Assessment of non-dietary, human exposure to pesticides

Hie Ling Wong

PhD

University of York

Environment

June 2018

Abstract

Assessment of non-dietary, human exposure to pesticides is an integral part of pesticide authorisation at the EU level. In this thesis, models were used to predict exposure of vulnerable human sub-populations to pesticides and thus to assess risks to health. Two high-quality pesticide usage datasets previously collected by Fera Science Ltd. and for EFSA were analysed. Trends in pesticide usage and major drivers of exposure and thus risk were identified, including any implications for regulatory procedures over the period investigated.

Residential exposure of pregnant women living at 100 and 1000 m downwind of treated orchards indicated improving fate (vapour pressure) and hazard profiles (reproductive/developmental toxicities) of pesticides applied in England and Wales over a 25-year period (1987, 1996, 2004 and 2012). Overall, results reflected the influence of changing policies during the 1990s and the ongoing review programme at national level.

Assessment of 50 agricultural professional operators across five cropping systems in Greece, Lithuania and the UK indicated a range of applications with potential for risk. Estimated exposure was significantly influenced by variations in agricultural practices and working behaviours involving the use of personal protective measures, including the extensive use of wettable powder formulations in Greece and large areas of land treated per day in Lithuania and the UK.

The 50 selected professional operators handled a range of active substances and/or co-formulants with known/possible endocrine disrupting activity during single spray days. At maximum, one operator handled five such active substances and ten such co-formulants in a single day. Thus, higher risk is expected in mixture than that predicted for single active substances.

Although the use of models in risk assessment has inherent uncertainties, these results add to the existing body of knowledge and allow a holistic assessment of the pesticide regulatory procedures over the period investigated.

Table of Contents

List of Tables

List of Figures

(Short titles)

List of Appendices

(Short titles)

Table legend

Figure legend

Acknowledgements

This work was sponsored by the Ministry of Education, Malaysia and University Malaysia Kelantan (UMK). The funding for this research is gratefully acknowledged. We also thank Fera Science Ltd. and the European Food Safety Authority for allowing use of their pesticide application data in this PhD study.

I would like to express my sincere gratitude to Professor Colin D. Brown for having supervised my PhD. Always approachable and encouraging, his patience and reliability have been very much appreciated and helped me maintain motivation and confidence throughout this study. I am also grateful to co-supervisors David Garthwaite and Dr Carmel Ramwell from Fera Science Ltd. for being very helpful and always available.

Finally, I would like to thank all the PhD students and staff of the Environmental Science research group for their support and good advice.

Author’s Declaration

Chapters of the present thesis have been written as papers for international peer-reviewed journals. The current publication status of the papers is presented in Table 1-1. All these papers have been reworked for a consistent style and format in this thesis. In addition, introductory and synthesising chapters have been added to briefly discuss about the whole research idea and to summarise the key findings, limitations, and recommendations for future research, respectively.

The papers have been written by the candidate as leading author, complemented by the suggestions and advice from the co-authors. Chapters 2 and 3 which are published, have also benefited from the comments of the anonymous referees as part of the review process, and copyright rests with the publishers.

The work in this thesis was undertaken as a PhD student at the Environment Department, University of York. Pesticide application data used in the research were collected by Fera Science Ltd. and for the European Food Safety Authority. I declare that this thesis is a presentation of original work and I am the sole author. This work has not previously been presented for an award at this, or any other, University. All sources are acknowledged as References.

Chapter 1 Introduction

Current agricultural activities rely to a large extent on the use of pesticides to secure yields and so help to meet demands from the rapid world-wide population growth, accelerated urbanisation, climate and dietary changes, and resource shortages (Schrijver, 2016). Agricultural activities are the primary target for pesticide applications with variability in loads in the environment explained by a range of factors including the physicochemical behaviour of active substances, agricultural practices, atmospheric conditions, nature of surfaces of application, and competing processes (Houbraken et al., 2016; Zhang et al., 2016; Villiot et al., 2018). During an application, 20-30% of pesticides may not reach the target area and are lost into the environment as spray drift (Villiot et al., 2018). After an application is complete, volatilisation followed by transport in the vapour phase may cause vapour drift from the treated plant and soil surfaces, accounting for as much as 90% of the applied dose at the extreme (Bedos et al., 2002). Pesticide drift may cause problems including damage to nearby plants, environmental contamination, illegal pesticide residues on food, and adverse effects on human health (Felsot et al., 2010; Hvezdova et al., 2018).

Studies on non-dietary exposure of humans to pesticides have been increasingly well documented over time. Upon contact with pesticides, active substances may dissolve and penetrate through the layer of wax on the skin and then enter into the blood stream (Herzfeld, 2017), whilst deposited soluble airborne chemicals in the lungs can be directly absorbed (ATSDR, 2005). Occupationally, professional agricultural operators may be confronted with particularly high exposure to complex mixtures of pesticides at levels hundreds of times greater than those for the general population (Sacchettini et al., 2015). There is also some evidence to indicate potential risks for residents living near to agricultural fields, particularly for sensitive sub-populations such as foetuses, children, pregnant and nursing mothers, and the elderly (Shirangi et al., 2010; Costa et al., 2014). The investigation of health issues related to exposure to pesticides can provide an important check on how pesticides have been and should be regulated (Andersson et al., 2014; Barnett et al., 2007). Nevertheless, poor exposure assessment remains a major limitation in the post-authorisation monitoring and epidemiological investigations (Mandic-Rajcevic et al., 2015; Kalliora et al., 2018).

Models that can simulate accurately scenarios for exposure of humans to pesticides are important tools in pesticide authorisation at the EU level. Much effort is expended to improve the existing exposure models to reflect current agricultural practices and scientific knowledge. For example, the UK Predictive Operator Exposure Model (UK POEM; UK MAFF, 1992) and the German Operator Exposure Model (the German model, Lundehn et al., 1992) were superseded recently by the harmonised Agricultural Operator Exposure Model (AOEM, Groβkopf et al., 2013a), and the Bystanders, Residents, Operators, and WorkerS Exposure models (BROWSE; Ellis et al., 2017) was introduced for regulatory application. Nevertheless, these models have some limitations mainly owing to sparcity of data and adopting reasonable worst-case assumptions, including a lack of exposure data for knapsack mixing/loading activities in the AOEM (Groβkopf et al., 2013b) and a maximum downwind distance of 10 m for pesticide vapour exposure in the BROWSE model (van den Berg et al., 2016). Whilst improvement to the existing models is needed as additional data become available, adjustable model parameters that allow exposure estimation for different scenarios are also important.

At the EU level, the control of pesticide use dates back to the first introduction of pesticide policies at this level in 1979 (Skevas et al., 2013). This was followed by Directive 91/414/EC that entered into force in 1993 and was repealed on 14 June 2011 with the Plant Protection Products Regulation (EC) 1107/2009 entering into force on 14 December 2009. Under the regulations, the authorisation of pesticide products is only granted if they have no immediate or delayed harmful effect on human health based on good agricultural practice and realistic conditions of use. Over time, persistent pesticides have been replaced by more biodegradable chemicals with currently about 400 active substances approved within the EU (Carvalho, 2017; Rieke et al., 2017). Despite much effort to minimise pesticide risk on human health, levels of exposure can be influenced by a wide variety of factors under actual use conditions. Equally, pesticide regulations usually require risk assessments on single active substances with additional, generally fewer data needed for commercial product formulations (Kienzler et al., 2016), whilst the CLP Regulation (EC) 1272/2008 on the classification, labelling and packaging of substances and mixtures transfers the responsibility to characterise toxicological hazard for pesticide co-formulants to industry. As such, mixture effects of pesticide chemicals comprising multiple active substances and/or co-formulants with similar toxicological endpoints have rarely been assessed to date.

The aim of this PhD is to assess the non-dietary exposure of vulnerable human populations to pesticides and to evaluate the efficiency of pesticide regulations in managing pesticide risk over the period investigated. The main objectives of this work are:

i. to identify the trends over 25 years (1987-2012) of pesticide usage and associated risk of exposure of pregnant women living at different distances downwind from treated orchards in England and Wales;
ii. to investigate how field practices in handling and applying pesticides influence the long-term exposure of agricultural professional operators to pesticides for different EU agricultural systems;
iii. to assess the real-world operator exposure to pesticide products/mixtures with potential endocrine activity comprising the range of active substances and co-formulants used in different EU agricultural systems; and
iv. to evaluate the major drivers of predicted exposure of target populations to pesticides including any implications for the regulatory assessment scheme.

Chapters of the present thesis have been prepared as stand-alone papers for submission to international peer-reviewed journals. The status of the different papers with regard to the publication process is presented in Table 1-1. An appendix is added at the end of this thesis with an initial evaluation of the mathematical model that is developed in *Chapter 2* for the prediction of airborne pesticide concentrations near to treated fields (Appendix 4).

Chapter 2 presents the patterns of pesticide usage in orchards over a 25-year period (1987-2012) in England and Wales, and the risk of environmental exposure to pesticides for pregnant women living at 100 and 1000 m downwind of treated orchards. A mathematical model is developed to predict levels of exposure to pesticides via indirect dermal contact with spray deposits and inhalation of volatilised pesticides. The impact of regulatory intervention in improving the fate and hazard profiles of pesticides over the period is investigated.

Chapter 3 reports the occupational exposure of professional agricultural operators to pesticides incurred during mixing/loading and application activities. The analysis considers five different cropping systems and regions in the EU. Levels of exposure are estimated using the harmonised Agricultural Operator Exposure Model (AOEM) and compared with the acceptable operator exposure level (AOEL) to assess the levels of risk associated with exposure to individual active substances applied. Any predicted exposures greater than the AOELs are investigated to identify the influencing factors including agricultural practices and working behaviours. The implications for operator exposure assessment within regulatory procedures are considered.

Chapter 4 presents the exposure of agricultural professional operators to constituents of all pesticide products applied on a single working days and comprising multiple active substances and/or co-formulants with known/possible endocrine disrupting activity. Levels of exposure to single chemicals are assessed using the AOEM and potential risk from such active substances is assessed using the lowest no observed (adverse) effect levels (NO(A)ELs) for endocrine disrupting effects and an assumption of concentration addition. Knowledge gaps in the current risk assessment for multiple pesticides with similar toxicological endpoints are identified.

Chapter 5 summarises the use of models for risk assessment, major drivers of exposure and associated risk, the implications for the regulatory assessment scheme, the limitations encountered, and the recommendations for further studies in the risk assessment of non-dietary, human exposure to pesticides.

Appendix 4 present an initial evaluation of the model developed for the prediction of airborne pesticide concentrations at a chosen distance downwind from a treated area. Field experimental data are used that were collected by the Swedish University of Agricultural Sciences during the periods of summer and autumn between 2008 and 2010 and five pesticide active substances. The results are analysed to determine the performance and limitations of the model and to identify any improvements to the model required for the future.

Table 1- 1. Publication status of the papers presented in the PhD thesis.

Chapter	Authors	Title	Status	Journal
2	Wong, H. L., Garthwaite, D. G., Ramwell, C. T. and Brown, C. D.	How does exposure to pesticides vary in space and time for residents living near to treated orchards?	Published	Environmental Science and Pollution Research 24 (2017) 26444-26461
3	Wong, H. L., Garthwaite, D. G., Ramwell, C. T. and Brown, C. D.	Assessment of exposure of professional agricultural operators to pesticides	Published	Science of the Total Environment 619-620 (2018) 874-882
4	Wong, H. L., Garthwaite, D. G., Ramwell, C. T. and Brown, C. D.	Assessment of occupational operator exposure to pesticide mixtures with endocrine disrupting activity	Submitted (June 2018)	Environmental Science and Pollution Research

Chapter 2 How does exposure to pesticides vary in space and time for resident living near to treated orchards?

Introduction

Pesticides are bioactive substances that have been widely used to improve agricultural production, reduce yield losses and maintain high product quality in order to meet the increasing demand for food from the world's growing population, particularly in intensive agricultural systems. Pesticides are chemical or biological agents designed to kill potential disease-causing organisms and control insects, other pests and weeds in both open and protected environments. Due to their intrinsic toxicity, it is necessary to quantify potential for transportation away from the point of application, exposure to humans and non-target ecosystems, and risk to human and ecological health. Pesticides are amongst the most highly regulated chemical classes due to the combination of bioactivity and use in open environments.

Spray drift and volatilisation followed by transport in the vapour phase are potential routes for dispersal of pesticides via the air. Spray drift is the downwind movement of spray droplets beyond the treated area at the time of application or soon after (Felsot et al., 2010). It is influenced by the nozzle and operating pressure of the equipment, height of the spray boom, and weather conditions at the time of application (Hofman and Solseng, 2001). After an application is complete, volatilisation followed by transport in the vapour phase can be an important pathway for pesticide emission from treated soil and plant surfaces, at the extreme accounting for as much as 90% of the applied dose over a period of a few days to several weeks (Bedos et al., 2002; Lichiheb et al., 2014). Sarigiannis et al. (2013) proposed that volatilisation from plant surfaces can be up to three times greater than that from soil, and volatilisation can be more important for total emissions of active substances compared to spray drift in the long term.

After entering into the atmosphere, spray drift can be transported by the wind before deposition of spray droplets locally while pesticide in the vapour phase following volatilisation can be transported over longer distances (Briand et al., 2002). Whilst much work has been done to measure downwind deposition of spray droplets, there is a lack of consistent methodology for quantifying airborne pesticide concentrations at a range of scales (Zivan et al., 2016; Lichiheb et al., 2016). Mathematical models are useful in complementing expensive and time-consuming field trials by including the complex processes that mediate the transfer of pesticides between different environmental compartments (Salcedo et al., 2017). A number of previous studies calculated vapour exposure using volatilisation models coupled with different dispersion modelling approaches including 3D Gaussian and a 2D version of OPS (Operational Atmospheric Transport Model for Priority Substances) (van den Berg et al., 2016). The BROWSE model (Bystanders, Residents, Operators and WorkerS Exposure models for plant protection products) is a recent development that combines a mechanistic volatilisation model and an advanced 3D dispersion model of OPS (van den Berg et al., 2016). Development of models for aerial transport and exposure to pesticides is still restricted by data availability. For example, the best data available while developing the airborne spray component of the BROWSE's orchard model did not give sufficient confidence in quantifying spray drift under different meteorological conditions and at different distances of exposure, implying that further experimental data are needed (Ellis et al., 2017).

There is evidence to suggest that residents living close to agricultural fields have greater exposure to pesticides compared to the general population, but very few studies have examined the dose-response relationships between exposure and health outcomes of interest (Shirangi et al., 2010). Sensitive sub-populations amongst residents could be at higher risk of health impacts than the general population and include foetuses, children, pregnant and nursing mothers, and the elderly (Costa et al., 2014). A systematic review and meta-analysis on residential exposure to pesticides and childhood leukaemia for 13 case-control studies published between 1987 and 2009 indicated stronger risk for exposure during pregnancy (meta-rate ratio (mRR): 2.19, 95% confidence intervals (CI): 1.92-2.50) compared to after pregnancy (mRR: 1.65, 95% CI: 1.33-2.05) (Van Maele-Fabry et al., 2011). Nevertheless, the study highlighted recall bias as a major limitation of case-control studies where questionnaire data are used to assess past exposure. Shirangi et al. (2010) suggested that residential proximity to pesticide applications during pregnancy could be associated with adverse reproductive outcomes in offspring. However, epidemiological evidence from 25 studies published between 1950 and 2007 was generally weak, primarily due to limitations in the assessment of exposure. The study suggested that future research should refine the methods on exposure modelling by incorporating environmental monitoring studies on pesticide drift. Weselak et al. (2007) reviewed epidemiological evidence on periconceptual pesticide exposures and developmental outcomes based on studies published between 1966 and 2005 and reported generally poor exposure estimations and limited evidence for causality in all the associations examined due to self-reported, indirect, or proxy exposure measures.

Regulatory assessments prior to authorisation of plant protection products require quantitative estimates of exposure to pesticides via the air for comparison with toxicological reference levels, below which no adverse health effects is expected (Galea et al., 2015). In Europe, the estimation of exposure to pesticides for operators, workers, residents and bystanders is underpinned by the guidance of EFSA (2014). However, sparcity of data on concentrations of volatilised pesticides in air has been noted as a limitation on exposure assessment (Ellis et al., 2010), as has a general lack of research into methods for estimating exposure and risk to the general public (Coscolla et al., 2017).

The Pesticide Authorisation Directive 91/414/EEC, ratified in 1993, legislated for a comprehensive review of plant protection products already on the market; of the ca. 1,000 active substances on the market in 1993 in at least one Member State, only around 250 (26%) passed the EU harmonised safety assessment, with the remainder either unsupported by industry (67%) or rejected following review (7%) (Balderacchi and Trevisan, 2010; EU Commission, 2009). These pesticides were mainly deregistered due to either their toxicity profile or restricted efficacy due to the development of resistance in the control target (Karabelas et al., 2009).

Post-authorisation monitoring schemes provide an important check that regulatory procedures are robust in the protection afforded to human health. In the UK, the Pesticide Incidents Appraisal Panel (PIAP) of the Health and Safety Executive (HSE) reviews incidents of alleged ill health that are attributed to pesticide exposure both at work and for members of the public (HSE, 2015). The Pesticide Incident Report 2012/13 (HSE, 2015) investigated 45 pesticide incidents (64% lower than the average for the previous ten years), with 15 complaints involving allegations of ill health of which 20-25% were classified as ‘confirmed’ or ‘likely’. An earlier scheme based on general practitioners estimated the prevalence and incidence of pesticide-related illness between 2004 and 2008. That study identified significant limitations in defining a pesticide-related cause of ill health because there is generally limited information on actual chemicals used and no routine confirmation of exposure through biological tests (Rushton and Mann, 2008). These are important caveats on the overall conclusion from post-authorisation monitoring that there is no evidence for widespread impacts of agricultural pesticides on human health in the UK.

Whilst much work considers the risks to human health from use of pesticides, there is a gap between risk assessment as part of regulatory procedures, post-authorisation monitoring, and longer-term epidemiological investigations. Regulatory assessments are the only place where exposure is routinely quantified, but this is done one chemical at a time and there is no oversight of total exposure to pesticides or of how this may be changing in time. Post-authorisation monitoring and epidemiological studies take a more holistic perspective on potential for health impacts, but have generally failed to include quantitative estimates of exposure. Thus an independent study of how exposure to pesticides varies in space and time provides an important check for the regulatory process.

This study investigates how pesticide usage and associated exposure and risk vary in space and time to provide a holistic evaluation of the impact of regulation. We selected off-target exposure to residents living close to treated areas as our test system, focusing on orchards which have relatively high usage of pesticides and treatments that are often directed into crop canopies, and pregnant women who are a vulnerable group because they may spend long periods at home and because some pesticides have potential for reproductive and/or developmental effects. We assessed variation in pesticide usage, exposure and risk (i) between orchard crops, (ii) between regions of England and Wales, (iii) across different seasons, and (iv) between different years over a time series spanning 25 years (1987-2012). Supplementary information for this study is provided as Appendix 1.

Methodology

Identification of potential routes/pathways of exposure

Cornelis et al. (2009) developed a GIS-based indicator for environmental exposure to pesticides, proposing the selection of cut-off values for the radii of zones around the site of application based on the decrease in airborne concentrations of pesticides. Following this procedure, two categories of proximity were identified in the current study, namely 0-200 m (central point at 100 m) and 0-2000 m (central point at 1000 m) such that airborne pesticide concentrations decreased by approximately 5-fold from 100 m to 1000 m.

Off-target movement of pesticides can result in contaminated food, water, air, dust, and soil and the potential for human exposure via inhalation, ingestion or dermal absorption through contact with contaminated surfaces (Sutton et al., 2011). Four pathways of exposure are considered in the standard EU risk assessment for residents which uses a model of residents living 8 m downwind from the middle of the last row in orchard crops (EFSA, 2014); these pathways are (i) spray drift resulting in direct exposure via dermal penetration and inhalation; (ii) spray drift causing deposits on the ground and other surfaces leading to dermal exposure; (iii) vapour dispersal leading to inhalation of airborne pesticides following volatilisation from residues on soil and/or the treated crop; and (iv) entry into treated crops causing exposure through direct contact with surface residues. Spray drift decreases very rapidly with distance from the treated field (Rautmann et al., 1999) and preliminary modelling showed that direct dermal and inhalation exposure from spray drift were insignificant contributors to total exposure for residents living 100 or 1000 m from the treated area due to the combination of rapid fallout of spray droplets from the air with increasing distance from the site of application (Sarigiannis et al., 2013; van de Zande et al., 2014), and short duration of exposure. As direct exposure to airborne spray droplets occurs only at the time of application or soon after, residents are mainly exposed to pesticides via the indirect dermal route from spray drift deposits (e.g. working, standing or sitting in a garden near to the application) and inhaled pesticide vapour that may occur continuously throughout the day (Felsot et al., 2010; Martin et al., 2008). We assumed that there was no entry of our target population into the treated crop. Calculations thus considered the potential for individuals living in the vicinity of treated orchards to be exposed via inhalation of pesticide vapour and indirect dermal contact with contaminated surfaces for a period of time following the application.

Pesticide usage data

Information on the use of plant protection products in the UK is required under EU legislation (EC Regulation 1185/09). Pesticide usage data have been collected systematically since 1965 by the Pesticide Usage Survey carried out by Fera Science Ltd. (formerly Central Science Laboratory, and the Food and Environment Research Agency). Field level data were not stored on relational databases until 1987. Prior to this only summary data from the published reports were stored on a relational database. The survey relies on a stratified random sample of farms to estimate total use, allowing comparability of data over time. For the current investigation, orchard data had been collected on a four-year rolling basis, i.e., 1987, 1992, 1996, 2000, 2004, 2008, and 2012. Collecting data via personal visits to the farms improves accuracy as surveyors can scrutinise all potential pesticide uses which might have occurred to ensure the farmers do not omit or forget anything important (Thomas, 1999; Eurostat, 2008).

In this study, we first evaluated changes in usage across all survey years and then selected four years for more detailed analysis to estimate changes in exposure and risk to health. The first orchard usage data were collected in 1983, but methodology was not consistent with subsequent studies. Hence, 1987 was chosen as the starting year and 1996, 2004, and 2012 were included to give approximately 8-year intervals up to the latest survey reported at the time of analysis. The main orchard crops grown in England and Wales are listed in Table 2-1 alongside the four regions of England and Wales included in the analysis on the basis that together they accounted for 95.8% of total orchard cultivation in 2012 (Figure A1-1). A total of 132 individual active substances are identified within the usage surveys as having been applied to major orchard crops in at least one of the years considered. The application rate, AR of an active substance for every application was one of the major factors in the exposure modelling. We estimated the average rate applied to each hectare of orchard from statistics for total amount applied and total area of each crop grown in a region. We calculated the exposure from applications of individual active substances based on monthly usage statistics. Hence, both treatments with a single substance in successive months or a single treatment with a product containing two active substances would both count as two applications in the exposure calculation.

Table 2- 1. Area of major orchard crops in four regions that accounted for 95.8% of total orchard cultivation in England and Wales in 2012 (Garthwaite et al. 2012).

Crop type	Crop grown area (ha)				
	Eastern	West Midlands	South-Eastern	South-Western	Total for England and Wales
Cherries	27	187	464	1	697
Cider apples/perry pears	83	5,244	41	2,731	8,619
Culinary apples (Bramley)	585	47	1,438	10	2,140
Culinary apples (others)	129	-	1	8	146
Dessert apples (Cox)	277	288	1,317	33	1,960
Dessert apples (others)	419	414	3,367	86	4,447
Other top fruit (incl. nuts)	45	-	131	36	213
Pears	340	88	1,295	24	1,757
Plums	160	170	426	150	973
Total grown area	2,065	6,438	8,480	3,079	20,952
% of total area	9.9	30.7	40.5	14.7	100.0

Models for pesticide fate and exposure

Exposure calculations predicted the maximum daily exposure (mg kg bw^{-1} day^{-1}) to each active substance applied to orchard crops, calculating the exposure as that for the first 24 hours after pesticide application. The EFSA assessment for residents' exposure to pesticides is currently based on the highest time-weighted average exposure for the first 24 hours after application via inhalation from vapour and 2 hours of dermal exposure to surface deposits (EFSA, 2014). The FOCUS Air group considered that the largest exposure would occur within a 24-hour period following application when taking into account the effects of dilution and dispersion of residues due to changing meteorological conditions (FOCUS, 2008). Here, we used a simplified additive method to calculate the exposure to and the cumulative reproductive and/or developmental risk associated with all pesticides applied to a single orchard crop type across a chosen year. Dissipation of active substances in soil and on plant surfaces was not included, so no attempt was made to estimate the change in exposure during the days/weeks after treatment.

A new model was developed to estimate exposure via inhalation of vapour, drawing on existing algorithms used in PEARL (Pesticide Emission Assessment at Regional and Local scales; van den Berg and Leistra, 2004), PELMO (Pesticide Leaching Model; Ferrari et al., 2005), and ISCST2 (Industrial Source Complex Short Term 2; US EPA, 1992a). Indirect dermal contact with contaminated ground was estimated from the equations provided by EFSA (2014) for systemic exposures of residents via dermal routes. Where parameters were set to default values, these are listed in Table A1-1.

Volatilisation from treated surfaces (source emission)

Algorithms from the PEARL and PELMO models were adjusted to estimate the rate of pesticide emissions after application from plant and soil surfaces, respectively. The PEARL model incorporates the concept of atmospheric resistance to pesticide volatilisation based on the thickness of laminar air boundary layers and diffusion of vapour from the plant surface to the turbulent air. It incorporates the effect of prevailing meteorological conditions on the initial estimation of pesticide volatilisation from crops in the field. PELMO estimates volatilisation from soil water by assuming negligibly low concentration of pesticide in the air above the soil (not including soil-air partitioning) (Wolters et al., 2003). Other competing processes for dissipation of pesticides in different environmental compartments were not included in our calculations so that leaching, transformation and wash-off from plant surfaces were all excluded, creating a more protective risk assessment.

The saturated vapour concentration of pesticide in the gas phase at the plant surface, C_{g,p_s} (g m^{-3}), depends on its substance-specific vapour pressure at the prevailing temperature. C_{g,p_s} is calculated using the Gas Law as described by van den Berg and Leistra (2004):

$$\boldsymbol{C_{g,p_s} = \frac{M \cdot VP(T)}{R \cdot T}} \qquad \textbf{(Eqn. 1)}$$

where M is the molecular mass (g mol^{-1}), $VP(T)$ is the vapour pressure of the pesticide (Pa) as a function of temperature based on PPDB (2017), R is the universal gas constant (Pa m^3 K^{-1} mol^{-1}), and T is the air temperature (K). The potential rate of volatilisation of pesticide from the leaf surface, J_{plant} (g m^{-2} day^{-1}) is calculated as:

$$\boldsymbol{J_{v,pot}} = \frac{\boldsymbol{C_{g,p_s} - C_{air}}}{\boldsymbol{r}} \qquad \textbf{(Eqn. 2)}$$

where C_{air} is the concentration in the turbulent air just outside the laminar air layer (g m^{-3}), and r is the resistance to transport from plant surface to atmosphere (d m^{-1}) calculated as the ratio of thickness of the boundary air layer, d (m) to the adjusted air diffusion coefficient, D_a (m^2 day^{-1}). It has been proposed that d ranges between 0.05 and 0.1 cm depending on the micrometeorological conditions (e.g. air velocity and turbulence) and surface properties (e.g. temperature and roughness) (Leistra and Wolters, 2004; FOCUS, 2008; Lichiheb et al., 2014; Houbraken et al., 2016). We used default values of 0.06 and 0.1 cm for the thickness of the boundary air layers on plant leaves and soil surfaces, respectively (van den Berg et al., 2016); sensitivity of rate of pesticide volatilisation to the value of d (Figure A1-2) illustrates the inversely proportional relationship (a doubling in d halves the emission rate). However, all the areic quantities such as fluxes are expressed per m^2 field surface (not plant surface). Consequently, the actual rate of pesticide volatilisation from plant surfaces, J_{plant} (g m^{-2} day^{-1}; maximum daily emission is the mass of pesticide per unit area of plant immediately after application) is estimated by taking into account the mass of pesticide on the plants:

$$\boldsymbol{J_{plant} = f_{mas} \cdot J_{v,pot}} \qquad \textbf{(Eqn. 3)}$$

with f_{mas} (dimensionless) is the factor to adjust amount of pesticide present on the plants as described by:

$$\boldsymbol{f_{mas} = \frac{A_p}{A_{p,ref}}} \qquad \textbf{(Eqn. 4)}$$

where A_p refers to the areic mass of pesticide on the plants (g m^{-2}) obtained by multiplying application rate, AR (g m^{-2}) with the crop interception factor, and $A_{p,ref}$ is the reference areic mass of pesticide on the plants. This assumes that thinner deposits on the leaves will be depleted sooner and the volatilising surface decreases along with the mass of pesticide in the deposit.

Algorithms from PELMO were used in the estimation of pesticide emission rates from exposed soil surfaces on a daily basis (Wolters et al., 2003; Ferrari et al., 2005):

$$\boldsymbol{J_{soil} = \frac{H' c_{sol}}{r}} \qquad \textbf{(Eqn. 5)}$$

where J_{soil} is the volatilisation rate from soil (g m^{-2} day^{-1}; maximum daily emission is the mass of pesticide per unit area of soil immediately after application), H' is the non-dimensional Henry's law constant, and c_{sol} is pesticide concentration in the soil pore water (g cm^{-3}), and r is the resistance to transport from the soil surface to the atmosphere as calculated in Eqn. 2 (d m^{-1})**.** Adjustments were required for three temperature-dependent parameters, namely D_a, H' and VP, while c_{sol} depends on application rate and the substance-specific organic carbon partition coefficient, K_{oc} (mL g^{-1}) with the use of default values for fraction of organic carbon, f_{oc} and dry soil bulk density (g cm^{-3}). According to Leistra et al. (2001), D_a was adjusted with:

$$\boldsymbol{D_a = D_{a,ref} \left(\frac{T}{T_{ref}}\right)^{1.75}} \qquad \textbf{(Eqn. 6)}$$

where $D_{a,ref}$ is the diffusion coefficient in air at 20°C, and T_{ref} is the reference temperature at 20°C. H' was adjusted with a $Q10$ factor that was derived as the median value of a range of factors (1.15-2.28) that have been reported for different active substances (Staudinger and Roberts, 2001; Feigenbrugel et al., 2004; Cetin et al., 2006). $Q10$ is defined as the ratio of degradation rates between the rates at 20° and 10°C (EFSA, 2007). According to Sarigiannis et al. (2013),

$$\boldsymbol{VP = VP_{ref} \cdot exp\left[-\frac{\Delta H_{vap}}{R}\left(\frac{1}{T} - \frac{1}{T_{ref}}\right)\right]} \qquad \textbf{(Eqn. 7)}$$

where VP_{ref} is the saturated vapour pressure of the substance at reference conditions (mPa), ΔH_{vap} is the molar enthalpy of evaporation (J mol^{-1}), R is the universal gas constant (J K^{-1} mol^{-1}), and T is the air temperature (K), and T_{ref} is the reference air temperature (K).

