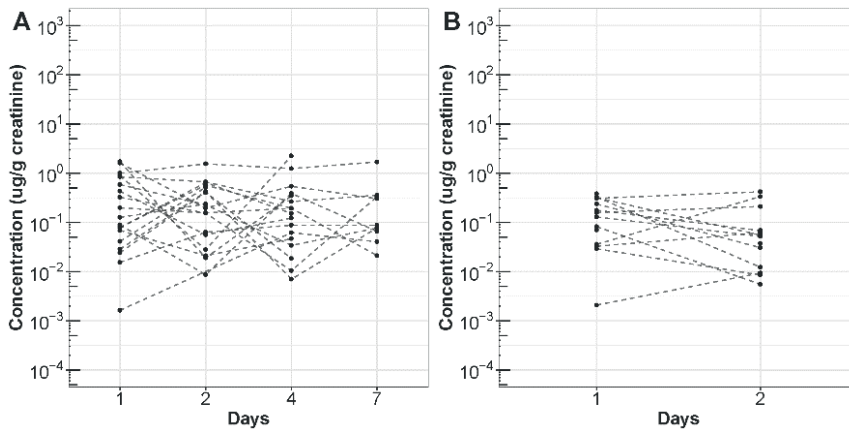


Fig.S4 Tebuconazole (biomarker) concentrations in Use period (A) and Non-use period (B) in the morning urine of residents from Non-farmer families. The x-axis represents the days the morning urine was collected. The y-axis represents the concentration in urine in $\mu\text{g/g}$ creatinine on a 10log scale. Each dotted line represents a subject and each dot is 1 measurement point.

Results from repeated measures correlation:

Use period -> Rho: -0.018 / p-value: 0.905 / 95% confidence interval: [-0.313, 0.280]

Non-use period -> Rho: -0.378 / p-value: 0.202 / 95% confidence interval: [-0.797, 0.286]

Tebuconazole – Farmer families

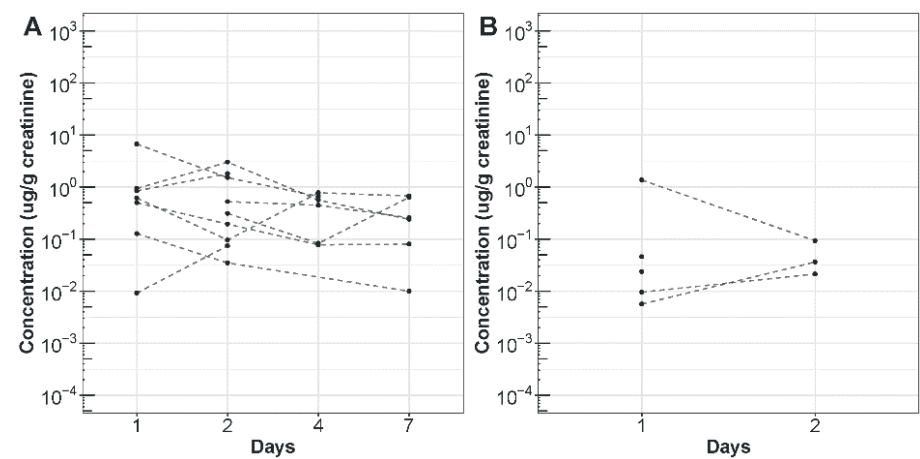


Fig.S5 Tebuconazole (biomarker) concentrations in Use period (A) and Non-use period (B) in the morning urine of residents from farmer families. The x-axis represents the days the morning urine was collected. The y-axis represents the concentration in urine in $\mu\text{g/g}$ creatinine on a 10log scale. Each dotted line represents a subject and each dot is 1 measurement point.

Results from repeated measures correlation:

Use period -> Rho: -0.392 / p-value: 0.087 / 95% confidence interval: [-0.726, 0.091]
Non-use period -> Insufficient pairs

Supplemental material I – Independent variables description

Table S7. List of independent variables included in the univariate and multivariate analyses

Type	Variables	Answer option
Categorical	Use period	Yes / No
	Use pesticides at least once	Yes/ No
	Type of floor = Smooth	Smooth / Rug or Carpet
	Owning pets	Yes/No
	Own a dog	Yes/No
	Own a cat	Yes/No
	Eat vegetables from garden	Yes/No
	Bring shoes inside	Yes/No
	Dry clothes outside	Yes/No
	Can smell pesticides	Yes/No
Numerical	Gender	Male / Female
	Age (y)	not applicable
	BMI (kg/m2)	not applicable
	Average time spent indoors (h)	not applicable
	Number of persons in home	not applicable
	Living room size (m2)	not applicable
	Air changes per hour of the home (1/h)	not applicable

References

1. Bakdash, J. Z., & Marusich, L. R. (2017). Repeated Measures Correlation. *Frontiers in psychology*, 8, 456. <https://doi.org/10.3389/fpsyg.2017.00456>
2. Mol et al., in preparation [methods paper]
3. Oerlemans A, Verscheijden LFM, Mol JGJ, Vermeulen RCH, Westerhout J, Roeleveld N, Russel FGM, Scheepers PTJ. Toxicokinetics of a urinary metabolite of tebuconazole following controlled oral and dermal administration in human volunteers. *Arch Toxicol*. 2019 Jul 29. doi: 10.1007/s00204-019-02523-5.



6

OBOMod - Integrated modelling framework for residents' exposure to pesticides

Daniel Figueiredo^{1*}, Roel Vermeulen^{1, 5}, Cor Jacobs², Henk Jan Holterman³, Jan C. van de Zande³, Frederik van den Berg², Gooijer, Y.M.⁴, Luuk Lageschaar⁴, Daan Buijtenhuijs¹, Esmeralda Krop¹, Anke Huss¹, Jan Duyzer⁶

¹ Institute for Risk Assessment Sciences, Division of Environmental Epidemiology, Utrecht University, Utrecht, the Netherlands

² Wageningen Environmental Research, Wageningen University & Research, Wageningen, the Netherlands

³ Wageningen Plant Research, Wageningen University & Research, Wageningen, the Netherlands

⁴ CLM Onderzoek en Advies BV, P.O. Box 62, 4100 AB, Culemborg, The Netherlands

⁵ Julius Centre for Public Health Sciences and Primary Care, University Medical Centre, Utrecht, the Netherlands

⁶ TNO Circular Economy and the Environment, Utrecht, the Netherlands

Published: Science of The Total Environment, Vol. 825, ID. 153798
doi: 10.1016/j.scitotenv.2022.153798

Abstract

Background: Pesticides can be transported from the site of application to homes via different routes and lead to exposure of residents, raising concerns regarding health effects. We built a deterministic model framework (OBOmod) to assess exposure of residents living near fields where pesticides are applied.

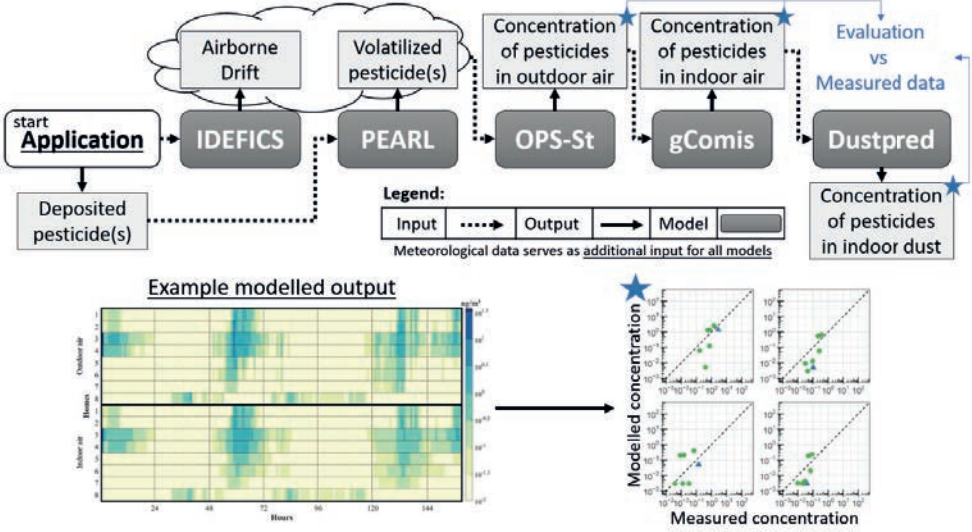
Methods: OBOmod connects five independent models operating on an hourly timescale and high spatial resolution (meters). Models include descriptions of spray drift, volatilization, atmospheric transport and dispersion, exchange between outdoor and indoor air and exchange between indoor air and dust. Fourteen bulb field applications under different weather conditions and comprising 12 pesticides were simulated. Each simulation included the first seven days after the application. The concentrations computed with OBOmod were compared with those measured in outdoor and indoor air and the amounts measured in indoor dust samples.

Results: Model evaluation indicated suitability of the developed framework to estimate outdoor and indoor air concentrations. For most pesticides, model accuracy was good. The framework explained about 30% to 95% of the temporal and spatial variability of air concentrations. For 20% of the simulations, the framework explained more than 35% of spatial variability of concentrations in dust. In general, OBOmod estimates remained within one order of magnitude from measured levels. Calculations showed that in addition to spray drift during application, volatilization from the field after spraying and pesticides in house dust are important routes for residents' exposure to pesticides.

Conclusions: Our framework covers many processes needed to calculate exposure of residents to pesticides. The evaluation phase shows that, with the exception of the dust model, the framework can be used in support of health and epidemiological studies, and can serve as a tool to support development of regulations and policy making regarding pesticide use.

Graphical abstract

OBOMod - Modelling framework to estimate resident's exposure to pesticides from spraying applications



Introduction

Exposure of residents to pesticides

Farmers, operators, workers, residents, and bystanders may be exposed to pesticides. In the past, assessment of the exposure was focussed on operators, workers, and bystanders (Waheed et al. 2017). In the last 10 years however, residents exposure has been an increasingly researched topic (PubMed 2021). This is likely due to growing concern among the population regarding pesticide usage (Calliera et al. 2019, Schaub et al. 2020, Zeitlin et al. 2021). But also due to efforts of policy makers to study residents' exposure (e.g. Health Council of the Netherlands 2014). A recent literature review by Dereumeux et al. stresses two important things: "There is evidence that residents living close to agricultural fields are more exposed to pesticides than the general population"; "Some epidemiological studies suggest an association between proximity to agricultural lands and a wide range of associated adverse health outcomes" (Cited from Dereumeux et al. 2020). Adding to this, it is known that i) part of the exposure of residents to pesticides is attributable to exposure via environmental routes (Cornelis et al. 2009), and ii) contrarily to dietary exposure, much of the environmental exposure is beyond the control of the average individual (Oates & Cohen 2011). These highlights the importance to understand and quantify the environmental exposure routes and feed this knowledge to regulatory entities.

Environmental routes contributing to exposure of residents

There are several environmental routes contributing to exposure of residents (Falette et al. 2018). One of the main routes to exposure of residents, living nearby agricultural fields where pesticides are applied, is the spray drift of pesticides through air (Holterman & van de Zande, 2010). During pesticide application, droplets can evaporate, drift and can remain airborne. Besides depositing on the target area, droplets can drift away and deposit in an off-target area (Steward et al. 2019). The percentage of the active ingredients that drift or evaporate before they reach the plants is highly dependent on physiochemical properties of the pesticides, weather conditions and the spraying conditions (Soheilifard et al. 2020).

A fraction of the deposited ingredient can then volatilize (Van den Berg et al. 1999, Langenbach et al. 2021), depending on its vapor pressure and several other parameters (e.g., absorption capacity to soil, penetration into leaves, degradation rates of the active material). The volatilized substance then moves with the wind (Zivan et al. 2016, Taylor et al. 2019).

The pesticide can then be transported via air in the direction of residences (Veludo et al. 2022) and there infiltrate into the house via openings such as open doors, windows, cracks, chimneys. Concentrations outside and inside the residence tends towards an equilibrium and, in theory, the concentration inside the house may reach the air concentration level outside if volatilization and meteorological conditions remain the same (Sangiorgi et al. 2013). However, this might often not be the case at all because of rapid changes of wind direction, source strength, atmospheric mixing, among others. To estimate short term indoor exposure (sometimes with the highest concentrations) it is also needed to have knowledge of the development of these processes in time, explicitly.

Finally, since in the indoor environment pesticides may be present in the gas-phase they can also be adsorbed to indoor dust particles (Butte, 2004). Dust particles can aggregate, and, in this state, pesticides can accumulate in the indoor environment. This can lead to exposure via contact with contaminated surfaces and/or incidental dust ingestion (Tames et al. 2020).

The need for modelling exposure through the different routes

To combine all of the aforementioned different routes of exposure, for a given spatial scale, models can play an important role: models allow to analyse and quantify exposure to a given pesticide (Butler Ellis et al. 2017), as well as generalize the results of observations and extrapolate results to other places with similar or different settings. Measurements, such as biomonitoring, have proven efficient to understand to what extent residents can be exposed. However, they may suffer from detection problems and limitations to the number of pesticides that can be assessed. In addition, they tend to be very time consuming and costly (Atabila et al. 2019) especially if the aim is to understand exposure of large populations, for many pesticides at the regional or even national scales. Models can be used to make exposure estimates on these scales.

Aim of the study

The aim of our study was to develop a modelling framework to estimate resident's exposure to pesticides from spraying applications. We focused on pesticide application using a boom sprayer since this is the most used technique in the Netherlands, in Europe and worldwide at large-scale farms (Fujimoto et al. 2016). In our framework, here forth named OBOMod, independent models are used to describe the processes in the causal chain of spraying, droplet drift during application, volatilization of deposited pesticides from vegetation and soil during and after spraying, gas and aerosol dispersion, exchange of pesticides between outdoor and indoor air and sorption of pesticides to

house dust. We describe each model individually and how they are connected in the framework. The OBOMod is applied to several case studies on different locations, for different pesticide mixtures and meteorological conditions. This allows us to test the versatility of the framework by simulating distinct real-life scenarios. Case study data with pesticide concentration measurements in outdoor and indoor air, and indoor dust were used to verify model results at different steps along the model chain. The novelty here is the integration of various pathways and evaluation of a framework fit for residential exposure assessment. We show how the OBOMod can be used and provide information so it can be applied in other studies.

Methods

The modelling framework

Five models were selected to build the OBOMod, to quantify contributions from the aforementioned pathways to residents' exposure (Figueiredo et al. 2018). The models are:

- Airborne spray drift: IDEFICS Model. Tests have been reported in several publications, such as Holterman et al. 1997, Holterman et al. 1998, Stallinga et al. 2008.
- Volatilisation: PEARL Model. Tests have been reported in several publications, such as Leistra & Wolters, 2004, Leistra et al., 2005, Leistra and van den Berg, 2007, Van den Berg et al. (2016a).
- atmospheric short term/short range transport: OPS_Ste Model. Tests have been reported in several publications, such as Van Jaarsveld 2004, Sauter et al. 2018. The potential use of OPS for pesticide transport has been highlighted in Van Den Berg et al. 2016 and Buttler Ellis et al. 2017.
- atmospheric transport from outdoors to indoors: gCOMIS Model. Tests have been reported in several publications, such as Phaff 1996, Borchellini & Furbringer 1999.
- sorption of pesticides to indoor dust: DUSTPRED Model. Tests have been reported by Weschler & Nazaroff 2010.

These models are well described in literature and a short explanation of each model can be found in Supplementary material A.

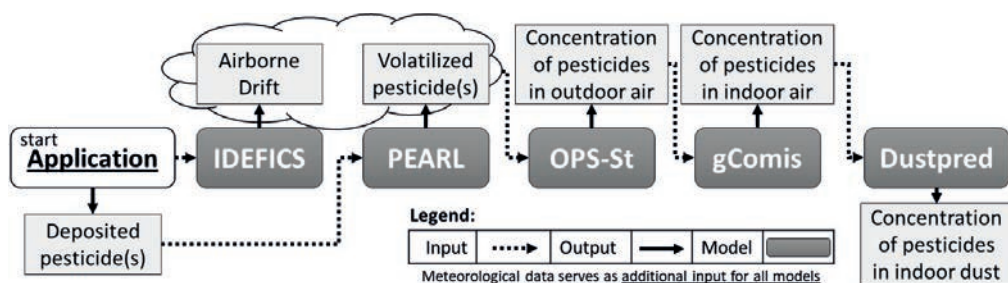


Fig 1. Integrated modelling framework (adapted from Figueiredo et al. 2021a).

As shown in Fig 1, the OBOMod follows the causal chain. It starts with the application where the IDEFICS model (Holterman et al. 1997), describes spray drift and calculates the deposition and concentration of spray droplets in air, up to five meters downwind of the sprayed area. Input to the model is parameters that were collected prior to the spraying event and based upon measurements (e.g. composition of the pesticide mixture in the tank, spray boom height, nozzle type and size and spray drop characteristics). The minimum set of data needed is i) day of spraying; ii) tank mixture; iii) sprayer and nozzle type. It is possible to run the model with “expert decision” input as long as one it’s clear about the quality of the input data. A detailed description of the droplet size distribution for each type of nozzles used in OBOMod can be found in Holterman & van de Zande 2019.

The PEARL model (Van den Berg et al. 2016b), quantifies volatilization from plants after the application. Inputs are physico-chemical properties of the pesticides and an estimate of the amount of deposited material (i.e. applied quantity minus primary drift). Furthermore, the model is driven by meteorological conditions. The computed volatilization is regarded as an emission source strength. Next, the OPS-St (Short term version of the Operational Priority Substances model) advanced Gaussian plume model (Sauter et al., 2015) is used to compute atmospheric transport, dispersion and resulting concentrations at receptor points around the fields. Aerosols already present in the background air were not taken into account. During application, the source strength input to OPS is taken to be the emission of pesticide mass in droplets as computed by IDEFICS at 5 m from the downwind edge of the applied field. IDEFICS can deal with any downwind distance, but larger distances take more computing time. The distance of 5 m was chosen to make sure that larger drops sedimented to the ground and that

only the smaller drops remained airborne. After application, the volatilization strength computed by PEARL is used as a source strength from the applied field. Concentrations calculated with the OPS-St model then serve as input to the ventilation model gComis (Feustel & Raynor-Hooson 1990). This model estimates concentrations in indoor air based on outdoor concentrations, using exchange rates between indoor and outdoor air. These rates are based on building characteristics obtained for each individual home and were assumed to be similar for gas-phase and particle-phase pesticides, given that larger particles will settle before reaching the home. Finally, an equation (Eq. (2) Weschler & Nazaroff 2010), here called Dustpred, is used to calculate the concentration of pesticides that will be present in indoor dust based on indoor air concentrations. All model inputs are described in more detail in (OBO 2019).

Wind erosion of particles from agricultural fields (Silva et al. 2019) was not considered in the modelling chain, since in the Netherlands this process is very unlikely to occur, given the high soil moisture content (Wösten et al. 2001) and the average height of the plant canopy, which serves as a barrier for erosion. For countries with low precipitation and low soil moisture content the wind erosion route might be of relevance, so it would need to be added to the OBOMod. The transport of pesticides via shoes, clothes and pets into the indoor environment was not included in the OBOMod either. Although hypothesized as important (Bradman et al. 2009), no model has been reported in the literature for this exposure route (take-home) of pesticides.

The models in the OBOMod are run independently, that is, they are connected solely via input-output information. Output is generated on an hourly basis, allowing us to look at both short (hours) and long-term (weeks) exposures. Spatial resolution is in meters and the model computes values for a-priori defined grids or receptor points.

General conditions and measured data

Fourteen spraying events under different meteorological conditions and settings and for various pesticide mixtures were simulated (Supplementary material B). All events were real spraying applications planned by the farmer and carried out during the OBO project (OBO 2019). These events occurred on selected fields described in Figueiredo et al. (2021a).

All planned spraying applications were carried out in the North-western part of the Netherlands, an area with intensive flower bulb growing. Spraying was performed in 2016 and 2017 during all months except September, October, November, and December. Temperatures ranged from 1°C in January to 32°C in July but were generally moderate

with an average of 14°C and a median of 16°C. Relative humidity ranged from 65 to 85%. Wind direction was predominantly from SW. Between hour variability was less than 10 degrees for 75% of all simulated hours. Day-to-day variability was high (usually more than 45 degrees). Wind speed during spraying was low in general and usually below 5 m/s at 10 m height (compliant with Dutch regulations for pesticide spraying). These observations were taken from nearby stations from the Dutch meteorological service KNMI. The observed wind speed, during the periods of application, is quite low for this area. But low wind speeds are, understandably, conditions that are favorable for farmers due to lower losses by drift to neighboring crops and surface water. In total, some 20 different active ingredients were sprayed, 45% being fungicides, 25% herbicides and 30% insecticides. These were applied on nine different flower species including tulips and lilies. Usually, sprayed mixtures contained two or three active ingredients. The choice of active ingredients and doses were made by the farmer.

In this study, 24-hour averaged samples of outdoor air were collected for a period of seven days for every home (total number of homes = 96), during and after the spraying event. Air was sampled through a standard PM10 inlet. We used a combination of a filter and XAD absorbent to collect volatile and particle bound pesticides, these were then pooled for chemical analysis. Also, one air sample was collected inside the homes on the day of spraying (i.e. day 1) (Figueiredo et al. 2021b). In addition, one week after the spraying event, one dust sample was collected in every home using a vacuum cleaner equipped with a special filter (Figueiredo et al. 2021c). It was used on a 4 to 6 m² surface depending on the available area (Figueiredo et al. 2019). This, vacuumed floor dust (VFD), is a good representation of pesticides in indoor dust (Curwin et al. 2005) and was used to evaluate the Dustpred model.

All samples were analysed for 46 active ingredients within a few weeks after sampling by using state of the art LC-MS methods (Figueiredo et al. 2021a). All experimental data and the results of our simulations can be found in the OBO technical report (OBO 2019). None of the pesticides were reported as being used indoors in the participating homes (see Supplementary material E from Figueiredo et al. 2021b). All measured pesticides and relevant physico-chemical properties are presented in Table 1.

Table 1. List of measured pesticides (active ingredients) and relevant physico-chemical characteristics.

Type	Pesticides	CAS RN	DT50 Soil ^a	Water solubility ^b	Vapor Pressure ^c
Herbicides	Asulam	3337-71-1	[2.1, 39]	962,000	1.9E-01
	Chloridazon	1698-60-8	[3.0, 173.9]	422	6.0E-02
	Chlorpropham	101-21-3	[2.8, 42.8]	110	2.4E+01
	Dimethenamid-P	163515-14-8	[5.0, 31.0]	1499	2.5E+00
	Linuron	330-55-2	[10.1, 168.4]	63.8	1.9E-01
	Metamitron	41394-05-2	[2.2, 44.5]	1770	8.6E-04
	Pendimethalin	40487-42-1	[39.8, 270.0]	0.33	1.3E+00
	S-metolachlor	51218-45-2	[3.6, 221]	530	4.2E+00
	Sulcotrione	99105-77-8	[1.2, 89.7]	165	5.0E-03
Insecticides	Terbuthylazine	5915-41-3	[6.43, 167.0]	6.6	9.0E-02
	Acetamiprid	135410-20-7	[0.8, 5.4]	2950	5.9E+00
	Cyhalothrin-lambda	91465-08-6	[10.1, 1000.0]	< 1	4.5E-04
	Deltamethrin	52918-63-5	[12.5, 231.0]	< 1	1.2E-05
	Flonicamid	158062-67-0	[0.7, 1.8]	5200	9.4E-04
	Fosthiazate	98886-44-3	[9.0, 17.0]	9000	5.6E-01
	Imidacloprid	138261-41-3	[77.0, 425.0]	610	2.1E-01
	Oxamyl	23135-22-0	[0.6, 19.4]	148,100	3.1E+01
	Pirimicarb	23103-98-2	[5.5, 274.0]	3100	9.7E-01
Fungicides	Pymetrozine	123312-89-0	[2.05, 183.0]	270	1.8E-03*
	Spirotetramat	203313-25-1	[0.05, 1.0]	30	6.0E-06*
	Thiacloprid	111988-49-9	[0.33, 16.8]	184	8.0E-07
	Azoxystrobin	131860-33-8	[35.2, 261.9]	7	1.1E-07
	Boscalid	188425-85-6	[27.0, 1214.4]	5	7.2E-04
	Carbendazim d	10605-21-7	[11.0, 120.0]	8	1.0E-04
	Cyprodinil	121552-61-2	[11.0, 98.0]	13	4.9E-01
	Difenoconazole	119446-68-3	[20.0, 456.0]	15	3.3E-05
	Dimethomorph	110488-70-5	[17.8, 599.1]	29	9.9E-01
Degradation products	Fludioxonil	131341-86-1	[8.0, 365.0]	2	3.9E-04
	Fluopicolide	239110-15-7	[77.0, 333.0]	3	8.0E-04
	Fluopyram	658066-35-4	[93.2, 717.0]	16	4.2E-03
	Flutolanil	66332-96-5	[60.4, 1000.0]	8	1.8E+00
	Kresoxim-methyl	143390-89-0	[0.37, 1.85]	2	2.3E-03
	Mepanipyrim	110235-47-7	[34.0, 253.9]	2	2.3E-02
	Prochloraz	67747-09-5	[22.1, 936.1]	27	1.5E-01
	Propamocarb	24579-73-5	14	900,000	7.3E+03
	Prothioconazole	178928-70-6	[0.04, 1.4]	23	4.5E-09*
Degradation products	Pyraclostrobin	175013-18-0	[4.2, 181.0]	2	2.6E-05
	Tebuconazole	107534-96-3	[25.8, 610.0]	36	1.7E-03
	Thiophanate-methyl	23564-05-8	[0.29, 3.3]	19	9.5E-03
	Toclofos-methyl	57018-04-9	[2.1, 16.4]	< 1	5.7E+01
	Trifloxystrobin	141517-21-7	[0.13, 2.83]	< 1	3.4E-03
	Fluopyram-benzamide	360-64-5	[6.7, 11.5]	ND	ND
	Metamitron-desamino	36993-94-9	[17.0, 39.7]	400	4.5E-04*
	Prothioconazole-desthio	120983-64-4	[4.56, 32.2]	51	1.1E-03*
	Spirotetramat-enol	203312-38-3	[0.02, 10.9]	2700	ND
	Trifloxystrobin-acid	252913-85-2	[21.1, 406.8]	21,000	5.5E-03**

* Estimated using EPI Suite™ (<https://www.epa.gov/tsca-screening-tools/epi-suite™-estimation-program-interface>)

** IUPAC Ref: CGA 321113

^a Half-life (degradation) in soil (days). Range of values from field and lab studies gathered from Lewis et al. 2016

^b Water solubility (at 20 °C [mg l⁻¹], integers presented) gathered from Lewis et al. 2016

^c Vapor pressure in millipascal (measured at 20°C or 25°C, depending on study) – collected from Pubchem (<https://pubchem.ncbi.nlm.nih.gov>)

^d Besides being a fungicide, carbendazim is also an environmental degradation product from thiophanate-methyl
ND (Not determined)

Testing model components of the framework

As a first step, we used measured outdoor air concentrations to test the IDEFICS-PEARL-OPS chain. In this step, we included only applications of which we had all required information (i.e. there was no input data missing). It should be noted that the input data for the PEARL model was obtained from data published in the literature and not by independent measurements. In addition, volatilization was assumed to be the only loss process, so the potential contribution of other processes on the plant surface, such as photo-transformation, penetration into the plant tissue and wash-off were not considered. Especially important here is that, apart from the selected field, no other agricultural field within an area of 250 m from homes applied the same pesticide in the same day. We considered contributions from distances above 250 m to be negligible (Gibbs et al. 2017, Figueiredo et al. 2021b) and we only considered volatilization from treated fields, not from off-target areas where pesticides could have been previously deposited after atmospheric dispersion.