Two parameters were shared between calculations for volatilisation from the two surfaces, namely the crop interception factor (*CI*) and monthly air temperature. For *CI*, emission rates of the pesticide from treated surfaces (plant and soil) were both estimated based on pesticide deposition at different growth stages (Leistra et al., 2001). *CI* values for apple trees were obtained from FOCUS (2000) and applied in calculations for all other orchard crops (Table A1-

2). The proportion of sprayed pesticide reaching the soil surface was calculated by difference. Mean monthly air temperatures for the past 35 years (1980-2015) were obtained from the Meteorological Office as regional climatic records and the 35 values for each month were averaged to derive monthly air temperature values to input into the calculations (Table A1-3).

The area source emission rate (Q_{act}, g m^{-2} s^{-1}) from all treated surfaces was calculated for each application of an active substance:

$$\boldsymbol{Q_{act}} = \frac{(\boldsymbol{J_{plant}} + \boldsymbol{J_{soil}})}{\mathbf{86{,}400}} \qquad \textbf{(Eqn. 8)}$$

where 86,400 converts the units of time from days to seconds.

Dispersion of volatilised pesticides downwind

A Gaussian diffusion model was used to estimate airborne concentrations of pesticide at different distances downwind of the emission source. ISCST2 was chosen because it is adaptable to various types of source emissions (i.e., point sources, volume sources, and area sources). The area source model of ISCST2 has frequently been used to assess the effects of pollutants on local air quality using emission rates and meteorological conditions as model inputs (Abdul-Wahab, 2004). It is adjustable for various parameters including height of crops (m), treated area (ha), wind speed (m s^{-1}), and mixing height (m).

By assuming that no crosswind (y=0) occurs at the area source and that atmospheric conditions are neutral, the total emission rate from both soil and plant surfaces was translated into airborne pesticide concentration at downwind distance, X (m) (measured from the downwind edge of the source area) by:

$$\boldsymbol{X} = \frac{\boldsymbol{Q_{act} \cdot V \cdot E \cdot X_o}}{\boldsymbol{4 \cdot \sqrt{2} \cdot U_s \cdot \sigma_z}} \qquad \textbf{(Eqn. 9)}$$

where Q_{act} is the area source emission rate (g m^{-2} s^{-1}), V is the vertical term (-), E is the error function term (-), X_o is the length of the side of the square area source (m), U_s is the wind speed (m s^{-1}), and σ_z is the vertical standard deviation (-).

The parameter, V was required to change the form of the vertical concentration distribution from Gaussian to rectangular (uniform concentration within the surface mixing layer) at downwind distances as follows:

$$\boldsymbol{V = exp[-0.5(\frac{z_r - h_e}{\sigma_z})^2] + exp[-0.5(\frac{z_r + h_e}{\sigma_z})^2] + \sum_{i=1}^{\infty}\{exp[-0.5\,(\frac{z_r - (2iz_i - he)}{\sigma_z})^2\ ] + exp[-0.5(\frac{z_r + (2iz_i - he)}{\sigma_z})^2] + exp[-0.5(\frac{z_r - (2iz_i + he)}{\sigma_z})^2] + exp[-0.5(\frac{z_r + (2iz_i + he)}{\sigma_z})^2]\}}$$

(Eqn. 10)

where h_e is the crop height (m), z_r is the adult height above ground (m), and z_i is the mixing height (m) adjusted based on crop height (Randerson, 1984) with:

$$\boldsymbol{z_i = \frac{0.3\,u^*}{f}}$$ **(Eqn. 11)**

where f is the Coriolis parameter (s^{-1} at 40° latitude) and u^* is friction velocity ($m\ s^{-1}$) calculated for the reference wind speed, $u(z)$ at 2.0 m above the ground using the logarithmic wind profile relationship:

$$\boldsymbol{u(z) = \frac{u*}{k} In\,(\frac{z}{z_0})}$$ **(Eqn. 12)**

where k is the von Karman's constant (dimensionless) and z_0 is the roughness parameter (m) approximated as 10% of the height of the crop surface.

The error function term, E is described by:

$$\boldsymbol{E = erf(\frac{r_o'+y}{\sqrt{2}\sigma_y}) + erf(\frac{r_o'-y}{\sqrt{2}\sigma_y})}$$ **(Eqn. 13)**

where $r_o{}'$ is the effective radius of area source $\frac{X_o}{\sqrt{\pi}}$ (m), and σ_y is the lateral vertical standard deviation.

The dispersion parameters were calculated according to a power-law fit to wind tunnel data (US EPA, 1992b):

$$\boldsymbol{\sigma_y = 0.73547\ X^{0.64931}}$$ **(Eqn. 14)**

$$\boldsymbol{\sigma_z = 0.28565\ X^{0.71285}}$$ **(Eqn. 15)**

Calculation of inhalation exposure

Concentrations in air derived from the air dispersion modelling were converted into individual exposures according to EFSA (2014):

$$\boldsymbol{SER_I} = \frac{\boldsymbol{VC \cdot IR \cdot IA}}{\boldsymbol{BW}} \qquad \textbf{(Eqn. 16)}$$

where SER_I is defined as the systemic exposure of residents via the inhalation route (mg kg bw^{-1} day^{-1}), VC is the estimated pesticide vapour concentration (mg m^{-3}) at the selected proximity, IR is inhalation rate (m^3 day^{-1}), IA is inhalation absorption (-), and BW is body weight (kg).

Inhalation rate was set to 13.8 m^3 day^{-1} based on default values for an adult female of 0.23 m^3 day^{-1} kg^{-1} daily inhalation rate of residents to vapours and 60 kg body weight for adults (US EPA, 2009; EFSA, 2010). A literature search was undertaken for information on absorption factors via the lungs following inhalation of pesticides; there is no consistent information on this process, so a default value of 100% absorption via inhalation was used (Ellis et al., 2013; EFSA, 2014; GroBkopf et al., 2013). Body weight for an adult female was set to 60 kg as recommended by EFSA (2014).

Calculation of indirect dermal exposure

Systemic exposure via the dermal route, SER_D (mg kg bw^{-1} day^{-1}) was calculated according to EFSA (2014):

$$\boldsymbol{SER_D} = \frac{\boldsymbol{AR \cdot D \cdot TTR \cdot TC \cdot H \cdot DA}}{\boldsymbol{BW}} \qquad \textbf{(Eqn. 17)}$$

where AR is the application rate (mg cm^{-2}), TTR is the turf transferable residue (-), TC is the transfer coefficient (cm^2 hr^{-1}), H is the exposure duration (hour), DA is the dermal absorption (-), and BW is the body weight (kg). D is the drift fraction which is calculated in accordance with crop growth stages:

For early growth stages, $\boldsymbol{D} = \left(\frac{\mathbf{3908.3}^*(\boldsymbol{X}^{-\mathbf{2.421}})}{\mathbf{100}}\right)$ **(Eqn. 18)**

For late growth stages, $\boldsymbol{D} = \left(\frac{\mathbf{298.83}^*(\boldsymbol{X}^{-\mathbf{1.8672}})}{\mathbf{100}}\right)$ **(Eqn. 19)**

For downward herbicide applications, $\boldsymbol{D} = \mathbf{2.7705}^{*}\left(\boldsymbol{X}^{-\mathbf{0.9787}}\right)$ **(Eqn. 20)**

where X is the selected downwind distance (m) (Rautmann et al., 1999).

Dermal absorption (DA) values for individual active substances (n=132) were extracted from the EFSA scientific reports on peer review of risk assessments for individual active substances, EFSA DAR and the Risk Characterisation Documents from the California Department of Pesticide Regulation; a default value of 75% was used for substances where no measured values were found (EFSA, 2012).

Calculation of total exposure

Estimated levels of exposure (mg kg bw^{-1} day^{-1}) to individual active substances for the two identified routes/pathways were summed to give an aggregated exposure:

$$\boldsymbol{\Sigma Exposure}_{(\boldsymbol{AS})} = \boldsymbol{Expsoure}_{(\boldsymbol{Inhaled\ vapour})} + \boldsymbol{Exposure}_{(\boldsymbol{indirect\ dermal})} \quad \textbf{(Eqn. 21)}$$

Subsequently, the total exposures to individual substances were summed to give an aggregated exposure for individual crops:

$$\boldsymbol{\Sigma Exposure}_{(\boldsymbol{crop\ type})} = \boldsymbol{Exposure}_{(\boldsymbol{AS_i})} + \cdots + \boldsymbol{Exposure}_{(\boldsymbol{AS_{i+n}})} \quad \textbf{(Eqn. 22)}$$

Timing of exposure to different compounds was not explicitly considered in the calculation and is discussed as a constraint on the methodology in “Discussion” section.

Risk estimation

Generally, regulatory risk assessment of pesticides in the EU is undertaken for single active substances or single pesticide products (Stehle and Schulz, 2015). The implementation of cumulative and combined exposures to pesticides is explicitly required by the regulatory agencies under Regulation (EC) 1107/2009 (Stein et al., 2014; Panizzi et al., 2017). The use of dose addition in regulatory risk assessment is considered sufficiently conservative as a default first tier approach for cumulative assessment, where the risk is deemed acceptable if the sum of all hazard quotients (HQ) ≤1 (Sarigiannis and Hansen, 2012; Stein et al., 2014). The risk from exposure to individual active substances was calculated based on the hazard quotient (HQ) approach:

$$\boldsymbol{HQ} = \frac{\boldsymbol{Exposure\ estimate\ for\ individual\ AS}}{\boldsymbol{Reference\ point}} \quad \textbf{(Eqn. 23)}$$

The reference point in this research refers to the no observed (adverse) effect level (NO(A)EL) for reproductive and/or developmental effects for individual substances. Reference points were extracted from four established toxicological databases, namely the EFSA Draft Risk Assessment Report (DAR) and Assessment Report (AR) (http://dar.efsa.europa.eu/dar-web/provision), the Joint Meeting on Pesticide Residues (JMPR) of the International Programme on Chemical Safety (IPCS INCHEM, http://www.inchem.org/pages/jmpr.html), the Integrated Risk Information System (IRIS, https://www.epa.gov/iris), and the Hazardous Substances Data Bank (HSDB) in the Toxicology Data Network (TOXNET, https://toxnet.nlm.nih.gov/newtoxnet/hsdb.htm).

One of the major issues in selecting the most relevant threshold for an individual active substance was the unclear boundary between reproductive and developmental effects for different periods of exposure (i.e. before pregnancy and during different trimesters). For instance, the EFSA DAR defines reproductive toxicities based on endpoints such as reduced offspring body weight or liver weight in two- and/or three-generation studies while developmental toxicities are assessed based on endpoints such as skeletal malformation, teratogenicity, and foetotoxicity. Meanwhile, the JMPR interprets the reproductive parameters as number of implants, resorptions, and dead foetuses, and developmental parameters refers to post-implantation variation in foetuses, and decreased viability indices. Generally, reproductive toxicity refers to any toxicological effects that may occur at different phases within the reproductive cycle while developmental toxicity refers to any effects in prenatal developmental studies and in one- or multi-generation studies (Wolterink et al., 2013). Since the test parameters were not uniquely classified, the lowest NO(A)ELs for reproductive and/or developmental effects were selected for use. As for the different thresholds in four different toxicological databases due to different study designs, the lowest NO(A)ELs for either reproductive or developmental toxicity were selected for use. This approach avoids any exclusion of potential higher toxicity for an individual active substance. It was found that 8 out of the 132 active substances applied to orchards in our dataset have no published toxicological thresholds for reproductive and/or developmental effects due to their chemical structure and here no NO(A)ELs was allocated (Table A1-4). For four active substances with significant use in at least one of the study years, the NO(A)EL were allocated based on either a major constituent in the compound (benzo-a-pyrene for tar oil), or similarity of chemical structures (dichlorprop-P/dichlorprop and mecoprop-P/mecoprop). Heptenophos has no data but is expected to be hazardous, so the NOAEL for chlorpyrifos was used, whilst the NOAEL for metiram was estimated by dividing the published LOAEL by two.

Studies on inhalation toxicity are lacking for most pesticides. Approximately 80% of inhalation risk assessments are based on route-extrapolated oral studies, whilst 20% of inhalation NOAEL data are route-extrapolated to dose (in mg kg bw^{-1} day^{-1}) from measured air concentrations (Salem and Katz, 2006). In the absence of data, the inhalation NOAEL is typically extrapolated from an oral study by assuming inhalation absorption is 100% of oral absorption due to the likelihood of higher absorbed dose via the inhalation route (Kegley and Conlisk, 2010).

Results

Pesticide usage

Figure 2-1 shows changes in total amount of pesticides applied to orchards in the four regions over a 25-year period with 4-year intervals. Data are shown with (Figure 2-1a) and without (Figure 2-1b) applications of tar oils as some of the associated rates of application were large and could mask changes in the other active substances used. Across the full period, the total amount of pesticide applied in any one year ranged between 2.0 and 21.0 kg ha^{-1}. Generally, there was greater usage of pesticide for orchards in the Eastern and South-Eastern regions compared to the West Midlands and South-Western regions. The total amount of pesticide applied was always greatest in 1987 and had decreased by 1992 and 1996 in all four regions. In contrast, no consistent changes were found for the later survey years (1996-2012) with some increases in total amounts applied in specific years between 2000 and 2012. The results revealed that the South-Western region had a large decrease in total applied amounts from 1987 to 1992, followed by a constant decline from 1992 to 2004 and inconsistent changes between 2004 and 2012. In contrast, total pesticide used in the South-Eastern region was approximately equal in 1987 and 2012 independent of whether or not tar oils were included.

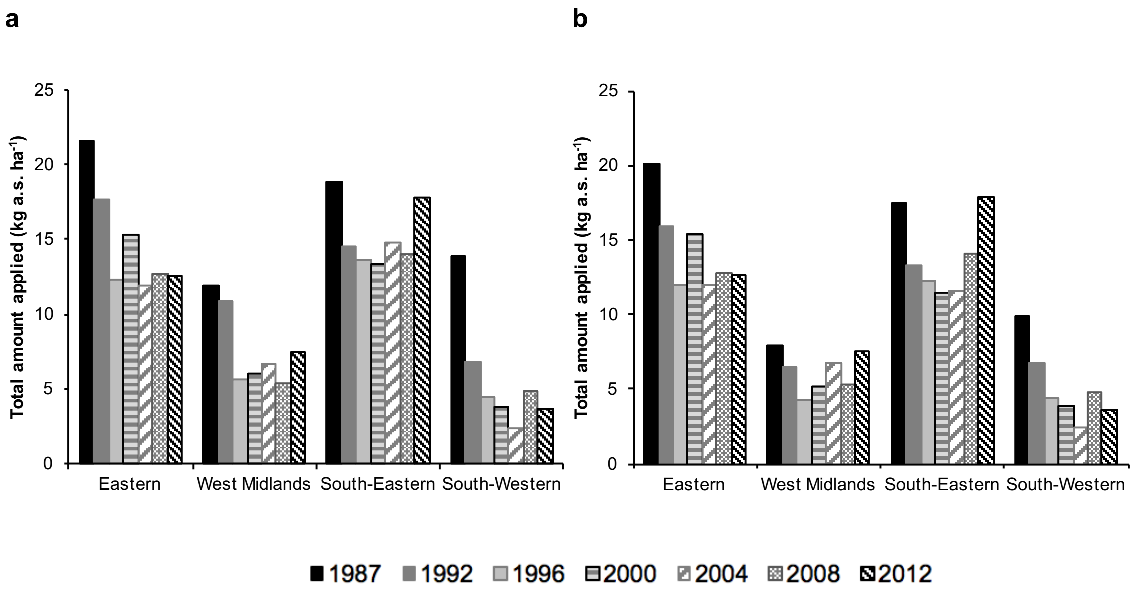


Figure 2- 1. Changes between 1987 and 2012 in total amount of pesticide applied to orchards cultivated in four regions of England and Wales. Data are shown either with tar oils included (a) or excluded (b).

The results were further analysed for four chosen years with approximately 8-year intervals from 1987 up to 2012 to investigate trends in pesticide usage for individual crop types. Tar oils were excluded from this analysis as they significantly skewed the total application amounts for plums and cherries in 1987 and to a lesser extent in 1996 and 2004. For instance, the highest application rate for plums in the South-Western region in 1987 (60.2 kg a.s. ha^{-1}) and cherries in the West Midlands region in 1987 (35.6 kg a.s. ha^{-1}) comprised 98.6 and 99.8% tar oils, respectively (Figure A1-3).

Total amount of pesticides applied to individual crop types was generally less than 30.0 kg a.s. ha^{-1} when tar oils were excluded (Figure 2-2). Some consistently low application amounts were identified for crops such as cherries, other top fruit and plums in all four regions (Figures 2-3b and A1-4b) although sample size was small due to the small area of each crop grown. The Eastern region showed declining trends of total application amounts for culinary apples (Bramley and others) and dessert apples (Cox) from 1987 to 2012. Meanwhile, the West Midlands and South-Western regions with relatively smaller pesticide usage showed no significant trends. Most crop types in the South-Eastern region had higher total application amounts in 2012 as compared to 2004. When tar oils were removed from the dataset, the greatest total amount of pesticide applied was for culinary apples (others) in the South-Eastern region in 2012 that comprised 71.5% captan, 8.3% chlorpyrifos, 6.0% dithianon, and 14.2% other substances.

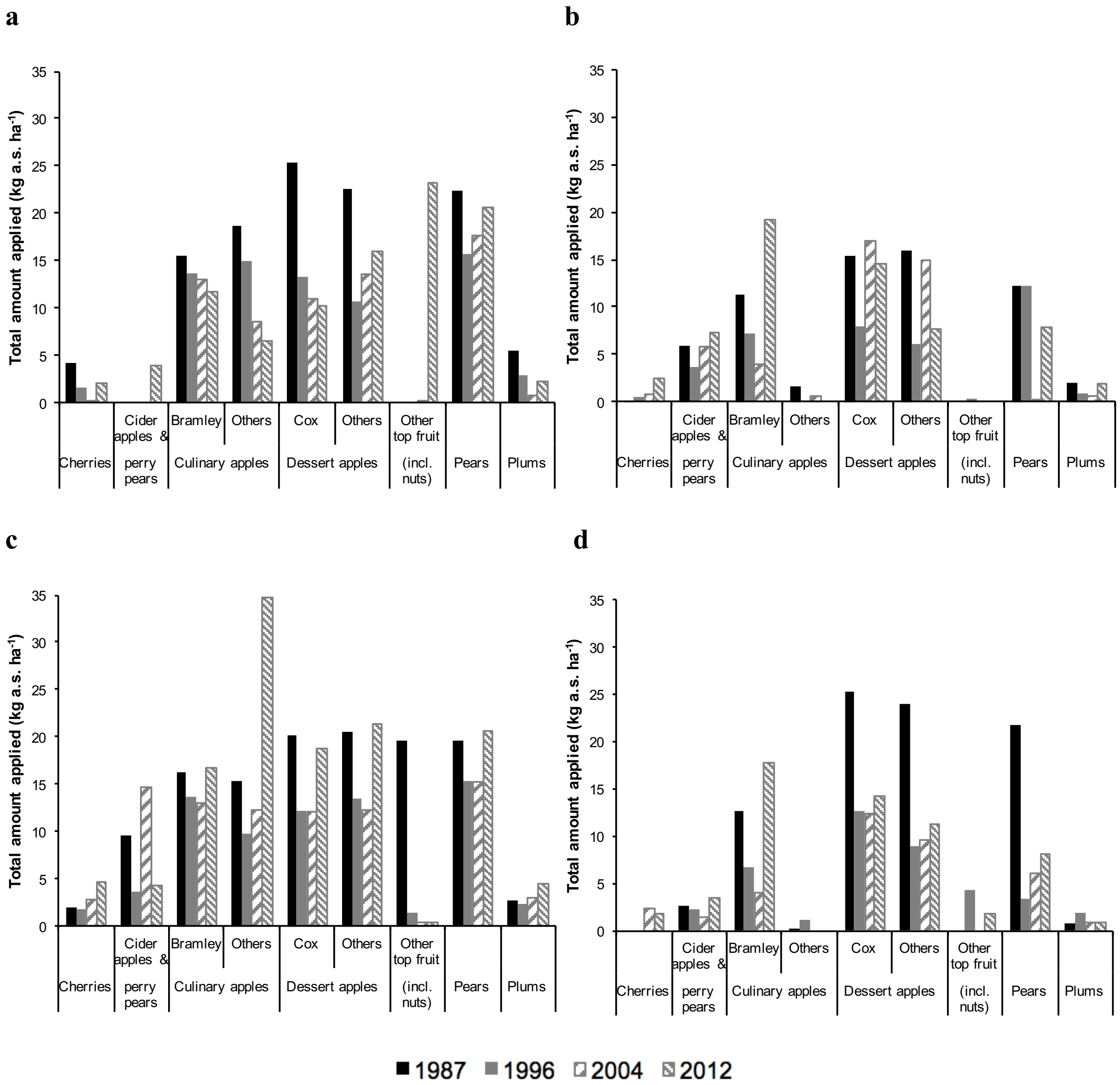


Figure 2- 2. Total amount of pesticide applied to major orchard crop types between 1987 and 2012 for Eastern (a), West Midlands (b), South-Eastern (c), and South-Western (d) regions. Blanks indicate that none of that orchard types were sampled in that region and tar oils are excluded from the data as large application rates obscure other trends.

Figure 2-3 presents the usage data as total number of applications of an active substance and as average rate of application across all treatments. There has generally been an increase in the number of applications of an active substance (Figure 2-3a), but this has been accompanied by a general decrease in the average rate of application (Figure 2-3b). The average application rate (Figure 2-3b) better explains the trends in pesticide usage with similar patterns to those shown in Figure 2-1, i.e. the highest average application rates and total applied amounts were in 1987 for all chosen regions (Figure A1-4).

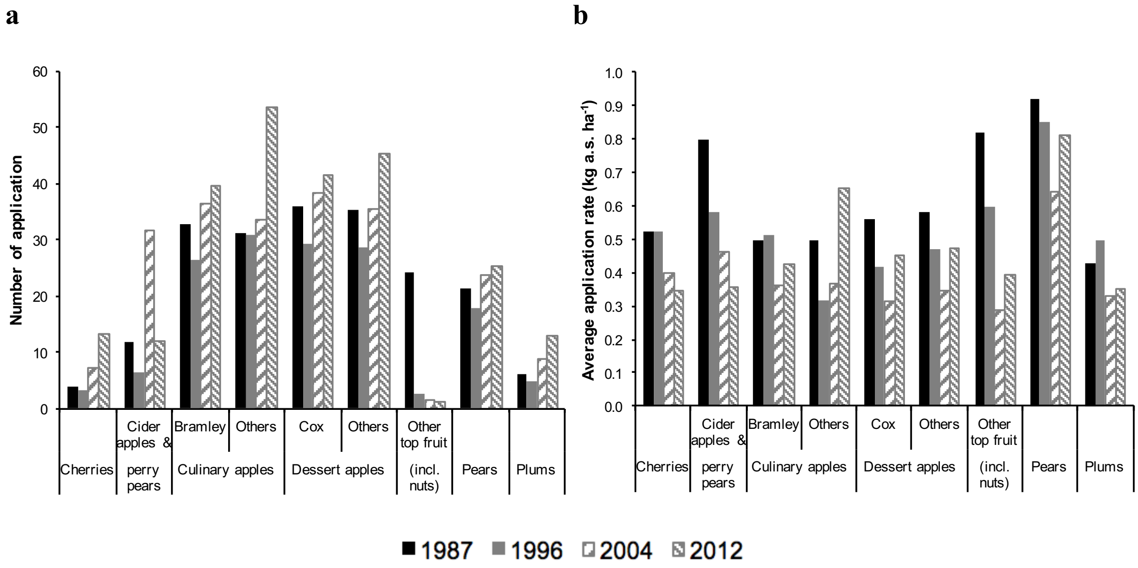


Figure 2- 3. Usage of pesticide for orchard crop types cultivated in the South-Eastern region with usage of tar oils excluded. Data are expressed as number of applications (a) defined as treated area divided by area grown, and average application rate (b) defined as total amount applied divided by number of applications. Here, application is defined as one treatment with one active substance, so successive treatments with a single active substance or a single treatment with a product containing two active substances would both count as two applications.

Aggregated exposures for residents living 100 m downwind

Aggregated exposure to pesticides via inhaled pesticide vapour and contact with contaminated ground were estimated for residents living 100 m downwind of individual crop types. Tar oils were included in all estimations of exposure and risk. Aggregated exposures to individual crop types were generally smaller than 2.0×10^{-3} mg kg bw^{-1} day^{-1} with most of the largest estimates in 1987 and values decreasing over the survey years (Figure 2-4). The Eastern and South-Western regions showed decreasing trends for most of the crop types while the West Midlands region showed less consistency in aggregated exposures. In comparison, the South-Eastern region indicated relatively high and constant exposures with small changes over the years. Overall, the exposures were smallest in 2012 with a couple of exceptions including culinary apples (Bramley) in the West Midlands region that increased approximately seven-fold from 2004 (1.4×10^{-4} mg kg bw^{-1} day^{-1}) to 2012 (9.6×10^{-4} mg kg bw^{-1} day^{-1}). In some cases, aggregated exposures greater than 2.0×10^{-3} mg kg bw^{-1} day^{-1} were strongly affected by tar oils, i.e., plums in the South-Western region in 1987 (6.1×10^{-3} mg kg bw^{-1} day^{-1}) and cherries in the West Midlands region in 1987 (3.6×10^{-3} mg kg bw^{-1} day^{-1}) where total exposure was approximately 99.5% attributable to tar oils.

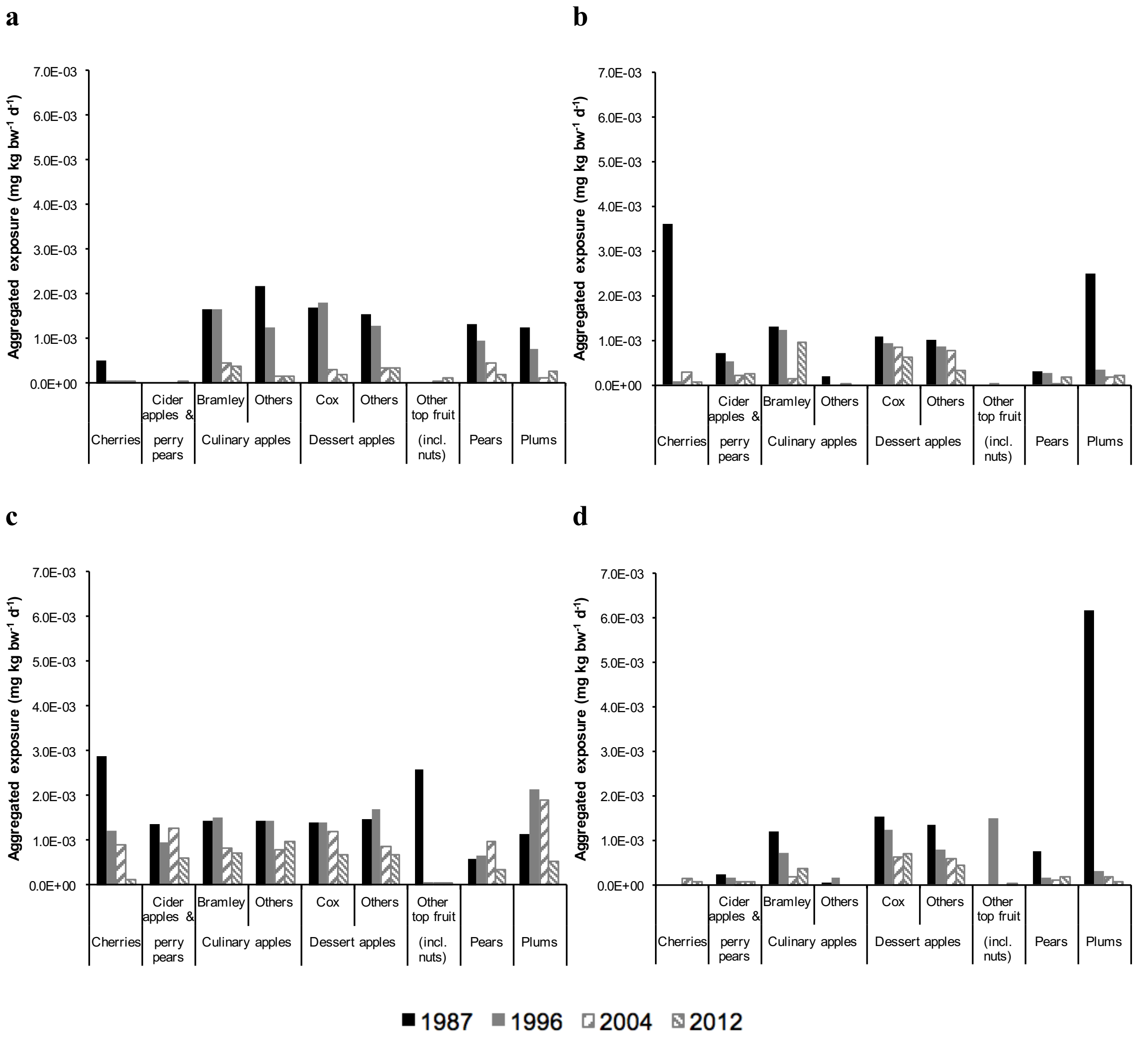


Figure 2- 4. Aggregated exposures to applied pesticide for residents living 100 m downwind of individual crop types. Data are shown for four years between 1987 and 2012 and for Eastern (a), West Midlands (b), South-Eastern (c), and South-Western (d) regions.

Aggregated hazard quotients for residents living 100 m downwind

Exposure estimates were converted into HQs using reproductive and/or developmental toxicities of the applied pesticides. Figure 2-5 shows that all aggregated HQs were at least two to three orders of magnitude smaller than 1, despite the inherent simplifications of assuming co-occurrence of exposure to all pesticides and additivity of effects. 1987 had the highest aggregated HQs and these decreased greatly by 1996, followed by smaller changes between 1996 and 2012. Generally, the Eastern, West Midlands, and South-Western regions had relatively lower aggregated HQs for most of the crop types compared to those for the South-Eastern region. Aggregated HQs were smallest in 2012 for most crop types, but with exceptions including culinary apples (Bramley) in the West Midlands region that increased approximately six-fold in 2012 ($6.2x10^{-4}$) when compared to 2004 ($9.9x10^{-5}$). For individual crop types with relatively larger aggregated HQs, results were influenced significantly by one or two dominant active substances. For instance, the highest aggregated HQ for plums in the South-Eastern region in 1987 ($6.8x10^{-3}$) comprised 95.6% demeton-S-methyl and 4.4% other substances; that for 1996 ($5.0x10^{-4}$) comprised 47.8% chlorpyrifos, 36.4% tar oil, 7.6% demeton-S-methyl, and 8.2% other substances; that for 2004 ($5.5x10^{-4}$) comprised 72.3% chlorpyrifos, 26.0% tar oil, and 1.7% other substances; and that for 2012 ($4.1x10^{-4}$) comprised 96.3% chlorpyrifos and 3.7% other substances.

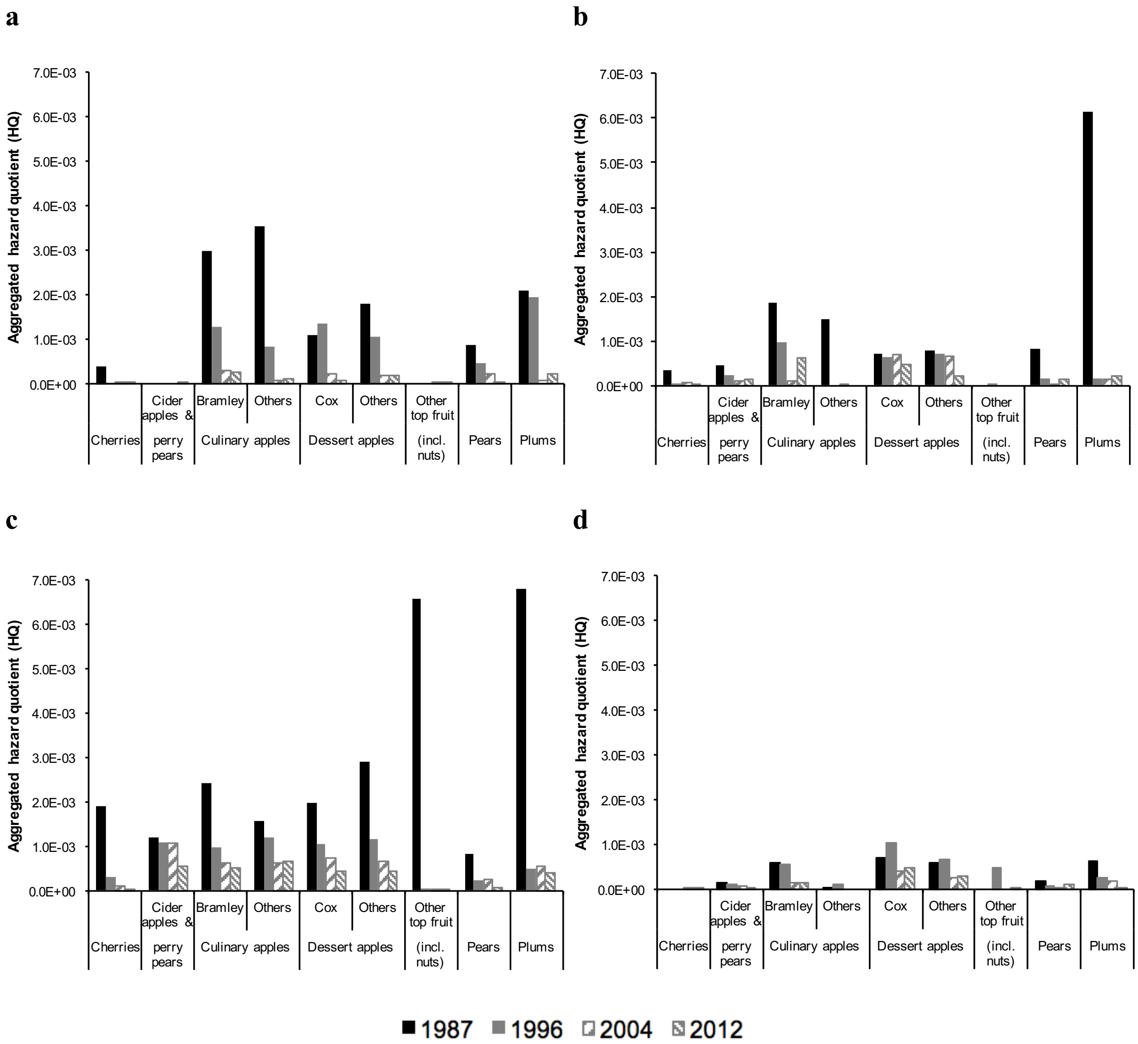


Figure 2- 5. Aggregated hazard quotients of reproductive and/or developmental toxicities to applied pesticide of resident pregnant women living 100 m downwind of individual crop types. Data are shown for four years between 1987 and 2012 and for Eastern (a), West Midlands (b), South-Eastern (c), and South-Western (d) regions.

Aggregated exposures and hazard quotients at 1000 m downwind

Aggregated exposures and risks to health were also estimated for residents living 1000 m from the treated orchard. Aggregated exposures to most of the crop types were smaller than 3.0×10^{-4} mg kg bw^{-1} day^{-1} (Figure A1-5) with exposure in 1987 and 1996 again estimated to be generally larger than that in 2004 and 2012. The estimations indicated decreasing trends in exposure for most crop types, particularly between 1996 and 2012. The aggregated exposures at 1000 m were converted into corresponding aggregated HQs and the results showed the same trends as at 100 m but with much smaller absolute values (Figure A1-6). Overall, the aggregated exposures and HQs at 1000 m for different crop types were approximately 5 to 16 times smaller than the equivalent values at 100 m.

Discussion

We applied consistent methodologies to compare year-on-year changes in pesticide usage, potential for residential exposure to pesticides, potential risk for reproductive or developmental effects on human health, as well as the major drivers of any changes over the past 30 years in England and Wales. It is important to note that aggregated exposures and risks summed daily values into a single measure even though exposure to different active substances will be widely dispersed in time; thus the data should not be taken as true estimates of daily exposure for direct comparison with daily dose thresholds for toxicity.

Based on four representative regions, average of total pesticide usage across the surveyed years showed a significant decrease from 1987 (66.2 kg a.s. ha^{-1}) to 1996 (49.8 kg a.s. ha^{-1}), followed by smaller changes through to 2012 (41.7 kg a.s. ha^{-1}) (Figure A1-7). This finding is supported by a time-series analysis of orchard fruit production in Great Britain with a decrease of approximately 22% in the mean usage from 1992 (42,000 kg) to 2008 (33,000 kg) (Cross, 2013). Our results show an average 13% increase in total usage in 2012 (41.7 kg a.s. ha^{-1}) compared to 2008 due to widespread application of fungicides (Figures A1-7 and A1-8) to control scab and powdery mildew in the wet weather conditions (Garthwaite et al., 2012). Our results are expressed as amount of pesticide applied to one hectare of crop, so are adjusted for any changes in the area of cultivated orchards over time (Thomas, 2003). There was a small but relatively consistent increase in the number of applications of individual active substances to crops; this was offset by a small, but relatively consistent decrease in average application rates over the surveyed years (Figures 2-3 and A1-4). This could reflect an increased uptake of reduced-rate applications at less than the maximum recommended label rate and the introduction of new molecules that are active at lower dose rates (Thomas, 2003).

We simplified the estimation of exposure by only considering that part of the dose received within 24 hours of the pesticide treatment. This should give a maximum dose when expressed on a daily basis. We further simplified within our aggregation procedure, by summing the daily doses and hazard quotients calculated for each individual treatment, independent of when those treatments occurred. Analysis shows that usage and thus exposure were significantly larger between April and July than for the remainder of the year (Figure A1-9). The relative sensitivity for reproductive and/or developmental outcomes of exposure pre-conception or during a specific trimester is unknown (Gonzalez-Alzaga et al., 2015). This is because the critical embryologic period is short and limited to the early stage of gestation before the diagnosis of pregnancy (Castilla et al., 2001). The peak in exposure each year suggests that temporal differentiation in health outcomes would be expected if such outcomes were associated with pesticide use (Li et al., 2014). The CHAMACOS study of associations (95% CI) of proximity to methyl bromide use within a 5 km radius during pregnancy (n=442) showed that the second trimester was a critical period for gestational growth and that exposure was associated with a decrease in means of birth weight (21.4 g), length (0.16 cm) and head circumferences (0.08 cm) (Gemmill et al., 2013). Despite the simplifications in producing aggregated estimates of risk, all values for the aggregated hazard quotient were two to three orders of magnitude or more smaller than one. Overall, this suggests a low level of risk to human health for the situation because co-occurrence of exposure to all pesticides applied to a single crop and additivity of effects from all individual active substances were implicit assumptions that will not hold true.

Figures 2-4 and 2-5 indicate that although there was no consistent change in total pesticide applied to orchard crops over time, there were small decreases in exposure and larger decreases in risk over time for most of the crop and region combinations. To investigate this further, data were normalised to express exposure per unit pesticide applied and risk per unit of exposure (Figure 2-6).

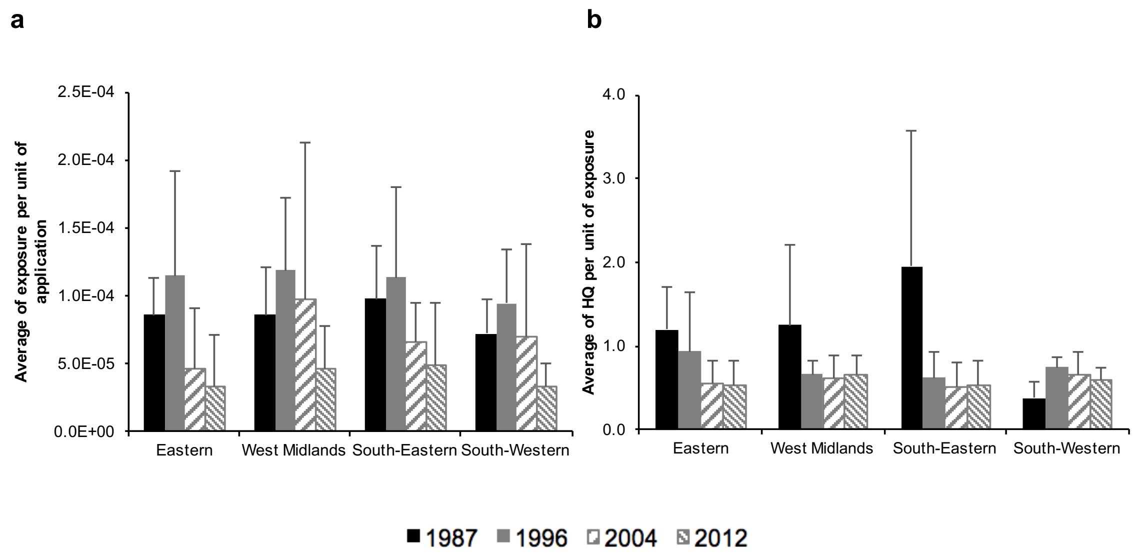


Figure 2- 6. Data for aggregated exposure normalised by expressing per kg of pesticide applied (a) and aggregated hazard quotient normalised by expressing per mg kg bw^{-1} day^{-1} of exposure (b). All data are for resident pregnant women living 100 m downwind of treated crops and are shown for four years between 1987 and 2012 and for Eastern (a), West Midlands (b), South-Eastern (c), and South-Western (d) regions. Error bars represent standard deviations of exposures and hazard quotients for identified crop types, respectively.

Overall, there was a small increase in estimated exposure per unit application between 1987 and 1996, but a steady decrease thereafter in all four regions (Figure 2-6a). In contrast, there was a relatively large decrease in risk per unit exposure between 1987 and 1996 for three of the four regions, with only small changes thereafter (Figure 2-6b). The decrease in risk per unit exposure between 1987 and 1996 can be attributed to the review and withdrawal from the market of compounds with relatively high toxicity for reproductive/developmental effects, including DDT, methidathion, azinphos-methyl, and cyhexatin. This initial impact of deregistrations after the introduction of Directive 91/414 is not apparent in the calculations for exposure per unit application (Figure 2-6a). However, it is interesting to note that this metric does decrease during the period 1996 to 2012, primarily due to the cessation of use of active substances with relatively higher volatility such as demeton-S-methyl, gamma-HCH, and fenitrothion. Over the full period considered, there has been a clear shift in the properties of pesticides applied to orchards away from compounds with large vapour pressures and small NO(A)ELs (high toxicity) (Figure A1-10). FOCUS (2008) proposed a vapour pressure trigger of >1.0×10^{-5} Pa to indicate those substances with potential for significant volatilisation from treated plant surfaces. 61% of the 76 compounds applied to orchards in 1987 had relatively large vapour pressure (>1.0×10^{-5} Pa) and relatively high reproductive/developmental toxicity (NO(A)EL <10 mg kg bw^{-1} day^{-1}); by 2012, this group of substances had reduced to 44% of the 54 compounds applied (Figure A1-10). The decreasing trend in total emission rate from treated surfaces and in the resulting concentration in air also indicates the improving fate profile of pesticides applied over the 25-year period (Figure A1-11). The sum of airborne concentrations for all pesticides at 100 m decreased by a factor of 3.5 from 1987 (0.14 mg m^{-3}) to 2012 (0.04 mg m^{-3}) with concentrations for individual pesticides in the range 4.3×10^{-17} to 1.3×10^{-2} mg m^{-3}. Zivan et al. (2016) measured chlorpyrifos in air collected 74 m downwind from a persimmon orchard in the range 6.3×10^{-4} to 2.0×10^{-3} mg m^{-3}, whilst Coscolla et al. (2010) detected 41 pesticides in ambient air in central France (2006-2008) with individual average concentrations ranging between 1.7×10^{-7} mg m^{-3} for vinclozolin and 2.5×10^{-5} mg m^{-3} for captan. Overall, the results reflect the influence of changing policies during the 1990s; Cross and Edwards-Jones (2006) found it impossible to identify any single policy leading to changes in pesticide risk over time, but the longer time series analysis possible in our study suggests that the introduction of European Directive 91/414 as well as the ongoing pesticides review programme at national level had a substantive effect in decreasing the overall toxicity profile of pesticides applied to orchards in the UK.

The present study estimated risk of applied pesticides based on maximum aggregated exposure on the first day after the application was made. This is likely to give the maximum daily dose of the pesticide (dose is expressed on a 'per day' basis) and indeed some studies show that volatilisation losses of pesticides including chlorpyrifos, prosulfocarb and trifluralin can be nearly complete within 24 hours (Rudel, 1997; Carlsen et al., 2006; Zivan et al., 2016). Volatilisation of other pesticides including fenpropimorph and parathion-methyl has been shown to proceed over several days or weeks after application (Rudel, 1997; Leistra et al., 2008; Kosikowska and Biziuk, 2010; Yusa et al., 2014). Whilst the fate of substances beyond the first day after application is not considered in the present work, more prolonged emission of pesticides is possible and could be considered in future studies to provide a more refined assessment of how exposure varies over time. The present work used the hazard quotient as a single figure to assess the risk to human health, combining the toxicity, amount and degree to which humans are exposed (Toronto Public Health, 2002). Relatively small exposures were estimated at our selected proximities due to the strong influence of proximity to spraying on magnitude of exposure. Ramaprasad et al. (2009) showed that children of agricultural operators living less than 61 m from an orchard had higher frequencies and greater levels of detectable urinary dimethyl thiophosphate levels than those living farther away. Our results also indicate higher potential hazard for inhalation exposure compared to dermal contact with spray deposits at distances farther downwind from treated orchards. This is due to longer duration of vapour drift as volatilization followed by aerial dispersion generally occurs over longer periods than spray drift and ground deposition (FOCUS, 2008). Active substances with greater volatility contributed more to total exposure at 1000 m compared to 100 m; for example, demeton-S-methyl applied to plums in the West Midlands region in 1987 contributed 15.0% and 25.0% of total exposure at 100 m and 1000 m, respectively. In contrast, exposure to spray droplets is less likely at greater proximities due to the relatively short time that droplets stay in the air; for example, duration in air is approximately 4 seconds for fine spray (200 microns in diameter) and 2 seconds for coarse spray (400 microns) to fall 3 m in still air (Klein et al., 2007).

Several limitations in data availability were encountered during the study. Atmospheric dispersion was the most significant transport pathways for volatilised pesticides yet it is poorly studied with most research focusing on measurements of downwind deposition of pesticide rather than airborne concentrations (Ellis et al., 2010; Zivan et al., 2016). Lack of data on airborne pesticide concentrations and spray deposition at different proximities from treated orchards has been noted previously as a constraint on model validation (Ellis et al., 2013). Our exposure estimates assume that residents receive 24 hours of exposure via inhalation of pesticide vapour and 2 hours of dermal exposure through activities on the contaminated ground; there is no consideration of structures that might interrupt pathways of exposure such as tree windbreaks, hedges, fences, or houses. We only considered toxicity for reproductive and/or developmental endpoints and did not consider all toxic mechanisms to assess overall potential for impact on health of residents. We also ignored some additional pathways of exposure such as dietary intake because these were assessed as relatively insignificant in the initial problem definition phase. Set against this, we summed daily exposures to all pesticides into a single aggregated value for exposure, even though these exposures will actually be widely spaced in time.

Conclusion

This study investigated trends in pesticide usage, exposure to pesticides via inhaled vapour and dermal contact with contaminated ground, and risk posed by pesticides applied to orchards for resident pregnant women living 100 or 1000 m downwind of treated areas. The exposure model is flexible and can be adjusted for a range of physicochemical properties of pesticides and atmospheric dispersion parameters. The model should be further validated and improved as field data become available for deposition and airborne concentrations of pesticides at greater distances from the site of application. The explicit calculation of exposures and the long time series of analysis add to the existing body of knowledge and allow a holistic assessment of the impact of pesticide regulation on use, exposure and risk. It is found that quantitative estimation of exposure can express the causal relationship between usage and associated risk in terms of space and time, which is a common caveat in post-authorisation monitoring and epidemiological investigations. There has not been a consistent change in usage over time, with a small increase in number of applications compensated in a small reduction in the average rate applied. Risk levels are generally small and have declined over time, with the cessation of use of several active substances with relatively high toxicity, and a net change to active substances with lower volatility. This evaluation of changes in pesticide use, exposure and risk over a 25-year time span can inform public debate about the effectiveness of regulatory interventions.

Chapter 3 Assessment of exposure of professional agricultural operators to pesticides

Introduction

Pesticides are widely used in agriculture to increase crop productivity and quality in order to meet the increasing demand for food from the world's growing population. Off-target movement of pesticides, however, may pose a risk to human health and the environment due to the intrinsic toxicity of this class of chemicals. Three major categories of human exposure to pesticides are identified, namely occupational, environmental, and dietary exposures (Mehrpour et al., 2014). Occupational exposure to pesticides is of particular interest in epidemiology because the exposure could be at levels hundreds of times greater than that for the general population (Sacchettini et al., 2015), and because this may cause excess risk for some diseases (Brouwer et al., 2016). For example, an association between occupational exposure and cancer was first reported around 50 years ago with higher prevalence of lung and skin cancers among farmers who used insecticides in vineyards (Mostafalou and Abdollahi, 2013). A review on the consequences of occupational exposure to pesticides on the male reproductive system proposed that the majority of pesticides could affect the system by mechanisms including reduction of sperm counts and density, inhibition of spermatogenesis, sperm DNA damage, and increasing abnormal sperm morphology (Mehrpour et al., 2014).

Agricultural operators are mainly exposed to pesticides during the preparation and application of the spray solution (Damalas and Abdollahzadeh, 2016). Due to spills and splashes, direct spray contact, or even drift, they are potentially exposed to pesticides via two routes of exposure, namely dermal absorption and respiratory inhalation (Gao et al., 2013; Moon et al., 2013; Ye et al., 2013; Damalas and Koutroubas, 2016). Whilst the dermal route is usually considered to constitute the major route of exposure to pesticides for agricultural operators (Zhao et al., 2015; Atabila et al., 2017), the inhalation route should not be neglected because of the presence of airborne spray droplets or vapour resulting from the spray preparation; the application could be dangerous as the lungs can rapidly absorb the dissolved pesticides into the bloodstream (Ogg et al., 2012; Choi et al., 2013). Generally, the operator is expected to engage in both mixing/loading and application tasks, and exposures via the dermal and inhalation routes arising from these tasks are summed to give the total potential exposure (EFSA, 2014).

The exposure of agricultural operators to pesticides could be influenced by a range of factors including the properties of the compound, agricultural factors (e.g. crop height, application equipment and technique), environmental factors (e.g. wind velocity and direction, temperature and relative humidity), protection measures, working behaviour, experience, and training (Aprea, 2012; Gao et al., 2013; Tsakirakis et al., 2014; Zhao et al., 2016). Generally, the levels of exposure during typical activities are predicted rather than measured due to complexities in measuring dose via different routes and limitations in biological monitoring together with the very wide range in climatic and working conditions that need to be considered (Colosio et al., 2012). Conventionally, the potential risk from human exposure to pesticide is expressed with a risk quotient which is the ratio of predicted exposure to a toxicological reference value that combines the risk with the amount and conditions of pesticide use (Cunha et al., 2012). Several predictive models are available to estimate operator exposure to pesticides including the EUROpean Predictive Operator Exposure Model (EUROPOEM), the UK Predictive Operator Exposure Model (UK POEM), the German Operator Exposure Model (German model), and the Bystanders, Residents, Operators, and WorkerS Exposure models (BROWSE) (Lammoglia et al., 2017).

Operator exposure must be estimated in the risk assessment for pesticides in accordance with EU Regulation (EC) 1107/2009 (Thouvenin et al., 2016). The exposure is normally estimated separately for mixing/loading and application tasks and for the recommended conditions of use (EFSA, 2014). Two operator exposure models were officially recommended by Regulation 1107/2009 for lower-tier risk assessment of agricultural operators to pesticides in the EU, namely the UK POEM (UK MAFF, 1992) and the German model (Lundehn et al., 1992) (NASDA, 2013). These are deterministic models derived from statistical analysis of data from exposure studies conducted before 1990. They have been superseded by the newly developed Agricultural Operator Exposure Model (AOEM; Groβkopf et al., 2013a). The AOEM is the first harmonised European operator exposure model, relying on empirical data from 34 exposure studies (1994-2009) to reflect agricultural practices and scientific knowledge. Despite the large database used for model development, the AOEM has some data gaps including the lack of exposure data for knapsack mixing/loading and hand-held applications in low crops (Groβkopf et al., 2013b).

European Union Directive 91/414/EEC concerning the placement of plant protection products on the market required that application of plant protection products following good practice should have no harmful effects on human health and no unacceptable influence on the environment. Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures ensures that the intrinsic toxicological potential of hazardous products is clearly communicated to users in the EU for the necessity of protection measures (Lichtenberg et al., 2015). In performing risk assessments of exposure to plant protection products in the EU, the zonal approach has been introduced by Regulation (EC) 1107/2009 for the evaluation and registration of plant protection products by taking into account national agronomics and regional differences (i.e. environmental conditions and application techniques) (Tsakirakis et al., 2014). The wide diversity of agriculture throughout the EU including farming practices and farm size incurs some challenges for European policy-makers in making decisions (EPRS, 2016).

This study investigates how field practice in handling and applying pesticides influences exposure for professional agricultural operators. To do this we apply information from a European database of pesticide application practices where, for the first time, all pesticide handling activities across individual working days were quantified for a large number of individuals and over protracted periods of up to a full year (Garthwaite et al., 2015). We select individuals from different cropping systems and different regulatory zones (northern, central, southern) of the EU and applied the AOEM (Groβkopf et al., 2013a) to assess levels of exposure for professional operators. We analyse results to determine differences in behaviours and patterns of exposure with cropping, region and working practices and compare exposures with Acceptable Operator Exposure Levels (AOELs) to investigate any implications for operator assessments within regulatory procedures. Supplementary information for this study is provided as Appendix 2.

Methodology

Pesticide application data

We used a dataset for pesticide application collected on behalf of the European Food Safety Authority (EFSA) in view of performing environmental risk assessments for pesticides in response to Regulation 1107/2009 (Garthwaite et al., 2015). Previous pesticide surveys undertaken within the EU provide little information on how pesticides are applied by agricultural operators or details of mitigation measures used to reduce exposure. In contrast, the EFSA dataset (Garthwaite et al., 2015) allows determination of risk of exposure from combined toxicity resulting from the cumulative non-dietary exposure of professional operators. The data were collected based on specifically designed survey forms in eight EU member states that together represent the three regulatory zones comprising Northern (Lithuania), Central (Belgium, Netherlands, Poland and United Kingdom) and Southern (Greece, Italy and Spain). Overall, the surveys collected information regarding >36,000 individual application events for operators on over 400 farms, with 645 sprayers used on nine different crops. A minimum of twenty fields were surveyed for each crop for between two and five crops in each member state, with at least two member states collecting information on each crop (Garthwaite et al., 2015). It is noteworthy that the data collected may not be representative of all farms in the sampled regions or across the country, but this should not limit the significance of the data collected since the aim of the survey was to collect data to improve models of operator and worker cumulative exposure; it was not intended to produce regional or national estimates of pesticide usage (Garthwaite et al., 2015).

We assessed the long-term patterns of professional agricultural operators' exposure to pesticides handled for Lithuania, the UK, and Greece to represent the three regulatory zones. These three member states were also the only ones that met the data quality requirements of our study with respect to finalised quality checking and data entry (Garthwaite et al., 2015). The data for other member states are generally poor because the budget was exceeded for the extra time needed in data management processes. The temporal unit of assessment was whole working days in 2012-2013; the periods of data collection were selected to quantify application practice across a cropping season, and up to one year where available (Garthwaite et al., 2015). Whilst the main thrust of the survey was to investigate the extent of a professional operator's exposure over a

12-month period, the period of data collection varied between cropping systems for various reasons; these included an unusually late spring and short growing season in Lithuania in 2013 and late contact with the operators in Greece whereby pesticide applications had already commenced (Garthwaite et al., 2015). Ten professional operators were chosen randomly whilst ensuring representation of different sizes of arable and orchard holdings in the UK (sum of area for all crops for arable system: 28-1040; orchard system: 16-121 ha) and Greece (arable system: 9-106 ha; orchard system: 1-9 ha) (Table A2-1). The surveyed farm sizes comprised classes A-F for the UK cropping systems (arable system: <50->500; orchard system: <10->80 ha), classes A-E for the Lithuanian arable system (<10->400 ha), and the Greek cropping systems (arable system: <2.4->4.5; orchard system: <0.5->1.9 ha) in order to represent operators' behaviours that may vary significantly between smaller and larger farms (Garthwaite et al., 2015). There are no data for orchards in Lithuania as no survey was carried out and this country was analysed for arable operators only (sum of area for all crops: 10-483 ha) (Table A2-1). The dataset for a single operator combined applications to all crops on the holding. The major crops were wheat, potatoes, and oilseed rape in Lithuania, citrus, grapes, and vegetables in Greece, and wheat, oilseed rape, sugar beet and apples in the UK (Garthwaite et al., 2015). Individual holdings comprised of different numbers of fields from 1 up to 70. The selected operators had spraying experience ranging from 3 to 54 years and differing levels of training in handling pesticides (Table A2-1). Overall, data were extracted for 50 randomly selected operators; the information for each application event comprised pesticide active substance, total amount of active substance handled, date of application, application technique, pesticide formulation, content of active substance in pesticide product, area treated per application, and PPE used.

Agricultural Operator Exposure Model (AOEM)

We employed the AOEM to estimate the levels of exposure during mixing/loading and application tasks because it reflects the latest scientific knowledge and application practices in the EU (Groβkopf et al., 2013a). The AOEM is developed to generate 75^{th}- and 95^{th}-percentile exposure based on the empirical data of 34 unpublished exposure studies that were conducted to Good Laboratory Practice standards between 1994 and 2009. In regulatory risk assessment, the 75^{th} percentile is used for assessing longer-term operator exposure to pesticides to provide a realistic upper estimate of daily exposure that will be exceeded very rarely over the course of a spraying season (EFSA, 2010). The 95th percentile is designed to support acute risk assessment as methodologies develop (EFSA, 2014).

The AOEM is usually applied to single active substances whereas here we applied it to all applications across a season; hence, we adopted algorithms from the AOEM to estimate the median exposure for all pesticides handled during each working day and over periods up to one year. The algorithms (Table 3-1) describe the dependency of exposure on the amount of pesticides handled. One constraint in these empirical equations is that any exponent greater than 1 ($\alpha > 1$) may result in a superlinear dependency on the amount of active substance handled and needs to be forced to 1 (Groβkopf et al., 2013a). Thus, we selected the algorithms with an exponent smaller than or equal to 1 where available ($\alpha \leq 1$) for four identified exposure situations, namely tank mixing/loading for vehicle-mounted/-trailed or hand-held spray equipment (tank ML), low crop application using vehicle-mounted/-trailed boom sprayers (LCTM AP), high crop application using vehicle-mounted/-trailed broadcast air-assisted sprayers (HCTM), and high crop application using hand-held spray equipment directed upwards (HCHH AP). Each exposure calculation comprised total exposures via dermal and inhalation routes. Dermal exposure was further segregated into protected or total exposure via hands and body dependent on whether PPE was used or not (Table 3-1). Here, total exposure refers to that without PPE use and protected exposure includes any PPE use (e.g. gloves and coveralls). The equation to calculate exposure to the head has a different structure that incorporates various types of PPE that modify exposure to differing extents.

Table 3- 1. Equations to predict median exposure to pesticides on a daily basis; the total amount of active substance (TA) is the major parameter for exposure, the slope α was set to 1 in case α >1; exposure is given in µg/person (Groβkopf et al., 2013a).