Given that these are evaluation steps we used concentrations measured outside close to the homes as input to the gComis model. The Gcomis model was therefore evaluated by comparing indoor concentrations calculated by gComis to concentrations measured indoors to verify the gComis calculations.

As a last step, we used measured indoor air concentrations to predict daily averaged concentrations of different pesticides in indoor dust and compared the average weekly concentration with the VFD. It should be noted that, VFD may also contain pesticides that accumulated before the sampling period. This aspect may lead to significant differences between calculated and observed concentrations in house dust.

The three evaluation steps

In summary, three model evaluation steps were considered:

- 1) IDEFICS, PEARL and OPS-ST, to calculate, respectively, droplet drift during spraying, volatilization from crop and dispersion of gaseous pesticides on day 1 to 7. The concentrations computed with this model suite are compared with the measured 24-hr (daily) air concentrations outside homes.
- 2) Gcomis, to calculate concentration inside homes on day 1 based upon concentrations measured outside. The concentrations computed with this model are compared with measured 24-hr average air concentrations inside homes.
- 3) Dustpred, to calculate daily content (mass) in house dust from measured concentrations in indoor air. The average concentrations computed with this model are compared with the those measured in VFD inside homes.

From the fourteen simulations, only five had specific pesticide mixtures being applied solely in the selected field (see Simulations 1-5, Supplementary material B). Therefore, evaluation for step 1 was solely done using data from these five applications.

In this way, we used concentrations measured outside the homes, concentrations measured inside homes and concentrations measured in indoor dust to test each submodel in the OBOMod. This approach allows us to reduce uncertainty throughout the model evaluation process, by avoiding errors propagated from other model steps.

Metrics used to assess the quality of model estimates

The statistical measure of the quality of model estimates was determined by the coefficient of determination (R^2 , or explained variance) between measured and modelled concentrations. Two additional metrics were used to assess the difference between modelled and measured values. We calculated the RMSE (Root Mean Squared Error) and the MAE (Mean absolute error). RMSE is analogous to the standard deviation (SD), since it accounts for the magnitude of the residuals, while MAE takes the average magnitude of the residuals. As proposed by Shmueli et al. (2016), we will use SD of the observations as a benchmark to compare with MAE and RMSE, given that SD is the amount of error that naturally occurs in the measured values. Metrics were computed from non-transformed data. Given the small number of paired samples above LOD for acetamiprid, efficiency metrics could not be calculated for this pesticide.

As additional data analysis, we i) investigated if there were systematic discrepancies between the modelled and the measured values (i.e. proportional bias) via modified Bland-Altman plots and ii) calculated Spearman correlation coefficients for gComis and Dustpred evaluation steps. This was done as a sensitivity analysis of model performance. Both indoor air and indoor dust are known to be influenced by sources and sinks present inside the home (e.g. resuspension, long-term accumulation, dragging in), which may cause the relation between measured and modelled data to be non-monotonic. The results from this sensitivity analysis can be consulted in Supplementary material C.

Temporal and spatial variability in concentrations

The quality of a model to estimate concentrations in outdoor air can be judged by looking at temporal (between days) and spatial (between homes) variability. For temporal variability, R^2 , MAE and RMSE were calculated for each pesticide and per home, using daily averages (see Table D.1, Supplementary material D). Scatter plots ($N = 29$) are presented for all measured vs modelled comparisons (see Fig D.1 in Supplementary material D) and a selection of representative cases ($N = 18$) is discussed here.

For spatial variability, R^2 , MAE and RMSE were calculated per pesticide and per day, again using daily averages of concentration (see Table D.2, Supplementary material D). Scatter plots ($N = 48$) were created for all measured vs modelled comparisons and are here discussed.

For indoor air and dust, where we had only one observation per home, metrics were calculated per pesticide but grouping the results from all homes into one single assessment. Here, R^2 refers to the proportion of spatial variability that we can explain with the model. Scatter plots of measured vs modelled data for both indoor air and dust, including all pesticides, can be found in Supplementary material E.

Results

Pesticides - summary of properties and measured concentrations

In the period that the pesticides were used on the selected fields they could be detected in nearly all 24 h outdoor air samples. Pesticide concentrations observed in outdoor air ranged from 0.003 (the detection limit for most pesticides) to 2750 ng/m³. Concentrations observed in indoor air were lower than those in outdoor air ranging from concentrations below the detection limit (<0.003 ng/m³) to 25 ng/m³ on the

day of application (Figueiredo et al. 2021b). Concentrations in vacuum cleaner floor dust ranged from 1 ng/g dust to 27000 ng/g dust (Figueiredo et al 2021c). Based on EFSA guidance documents (EFSA 2014), solely chlorpropham and propamocarb are considered highly volatile compounds (see Table 1, vapor pressure > 10 mPa). The remaining pesticides are considered to have low volatility, although pendimethalin can be considered moderately volatile (Lewis et al. 2016). The half-life of the pesticides in soil (DT50 in Table 1) could also be a parameter that plays a role in the outcome of model simulations. It appears however that the reported half-life in soil is quite variable for most compounds, so we did not take this parameter into account when interpreting results. Finally, 13 of the measured pesticides have high water solubility (i.e. amount of chemical substance that can dissolve in water). These group (see Table 1, water solubility > 500) have higher volatilization potential if the plant leaves are wet, since volatilization occurs at the water – air interface.

Example output of simulations

As an example, we show in detail how the OBomod is setup for one simulation run (Fig 2) for the pesticide trifloxystrobin, a low volatility fungicide used to control diseases such as mildew and blight in flower bulb growing. In the left panel, a field where application takes place is shown and the eight neighbouring study homes. In the right panel, the wind rose, is displayed for each of the seven days after application. These show the frequency of the occurrence of a certain wind direction (degrees) and wind velocity (m/s). Immediately after spraying, volatilization from the field starts and is modelled during the next seven days. Spray drift takes place only during spraying, at Day 1.

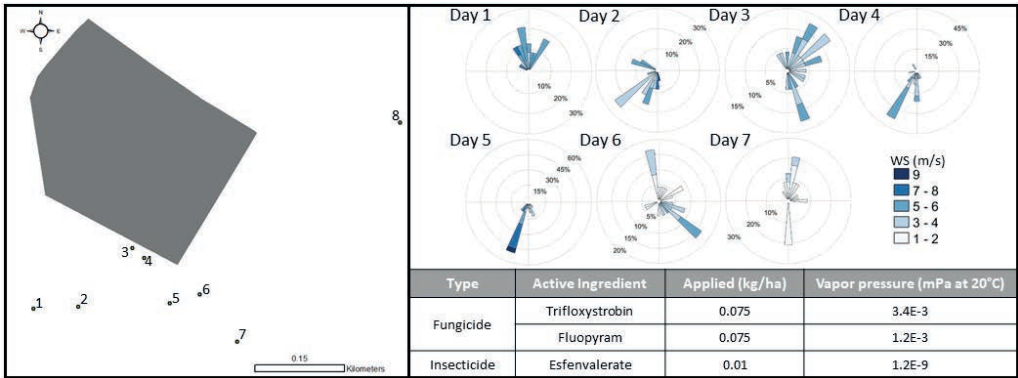


Fig 2. Simulation 4 setup. In the left: The field in grey and the homes as dots. In the upper right: The wind direction (% of the day that was blowing from) and speed (WS – Wind speed) each day during the 7 simulated days. In the bottom right: the applied mixture of pesticides.

Outdoor and indoor air

We can see from the modelled concentration in outdoor and indoor air (Fig 3) that homes downwind of application (homes 1 to 4) are exposed to higher concentrations than other homes during the first hour (when spraying occurs), with homes closer to the field, homes 3 and 4, showing the highest values in outdoor air, 38 and 29 ng/m^3 , respectively.

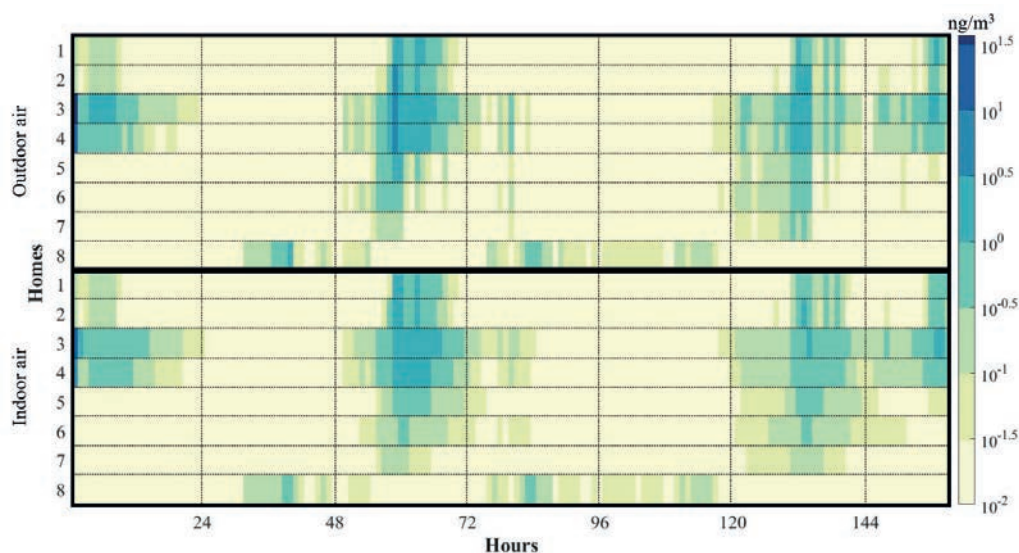


Fig 3. Modelled Trifloxystrobin, hourly averaged, concentration in outdoor air and indoor air for each home. These are the results of simulation 4, which the setup is shown in Fig 2. In the x axis, the hour since application (hour = 1). In the y axis the homes. The colour represents the modelled concentration in ng/m^3 .

On Day 2, the wind direction shifted and blew mainly from the South-West (Right Panel – Fig 2), resulting in an increase of concentration for home 8 (average 0.2 ng/m^3 , Day 2) and almost no exposure near the other homes. Air concentrations vary within the one-week period, by a factor of six between the lowest and highest modelled concentrations. We can see also that modelled concentrations in outdoor and indoor air are very similar.

Spray drift and volatilization

From the modelled trifloxystrobin data we can infer what would be the most relevant exposure route: spray drift or evaporation of active ingredient deposited (afterwards). If we focus on the homes that are predominantly downwind (Left Panel – Fig 1, Homes

1 to 4) from the treated area and take the full week into account, it can be seen that total exposure (defined here as concentration \times hours exposed) via volatilization is higher than the exposure via spray drift (during application). This is illustrated with an example, based on real spraying applications [Supplementary material B, Simulation 4]. In this case, taking cumulative exposure due to volatilization as the multiplication of exposed time (all 7 days) by the arithmetic mean of air concentrations, we end up with concentrations (in ng/m^3) of 20.9, 20.61, 97.2 and 75.1 for homes 1, 2, 3 and 4, respectively. Exposure due to drift, that only happens in the first hour, amounts (in ng/m^3) to 0.26, 0.27, 37.7 and 29.7 for homes 1, 2, 3 and 4, respectively. Thus, for all homes, the exposure caused by drift in the first hour is lower than the cumulative exposure due to volatilization. The result in this example also holds true if we take 7 days median (instead of mean) concentration as hourly exposure.

Indoor dust

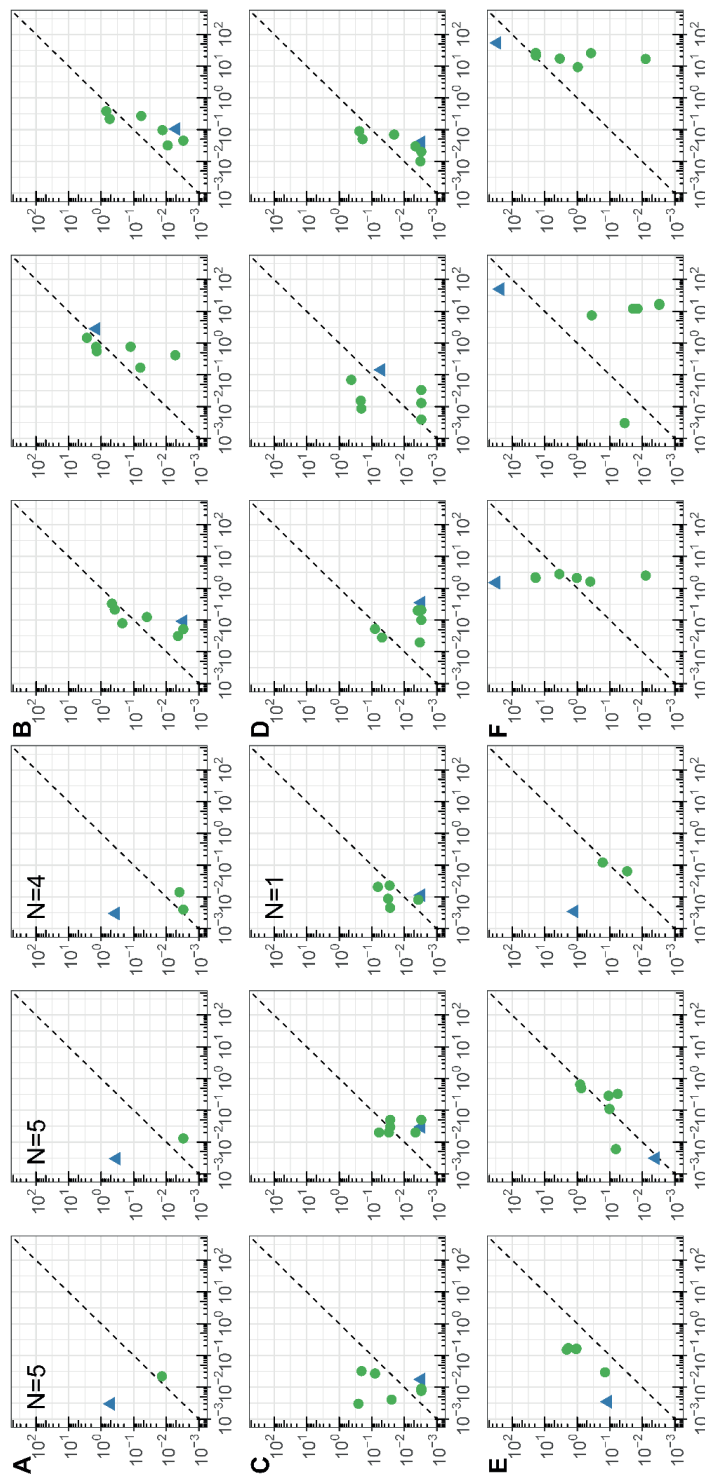
In contrast with concentrations in air, indoor dust concentrations are calculated from daily averaged indoor air concentrations instead of hourly values. The modelled concentrations in dust are quite variable. Large differences occur between the concentrations on different days, with values typically varying between about 10 and 100 ng/g of dust. This variability in modelled values is solely caused by the daily variability of indoor air concentrations (Figure 3), given that the remaining parameters from the Dustpred model are fixed. Modelled trifloxystrobin concentrations in indoor dust can be consulted in Supplementary material F. In short, homes 3 and 4 are consistently more exposed (higher concentrations in dust) than the other homes.

Testing individual model components of the framework

Step 1: Outdoor air

Temporal variability

For several homes (28%) the explained temporal variability (R^2) in concentrations by the model was higher than 0.7. For 24% the R^2 ranged between 0.35 and 0.7 and for the remaining homes the R^2 was below 0.35 (for each individual R^2 see Table D.1 Supplementary material D). A selection of representative cases for model and measured data comparison, per pesticide and per home, is presented in Fig 4. We can see that for some pesticides, such as fluopyram (panel B in Fig. 4) and mepanipyrin (panel E in Fig. 4), most of the data points are close to the 1:1 line, indicating good agreement between measured and modelled data. However, for lower concentrations of fluopyram, the model underestimates concentrations (model < measured). For



Legend: A=Acetamiprid, B= Fluopyram, C= Tebuconazole, D= Trifloxystrobin, E= Mepanipyrim, F= Chlorpropham
Fig 4. Measured versus modelled outdoor air concentrations per pesticide and per home – Selection of 3 examples per pesticide and only cases for which no other applications in the vicinity were done at the same time as the application on the selected field (Simulation 1 to 5). Each panel corresponds to a different pesticide (see legend). Each plot is a different home. For each plot, in the x axis, the measured concentration in ng/m³ and in the y axis, the modelled concentration in ng/m³. Both x and y axis are in the logarithmic scale (base 10). The blue triangle is day 1, the day of spraying. The dashed black line is the 1:1 line (i.e. identity line). N = refers to the number of pairs where both the measured and modelled values are below the detection limit of the targeted pesticide (i.e. concentrations < 0.003 ng/m³).

acetamiprid (panel A in Fig. 4) there is also good agreement, but most of the modelled and measured concentrations are below the detection limit (LOD). The exception here is an overestimation of acetamiprid concentrations in the day of spraying (day 1).

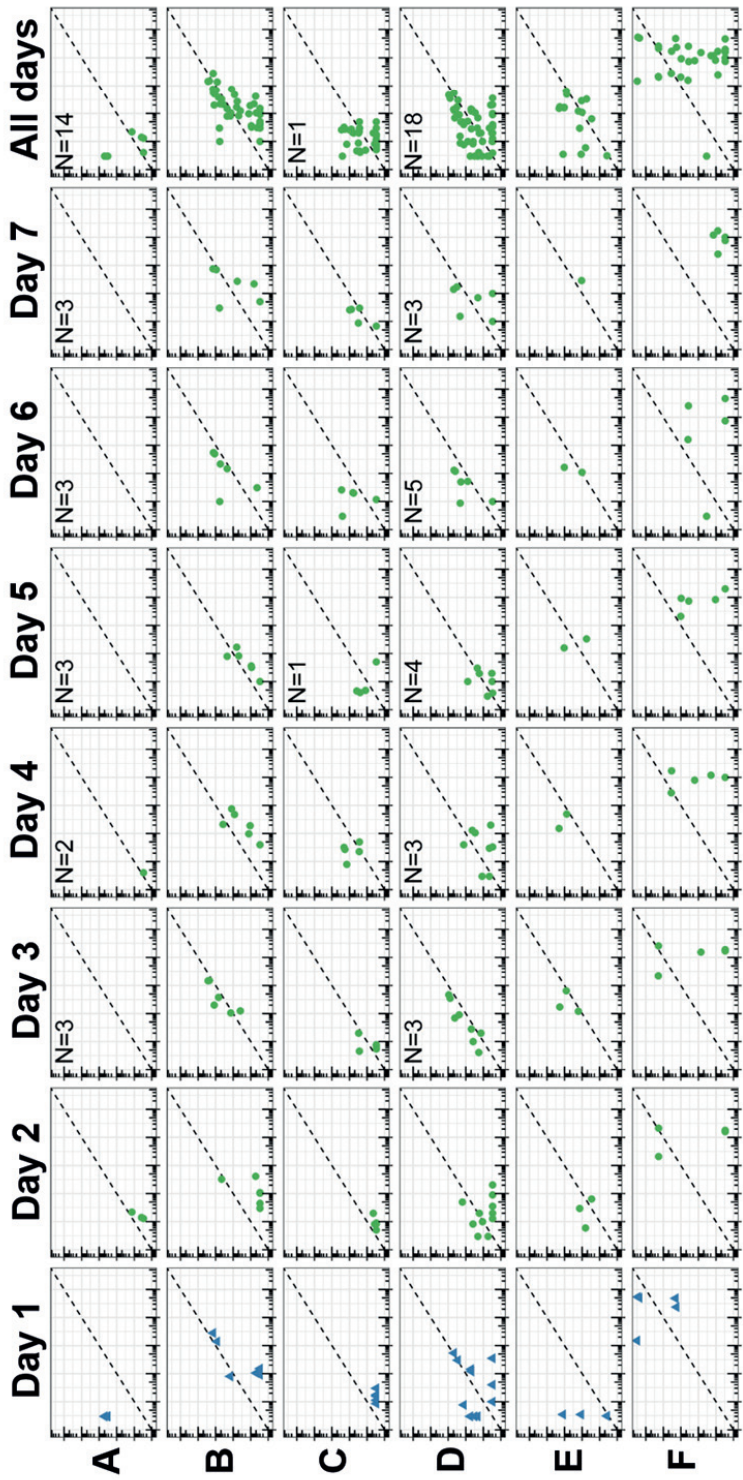
For chlorpropham (panel F in Fig. 4), the model overestimates concentrations in day 1 and underestimates concentrations for all homes in most of the consequent days. Finally, for both tebuconazole (panel C in Fig. 4) and trifloxystrobin (panel D in Fig. 4) we have a similar outcome. For some homes, most of the dots are close to the 1:1 line, whereas for other homes there is a systematic underestimation of concentrations (values below 1:1 line in panel D). All scatter plots and a detailed summary of model quality metrics calculated per pesticide and per home can be consulted in Supplementary material D.

Spatial variability

Modelled and measured data comparisons, per pesticide and per day, are presented in Figure 5. There is a lot of variability on model agreement between the different days, with the R^2 values ranging from 0.05 to 0.995 (see Table D.2 Supplementary material D, for all calculated R^2). There is also quite some variation in model performance between the different pesticides (A to F in Figure 5). For acetamiprid (A in Figure 5), we cannot draw any conclusions on model performance. Although most of the times both modelled and measured values are below the LOD, we do not know how the model performs for very low concentrations ($< \text{LOD}$).

For fluopyram (B in Figure 5), the model explains between 60% to 70% of the spatial variability in concentrations for the first 5 days, but only 15% on the last two days of measurements. The model often underpredicts fluopyram concentrations when measured values are below 10^{-1} ng/m^3 (B – All days, Fig 5). For tebuconazole and trifloxystrobin (C and D in Figure 5, respectively) we see that the explained variance is high for some days, such as days 3 and 6. Whereas for other days the R^2 is quite low, such as days 1 and 4. For mepanipyrim (E in Figure 5), when comparing Day 1 with all days, the model seems to perform reasonably well with the exception on day 1. Finally, for chlorpropham the model seems to explain on average 40% of the spatial variability in concentrations.

Regarding accuracy (i.e. how close the modelled value is to the measured value), the model performs well for fluopyram and trifloxystrobin. Most values are within one SD from the true mean (i.e. $\text{MAE} < \text{SD}$). However, for both of those pesticides (B and D in Figure 5), the RMSE indicates that the deviation between modelled and measured values is not similar on all days ($\text{RMSE} > \text{MAE}$). For tebuconazole (C in Figure 5), most



Legend: A=Acetamidrid, B= Fluopyram, C= Tebuconazole, D= Trifloxystrobin, E= Mepanipyrim, F= Chlorpropham

Fig 5. Modelled vs measured concentration in outdoor air, per pesticide and per day. Each row is a different pesticide (see legend). Each column is a different day. Last column includes all days (day 1 to day 7). For each plot, in the x axis the measured concentration and in the y axis the modelled concentration. Both x and y axis are in the logarithmic scale (base 10). Each point within a plot is the 1:1 line (i.e. identity line). N = refers to the number of pairs where both the measured and modelled values are below the detection limit of the targeted pesticide (concentrations < 0.003 ng/m3).

of the predicted values are in the same order of magnitude as the measured values and are on average around one SD from the mean, except for days 4 and 6. The RMSE indicates that there is not much difference in the magnitude of the residuals (RMSE \approx MAE). For both mepanipyrim and chlorpropham (E and F in Figure 5) most of the predicted values are within the same order of magnitude as the measured values, but the average of residuals is for most cases quite high (MAE \approx between 2 and 4 times the SD). The RMSE indicates that there is not much difference in the magnitude of the residuals (RMSE \approx MAE).