Tank ML	$\mathbf{log}\, \boldsymbol{exposure} = \boldsymbol{\alpha} \cdot \mathbf{log}\, \boldsymbol{TA} + [\boldsymbol{formulation\ type}] + \boldsymbol{constant}$
Total hands	$\log DE_{ML(H)} = 0.71 \cdot \log TA + 0.57\,[liquid] + 1.55\,[WP] - 0.34\,[glove\ wash] + 2.73$
Protected hands	$\log DE_{ML(Hp)} = 0.39 \cdot \log TA + 0.17\,[liquid] + 1.74\,[WP] + 1.02$
Total body	$\log DE_{ML(B)} = 0.71 \cdot \log TA + 0.24\,[liquid] + 1.69\,[WP] + 2.87$
Protected body	$\log DE_{ML(Bp)} = 0.95 \cdot \log TA - 0.05\,[liquid] + 1.99\,[WP] + 0.87$
Head	$\log DE_{ML(C)} = \log TA + 0.55\,[liquid] + 1.31\,[WP] + 1.52\,[no\ face\ shield] - 1.07$
Inhalation	$\log IE_{ML} = 0.53 \cdot \log TA - 0.73\,[liquid] + 2.26\,[WP] + 0.61$
LCTM AP[a]	$\mathbf{log}\, \boldsymbol{exposure} = \boldsymbol{\alpha} \cdot \mathbf{log}\, \boldsymbol{TA} + [\boldsymbol{droplet}] + [\boldsymbol{equipment}] + \boldsymbol{constant}$
Total hands	$\log DE_{AP(H)} = \log TA + 1.43\,[normal\ droplet] - 1.41\,[normal\ equipment] + 1.30$
Protected hands	$\log DE_{AP(Hp)} = \log TA + 1.46\,[normal\ droplet] - 0.61\,[normal\ equipment] - 0.67$
Total body	$\log DE_{AP(B)} = \log TA + 0.56\,[normal\ droplet] - 1.62\,[normal\ equipment] + 2.52$
Protected body	$\log DE_{AP(Bp)} = log\ TA + 0.34\,[normal\ droplet] - 0.94\,[normal\ equipment] + 0.49$
Head	$\log DE_{AP(C)} = \log TA + 0.32\,[normal\ droplet] - 0.22\,[normal\ equipment] - 0.22$
Inhalation	$\log IE_{AP} = 0.46 \cdot \log TA + 0.13\,[normal\ droplet] + 0.65\,[normal\ equipment] - 0.89$
HCTM AP	$\mathbf{log}\, \boldsymbol{exposure} = \boldsymbol{\alpha} \cdot \mathbf{log}\, \boldsymbol{TA} + [\boldsymbol{cabin}] + \boldsymbol{constant}$
Total hands	$\log DE_{AP(H)} = 0.49 \cdot \log TA + 0.89\,[no\ cabin] + 2.29$
Protected hands	$\log DE_{AP(Hp)} = 0.88 \cdot \log TA + 1.18$[c]
Total body	$\log DE_{AP(B)} = \log TA + 0.86\,[no\ cabin] + 2.86$
Protected body	$\log DE_{AP(Bp)} = \log TA + 0.50\,[no\ cabin] + 1.30$
Head	$\log DE_{AP(C)} = \log TA + 1.46\,[no\ cabin] + 0.82$
Inhalation	$\log IE_{AP} = 0.63 \cdot \log TA + 1.00\,[no\ cabin] + 0.51$
HCHH AP[b]	$\mathbf{log}\, \boldsymbol{exposure} = \boldsymbol{\alpha} \cdot \mathbf{log}\, \boldsymbol{TA} + [\boldsymbol{culture}] + \boldsymbol{constant}$
Total hands	$\log DE_{AP(H)} = \log TA - 0.94\,[normal\ culture] + 4.02$
Protected hands	$\log DE_{AP(Hp)} = \log TA - 1.26\,[normal\ culture] + 1.90$
Total body	$\log DE_{AP(B)} = 0.32 \cdot \log TA - 1.50\,[normal\ culture] + 5.75$
Protected body	$\log DE_{AP(Bp)} = \log TA - 1.48\,[normal\ culture] + 3.72$
Head	$\log DE_{AP(C)} = 0.34 \cdot \log TA - 1.18\,[normal\ culture] + 2.87$
Inhalation	$\log IE_{AP} = 0.74 \cdot \log TA - 0.57\,[normal\ culture] + 2.13$

AP, application; ML, mixing/loading; DE, dermal exposure; IE, inhalation exposure; H, total hands; Hp: protected hands; B, total body; Bp, protected body; C, head; WP, wettable powder formulation

[a] For LCTM AP, the droplet sizes are grouped into 'normal' and 'coarse' subsets with the latter size being chosen when drift reducing nozzles are used; the 'normal' and 'small' equipment subsets are used with the small equipment for treatment in small areas/high crops.

[b] For HCHH AP, the 'normal' and 'dense' culture subsets with the dense culture refers to unavoidable direct contact with sprayed crop during applications.

[c] The dependency of the factor [cabin] was not significant.

Exposure calculation

Total exposure of an operator to individual active substances handled across a whole working day (mg kg bw^{-1} day^{-1}) comprised of dermal (DE, mg kg bw^{-1} day^{-1}) and inhalation (IE, mg kg bw^{-1} day^{-1}) routes for both mixing/loading (ML) and application (AP) tasks:

$$\boldsymbol{Exposure_{ML}} = \frac{((DE_{ML(H\ or\ Hp)} + DE_{ML(B\ or\ Bp)} + DE_{ML(C)}) \times DA_{ML}) + (IE_{ML} \times IA_{ML})}{BW \times UF} \quad \textbf{(Eqn. 24)}$$

$$\boldsymbol{Exposure_{AP}} = \frac{((DE_{AP(H\ or\ Hp)} + DE_{AP(B\ or\ Bp)} + DE_{AP(C)}) \times DA_{AP}) + (IE_{AP} \times IA_{AP})}{BW \times UF} \quad \textbf{(Eqn. 25)}$$

$$\boldsymbol{Total\ exposure = Exposure_{ML} + Exposure_{AP}} \quad \textbf{(Eqn. 26)}$$

where subscripts H and Hp are exposures via total hands and protected hands respectively, B and Bp are exposures via total body and protected body respectively, and C is exposure to the head. BW is the body weight of an operator (75 kg as a default), and UF is the unit conversion factor from µg to mg (1000). Dermal absorption (DA, %) defines absorption of pesticide via skin surfaces and is a function of the percentage of active substance(s) in the product (EFSA, 2012; So et al., 2014); DA_{ML} is assumed to be 25 and 75% for formulated products that contain proportions of active substances >5% and ≤5%, respectively; DA_{AP} is 75% with active substance ≤5% in the spray solution; and DA is 10% during both tasks for active substances with log octanol-water coefficient (P_{ow}) <-1 or >4 together with molecular weight greater than 500 g mol^{-1}. Inhalation absorption (IA, %) refers to the adjustment of inhalation uptake for the use of respirators based on protection factors reported by EFSA (2010); values are 10% for a power-assisted respirator, 25% for a valved filtering half mask, reusable half mask with filters, disposable filtering half mask, or full-face mask, and 100% for no respirator use for both IA_{ML} and IA_{AP}, separately. IA_{AP} is 100% for all LCTM and HCTM sprayers independent of the cabin status.

All handled pesticides were classified into three major formulation types to determine potential exposure during tank mixing/loading (Table 3-2), namely wettable powders which have relatively larger exposure, liquid formulations which have intermediate exposure, and wettable granules which have relatively smaller exposure (Groβkopf et al., 2013b). Two formulation categories were removed from the analyses, namely rodenticide bait (ready for use) and others (unknown). All LCTM and HCTM applications were grouped into two classes for sprayers with the presence of a cabin (i.e. cab with no filter, cab with carbon filter and closed cab) and sprayers with no cabin (open and no cab). Exposure to pesticides during application in a cabin and/or with PPE use was calculated using the equation for protected exposure, and with no cabin and no PPE use was calculated based on the equation for total exposure.

Table 3- 2. Classification of pesticide formulations into wettable powder, liquid and wettable granule groups included in the AOEM model.

Wettable Powder	Liquid	Wettable Granule
dustable powder (DP), wettable powder (WP), water-soluble powder (SP)	capsule suspension (CS), emulsifiable concentrate (EC), emulsion-oil in water (EW), microemulsion (ME), oil dispersion (OD), oil miscible flowable (OF), oil miscible liquid (OL), soluble concentrate (SL), suspension concentrate (SC), suspo-emulsion (SE)	Granule (GR), tablet (TB), water dispersible (WG), water soluble granules (SG)

Several assumptions were made during the study. We assumed that the listed PPE were worn continuously during the mixing/loading and/or application tasks because no data were collected for individual applications. For a number of holdings where there was no information collected on the use of PPE for an individual application method, we assumed that the operators used the same types of PPE as used for other application methods on the same holdings. Where the use of specific types of PPE were not listed in the survey, we assumed that the operators did not wear PPE during either mixing/loading or application tasks. For a small number of applications in the UK where dates of application were not recorded, the summed exposure to the same active substance on the same working day could not be calculated and these remained as separate applications.

Comparison between predicted exposure and the respective AOELs

Exposure was combined for all applications of a single active substance on a single working day and this value was compared with the respective Acceptable Operator Exposure Level (AOEL, mg kg bw^{-1} day^{-1}) established during EU regulatory assessment. The AOEL is the maximum amount of an active substance to which an operator may be exposed internally without causing any adverse health effects (Marrs and Ballantyne, 2004). It is usually derived from the no observed adverse effect level based on the most relevant sub-acute or sub-chronic toxicity study divided by a safety factor (100) to account for differences in sensitivity between test animals and humans, and the variation in sensitivity between individuals (Matthews, 2002). We extracted the AOELs for a total of 180 substances from the EU Pesticides Database (2016), Pesticide Properties Database (PPDB, 2017), and Bio-Pesticides Database (BPDB, 2017). Three active substances where AOELs were not available were removed from the analyses, namely calcium and derivatives, sulphur, and paraffin oil.

Results

Pesticide application data

Table 3-3 summaries application data for the 50 professional operators from different cropping systems in Lithuania, the UK and Greece. The total number of active substances handled by the selected operators was larger in the arable system of the UK (24-66 compounds) and smaller for those in Lithuania (4-24 compounds). Operators in the cropping systems of Greece and the orchard system of the UK generally handled around 20 different active substances over the cropping season. The total mass of pesticides handled over the survey period was largest in the UK arable (median: 580 kg a.s.) and orchard system (437 kg a.s.), intermediate for the arable systems in Greece (151 kg a.s.) and Lithuania (77 kg a.s.), and smallest in the Greek orchard system (22 kg a.s.).

Figure 3-1 shows cumulative frequency distributions of the area treated with a single active substance on single working days. The percentage of days when at least one treatment occurred varied across the selected operators, with some operators in the Greek arable system and the UK orchard system applying pesticides on ca. 40% of all days covered by the survey period (Table A2-1); more commonly, operators carried out spraying on ca. 20% of days. EFSA (2014) proposed representative values of 50 and 10 ha for the area of arable and orchard crop, respectively, treated with an individual active substance in a single day using vehicle-mounted equipment (EFSA, 2014). Median values for area treated with an individual active substance in one day were below the EFSA values in all cropping systems. However, the EFSA values were exceeded at the 95th percentile in UK arable and orchard systems (132 and 19 ha day^{-1}, respectively) and in the Lithuanian arable system (103 ha day^{-1}) (Table 3-4). The absolute maximum area treated by a single operator on one day was 199 ha on one of the UK arable holdings, necessitating 11 separate mixing/loading procedures across the day.

Table 3- 3. Summary of application data for 50 selected professional operators showing the total number and total mass of active substances handled during the survey period.

Holding code	LTAB	UKAB	GRAB	UKOR	GROR
Total number of active substances handled					
01	15	33	19	6	20
02	7	29	20	30	3
03	24	34	20	23	33
04	7	24	13	17	16
05	15	27	17	23	32
06	18	48	13	25	14
07	9	49	21	41	23
08	7	55	19	18	15
09	4	30	8	12	19
10	18	66	12	26	14
Median	12	34	18	23	18
Total mass of active substances handled					
01	166.0	103.5	268.5	131.4	21.1
02	27.8	184.3	191.4	275.6	1.9
03	808.7	926.1	122.6	557.4	69.8
04	7.3	64.1	11.6	452.0	16.9
05	431.6	249.2	148.2	422.2	68.9
06	410.2	911.6	153.1	876.7	17.6
07	53.1	3128.8	423.7	1051.5	35.3
08	18.1	2547.4	188.2	819.7	21.8
09	3.2	93.8	67.4	331.0	10.4
10	99.9	2088.8	38.8	380.2	25.3
Median	76.5	580.4	150.7	437.1	21.5

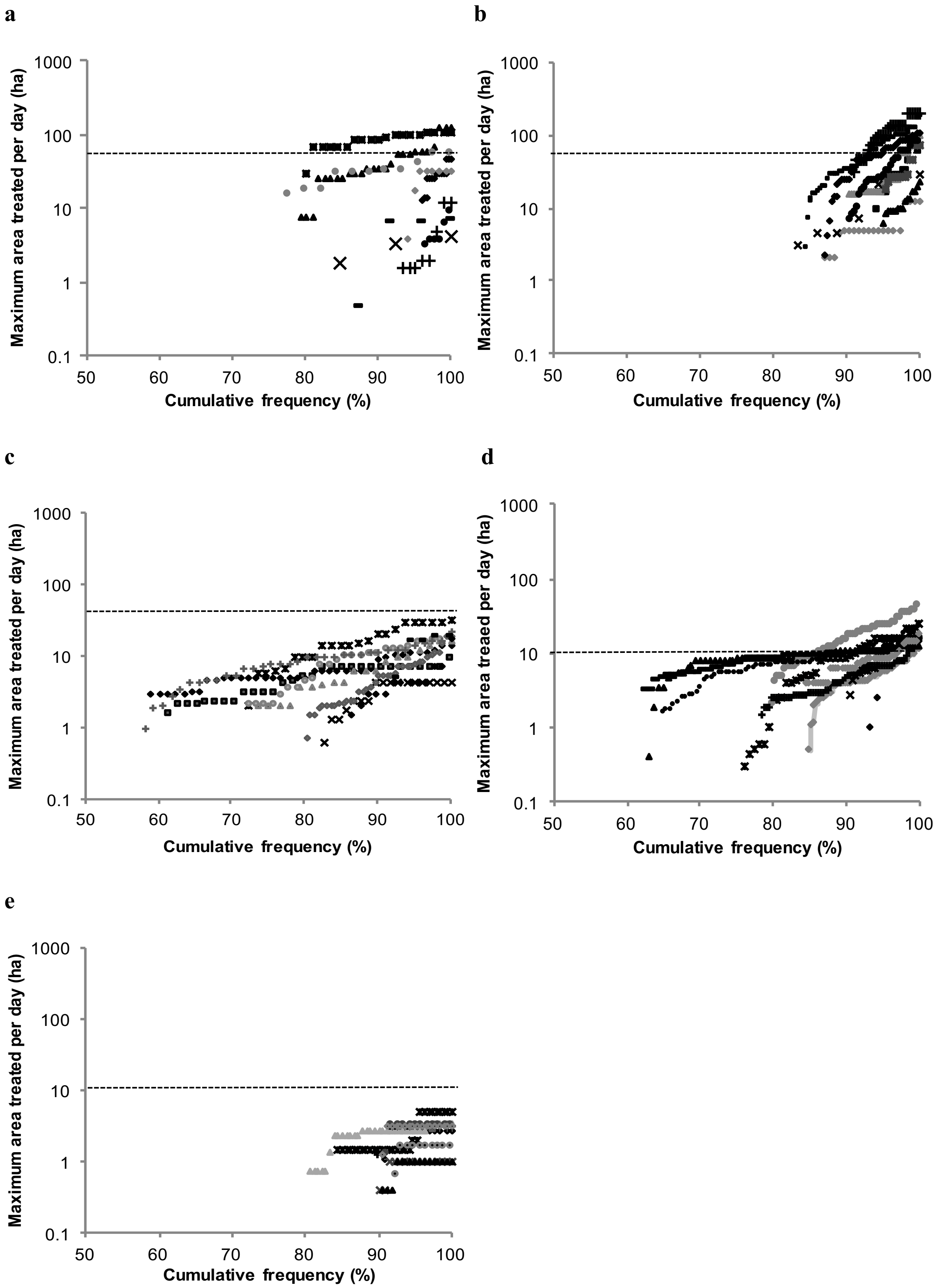


Figure 3- 1. Cumulative frequency distributions of maximum areas treated with a single active substance on a single working day for arable operators in Lithuania (a), the UK (b) and Greece (c), and orchard operators in the UK (d) and Greece (e). The EFSA default values for total area treated per day with individual substances (50 and 10 ha day^{-1} in arable and orchard systems, respectively) is indicated by the dashed lines. Different symbols represent individual operators and each value shown is one substance applied on a single working day.

Table 3- 4. Comparison between areas treated with individual active substances on a single spray day expressed as 50th, 75th and 95th percentiles, and the EFSA default values (EFSA, 2014).

Cropping system	Area treated per active substance per day (ha)					
	Summary of database information (percentile)					EFSA value[a]
	25th	50th	75th	95th	Maximum	
Lithuania arable	7.8	29.8	47.0	102.9	129.6	50.0
UK arable	14.5	26.2	58.6	132.2	198.7	50.0
Greek arable	2.8	5.0	9.3	19.6	30.7	50.0
UK orchard	4.0	6.9	10.1	18.5	42.8	10.0
Greek orchard	1.5	2.7	3.2	5.0	5.0	10.0

[a] For vehicle-mounted equipment.

Estimated total exposure for professional operators

Figure 3-2 shows that the total exposure per working day for the selected operators estimated for the full study period varied across the different cropping systems. Here, the exposure is expressed for all days with applications to correct for differences in the cropping period with applications across different operators. Overall, the medians of total daily exposure were largest in the Greek arable system (9.7×10^{-3} mg kg bw^{-1} day^{-1}) and orchard system (7.7×10^{-3} mg kg bw^{-1} day^{-1}), intermediate for the UK orchard system (6.9×10^{-3} mg kg bw^{-1} day^{-1}) and arable system (1.8×10^{-3} mg kg bw^{-1} day^{-1}), and smallest for the Lithuanian arable system (1.1×10^{-3} mg kg bw^{-1} day^{-1}). For individual cropping systems, the variance around the mean daily exposure for the 10 operators was largest in the UK cropping systems (coefficients of variation 116% and 105% for arable and orchard systems, respectively), intermediate for the arable systems in Lithuania (93%) and Greece (73%), and smallest in the Greek orchard system (43%).

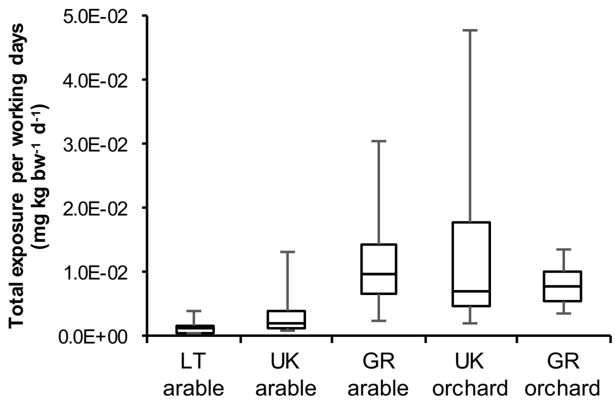


Figure 3- 2. Estimated exposures for 10 randomly selected professional operators from the cropping systems in Lithuania, the UK and Greece. Values are calculated for individual operators based on the respective total number of working days. Boxes show the median and quartiles, and whiskers show the range.

Comparison of levels of exposure with the respective AOEL

Figure 3-3 categorises all applications made by each individual operator according to ratios between the predicted exposure and the respective AOEL for each active substance handled on a single working day. Here, the same substance applied several times on the same working day is considered as one application whereas the same active substance applied on successive days counts as two applications. Overall, Greek cropping systems had the largest number of applications with AOELs exceeded (estimated exposure: AOEL >1.0) and the Lithuanian arable system had the least. There were seven arable and eight orchard operators in the Greek cropping systems where at least one application exceeded the AOEL, four arable and nine orchard operators in the UK cropping systems, and two operators in the Lithuanian arable system. Table 3-5 shows that the percentage of applications with AOEL exceeded were larger in Greek cropping systems compared to the UK and Lithuania. Generally, most of the applications had exposure estimates that were at least a factor of 10 smaller than the respective AOELs.

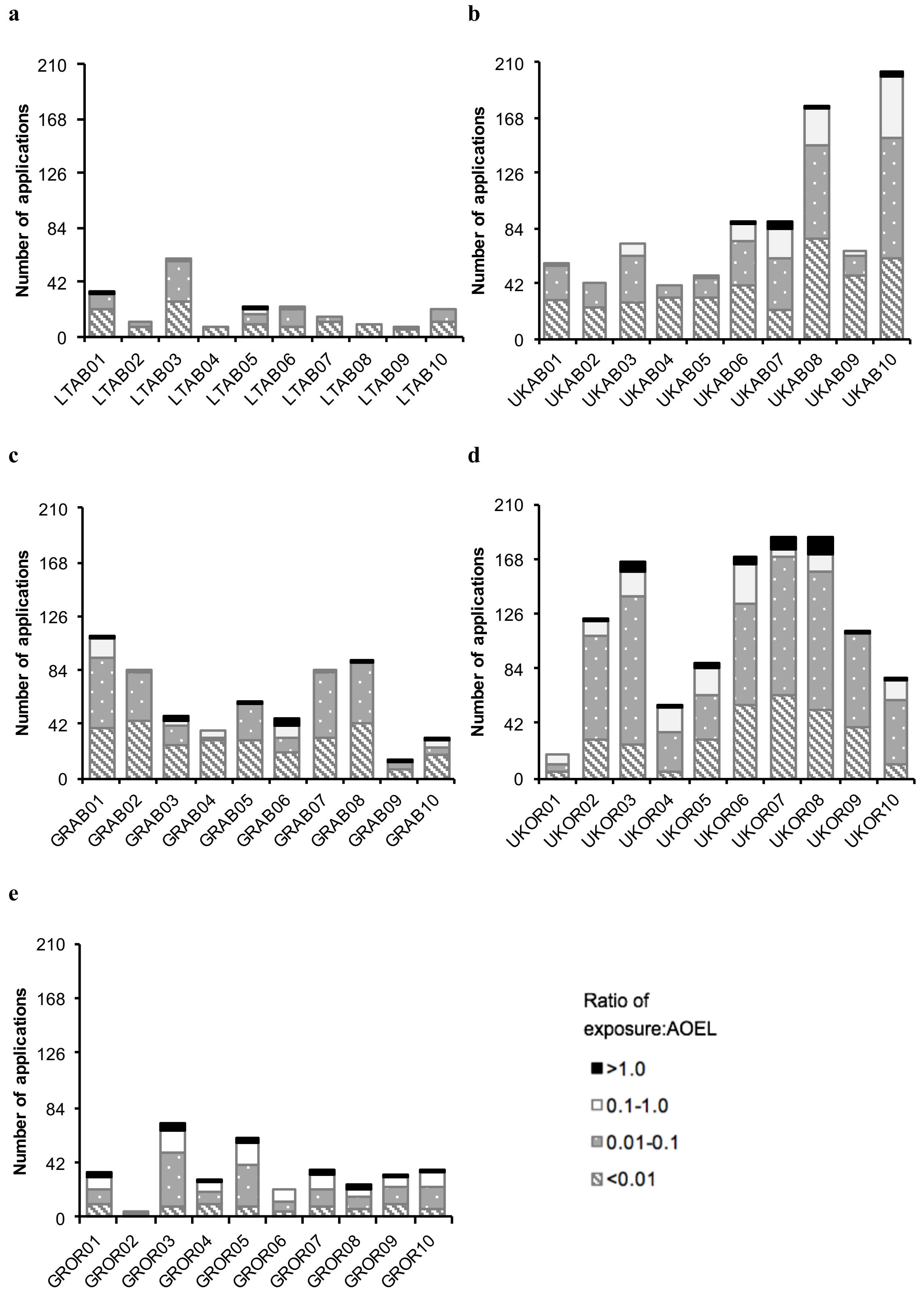


Figure 3- 3. Bar charts showing the total number of applications made by a single operator (each bar is one operator) and how these applications classify into instances where predicted exposure:AOEL was >1.0, 0.1-1.0, 0.01-0.1, or <0.01. Separate charts show the data for the arable systems of Lithuania (a), the UK (b), Greece (c), and the orchard systems of the UK (d) and Greece (e). Each individual application refers to one active substance applied on a single working day.

Table 3- 5. Summary of instances in the different cropping systems when predicted exposure exceeded the AOEL.

Cropping system	No. of operators with any instance of exposure > AOEL	Applications with AOEL exceeded (% of total number of applications)
Lithuania arable	2	2.9-4.5
UK arable	4	1.1-5.6
Greece arable	7	1.1-14.3
UK orchard	9	0.8-6.5
Greece orchard	8	2.8-16.0

Discussion

The structure of agriculture varies across the EU due to differences in topography, geology, climate, natural resources, infrastructure, and social customs. In this study, the size of farm holding was largest in the UK (median areas of 165 and 38 ha for arable and orchard systems, respectively), intermediate for the Lithuanian arable system (44 ha), and smallest for Greece (arable 32 ha; orchard 3 ha) (Table A2-1). Individuals spent different amounts of time spraying crops with an absolute range across all holdings of 1 to 418 hours over the period investigated (Table A2-2). Cumulative time spent spraying was longest in the UK orchard system (median 306 hours; 95th percentile 412 hours) and arable system (median 75 hours; 95th percentile 308 hours). The total amount of active substance handled during each working day is the dominant input parameter for estimating operator exposure within the AOEM (Groβkopf et al., 2013a).

Figure 3-3 indicates the potential risk of exposure to pesticides handled amongst the selected professional operators with some applications generating predicted exposures where the AOEL was exceeded. Exposures during mixing/loading tasks were larger than those during application (Figure A2-1), and varied by formulation type (Table 3-1) with wettable powder > liquid > wettable granule formulations. Moon et al. (2013) undertook a risk assessment of operator exposure to pesticides in apple orchards and proposed a greater dermal exposure during mixing/loading of wettable powders (0.003-0.007% of total prepared amount) when compared to liquid formulations (0.001-0.002%) due to direct contact with fine pesticide powders when tearing the pouch and pouring into the mixing tank. In comparison, wettable granules are formulated to be non-dusty and have relatively lower potential for exposure (Zhao et al., 2015). The exposure calculations for mixing/loading of wettable powders in AOEM rely on just two exposure studies for hand-held applications to citrus in Spain with similar application conditions and equipment (Groβkopf et al., 2013b). Given the dominance of wettable powders in the exposure estimates, priority should be given to improving the statistical power of the AOEM model with more studies on the exposure to different formulations using tractor-mounted and hand-held equipment (Groβkopf et al., 2013a).

A dramatic shift from wettable powder formulations to wettable granules was identified previously in a study on advances in agrochemical formulation (Mulqueen, 2003). Nevertheless, the current study indicates significant use of wettable powder pesticides in Greece, whilst liquid formulations were more commonly used in the UK and Lithuania, and there was relatively little use of wettable granules in any of the cropping systems. There is a range of potential factors that could influence the physical forms (solid/liquid) of a pesticide product including the application technique, customer acceptability and business need, and the regional market requirements (Mulqueen, 2003; Green and Beestman, 2007).

Generally, the predicted exposures for the HCTM applications in orchard systems were high compared to LCTM applications in arable systems. Whereas cabin status was identified previously as having no great impact on the operator's exposure to pesticides and was therefore excluded from the LCTM scenario of the AOEM, it was identified as an important influence in the HCTM scenario (Groβkopf et al., 2013a). In the present study, we classified the HCTM sprayers into two major groups for sprayers with and without cabins. This classification contributes significantly to those exposures with AOELs exceeded amongst the orchard operators, particularly amongst the Greek operators where none of the HCTM sprayers in our sample set were fitted with cabins (Table A2-1). Eight out of ten cabins in both UK cropping systems and a smaller proportion in the Lithuanian and Greek arable systems were fitted with carbon filters (Table A2-1); this exposure reduction measure is not included into the AOEM so it is likely that exposure during application is overestimated for these operators.

Occupational exposure to pesticides is affected significantly by working practices relating to the use of PPE. Agricultural operators are protected by the requirements on PPE as proposed by regulations to reduce the exposure to levels deemed acceptable (Woodruff et al., 1994). The requirements are usually determined based on the intrinsic toxicological properties and exposure profile of the products (e.g. formulation types and application scenarios) (Lichtenberg et al., 2015). Whilst the use of PPE is considered in the AOEM, there are some limitations in the exposure calculations due to the lack of data for inhalation routes both during mixing/loading and application tasks and for exposure to the head during application when protected by PPE (Groβkopf et al., 2013a). Overall, the EFSA dataset indicates that the selected professional operators generally wore gloves and protective clothing during mixing/loading activities with less PPE used during applications (Table A2-3). During mixing/loading activities, there was slightly higher use of face shields for liquid pesticides and respirators for solid pesticides (i.e. wettable powders and wettable granules). For the application tasks, there was less implementation of PPE in the UK and Lithuania due to the presence of cabins as compared to Greece where open tractors are more common (Table A2-1). Lichtenberg et al. (2015) proposed that the use of respirators for inhalable droplets during mixing/loading of liquid pesticides is less relevant compared to use for powder/dust pesticides and that the assigned PPE can be omitted when spraying occurs from a closed cabin. In practice, the use of PPE could be affected by other factors including personal preference, availability in the workplace, toxicity of pesticide, and thermal comfort (MacFarlane et al., 2013).

In the regulatory risk assessment, predicted total absorbed doses (sum of skin and respiratory absorbed doses) of agricultural operators to pesticides should not be greater than the AOEL for an individual active substance or combination of active substances formulated into a single product. EFSA (2014) proposed default assumptions that the total area treated with each substance per day using vehicle-mounted equipment be taken as 50 and 10 ha for arable and orchard crops, respectively. However, these values were exceeded relatively frequently for at least one compound per working day for some operators from the UK and Lithuanian cropping systems (Figure 3-1). It is known that the area treated is influenced by the type of equipment used (for example, newer sprayers may allow spraying with a stable boom at faster ground speeds) and EFSA (2014) states that values were derived based on "relatively simple and older model". Equipment used by the operators ranged from 1 to 43 years old, but nearly 50% of operators from the orchard systems used equipment that was at least 20 years old (Table A2-4). The representative values for area treated from EFSA guidance are intended to be towards the upper end of the range in values occurring in the field and not the absolute maxima. Nevertheless, the analysis presented here suggests a need to review how representative these values are for spraying practice across the whole of the EU.

According to Regulation (EC) No 1107/2009, the AOEL is used as a limit in the authorisation process of the use of any active substances, and further work or ultimately no authorisation is triggered if the exposure estimate exceeds the AOEL (Aprea et al., 2016; Thouvenin et al., 2016). The AOEL is generally derived from the most sensitive no observed adverse effect level for relevant endpoints based on an oral short-term toxicity study as a default procedure (i.e. 90-day study or occasionally 1-year study) (European Commission, 2006). In practice, an agricultural operator's exposure to pesticides occurs mainly through the dermal route, and to a lesser extent through the inhalation route (CTGB, 2016). Route-to-route extrapolation is only appropriate if the type and extent of effects of a substance are independent of the route of exposure (European Commission, 2006). We did not adjust the AOEL for route of exposure, so uncertainties are introduced because of the lack of information on any association between adverse effect and route of exposure, as well as by the repeated dose that is used in most toxicity studies to determine the no observed adverse effect level.

Our study indicates that a few relatively hazardous substances contributed significantly to the working days with estimated exposures greater than the AOELs (Table A2-3); these included diquat, glufosinate-ammonium, prosulfocarb, chlorothalonil, and chlorpyrifos, all of which have AOEL <0.1 mg kg bw^{-1} day^{-1}. Chlorpyrifos made a significant contribution to those exposures where AOELs were exceeded in the UK orchard system, but all uses in the UK were withdrawn with effect from April 2016 except use as a drench for brassica seedlings. Besides this restriction on use of chlorpyrifos, several other active substances have been restricted or removed from the market in one or more of the member states since the period of data collection including amitrole, carbendazim, flusilazole, ioxynil, and tepraloxydim. However, only amitrole was associated with a single exceedance of the AOEL in the UK orchard cropping system (Table A2-3).

Limitations within the current study include the reliance on the assumptions and underpinning data embedded into the AOEM and the derivation of regulatory AOEL values. A particular constraint within the AOEM is the relatively simple treatment of protection factors to incorporate efficiency of personal protective equipment and the influence of cabin design on exposure under different field conditions. There is a clear need for validation of exposure predictions against field measurements and biological monitoring, and this should include generation of data for modern spray machinery and in a range of countries with different cropping, environmental and cultural conditions. Three active substances where AOELs were not available were removed from the analyses, namely calcium and derivatives, sulphur, and paraffin oil. The data collection was designed to make broad comparisons across cropping systems and countries and did not allow direct comparison of individual crop types because a particular crop may only have been grown on a small number of holdings. A direct comparison of pesticide usage and application practice between individual crops would be useful to add into any future study.