Step 2: Indoor air

Model performance metrics for the gComis evaluation step are presented in Table 2. Here, we can see that for 32% of pesticides the R^2 was above 0.35, while for the remaining 68% was below this value. The average R^2 was 0.3. For most cases ($N = 15$ pesticides) model accuracy is good, given that $MAE < SD$.

Table 2. Estimating indoor air concentrations - model efficiency per pesticide. Pesticides are ordered by vapor pressure (higher to lower).

Pesticide	Paired-N	Measured		Model efficiency		
		Mean	SD	R ²	MAE	RMSE
Propamocarb	4	0.513	0.734	0.968	0.259	0.453
Chlorpropham	16	5.251	6.425	0.018	21.45	37.781
S-Metolachlor	16	0.531	1.045	0.032	0.944	1.396
Fluopyram-benzamide	13	0.056	0.059	0.69	0.103	0.158
Pendimethalin	16	1.49	1.865	0.006	7.496	10.059
Dimethenamid-P	14	0.092	0.075	0.294	0.127	0.208
Tolclofos-methyl	15	1.067	2.758	0.152	0.305	0.523
Prochloraz	12	0.06	0.1	0.348	0.011	0.02
Carbendazim	13	0.372	0.67	0.223	0.176	0.359
Linuron	14	0.027	0.027	0.483	0.047	0.09
Mepanipyrim	6	0.062	0.077	<0.01	0.047	0.088
Trifloxystrobin	6	0.009	0.006	0.155	0.01	0.011
Trifloxystrobin-acid	4	0.073	0.106	0.814	0.173	0.213
Kresoxim-methyl	9	0.062	0.059	0.433	0.042	0.06
Tebuconazole	9	0.132	0.171	0.088	0.1	0.171
Fluopyram	11	0.155	0.26	0.476	0.409	0.803
Flonicamid	10	0.077	0.058	0.251	0.149	0.268
Metamitron	8	0.17	0.216	0.051	0.137	0.233
Boscalid	9	0.031	0.019	0.009	0.015	0.023
Prothioconazole-desthio	14	0.066	0.084	0.261	0.078	0.095
Lambda-cyhalotrin	3	0.079	0.048	0.356	0.035	0.05
Difenoconazole	5	0.075	0.068	0.047	0.086	0.104
Pyraclostrobin	13	0.112	0.217	0.14	0.021	0.03
Deltamethrin	6	0.015	0.009	0.168	0.007	0.009
Azoxystrobin	7	0.069	0.108	<0.01	0.029	0.061

Paired-N – Number of modelled and measured paired values, for the homes with quantifiable samples for the given pesticides (first column). SD – Standard deviation (ng/m³); R² – coefficient of determination (-); MAE – Mean absolute error (ng/m³); RMSE – Root mean square error (ng/m³)

For the remaining 10 pesticides, MAE is 2xSD as a maximum, except for chlorpropham and pendimethalin, where MAE is much higher than SD. For almost all cases (80%) where MAE < SD, RMSE is either lower or quasi-equal to SD. Finally, for almost all pesticides, the RMSE was slightly higher than MAE, indicating that for some homes the predicted values are further away from the measured value compared to other homes (RMSE > MAE). Here, the difference between RMSE and MAE was often lower for less volatile pesticides, such as deltamethrin, pyraclostrobin and difenoconazole.

Step 3: Indoor dust

Results of the Dustpred evaluation step are presented in Table 3. Overall, the capacity to explain spatial variability of pesticide concentrations in indoor dust was low (average R^2 of 0.2). The model explained more than 35% of spatial variability for 4 pesticides out of the 18. Here, $R^2 > 0.75$ for difenoconazole and kresoxim-methyl. For some pesticides (N=8) model accuracy is good, given that MAE < SD. However, for other pesticides, specially more volatile ones such as pendimethalin, s-metolachlor and chlorpropham, MAE can be more than 1 order of magnitude higher than SD. Like the indoor air evaluation step, the difference between RMSE and MAE was often lower for less volatile pesticides, such as azoxystrobin, fludioxonil and flonicamid.

Table 3. Estimating indoor dust concentrations - model efficiency per pesticide. Pesticides are ordered by vapor pressure (higher to lower).

Pesticide	Paired-N	Measured		Model efficiency		
		Mean	SD	R^2	MAE	RMSE
Chlorpropham	9	104	84	0.015	580	1272
S-Metolachlor	5	12	8	0.572	1305	2187
Pendimethalin	27	33	52	0.039	852	1453
Tolclofos-methyl	9	20	14	0.011	18	22
Prochloraz	27	23	29	0.009	24	38
Carbendazim	27	157	140	0.002	134	190
Linuron	6	8	3	0.325	6	9
Kresoxim-methyl	8	29	44	0.769	7	9
Tebuconazole	27	20	30	0.05	13	21
Fluopyram	27	4	9	0.178	15	21
Flonicamid	27	4	7	0.077	7	12
Metamitron	6	75	99	0.149	140	282
Boscalid	27	26	35	0.158	17	27
Prothioconazole-desthio	27	6	12	0.001	23	27
Fludioxonil	4	10	10	0.439	28	32
Difenoconazole	5	13	12	0.911	25	32
Pyraclostrobin	27	44	50	0.04	45	63
Azoxystrobin	12	6	10	0.04	14	22

Paired-N – Number of modelled and measured paired values, for the homes with quantifiable samples for the given pesticides (first column). SD – Standard deviation (ng/m^3); R^2 – coefficient of determination (-); MAE – Mean absolute error (ng/m^3); RMSE – Root mean square error (ng/m^3)

Discussion

In this study, we developed and tested a new modelling framework to estimate residents' exposure to pesticides resulting from boom sprayer applications. Results show the suitability of the framework to estimate concentrations in outdoor and indoor air for different pesticide mixtures and meteorological conditions. Estimating concentrations in indoor dust remains challenging.

Atmospheric transport and dispersion of pesticides

In the first step of the framework evaluation we explained a large portion of the variance in outside air concentrations due to vapor drift during application and vaporization after application. The model seems to tackle well both spatial and temporal variability (day to day variations) for some pesticides, such as fluopyram and mepanipyrim. For other pesticides, like chlorpropham, the explained spatial variance was lower (~40%). Unexplained variance might be related to factors that were not included in the modelling chain, such as: processes on the plant surface, such as photo-transformation, penetration into the plant tissue and wash-off; the effect of the formulation of the pesticide on the vapor pressure of the pesticide, pesticide volatilization from fields planted and sprayed in the periods before or during our study; the influence of obstacles (e.g. built environment); particle-bound pesticides that travel long distances (Sanusi et al. 1999); emissions related to pesticide use in bulb disinfection in the area (Brouwer et al. 1994) or residential use (Deziel et al. 2017).

However, we hypothesize that from these, effects on volatilization from fields and bulb disinfection are the most likely factors influencing air concentration differences between homes at local scale (< 250m) in our setting. Bulb disinfection contribution is also postulated by Figueiredo et al. (2021c) who focused on pesticide concentrations in indoor dust. The other factors are more likely contributors to the overall background of pesticide concentrations (Degrendele et al. 2016) and will hardly affect variance in this study. Hence, most of these compounds will show small concentration gradients outside source areas and consequently will not show large differences in concentration between homes located relatively close to each other (few hundred meters).

Regarding accuracy, the model seems to overall perform reasonably well. Interestingly, within the pesticides sprayed, model accuracy was lower for the more volatile ones, such as chlorpropham. But as mentioned above this could be related to bulb disinfection in the area. Larger residuals for this group might be explained by many of the aforementioned factors that have direct influence on the volatilization processes and therefore have greater effect on the calculations for more volatile pesticides.

Exchange of pesticides between outside and inside air

In the second evaluation step, going from concentrations in outdoor to indoor air, we explained more than 40% of the variance for 8 different pesticides concentrations in the homes. Figueiredo et al. (2021b) showed that, in the studied locations, measured outdoor and indoor concentrations correlated moderately. Therefore, it does not come as a surprise that for several other pesticides we cannot explain more than 30% of the variability in indoor air concentrations between homes. Additionally, some unexplained variability is to be expected, given that not all indoor sources and sinks of pesticides were accounted for. As a source, resuspension of particle-attached pesticides should be included in gComis model and as a sink (i.e. indoor loss processes) deposition and absorption to surfaces, such as walls (Wei et al. 2019) should also be included.

Independently of the above missing sources and sinks, model accuracy was good for nearly all pesticides, with predicted concentrations often lower than one SD from the true mean. A few large deviations were found between modelled and measured concentrations, that could not be explained. However, one hypothesis here is that our model is not predicting the total measured fraction. Our measured samples include pesticides in the gas-phase and absorbed to particles smaller than 10 μm . It is possible that the difference between measured and modelled could be explained by the contribution of particle-attached pesticides that were already present indoors. Apart from those, almost all modelled concentrations were in the same order of magnitude as the ones measured.

In a recent study, Pelletier et al (2017) showed that exposure to semi-volatile organic compounds was mainly driven by indoor concentrations. Therefore, an increase in the precision of estimates of concentration inside homes will reduce the uncertainty in exposure estimates of persons. Here, we show that modelling this step is relevant because concentrations were not equal between indoor and outdoor. The differences varied per pesticide. This step becomes especially important for exposure routes that are largely influenced by indoor air concentrations, such as inhalation and dermal skin uptake (Shi & Zhao 2014). Modelling indoor air concentrations might be less relevant for areas with no local sources, where concentrations are more or less constant and both outdoor and indoor concentrations are equal to background levels.

To the best of our knowledge this is the first time a ventilation model is integrated in an approach to estimate concentrations of pesticides in indoor air. We see that the use of this model is important when estimating quantitative levels, and it is more relevant when looking at a small time-windows of exposure (i.e. finer time resolution), when

balance between both environments is not yet reached. This phenomenon is shown in other studies (e.g. Table 3 - Raeppl et al. 2016). Nevertheless, for epidemiological purposes where relative ranking is the norm, using outdoor air concentrations as a proxy for indoor concentrations could still be valid. This may be concluded from comparisons done between indoor and outdoor concentrations (Figueiredo et al. 2021b) as well as the model simulations done in our study.

Estimating concentrations in indoor dust

In the last evaluation step, when comparing the modelled and measured data, the model could explain only a very small part of the spatial variability in the measured concentrations in VFD. Contrarily from the previous two steps, explained variability was only high for two pesticides, difenoconazole and kresoxim-methyl. Model accuracy was also not as good as the previous two evaluation steps, especially for more volatile pesticides. We found that the main advantage of the model is its simplicity and limited number of input parameters when compared to other more complex models for semi-volatile compounds such as the ones presented by Liang et al. 2019 or Wei et al. 2019. Concentrations in indoor dust are largely driven by the dust-air partition coefficient (used in the Dustpred model). There are however other factors that influence the pesticide presence in VFD. These were not considered due to lack of available data. These include the half-life of the pesticide in the indoor environment (Li et al. 2019), which is known to be quite variable and the influence of the take-home pathway (i.e. pesticides in clothing, shoes and brought by pets) (Teyssiere et al. 2020). The relevance of the latter process is still an unknown. However, by choosing VFD over dust from doormats as evaluation, we minimized the influence of the take home pathway, assuming that most particles get trapped in the doormat.

The main limitation however is not related to these factors, but to the complexity of the dust matrix. Pesticide levels in indoor dust are not just a reflection of current nearby applications but also i) applications done in the past and ii) pesticide use in other areas and transported through air across longer distances (Fuhrmann et al. 2020). These will eventually deposit (settle) indoors (Quirós-Alcalá et al. 2011) and accumulate in indoor dust (Rull & Ritz 2003, Rothlein et al. 2006).

The influence of past applications and degradation on pesticides present in the indoor environment remains one of the most challenging problems. It is key to better understand lifetime exposure of residents via the dermal pathway and inhalation of small contaminated particles.

Estimating residents' exposure to pesticides

Several studies have shown that during spraying, pesticides will drift outside the application area (e.g. Coronado et al. 2011, van de Zande et al. 2012). However, the observation that volatilization leads to detectable concentrations, even seven days after application, also observed by Van den Berg et al. (1995), emphasizes the need to include this route in exposure studies. At the same time, it illustrates the necessity to study differences in exposure resulting from primary drift following application and the exposure resulting from volatilization lasting for days (and perhaps much longer for some pesticides). The latter may as such be a larger contributor to residential exposure than droplet drift during application. This will depend on the pesticide persistence in the environment (Socorro et al. 2016) and physicochemical properties, notably the potential to volatilize. As we have seen in the example provided here, there is a possibility that long-term cumulative exposure to volatilization is higher than cumulative short-term exposures to drift. In a future study we will investigate differences in exposure resulting from primary and secondary drift more systematically by including more pesticides, simulate for more days, multiple applications and different climate scenarios.

The above is an indication that both routes may at least be equally important in evaluation frameworks. Regulation however is focused on reducing spray drift as a means to reduce exposure of surface water and ground level close to fields. Volatilization is not directly affected by these regulations. Therefore, to limit the contribution of volatilization, we would need to reduce the amount sprayed/used or/and use pesticide that degrade faster in the environment, always taking into account possible transformation products. The modelling framework can support the development of guidelines considering not just spray drift but also volatilization (e.g. Boesten et al. 2021).

In general, the modelling framework seems capable of simulating spray drift, vaporization and atmospheric transport and dispersion of different pesticide mixtures for different meteorological conditions reasonably well. The framework explained about 30% to 95% of the temporal and spatial variability of air concentrations, respectively. Environmental concentration estimates given here are likely a better exposure proxy and closer to reality than earlier exposure proxies used for health studies, such as buffers of agricultural fields surrounding homes (e.g. Ward et al. 2006), proximity to fields (e.g. Bukalasa et al. 2017), remote sensing (e.g. Wan 2015) and many others. These exposure proxies do not include the impact of meteorological conditions and physico-chemical properties.

The results of the first two evaluation steps (i.e. estimating outdoor and indoor air concentrations) show moderate to good accuracy of the model for most pesticides, except chlorpropham. This part of the framework currently can be used for estimating exposure of residents to pesticides. This may be done for individual pesticides or mixtures and can include single or multiple fields, depending on existing spraying applications and availability of input data. However, estimating concentrations of pesticides in indoor dust proved to be difficult. This could be related to the adequacy of the Dustpred model for the situations we tried to simulate here. It could be that accumulation of pesticides in dust from previous applications or applications further away plays a large role. So, at this stage, evaluation showed weaknesses in the model for this step and the Dustpred model should only be used for pesticides that degrade rapidly in the environment, thus not being affected by “historical” use, residential use (Meftaul et al. 2020) and long-range transport.

Modelling framework - strengths and limitations

Our modelling framework has several strengths. Firstly, it was developed by collecting already built and verified models and each step was evaluated independently, therefore avoiding possible errors propagated between models. Secondly, the fact that the models are connected solely by input and output gives a great flexibility for improvement and adjustments in future research, as well as for running only parts of the framework if needed. Finally, simplifications can be done in all models to reduce the number of input parameters, adjust resolution (i.e. m to km) and use the model to estimate pesticide exposures for both local and national scales.

Regarding the use of the framework, the model with the largest limitation is the Dustpred model. It is likely related to the inherent complexity of the dust matrix and all factors influencing concentrations in this medium. Nevertheless, as dust can be an important exposure source, additional steps need to be taken to improve indoor dust models through either deterministic or empirical modelling. We know that improvement may be achieved by adding information regarding historical pesticide use, residential use (Glorennec et al. 2017) and the direct influence of indoor sources and sinks, as mentioned by Sukiene et al. (2017), when it becomes available. One of the main problems to also tackle is the take-home pathway (such as drag) (Figueiredo et al. 2021cc).

Other limitations of the framework are related to the volatilization model. In the current version of this model, the effect of the formulation on the behavior of the pesticide on the plant surface is not taken into account. To remedy this, model concepts for the

description of this effect would have to be developed and tested.

In many cases, the required model input is incomplete. Missing values need to be estimated (e.g. Leistra 2011) or obtained from measurements published in the scientific literature or reported in EFSA peer reviews of the active substances of the plant protection product. However, there can be uncertainty in the value for a substance property, such as the vapor pressure, as sometimes different values are reported in the literature. In addition, the lack of information of the effect of the formulation on the actual vapor pressure adds to this uncertainty. It is important to establish what are possible ranges for the input parameters, so as to know how much uncertainty there is in the model chain. The temporal and or spatial resolution of input data, such as meteorological data, needs also further attention as the impact of some variables may not be possible to assess when using data at lower resolution. A sensitivity analysis considering all relevant input variables at different spatial or temporal resolution would help to identify the scale at which these variables should be measured preferably and to define the parts of the model that need further improvement. These steps will be included in future OBOMod iterations.

The use of the model framework depends also on the availability of relevant data. Inclusion of data on these properties, e.g. on other relevant processes on the plant surface, such as penetration of the substance into the plant tissue, photo-transformation and wash-off in the dossiers submitted for registration in the EU would be needed to further improve the assessment of the exposure of residents as a result of agricultural use of pesticides. In a next step, dedicated field experiments on the emission and atmospheric transport of agricultural pesticides are needed to evaluate the improvement of the OBO model framework using the improved set of input values. Also, uncertainty (individual and propagation) as well as sensitivity analysis on certain input parameters will be studied. This hopefully leads to further improvements of the OBOMod.

Concluding remarks

An integrated framework based on different existing deterministic models is used to estimate residents' exposure to pesticides.

We estimated the exposure to pesticides in homes near agricultural sites using models describing air-borne drift, volatilization, atmospheric transport and dispersion, exchange between outdoor and indoor air in residential areas close to treated fields.

From the comparison between modelled and measured concentrations in air we conclude that, in general, the predicted 24-h exposure concentrations of residents to pesticides in air were in the same order of magnitude as those measured. Some studies showed that house dust seems to be an important exposure route. However, predictions of concentrations in this medium remain difficult. Another important finding is that especially for the volatile compounds considered in this study, the cumulative exposure due to volatilization after application may be larger than exposure to droplet drift during application.

The framework can be used in local settings at a range of a few kilometres away from the source to quantitatively estimate exposure via air. The framework can be used for different purposes. It can be used to link to different health outcomes and improve epidemiological studies. It can be used to help public health policy makers by simulating worst case scenarios or integrate with toxicology data to allow for a more complete assessment of human health risk from pesticides. Finally, it can also be used to quantify relative contributions from exposure pathways, and so support development of regulations (e.g. quantity applied) regarding pesticide application.

Acknowledgments

This study was funded by the Dutch Ministry of Infrastructure and Water Management and the Ministry of Agriculture, Nature and Food Quality. This work was commissioned by the Dutch National Institute for Public Health and the Environment (RIVM). We would like to thank all participants and growers for their willingness to participate in this study, the stakeholders for continuous feedback given and all the parties involved in the OBO study group.

References

- Atabila, A., Phung, D. T., Hogarh, J. N., Osei-Fosu, P., Sadler, R., Connell, D., & Chu, C. (2017). Dermal exposure of applicators to chlorpyrifos on rice farms in Ghana. *Chemosphere*, 178, 350–358. <https://doi.org/10.1016/j.chemosphere.2017.03.062>
- Boesten, J. J. T. I., Adriaanse, P. I., Holterman, H. J., ter Horst, M. M. S., Tiktak, A., van der Zande, J. C., & Wipfler, L. (2021). Scenarios for exposure of aquatic organisms to plant protection products in the Netherlands: Part 2: Sideways and upward spraying in Dutch fruit crops (final report). (Wageningen Environmental Research report; No. 3100). Wageningen Environmental Research. <https://doi.org/10.18174/549658>
- Borchiellini R., Furbinger J., 1999: "An evaluation exercise of a multizone air flow model." *Energy and Buildings*, Vol 30, No 1,35-5 1
- Bradman, A., Salvatore, A., Boeniger, M. et al. Community-based intervention to reduce pesticide exposure to farmworkers and potential take-home exposure to their families. *J Expo Sci Environ Epidemiol* 19, 79–89 (2009). <https://doi.org/10.1038/jes.2008.18>
- Brouwer, D. H., Brouwer, E. J., & van Hemmen, J. J. (1994). Estimation of long-term exposure to pesticides. *American Journal of Industrial Medicine*, 25(4), 573–588. <https://doi.org/10.1002/ajim.4700250411>
- Bukalasa, J.S., Brunekreef, B., Brouwer, M., Vermeulen, R., de Jongste, J.C., van Rossem, L., Vonk, J.M., Wijga, A., Huss, A., Gehring, U., 2017. Proximity to agricultural fields as proxy for environmental exposure to pesticides among children: the PIAMA birth cohort. *Sci. Total Environ.* 595, 515–520. <https://doi.org/10.1016/j.scitotenv.2017.03.269>
- Butler Ellis, M. C., van de Zande, J. C., van den Berg, F., Kennedy, M. C., O'Sullivan, C. M., Jacobs, C. M., Fragkoulis, G., Spanoghe, P., Gerritsen-Ebben, R., Frewer, L. J., & Charistou, A. (2017). The BROWSE model for predicting exposures of residents and bystanders to agricultural use of plant protection products: An overview. *Biosystems Engineering*, 154, 92–104. <https://doi.org/10.1016/j.biosystemseng.2016.08.017>
- Butte, W. (2004). Sources and Impacts of Pesticides in Indoor Environments. *Handbook of Environmental Chemistry*, 4, 89–116. <https://doi.org/10.1007/b94832>
- Calliera, M., Luzzani, G., Sacchettini, G., & Capri, E. (2019). Residents perceptions of non-dietary pesticide exposure risk. Knowledge gaps and challenges for targeted awareness-raising material in Italy. *Science of the Total Environment*, 685(June), 775–785. <https://doi.org/10.1016/j.scitotenv.2019.06.223>
- Cornelis, C., Schoeters, G., Kellen, E., Buntinx, F., & Zeegers, M. (2009). Development of a GIS-based indicator for environmental pesticide exposure and its application to a Belgian case-control study on bladder cancer. *International Journal of Hygiene and Environmental Health*, 212(2), 172–185. <https://doi.org/10.1016/j.ijheh.2008.06.001>
- Coronado, G. D., Livaudais, J., Hanisch, R., & Tekeste, T. (2011). Take-Home Route of Pesticide

- Exposure. *Encyclopedia of Environmental Health*, 1, 312–324. <https://doi.org/10.1016/B978-0-444-52272-6.00641-3>
- Curwin, B. D., Hein, M. J., Sanderson, W. T., Nishioka, M. G., Reynolds, S. J., Ward, E. M., & Alavanja, M. C. (2005). Pesticide contamination inside farm and nonfarm homes. *Journal of Occupational and Environmental Hygiene*, 2(7), 357–367. <https://doi.org/10.1080/15459620591001606>
- Degrendele, C., Okonski, K., Melymuk, L., Landlová, L., Kukučka, P., Audy, O., ... Klánová, J. (2016). Pesticides in the atmosphere: A comparison of gas-particle partitioning and particle size distribution of legacy and current-use pesticides. *Atmospheric Chemistry and Physics*, 16(3), 1531–1544. <https://doi.org/10.5194/acp-16-1531-2016>
- Dereumeaux, C., Fillol, C., Quenel, P., & Denys, S. (2020). Pesticide exposures for residents living close to agricultural lands: A review. *Environment International*, 134 (November 2019), 105210. <https://doi.org/10.1016/j.envint.2019.105210>
- Deziel, N. C., Beane Freeman, L. E., Graubard, B. I., Jones, R. R., Hoppin, J. A., Thomas, K., ... Friesen, M. C. (2017). Relative contributions of agricultural drift, para-occupational, and residential use exposure pathways to house dust pesticide concentrations: Meta-regression of published data. *Environmental Health Perspectives*, 125(3), 296–305. <https://doi.org/10.1289/EHP426>
- EFSA (European Food Safety Authority), 2014. Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. *EFSA Journal* 2014;12(10):3874, 55 pp.12, <https://doi.org/10.2903/j.efsa.2014.3874>
- Falette, N., Kiss, A., Bayle, M.-L., Bouaoun, L., Scalbert, A., & Fervers, B. (2018). Seasonal variations of exposure to agricultural pesticides in residents proximate to vineyards: SIGEXPOSOME study. *Revue d'Épidémiologie et de Santé Publique*, 66, S340. <https://doi.org/10.1016/j.respe.2018.05.279>
- Feustel, H. E., & Raynor-Hooson, A. (1990). COMIS Fundamentals. Air Infiltration and Ventilation Centre, Technical Note 29, Lawrence Berkeley Laboratory Report, LBL-28560.
- Figueiredo, D. M., Vermeulen, R. C., Duyzer, J. (2018). An integrated modelling framework to estimate residents exposure to pesticides from boom sprayer applications. ISEE Young conference. <https://doi.org/10.1136/oemed-2018-iseeabstracts.84>
- Figueiredo, D. M., Nijssen, R., Krop, E., Buijtenhuijs, D., Duyzer, J., Huss, A., Mol, H., Vermeulen, R. C. H. (2019). Pesticides in indoor dust – A possible important route for residents' exposure, *Environmental Epidemiology*: October 2019 - Volume 3 - Issue - p 122 <https://doi.org/10.1097/01.EE9.0000607072.50712.0a>
- Figueiredo, D. M., Krop, E. J., Duyzer, J., Gerritsen-Ebben, R. M., Gooijer, Y. M., Holterman, H. J., Huss, A., Jacobs, C. M., Kivits, C. M., Kruijne, R., Mol, H. J., Oerlemans, A., Sauer, P. J., Scheepers, P. T., van de Zande, J. C., van den Berg, F., Wenneker, M., & Vermeulen, R. C. (2021a). Research on exposure of residents to pesticides in The Netherlands: Study Protocol (Preprint). *JMIR Research Protocols*, 10. <https://doi.org/10.2196/27883>
- Figueiredo, D. M., Duyzer, J., Huss, A., Krop, E. J. M., Gooijer, Y., & Vermeulen, R. C. H. (2021b). Spatio-temporal variation of outdoor and indoor pesticide air concentrations in homes near