Conclusion

This study allows an evaluation of the European regulatory exposure assessment against a high-quality dataset on operator practices across three member states and two cropping systems. The dominant influences on estimated exposure were the extensive use of wettable powder formulations in Greece and multiple mixing and loading activities associated with large areas of crop treated with a pesticide product each day in the UK and Lithuania. The model predicted clear differences in exposure across the different systems, driven by variations in agricultural practices and working behaviours, and there were some applications that generated predicted daily exposures that exceeded the AOEL, particularly for more hazardous active substances. Agricultural operators have limited control over the toxicity of products that they apply, but their use of pesticides can be regarded as safe through the adoption of effective exposure mitigation measures, including the use of PPE during mixing and loading and undertaking application activities from a closed cabin. Study results can be used to evaluate current assumptions in regulatory exposure calculations and to identify situations with potential risk that require further analysis including measurements of exposure to validate model estimations.

Chapter 4 Assessment of occupational exposure to pesticide mixtures with endocrine disrupting activity

Introduction

Agricultural operators can be exposed to complex mixtures of pesticides when applying tank mixes of two or more products or when making sequential applications of different products (Panizzi et al., 2017). Complexity of mixtures to which operators are exposed may be further increased because pesticide products comprise both the declared active substances that control the target pests/plant diseases and co-formulants that aid application and/or improve the effectiveness of the product (Yusoff et al., 2016). To date, little is known about the risk from cumulative exposure to different combinations of pesticides in mixtures (Kienzler et al., 2016).

Pesticides with endocrine disrupting activity are of particular health concern because the endocrine system regulates the secretion of almost all hormones that control the metabolism and function of the body, influencing almost every cell, organ and function of an organism (EFSA, 2013a). They can interfere with the function of the hormone system, thus dysregulating homeostatic mechanisms, reproduction and development (Sidorkiewicz et al., 2017). Numerous studies have suggested effects from occupational exposure to endocrine disrupting pesticides on the reproductive system including reduced semen quality and lower luteinizing hormone (Hossain et al., 2010; Mehrpour et al., 2014; Cremonese et al., 2017). Other studies suggest higher risk of hypospadias, and allergic and non-allergic wheeze (Rocheleau et al., 2009; Mesnage et al., 2017). Pesticides with endocrine disrupting activity can instigate effects at very low doses that are not always predicted from tests at higher doses (Futran Furhrman et al., 2015). Similarly, chemicals that are present individually at ineffective doses can produce substantial effects when combined in mixtures (Christiansen et al., 2012; Hass et al., 2012).

Cumulative risk from exposure to mixtures of pesticides that can produce common adverse effects on the same target organ or organ system is a particular concern (EFSA, 2013b); concentration/dose addition is generally used as the default first tier approach for hazard quantification (Sarigiannis and Hansen, 2012). For instance, good agreement was found between observed and predicted effects on sexual development in rats based on dose-additivity for a mixture of five low-dose endocrine disrupting pesticides comprising epoxiconazole, mancozeb, prochloraz, tebuconazole and procymidone (Hass et al., 2012). Generally, the concentration/dose addition approach is considered sufficiently conservative to assess the risk from combined exposure to multiple chemicals, irrespective of the similarity and dissimilarity of their mechanisms or modes of action in the mixtures (Kienzler et al., 2016).

European pesticide regulations require risk assessments that usually focus on the declared active substances with additional, but generally fewer, data requirements for commercial product formulations (Kienzler et al., 2016). Regulation (EC) 1107/2009 concerning the placing of plant protection products on the market requires that individual active substances to be included in pesticide products should have no harmful effect on human health nor the environment on the basis of harmonised criteria at Community level. Meanwhile, pesticide co-formulants are authorised in the Member States with responsibility for characterising toxicological hazard transferred to industry under the CLP Regulation (EC) 1272/2008 on the classification, labelling and packaging of substances and mixtures (Hernandez and Tsatsakis, 2017). The potential for mixture effects from different combinations of pesticides applied in multiple products is not covered within pesticide regulation and has rarely been tested (Kienzler et al., 2016;).

Professional agricultural and horticultural operators often handle large amounts of pesticides and thus have high potential for exposure to multiple products with similar toxicological endpoints. They thus represent a vulnerable group for combined effects of pesticide mixtures. This study investigates actual scenarios of pesticide use for professional operators in order to: determine the pesticide mixtures to which individuals are potentially exposed; quantify the exposure to and risk from pesticide active substances with known/possible endocrine disrupting activity; and investigate whether co-formulants in pesticide products might be an additional source of exposure to endocrine disruptors. To do this, we analyse usage of known and possible endocrine disrupting substances over an agricultural season for a total of 50 professional operators from different cropping systems in Greece, Lithuania, and the UK. Exposure of operators is assessed on a daily basis using the Agricultural Operator Exposure Model (AOEM; Groβkopf et al., 2013a) and potential risk is assessed using the lowest no observed (adverse) effect levels (NO(A)ELs) for endocrine disrupting effects and an assumption of concentration addition. We analyse results to determine gaps in knowledge in the current risk assessment. Supplementary information for this study is provided as Appendix 3.

Methodology

Pesticide application data

We used a dataset of pesticide applications made by professional operators that was collected on behalf of the European Food Safety Authority (EFSA) with the purpose of addressing cumulative exposure and potential for combined, non-dietary effects of pesticide products (Garthwaite et al., 2015). The dataset comprises long-term records of all pesticide handling activities for a large number (> 400) of professional operators, including details on the pesticide products used, application methods, and personal protective measures. This allows in-depth investigations of operators' exposure during mixing/loading and application tasks. Based on an earlier study (Wong et al., 2018), a total of 50 professional operators were randomly selected to give ten individuals each from arable and orchard farming systems in the UK and Greece, and a further ten from arable agriculture in Lithuania. These countries were selected as having robust data quality (Garthwaite et al., 2015). Data for each operator covered all pesticide spraying and handling activities over an agricultural season (2012/13) and comprised crop, pesticide product, area applied, mass applied, volume applied, spray equipment and personal protective equipment.

Identification of pesticides with endocrine disrupting activity

An endocrine disruptor is defined as "an exogenous substance or mixture that alters the functions of the endocrine system and consequently cause adverse effects in an intact organism, or its progeny, or (sub) populations" whilst a possible endocrine disruptor is "an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub) populations" (WHO/IPCS, 2002). We classified the declared active substances of products applied in our dataset for their known or possible endocrine disrupting activity based on the Pesticide Properties Database (PPDB, 2018), which is an international database for pesticide risk assessments and management that is endorsed by the International Union of Pure and Applied Chemistry and promoted by major organisations including the Food and Agricultural Organisation (Lewis et al., 2016). Four triazole fungicides had no relevant data available (i.e. difenoconazole, metconazole, paclobutrazol, and tebuconazole; Table A3-1), but were included here because studies have identified that triazoles and structurally similar chemicals are potential endocrine disruptors (Andersen et al., 2002; Marx-Stoelting et al., 2014; Lv et al., 2017; Teng et al., 2018).

Determination of whether or not co-formulant chemicals have potential for endocrine disrupting activity was undertaken for a single, exemplar scenario (UK orchards). A total of 93 pesticide products that were applied by at least one operator from the UK orchard system were identified for their co-formulants based on individual material safety data sheets (MSDS). Where no MSDS was found, the most similar product from the same manufacturing company and formulation type was substituted. Afterwards, individual co-formulants were assessed for their potential endocrine disrupting activity based on their chemical abstract service numbers (CAS No.) in accordance with the Hazardous Substances Data Bank in the Toxicological Data Network (TOXNET, https://toxnet.nlm.nih.gov/newtoxnet/hsdb.htm) and the PPDB (2018). We extracted all endocrine-relevant data from animal-based studies including information on different routes and durations of exposure as there is limited toxicological data for co-formulants (Table A3-2). Co-formulants where no data were found to indicate endocrine disrupting properties were assumed not to be active as endocrine disruptors.

Quantification of exposure

Professional operators are mainly exposed to pesticide products during mixing/loading and application tasks via two major routes, namely dermal absorption and respiratory inhalation (Damalas and Abdollahzadeh, 2016). These exposure scenarios are included within the harmonised Agricultural Operator Exposure Model to reflect agricultural practices in the EU (AOEM; Groβkopf et al., 2013a). The AOEM is based upon empirical data from 34 exposure studies conducted between 1994 and 2009. The model allows the adjustment of a range of exposure parameters including the formulation type (liquid, wettable powder, wettable granule), personal protective equipment (PPE; gloves, face shield, coverall), and application equipment (knapsack, vehicle-mounted tractors, cabin status) (Groβkopf et al., 2013a). Here, we employed the AOEM to assess the median exposures of operators to individual active substances with known/possible endocrine disrupting activity during mixing/loading and application tasks across individual spray days (Table 3-1).

In the AOEM algorithms, the total mass of active substance handled during a day is the dominant input parameter to the exposure modelling. However, pesticide products consist of the declared active substance plus co-formulants that may be hazardous in themselves. The AOEM algorithms were also adopted to assess the occupational exposure to any co-formulants that were identified on the MSDS for the respective product and that were identified as having possible endocrine disrupting activity. The MSDS rarely gives precise information on the exact proportions of different co-formulants, so we used the mean value where a range was given (e.g. 3% for "1-5%") and the defining number for compositional formulations (e.g. 5% for "<5%", "≤5%" or ">5%"). Exposure to individual co-formulants was calculated as for active substances, considering exposure to the hands, body, head, and via inhalation; the influence of any personal protective equipment and/or equipment design was included in the calculation and adjustments for dermal and inhalation absorptions were based on the content of individual co-formulants in the products. Full details of the exposure model are provided in Wong et al. (2018). The total exposures to active substances and co-formulants with known/possible endocrine disrupting activity were summed separately for each individual spray day.

Risk estimation

According to EFSA (2013b), the combined effects of individual pesticide active substances should be determined based on their toxicological profiles where experimental measurements of combined effects are not available. To estimate risk from exposure to multiple active substances with known/possible endocrine disrupting activity handled on a single spray day, we adopted an application of the concept of concentration addition to calculate the combined dosages in the mixture based on the point of departure index (PODI) (Christiansen et al., 2012):

$$\boldsymbol{PODI} = \sum_{\boldsymbol{i}=\boldsymbol{1}}^{\boldsymbol{n}} \left[\frac{\boldsymbol{EL_i}}{\left(\frac{\boldsymbol{POD_i}}{\boldsymbol{UF}}\right)}\right] \qquad \textbf{(Eqn. 27)}$$

where EL is the estimated exposure level (mg kg bw^{-1} day^{-1}) and POD is the point of departure for endocrine disrupting effects (NO(A)ELs in mg kg bw^{-1} day^{-1}). UF is the default uncertainty factor of 100, frequently characterised as a factor of 10 for interspecies extrapolation and a further factor of 10 for different sensitivities among humans (Bang et al., 2012). A PODI >1 indicates that significant effects are possible.

For the POD, we extracted the short-term NO(A)ELs (subacute or subchronic) for endocrine disrupting effects from six established toxicological databases, namely the EFSA Draft Risk Assessment Report and Assessment Report (http://dar.efsa.europa.eu/dar-web/provision), the Joint Meeting on Pesticide Residues of the International Programme on Chemical Safety, http://www.inchem.org/pages/jmpr.html), the Hazardous Substances Data Bank of TOXNET, the Integrated Risk Information System (https://www.epa.gov/iris), the EPA Endocrine Disruptor Screening Program Tier 1 screening determinations and associated data evaluation records (https://www.epa.gov/endocrine-disruption/endocrine-disruptor-screening-program-tier-1-screening-determinations-and) the European Commission (EC) Endocrine Disruptors Database (EDS, http://ec.europa.eu/environment/chemicals/endocrine/strategy/substances_en.htm), ECHA Classification and Labelling report, and other open literature (Table A3-3). Active substances that lacked a short-term NO(A)EL were assessed against individual chronic NO(A)ELs for endocrine disrupting effects; this was necessary for captan, chlorothalonil, flusilazole, linuron, paclobutrazol, propiconazole and pyriproxyfen. When neither short-term nor chronic NO(A)ELs were available (i.e. for deltamethrin and s-metolachlor), the lowest observed (adverse) effect levels (LO(A)ELs) for endocrine disrupting effects were applied with an adjusted uncertainty factor of 1000 (Bullock and Ignacio, 2006) (Table A3-3).

A major challenge was encountered during the identification and extraction of NO(A)ELs for endocrine disrupting effects. As the disrupting process may affect different endpoints due to an alteration of function of the endocrine system, it is often difficult to assess the endocrine mediated mechanism or mode of action (Marx-Stoelting et al., 2014). The endocrine system communicates with the nervous and immune systems via multiple common pathways, so chemical exposure may affect the function of these systems together (Liu et al., 2006). For instance, observed effects on testicular and uterine weight in test organisms could be due to endocrine disruption even though no mechanistic evidence is available (Ewence et al., 2013). The problem associated with determining adversity and risk from endocrine disruptor compounds remains unresolved (Futran Fuhrman et al., 2015). Hence, we extracted NO(A)ELs for any observed (adverse) effects on the thyroid, adrenal, pancreas, pituitary, prostate, gonad (testes and ovaries), hormones, spleen, and growth retardation for the current assessment (Table A3-3).

Results

Pesticide application data

The pesticide programmes used across five cropping systems included eight active substances that are known to have endocrine disrupting activity (Table 4-1), comprising bifenthrin, bromoxynil, deltamethrin, fenoxycarb, ioxynil, picloram, tau-fluvalinate, and triadimenol (PPDB, 2018). All systems included applications of at least one such substance, with a maximum of six active substances with known endocrine disrupting activity applied in the UK arable system. More than half (48-67% across the different cropping systems) of active substances with known/possible activity were fungicides, with 13-35% insecticides and 10-28% herbicides (Table 4-1).

Table 4- 1. Summary of pesticide active substances (AS) with known/possible endocrine disrupting activity (PPDB, 2018) used in the different cropping systems and classified by pesticide type.

Cropping system	Number of AS with endocrine activity		Number of AS with known/possible endocrine activity used on different targets		
	Known	Possible	Fungicides	Herbicides	Insecticides
Lithuania arable	2	15	9	3	5
UK arable	6	23	14	8	7
Greece arable	1	10	6	2	3
UK orchard	1	14	10	3	2
Greece orchard	2	18	11	2	7
All systems combined	8	40	25	11	12

Overall, the UK cropping systems were treated with a larger number of active substances with known/possible endocrine disrupting activity during the survey period (medians of 11 and 10 chemicals for arable and orchard systems, respectively) than the Greek cropping systems (6 and 5 chemicals for orchard and arable systems, respectively) and the Lithuanian arable system

(4 chemicals) (Figure 4-1a). The masses of identified active substances applied were also largest in the UK (medians of 305 and 256 kg a.s. for orchard and arable systems, respectively) (Figure 4-1b). Active substances with known/possible endocrine disrupting activity were handled relatively frequently with 86% of the 50 professional operators handling at least one such substance on more than 50% of total spray days during the period investigated (Figure 4-1c), and up to five identified active substances applied on a single day in the UK orchard system (Figure 4-1d).

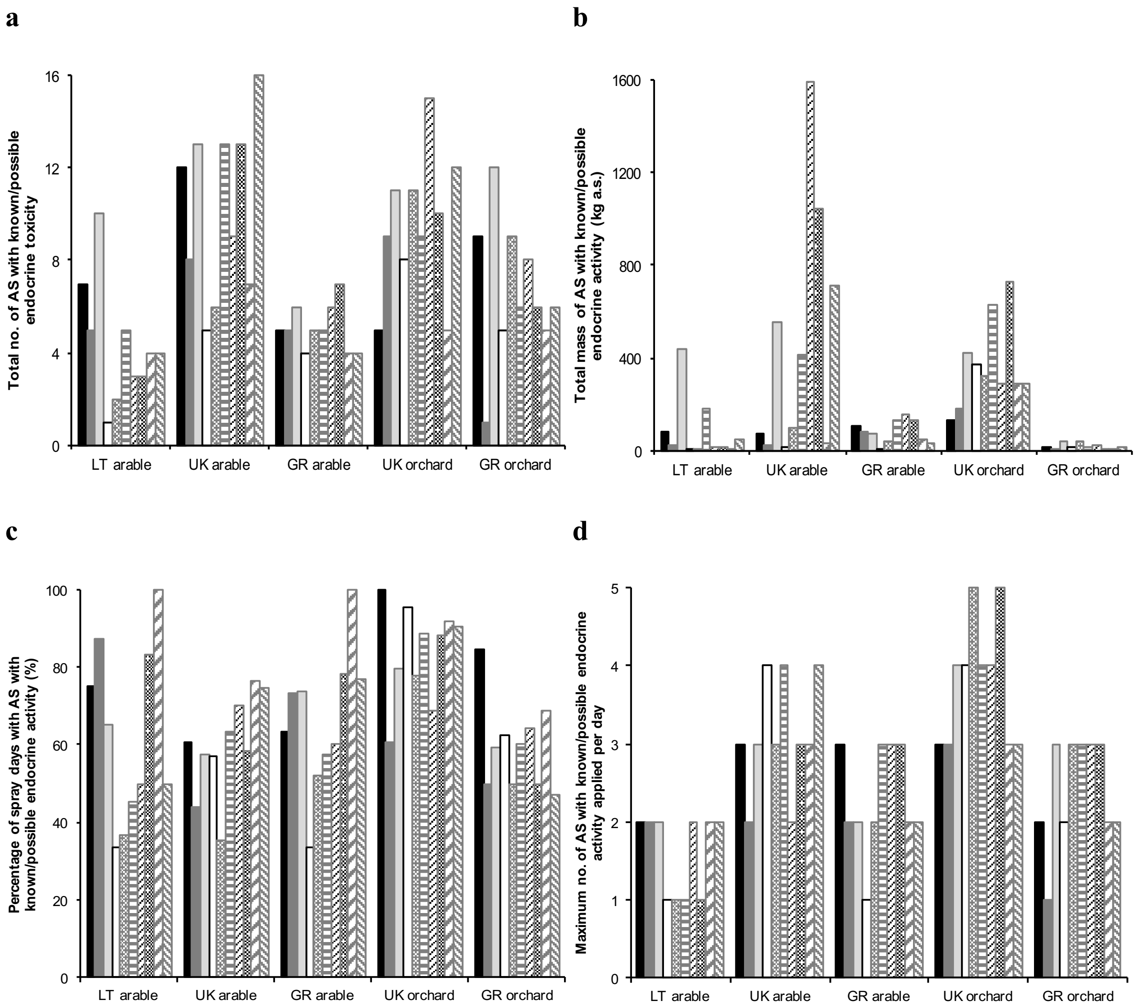


Figure 4- 1. Application data for 50 professional operators from the cropping systems in Lithuania, the UK and Greece expressed as total number (a), total mass (b), percentage of spray days (c), and maximum number applied on a single day (d) of active substances (AS) with known/possible endocrine disrupting activity.

Predicted exposure and risk from active substances with known/possible endocrine disrupting activity

Figure 4-2 shows that the estimated exposure to active substances with known/possible endocrine disrupting activity on single spray days varied greatly across the 50 selected professional operators. Overall, all operators had at least one spray day with predicted exposure to such active substances over the survey period. At median level, the predicted daily exposure was generally larger amongst the orchard operators from the UK ($1.1x10^{-3}$ - $5.1x10^{-2}$ mg kg bw^{-1} day^{-1}) and Greece ($2.4x10^{-4}$ - $2.2x10^{-2}$ mg kg bw^{-1} day^{-1}) compared to individuals working in arable systems in Greece ($8.3x10^{-5}$ - $2.0x10^{-2}$ mg kg bw^{-1} day^{-1}), the UK ($1.1x10^{-4}$ - $3.7x10^{-3}$ mg kg bw^{-1} day^{-1}), and Lithuania ($8.7x10^{-5}$ - $1.6x10^{-3}$ mg kg bw^{-1} day^{-1}). Over the survey period, the Greek arable operators had relatively larger variance around mean daily exposure (coefficients of variation 103-340%), whilst variance was intermediate for those from the orchard systems in the UK and Greece (78-232% and 88-180%, respectively), and relatively smaller amongst the arable operators from Lithuania and the UK (51-148% and 62-116%).

Figure 4-3 shows the predicted risk per spray day from exposure to active substances with known/possible endocrine disrupting activity across the 50 selected operators. Generally, the Greek and UK orchard operators had larger risk estimates (medians of PODI $5.0x10^{-3}$ - $5.5x10^{-1}$ and $7.6x10^{-3}$ - $2.2x10^{-1}$, respectively) than those from arable systems of Lithuania and the UK ($8.6x10^{-4}$ - $2.4x10^{-1}$ and $1.1x10^{-3}$ - $3.3x10^{-2}$, respectively). Overall, 14 of the 50 operators had at least one spray day with PODI >1; the largest number of individuals meeting this criterion were from the Greek cropping systems (five and four operators for arable and orchard systems, respectively) and the least for the UK cropping systems (only one operator in each system). Individuals with maximum PODIs >1 generally had larger variance around mean daily PODI over the survey period; for example, three Lithuanian arable operators with maximum PODIs of 3.5, 5.6 and 4.1 had estimated coefficients of variation 233, 398 and 263%, respectively (Figure 4-3a).

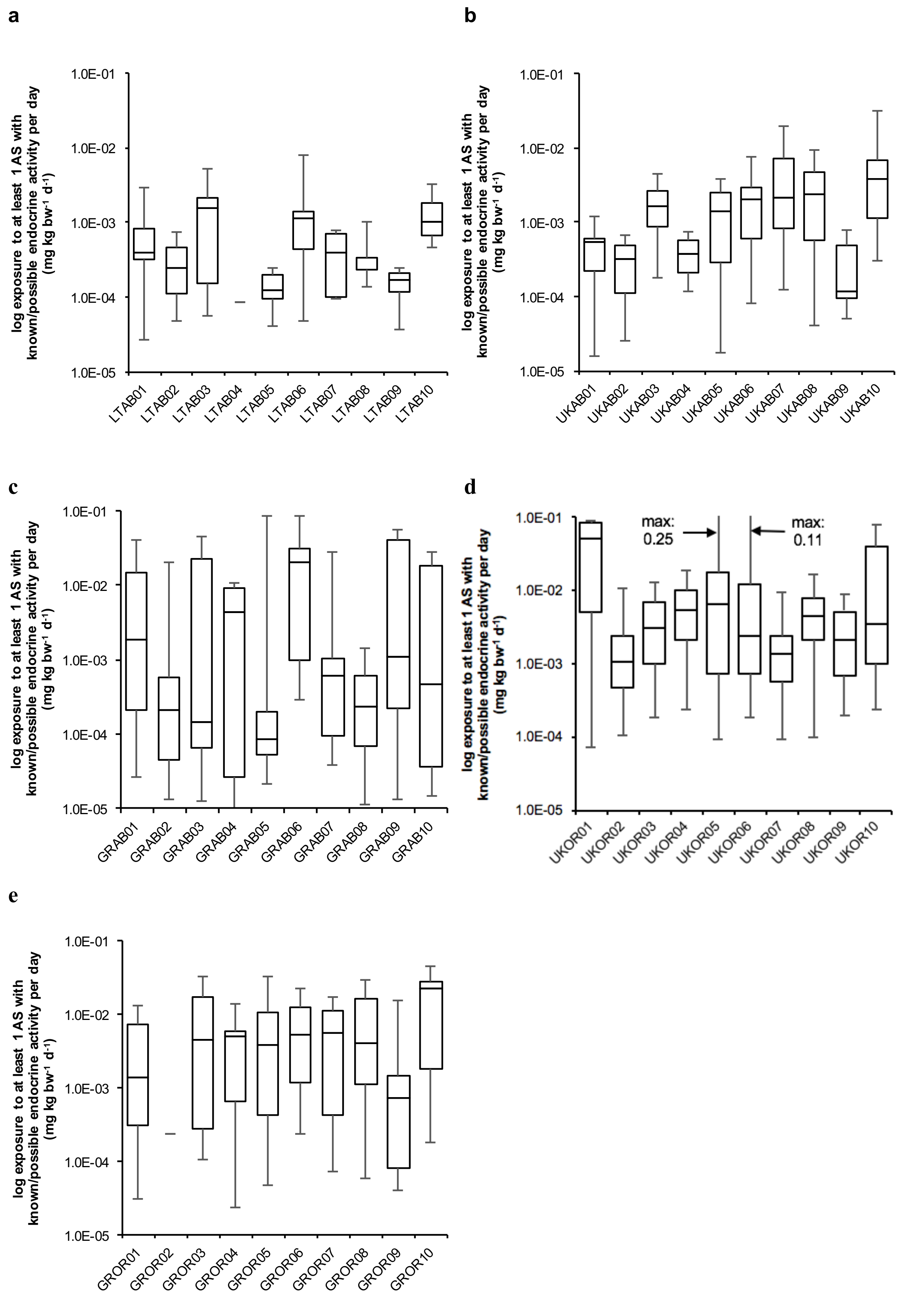
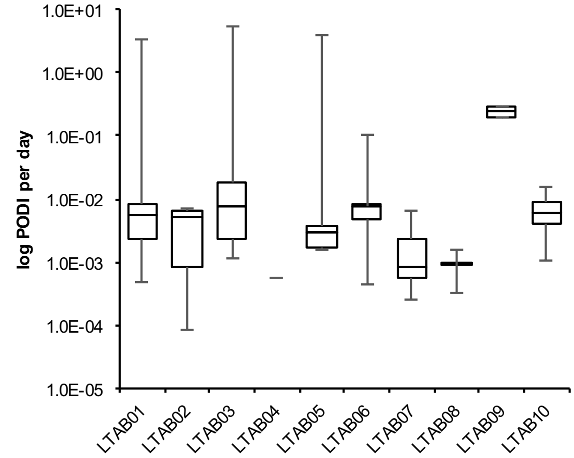
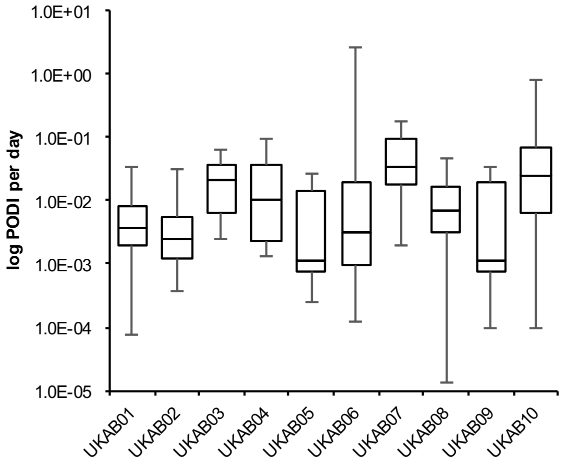


Figure 4- 2. Estimated total exposure on individual spray days when at least one active substance with known/possible endocrine disrupting activity was applied. Data are shown for individual operators from the arable systems in Lithuania (a), the UK (b) and Greece (c), and the orchard systems in the UK (d) and Greece (e). Boxes show the median and quartiles, and whiskers show the range.

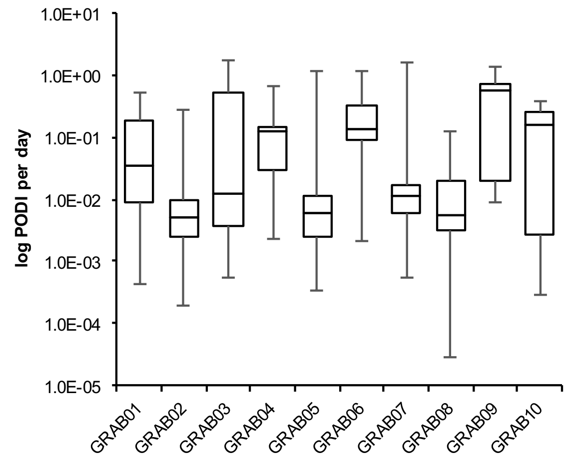
a



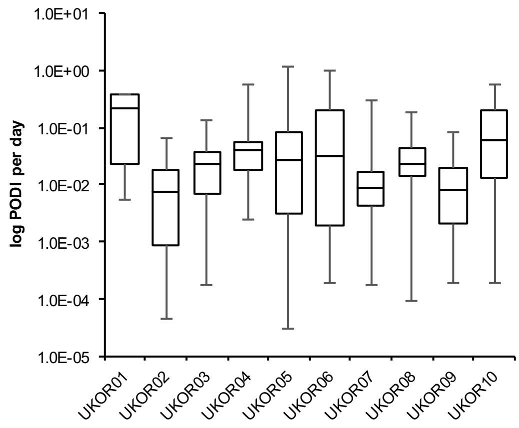
b



c



d



e

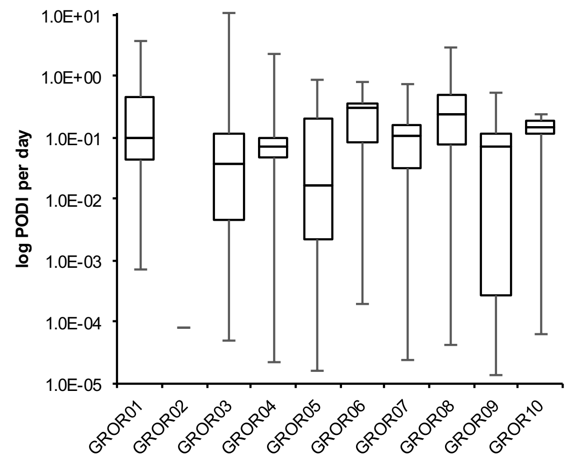


Figure 4- 3. Estimated risk from exposure on individual spray days when at least one active substance with known/possible endocrine disrupting activity was applied. Data are shown for individual operators from the arable systems in Lithuania (a), the UK (b) and Greece (c), and the orchard systems in the UK (d) and Greece (e). Boxes show the median and quartiles, and whiskers show the range.

Figure 4-4 shows cumulative frequency distributions for estimates of total exposure and total risk on single spray days and for individual operators from the five cropping systems. Across all of the operators, at least one active substance with known/possible endocrine disrupting activity was applied on ca. 60 to 80% of the total spray days that were recorded in the database. On single spray days, the total exposure to such active substances varied greatly across all operators, ranging between 6.7×10^{-6} and 2.7×10^{-1} mg kg bw^{-1} day^{-1} (Figure 4-4a). Estimated exposure was largest for the UK orchard system at all points on the cumulative frequency distribution (Figure 4-4a). For example, at the 95th percentile, estimated exposure in the UK orchard system (4.1×10^{-2} mg kg bw^{-1} day^{-1}) was more than an order of magnitude larger than that in the Lithuanian arable system (2.6×10^{-3} mg kg bw^{-1} day^{-1}). Estimated risk was only largest for UK orchards up to the 60th percentile (Figure 4-4b); at percentiles above this, risk was always largest in the Greek orchard system mainly due to the applications of a few relatively hazardous substances (e.g. deltamethrin and chlorpyrifos-methyl with points of departure for endocrine disrupting activity of 0.001 and 1.0 mg kg bw^{-1} day^{-1}, respectively). At the 95th percentile of the distribution, the Greek cropping system had largest estimated risk (PODI of ca. 5.3×10^{-1} in each system), whilst this was intermediate for the UK orchard system and the Lithuanian arable system (3.0×10^{-1} and 2.5×10^{-1}, respectively), and least for the UK arable system (9.0×10^{-2}; Table 4-2). All five cropping systems had at least one operator with a point of departure index for endocrine disrupting effects on a single spray day greater than one (maximum PODIs ranged between 1.2 and 10.7; Table 4-2).