- agricultural fields. *Atmospheric Environment*, 262(June), 118612. <https://doi.org/10.1016/j.atmosenv.2021.118612>
- Figueiredo, D. M., Nijssen, R., Krop, E. J. M., Buijtenhuijs, D., Gooijer, Y., Lageschaar, L., Duyzer, J., Huss, A., Mol, H., Vermeulen, R. C.H. (2021c). Pesticides in Doormat and Floor Dust from Homes Close to Treated Fields: Spatio-Temporal Variance and Determinants of Occurrence and Concentrations (2021). <http://dx.doi.org/10.2139/ssrn.3951730>
- Freeman, L. E. B., Bonner, M. R., Blair, A., Hoppin, J. A., Sandler, D. P., Lubin, J. H., ... Alavanja, M. C. R. (2005). Cancer incidence among male pesticide applicators in the agricultural health study cohort exposed to diazinon. *American Journal of Epidemiology*, 162(11), 1070–1079. <https://doi.org/10.1093/aje/kwi321>
- Fuhrmann, S., Klánová, J., Přibyllová, P., Kohoutek, J., Dalvie, M. A., Rössli, M., Degrendele, C., 2020. Qualitative assessment of 27 current-use pesticides in air at 20 sampling sites across Africa.. *Chemosphere* 258, 127–333. <https://doi.org/10.1016/j.chemosphere.2020.127333>
- Fujimoto, A., Satow, T., & Kishimoto, T. (2016). Simulation of spray distribution with boom sprayer considering effect of wind for agricultural cloud computing analysis. *Engineering in Agriculture, Environment and Food*, 9(4), 305–310. <https://doi.org/10.1016/j.eaef.2016.04.001>
- Gibbs, J.L., Yost, M.G., Negrete, M., Fenske, R.A., 2017. Passive sampling for indoor and outdoor exposures to chlorpyrifos, azinphos-methyl, and oxygen analogs in a rural agricultural community.. *Environ. Health Perspect.* 125, 333–341. <https://doi.org/10.1289/ehp425>
- Glorennec, P., Serrano, T., Fravallo, M., Warembourg, C., Monfort, C., Cordier, S., ... Chevrier, C. (2017). Determinants of children's exposure to pyrethroid insecticides in western France. *Environment International*, 104(April), 76–82. <https://doi.org/10.1016/j.envint.2017.04.007>
- Health Council of the Netherlands. Crop protection and local residents. The Hague: Health Council of the Netherlands, 2014; publication no. 2014/02E
- Holterman, H.J., Zande, J.C. van de, Porskamp, H.A.J., Huijsmans, J.F.M. 1997. Modelling spray drift from boom sprayers. *Computers and Electronics in Agriculture* 19(1997): p1-22.
- Holterman H J, Michielsen J M G P, Van de Zande J C. 1998. Spray drift in crop protection: validation and usage of a drift model. Paper presented at the International Conference on Agricultural Engineering (AgEng), Oslo (Norway), August 24-27, 1998, Paper no. 98-A-012, 9 pp
- Holterman, H.J. & J.C. van de Zande, 2010. The Cascade Drift Model: First results of a realistic study on regional pesticide deposition. *Aspects of Applied Biology* 99, International advances in pesticide application. 2010. 367-374. <https://edepot.wur.nl/169059>
- Holterman, H.J., van de Zande, J.C. 2019. Spray drift simulations to estimate the exposure of residents to pesticides close to a sprayed field. Wageningen Research, Report WPR-878. <https://doi.org/10.18174/467149>
- Langenbach, T., de Campos, T.M.P., & Caldas, L.Q. (2021). Why Airborne Pesticides Are So Dangerous [Online First], IntechOpen, <https://doi.org/10.5772/intechopen.95581>
- Leistra, M., Wolters A. (2004). Computations on the volatilisation of the fungicide fenpropimorph

- from plants in a wind tunnel. *Water Air Soil Pollut.*, 157, pp. 133-148. <https://doi.org/10.1023/B:WATE.0000038883.86688.83>
- Leistra, M., Smelt, J.H. and F. van den Berg, 2005. Measured and computed volatilisation of the fungicide fenpropimorph from a sugar beet crop. *Pest Management Science* 61: 151-158. <https://doi.org/10.1002/ps.964>
- Leistra, M. and F. van den Berg, 2007. Volatilization of parathion and chlorothalonil from a potato crop simulated by the PEARL model. *Environ. Sci. Technol.* 41: 2243-2248. <https://doi.org/10.1021/es0627242>
- Leistra, M., 2011. Methods for estimating the vapour pressure of organic chemicals. Report 2215. Alterra, Wageningen, the Netherlands
- Lewis, K.A., Tzilivakis, J., Warner, D. and Green, A. (2016) An international database for pesticide risk assessments and management. *Human and Ecological Risk Assessment: An International Journal*, 22(4), 1050-1064. <https://doi.org/10.1080/10807039.2015.1133242>
- Li, L., Qiu, Y., Gustafsson, Å., Krais, A. M., Weiss, J. M., Lundh, T., & Bergman, Å. (2019). Characterization of residential household dust from Shanghai by particle size and analysis of organophosphorus flame retardants and metals. *Environmental Sciences Europe*, 31(1). <https://doi.org/10.1186/s12302-019-0279-9>
- Liang, Y., Bi, C., Wang, X., & Xu, Y. (2019). A general mechanistic model for predicting the fate and transport of phthalates in indoor environments. *Indoor Air*, 29(1), 55–69. <https://doi.org/10.1111/ina.12514>
- Meftaul, I. M., Venkateswarlu, K., Dharmarajan, R., Annamalai, P., & Megharaj, M. (2020). Pesticides in the urban environment: A potential threat that knocks at the door. *Science of the Total Environment*, 711, 134612. <https://doi.org/10.1016/j.scitotenv.2019.134612>
- Oates, L., & Cohen, M. (2011). Assessing diet as a modifiable risk factor for pesticide exposure. *International journal of environmental research and public health*, 8(6), 1792–1804. <https://doi.org/10.3390/ijerph8061792>
- OBO (2019). Research on exposure of residents to pesticides in the Netherlands: OBO flower bulbs. <https://www.rijksoverheid.nl/binaries/rijksoverheid/documenten/rapporten/2019/04/10/bijlage-1-onderzoeksrapport-obo/bijlage-1-onderzoeksrapport-obo.pdf>
- Pelletier, M., Bonvallot, N., Ramalho, O., Mandin, C., Wei, W., Raffy, G., ... Glorennec, P. (2017). Indoor residential exposure to semi-volatile organic compounds in France. *Environment International*, 109(September), 81–88. <https://doi.org/10.1016/j.envint.2017.08.024>
- Phaff, J.C., 1996. "Final Report Annex 23 - Multizone Ventilation Models: Participation of TNO Bouw. Examples," Report 96-BB1-R1086. TNO
- Pubmed 2021. <https://pubmed.ncbi.nlm.nih.gov/?term=pesticide+exposure+resident> [accessed on 30-09-2021]
- Quirós-Alcalá, L., Bradman, A., Nishioka, M., Harnly, M. E., Hubbard, A., Mckone, T.E., Ferber, J., Eskenazi, B. (2011). Pesticides in house dust from urban and farmworker households in California: An observational

- measurement study. *Environ. Health* 2011, <https://doi.org/10.10186/1476-069X-10-19>
- Raeppele, C., Salqu bre, G., Millet, M., & Appenzeller, B. M. R. (2016). Pesticide detection in air samples from contrasted houses and in their inhabitants' hair. *Science of The Total Environment*, 544, 845–852. <https://doi.org/10.1016/j.scitotenv.2015.12.020>
- Rothlein, J., Rohlman, D., Lasarev, M., Phillips, J., Muniz, J & Linda McCauley (2006). Organophosphate Pesticide Exposure and Neurobehavioral Performance in Agricultural and Nonagricultural Hispanic Workers. *Environmental Health Perspectives* 114:5 CID: <https://doi.org/10.1289/ehp.8182>
- Rull, R. P., & Ritz, B. (2003). Historical pesticide exposure in California using pesticide use reports and land-use surveys: An assessment of misclassification error and bias. *Environmental Health Perspectives*, 111(13), 1582–1589. <https://doi.org/10.1289/ehp.6118>
- Sangiorgi, G., Ferrero, L., Ferrini, B. S., Lo Porto, C., Perrone, M. G., Zangrando, R., ... Bolzacchini, E. (2013). Indoor airborne particle sources and semi-volatile partitioning effect of outdoor fine PM in offices. *Atmospheric Environment*, 65, 205–214. <https://doi.org/10.1016/j.atmosenv.2012.10.050>
- Sanusi, A., Millet, M., Mirabel, P., & Wortham, H. (1999). Gas-particle partitioning of pesticides in atmospheric samples. *Atmospheric Environment*, 33(29), 4941–4951. [https://doi.org/10.1016/S1352-2310\(99\)00275-7](https://doi.org/10.1016/S1352-2310(99)00275-7)
- Sauter, F., M. van Zanten, E. van der Swaluw, J. Aben, F.de Leeuw, H.van Jaarsveld (2015). 'The OPS-model. Description of OPS 4.5.0', Bilthoven, Rijksinstituut voor Volksgezondheid en Milieu, <http://www.rivm.nl/media/ops/OPS-model.pdf>
- Sauter, F., Van Zanten, M., Van der Swaluw, E., Aben, J., De Leeuw, F., Van Jaarsveld, H. (2018). The OPS-Model. Description of OPS 4.5.2. RIVM (National Institute for Public Health and the Environment), Bilthoven. <https://www.rivm.nl/media/ops/v4.5.2/OPS-model-v4.5.2.pdf>
- Schaub, S., Huber, R., Finger, R (2020). Tracking societal concerns on pesticides – a Google Trends analysis *Environ. Res. Lett.* 15 084049. <https://doi.org/10.1088/1748-9326/ab9af5>
- Shi, S., Li, Y., & Zhao, B. (2014). Deposition velocity of fine and ultrafine particles onto manikin surfaces in indoor environment of different facial air speeds. *Building and Environment*, 81, 388–395. <https://doi.org/10.1016/j.buildenv.2014.07.017>
- Silva, V., Mol, H. G. J., Zomer, P., Tienstra, M., Ritsema, C. J., & Geissen, V. (2019). Pesticide residues in European agricultural soils – A hidden reality unfolded. *Science of The Total Environment*, 653, 1532–1545. <https://doi.org/10.1016/j.scitotenv.2018.10.441>
- Shmueli, G., Bruce, P. C., Stephens, M., & Patel, N. R. (2016). *Data Mining for Business Analytics: Concepts, Techniques, and Applications with JMP Pro* (3rd Edition). Wiley.
- Socorro, J., Durand, A., Temime-Roussel, B., Gligorovski, S., Wortham, H & Quivet, E. (2016) The persistence of pesticides in atmospheric particulate phase: An emerging air quality issue. *Sci. Rep.* 6, 33456; <https://doi.org/10.1038/srep33456>
- Soheilifard, F., Afshin, M., Raini, M.G., Taki, M., van Zelm, R., 2020. Chemical footprint of pesticides used in citrus orchards based on canopy deposition and off-target losses. *Science of The Total*

- Environment 732, 118–139. <https://doi.org/10.1016/j.scitotenv.2020.139118>
- Stallinga, H., Holterman, H. J., Michielsen, J. G. P., & van Velde, P. (2008). A two-year experimental study on airborne drift using active and passive sampling. 1-8. In: Applied Biology 84. Alexander, L. S., Carpenter, P. I., Cooper, S. E., Glass, C. R., Andersen, P. G., Magri, B., Robinson, T. H., Stock, D., Taylor, W. A., Thornhill, E. W. & Zande, J. C. (eds.). Warwick, UK: Association of Applied Biologists, Vol. 84. p. 1-8
- Steward, B. L., Hanna, H. M., Dixon, P. M., & Mompremier, R. K. (2019). Measuring and modelling the movement of spray droplets into off-target areas. 2019 ASABE Annual International Meeting. 1901496. <https://doi.org/10.13031/aim.201901496>
- Sukiene, V., von Goetz, N., Gerecke, A.C., Bakker, M.I., Delmaar, C.J., Hungerbuhler, K. (2017). Direct and air-mediated transfer of labeled SVOCs from indoor sources to dust. Environ. Sci. Technol. 51 (6), 3269–3277.
- Tames, F., Miglioranza, K. S. B., Nuñez, M. R., & Carreras, H. (2020). Indoor persistent organic pollutants in agricultural areas from Argentina. Indoor Air, (January), 1–10. <https://doi.org/10.1111/ina.12649>
- Taylor, M., Lyons, S. M., Davie-Martin, C. L., Geoghegan, T. S., & Hageman, K. J. (2020). Understanding Trends in Pesticide Volatilization from Agricultural Fields Using the Pesticide Loss via Volatilization Model. Environmental Science & Technology, 54(4), 2202–2209. <https://doi.org/10.1021/acs.est.9b04762>
- Teyssie R, Manangama G, Baldi I, Carles C, Brochard P, Bedos C, et al. (2020) Assessment of residential exposures to agricultural pesticides: A scoping review. PLoS ONE 15(4): e0232258. <https://doi.org/10.1371/journal.pone.0232258>
- Tsatsakis, A., Tyshko, N. V., Docea, A. O., Shestakova, S. I., Sidorova, Y. S., Petrov, N. A., ... Tutelyan, V. A. (2019). The effect of chronic vitamin deficiency and long term very low dose exposure to 6 pesticides mixture on neurological outcomes – A real-life risk simulation approach. Toxicology Letters, 315(May), 96–106. <https://doi.org/10.1016/j.toxlet.2019.07.026>
- Van den Berg, F., R. Kubiak, W.G. Benjey, M.S. Majewski, S.R. Yates, G.L. Reeves, J.H. Smelt, A.M.A. Van der Linden, 1999. Emission of pesticides into the air. Water, Air and Soil Pollution 115: 195–218. <https://doi.org/10.1023/A:1005234329622>
- van den Berg, F., Bor, G., Smidt, R. A., van de Peppel-Groen, A. E., Smelt, J. H., Müller, T. & Maurer, T., 1995, Volatilization of parathion and chlorothalonil after spraying onto a potato crop. Wageningen: DLO Winand Staring Centre. 59 p.
- van den Berg, F. C.M.J. Jacobs, M.C. Butler-Ellis, P. Spanoghe, P., K. Doan Ngoc and G. Fragkoulis, (2016a). Modelling exposure of workers, residents and bystanders to vapour of plant protection products after application to crops. Sci. Total Environ. 573, 1010-1020. <https://doi.org/10.1016/j.scitotenv.2016.08.180>
- van den Berg, F., Tiktak, A., Boesten, J. J. T. I., & van der Linden, A. M. A. (2016b). PEARL model for pesticide behaviour and emissions in soil-plant system: description of processes. Wageningen: Statutory Research Tasks Unit for Nature & the Environment (Wot-technical report 61) – 134.

- Van Jaarsveld J.A. (2004) Description and validation of OPS-Pro 4.1, RIVM report 500045001/2004. <https://www.rivm.nl/bibliotheek/rapporten/500045001.pdf>
- Veludo, A.F., Figueiredo, D.M., Degrendele, C., Masinyana, L., Curchod, L., Kohoutek, J., Kukučka, P., Martiník, J., Příbylová, P., Klánová, J., Dalvie, M.A., Rösli, M., Fuhrmann, S., 2022. Seasonal variations in air concentrations of 27 organochlorine pesticides (OCPs) and 25 current-use pesticides (CUPs) across three agricultural areas of South Africa. *Chemosphere* 289, 133–162. <https://doi.org/10.1016/j.chemosphere.2021.133162>
- Waheed, S., Halsall, C., Sweetman, A. J., Jones, K. C., & Malik, R. N. (2017). Pesticides contaminated dust exposure, risk diagnosis and exposure markers in occupational and residential settings of Lahore, Pakistan. *Environmental Toxicology and Pharmacology*, 56(November), 375–382. <https://doi.org/10.1016/j.etap.2017.11.003>
- Wan, N. (2015). Pesticides exposure modeling based on GIS and remote sensing land use data. *Applied Geography*, 56, 99–106. <https://doi.org/10.1016/j.apgeog.2014.11.012>
- Ward M. H., Lubin J., Giglierano J., Colt J. S., Wolter C., Bekiroglu N., Camann D., Hartge P., Nuckols J. R.. Proximity to crops and residential exposure to agricultural herbicides in Iowa, *Environ. Health Perspect.*, 2006, vol. 114 6 (pg. 893-897)
- Wei, W., Ramalho, O., & Mandin, C. (2019). A long-term dynamic model for predicting the concentration of semi-volatile organic compounds in indoor environments: Application to phthalates. *Building and Environment*, 148(October 2018), 11–19. <https://doi.org/10.1016/j.buildenv.2018.10.044>
- Weschler, C. J., & Nazaroff, W. W. (2010). SVOC partitioning between the gas phase and settled dust indoors. *Atmospheric Environment*, 44(30), 3609–3620. <https://doi.org/10.1016/j.atmosenv.2010.06.029>
- Wösten J.H.M., Veerman G.J., De Groot W.J.M., Stolte J. 2001. Waterretentie- en doorlatendheidskarakteristieken van boven- en ondergronden in Nederland: de Staringreeks - Vernieuwde uitgave 2001. Wageningen: Alterra. Report no. 153. 86 pp. <https://www.wur.nl/nl/Publicatie-details.htm?publicationId=publication-way-333133353539>
- Zande, J.C. van de, H.J. Holterman & J.F.M. Huijsmans (2012). Spray drift assessment of exposure of aquatic organisms to plant protection products in the Netherlands. Part 1: Field crops and downward spraying. Wageningen UR Plant Research International, Plant Research International Report 419, Wageningen. 84p. <https://edepot.wur.nl/243240>
- Zeitlin, Jonathan and Weimer, Maria and van der Duin, David and Kuhn, Theresa and Jensen, Martin Dybdahl, Reforming EU Pesticides Regulation, Rebuilding Public Support: Evidence from Survey Experiments in Six Member States (June 8, 2021). Amsterdam Centre for European Studies Research Paper No. 2021/03, Available at SSRN: <https://ssrn.com/abstract=3862421> or <http://dx.doi.org/10.2139/ssrn.3862421>
- Zivan, O., Segal-Rosenheimer, M., & Dubowski, Y. (2016). Airborne organophosphate pesticides drift in Mediterranean climate: The importance of secondary drift. *Atmospheric Environment*, 127, 155–162. <https://doi.org/10.1016/j.atmosenv.2015.12.003>

Supplementary material A – Explanation of the models used in the modelling framework

IDEFICS - Model for Spray Drift

The model chosen to study spray drift is IDEFICS, since it was determined to be a useful tool to investigate spray drift under varying conditions (Holterman et al. 2010). This model was never used in any existing framework. It is a mixed 2-3-dimensional physical model for spray applications with boom sprayers that describe the trajectories of drops successively by combining deterministic models for the motions of droplets combined with statistical variations of air turbulence (Holterman et al. 1997). The model basically is two-dimensional (2D), but close to the spray nozzle the model is 3D, incorporating the sprayer driving speed and entrained air-currents below the nozzle.

Some of the inputs can be deducted from other applications (e.g. nozzle height above crop) or given an arbitrary distribution (e.g. droplet size spectrum). The output of the IDEFICS model that we used is the vertical distribution of airborne spray drops and vapour at a fixed position downwind. It is important to note that spray boom height, wind speed, nozzle type and spray pressure are the major factors affecting spray drift.

For inquiries regarding the use the IDEFICS model in other studies please contact dr.ir. HJ (Henk Jan) Holterman at henkjan.holterman@wur.nl

PEARL - Model for Volatilization

The model chosen to calculate the rate and extent of volatilization is PEARL (Pesticide Emission Assessment at Regional and Local Scales). PEARL is a one-dimensional numerical model of pesticide behaviour in the soil-plant system (Van den Berg et al. 2016).

In the PEARL model, model concepts have been implemented for the relevant processes on the plant leaves, volatilisation, penetration into the plant leaves, photo-transformation under the influence of sunlight and wash-off from plant leaves due to rainfall. The volatilization from soil and plants surfaces depends on the physic-chemical properties of the pesticide and the prevailing meteorological conditions

The PEARL has already been used in combination with the OPS model to assess the vapour exposure of residents and bystanders in the BROWSE project (Butler Ellis et al. 2017). Pesticide volatilization can occur from soil or plant surfaces. In this study only volatilisation from plant surfaces was considered. This decision was made by experts

after analysing the photos taken from the fields growing stage when applications occurred. Experts determined that for all locations at least 2/3 of the fields were covered with crop. Therefore, the soil cover fraction by the crop was set as 0.66. The volatilization from soil (bare soil, 1/3 of the field area) was considered negligible. Some of the inputs are known from literature (e.g. Koa, Kow), others are collected from the field and other are tested arbitrarily if not known (e.g. Molar enthalpy of sorption and rooting depth).

This model is not yet available for external users.

OPS - Model for Dispersion

For a description of atmospheric transport and dispersion the model chosen is OPS-St (Short term version of OPS, Operational Priority Substances model, for computations up to ~50km from the source). This special model version, with interfaces to PEARL, is used on an hourly basis and computes concentrations and deposition for a limited area. The model can be described as an advanced Gaussian plume model. This model type is based on the standard Gaussian plume equation, but takes into account the development and dynamics of the atmospheric boundary layer including the properties close to the surface, such as near-surface profiles of meteorological variables and continuous stability functions (Holmes and Morawska, 2006). After application, the source strength in OPS-st is taken to be the volatilization rate computed by PEARL. To ensure consistent use of meteorological conditions in OPS-st and PEARL (wind speed and direction, temperature, humidity, radiation) on an hourly basis, meteorological conditions are pre-processed by OPS, which generates the meteorological input file for PEARL during an OPS run. After the completion of the PEARL calculations, OPS resumes the run using the calculated emission rates as input. The output of the OPS-St model that we are interested in is the concentration in air at specific receptor points, located outside homes.

The version used here is intimately linked (offline coupling) with PEARL. But it belongs to the OPS model family (based on the similar physics). The general (not coupled) OPS model can be requested (freely available) from <https://www.rivm.nl/operationele-prioritaire-stoffen-model/beschikbaarstelling-en-support>

gComis - Model for Outdoor to Indoor concentrations in air

The selected model to tackle the outdoor and indoor mass exchange was the gComis (Feustel & Smith 1997) ventilation model. This is a zone model that uses air flow based on building characteristics to estimate indoor concentrations based on outdoor

concentrations. Ventilation is simulated quasi static, and often used for time series of seconds up to years for buildings with a few or several zones (rooms or parts of rooms) (Feustel 1998).

Small particles were simulated as having “gas behaviour”, meaning that settling velocity was not taken into account in the gComis model.

There are several outputs given by the model, such as ventilation flowrates, air change rates, air velocities in openings, heat transfer by ventilation and ventilation heat losses. However, the output of the gComis model that we are interested in is the concentrations (in time) for the indoor environment.

For inquiries regarding the use the gComis model in other studies please contact Daniel Figueiredo at d.m.figueiredo@uu.nl

Dustpred - Model for concentrations of pesticides in indoor dust

The selected model to calculate the concentrations of different pesticides in indoor dust, here named Dustpred, was Equation - 2 from Weschler & Nazaroff et al. 2010. The equation is as follows:

Where: $X_{dust,pred}$ - Prediction of a targeted SVOC mass fraction in dust; C_g - Gaseous concentration; K_{oa} - Octanol-air partition coefficient; f_{om_dust} - Fraction of the dust that is organic matter; ρ_{dust} - Density of dust.

The fraction of dust that is organic matter is 0.2. It is based on the values reported by Weschler & Nazaroff et al. 2010.

The output of the Dustpred model that we are interested in is the concentrations of a given pesticide in indoor dust.