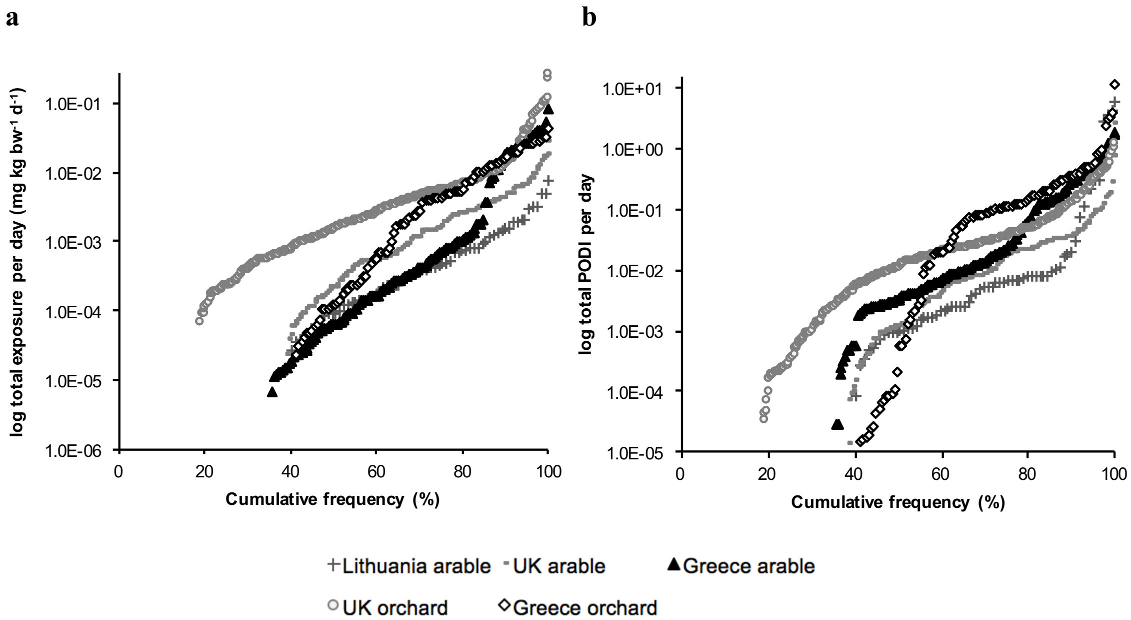


Figure 4- 4. Cumulative frequency distributions of total exposure (a) and total risk expressed as the PODI (b) on single spray days with at least one active substance with known/possible endocrine disrupting activity applied by 50 individual operators across the cropping systems. Each data point represents the value for an individual operator on a single day.

Table 4- 2. Distribution of predicted total risk (expressed as the PODI) from exposure to active substances with known/possible endocrine disrupting activity. Different percentiles and the maximum are given for the five cropping systems based on 10 operators and all spray days with at least one active substance applied.

	Total PODI per spray day (percentile)				
Cropping system	25th	50th	75th	95th	Maximum
Lithuania arable	-	9.53×10^{-4}	6.29×10^{-3}	2.47×10^{-1}	5.58
UK arable	-	1.27×10^{-3}	1.80×10^{-2}	9.02×10^{-2}	2.61
Greece arable	-	3.25×10^{-3}	2.15×10^{-2}	5.32×10^{-1}	1.74
UK orchard	3.37×10^{-4}	1.05×10^{-2}	3.44×10^{-2}	3.03×10^{-1}	1.15
Greece orchard	-	5.28×10^{-4}	1.06×10^{-1}	5.28×10^{-1}	10.72

Predicted exposure to pesticide co-formulants with possible endocrine disrupting activity

Figure 4-5 shows that co-formulants increased the complexity of potential exposure of the UK orchard operators to mixtures of chemicals with possible endocrine disrupting activity. At maximum, one operator applied five such active substances and ten such co-formulants on a single spray day. Only one active substance classified as having known endocrine disrupting activity was applied by any of the ten operators working in UK orchards. Figure 4-6 shows that estimated exposure of operators to co-formulants classified as having possible endocrine activity was at a level lower than that for active substances; exposure to co-formulants contributed up to ca. 0.1 mg kg bw^{-1} and 46% of an individual's total exposure to pesticides with endocrine disrupting activity over the survey period.

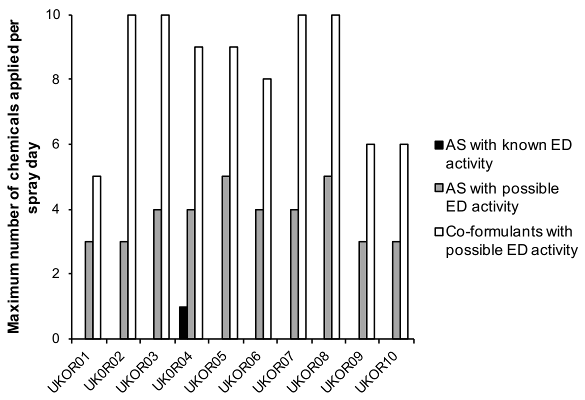


Figure 4- 5. Maximum number of active substances and co-formulants with known or possible endocrine disrupting activity applied on a single spray day for ten operators working in UK orchards.

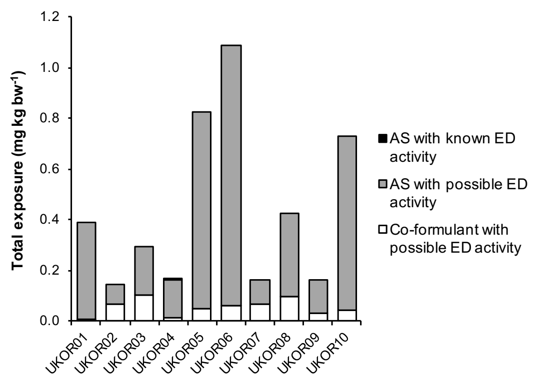


Figure 4- 6. Predicted total exposure to active substances and co-formulants with known/possible endocrine disrupting activity over the survey period for 10 operators working in UK orchards.

Discussion

Professional agricultural operators across five agricultural systems in three European member states were potentially exposed on single spray days to complex mixtures of active substances and co-formulants with known/possible endocrine disrupting activity (Figures 4-1d and 4-5). The majority of active substances identified as having known/possible endocrine disrupting activity were fungicides (48-67% of total active substances across the five agricultural systems; Table 4-1). In a review of recent literature on the effects of pesticide mixtures in human and animal models based on 78 studies published between 2000 and 2014, mixture effects of fungicides were associated predominantly with endocrine regulation and/or reproduction (Rizzati et al., 2016). Figure A3-1 compares the relative contributions of fungicides, herbicides, and insecticides to the use, exposure and risk associated with endocrine disrupting activity. Overall, fungicides made the largest contribution to total usage and associated exposure across all cropping systems (48-67% and 58-99%, respectively) compared to herbicides (10-28% and 0.7-38%) and insecticides (13-35% and 0.2-26%; Figures A3-1a and A3-1b). In contrast, insecticides and fungicides contributed similarly to risk across the five systems as a whole (Figure A3-1c). Fungicides were the major component of risk in the Greek arable system and the UK cropping systems (64% and ca. 50% of total PODI in each system, respectively), whereas insecticides dominated the risk profile in the Lithuanian arable system and the Greek orchard system (94% and 79% of total PODI, respectively). Herbicides contributed least to the risk associated with endocrine disrupting activity, representing at maximum, 22% of the PODI in the UK orchard system.

Figures 4-1d and 4-5 indicate that the professional operators in our dataset can be exposed to up to five active substances with known/possible endocrine disrupting activity on a single spray day, with predicted exposure ranging between 6.7×10^{-6} and 2.7×10^{-1} mg kg bw^{-1} day^{-1} (Figure 4-4a). Table 4-2 indicates that all cropping systems had at least one operator with potential risk from exposure to active substances with known/possible endocrine disrupting activity indicated by a point of departure index greater than 1 on a spray day. The instances with potential risk are primarily due to uses of deltamethrin where the LO(A)EL had to be used as the point of departure, and uses of mancozeb and copper oxychloride where the AOEM estimates larger exposure because they are formulated as wettable powders. Many of the copper oxychloride formulations are no longer approved as plant protection products, although growers can continue to use copper oxychloride based products as foliar feeds. Predicted concentrations below individual points of departure do not mean that there is no risk as the NOAELs cannot be equated with zero-effect levels (Kortenkamp et al., 2007). The endocrine system usually responds to hormone concentrations of parts-per-trillion and parts-per-billion and endocrine disruptors can coexist in the system to cause low-dose effects that are not predicted at higher dose (Vandenberg et al., 2012). A minor change in the concentration of an endocrine disrupting chemical can induce significant changes in biological endpoints even though the dose is small (Futran Fuhrman et al., 2015). Currently, risk assessment methodologies do not sufficiently assess the hazard associated with low-dose exposure to endocrine active substances (Melching-Kollmuss et al., 2017) and the lack of a universal definition for “low dose” is one obstacle to this.

Based on the UK orchard system, Figures 4-5 and 4-6 indicate that professional operators can be simultaneously exposed to multiple co-formulants with possible endocrine disrupting activity; levels of exposure are generally lower than for the declared active substances, with co-formulants accounting for up to 46% of total exposure at maximum due to their relatively smaller proportions in the products. The AOEM was developed to simulate active substances and the algorithms of the model might require modification for co-formulants such as surfactants that have an amphiphilic structure consisting of a long-chain hydrocarbon and an ionic or highly polar group (Castro et al., 2014). Co-formulants are usually assessed for acute ocular and dermal properties, but there is no specific requirement for medium- and long-term regulatory experiments on mammals and acceptable daily intake values are not required to be established (Defarge et al., 2016). It was not possible to estimate risk from exposure to co-formulants here because of the lack of appropriate experimental endpoints; the total risk associated with use of the products will thus be greater than that reported here based on the active substances alone.

In the EU, pesticide formulations are typically registered at the national level and require more risk assessment data for the declared active substances than for the authorisation of co-formulants (Kienzler et al., 2016). It is usually the responsibility of industry to classify the co-formulants and this may result in different classifications, labelling, and levels of protection for substances with identical CAS numbers (Lichtenberg et al., 2015). The lack of complete disclosure of identity and concentrations of co-formulants and formulation ingredients coupled with inadequate analytical methods constrain a comprehensive risk assessment for commercial plant protection products (Mullin et al., 2016).

There is currently no consensus on a science-based approach to the assessment of endocrine disrupting properties (Marx-Stoelting et al., 2016). The assessment is affected by different issues including the existence of safe thresholds for adverse effects, the significance of dose-response relationships, and the influence of different modes of action (Solecki et al., 2017). The adoption of scientific criteria for endocrine disruptors needs a clear definition of the hazard as the first step to developing test methods, identifying hazardous chemicals, and managing risk for regulatory purposes (Slama et al., 2016). Typically, chemicals with observed endocrine effects in experimental animals based on the test guidelines of Organisation for Economic Co-operation and Development need to be addressed for their relevance to humans including consideration of species, strain, exposure route (OECD, 2012), and species-specific differences such as endocrine signalling, toxicokinetics, and bio-transformation (Testai et al., 2013). The dose thresholds/guidance values for "Specific Target Organ Toxicity Repeated Exposure" were used to determine whether the hazardous property of endocrine disruption should be identified for regulatory purposes in accordance with the CLP Regulation (Ewence et al., 2015). Nevertheless, the OECD framework is inadequate for the identification of all aspects of endocrine disrupting effects, because it mainly focuses on estrogenicity, anti-androgenicity, and thyroid disruption (Manibusan and Touart, 2017).

Conclusion

Professional agricultural operators handling plant protection products can be exposed to complex mixtures of chemicals comprising both the declared active substances and co-formulants, and some of these chemicals have known/possible endocrine disrupting activity. At the extremes, our results show that exposure to pesticide active substances can result in risk quotients for mixtures handled on a single day that indicate potential for risk (i.e. point of departure index greater than 1). Additional risk might also be expected from simultaneous exposure of operators to pesticide co-formulants with endocrine disrupting activity. This study suggests the need for clarity on the identification of endocrine disrupting activity, particularly as many of the substances considered in this study were classified as having “possible” rather than “known” endocrine disrupting activity. Further work is also required on risk assessment for pesticide co-formulants, particularly where complex mixtures can occur with multiple active substances and co-formulants that have similar toxicological endpoints.

Chapter 5 Conclusion and Perspectives

Literature review

Pesticides are widely used in agriculture to control a range of pests and crop diseases. Due to the intrinsic toxicity of this class of chemicals, off-target movement of pesticides may pose a risk to human health. Risk assessment for non-dietary, human exposure to pesticides is an integral part of pesticide authorisation at the EU level, with a range of models introduced for regulatory application. Typically, investigation of association between pesticide exposure and health issues provides an important check for the regulatory process in minimising pesticide risk. Nevertheless, a review of the literature has identified exposure estimation as a major gap between risk assessment as part of regulatory procedures, post-authorisation monitoring, and epidemiological investigations:

1. Much effort is expended in epidemiology to express major associations between exposure of vulnerable humans to a range of pesticides and ill health. Pregnant women are of particular concern because they may spend long periods at home and are susceptible to pesticides that have the potential to cause adverse reproductive and developmental effects. However, the strength of evidence for any association with birth outcomes is generally weak because of methodological limitations including the relative weakness in measurement and prediction of exposure.

2. Occupationally, agricultural operators can be exposed to complex mixtures of pesticides during mixing/loading and application activities at levels much higher than the general population. Operator exposure can be influenced by a wide range of factors under actual conditions of use and thus is generally predicted rather than measured. A range of models is available to assess the operator exposure, however, the major drivers of exposure have rarely been assessed against agricultural practices under field conditions.

3. European pesticide regulations require risk assessment that usually focuses on the declared active substances with generally fewer data requirements for co-formulants. Regulatory assessment is the only place where exposure is routinely quantified, but this is done one active substance at a time and there is no oversight of total exposure to pesticides or of how this may be changing in time. In mixtures, active substances and/or co-formulants with similar

toxicological endpoints may cause combined effects at levels higher than that predicted for single active substances. Nevertheless, mixture toxicities of multiple active substances and/or co-formulants, other than those occurring in tank mixes, have typically been ignored within the regulatory assessment scheme.

4. Exposure models that can describe the complex interactions between agronomic and environmental conditions and pesticide exposure are important tools in regulatory risk assessment that can be used to supplement limited field measurements in a cost-effective way. Nevertheless, the existing models have some limitations including limited data for some pathways of operator exposure in the AOEM and the maximum distance of 10 m for residential exposure in the BROWSE models. Improvement to the models is necessary as additional data become available, and adjustable parameters are also important to simulate different situations more accurately.

5. Pesticide risk is typically assessed against the respective lowest NO(A)EL value, with a range of established toxicological databases available. For the identification of the lowest relevant value, however, there are currently no scientific criteria to define different health diseases including a clear boundary between reproductive and developmental effects or of endocrine induced effects. Questions remain concerning inherent uncertainties in the NO(A)ELs and the impact on the risk assessment.

The aim of this PhD study was to assess non-dietary exposure of vulnerable humans to pesticides and to evaluate the regulatory process in managing pesticide risk over time. A mathematical model for pesticide volatilisation and aerial dispersion was developed and the harmonised Agricultural Operator Exposure Model (AOEM) was used to quantify the levels of exposure and thus risk for residents and professional agricultural operators, respectively. Two high-quality pesticide application datasets previously collected by Fera Science Ltd. and for EFSA at the UK and the EU levels, respectively were used to drive the analyses. Trends in pesticide usage and major drivers of exposures and thus risks were identified, including any implications for the regulatory assessment scheme over the period investigated. The main conclusions of this thesis can be summarised as follows.

Use of models for risk assessment

In this thesis, the use of models for risk assessment enabled non-dietary routes of human exposure to pesticides to be quantified across a range of agronomic and environmental conditions, which is a common requirement in post-authorisation monitoring and epidemiological studies. Model simulation can supplement the available exposure data cost-effectively, but there are inherent limitations owing to the embedded assumptions and data availability at the time of model development.

In Chapter 2, a mathematical model was developed that allows estimation of exposure to pesticides for residents living at different distances from treated fields. The model consists of three components, namely pesticide volatilisation and aerial dispersion, deposition of spray droplets, and then residential exposure. For modelling purposes, the following assumptions were made: (i) two major routes of exposure were considered dominant, namely vapour inhalation and indirect dermal contact with contaminated ground, (ii) maximum daily exposure was estimated for the first day after an application is completed, and (iii) no other dissipation pathways or competing processes on treated surfaces were included as the simulation only considered the first day after treatment. The developed model provides a promising starting point to estimate pesticide exposure and associated risk for residents living at different proximities from treated fields. The explicit calculations can be used as an improvement to the relatively weak exposure prediction and measurement in epidemiological methodologies. Nevertheless, a complete evaluation of the model is required and is discussed further below.

In Chapters 3 and 4, the use of the AOEM allows simulation of a range of parameters to reflect latest agricultural practices and scientific knowledge including the use of different pesticide formulations, application methods, and protective measures under field conditions. More field measurements are needed to improve the statistical power of the estimated dominance of wettable powder formulations in the AOEM as this relied on just two exposure studies for hand-held applications. The AOEM was developed based on empirical data and application is thus restricted to situations that are covered by the measurements. A range of assumptions are adopted in the model including: use of LCTM situation for arable crops and HCTM situation for orchard crops treated with vehicle-mounted/vehicle-trailed sprayers; use of HCHH situation for orchard crops treated with hand-held equipment; use of tank mixing/loading situation for all vehicle-mounted/-trailed sprayers and hand-held equipment; a relatively simple treatment of protection levels to incorporate the efficiency of PPE use; and an assumption of 100% inhalation absorption independent of the cabin status, which is a dominant parameter for relatively higher exposure estimates in HCTM applications.

In Chapter 4, the AOEM algorithms were used to predict exposures from individual active substances and co-formulants with known/possible endocrine disrupting activity. However, the algorithms were developed for active substances that have different chemical structures and thus properties compared to co-formulants. Co-formulants such as surfactants have an amphiphilic structure consisting of a long-chain hydrocarbon and a highly polar group, which is typically designed to aid application and/or improve the effectiveness of the product. Therefore, errors are possible when using the AOEM for co-formulants and tests would be required to identify the appropriateness and accuracy of such use.

Model evaluation

In Chapter 2, the developed mathematical model was not evaluated as data were not available at the time of model development. Subsequently, a small unpublished dataset collected by the Swedish University of Agricultural Sciences during summer and autumn 2008 to 2010 became available for a preliminary evaluation as presented in Appendix 4. Five of six measured active substances were selected for the evaluation, namely fenpropimorph, lindane, pendimethalin, pirimicarb, and prosulfocarb. Results for the first day after application were calculated to match the model outputs, thus all variables were averaged to derive daily values including wind speeds, air temperatures, and measured airborne concentrations at a chosen height of 1.0 m above ground.

Results indicated that model outputs for concentrations of pesticides in air matched field observations to within an order of magnitude in most cases (Table A4-4), with ca. 86% of total comparisons lying within a factor of ten during the periods of summer and autumn (Table A4-5). The factor of ten for comparison was modified from a factor of two that was used to evaluate an urban air quality model (Derwent et al., 2010); this allows for uncertainties introduced by a variety of agronomic and environmental variables that were not parameterised in the developed model. Meanwhile, the correlation coefficients of the scatter plots indicated relatively poor correlations between the model outputs and field observations with R^2 values of 0.21 and 0.59

during the summer and autumn, respectively (Figure A4-6). More processes would need to be tested and factored into the model for a more accurate estimation, including the consideration of formulation effects and dissipation pathways other than volatilisation on treated surfaces.

Overall, the preliminary evaluation indicated that the developed model for pesticide volatilisation and aerial dispersion is a promising starting point to measure the residential exposure to pesticides, helping to address a common gap in epidemiological studies. The model enables the quantification of total inhalation exposure from a large number of active substances and applications at different proximities from treated fields. Meanwhile, deposition of spray droplets and thus indirect dermal contact with contaminated ground could not be assessed due to lack of data for locations remote from the treated area. More field data measuring agronomic and environmental conditions, airborne concentrations, and spray deposits for a range of active substances and at larger proximities, would supplement the limited data in the initial evaluation, improving current understanding of the influences of pesticide properties and environmental conditions on fate and allowing a more complete evaluation of the model. Detailed information on the preliminary evaluation comprising an introduction, methodology, results, discussion, and conclusion for this work are included in Appendix 4.

Major drivers of pesticide exposure and risk

In general, resident pregnant women living in the vicinity of treated fields had exposure estimates at levels relatively smaller than those for the professional operators who are directly involved in pesticide handling activities. Residents usually take no action to avoid or to control pesticide exposure and might be present in the home for up to 24 h per day (longer-term exposure; EFSA, 2014), whilst the professional operators generally handle large amounts and complex mixtures of pesticides during mixing/loading and application tasks.

In Chapter 2, results regarding resident pregnant women confirmed the impact of regulatory intervention in improving fate and hazard profiles of pesticides applied in orchards in England and Wales over a 25-year period (1987, 1996, 2004 and 2012). Based on four regions and nine orchard crops, there was significant decrease in total pesticide usage from 1987 to 1996, followed by smaller changes through to 2012 (Figure A1-7). This was attributable to reduced-rate applications at less than the maximum recommended label rate and the introduction of new molecules that are active at lower dose rates. There were also overall decreasing trends in total pesticide emission rate, the estimated exposure per unit application, and the risk per unit exposure across four chosen years (Figures 2-6 and A1-11). The analysis showed a clear shift in the properties of pesticides applied to orchards away from active substances with relatively high volatility and high reproductive/developmental toxicity from 1987 to 2012 (Figure A1-10). At 1000 m from treated fields, active substances with higher volatility contributed more to total exposure compared to that at 100 m. Hazard quotients for reproductive/developmental effects at 1000 m were 5 to 16 times smaller than those at 100 m, indicating the strong influence of proximity on magnitude of exposure and thus risk. Meanwhile, the relatively larger hazard quotients in the analysis were driven by one or two dominant active substances with relatively high toxicity for reproductive/developmental effects, with a number of hazardous substances that have been restricted or removed from the market over the period investigated.

In Chapter 3, analysis of 50 professional operators from cropping systems in Greece, Lithuania, and the UK identified agricultural practices as the dominant influence on their estimated daily exposures between 2012 and 2013. In Greece, the extensive use of wettable powder formulations contributed significantly to the relatively larger exposure estimates in agreement with empirical data (exposure due to wettable powder > liquid > wettable granule formulations). Meanwhile, the UK and Lithuania were influenced by the total area of land treated with each active substance per day as this frequently exceeded the regulatory assumptions suggested by EFSA (50 and 10 ha using vehicle-mounted equipment for arable and orchard crops, respectively; Figure 3-1). There were also influences of individual working behaviours involving the use of PPE, and the use of several hazardous active substances that have been restricted or removed from the market since the period of data collection. Crop types might influence operator exposure through different pesticide usage and application practices, but such influence was not assessed because a particular crop may have only been grown on a small number of holdings.

In Chapter 4, further analysis regarding the 50 selected professional agricultural operators indicated that individuals handled multiple active substances and/or co-formulants with known or possible endocrine disrupting activity during a single spray day. Across five cropping systems, the analysis identified eight active substances with known endocrine disrupting activity, whilst 40 other substances and 27 co-formulants were classified as having possible endocrine disrupting activity (Tables A3-1 and A3-2). In mixtures, all pesticide constituents with similar toxicological endpoints have potential to cause combined effects at levels higher than those predicted for individual active substances alone. At maximum, one operator handled five active substances with known/possible endocrine disrupting activity and ten co-formulants with possible activity in a single day (Figures 4-1d and 4-5). In everyday life, the operators can also be exposed to other classes of endocrine disrupting chemicals through their use in detergents, industrial and household products, brominated flame retardants, plastics, and as ingredients in personal care products based on varied lifestyle choices (Darbre, 2017). A review on endocrine disruptors and their possible impacts on human health demonstrated that previous studies on endocrine disruptors mainly focused on steroid hormones, synthetic steroids, polychlorinated dibenzo dioxins, and biphenyls with generally little work on alkylphenol ethoxylate, gonadotropin compounds, and pesticides due to their dependency upon diverse applications (Kabir et al., 2015). In a case-control study conducted by Den Hond et al. (2015) to investigate the association between endocrine disrupting chemicals and male fertility based on semen analysis for 163 patients, chlorinated pesticides from historical source (chlordane and hexachlorobenzene) and emerging chemical brominated flame retardants (polybrominated diphenylethers, BDE209) were identified as risk factors for subfertility compared to other endocrine disruptors including phthalates, triclosan and bisphenol A. In Chapter 4, pesticides appear as a major risk factor for the agricultural operators who may frequently handle large amount of endocrine disrupting chemicals during single spraying days compared to other sources like dietary intake, but should this be further investigated in the future studies.

Overall, regulatory interventions were a common driver of human exposure to pesticides. In Chapters 2 and 3, the analysis indicated improving pesticide hazard profile through the review and removal of hazardous active substances from the market over the period investigated. In Chapter 4, the analysis indicated the need to account for combined effects of multiple pesticide constituents with similar toxicological endpoints in regulatory risk assessment. On the other hand, the operator exposures in Chapters 3 and 4 were also driven by agricultural practices including the choices of pesticide formulations, application methods, and multiple applications of pesticide products on single spraying days. Generally, operator exposure at work can be minimised through working behaviour involving the use of PPE, whereas residents have very limited control over pesticide exposure in their daily activities.

Implications within regulatory procedures

Much work is expended to improve risk assessment and thus authorisation of pesticide active substances. Overall, results of this study confirmed the significant impact of Directive 91/414/EC and Regulation (EC) 1107/2009 in minimising pesticide risk over the period investigated. Persistent and hazardous active substances have been gradually removed from the market, with a reduction from ca. 1,000 substances in 1993 to currently about 400 substances approved within the EU.

In Chapter 3, the total area of land treated with each active substance per day was assessed against EFSA default assumptions that were derived based on relatively simple and older data. These representative values are intended to be towards the upper end of the range in values occurring in the field and not the absolute maxima. Nevertheless, there is a need to review how representative these values are for current spraying practice across the whole of the EU. To a lesser extent, the analysis also showed the need to account for the effects of formulation type in the pesticide risk assessment.

In Chapter 4, the analysis confirmed that active substances and/or co-formulants can have similar toxicological endpoints that may cause combined effects in mixtures. Meanwhile, the substance-driven risk assessment has typically ignored such combined effects in the authorisation of pesticide products and formulations. Until now, there is no specific regulatory requirement for medium- and long-term mammal experiments to establish acceptable daily intake values for co-formulants. The identification of co-formulants here based on the material safety data sheets showed a need to disclose the exact information on co-formulants for risk assessment purposes. It also showed a need to have one authority responsible for authorising both active substances and co-formulants, whereas to date these have been approved at the EU and the national levels, respectively.

Hazard-based inclusion criteria do not provide a science-based approach to assess health issues of concern, including the identification of reproductive and developmental endpoints (Chapter 2), or of known and possible endocrine disrupting activities (Chapter 4). The regulatory use of AOEL as a limit in the authorisation process of the use of any active substances is an internal dose (Chapter 3), whilst the major route of exposure in the post-marketing phase is the skin; hence, risk assessment can be carried out only by conducting dermal exposure studies (Mandic-Rajcevic et al., 2015).

The current pesticide regulatory system does not require post-registration monitoring to provide real exposure information for non-dietary and environmental risks at the EU level (EFSA, 2018). Pre-registration studies are usually conducted based on all the recommendations for use (e.g. the representative recommended rate of application and the likely maximum area of crop treatable in a working day), so post-registration surveillance studies are important to ensure representation of actual use conditions and exposure variability (e.g. use of protective clothing and equipment) in exposure assessment (OECD, 1997). The monitoring data including post marketing vigilance by applicants can be used to refine the hazard assessment and the exposure estimates, and/or to guide risk management to revisit approval conditions (EFSA, 2018).

Limitations in analyses

In this thesis, the longer-term analysis of pesticide application data and explicit exposure estimations add to the existing body of knowledge and allow a holistic assessment of the effectiveness of regulatory interventions in minimising pesticide risk within the EU over the period investigated. Nevertheless, several inherent limitations are present within the analyses. In Chapter 2, results regarding residential exposure were summed into single measures to give total exposure and total risk estimates associated with individual crops. However, the implicit assumption of co-occurrence of exposure to all pesticides applied to a single crop and additivity of such effects will not hold true. Under field conditions, the exposure to individual active substances will be widely dispersed in time whilst this is not considered in the present work. The analysis indicated the strong influence of proximity to the sprayed area on magnitude of residential exposure and thus risk, however, such influence could not be verified due to the lack of data on airborne pesticide concentrations and spray deposits at the selected proximities. Results suggested a temporal differentiation in health outcomes for the estimated peak exposure between April and July each survey year, but this could not be assessed without relevant health data. Other inherent limitations were also introduced in the analysis, including no consideration of the fate of substances beyond the first day after application, of the structures that might interrupt pathways of exposure, of different mechanisms between reproductive and developmental toxicities, and of additional exposure pathways such as dietary intake.

In Chapter 3, major limitations within the analysis of operator exposure during mixing/loading and application activities resulted from the relatively simple treatment of protection factors to incorporate efficiency of PPE use and the influence of cabin design on exposure under field conditions. The AOEL that was used as a safety threshold is derived based on the most sensitive NO(A)EL for relevant endpoints and is thus not appropriate to inform actual level of risk. Uncertainties were also introduced because there was no adjustment to the AOELs for route of exposure, or for the use of repeated dose in the determination of the values in most toxicity studies.

The analysis in Chapter 4 confirmed that co-formulants may share similar toxicological endpoints as their declared active substances and may increase toxicities of pesticide products in mixtures. Nevertheless, errors are possible with the use of the AOEM for co-formulants as the model was developed for active substances with different chemical structures and thus different characteristics. As co-formulants are usually assessed for acute ocular and dermal properties, additional toxicity attributed by co-formulants could not be assessed due to the lack of appropriate toxicological data.

The identification of the lowest NOAEL for a specific health issue from a range of toxicological datasets remains a challenge, including the definition of safety thresholds for adverse effects and determination of relevant toxicological endpoints. Inherent uncertainties were also introduced through data extrapolation from LO(A)ELs and chronic NO(A)ELs where short-term NO(A)ELs were lacking and through inter-species extrapolation from test animals to humans.

Further research

This PhD study reports useful information on the use of models for risk assessment on non-dietary routes of pesticide exposure for two vulnerable human sub-populations, comprising resident pregnant women and agricultural professional operators. Nevertheless, models consist of inherent uncertainties that depend on scientific data availability and assessment assumptions (Beronius and Agerstrand, 2017). More data on pesticide airborne concentrations and spray depositions for a range of active substances and at larger distances from treated areas would permit a complete evaluation and thus overall improvement to the developed mathematical model for residential exposure. The use of the harmonised AOEM would require further refinement for a range of assumptions that were applied in practice for a more accurate estimation, including the relatively simple incorporation of protection efficiency for the PPE use and 100% inhalation absorption independent of cabin status during application. The use of the AOEM algorithms to predict exposure from co-formulants would need to be tested for its appropriateness and accuracy of use for the future.