The set of equations are described in: “Weschler, C. J., & Nazaroff, W. W. (2010). SVOC partitioning between the gas phase and settled dust indoors. *Atmospheric Environment*, 44(30), 3609–3620. <https://doi.org/10.1016/j.atmosenv.2010.06.029>”

Supplementary material B – Meteorological conditions and pesticide mixtures for each performed simulation

Table B1. Meteorological conditions for each of the 14 simulations, on day 1 and remaining week (days 2 to 7)

Sim	Month	Day 1 - Mean (Min, Max)			Days 2 to 7 - Mean (Min, Max)		
		Temp (°C)	Hum (%)	WS (m/s)	Temp (°C)	Hum (%)	WS (m/s)
1	February	5 (3,6)	87 (79,95)	6 (2,12)	6 (3,9)	92 (72,98)	8 (2,14)
2	June	24 (18,30)	65 (44,93)	2 (1,6)	20 (14,28)	70 (43,98)	6 (2,10)
3	March	16 (12,22)	62 (46,74)	5 (3,7)	10 (5,21)	78 (50,98)	4 (1,10)
4	April	9 (4,13)	76 (48,94)	5 (2,8)	7 (0,12)	76 (39,95)	5 (0,10)
5	May	22 (17,26)	57 (46,74)	5 (4,7)	19 (9,30)	63 (35,95)	4 (0,9)
6	May	17 (12,24)	73 (38,97)	4 (1,8)	17 (9,31)	79 (32,98)	4 (1,8)
7	May	13 (10,16)	80 (61,95)	3 (1,5)	16 (12,20)	84 (71,99)	5 (2,8)
8	July	23 (17,32)	72 (37,96)	6 (2,8)	19 (14,23)	87 (62,98)	3 (0,7)
9	May	9 (7,11)	68 (60,79)	3 (1,5)	14 (7,21)	72 (36,98)	5 (2,9)
10	January	4 (4,5)	88 (83,98)	3 (2,6)	5 (1,11)	86 (79,98)	4 (0,7)
11	June	19 (16,25)	70 (51,83)	5 (3,10)	19 (12,27)	77 (48,99)	4 (1,9)
12	May	9 (7,12)	68 (60,79)	3 (1,5)	14 (7,22)	73 (36,98)	5 (2,9)
13	August	18 (15,20)	75 (64,89)	5 (3,7)	18 (12,21)	79 (48,96)	7 (0,14)
14	August	20 (17,23)	76 (54,91)	3 (2,5)	17 (10,22)	84 (64,99)	5 (0,9)

Sim – Simulation / Temp – Temperature / Hum – Relative Humidity / WS – Wind speed

Table B2. Pesticide mixtures for each performed simulation

Simulation*	Pesticide mixtures					
1	Chlorpropham	Pendimethalin				
2	Acetamiprid	Esfenvalerate	Mancozeb	Mepanipyrim		
3	Folpet	Tebuconazole				
4	Esfenvalerate	Fluopyram	Trifloxystrobin			
5	Trifloxystrobin					
6	Acetamiprid					
7	Folpet	Mancozeb	Tebuconazole	Thiacloprid		
8	Flonicamid	Fluopyram	Trifloxystrobin			
9	Chlorpropham	Pendimethalin				
10	Mancozeb	Tebuconazole				
11	Chlorothalonil	Esfenvalerate	Mancozeb	Prochloraz		
12	Lambda-Cyhalotrin	Mancozeb	Flonicamid	Tebuconazole		
13	Asulam	Lambda-Cyhalotrin	Metamitron	Quinmerac		
14	Asulam	Lambda-Cyhalotrin	Mancozeb	Metamitron	Pymetrozine	Quinmerac

*Simulations 1-5 are the only ones where no other applications occurred at the time of the planned application.

Supplementary material C – Modelled vs Measured concentrations for indoor air and indoor dust

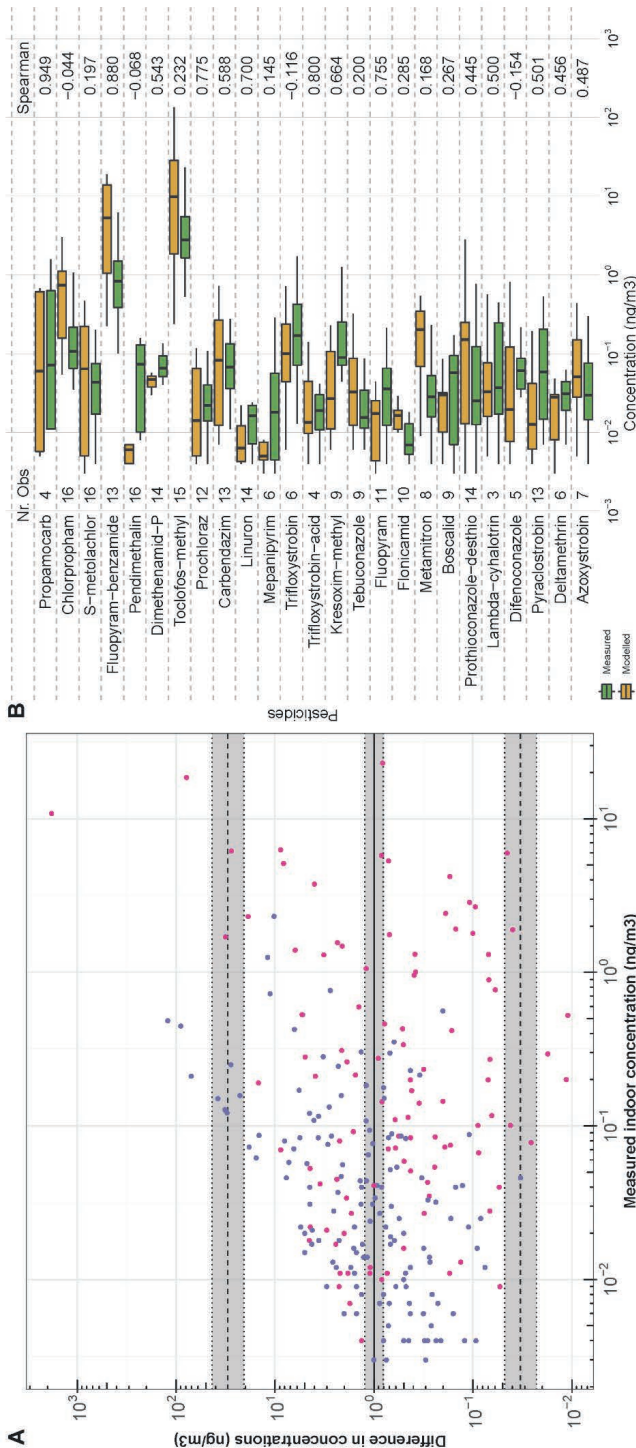


Fig C1. Modelled vs measured concentration in indoor air. Modelled indoor concentration using gComis and having measured outdoor values as input. In panel A, all paired modelled and measured points are plotted together in a Bland-Atman plot. On the x axis, the measured concentration in indoor air. On the y axis, the difference between the modelled and measured concentrations in indoor air. Both x and y axis are normalized in the logarithmic scale (base 10). The darker dots are pesticides with vapour pressure < 0.1 mPa at 20°C. The black line is the mean difference. The dashed lines are the lower (-1.96 standard deviation) and upper limit (+1.96 standard deviation), with the shaded area (delimited by dotted lines) being the 95% CI. In panel B, the modelled and measured data are plotted per pesticide. In green, the measured data and in yellow, the modelled data. On the x axis, concentration is presented in the logarithmic scale (base 10). On the y axis, the names of the pesticides are listed by order of decreasing (top to bottom) vapour pressure. On the y axis, Nr. Obs, refers to the number of observations in each boxplot. On the y axis, Spearman Rho, refers to the spearman correlation calculated between paired modelled and measured data for each pesticide. Summary statistics in boxplots (min, max, 1st and 3rd quartile and median).

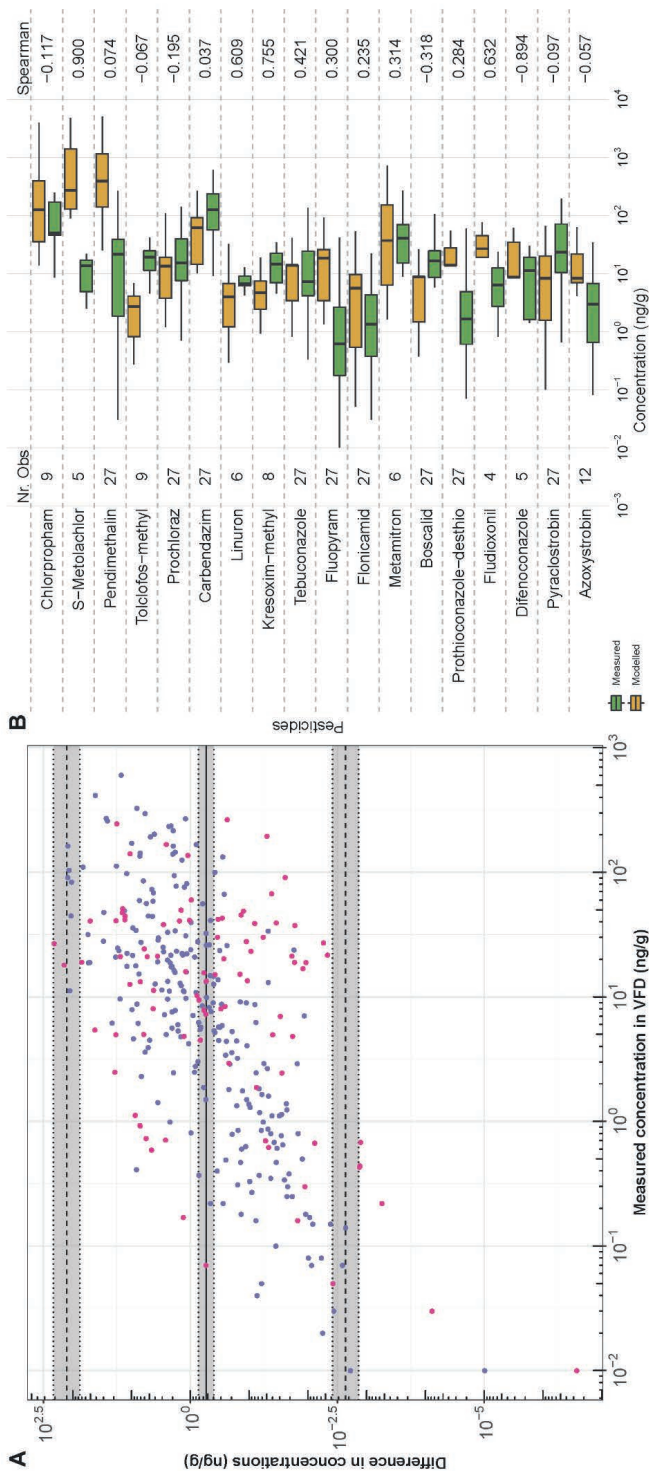
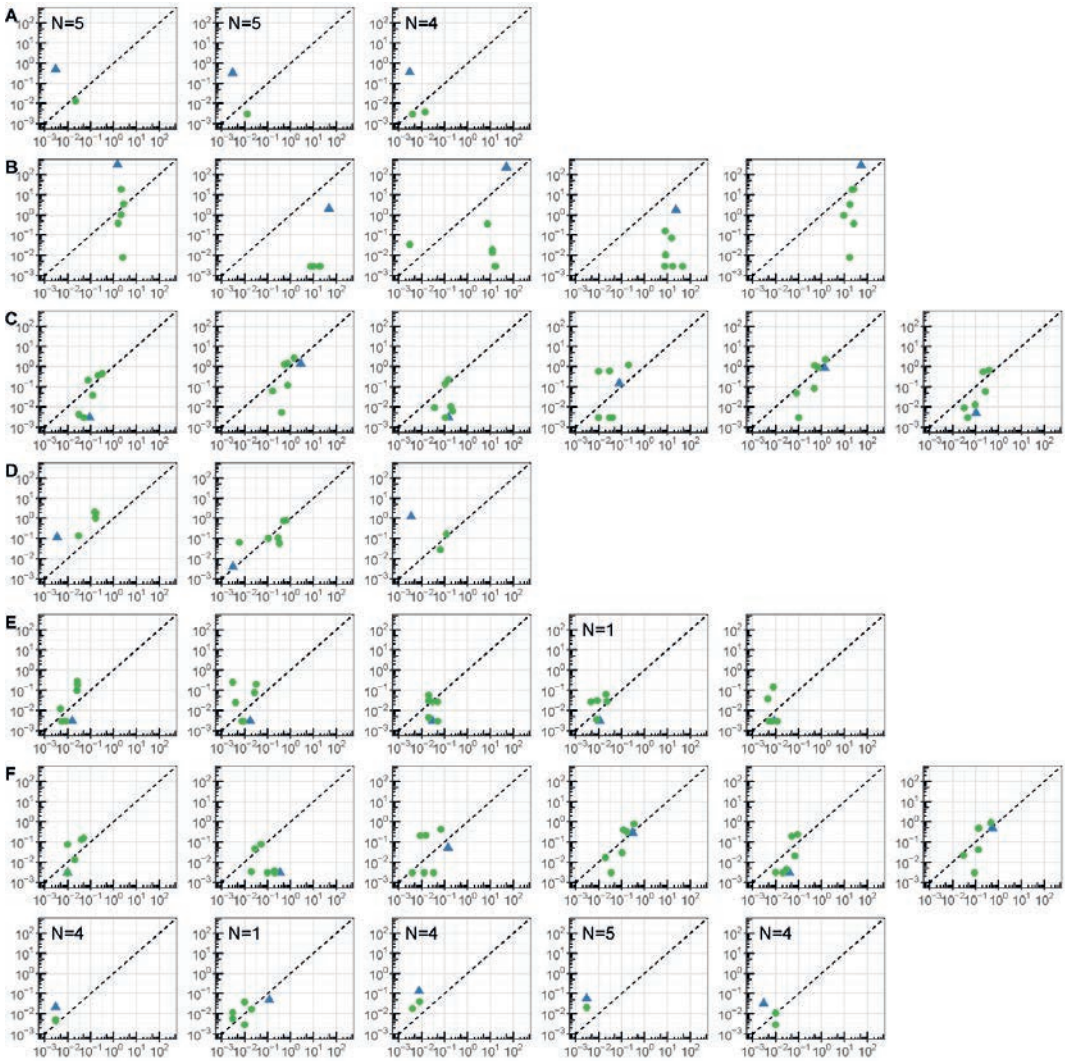


Fig C2. Modelled vs measured concentration in indoor dust. In panel A, all paired modelled and measured points are plotted together in a Bland-Atman plot. On the x axis, the measured concentrations in indoor dust (VFD). On the y axis, the difference between the modelled and measured concentrations in indoor dust. Both x and y axis are normalized in the logarithmic scale (base 10). The darker dots are pesticides with vapour pressure < 0.1 mPa at 20°C. The black line is the mean difference. The dashed lines are the lower (-1.96 standard deviation) and upper limit (+1.96 standard deviation), with the shaded area (delimited by dotted lines) being the 95% CI. In panel B, the modelled and measured data are plotted per pesticide. In green, the measured data and in yellow, the modelled data. On the x axis, concentration is presented in the logarithmic scale (base 10). On the y axis, the names of the pesticides are listed by order of decreasing (top to bottom) vapour pressure. On the y axis, Nr. Obs, refers to the number of observations in each boxplot. Also on the y axis, Spearman Rho, refers to the spearman correlation calculated between paired modelled and measured data for each pesticide. Summary statistics in boxplots (min, max, 1st and 3rd quartile and median).

Supplementary material D – Modelled vs Measured concentrations for outdoor air, per pesticide and per home.



Legend: A=Acetamidiprid, B=Chlorpropham, C=Fluopyram, D=Mepanipirim, E=Tebuconazole, F=Trifloxystrobin

Figure D1. Modelled vs measured concentration in outdoor air, per pesticide and per home. Each row is a different pesticide (see legend). Each plot is a different home. For each plot, in the x axis, the measured concentration in ng/m³ and in the y axis, the modelled concentration in ng/m³. Both x and y axis are in the logarithmic scale (base 10). The blue triangle is day 1, the day of spraying. The dashed black line is the 1:1 line (i.e. identity line). N = refers to the number of pairs where both the measured and modelled values are below the detection limit of the targeted pesticide (i.e. both < 0.003 ng/m³).

Supplementary material D1. Model efficiency - Temporal variability of outdoor air concentrations.

Pesticide ^a	Paired-N	Measured		Model efficiency		
		Mean	SD	R2 (^b)	MAE (^b)	RMSE (^b)
Chlorpropham	7	2.114	0.460	0.003 (+0.175)	6.599 (+43.581)	9.918 (108.237)
	7	18.929	13.767	<0.01 (+0.622)	14.08 (+4.557)	14.948 (7.267)
	7	16.343	15.906	0.073 (-0.038)	10.672 (+24.582)	12.121 (57.856)
	7	17.986	13.893	0.141 (-0.141)	17.031 (+0.664)	21.859 (-0.026)
	7	24.301	14.251	0.071 (+0.289)	12.277 (+31.377)	14.324 (74.330)
Fluopyram	7	0.130	0.104	0.737 (-0.126)	0.102 (-0.002)	0.115 (-0.004)
	7	0.988	0.894	0.383 (+0.016)	0.649 (+0.107)	0.74 (0.126)
	7	0.137	0.060	0.005 (-0.005)	0.106 (+0.006)	0.127 (0.003)
	7	0.057	0.067	0.112 (+0.019)	0.380 (-0.045)	0.541 (-0.040)
	7	0.680	0.572	0.731 (-0.005)	0.367 (+0.028)	0.459 (0.017)
	7	0.163	0.129	0.762 (-0.075)	0.168 (-0.010)	0.210 (-0.012)
Mepanipyrim	6	0.113	0.075	0.914 (-0.100)	1.117 (-0.167)	1.294 (-0.112)
	7	0.268	0.246	0.351 (+0.301)	0.157 (-0.022)	0.185 (-0.014)
	3	0.063	0.058	1.000 (-0.371)	0.040 (+0.392)	0.041 (0.661)
Tebuconazole	7	0.016	0.010	0.805 (-0.221)	0.084 (-0.010)	0.128 (-0.01)
	7	0.014	0.012	0.031 (-0.029)	0.085 (-0.010)	0.128 (-0.01)
	7	0.031	0.013	0.103 (-0.018)	0.023 (0.001)	0.028
	7	0.011	0.008	0.424 (-0.171)	0.017 (-0.002)	0.023 (-0.002)
	7	0.007	0.002	0.023 (+0.021)	0.032 (-0.004)	0.058 (-0.005)
Trifloxystrobin	7	0.021	0.017	0.543 (+0.049)	0.049 (-0.006)	0.065 (-0.005)
	7	0.136	0.121	0.197 (+0.062)	0.093 (0.036)	0.122 (0.051)
	7	0.041	0.05	0.141 (-0.024)	0.133 (-0.005)	0.187 (-0.010)
	7	0.157	0.126	0.710 (+0.002)	0.167 (-0.022)	0.228 (-0.017)
	7	0.044	0.028	0.659 (-0.117)	0.065 (-0.004)	0.088 (-0.005)
	7	0.217	0.198	0.424 (+0.032)	0.229 (-0.024)	0.289 (-0.020)
	2	< LOD	nd	nd	0.001 (0.002)	0.001 (0.006)
	6	0.024	0.043	0.191 (+0.267)	0.008 (0.009)	0.013 (0.016)
	3	0.005	0.002	0.871 (+0.023)	0.008 (0.016)	0.014 (0.034)
	2	< LOD	nd	nd	0.003 (0.007)	0.007 (0.014)
	3	0.005	0.003	0.400 (-0.391)	0.001 (0.004)	0.003 (0.008)

SD – Standard deviation (ng/m³); R² – coefficient of determination (-); MAE – Mean absolute error (ng/m³); RMSE – Root mean square error (ng/m³); ^a Each row corresponds to a different home; ^b Values including day 1 (day of spraying) in the dataset; nd – not determined given either i) small number of paired samples (Paired-N<3) or ii) values below detection limit

Supplementary material D2. Model efficiency - Spatial variability of outdoor air concentrations.

Pesticide	Day	Paired-N	Measured		Model efficiency		
			Mean	SD	R2	MAE	RMSE
Fluopyram	Fl1	6	0.770	1.119	0.650	0.394	0.622
	2	6	0.171	0.159	0.706	0.137	0.195
	3	6	0.63	0.671	0.700	0.586	0.751
	4	6	0.296	0.273	0.577	0.249	0.323
	5	6	0.068	0.056	0.728	0.056	0.075
	6	6	0.243	0.234	0.157	0.493	0.556
	7	6	0.338	0.317	0.168	0.328	0.397
Tebuconazole	1	5	0.017	0.008	NA	0.014	0.016
	2	5	0.010	0.006	0.425	0.005	0.005
	3	5	0.009	0.006	0.629	0.008	0.012
	4	5	0.028	0.015	0.051	0.091	0.119
	5	5	0.013	0.021	0.162	0.021	0.023
	6	5	0.016	0.009	0.995	0.114	0.153
	7	5	0.020	0.011	0.155	0.037	0.046
Trifloxystrobin	1	11	0.138	0.182	0.046	0.078	0.12
	2	11	0.042	0.06	0.046	0.047	0.076
	3	11	0.095	0.158	0.909	0.137	0.231
	4	11	0.050	0.066	0.224	0.047	0.075
	5	11	0.010	0.009	0.498	0.004	0.006
	6	11	0.035	0.048	0.795	0.092	0.155
	7	11	0.048	0.062	0.450	0.081	0.137
Mepanipyrim	1	3	0.003	0.000	0.838	0.442	0.704
	2	3	0.033	0.029	0.111	0.068	0.075
	3	3	0.314	0.291	0.134	0.64	0.994
	4	2	0.323	0.243	nd	1.103	1.386
	5	3	0.244	0.122	1.000	0.599	0.682
	6	3	0.137	0.038	1.000	0.452	0.634
	7	1	0.285	nd	nd	0.177	0.177
Chlorpropham	1	5	35.365	22.386	0.444	120.578	149.804
	2	5	14.855	7.437	nd	16.895	16.915
	3	5	15.894	8.641	0.551	14.54	15.257
	4	5	9.966	5.266	0.302	10.851	11.075
	5	5	9.404	6.538	0.053	7.862	7.883
	6	5	16.25	19.755	0.178	20.117	26.744
	7	5	9.808	5.314	0.457	11.628	12.114

SD – Standard deviation (ng/m³); R2 – coefficient of determination (-); MAE – Mean absolute error (ng/m³); RMSE – Root mean square error (ng/m³); nd – not determined given either i) small number of paired samples (Paired-N<3) or ii) values below detection limit.

Supplementary material E – Scatter-Plots of modelled vs measured concentrations for indoor air and indoor dust, including all pesticides.

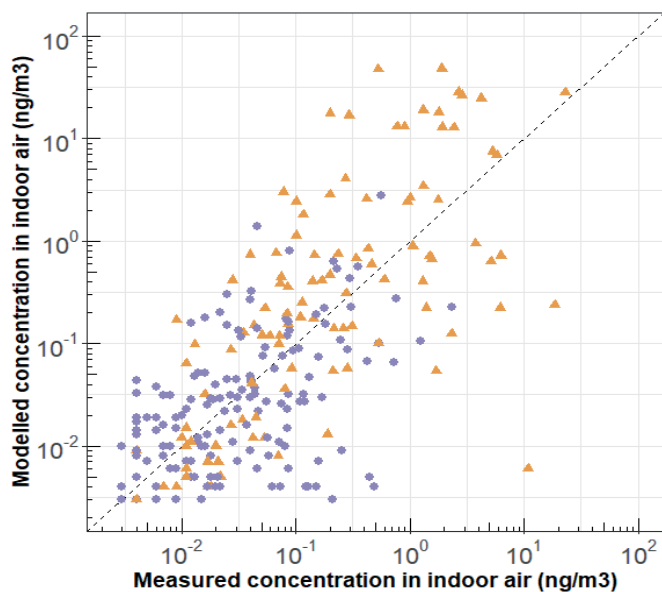


Figure E1. Modelled vs measured concentration in indoor air. Modelled indoor concentration using gComis and having measured outdoor values as input. In the x axis, the measured concentration in indoor air. In the y axis, the modelled concentration in indoor air. Both x and y axis are in the logarithmic scale (base 10). The darker dots are pesticides with vapour pressure < 0.1 mPa at 20°C. The dashed black line is the 1:1 line (i.e. identity line).

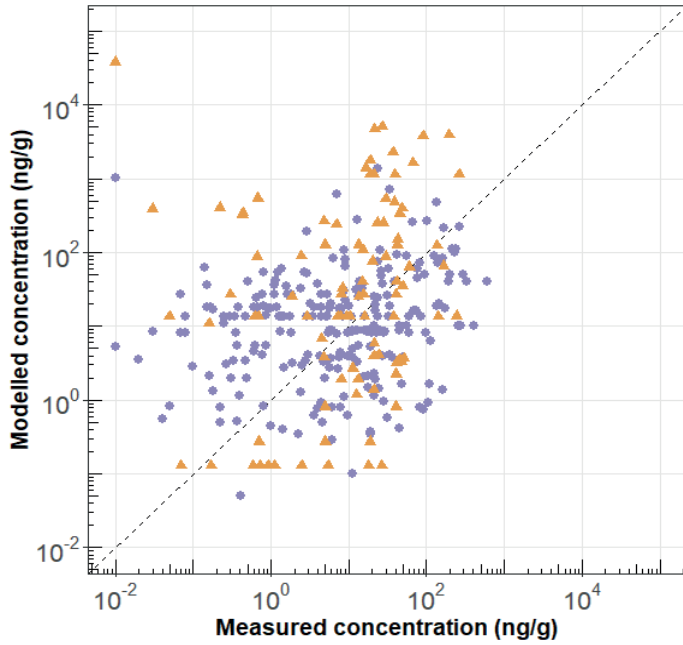


Figure E2. Modelled vs measured concentration in indoor dust. In the x axis, the measured concentration in indoor dust. In the y axis, the modelled concentration in indoor dust. Both x and y axis are in the logarithmic scale (base 10). The darker dots are pesticides with vapour pressure < 0.1 mPa at 20°C . The dashed black line is the 1:1 line (i.e. identity line).

Supplementary material F – Modelled Trifloxystrobin daily concentration in indoor dust for each home

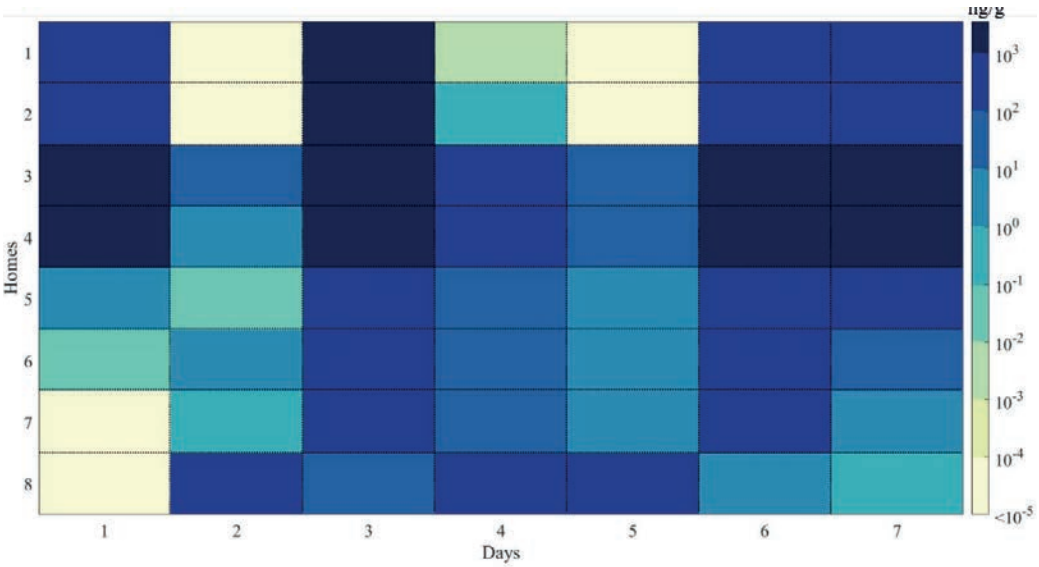


Figure F1. Modelled Trifloxystrobin daily concentration in indoor dust for each home. These are the results of simulation 4, having the daily average modelled concentrations in indoor air as input. In the x axis, the days. In the y axis the homes. The colour represents the modelled values in ng/g of dust.



7

General discussion



Pesticides are essential for food production (Rani et al. 2021). Even in organic farming, a limited range of pesticides are allowed (Hillocks 2012). These chemicals, or more accurate, the active ingredient(s) present in these, are used to repel, control (e.g. protection) or kill different organisms or diseases. The application of pesticides, especially in agricultural fields close to neighboring homes, has led to increased concerns from citizens about their potential environmental exposure and related health effects. To understand the potential health implications of environmental exposure to current-use pesticides it is necessary to characterize their sources and estimate their magnitude.

The aims of this thesis were to i) understand spatial and temporal variation in residential pesticide exposures; ii) study the relevance of the different exposure routes contributing to residential pesticide exposure; iii) study possible determinants of pesticide occurrence and concentrations in the different matrixes (e.g. air, house dust) and iv) improve existing modelling approaches for residential exposures to pesticides. The presented work was made possible through the analysis of collected environmental and personal samples within the OBO-study, the use of detailed data on spraying applications and use of verified deterministic models. Ultimately, this thesis contributed to advancing the knowledge in the field of environmental exposure to pesticides, by answering some open research questions and by identifying additional knowledge gaps.

Our main findings showed that for most of the studied pesticides, both occurrence and concentrations, are higher inside and outside the homes of people living close to bulb fields compared to homes further away. Concentrations are also higher during the application period (i.e. spraying season) when compared to the non-application period, although this difference was less pronounced for pesticides in indoor dust. The correlations found between urinary concentrations of one of the pesticides with the concentrations of its parent compound (carbendazim) in handwipes is an indication that i) indoor exposure to pesticides in house dust (via contact to contaminated surfaces) can occur and ii) pesticides used in neighboring fields can lead to uptake. Our modelling efforts resulted in the creation of a framework that, after comparison with field measurements, was shown to be suitable for estimating residential exposure to pesticides present in outdoor and indoor air, from boom spraying applications, on a high spatial (meters) and temporal (hours) resolution.

“The more I learn, the more I realize how much I don’t know.” - Albert Einstein

Interpreting pesticide data

Let's put it this way...exposure to pesticides is not easy to study. Contrarily to many other compounds, pesticides vary largely in their chemical and physical properties, such as their degradation time and capacity to evaporate, making pesticides quite a heterogeneous group of chemicals. Also, as highlighted by Lushchak et al. (2018), the toxicological mode of action is diverse and often cannot be specifically classified. Consequently, interpretation of data likely needs to be done per compound or per (chemical) groups sharing similar properties. Moreover, other factors can also weigh heavily in the interpretation. For example, new regulatory guidelines might enforce new maximum application dosages (Lee et al. 2019) which will directly affect the concentrations of some pesticides in the environment. Some pesticides can be taken off the market, which can directly affect occurrence; some might have other uses, such as wood preservatives (Patrick-Iwuanyanwu et al. 2020) or impregnated in flea collars (Yimam & Mohebalı 2020) which can influence concentrations. All these factors lead to a necessity for a more careful interpretation of study results (Ludvigsen & Lode 2002). During this study I have kept this in mind and always tried to avoid simplistic generalizations, except if there were indeed commonalities between the different pesticides and evidence based generalizations could indeed be made.

Residential exposure to pesticides

Pesticide exposure is assessed in different ways depending on the main goal of the study. In an epidemiological context, where we try to “find the causes of health outcomes and diseases in populations” (cited from CDC), environmental exposure to pesticides is usually determined by using proxies, such as total area of crops surrounding a residence, most probable applied dosage and distance/proximity to agricultural fields (Cecchi et al. 2021). Sometimes these proxies are used in combination (VoPham et al. 2015, Simões et al. 2022). Yet, this is not necessarily the optimal approach to characterize exposure, as pointed out in a review by Dereumeaux et al. (2020), since for instance it does not account for meteorological conditions (wind direction, wind speed, precipitation, etc.) and pesticide physico-chemical properties. But, in most cases, it is the only approach given the available data (Gunier et al. 2011). For example, to link past exposure to health end points using both retrospective cohort studies and case-control studies we need data from previous years. These data include crop location and type, applied mixtures, quantity applied, amongst others from farmer diaries or

registries. However, this information is often scarce or non-existent. On the other hand, in exposure studies, such as the OBO-study, where we “aim to determine the types, levels, and combinations of exposures people experience” (cited from NIEHS), personal monitoring, environmental monitoring and modelling of exposures are preferred. The reason for this preference is the focus on current practices, duration, frequency and concentrations of exposure(s) (Nieuwenhuijsen 2015).

Environmental and personal sampling were performed at the homes included in the OBO-study in order to assess residential exposure to pesticides. Air samples were collected outside and inside the homes. In parallel, indoor dust samples, handwipe samples and urine samples were collected.

Environmental sampling

Data collected with active air samplers (AAS) capture both gas and particle-phase pesticides resulting from spray drift, pesticide deposition and consequent volatilization. This is due to the capacity of the AAS to capture high temporal resolution data, given that we can control the influx volume and therefore sample large quantities of air in a short period of time (Hayward et al. 2010a). This is not possible with passive air samplers (PAS), where the air sampling volume is determined by natural air flow and as a result it takes longer to have enough material for detection (Gamboa et al. 2020). For pesticide exposure via air, AAS seem ideal when studying short periods, where the interest is on acute exposures. But, for longer periods of sampling, PAS have been indicated to perform as well as AAS and be a more economically viable solution (Lévy et al. 2018, Climent et al. 2019). The main drawback of using PAS is the variability of air sampling rates, which change depending on meteorological conditions, such as wind speed and humidity. As a consequence, PAS samples have different air sampling rates (except if deployed close to each other), which leads to complexities in the interpretation of the data.

The dust collected via vacuuming of the floor captures long-term exposure to pesticides, a result of accumulation in the indoor environment. The main hypothesized reason for this accumulation, is that pesticides are “protected” from water, microbial and photodegradation (Simaremare et al. 2021, Kuiper et al. 2022) when inside the home. Also, as stressed by Ritz and Rull (2008), accumulation is dependent on the chemical properties of the substances, such as vapor pressure. Other factors, such as type of home ventilation (Rudel et al. 2003), domestic use (Audy et al. 2018) and

type of flooring (Obendorf et al. 2005) are also often mentioned in literature as having influence in indoor pesticide accumulation.

We used polypropylene doormats as used by Nishioka et al. (2002) as effective approach for trapping soil and dust particles. The dust collected via doormats captured short term exposure to particle-phase pesticides, a result of particles being trapped in the doormat during a one week period. Previous studies that have used this sampling technique focused on other pesticides than those measured in the OBO study (Lewis et al. 1994, Ganser 2006). Thus, comparison with our results was not possible.

For exposure via dust, doormats seem to be a better proxy for exposure assessment studies, given that it can capture exposure in a defined period of time, whereas vacuuming floors might be more appropriate for health assessment studies, since it captures cumulative (past and current) exposures (Deziel 2019).

It is important to stress that there are several other ways to collect indoor dust, and each one has its functionality. For example, surface wipes and electrostatic dust collectors (EDCs) have also been employed before. These are simple and cost-effective sampling methods. However, EDCs are known to only characterize settling dust (Viegas et al. 2021) and therefore do not capture chemical accumulation in surfaces (e.g. floor), which is one of the most important exposure sources for hand-to-mouth ingestion and dermal contact. On the other end, surface wipes do capture accumulation on surfaces, but the downside is that different surfaces will trap particle and gas-phase pesticides in different ways depending on the properties of the surface film. So, chemical loading will vary largely between objects (Fan et al. 2022), therefore making it difficult to quantify exposure.

Personal sampling

Personal handwipes seemed to be efficient in capturing short-term exposure to pesticides, but it solely captures the dermal contact route (Geno et al. 1996). Other studies, performed in both occupational and non-occupational settings, have also indicated handwipes as a suitable technique to assess individual exposure. Several of these studies have collected urinary data in parallel and found that detection of a certain pesticide in hand wipes was significantly associated with its main metabolites in urine (Curwin et al. 2005, López-Gálvez et al. 2020, Kunno et al. 2020). Therefore, to characterize the dermal contact exposure route, personal handwipes might be a good

proxy, given the high detection frequency and the correlation with urinary biomarkers. However, they only address short exposure windows and there is a high variability associated with the time of sample collection.

We also performed biological monitoring in order to determine personal exposure for a few selected pesticides. We chose to sample urine over blood, given that collection of urine samples is less invasive, urine is easier to collect and available in sufficient quantity. Urine samples seemed to be efficient on capturing short-term exposure to pesticides. This was expected, since urinary biomarkers are taken as the golden standard for reflecting short-term exposures from all the different routes. The main downside of urinary concentrations, and often overlooked, is that there is a large temporal (almost daily) variability. For example, as pointed out by Norén et al. (2020), urinary concentrations can vary due to differences in: used analytical methods, population characteristics, urine dilution correction methods, sampling years, amongst others.

It is important to mention that hair samples from a few participants (N=19) were also collected as an add-on to the OBO-study, but no conclusions were drawn from the outcomes of these samples. Hair has been used to obtain information on exposure at a personal level for a larger number of pesticides over a longer time period (Schummer 2012, Hardy 2015), therefore reflecting long-term (chronic) exposure. However, at this stage, there are still some knowledge gaps. The main two being that i) it is difficult to translate concentrations in hair to actual exposure (oral/inhalation/dermal intake) and ii) it is not possible to determine which time-frame the concentrations established refers to. In a recent study, Hardy et al. (2021) postulates that hair may contain chemicals that have been present for a short time (days) to over a period of weeks to months, depending on the length of the hair strand.

Pesticide concentrations in air and dust

We have seen that, in general, the observed concentrations in air and dust show a wide variations in concentrations covering sometimes several orders of magnitude. Concentrations in air varied within six orders of magnitude. For dust, concentrations varied within four orders of magnitude. It comes as no surprise that environmental exposure is overall one order of magnitude higher in the period when pesticides are being applied and higher closer to fields. Similar contrasts were also observed in several other studies that performed air sampling (Hayward et al. 2010b, Carratalá et al. 2017, Wang et al. 2021, Veludo et al. 2022). However, contrary to concentrations in outdoor

and indoor air, indoor dust concentrations were rather constant across the sampling periods (use and non-use) and across homes. A less pronounced spatial and temporal variability in pesticides' concentration in dust were also observed in other studies (Golla et al. 2012, Hung et al. 2018). The concentrations of measured pesticides inside and outside the control homes indicates an exposure to these homes that is not driven by local spraying applications, but most likely a combination of long-range transport (Zhan et al. 2021), pesticide use in open spaces like lawns and gardens (Meftaul et al. 2020) and household use (Grey et al. 2005). These findings are in line with previous studies that have also detected several pesticides in house dust collected from urban homes (Quirós-Alcalá et al. 2011, Velázquez-Gómez et al. 2019). Moreover, Béranger et al. (2019) has found current-used pesticides in house dust from urban areas with a "zero-pesticide-use" policy in place. So, residents are exposed throughout the year to several pesticides, independently of where they live.

It is important to stress that the above findings might not be valid for pesticides solely reported as used in bulb disinfection. These pesticides are bound to the location and time where the bulb disinfection occurs and therefore exposure frequency and magnitude is expected to be different from those sprayed in the agricultural fields. Our results indicate this, but do not allow for a validation of this hypothesis given that we did not have information on the exact locations, quantity and frequency that these specific pesticides were used.

Exposure to pesticides – mixtures, routes and determinants

Although we know that for many pesticides the exposure timeframe is all year round, we do not know if there are adverse health effects due to continuous exposure to pesticide mixtures (sometimes called cocktails), even if they are present in low environmental concentrations. In the OBO-study, we compared urinary pesticide levels from our participants with those from volunteers that received a single dose just below the acceptable daily intake (ADI¹) (Oerlemans et al. 2019). For the five different pesticides measured in urine, the observed levels of biomarkers were lower compared to those in the volunteers (OBO 2019). However, these results cannot be generalized to other pesticides because both exposure profile and the ADI are unique for each pesticide. Moreover, we are assessing pesticides individually, given that potential "combined

1 "The maximum amount of a chemical that can be ingested daily over a lifetime with no appreciable health risk" (Cited from Dennis & Wilson 2003).

effects” and a-priori defined mixture thresholds are not known for these compounds. So, conclusions on health risks from the pesticide mixtures present in this study cannot be drawn. Conclusions can also not be drawn for more susceptible subpopulations, like toddlers and young children (Meftaul et al. 2020), since they have a likely higher exposure burden due to hand-to-mouth action, dermal contact to surfaces and time they spend close to the ground (Wilson et al. 2013).

The body of knowledge on combined effects from pesticide mixtures has doubled in the last 10 years (Pubmed 2022). In an extensive review, Rizzati et al (2016) highlights that it is of utmost importance to study these combined effects, even at low doses (Damalas & Eleftherohorinos, 2011). As an example, in a recent study, He et al. (2022) concluded that exposure to some pesticides at low-dosage causes changes in neuronal morphology and synapse, observed in autism spectrum disorder. This example is not the exception, as there are other studies finding other low-dose effects from pesticide mixtures (Lukowicz et al. 2018, Mesnage et al. 2021). Conversely, as pointed out by Hernández et al. (2017), no significant effects were found for a different set of studied pesticide mixtures.

Despite the above efforts, the effect of pesticide mixtures is still poorly understood (Siviter et al. 2021). Given the number of authorized products, there are a lot of possible mixtures that one might be exposed to, and these can occur at different exposure levels, exposure periods and exposure frequencies. The question becomes: Which pesticide combinations to study first? To address this, we need to i) assess the levels amongst different environmental matrixes; ii) identify reoccurring environmental mixtures and iii) understand spatial and temporal variability of pesticide concentrations. These three aspects are a step into decision support and prioritization for future studies looking into assessing combined exposure and mixture effects.

To further improve our understanding on spatial and temporal variability of pesticides, we tried to identify possible determinants for occurrence and concentrations of pesticides in air and dust during the period when pesticides are sprayed in the agricultural fields. Residents’ outdoor exposure to pesticides in air seems to be mainly driven by wind direction, evaporation and total agricultural area surrounding a given home, which is in agreement with the mathematical formulation from already existing deterministic models (e.g. Butler Ellis et al. 2017). On the other hand, residents’ exposure to pesticides in the indoor environment, specially to contaminated dust, is more complex. We noticed that it is possible to predict occurrence of a given pesticide in indoor dust based on the pesticides vapor pressure and half-life in soil, distance to agricultural fields and observed air concentrations. But, it is difficult to predict the

concentration range (magnitude of variation in exposure). This difficulty is not limited to pesticides, as it is also indicated as a major challenge in other fields focusing on plastic additives, industrial chemicals, combustion by-products and many other compounds (Melymuk et al. 2020). For pesticides, the reason is that concentrations in indoor dust seem to be driven by a combination of many factors which differ depending on the pesticide in question (Teyssere et al. 2021). Some of these factors remain difficult to estimate, such as carriage of pesticides into home via contaminated clothing and shoes (take-home route, Deziel et al. 2015) or the degradation time of a certain pesticide in the indoor environment (Mahler et al. 2009), especially in shaded areas.

Exposure to pesticides via inhalation has received the most attention to date, but as our results suggest, there are other exposure pathways, specially involving the dust matrix, such as dust ingestion and dermal contact, that are likely to be of equivalent or sometimes even greater importance for residential exposure. Given that there is a high potential for exposure to pesticides via post application processes, such as volatilization and contaminated dust, the need to develop and validate models for prediction of multipath is evident. To tackle this, we developed a modelling framework.

In real-life scenarios simulated by the modelling framework we have seen that, for pesticides with a reasonably large potential to volatilize, the cumulative exposure due to volatilization after application may sometimes be larger than exposure to droplet drift during application. This needs further evaluation, especially in the regulatory framework, which is primarily focused on reducing exposure by reducing spray drift (e.g. OJEU 2009). Volatilization is driven by the total amount used which may not be reduced by drift reducing measures. Here, the framework could provide input for developing guidelines taking into account volatilization.

“Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less.” - Marie Curie

Modelling exposure to pesticides from boom spraying applications

Substantial progress was made in creating an integrated model framework that consists of a chain of connected models that predict concentrations in both air and dust on an hourly basis. Model verification indicated that the framework could be suitable for estimating residential pesticide exposure via air on a high spatial and temporal resolution, for both outdoor and indoor environments. The modelling framework

is in general not yet suitable to predict concentrations for pesticides in indoor dust. Though, pesticides that break down or dissipate rapidly in the environment may be estimated with reasonable accuracy, given that these are less influenced by past-usage and indoor accumulation.

As discussed in the previous section, the low proportion of variance explained of pesticide concentrations in dust by the dust module, could be explained, because current models do not account for other sources and sinks of pesticides. Given the potential importance of the dust matrix in explaining residential exposure, the development of a model capable to include all the major determinants for pesticides concentrations in indoor dust is of utmost importance. But, before we can talk about development of such model, we have to take a step back... and look in great detail at the different influencing factors, starting with the composition of house dust.

House dust usually “arises from external sources, including dust that originates from aerosol, soil and street dust, as well as dust generated within the house” (cited from Fergusson et al. 1986). It is therefore a heterogeneous mixture of particles, hair, fibers, biologically-derived material (e.g. moulds and animal fur), ash, among other components. This is the first layer of complexity when determining pesticide concentrations in house dust. The second layer of complexity is related to the adsorption and desorption of pesticides to different particle size fractions. As showed by Coscollà et al., some pesticides are mainly bound to particles with a diameter $< 1\mu\text{m}$, but others present bimodal pesticide size distribution with peaks on the fine–coarse ($1\text{--}10\mu\text{m}$) and ultrafine–fine ($< 1\mu\text{m}$) fractions (Coscollà et al. 2008, Coscollà et al. 2013). The third and final layer of complexity has to do with the processes and factors that influence i) transport, such as wind erosion and take-home route; ii) deposition and resuspension, such as the size of the particles and disturbance of surfaces; iii) accumulation (or not), such as vacuum cleaning and type of flooring and iv) degradation of pesticides in the indoor environment.

Sorption of gas-phase pesticides to dust particles was included in our model and more recently we added settling of particle-phase pesticides into the equation. Nevertheless, there is still a long road ahead before we can predict pesticide concentrations in indoor dust with an acceptable degree of certainty.

During our study, for most cases, wind was not blowing towards the homes during the spraying application, so our simulations did not capture “worst-case scenarios”. Also, if there is an emerging pest that needs to be treated, an application might take place that is not according to guidelines. In the OBO-study, a sensitivity analysis simulating

unfavorable meteorological conditions was performed, and found that drift exposure may be more than a factor of ten higher than exposure observed in this study when wind was blowing towards the homes during spraying.

During spraying applications there is a multitude of combinations of tank mixtures, nozzle features, meteorological conditions, field sizes and other factors that vary between applications. Therefore, each spraying application may lead to a different exposure profile. The question is “How often do worst-case scenarios occur out of all the possible parameters combination”. An important exercise will be to perform all possible combinations or a random selection of these. These would allow us to ascertain how often can exposure be higher than a-priori defined thresholds. It would also help to identify exposure ranges and develop probability functions based on real-life settings.

In order to perform the aforementioned exercise, one has to first define a worst-case scenario. This always occurs when the homes are downwind from pesticide sprayings and are located in the plume axis (where concentration is the highest). But, regarding climatic conditions, defining worst-case scenario is not a trivial task. From an atmospheric point of view, low wind speeds and stable conditions should be in place, which will strongly reduce vertical mixing during pesticide drift. However, stable conditions (usually night-time) often imply conditions with comparatively low temperatures and coupled low volatilization. The first step would be to identify a combination of variables that lead to maximum exposure. Once this set is defined, we would need to check how often these conditions are met within the full set of possible combinations. For the Netherlands, this can be done by using the hourly resolution meteorological data available from KNMI stations (KNMI).

It is not yet possible to predict the environmental exposure of all residents near bulb fields and other crops with downward spraying, via both air and house dust, for all pesticides and all locations in the Netherlands. There are three main reasons behind this: i) lack of specificity in input data; ii) current parametrization of the dust model and iii) difficulty to account for variability in background concentrations. Regarding the first two, our research offers the components to develop and extrapolate models for residential pesticide exposures and thus may represent a way to upscale pesticide exposure assessment for large scale population studies. This can be done, for example, by testing which input variables drive model results the most and which variables have little influence on the outcome. Such a sensitivity study would allow us to simplify our framework while maintaining a certain degree of certainty in the outcome.

Regarding background concentrations, it is known that several current-use pesticides are persistent enough to be carried for long distances (Balmer et al. 2019). Therefore, we would need to put in place a monitoring system that would help us identify what is the spatial and temporal variability of background concentrations. This could consist of active or passive sampling devices placed across the Netherlands and capturing all cardinal wind directions. Ideal locations would be far from agricultural fields, but also from residential homes and other green spaces where pesticides spraying can still occur.

“For my part I know nothing with any certainty, but the sight of the stars makes me dream.” - Vincent Van Gogh

Knowledge gaps...What is next?

One of our main findings translates into higher concentrations closer to fields and higher concentrations during the application period. Despite the size of this study, the sample size and selected agricultural setting limits generalization of these results for all different areas and populations in the Netherlands. In particular for areas close to fields where sideways or upward spraying techniques are used (such as fruit orchards), spatial distribution might be quite different, given that these have higher emissions due to larger drift. Further research should focus on assessing exposure from this type of spraying applications.

Currently, the existing exposure gradients for house dust are poorly described and routes leading to pesticides in dust (e.g. take-home route) are less well understood. As pesticides in house dust can potentially form an important source of exposure (especially for children), more information on the pesticide levels in house dust and its driving factors (accumulation in shaded areas, absorption of gaseous pesticides to house dust) needs to be collected.

Given the measurable concentrations of almost all pesticides in environmental and personal samples, and the correlations found between handwipe and urinary concentrations, the current results need to be explored in relation to possible adverse health effects. Here an example on how this can be done: First, by studying possible mixture effects from the most detectable pesticides in our study and identify underlying dose-response relationships. This can be done via *in silico* models (Barh et al. 2014) complemented with research done in experimental or laboratory settings (e.g. *in vivo*

testing) for a set of disease markers (Taxvig et al. 2013). Adverse outcome pathways (AOPs) can be used to better understand the mode of action of pesticides and support rational identification of these effect markers for *a-priori* identified disease-relevant endpoints, such as oxidative stress (Marins et al. 2020) and thyroid hormone disruption (Leemans et al. 2019). Second, by translating those results to population level. This can be done by estimating exposure of a given population to these mixtures and link to disease incidence of an *a-priori* defined health endpoint (e.g. prospective study).

The developed modelling framework is still a set of proprietary models. To apply the integrated modelling framework to estimate population level exposures we need to simplify the framework and move to an open-source approach, making it more easily adaptable, transparent, and accessible to everyone. At this point in time, the mathematical formulations used in the different models are being transferred to an open-source R package. The dust module is being further developed and simplifications, such as reducing the number of necessary input data, are being considered. This will allow computing efficiency to be increased. After this, estimates over longer time scales (such as annual averages) for indoor and outdoor air concentrations can be calculated. Such results can be used to highlight residential exposure hotspots on a national scale and serve as input for epidemiological studies.

Finally, as discussed before, several studies have shown that we are exposed to a cocktail of pesticides, both persistent pesticides used earlier and current-use pesticides. Our study added to the body of research evidence that even for current-use pesticides, exposure occurs all-year round. It is important to focus not only on the magnitude of exposure, but also on the dimensionality of exposure (pesticide mixtures). Within our study, concentrations were in the order of nanograms per medium for most of the targeted pesticides. These environmental concentrations can be considered low, but cannot be taken as an indication of an increased likelihood for adverse health effects in the Dutch population. To answer whether an excess risk exists, studies on mixtures in relation to possible adverse health effects are needed. Particularly, for pesticides with the same mode of action and frequently detected in our samples, health effect studies are warranted.