Risk assessment for residential exposure based on maximum dose within 24 h of pesticide treatment is a worst-case assumption. In reality, residents can be exposed to some kinds of pesticides at lower concentrations over a period of a few days to several weeks after an application is complete. Consideration of pesticide fate after entering different environmental compartments would be useful to add to the existing knowledge about cumulative residential exposure beyond the first day after application, while other refinements of limitations are possible for the future as discussed in the previous section. For the occupational risk assessment, some aspects of operator exposure would be useful to add into any further study including the incorporation of more specific protection factors for the PPE use and inhalation absorption based on cabin design when additional data and improved scientific knowledge become available.

Mixture risk assessment of pesticide constituents comprising multiple active substances and/or co-formulants with similar toxicological endpoints appeared to be a major gap in current regulatory risk assessment at the EU level (Chapter 4). Neglecting such mixture effects may miss higher risk than that predicted for single active substances alone. More toxicological studies are required to understand the combined effects of multiple active substances with similar toxicological endpoints in every potential combination. Equally, experimental data are needed to understand the chemical behaviours of individual co-formulants and their interactions with active substances in a range of mixtures. The general lack of toxicological data for co-formulants would need to be addressed based on medium- and long-term mammal experiments for risk assessment purposes.

An important issue concerning the need for clear definition of hazard and thus scientific criteria in the risk assessment was also raised in this thesis. In Chapter 2, there was an unclear boundary between reproductive and developmental outcomes for different windows of exposure, i.e. before pregnancy and during different trimesters. In Chapter 4, there are no agreed scientific criteria to identify the endocrine mediated mechanisms and thus endpoints, whilst 48 of 180 active substances were identified with known/possible endocrine disrupting activity (Table A3-1; Chapter 3). Inclusion of all possible health endpoints in this thesis would be over conservative (e.g. spleen effects and growth retardation for endocrine disrupting effects), thus identification of endpoints based on a science-based approach would permit a more realistic estimation when a consensus becomes available in the future.

Some aspects of the exposure assessment that lie outside the remit of this thesis would deserve further research. Predicted pesticide risks with exposures below the respective safety thresholds did not mean risks are impossible or negligible. Validation of exposure predictions against biological monitoring and health data is necessary to evaluate the model simulations, but there are relatively scarce data to date.

Appendices

Appendix 1 Supplementary Chapter 2

Table A1- 1. Default parameter values used in modelling exposure to residents.

Parameter	Default value
Adult height, z_r	1.4 m
Body weight, BW	60 kg (for adult as recommended by EFSA, 2014)
Concentration in the turbulent air outside the laminar air layer, C_{air}	Set as zero (= 0 g m^{-3})
Coriolis parameter, f	$9.374\text{x}10^{-5}$ s^{-1} (at 40° latitude)
Crop height, h_e	2.0 m (for orchard crop)
Diffusion coefficient in air at 20°C, $D_{a,ref}$	0.43 m^2 d^{-1} (BROWSE[a])
Dry soil bulk density	1.1 g cm^{-3}
Fraction of organic carbon, f_{oc}	0.02 g g^{-1}
$Q10$ factor	1.78 (for every 10°C increase or decrease)
Indirect dermal exposure duration, H	2 hrs (EFSA, 2014)
Inhalation rate, IR	13.8 m^3 d^{-1} (for adult as recommended by US EPA)
Inhalation absorption, IA	100% (= 1.0)
Molar enthalpy of evaporation, ΔH_{vap}	95,000 J mol^{-1}
Reference aeric mass of pesticide on the plants, $A_{p,ref}$	1.0 x 10^{-4} kg m^{-2} (= 1 kg ha^{-1})
Soil water content	0.3 g g^{-1}
Transfer coefficient, TC	7,300 cm^2 hr^{-1} (for adult as recommended by EFSA, 2014)
Turf transferable residues, TTR	5 % (= 0.05 for products applied in liquid sprays as recommended by EFSA, 2014)
Treated area	200 x 200 m
Universal gas constant, R	8.314 Pa m^3 K^{-1} mol^{-1}
von Karman's constant, k	0.4
Wind speed, $u(z)$	2.8 m s^{-1} at 2.0 m above the ground (BROWSE[a])

[a] BROWSE refers to the Bystanders, Residents, Operators and WorkerS Exposure models for plant protection products (Ellis et al., 2013).

Table A1- 2. Main stages of apple development and associated interception factors for pesticide applied to the canopy (Olesen and Jensen, 2013; Jensen and Spliid, 2003).

Apple	Without leaves	Flowering	Leaf development	Full foliage
Month	November-March	April	May-June	July-Oct
CI (%)	50	65	70	80
Fraction on plant	0.5	0.65	0.7	0.8
Fraction on soil	0.5	0.35	0.3	0.2

Table A1- 3. Average monthly temperature between 1980 and 2015 for the regions considered in the study (Met Office, 2015).

Month	Eastern	West Midlands	South-Eastern	South-Western
January	4.2	3.9	4.6	4.8
February	4.4	4.0	4.6	4.7
March	6.5	6.1	6.7	6.4
April	8.8	8.2	8.9	8.3
May	11.9	11.2	12.0	11.2
June	14.8	14.1	14.8	13.8
July	17.2	16.3	17.1	15.8
August	17.1	16.0	16.9	15.7
September	14.6	13.6	14.5	13.7
October	11.1	10.2	11.2	10.7
November	7.2	6.7	7.5	7.5
December	4.8	4.4	5.2	5.4

Table A1- 4. Pesticide active substances with no NO(A)ELs for reproductive and/or developmental effects reported in the literature or reported in concentration unit other than daily exposure.

No.	Active substance
1	Alloxydim-sodium
2	Benodanil
3	Ditalimfos
4	Nitrothal-isopropyl
5	Nuarimol
6	Propyzamide
7	Pyrifenox
8	Tetradifon

Figure A1- 1. Map of regions in the UK derived from the Office for National Statistics (2011).

a

b

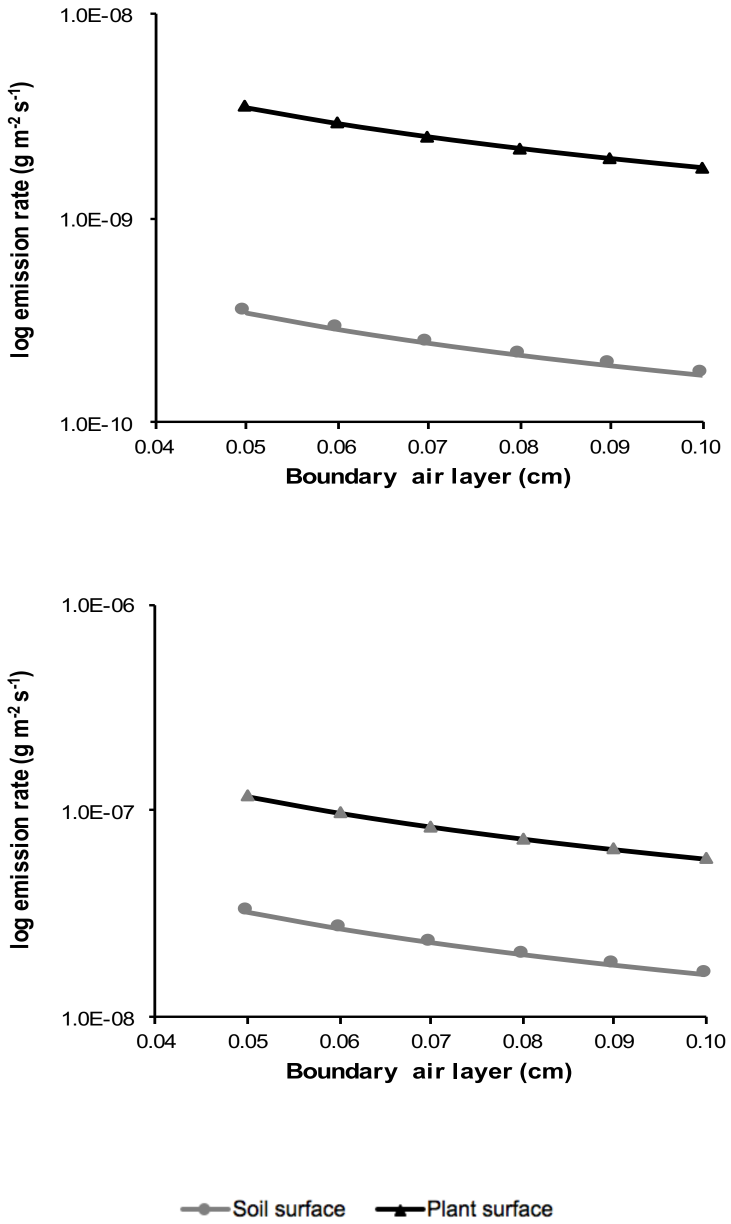


Figure A1- 2. Sensitivity analysis for the effect of boundary air layers on the emission rates of active substances with low volatility (propyzamide; VP: 5.8×10^{-5} Pa) (a) and medium volatility (chlorpyrifos; VP: 1.43×10^{-3} Pa) (b) from the treated surfaces.

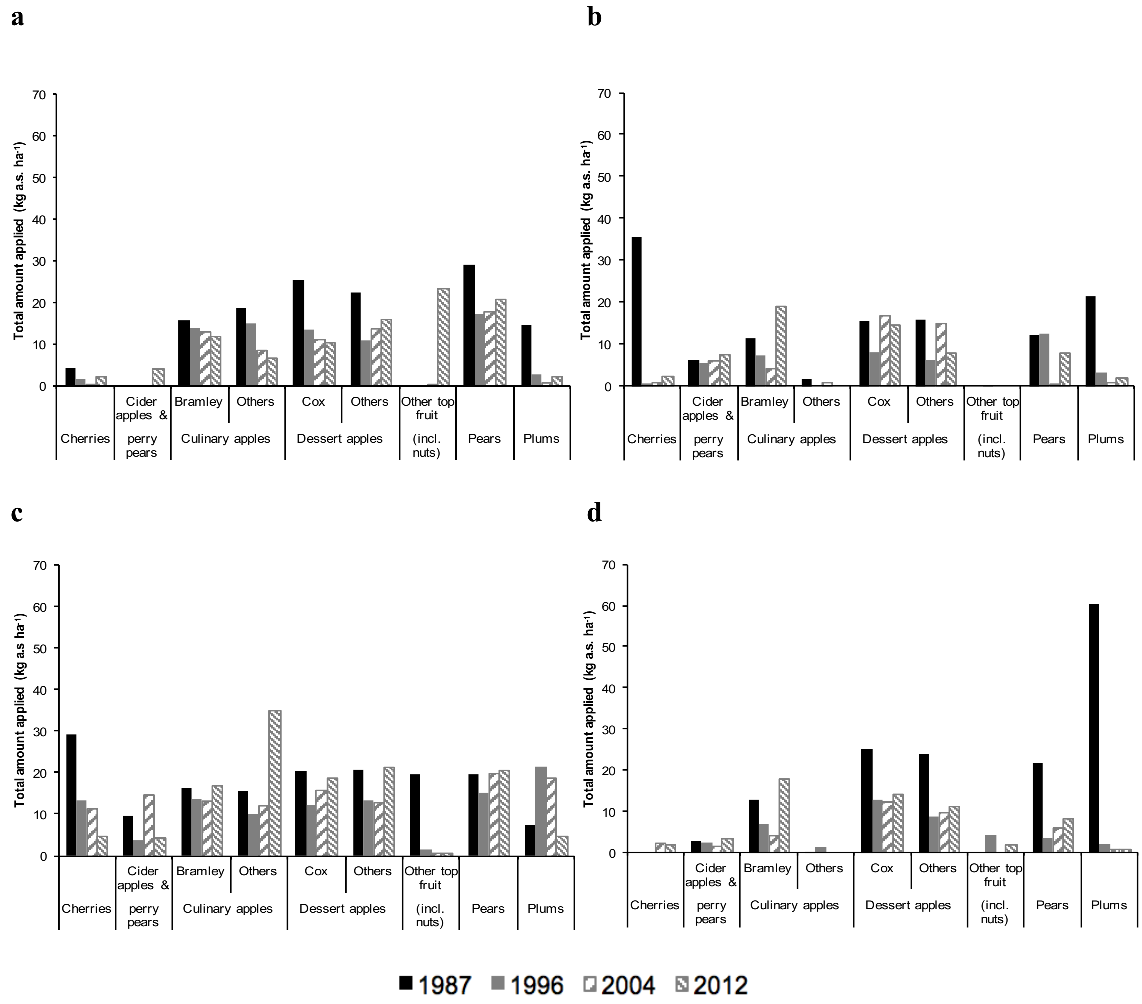


Figure A1- 3. Total amount of pesticide (including tar oils) applied to major orchard crop types between 1987 and 2012 for Eastern (a), West Midlands (b), South-Eastern (c), and South-Western (d) regions. Blanks indicate that none of that orchard type was sampled in that region.

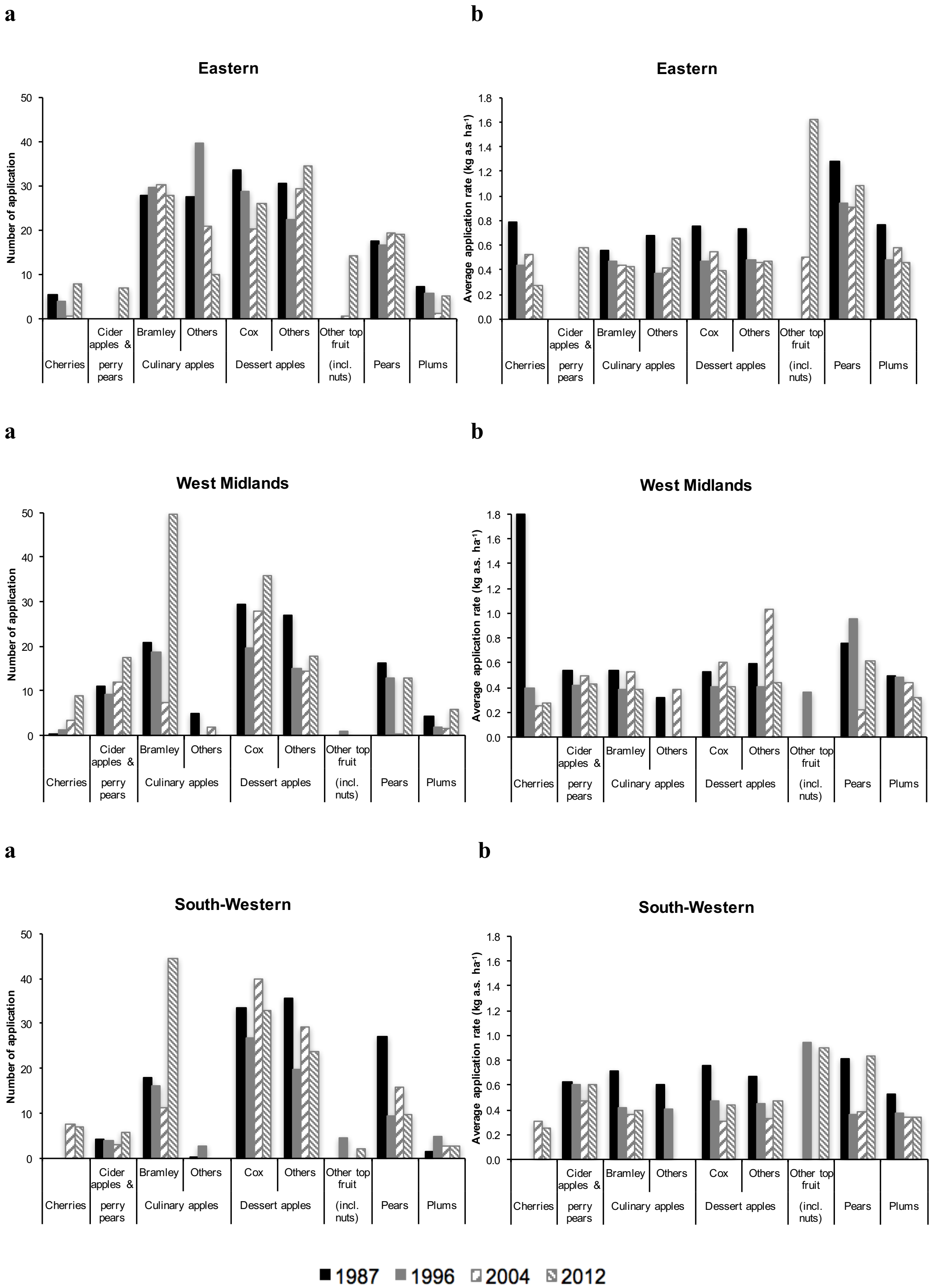


Figure A1- 4. Usage of pesticide for orchard crop types cultivated in the Eastern, West Midlands, and South-Western regions with usage of tar oils excluded. Data are expressed as number of applications (a) defined as treated area divided by area grown, and average application rate (b) defined as total amount applied divided by number of applications. Here, application is defined as one treatment with one active substance, so successive treatments with a single active substance or a single treatment with a product containing two active substances would both count as two applications.

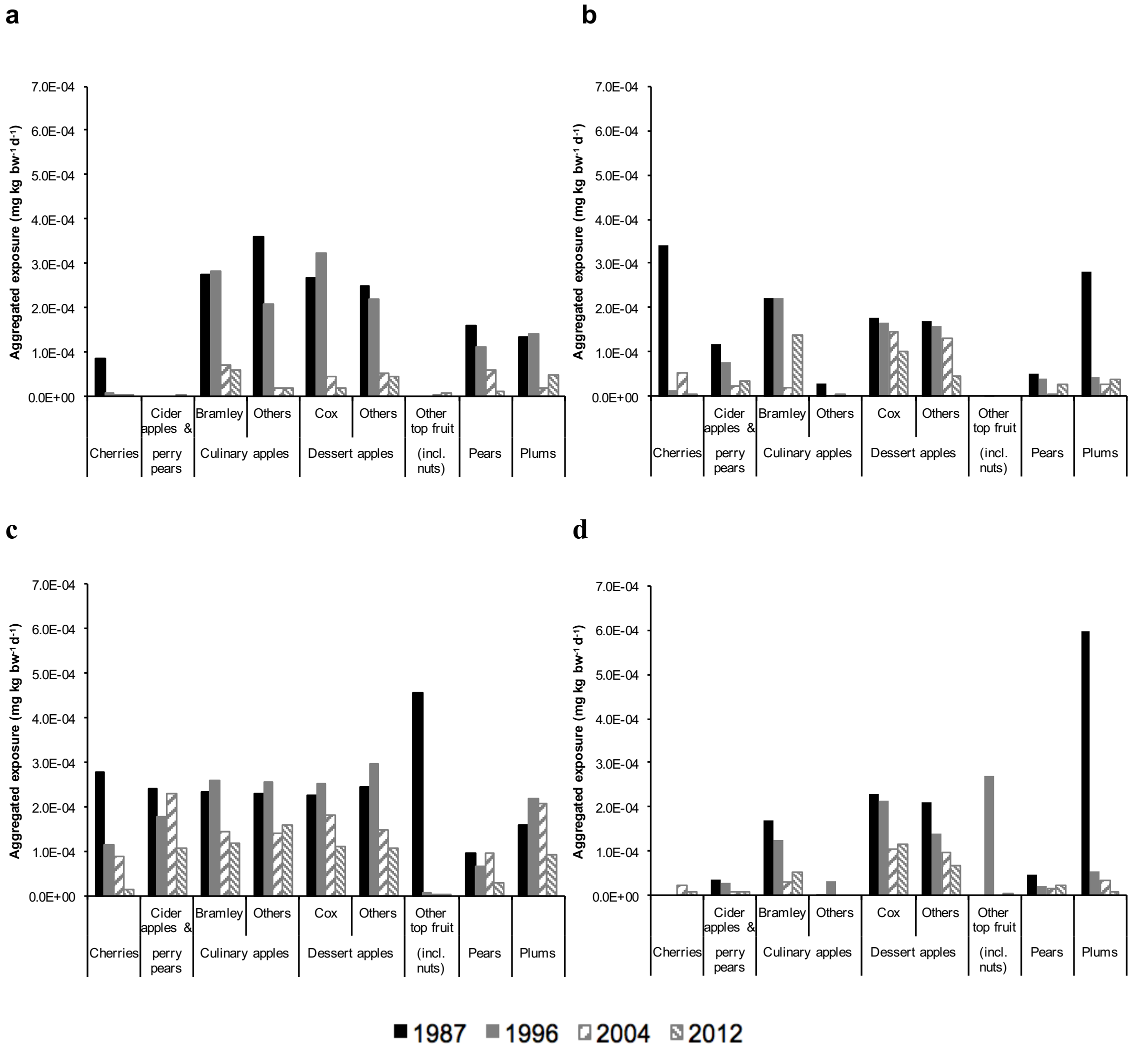


Figure A1- 5. Aggregated exposures to applied pesticide for residents living 1000 m downwind of individual crop types. Data are shown for four years between 1987 and 2012 for Eastern (a), West Midlands (b), South-Eastern (c), and South-Western (d) regions.

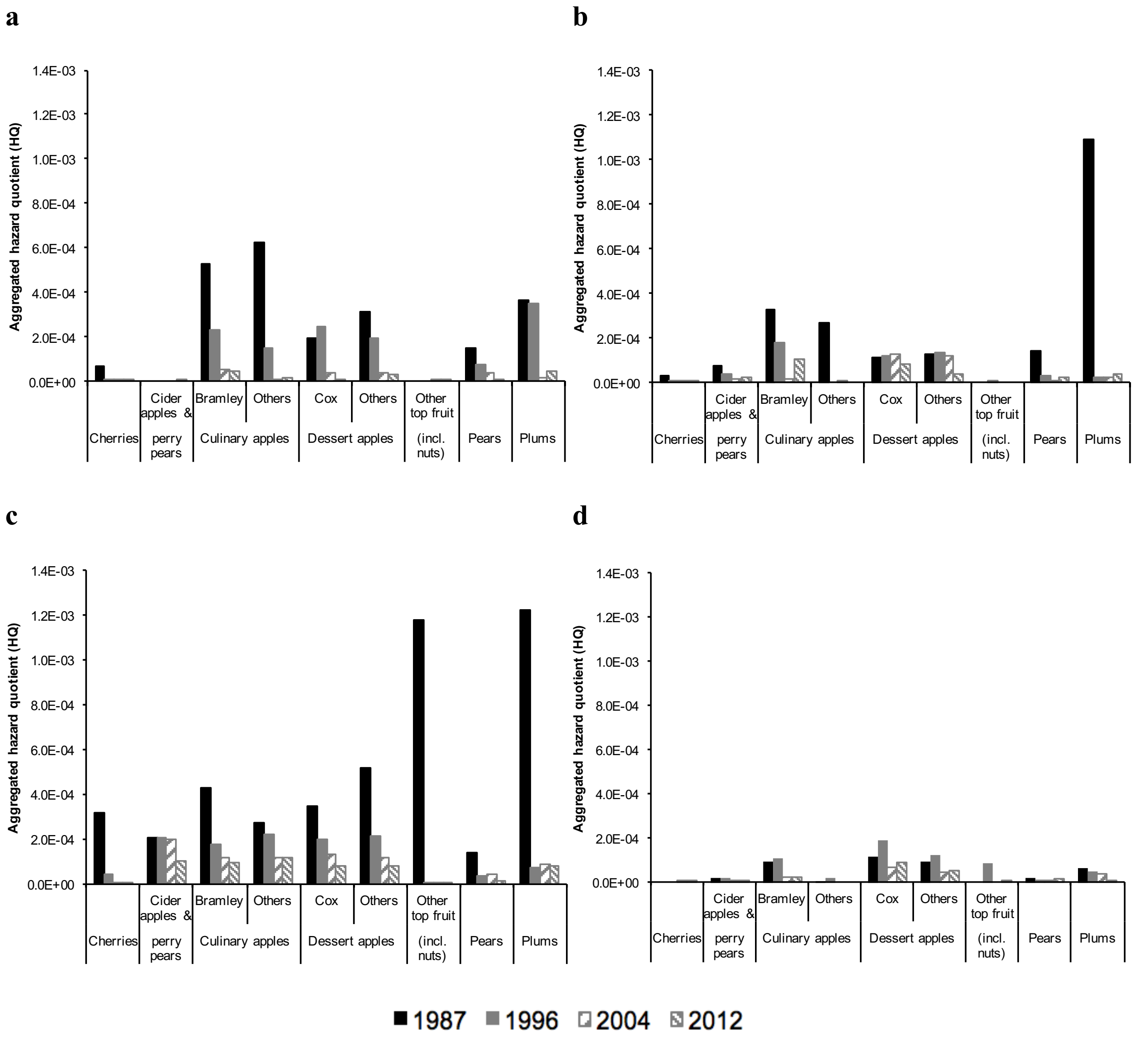


Figure A1- 6. Aggregated hazard quotients based on reproductive/developmental toxicity for pesticide exposure to resident pregnant women living 1000 m downwind of individual crop types. Data are shown for four years between 1987 and 2012 and for Eastern (a), West Midlands (b), South-Eastern (c), and South-Western (d) regions.

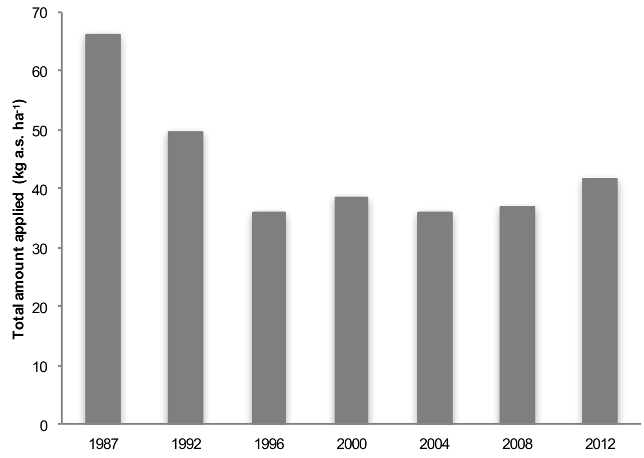


Figure A1- 7. Average of total amount of pesticide applied to all crop types in four regions in England and Wales at approximately 4-year intervals between 1987 and 2012.

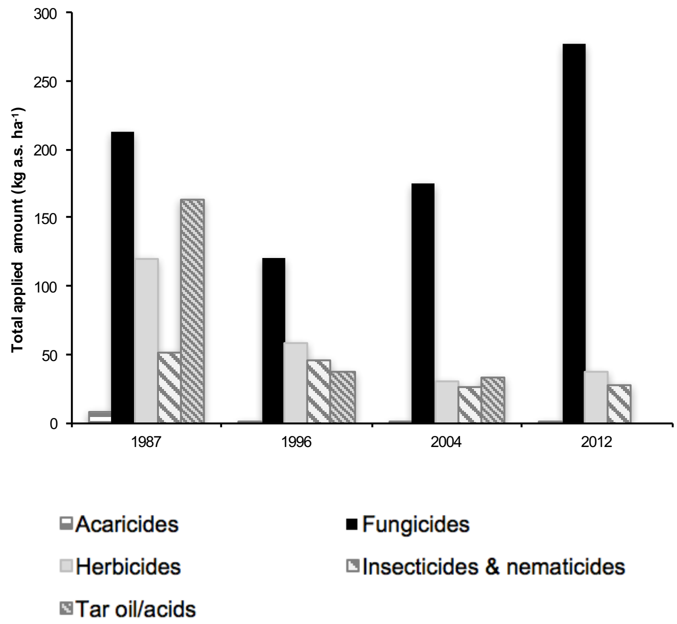


Figure A1- 8. Total amount of pesticide applied in four regions in England and Wales for 4 years between 1987 and 2012 based on pesticide chemical groups.

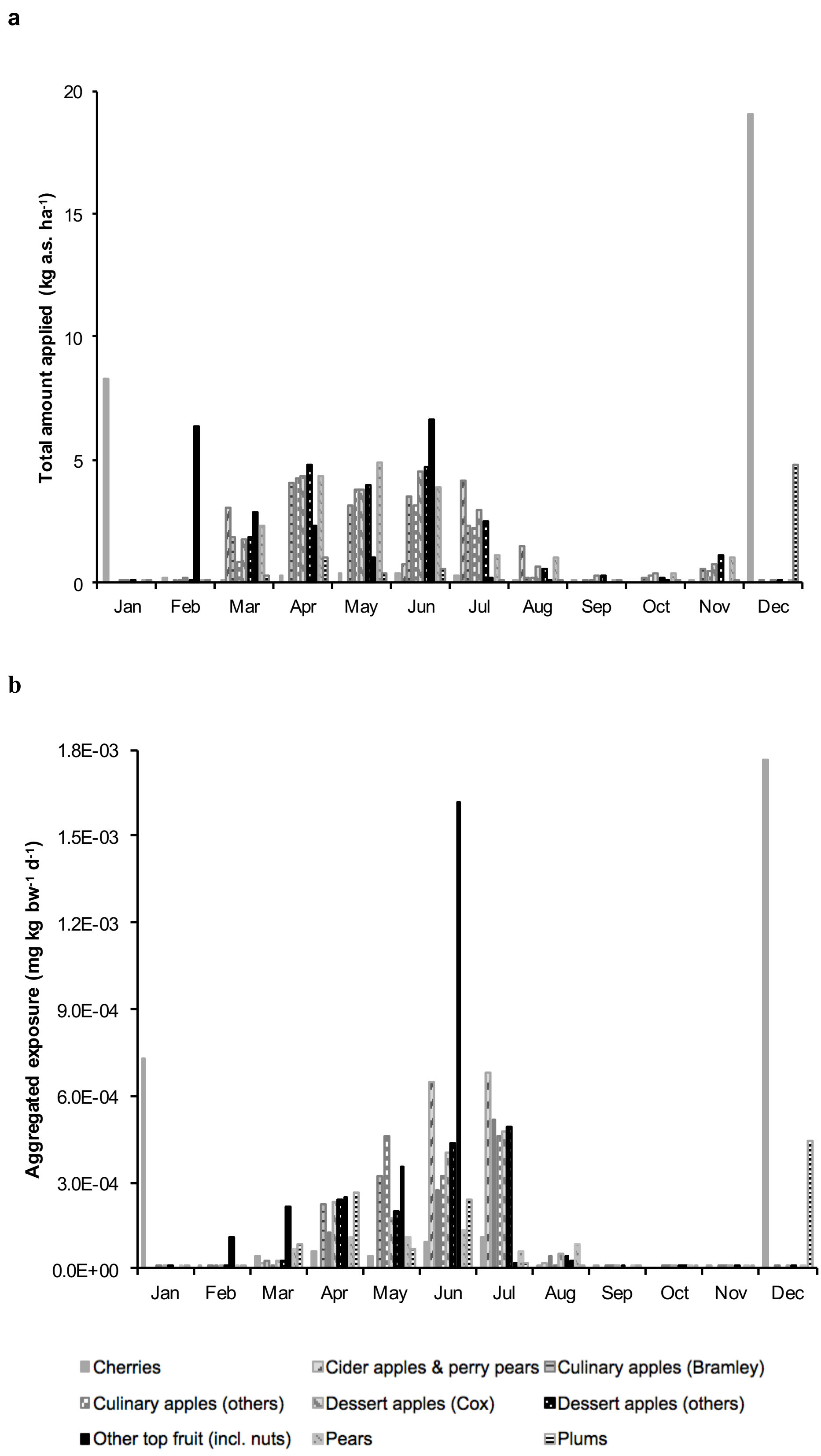


Figure A1- 9. Monthly estimates for total amount of pesticide applied to orchards in the South-Eastern region (a) and aggregated exposures for resident pregnant women living 100 m downwind of individual crop types (b) in 1987.