“The wise man is one who knows what he does not know”. - Lao Zi

References

- Audy, O., Melymuk, L., Venier, M., Vojta, S., Becanova, J., Romanak, K., Vykoukalova, M., Prokes, R., Kukucka, P., Diamond, M. L., & Klanova, J. (2018). PCBs and organochlorine pesticides in indoor environments - A comparison of indoor contamination in Canada and Czech Republic. *Chemosphere*, 206, 622–631. <https://doi.org/https://doi.org/10.1016/j.chemosphere.2018.05.016>
- Balmer, J. E., Morris, A. D., Hung, H., Jantunen, L., Vorkamp, K., Rigét, F., Evans, M., Houde, M., & Muir, D. C. G. (2019). Levels and trends of current-use pesticides (CUPs) in the arctic: An updated review, 2010–2018. *Emerging Contaminants*, 5, 70–88. <https://doi.org/https://doi.org/10.1016/j.emcon.2019.02.002>
- Barh, D., Chaitankar, V., Yiannakopoulou, E. C., Salawu, E. O., Chowbina, S., Ghosh, P., & Azevedo, V. (2014). In Silico Models: From Simple Networks to Complex Diseases. *Animal Biotechnology*, 385–404. <https://doi.org/10.1016/B978-0-12-416002-6.00021-3>
- Béranger, R., Billoir, E., Nuckols, J. R., Blain, J., Millet, M., Bayle, M.-L., ... Fervers, B. (2019). Agricultural and domestic pesticides in house dust from different agricultural areas in France. *Environmental Science and Pollution Research*. <https://doi.org/10.1007/s11356-019-05313-9>
- Butler Ellis, M. C., van den Berg, E., van de Zande, J. C., Kennedy, M. C., Charistou, A. N., Arapaki, N. S., Butler, A. H., Machera, K. A., & Jacobs, C. M. (2017). The BROWSE model for predicting exposures of residents and bystanders to agricultural use of pesticides: Comparison with experimental data and other exposure models. *Biosystems Engineering*, 154, 122–136. <https://doi.org/10.1016/j.biosystemseng.2016.09.002>
- Caratalá, A., Moreno-González, R., & León, V. M. (2017). Occurrence and seasonal distribution of polycyclic aromatic hydrocarbons and legacy and current-use pesticides in air from a Mediterranean coastal lagoon (Mar Menor, SE Spain). *Chemosphere*, 167, 382–395. <https://doi.org/10.1016/j.chemosphere.2016.09.157>
- CDC. Centers for Disease Control and Prevention. <https://www.cdc.gov/careerpaths/k12teacherroadmap/epidemiology.html> [last accessed February 2022]
- Cecchi, A., Alvarez, G., Quidel, N., Bertone, M. C., Anderle, S., Sabino, G., ... Rovedatti, M. G. (2021). Residential proximity to pesticide applications in Argentine Patagonia: impact on pregnancy and newborn parameters. *Environmental Science and Pollution Research*. <https://doi.org/10.1007/s11356-021-14574-2>
- Clark L.M. (2004). Assessment of pesticide residues in farmers' house dust and educational intervention to improve pesticide handling practices. Master's Thesis, Marine Estuarine and Environmental Science, University of Maryland, College Park, MD.
- Climent, M. J., Coscollà, C., López, A., Barra, R., & Urrutia, R. (2019). Legacy and current-use pesticides (CUPs) in the atmosphere of a rural area in central Chile, using passive air samplers. *Science of the Total Environment*, 662, 646–654. <https://doi.org/10.1016/j.scitotenv.2019.01.302>
- Coscollà, C., Yusà, V., Martí, P., & Pastor, A. (2008). Analysis of currently used pesticides in fine airborne

- particulate matter (PM 2.5) by pressurized liquid extraction and liquid chromatography-tandem mass spectrometry. *Journal of chromatography. A*, 1200(2), 100–107. <https://doi.org/10.1016/j.chroma.2008.05.075>
- Coscollà, C., Yahyaoui, A., Colin, P., Robin, C., Martinon, L., Val, S., Baeza-Squiban, A., Mellouki, A., & Yusà, V. (2013). Particle size distributions of currently used pesticides in a rural atmosphere of France. *Atmospheric Environment*, 81, 32–38. <https://doi.org/10.1016/j.atmosenv.2013.08.057>
- Curwin, B. D., Hein, M. J., Sanderson, W. T., Barr, D. B., Heederik, D., Reynolds, S. J., ... Alavanja, M. C. (2005). Urinary and hand wipe pesticide levels among farmers and nonfarmers in Iowa. *Journal of Exposure Science & Environmental Epidemiology*, 15(6), 500–508. <https://doi.org/10.1038/sj.jea.7500428>
- Damalas, C. A., & Eleftherohorinos, I. G. (2011). Pesticide exposure, safety issues, and risk assessment indicators. *International journal of environmental research and public health*, 8(5), 1402–1419. <https://doi.org/10.3390/ijerph8051402>
- Dennis, M. J., & Wilson, L. A. (2003). *NITRATES AND NITRITES* (B. B. T.-E. of F. S. and N. (Second E. Caballero (ed.); pp. 4136–4141). Academic Press. <https://doi.org/10.1016/B0-12-227055-X/00830-0>
- Dereumeaux, C., Fillol, C., Quenel, P., & Denys, S. (2020). Pesticide exposures for residents living close to agricultural lands: A review. *Environment International*, 134(May 2019), 105210. <https://doi.org/10.1016/j.envint.2019.105210>
- Deziel N. C. (2019). Methods for Quantifying Residential Pesticide Exposure, *Environmental Epidemiology: October 2019 - Volume 3 - Issue - p 97-98* <https://doi.org/10.1097/01.EE9.0000606760.33404.0b>
- Deziel, N. C., Friesen, M. C., Hoppin, J. A., Hines, C. J., Thomas, K., & Beane Freeman, L. E. (2015). A Review of Nonoccupational Pathways for Pesticide Exposure in Women Living in Agricultural Areas. *Environmental Health Perspectives*, 123(6), 515–524. <https://doi.org/10.1289/ehp.1408273>
- Fan, Y., Chen, Q., Wang, Z., Zhang, X., Zhao, J., Huang, X., Wei, P., Hu, P., & Cao, Z. (2022). Identifying dermal exposure as the dominant pathway of children's exposure to flame retardants in kindergartens. *Science of The Total Environment*, 808, 152004. <https://doi.org/https://doi.org/10.1016/j.scitotenv.2021.152004>
- Fergusson, J. E., Forbes, E. A., Schroeder, R. J., & Ryan, D. E. (1986). The elemental composition and sources of house dust and street dust. *Science of The Total Environment*, 50, 217–221. [https://doi.org/https://doi.org/10.1016/0048-9697\(86\)90363-3](https://doi.org/https://doi.org/10.1016/0048-9697(86)90363-3)
- Gamboa, L. C., Diaz, K. S., Ruepert, C., & van Wendel de Joode, B. (2020). Passive monitoring techniques to evaluate environmental pesticide exposure: Results from the Infant's Environmental Health study (ISA). *Environmental Research*, 184, 109243. <https://doi.org/10.1016/j.envres.2020.109243>
- Ganser L.M. (2006). Assessing the potential for doormats to reduce pesticide residues in the home [Master's thesis]. College Park, MD: University of Maryland
- Geno, P. W., Camann, D. E., Harding, H. J., Villalobos, K., & Lewis, R. G. (1996). Handwipe sampling and analysis procedure for the measurement of dermal contact with pesticides. *Archives*

- of Environmental Contamination and Toxicology, 30(1), 132–138. <https://doi.org/10.1007/bf00211339>
- Golla, V., Curwin, B., Sanderson, W., & Nishioka, M. (2012). Pesticide Concentrations in Vacuum Dust from Farm Homes: Variation between Planting and Nonplanting Seasons. *ISRN Public Health*, 2012, 1–10. <https://doi.org/10.5402/2012/539397>
- Grey, C. N. B., Nieuwenhuijsen, M. J., & Golding, J. (2005). The use and disposal of household pesticides. *Environmental Research*, 97(1), 109–115. <https://doi.org/10.1016/j.envres.2004.07.008>
- Gunier, R. B., Ward, M. H., Airola, M., Bell, E. M., Colt, J., Nishioka, M., Buffler, P. A., Reynolds, P., Rull, R. P., Hertz, A., Metayer, C., & Nuckols, J. R. (2011). Determinants of agricultural pesticide concentrations in carpet dust. *Environmental health perspectives*, 119(7), 970–976. <https://doi.org/10.1289/ehp.1002532>
- Hardy, E. M., Duca, R. C., Salquebre, G., & Appenzeller, B. M. (2015). Multi-residue analysis of organic pollutants in hair and urine for matrices comparison. *Forensic science international*, 249, 6–19. <https://doi.org/10.1016/j.forsciint.2014.12.003>
- Hardy, E. M., Dereumeaux, C., Guldner, L., Briand, O., Vandentorren, S., Oleko, A., Zaros, C., & Appenzeller, B. M. R. (2021). Hair versus urine for the biomonitoring of pesticide exposure: Results from a pilot cohort study on pregnant women. *Environment International*, 152, 106481. <https://doi.org/10.1016/j.envint.2021.106481>
- Hayward, S. J., Gouin, T., & Wania, F. (2010a). Comparison of four active and passive sampling techniques for pesticides in air. *Environmental Science and Technology*, 44(9), 3410–3416. <https://doi.org/10.1021/es902512hv>
- Hayward, S. J., Gouin, T., & Wania, F. (2010b). Levels and Seasonal Variability of Pesticides in the Rural Atmosphere of Southern Ontario. *Journal of Agricultural and Food Chemistry*, 58(2), 1077–1084. <https://doi.org/10.1021/jf902898f>
- He, X., Tu, Y., Song, Y., Yang, G., & You, M. (2022). The relationship between pesticide exposure during critical neurodevelopment and autism spectrum disorder: A narrative review. *Environmental Research*, 203, 111902. <https://doi.org/10.1016/j.envres.2021.111902>
- Hernández, A. F., Gil, F., & Lacasaña, M. (2017). Toxicological interactions of pesticide mixtures : an update. *Archives of Toxicology*, 91(10), 3211–3223. <https://doi.org/10.1007/s00204-017-2043-5>
- Hillocks, R. J. (2012). Farming with fewer pesticides: EU pesticide review and resulting challenges for UK agriculture. *Crop Protection*, 31(1), 85–93. <https://doi.org/10.1016/j.cropro.2011.08.008>
- Hung, C.-C., Huang, F.-J., Yang, Y.-Q., Hsieh, C.-J., Tseng, C.-C., & Yiin, L.-M. (2018). Pesticides in indoor and outdoor residential dust: a pilot study in a rural county of Taiwan. *Environmental Science and Pollution Research*, 25(23), 23349–23356. <https://doi.org/10.1007/s11356-018-2413-4>
- KNMI. Het koninklijk nederlands meteorologisch instituut. <https://www.knmi.nl/nederland-nu/klimatologie-metingen-en-waarnemingen> [last accessed February 2022]
- Kuiper, G., Young, B. N., Wemott, S., Erlandson, G., Martinez, N., Mendoza, J., Dooley, G., Quinn, C., Benka-Coker, W. O., & Magzamen, S. (2022). Factors Associated with Levels of Organophosphate

- Pesticides in Household Dust in Agricultural Communities. *International Journal of Environmental Research and Public Health*, 19(2). <https://doi.org/10.3390/ijerph19020862>
- Kunno, J., Ong-Artborirak, P., Panicharoen, P., Robson, M. G., & Siri Wong, W. (2020). Pyrethroid Insecticides in Households from Urban Areas: An Association of the 3-PBA Metabolite and Hand Wipes. *Annals of global health*, 86(1), 55. <https://doi.org/10.5334/aogh.2746>
- Lee, R., den Uyl, R., & Runhaar, H. (2019). Assessment of policy instruments for pesticide use reduction in Europe; Learning from a systematic literature review. *Crop Protection*, 126, 104929. <https://doi.org/https://doi.org/10.1016/j.cropro.2019.104929>
- Leemans, M., Couderq, S., Demeneix, B., & Fini, J.-B. (2019). Pesticides With Potential Thyroid Hormone-Disrupting Effects: A Review of Recent Data. *Frontiers in Endocrinology*, 10. <https://doi.org/10.3389/fendo.2019.00743>
- Lévy M., Al-Alam J., Ridacker C., Massemin S., Millet M. (2018). Use of XAD®-2 passive air samplers for monitoring environmental trends of PAHs, PCBs and pesticides in three different sites in Strasbourg and its vicinity (east of France). *Atmos. Environ.*, 195 (2018), pp. 12-23. <https://doi.org/10.1016/j.atmosenv.2018.09.052>
- Lewis, R.G., Fortmann, R.C. & Camann, D.E. (1994). Evaluation of methods for monitoring the potential exposure of small children to pesticides in the residential environment. *Arch. Environ. Contam. Toxicol.* 26, 37–46. <https://doi.org/10.1007/BF00212792>
- López-Gálvez, N., Wagoner, R., Canales, R. A., de Zapien, J., Calafat, A. M., Ospina, M., Rosales, C., & Beamer, P. (2020). Evaluating imidacloprid exposure among grape field male workers using biological and environmental assessment tools: An exploratory study. *International Journal of Hygiene and Environmental Health*, 230, 113625. <https://doi.org/10.1016/j.ijheh.2020.113625>
- Ludvigsen, G. H., & Lode, O. (2002). Trends of pesticides in Norwegian streams and rivers (1996–2000). *International Journal of Environmental Analytical Chemistry*, 82(8–9), 631–643. <https://doi.org/10.1080/0306731021000062982>
- Lukowicz, C., Simatos, S. E., Régnier, M., Polizzi, A., Lasserre, F., Montagner, A., Lippi, Y., Jamin, E. L., Martin, J. F., Naylies, C., Canlet, C., Debrauwer, L., Bertrand-Michel, J., Saati, T. Al, Théodorou, V., Loiseau, N., Lakhal, L. M., Guillou, H., & Gamet-Payastre, L. (2018). Metabolic effects of achronic dietary exposure to a low-dose pesticide cocktail in mice: Sexual dimorphism and role of the constitutive and rostrane receptor. *Environmental Health Perspectives*, 126(6), 1–18. <https://doi.org/10.1289/EHP2877>
- Lushchak, V. I., Matviishyn, T. M., Husak, V. V., Storey, J. M., & Storey, K. B. (2018). Pesticide toxicity: a mechanistic approach. *EXCLI journal*, 17, 1101–1136. <https://doi.org/10.17179/excli2018-1710>
- Mahler, B.J., Van Metre, P.C., Wilson, J.T. and Musgrove, M. (2009) Fipronil and its degradates in indoor and outdoor dust, *Environ. Sci. Technol.*, 43, 5665–5670. <https://doi.org/10.1021/es901292a>
- Marins, A. T., Cerezer, C., Leitemperger, J. W., Severo, E. S., Costa, M. D., Fontoura, D. O., ... Loro, V. L. (2020). A mixture of pesticides at environmental concentrations induces oxidative stress and cholinergic effects in the neotropical fish *Rhamdia quelen*. *Ecotoxicology*, 30(1), 164–174. <https://doi.org/10.1007/s10646-020-02000-0>

doi.org/10.1007/s10646-020-02300-6

- Meftaul, I., Venkateswarlu, K., Dharmarajan, R., Annamalai, P., & Megharaj, M. (2020). Pesticides in the urban environment: A potential threat that knocks at the door. *Science of The Total Environment*, 711, 134612. <https://doi.org/doi.org/10.1016/j.scitotenv.2019.134612>
- Melymuk, L., Demirtepe, H., & Jílková, S. R. (2020). Indoor dust and associated chemical exposures. *Current Opinion in Environmental Science & Health*, 15, 1–6. <https://doi.org/10.1016/j.coesh.2020.01.005>
- Mesnager, R., Teixeira, M., Mandrioli, D., Falcioni, L., Ibragim, M., Ducarmon, Q. R., Zwiittink, R. D., Amiel, C., Panoff, J. M., Bourne, E., Savage, E., Mein, C. A., Belpoggi, F., & Antoniou, M. N. (2021). Multi-omics phenotyping of the gut-liver axis reveals metabolic perturbations from a low-dose pesticide mixture in rats. *Communications Biology*, 4(1). <https://doi.org/10.1038/s42003-021-01990-w>
- NIEHS. National Institute of Environmental Health Sciences. <https://www.niehs.nih.gov/health/topics/science/exposure/index.cfm> [last accessed February 2022]
- Nieuwenhuijsen, M. J. (Ed.). (2015). *Exposure assessment in environmental epidemiology*. Oxford University Press, USA. ISBN : 9780199378784
- Nishioka M.G., Lewis R.G., Brinkman M.C., Burkholder H.M. (2002). Foot transfer of lawn-applied pesticides from turf to carpet: Comparison of semivolatile chlorpyrifos with nonvolatile chlorothalonil. *Bull Environ Contam Toxicol*. 68(1): 64-71 (2002). <https://doi.org/10.1007/s00128-001-0220-x>
- Norén, E., Lindh, C., Rylander, L., Glynn, A., Axelsson, J., Littorin, M., Faniband, M., Larsson, E., & Nielsen, C. (2020). Concentrations and temporal trends in pesticide biomarkers in urine of Swedish adolescents, 2000-2017. *Journal of exposure science & environmental epidemiology*, 30(4), 756–767. <https://doi.org/10.1038/s41370-020-0212-8>
- Obendorf, S. K., Lemley, A. T., Hedge, A., Kline, A. A., Tan, K., & Dokuchayeva, T. (2005). Distribution of Pesticide Residues Within Homes in Central New York State. *Archives of Environmental Contamination and Toxicology*, 50(1), 31–44. <https://doi.org/10.1007/s00244-004-0185-y>
- OBO (2019). Research on exposure of residents to pesticides in the Netherlands: OBO flower bulbs. <https://www.rijksoverheid.nl/binaries/rijksoverheid/documenten/rapporten/2019/04/10/bijlage-1-onderzoeksrapport-obo/bijlage-1-onderzoeksrapport-obo.pdf> [last accessed February 2022]
- Oerlemans, A., Verscheijden, L., Mol, J., Vermeulen, R., Westerhout, J., Roeleveld, N., Russel, F., & Scheepers, P. (2019). Toxicokinetics of a urinary metabolite of tebuconazole following controlled oral and dermal administration in human volunteers. *Archives of toxicology*, 93(9), 2545–2553. <https://doi.org/10.1007/s00204-019-02523-5>
- OJEU. Official Journal of the European Union (2009). Directive 2009/128/EC of the european parliament and of the council, establishing a framework for community action to achieve the sustainable use of pesticides.

- Patrick-Iwuanyanwu, K. C., Bekibele, G. E., Egbuna, C., & Anacletus, F. C. (2020). Toxicological changes in female wistar albino rats exposed to solignum: A permethrin-containing wood preservative. *Current Topics in Toxicology*, 16(October), 183–194. <https://doi.org/10.31300/CTTX.16.2020.183-194>
- Pubmed. <https://pubmed.ncbi.nlm.nih.gov/?term=pesticide+mixture+effect&filter=years.2012-2022> [last accessed February 2022]
- Quirós-Alcalá, L., Bradman, A., Nishioka, M., Harnly, M. E., Hubbard, A., McKone, T. E., Ferber, J., & Eskenazi, B. (2011). Pesticides in house dust from urban and farmworker households in California: an observational measurement study. *Environmental health : a global access science source*, 10, 19. <https://doi.org/10.1186/1476-069X-10-19>
- Rani, L., Thapa, K., Kanojia, N., Sharma, N., Singh, S., Grewal, A. S., Srivastav, A. L., & Kaushal, J. (2021). An extensive review on the consequences of chemical pesticides on human health and environment. *Journal of Cleaner Production*, 283, 124657. <https://doi.org/10.1016/j.jclepro.2020.124657>
- Ritz, B., & Rull, R. P. (2008). Assessment of environmental exposures from agricultural pesticides in childhood leukaemia studies: challenges and opportunities. *Radiation Protection Dosimetry*, 132(2), 148–155. <https://doi.org/10.1093/rpd/ncn268>
- Rizzati, V., Briand, O., Guillou, H., & Gamet-Payraastre, L. (2016). Effects of pesticide mixtures in human and animal models: An update of the recent literature. *Chemico-Biological Interactions*, 254, 231–246. <https://doi.org/10.1016/j.cbi.2016.06.003>
- Rudel, R. A., Camann, D. E., Spengler, J. D., Korn, L. R., & Brody, J. G. (2003). Phthalates, Alkylphenols, Pesticides, Polybrominated Diphenyl Ethers, and Other Endocrine-Disrupting Compounds in Indoor Air and Dust. *Environmental Science & Technology*, 37(20), 4543–4553. <https://doi.org/10.1021/es0264596>
- Schummer, C., Salqu bre, G., Briand, O., Millet, M., & Appenzeller, B. M. (2012). Determination of farm workers' exposure to pesticides by hair analysis. *Toxicology letters*, 210(2), 203–210. <https://doi.org/10.1016/j.toxlet.2011.11.019>
- Simaremare, S., Hung, C., Yu, T., Hsieh, C., & Yiin, L. (2021). Association between Pesticides in House Dust and Residential Proximity to Farmland in a Rural Region of Taiwan. <https://doi.org/10.3390/toxics9080180>
- Sim es, M., Huss, A., Brouwer, M., Krop, E., Janssen, N., & Vermeulen, R. (2022). Residential proximity to crops and agricultural pesticide use and cause-specific mortality: A prospective census-based cohort study in the Netherlands. *Science of The Total Environment*, 817, 152932. <https://doi.org/10.1016/j.scitotenv.2022.152932>
- Siviter, H., Bailes, E.J., Martin, C.D., Oliver, T.R., Koricheva, J., Leadbeater, E., Brown, M.J.F. (2021). Agrochemicals interact synergistically to increase bee mortality. *Nature* 596, 389–392. <https://doi.org/10.1038/s41586-021-03787-7>.
- Taxvig, C., Hadrup, N., Boberg, J., Axelstad, M., Bossi, R., Bonefeld-J rgensen, E. C., &

- Vinggaard, A. M. (2013). In vitro - in vivo correlations for endocrine activity of a mixture of currently used pesticides. *Toxicology and Applied Pharmacology*, 272(3), 757–766. <https://doi.org/10.1016/j.taap.2013.07.028>
- Teyssiere, R., Manangama, G., Baldi, I., Carles, C., Brochard, P., Bedos, C., & Delva, F. (2021). Determinants of non-dietary exposure to agricultural pesticides in populations living close to fields: A systematic review. *Science of The Total Environment*, 761, 143294. <https://doi.org/10.1016/j.scitotenv.2020.143294>
- Velázquez-Gómez, M., Hurtado-Fernández, E., & Lacorte, S. (2019). Differential occurrence, profiles and uptake of dust contaminants in the Barcelona urban area. *Science of The Total Environment*, 648, 1354–1370. <https://doi.org/10.1016/j.scitotenv.2018.08.058>
- Veludo, A. F., Martins Figueiredo, D., Degrendele, C., Masinyana, L., Curchod, L., Kohoutek, J., Kukučka, P., Martiník, J., Přibyllová, P., Klánová, J., Dalvie, M. A., Rössli, M., & Fuhrmann, S. (2022). Seasonal variations in air concentrations of 27 organochlorine pesticides (OCPs) and 25 current-use pesticides (CUPs) across three agricultural areas of South Africa. *Chemosphere*, 289, 133162. <https://doi.org/10.1016/j.chemosphere.2021.133162>
- Viegas, C., Dias, M., Almeida, B., Vicente, E., Candeias, C., Aranha Caetano, L., Carolino, E., & Alves, C. (2021). Loading Rates of Dust and Bioburden in Dwellings in an Inland City of Southern Europe. In *Atmosphere* (Vol. 12, Issue 3). <https://doi.org/10.3390/atmos12030378>
- VoPham, T., Wilson, J. P., Ruddell, D., Rashed, T., Brooks, M. M., Yuan, J. M., Talbott, E. O., Chang, C. C. H., & Weissfeld, J. L. (2015). Linking pesticides and human health: A geographic information system (GIS) and Landsat remote sensing method to estimate agricultural pesticide exposure. *Applied Geography*, 62, 171–181. <https://doi.org/10.1016/j.apgeog.2015.04.009>
- Wang, S., Salamova, A., & Venier, M. (2021). Occurrence, Spatial, and Seasonal Variations, and Gas-Particle Partitioning of Atmospheric Current-Use Pesticides (CUPs) in the Great Lakes Basin. *Environmental Science and Technology*, 55(6), 3539–3548. <https://doi.org/10.1021/acs.est.0c06470>
- Wilson, R., Jones-Otazo, H., Petrovic, S., Mitchell, I., Bonvalot, Y., Williams, D., & Richardson, G. M. (2013). Revisiting Dust and Soil Ingestion Rates Based on Hand-to-Mouth Transfer. *Human and Ecological Risk Assessment*, 19(1), 158–188. <https://doi.org/10.1080/10807039.2012.685807>
- Yimam, Y., & Mohebal, M. (2020). Effectiveness of insecticide-impregnated dog collars in reducing incidence rate of canine visceral leishmaniasis: A systematic review and meta-analysis. *PLoS ONE*, 15(9 September 2020), 1–15. <https://doi.org/10.1371/journal.pone.0238601>
- Zhan, L., Cheng, H., Zhong, G., Sun, Y., Jiang, H., Zhao, S., Zhang, G., & Wang, Z. (2021). Occurrence of atmospheric current-use and historic-use pesticides at a CAWNET background site in central China. *Science of The Total Environment*, 775, 145802. <https://doi.org/10.1016/j.scitotenv.2021.145802>



Appendices



English summary

In the Netherlands, the application of pesticides on agricultural fields has raised concerns from residents living close to these. Several studies focusing on the association between pesticide exposure and health effects have indicated an increased risk for certain diseases. Most of these studies focus on occupationally exposed populations, where people perform jobs that involve handling pesticides or work in fields where these are routinely used. Although exposures are lower in the general population, there are studies performed in non-occupational settings that find links between exposure to pesticides and increased risk for a certain disease. To understand if a certain disease is related to an exposure to any given chemical, we first need to identify the exposed vs non-exposed population and also understand the levels, duration and frequency of exposure. In occupational settings, exposure is often assigned based on operator or worker reporting practices, and this knowledge drives the exposure ranking. But, in non-occupational settings, such as residents living close to agricultural fields, the main drivers of exposure are different. Residents are likely to be exposed to lower levels but for a longer duration due to spray drift and volatilization of pesticides from nearby agricultural land. Also, other populations are exposed, such as children, who may be more vulnerable. The possible accumulation of pesticides in the home environment may also contribute to the levels and duration of exposure.

To address the above and investigate residents' exposure to pesticides the "Onderzoek Bestrijdingsmiddelen en Omwonenden" (OBO-study) was developed. This study was commissioned by the National Institute for Public Health and the Environment (RIVM) and it aimed to assess pesticide exposure for residents living close (< 250 meters) to agricultural fields and to better understand the possible routes of environmental exposure. This thesis was developed as part of the OBO study.

This thesis

The theme of my thesis revolves around the characterization and quantification of residential exposure to pesticides. It is an exposure assessment study among residents living close to agricultural land, with focus on areas with bulb crops. The aim is on investigating residents' environmental exposure to pesticides by studying drivers of this exposure as well as temporal and spatial variability in environmental pesticides concentration. This is achieved by collecting and analyzing patterns in environmental and personal exposure data and estimating environmental concentrations using a deterministic modelling framework.

Chapter 2 details the protocol for the OBO study. This was an observational study conducted between 2016 and 2019 and involved residents living in the vicinity (<250 meters) of agricultural fields (flower bulbs) and residents living more than 500 meters away from any agricultural fields (controls). Residential exposures were measured in spraying and non-spraying periods. We assessed 96 homes and 192 participants, including 7 growers and 28 controls. We followed 14 pesticide applications, applying 20 active ingredients. We collected 1728 environmental samples: 1018 air, 445 dust, 265 soil and 2597 personal samples: 2485 urine and 112 hand wipes. Environmental samples were analyzed for 46 prioritized pesticides. Urine samples were analyzed for biomarkers of a subset of 5 pesticides. Chapter 2 describes, to the best of our knowledge, the first study on residents' exposure to pesticides addressing all major nondietary exposure sources and routes (air, soil, dust). This chapter provides the methodology used to study residential exposure to pesticides and a list of (practical) lessons learned.

Chapter 3 describes the spatial and temporal variation of 46 different current-use pesticide concentrations in air outside and inside homes located close (<250m) and further away from treated fields. From the 46 pesticides, 11 were actively used on nearby fields, 3 were used in bulb disinfection and 6 were degradation products. In this chapter we described that most pesticide concentrations were 5–10 times higher in outdoor air during spraying periods when compared with non-spraying periods. Concentrations were overall higher closer to the fields (<250 m) than further away. Correlations between indoor and outdoor air concentrations were low for some less volatile pesticides, indicating that for these pesticides group exposure levels can be quite different between inside and outside the home. Chapter 3 also highlighted that environmental exposure to pesticides via air is not limited to the day of application and may occur year-round and that factors influencing the local fate of pesticides in air may differ significantly between compounds.

Chapter 4 focuses on the indoor dust matrix and what it means for residential pesticide exposure. This is one of the least studied matrixes in residential exposure assessment of pesticides and hence filled an important knowledge gap regarding information on occurrence, levels and determinants of pesticides in dust in residential homes. These gaps were addressed by collecting house dust that was vacuumed in all homes from floors (VFD) and from newly placed clean doormats (DDM). This was the first time these matrixes were studied in parallel. Pesticides were found in indoor dust of all homes included in our study and we found that people living close to fields were exposed year-round to pesticides in house dust. In this chapter we studied the determinants

of occurrence and concentration of pesticides in VFD. We showed that the main determinants were like the ones included in current deterministic models, namely PEARL and OPS, and that we succeeded in accurately predicting occurrence of a given pesticide in dust. An important aspect of this study is highlighting that DDM might be a better proxy for pesticides in indoor dust for exposure assessment studies, given that it can be deployed for a certain period and capture exposure in a clearly defined time-frame, whilst VFD might be more appropriate for health assessment, given that it captures both past and current exposures. This is a result of indoor accumulation and slower indoor degradation of sprayed pesticides.

Chapter 5 describes the personal exposure in the residential setting. Handwipes and urine samples were collected in parallel from a subset population within the OBO-study. This study aimed on elucidating if there were personal exposure differences between spraying and non-spraying periods. Hand wipes were analyzed for the parent compound and urines samples for the corresponding urinary metabolite of the five applied pesticides. Concentrations in hand wipes were overall higher in pesticide use periods compared to non-use periods and higher in farmer families compared to non-farmer families. This chapter informs on determinants that were shown to influence variability of pesticide concentrations in handwipes, such as floor age, owning a pet and time of sampling. These have also been postulated in other studies, but with focus on indoor dust levels. The most important finding is a strong correlation between carbendazim in urine and handwipes, which is an indication of non-occupational dermal exposure via contaminated indoor surfaces.

Chapter 6 details a deterministic model framework (OBOmod) to assess exposure of residents living near fields where pesticides are applied. This chapter describes the first ever framework to include all major physical processes in residential exposure to pesticides. It includes five independent models that describe levels in the environment from the moment pesticides are released by the boom sprayer until they end up in the air and house dust. In this study we simulate fourteen bulb field applications under different weather conditions and comprising 12 pesticides. Modelled values were compared with concentrations measured in Chapter 3 (air) and Chapter 4 (house dust). The model evaluation shows that, with the exception of the dust model, the framework can be used in support of health and epidemiological studies, and can serve as a tool to support development of regulations and policy making regarding pesticide use. A very relevant finding that resulted from our simulations shows that, for some pesticides, cumulative exposure due to volatilization after application may be larger than exposure to droplet drift during application.

Chapter 7 focuses on the findings from each chapter in the light of previous works and describes future research paths. The work presented in this thesis represents the initial step into a more comprehensive assessment of residential pesticide exposure in the Dutch population. From the identified knowledge gaps and based on work from other academic peers, my recommendation for further improving residential exposure assessment to pesticides can be summarized in four points: 1) Perform research in areas where sideways or upward spraying techniques are used (such as fruit trees), given that these have higher emissions due to a higher drift potential. This would allow us to assess exposure levels related to these type of techniques, in addition to the downward spraying technique studied in OBO, and evaluate current models; 2) Focus more on pesticide levels in house dust since i) this route might be of relevance for residential exposures and should therefore be included in epidemiological studies, ii) it is a mirror of long-term exposure and iii) it can be especially important in exposure of more vulnerable populations, like toddlers, considering that they spent a great amount of time close to the ground; 3) Improve the current OBO modelling framework, by means of implementation and verification of a new dust module and spray drift for other types of spraying techniques and by making the OBOmod accessible to all; 4) It is time to focus on the dimensionality (co-occurrence) of pesticides (pesticide mixtures). Studies on mixtures in relation to possible adverse health effects are needed. Particularly, for pesticides with the same mode of action and which are frequently detected in our samples.

Nederlandse samenvatting

In Nederland heeft de toepassing van bestrijdingsmiddelen op landbouwpercelen tot zorgen gewekt bij omwonenden. Verschillende onderzoeken die zich richten op het verband tussen blootstelling aan pesticiden en gezondheidseffecten hebben een verhoogd risico op bepaalde ziekten aangetoond. De meeste van deze onderzoeken zijn gericht op beroepsmatig blootgestelde populaties, waar mensen beroepen uitoefenen waarbij ze met pesticiden omgaan of in velden werken waar deze routinematig worden gebruikt. Hoewel de blootstellingen lager zijn in de algemene bevolking, zijn er onderzoeken in niet-beroepsmatige blootgestelde populaties (omwonenden) die verbanden hebben laten zien tussen blootstelling aan pesticiden en een verhoogd risico op een bepaalde ziekte. Om te begrijpen of een bepaalde ziekte verband houdt met blootstelling aan een bepaalde chemische stof, moeten we eerst de blootgestelde versus niet-blootgestelde populatie identificeren en ook de concentraties, duur en frequentie van blootstelling begrijpen. In studies naar beroepsmatige blootstelling, wordt de blootstelling vaak toegewezen op basis van het rapporteren van werkomstandigheden en gebruikspraktijken van operators of werknemers. Deze informatie wordt vervolgens gebruikt in algoritmes om tot een blootstellingschatting te komen. Maar, in niet-beroepsmatige blootgestelde populaties, zoals bewoners die dicht bij landbouwvelden wonen, zijn de belangrijkste oorzaken van persticidenblootstelling anders. Bewoners worden daardoor blootgesteld aan lagere concentraties, maar voor een langere duur als gevolg van sproeinevel en vervluchting van pesticiden uit nabijgelegen landbouwgrond.

De mogelijke ophoping van pesticiden in de woonomgeving kan ook bijdragen aan de concentratie en duur van blootstelling. Bovendien zouden bepaalde subgroepen, zoals kinderen, blootgesteld kunnen worden aan hogere concentraties aan pesticiden gegeven het nauw en frequent contact met het vloeroppervlak.

Om de blootstelling van bewoners aan bestrijdingsmiddelen te onderzoeken is het Onderzoek Bestrijdingsmiddelen en Omwonenden (OBO-onderzoek) gestart. Dit onderzoek is uitgevoerd in opdracht van het Rijksinstituut voor Volksgezondheid en Milieu (RIVM) en had tot doel de blootstelling aan pesticiden van omwonenden (< 250 meter) van landbouwgronden te bepalen en de mogelijke routes van milieublootstelling beter te begrijpen. Dit proefschrift is onderdeel van het OBO-onderzoek.

Dit proefschrift

Het thema van mijn proefschrift draait om de karakterisering en kwantificering van blootstelling aan pesticiden van omwonenden. Het onderzoek is uitgevoerd onder omwonenden die in de buurt van landbouwgrond (bloembollen) wonen. Het doel van het onderzoek is om de milieublootstelling van bewoners aan pesticiden te onderzoeken door de determinanten van deze blootstelling te identificeren, evenals de temporele en ruimtelijke variabiliteit in de concentratie van pesticiden in de woonomgeving te bepalen. Dit is gedaan door het verzamelen van milieu- en persoonlijke blootstellingsgegevens en door milieuconcentraties te schatten met behulp van een deterministisch modelleringskader.

Hoofdstuk 2 beschrijft het protocol voor de OBO-onderzoek. Dit was een observationele studie uitgevoerd tussen 2016 en 2019 en het betrof bewoners die in de buurt van landbouwvelden (bloembollen) woonden (<250 meters) en bewoners die meer dan 500 meter verwijderd waren van landbouwgronden (controles). Blootstelling aan pesticiden bij omwonenden werd gemeten in zowel spuit- en niet-spuitperioden. We beoordeelden 96 woningen en 192 deelnemers, waaronder 7 telers en 28 controles. We volgden in totaal 14 toepassingen van pesticiden, waarbij in totaal 20 pesticiden werden verpoten. We verzamelden 1728 omgevingsmonsters: 1018 lucht-, 445 stof-, 265 grond- en 2597 persoonlijke monsters: 2485 urine en 112 handveegmonsters. De omgevingsmetingen werden geanalyseerd voor 46 geprioriteerde pesticiden. Urinemonsters werden geanalyseerd op biomarkers van een subset van 5 pesticiden. Hoofdstuk 2 beschrijft, voor zover wij weten, het eerste onderzoek naar de blootstelling van bewoners aan pesticiden, waarbij alle belangrijke bronnen en routes van blootstelling buiten voeding (lucht, bodem, stof) zijn onderzocht. Dit hoofdstuk wordt de methodologie gepresenteerd die is gebruikt om de blootstelling aan pesticiden in woningen te bestuderen en worden een aantal (praktische) geleerde lessen gepresenteerd.

Hoofdstuk 3 beschrijft de ruimtelijke en temporele concentratie van 46 verschillende, huidige gebruikte pesticiden in de lucht binnenshuis en buitenshuis van woningen dichtbij (< 250m) en verder weg van behandelde landbouwvelden. Van de 46 bestrijdingsmiddelen werden er 11 actief gebruikt op nabijgelegen velden, 3 werden gebruikt voor de desinfectie van bollen en 6 waren afbraakproducten. In dit hoofdstuk hebben we beschreven dat de meeste pesticiden concentraties 5-10 keer hoger waren in de buitenlucht tijdens spuitperioden in vergelijking met niet-spuitperioden. Over het algemeen waren de concentraties dicht bij de velden (<250 m) hoger dan verder weg. De correlaties tussen de binnen- en buitenluchtconcentraties waren laag voor

sommige minder vluchtige pesticiden, wat aangeeft dat voor laatste genoemde groep van pesticiden de blootstellingsniveaus behoorlijk kunnen verschillen tussen binnen en buiten het huis. Hoofdstuk 3 wees ook uit dat milieublootstelling aan pesticiden via de lucht niet beperkt is tot de dag van toepassing maar het hele jaar door kan voorkomen en dat factoren die het lot van pesticiden in de lucht beïnvloeden aanzienlijk kunnen verschillen tussen pesticiden.

Het onderzoek beschreven in hoofdstuk 4 was gericht op huisstof en de bijdrage daarvan aan de blootstelling aan pesticiden van omwonenden. Huisstof is een van de minst bestudeerde matrices voor de beoordeling van de blootstelling aan pesticiden in woningen en vult daarom een belangrijke kennislacune op met betrekking tot informatie over het voorkomen, de concentraties en determinanten van pesticiden in stof in huizen. De kennislacune is geadresseerd door huisstof te verzamelen in alle woningen door twee methodes: stofzuigen van vloeren (VFD) en door het plaatsen van nieuwe schone deurmatten (DDM). Dit was de eerste keer dat deze matrices parallel werden bestudeerd. Pesticiden werden aangetroffen in huisstof van alle huizen die in ons onderzoek waren opgenomen. Deze pesticiden werden niet alleen aangetroffen tijdens het spuitseizoen maar konden ook buiten het spuitseizoen worden gevonden. De belangrijkste determinanten van het voorkomen van pesticiden in VFD en DDM waren vergelijkbaar met die in de huidige deterministische modellen, namelijk PEARL en OPS. Een belangrijke bevinding van deze studie is dat DDM een betere benadering is voor pesticiden in huisstof in een blootstellingsbeoordelingsonderzoek, omdat het voor een bepaalde periode kan worden ingezet waardoor duidelijk is over welke tijdsperiode de pesticiden zich hebben verzameld in het huisstof. Echter DDM mist daardoor mogelijke accumulatie van pesticiden over een langere tijd. VFD is daarom mogelijk geschikter voor gezondheidsstudies, aangezien het zowel eerdere als huidige blootstellingen reflecteert.

Hoofdstuk 5 beschrijft de persoonlijke blootstelling van omwonenden. Handveeg- en urinemonsters werden parallel verzameld uit een subgroep van de deelnemers aan de OBO-studie. Het doel van dit onderzoek was om na te gaan of er persoonlijke blootstellingsverschillen waren tussen spuit- en niet-spuitperioden. Handveegmonsters werden geanalyseerd op de pesticiden en de urinemonsters op de overeenkomstige urinaire metaboliet(en) van vijf toegepaste pesticiden. De concentraties in veegmonsters waren over het algemeen hoger in perioden waarin pesticiden werden gebruikt op het veld in vergelijking met perioden van niet-gebruik en hoger in boerenfamilies dan in niet-boerengezinnen. Dit hoofdstuk beschrijft ook de determinanten waarvan is aangetoond dat ze de variabiliteit van pesticideconcentraties in veegmonsters

beïnvloeden, zoals de leeftijd van de vloer, het bezit van een huisdier en het tijdstip van bemonstering. Deze zijn ook gepostuleerd in andere onderzoeken, maar met de nadruk op stofniveaus binnenshuis. De belangrijkste bevinding is een sterke correlatie tussen carbendazim in urine en handveegmonsters, wat een indicatie is van niet-beroepsmatige huidblootstelling via besmette binnenoppervlakken.

Hoofdstuk 6 beschrijft een deterministisch model (OBOmod) om de blootstelling te modelleren van bewoners die in de buurt van velden wonen waar pesticiden worden toegepast. Dit hoofdstuk beschrijft het allereerste modelraamwerk dat alle belangrijke fysieke processen voor de blootstelling aan pesticiden van omwonenden omvat. Het raamwerk bestaat uit vijf onafhankelijke modellen die de niveaus in de omgeving beschrijven vanaf het moment dat bestrijdingsmiddelen vrijkomen vanuit de spuitboom totdat ze in de binnenlucht en het huisstof terechtkomen. In deze studie simuleren we veertien pesticidentoepassingen op bollenvelden bij verschillende weersomstandigheden. In het totaal werden er 12 verschillende bestrijdingsmiddelen verspoten tijdens deze toepassingen. De gemodelleerde waarden zijn vergeleken met de concentraties zoals beschreven in hoofdstuk 3 (lucht) en hoofdstuk 4 (huisstof). Uit de modevaluatie blijkt dat, met uitzondering van het stofmodel, het raamwerk kan worden gebruikt ter ondersteuning van gezondheids- en epidemiologische studies, en kan dienen als een hulpmiddel ter ondersteuning van de ontwikkeling van regelgeving en beleidsvorming met betrekking tot het gebruik van pesticiden. Een zeer relevante bevinding die uit onze simulaties voortvloeide, is dat voor sommige pesticiden de cumulatieve blootstelling als gevolg van vervluchtiging na toepassing groter kan zijn dan de blootstelling aan druppeldrift tijdens de toepassing.

Hoofdstuk 7 worden de bevindingen van elk hoofdstuk besproken in het licht van eerder werk en worden toekomstige onderzoekspaden beschreven. Het werk dat in dit proefschrift is gepresenteerd vormt de eerste stap naar een meer uitgebreide beoordeling van de blootstelling aan pesticiden in de Nederlandse bevolking. Op basis van de geïdentificeerde kennislacunes en op basis van werk van andere academische vakgenoten, kan mijn aanbeveling voor het verder verbeteren van de beoordeling van de blootstelling aan pesticiden bij omwonenden worden samengevat in vier punten: 1) Voer onderzoek uit in gebieden waar zijwaartse of opwaartse spuittechnieken worden gebruikt (zoals fruitbomen), aangezien deze een hogere emissie hebben vanwege een hoger driftpotentieel. Dit zou ons in staat stellen om blootstellingsniveaus gerelateerd aan dit soort technieken, naast de in dit onderzoek bestudeerde neerwaartse spuittechnieken, te beoordelen en huidige modellen te evalueren; 2) Focus meer op pesticideniveaus in huisstof, aangezien i) deze route van belang is voor omwonenden

en daarom meegenomen moet worden in gezondheidkundigonderzoek, ii) het een spiegel is van de langdurige blootstelling en iii) het vooral belangrijk kan zijn voor de blootstelling van meer kwetsbare populaties, zoals peuters, aangezien ze veel meer contact met het vloeroppervlak hebben en meer huisstof via hand-mond gedrag binnenkrijgen; 3) Verbeteren van het huidige OBO-model door implementatie en verificatie van een nieuwe huistofmodule en het includeren van spuitdrift voor andere soorten spuittechnieken dan neerwaardse spuitboom bespuitingen en door de OBOMod voor iedereen toegankelijk te maken; 4) Het is tijd om te focussen op de dimensionaliteit (gelijktijdig voorkomen) van blootstelling (bestrijdingsmiddelenmengsels). Onderzoek naar mengsels in relatie tot mogelijke nadelige gezondheidseffecten is nodig. Met name voor bestrijdingsmiddelen met hetzelfde werkingsmechanisme die veelvuldig in onze monsters worden aangetroffen.

Acknowledgement

I would like to start by acknowledging three professors from my previous university that through their lectures and occasional discussion, sparked my interest in research and indirectly motivated me to pursue a PhD. These are Prof. Dr. Aires dos Santos, Prof. Dr. Tiago Domingos and Prof. Dr. João Canário.

Coming to the Netherlands for a PhD was a great decision. Once I arrived I rapidly saw myself surrounded by great colleagues, which were a pillar of strength along my PhD journey. For that, I thank all colleagues that some way or another had an positive effect on my development as a researcher, as a supervisor and as a teacher.

Roel: I think in the beginning of our discussions you probably though “Ohh my, he as all these thoughts and ideas, but he needs to focus and prioritize”. Well, I can now say with confidence that by learning with you I have definitely improved on those skills. You were a promotor that ended up being also a second daily supervisor. Maybe you ended up seeing more of me than you would have liked :). Thank you for also giving me the freedom to work in more than one topic and in multiple little side projects. I am grateful that I had you as supervisor and I am looking forward to continue working with you in the future.

Jan: We had months with maybe once a week meetings where we would discuss topics related to dispersion modelling, atmospheric stability and others alike. And other long periods without any interaction. I enjoyed your approach on supervision – “Only meet if there is something important to discuss”. Our discussions helped me to elevate my thought process and to not take what other experts say for granted. I also want to thank you for the informal talks we would have about things that were not just work, such as life plans, vacation, music and so on. These were moments that relieved stress and I valued them a lot during my PhD journey.

319b: To all the friends I shared the 319b office...a huge thank you. Calvin, Ilse, Jules, Marije, Edith, Joseph, you have been more than colleagues at work, you are awesome friends. There are really not enough “thank you” for everything we have shared - Thank you Calvin for sparking my interest and educating me in special beers, whisky, coffee and the occasional off-work culinary fun and house moving. Thank you Jules for the carnival time, the talks about football and wie is de mol, and the occasional off-work board game fun. Thank you Marije for all the laughs, the talks about travelling and of course allowing us to stay at your place during the summer. Thank you Ilse, for the

support at the end of my PhD and for the off-work talks, drinks, and so on...Thank you all!...

Esmeralda and Daan: I could have not asked for a better duo as OBO colleagues. It would have been very difficult for me to succeed without your constant help and motivation in that first year. I am grateful to still be in contact with both of you and hope to keep our friendship forever.

Mariana, Nahid & Liese: You have been a support group in my first two years of PhD and I will always cherish those lunches at the UMC canteen where we would openly talk about our conquests and frustrations inside and outside work.

Maciek & Samuel: Our interaction was more constant in the last year of my PhD with us sharing regular football matches and the euro and world cup IRAS tournament, but also, in the case of Samuel, common research interests. One day I hope to be able to reunite the football team for a match and have some beers after. Those were great moments of relaxation.

Anke: We started working together about 2 years ago for my post-doc, but I want to acknowledge you here, because you 1) gave me motivation and enough time to finish my PhD thesis and 2) taught me how to say "no" to tasks that would end up being too much for my plate. I look forward to keep working with you for many years to come.

Ingrid, Christina, Petra, Djoeka, Ed: Thank you for all your help during my PhD, it was pivotal for me to succeed.

Mieke: You saw my eagerness to teach and supervise and you supported that side of my PhD without asking much in return. Without you I think I would have not been able to advance as fast as I did in my supervisor and teacher skills.

Finally...

Doce: As you know you were one of the main reasons I moved to the Netherlands. You were always there in the most stressful periods and you never stopped encouraging me. You also taught me to not overwork...which I still fail to do sometimes. Thank you for your companionship. I love you.

To my family: I love you. I could not have achieved this step in my career without your hard work and unwavering support. Thank you.

Curriculum vitae

Daniel was born in Cascais (Lisbon), Portugal on June 18, 1992. He graduated in 2015 from Instituto Superior Técnico (IST-Lisbon) majoring in environmental engineering (specialization in environmental modelling and management). In 2016, Daniel started pursuing a doctorate degree at the Institute for Risk Assessment Sciences (IRAS) at Utrecht University, producing the works presented in this thesis. During this time he has also contributed heavily in the report for the OBO-project (Research on exposure of residents to pesticides). Since 2020, Daniel has started his postdoctoral research at IRAS on Horizon2020 SPRINT project, where he focuses on modelling exposure to pesticides in Europe and developing a Global Health Risk Assessment Toolbox to assess impacts of these on environment and human health. Meanwhile, he has also joined the NWO funded VHP4Safety project, where he is developing an exposome (exposure throughout lifetime) scenario generator for pesticides. Since the start of his academic career, Daniel has published 13 articles; supervised 8 master projects, supervised 5 case-studies for bachelors and master courses, supervised college students in the U-talent program, gave theoretical and practical lessons in different subjects, such as deterministic and stochastic modelling, spatial interpolation and climate change. Finally, Daniel was also organizer of IRAS sports (2018-2020), a member of the IRAS Party Committee (2018-2021), organizer of IRAS Buddy system – quarantine (2020-2022) and a Member of the Diversity Safety, Inclusiveness workgroup (2022-ongoing).



Utrecht University

Institute for Risk
Assessment Sciences (IRAS)