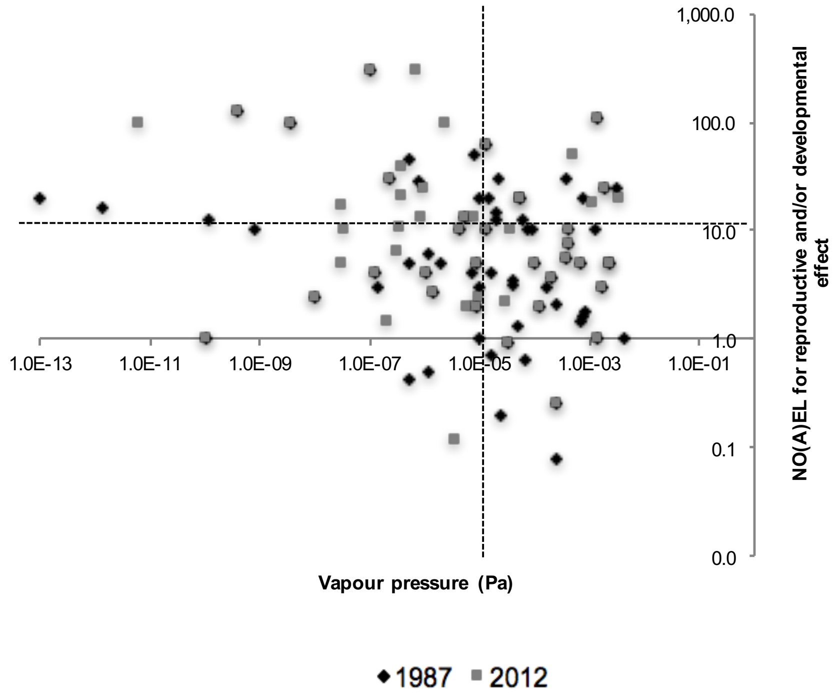


Figure A1- 10. Plot of NO(A)ELs of reproductive and/or developmental toxicity and vapour pressure of individual active substances; plot is divided into approximate quadrants using divisions at 10 mg kg bw^{-1} day^{-1} and 1.0x10^{-5} Pa.

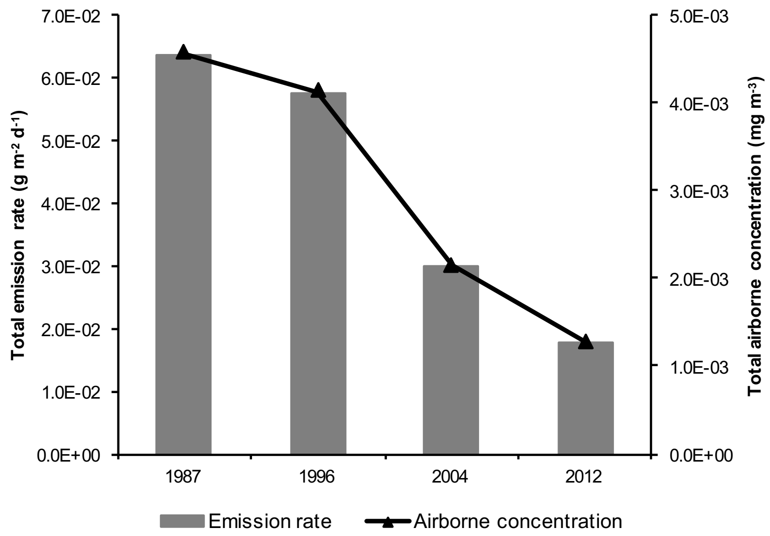


Figure A1- 11. Total emission rates of applied pesticides and their respective airborne concentrations at 100 m downwind in four regions in England and Wales for 4 years between 1987 and 2012.

Appendix 2 Supplementary Chapter 3

Table A2- 1. Information on the holding, operator details and agricultural practices for 50 selected professional operators.

Operator code	Total crop grown area (ha)	Crop type	Age	Spray experience (year)	Nationally recognized spray certificate type (year of most recent training)	Date range for data collection	Total number of spray days	Method of application	Sprayer cab type
Lithuania arable (LTAB)									
LTAB01	129	Barley, other cereals, oilseed rape, wheat	65	40	Theory (2008)	05/09/2012 – 13/09/2013	16	HD - hydraulic boom (downwards)	Closed cab
LTAB02	24	Other cereals, peas (dry), potatoes	44	6	Theory and Practical (2013)	06/05/2013 – 01/08/2013	8	HD	Closed cab with no filter
LTAB03	416	Potatoes, oilseed rape, wheat	29	5	Theory (2013)	18/05/2013 – 15/09/2013	26	HD	Closed cab
LTAB04	10	Barley, oilseed rape, wheat	43	12	Theory (2012)	19/05/2013 – 31/05/2013	3	HD	Closed cab
LTAB05	483	Maize, potatoes, oilseed rape, wheat	49	16	Theory (2013)	18/04/2013 – 15/07/2013	19	HD	Closed cab with carbon filter
LTAB06	244	Barley, maize, other kind of root and tuber vegetables except sugar beet, potatoes, oilseed rape, wheat	39	14	Theory (2012)	15/05/2013 – 28/06/2013	11	HD	Closed cab with carbon filter
LTAB07	34	Barley, grass, oats, other cereals, potatoes, wheat	48	15	Theory and Practical (2009)	12/05/2013 – 22/08/2013	8	HD	Closed cab

LTAB08	13	Barley, potatoes, wheat	44	14	Theory (2012)	01/05/2013 – 28/09/2013	6	HD	Closed cab
LTAB09	18	Barley, oats, potatoes, wheat	55	18	Theory (2011)	01/06/2013 – 24/06/2013	4	HD	Closed cab
LTAB10	53	Potatoes, wheat	54	12	Theory (2011)	08/05/2013 – 03/09/2013	8	HD	Closed cab
UK arable (UKAB)									
UKAB01	28	Head cabbage, potatoes, wheat	55	35	No	24/04/2013 – 18/09/2013	20	HD	Closed cab
UKAB02	112	Peas (dry), sugar beet, wheat	33	10	Theory (2013)	11/10/2012 – 04/07/2013	16	HD	Closed cab with carbon filter
UKAB03	235	Peas (dry), potatoes, oilseed rape, sugar beet, wheat	44	25	Theory and Practical (1992)	01/11/2012 – 06/10/2013	33	HD	Closed cab with carbon filter
UKAB04	39	Sugar beet, wheat	57	41	Theory and Practical (2013)	16/05/2013 – 20/06/2013	7	HD	Closed cab with carbon filter
UKAB05	120	Oilseed rape, sugar beet, wheat	42	20	Theory (2012)	26/08/2012 – 06/08/2013	17	HD	Closed cab with carbon filter
UKAB06	210	Barley, beans (dry), oilseed rape, sugar beet, wheat	33	13	Theory and Practical (2013)	27/09/2012 – 01/08/2013	30	HD	Closed cab with carbon filter
UKAB07	374	Potatoes, sugar beet, wheat	45	25	Theory (2012)	31/10/2012 – 17/09/2013	30	HD	Closed cab with carbon filter
UKAB08	1040	Barley, beans (dry), oilseed rape, sugar beet, wheat	21	3	Theory and Practical (2013)	11/09/2012 – 04/09/2013	57	HD	Closed cab with carbon filter
UKAB09	67	Beans (dry), oilseed rape, sugar beet, wheat	51	-	Theory and Practical (2013)	03/09/2012 – 06/08/2013	17	HD	Closed cab with carbon filter

UKAB10	663	Barley, beans (dry), oilseed rape, sugar beet, wheat	55	35	No	18/09/2012 – 12/09/2013	47	HD	No cab
Greek arable (GRAB)									
GRAB01	41	Maize, tomatoes	53	25	No	10/04/2013 – 08/07/2013	38	HD	No cab
GRAB02	27	Tomatoes	52	30	No	25/04/2013 – 09/07/2013	30	BA, HD	Closed cab with carbon filter
GRAB03	25	Maize, tomatoes	55	35	No	27/04/2013 – 04/07/2013	19	BA, HD	No cab
GRAB04	9	Maize, tomatoes, wine grapes	38	22	No	07/04/2013 – 12/07/2013	18	BA, HD	Closed cab
GRAB05	86	Maize, peppers, tomatoes	31	11	No	15/04/2013 – 02/07/2013	23	BA, HD	BA - closed cab with carbon filter; HD - no cab
GRAB06	106	Maize, tomatoes	34	15	No	09/04/2013 – 08/07/2013	26	BA, HD	Closed cab
GRAB07	40	Maize, tomatoes	53	35	No	18/04/2013 – 07/07/2013	35	BA, HD	Closed cab
GRAB08	36	Maize, peppers, potatoes, tomatoes	42	27	No	07/04/2013 – 05/10/2013	37	BA, HD	Closed cab
GRAB09	25	Maize, tomatoes	58	30	No	22/04/2013 – 15/06/2013	5	BA, HD	No cab
GRAB10	27	Maize, tomatoes	40	20	No	05/04/2013 – 01/07/2013	13	BA, HD	Closed cab with carbon filter
UK orchard (UKOR)									
UKOR01	16	Apples, pears, plums	69	54	No	28/03/2013 – 11/07/2013	8	BA – broadcast air assisted	Closed cab with carbon filter
UKOR02	30	Apples, hops (dried, including	54	30	Theory (2013)	25/10/2012 –	61	BA, HD	Closed cab with

		hop pellets unconcentrated)				27/11/2013			carbon filter
UKOR03	35	Apples	54	20	Theory and Practical (2013)	26/03/2013 – 29/08/2013	59	BA, HD	BA - closed cab with carbon filter; BA – no cab
UKOR04	17	Apples, pears	63	40	Theory and Practical (2013)	10/04/2013 – 28/11/2013	23	BA, HD	Closed cab with carbon filter
UKOR05	24	Apples, pears, plums	52	-	Theory (2013)	06/03/2013 – 31/07/2013	36	BA, HD	Closed cab with carbon filter
UKOR06	43	Apples	61	43	Theory (2013)	24/10/2012 – 02/09/2013	63	BA, HD	Closed cab with carbon filter
UKOR07	52	Apples, cherries, currants (red, black and white), hops (dried, including hop pellets unconcentrated), pears	50	30	Theory (2013)	12/10/2012 – 31/08/2013	71	BA, HD	Closed cab
UKOR08	121	Apples, currants (red, black and white), gooseberries, pears, plums	32	6	Theory (2013)	05/03/2013 – 15/09/2013	69	BA	Closed cab with carbon filter
UKOR09	112	Apples, pears, plums	30	3	Theory (2013)	10/04/2013 – 13/08/2013	49	BA	Closed cab with carbon filter
UKOR10	41	Apples, currants (red, black and white)	56	36	Theory (2013)	05/03/2013 – 04/12/2013	43	BA, HD	Closed cab
Greek orchard (GROR)									
GROR01	3	Wine grapes	54	30	Theory (2008)	28/03/2013 – 04/08/2013	13	HD	No cab
GROR02	7	Wine grapes	38	18	Theory (2009)	12/02/2013 – 25/03/2013	2	LA – lance sprayer	No cab

GROR03	9	Peaches, pears, wine grapes	53	28	Theory (2009)	12//02/2013 – 10/08/2013	36	BA, LA	No cab
GROR04	1	Wine grapes	62	50	Theory (2009)	05/03/2013 – 03/08/2013	16	BA, HD, LA	No cab
GROR05	6	Pears, wine grapes	60	45	Theory (2009)	28/01/2013 – 02/08/2013	30	BA, HD, KN	No cab
GROR06	2	Wine grapes	62	34	No	19/03/2013 – 15/07/2013	10	HD, LA	No cab
GROR07	3	Wine grapes	42	10	Theory (2009)	02/04/2013 – 07/08/2013	14	BD, HD	No cab
GROR08	3	Wine grapes	38	20	Theory (2009)	19/03/2013 – 20/07/2013	12	BA, HD, LA	No cab
GROR09	1	Wine grapes	36	25	Theory (2009)	10/03/2013 – 15/08/2013	16	BA, HD	No cab
GROR10	3	Wine grapes	70	40	Theory (2009)	01/03/2013 – 18/08/2013	17	BA, HD	No cab

Table A2- 2. Total number of hours spent spraying during the surveyed period for each individual operator, together with the median, 75th and 95th percentiles for each cropping system.

Holding code	LTAB	UKAB	GRAB	UKOR	GROR
01	44	125	132	43	52
02	16	85	78	316	14
03	145	64	57	418	72
04	1	20	33	127	32
05	141	54	159	193	103
06	48	65	79	390	20
07	9	360	138	293	77
08	7	244	103	379	63
09	5	30	26	404	36
10	49	225	26	295	63
Median	30	75	79	306	58
75th perc.	49	200	125	387	70
95th perc.	143	308	150	412	91

Table A2- 3. Details of all applications with predicted exposure in excess of the AOEL.

Holding code	Date	Crop type	Active substance	Form-ulation	Area treated (ha d^{-1})	AOEL (mg kg bw^{-1} d^{-1})	Exposure: AOEL	PPE use		
								Mixing/loading – liquid formulations	Mixing/loading – solid formulations	Application
Lithuania arable (LTAB)										
01	28/05/2013	Wheat	Spiroxamine	EC	47.0	0.0006	1.3	Normal workwear; Gloves-non specified rubber		Normal workwear
05	15/07/2013	Potatoes, oilseed rape	Diquat	SL	129.6	0.001	3.0	Workwear: breathable (cotton/polyester); Gloves-non specified rubber; Face shield		None
UK arable (UKAB)										
06	12/11/2012	Wheat	Prosulfocarb	EC	41.7	0.007	1.2	Type 6 (e.g. Tyvek Classic/Kleeguard T56; Gloves-nitrile		Type 6 (e.g. Tyvek Classic/Kleeguard T56
07	16/05/2013	Potatoes	Diquat	SL	72.7	0.001	1.8	Type 6 (e.g. Tyvek Classic/Kleeguard T56; Face shield; Gloves-nitrile		Long clothes
	22/05/2013	Potatoes	Diquat	SL	59.5	0.001	1.5			
	03/09/2013	Potatoes	Diquat	SL	99.4	0.001	1.8			
	10/09/2013	Potatoes	Glufosinate-ammonium	SL	99.4	0.0021	1.2			
	02/07/2013	Potatoes	Cymoxanil	WP	132.2	0.01	4.6		Type 6 (e.g. Tyvek Classic/Kleeguard T56; Gloves-nitrile; Respirator-half mask, reusable with	

									filters	
08	15/08/2013	Beans (dry)	Diquat	SL	43.4	0.001	2.5	Apron; Gloves-nitrile		Normal workwear
	16/08/2013	Beans (dry)	Diquat	SL	46.0	0.001	2.6			
	04/09/2013	Beans (dry)	Diquat	SL	29.6	0.001	1.9			
10	08/04/2013	Barley	Prosulfocarb	EC	105.0	0.007	10.0	Type 6 (e.g. Tyvek Classic/Kleeguard T56; Gloves-nitrile		Workwear: breathable (cotton/polyester)
	30/04/2013	Wheat	Chlorothalonil	SC	80.8	0.009	1.4			
	13/05/2013	Wheat	Chlorothalonil	SC	43.3 [a)]	0.009	1.6			
	29/08/2013	Beans (dry)	Diquat	SL	12.2	0.001	2.1			
Greece arable (GRAB)										
01	18/06/2013	Tomatoes	Mancozeb	WP	5.9	0.035	1.1		Type 6 (e.g. Tyvek Classic/Kleeguard T56; Gloves-nitrile; Respirator-disposable filtering half mask	Long sleeved shirt, full length trousers; Respirator-disposable filtering half mask
	22/06/2013	Tomatoes	Mancozeb	WP	5.8	0.035	1.1			
03	12/05/2013	Tomatoes	Mancozeb	WP	5.9	0.035	1.2		Type 6 (e.g. Tyvek Classic/Kleeguard T56; Gloves-nitrile; Respirator-power assisted	Type 6 (e.g. Tyvek Classic/Kleeguard T56; Gloves-nitrile
	05/06/2013	Tomatoes	Cymoxanil [b)]	WP	13.5	0.01	1.8			
	05/06/2013	Tomatoes	Mancozeb [b)]	WP	13.5	0.035	1.2			
	11/06/2013	Tomatoes	Mancozeb	WP	9.4	0.035	1.3			
05	12/06/2013	Tomatoes	Cymoxanil [b)]	WP	28.7	0.01	3.5		Type 6 (e.g. Tyvek Classic/Kleeguard T56; Gloves-nitrile; Respirator-valved filtering half mask	Long sleeved shirt, full length trousers
	12/06/2013	Tomatoes	Mancozeb [b)]	WP	28.7	0.035	2.5			
06	10/04/2013	Tomatoes	Mancozeb	WP	4.3	0.035	1.1		Workwear: breathable (cotton/polyester);	Long sleeved shirt, full length trousers
	10/05/2013	Tomatoes	Mancozeb	WP	11.8	0.035	2.5			
	25/05/2013	Tomatoes	Cymoxanil	WP	16.0	0.01	1.4			

	04/06/2013	Tomatoes	Cymoxanil	WP	16.8	0.01	1.5		Gloves-nitrile; Respirator-full face mask	
	07/06/2013	Tomatoes	Cymoxanil	WP	2.0	0.01	1.0			
	14/06/2013	Tomatoes	Cymoxanil	WP	10.3	0.01	1.4			
08	10/09/2013	Potatoes	Propineb	WP	8.0	0.003	7.5		Type 6 (e.g. Tyvek Classic/Kleeguard T56; Gloves-nitrile latex; Respirator-full mask	Long sleeved shirt, full length trousers
09	27/05/2013	Tomatoes	Mancozeb	WP	20.2	0.035	1.6		Type 6 (e.g. Tyvek Classic/Kleeguard T56; Gloves-nitrile; Respirator-full mask	Type 6 (e.g. Tyvek Classic/Kleeguard T56; Gloves-nitrile; Respirator-full mask
	08/06/2013	Tomatoes	Mancozeb	WP	17.0	0.035	1.2			
10	04/06/2013	Tomatoes	Cymoxanil	WP	6.8	0.01	1.2		Type 6 (e.g. Tyvek Classic/Kleeguard T56; Gloves-nitrile; Respirator-disposable filtering half mask	Long sleeved shirt, full length trousers
UK orchard (UKOR)										
02	14/03/2013	Apples	Chlorpyrifos	EC	4.4 [a)]	0.001	2.2	Normal workwear; Gloves-nitrile		Normal workwear
03	29/04/2013	Apples	Chlorpyrifos	EC	10.4	0.001	2.3	Type 6 (e.g. Tyvek Classic/Kleeguard T56); Face shield; Gloves-nitrile		Normal workwear; Gloves-nitrile
	30/04/2013	Apples	Chlorpyrifos	EC	7.6	0.001	1.7			
	02/05/2013	Apples	Chlorpyrifos	EC	8.4	0.001	1.9			
	28/05/2013	Apples	Chlorpyrifos	EC	10.4	0.001	4.4			
	29/05/2013	Apples	Chlorpyrifos	EC	7.6	0.001	3.2			
	03/07/2013	Apples	Chlorpyrifos	EC	10.4	0.001	4.4			
	04/07/2013	Apples	Chlorpyrifos	EC	7.6	0.001	3.2			
04	22/07/2013	Apples	Chlorpyrifos	WG	6.0	0.001	2.5		Type 6 (e.g. Tyvek Classic/Kleeguard T56); Face shield; Gloves-nitrile;	Workwear: breathable (cotton/polyester)

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>Respirator-valved filled filtering half mask</td><td></td></tr>
<tr><td rowspan="3">05</td><td>07/03/2013</td><td>Apples, pears</td><td>Copper oxychloride</td><td>WP</td><td>11.2</td><td>0.25</td><td>1.1</td><td>Long clothes; Respirator-half mask, reusable with filters</td><td></td><td rowspan="3">Workwear: breathable (cotton/polyester)</td></tr>
<tr><td>06/06/2013</td><td>Apples</td><td>Chlorpyrifos</td><td>EC</td><td>15.0</td><td>0.001</td><td>4.7</td><td rowspan="2"></td><td rowspan="2">Workwear: breathable (cotton/polyester)</td></tr>
<tr><td>31/07/2013</td><td>Apples</td><td>Chlorpyrifos</td><td>EC</td><td>15.0</td><td>0.001</td><td>6.6</td></tr>
<tr><td rowspan="7">06</td><td>24/10/2012</td><td>Apples</td><td>Chlorpyrifos</td><td>EC</td><td>13.7</td><td>0.001</td><td>4.7</td><td rowspan="7">Long clothes; Gloves-nitrile</td><td rowspan="7"></td><td rowspan="7">Long clothes</td></tr>
<tr><td>08/11/2012</td><td>Apples</td><td>Amitrole</td><td>SL</td><td>8.1</td><td>0.001</td><td>1.1</td></tr>
<tr><td>15/04/2013</td><td>Apples</td><td>Chlorpyrifos</td><td>EC</td><td>5.6</td><td>0.001</td><td>2.0</td></tr>
<tr><td>16/04/2013</td><td>Apples</td><td>Chlorpyrifos</td><td>EC</td><td>18.2</td><td>0.001</td><td>6.0</td></tr>
<tr><td>23/04/2013</td><td>Apples</td><td>Chlorpyrifos</td><td>EC</td><td>8.3</td><td>0.001</td><td>2.9</td></tr>
<tr><td>24/04/2013</td><td>Apples</td><td>Chlorpyrifos</td><td>EC</td><td>10.7</td><td>0.001</td><td>3.7</td></tr>
<tr><td>07/05/2013</td><td>Apples</td><td>Chlorpyrifos</td><td>EC</td><td>42.8</td><td>0.001</td><td>13.5</td></tr>
<tr><td rowspan="5">07</td><td>04/04/2013</td><td>Pears</td><td>Chlorpyrifos</td><td>WG</td><td>2.4</td><td>0.001</td><td>1.0</td><td rowspan="5"></td><td rowspan="5">Apron; Face shield; Gloves-nitrile; Respirator-disposable filtering half mask</td><td rowspan="5">Normal workwear</td></tr>
<tr><td>24/04/2013</td><td>Currants (red, black, and white)</td><td>Chlorpyrifos</td><td>WG</td><td>6.6</td><td>0.001</td><td>2.3</td></tr>
<tr><td>31/05/2013</td><td>Currants (red, black, and white)</td><td>Tebufenpyrad</td><td>WP</td><td>7.4</td><td>0.01</td><td>1.3</td></tr>
<tr><td>19/07/2013</td><td>Hops (dried, including hop pellets unconcentr ated)</td><td>Flonicamid</td><td>WG</td><td>1.5</td><td>0.025</td><td>2.0</td></tr>
<tr><td>20/07/2013</td><td>Hops (dried, including hop pellets</td><td>Flonicamid</td><td>WG</td><td>5.5</td><td>0.025</td><td>3.5</td></tr>
</table>

		unconcentrated)								
	24/07/2013	Hops (dried, including hop pellets unconcentrated)	Flonicamid	WG	3.0	0.025	3.9			
	09/05/2013	Apples	Chlorpyrifos	EC	6.7	0.001	1.5	Normal workwear; Face shield; Gloves-nitrile		
	26/06/2013	Pears	Chlorpyrifos	EC	2.4	0.001	1.2			
	29/06/2013	Pears	Chlorpyrifos	EC	2.4	0.001	1.1			
08	30/04/2013	Apples	Chlorpyrifos	EC	13.5	0.001	2.9	Type 6 (e.g. Tyvek Classic/Kleeguard T56); Face shield; Gloves-nitrile		Long clothes
	03/05/2013	Apples	Chlorpyrifos	EC	16.7	0.001	3.6			
	17/05/2013	Plums	Chlorpyrifos	EC	6.9	0.001	3.0			
	04/06/2013	Apples	Chlorpyrifos	EC	3.2	0.001	1.5			
	05/06/2013	Apples	Chlorpyrifos	EC	6.6	0.001	2.9			
	21/06/2013	Plums	Chlorpyrifos	EC	6.9	0.001	3.0			
	01/07/2013	Apples	Chlorpyrifos	EC	8.4	0.001	3.6			
	02/07/2013	Apples	Chlorpyrifos	EC	4.9	0.001	2.2			
	12/07/2013	Plums	Chlorpyrifos	EC	6.9	0.001	3.0			
	22/07/2013	Apples	Chlorpyrifos	EC	4.4	0.001	2.0			
	25/07/2013	Apples	Chlorpyrifos	EC	9.8	0.001	4.1			
	26/07/2013	Apples	Chlorpyrifos	EC	3.5	0.001	1.6			
09	10/04/2013	Apples	Dithianon	SC	93.6	0.0135	1.0	Type 6 (e.g. Tyvek Classic/Kleeguard T56); Face shield; Gloves-nitrile		Normal workwear
	17/04/2013	Plums	Chlorpyrifos	EC	13.4	0.001	4.2			
10	03/05/2013	Apples	Chlorpyrifos	EC	18.6	0.001	3.9	Type 6 (e.g. Tyvek Classic/Kleeguard T56); Face shield; Gloves-nitrile		Long clothes
Greece orchard (GROR)										
01	20/04/2013	Wine	Chlorpyrifos	CS	2.7	0.001	1.4	Workwear:		Workwear: rainwear 2

		grapes						rainwear 2 piece (vinyl, Goretex etc); Gloves-latex; Respirator-disposable filtering half mask		piece (vinyl, Goretex etc); Gloves-latex; Respirator-full face mask
	29/06/2013	Wine grapes	Chlorpyrifos	CS	2.7	0.001	3.5			
	04/08/2013	Wine grapes	Chlorpyrifos	CS	2.7	0.001	2.2			
03	27/02/2013	Peaches	Ziram	WP	2.4	0.015	2.2		Workwear: rainwear 2 piece (vinyl, Goretex etc); Gloves-nitrile; Respirator-full face mask	Workwear: rainwear 2 piece (vinyl, Goretex etc); Gloves-nitrile; Respirator-full face mask
	08/03/2013	Peaches	Formetanate	WP	0.8	0.004	1.5			
	08/04/2013	Peaches	Ziram	WP	2.4	0.015	2.2			
	23/05/2013	Pears	Chlorpyrifos	EC	2.8	0.001	4.5	Workwear: rainwear 2 piece (vinyl, Goretex etc); Gloves-nitrile; Respirator-full face mask		
	17/06/2013	Wine grapes	Chlorpyrifos	CS	3.5	0.001	5.5			
	04/07/2013	Pears	Chlorpyrifos	EC	2.8	0.001	4.6			
04	22/04/2013	Wine grapes	Propineb	WP	1.0	0.003	3.2	Workwear: rainwear 2 piece (vinyl, Goretex etc); Gloves-nitrile; Respirator-full face mask		Workwear: rainwear 2 piece (vinyl, Goretex etc); Gloves-nitrile; Respirator-full face mask
05	10/05/2013	Wine grapes	Chlorpyrifos	CS	5.0	0.001	7.7	Long sleeved shirt, full length trousers; Gloves-nitrile; Respirator-full face mask		Long sleeved shirt, full length trousers; Gloves-nitrile; Respirator-full face mask
	22/05/2013	Pears	Chlorpyrifos	EC	1.5	0.001	3.5			
	18/06/2013	Wine grapes	Chlorpyrifos	CS	5.0	0.001	6.2			
07	01/05/2013	Wine grapes	Chlorpyrifos	CS	3.2	0.001	2.5	Long sleeved shirt, full length trousers; Gloves-nitrile; Respirator-full face mask		Long sleeved shirt, full length trousers; Gloves-nitrile; Respirator-full face mask
	07/06/2013	Wine grapes	Chlorpyrifos	CS	3.2	0.001	2.5			
	01/07/2013	Wine	Chlorpyrifos	CS	3.2	0.001	5.5			

		grapes								
	03/08/2013	Wine grapes	Chlorpyrifos	CS	3.2	0.001	4.7			
08	26/04/2013	Wine grapes	Chlorpyrifos	CS	3.2	0.001	2.2	Long sleeved shirt, full length trousers; Gloves-nitrile; Respirator-full face mask		Long sleeved shirt, full length trousers; Gloves-nitrile; Respirator-full face mask
	06/06/2013	Wine grapes	Chlorpyrifos	CS	3.2	0.001	4.0			
	04/07/2013	Wine grapes	Chlorpyrifos	CS	3.2	0.001	4.0			
	20/07/2013	Wine grapes	Chlorpyrifos	CS	3.2	0.001	4.7			
09	20/04/2013	Wine grapes	Propineb	WP	1.0	0.003	1.9	Long sleeved shirt, full length trousers; Gloves-nitrile; Respirator-full face mask		Long sleeved shirt, full length trousers; Gloves-nitrile; Respirator-full face mask
10	20/07/2013	Wine grapes	Cymoxanil	WP	3.2	0.01	1.5		Long sleeved shirt, full length trousers; Gloves-nitrile	Long sleeved shirt, full length trousers; Gloves-nitrile

a) The maximum area treated for a single active substance that applied more than one application across a day.

b) Estimated exposures with AOELs exceeded for different types of active substance on the same working day.

Table A2- 4. Summary of age of sprayers (all in years) for the selected holdings.

Holding code	LTAB (BA only)	UKAB (BA only)	GRAB (BA & HD)	UKOR (BA & HD)	GROR (BA, HD, KN & LA)
01	1	1	-	BA: 22	HD: 3 & 12
02	13	17	BA: 3 HD: 5	BA: 1 & 30 HD: 30	LA: 10
03	4	5	-	BA: 9 & 15 HD: 43	BA: 5 LA: 5
04	3	10	BA: 15	BA: 4 HD: 4	BA: 20 HD: 7 LA: 2
05	-	20	-	BA: 5 HD: 18	BA: 20 HD: 20
06	4	5	HD: 9	BA: 3 HD: 8	HD: 20 LA: 10
07	15	5	-	BA: 2 & 7 HD: 30	BA: 6 HD: 15
08	6	1	-	BA: 3 HD: 10	BA: 11 HD: 30 LA: 20
09	3	14	-	BA: 2, 3 & 5 HD: 40	BA: 10 HD: 15
10	2	3	BA: 5	BA: 4 HD: 5	BA: 10 HD:4

BA-broadcast-air assisted sprayer; HD-hydraulic boom sprayer (downward); KN-knapsack sprayer; LA-lance sprayer

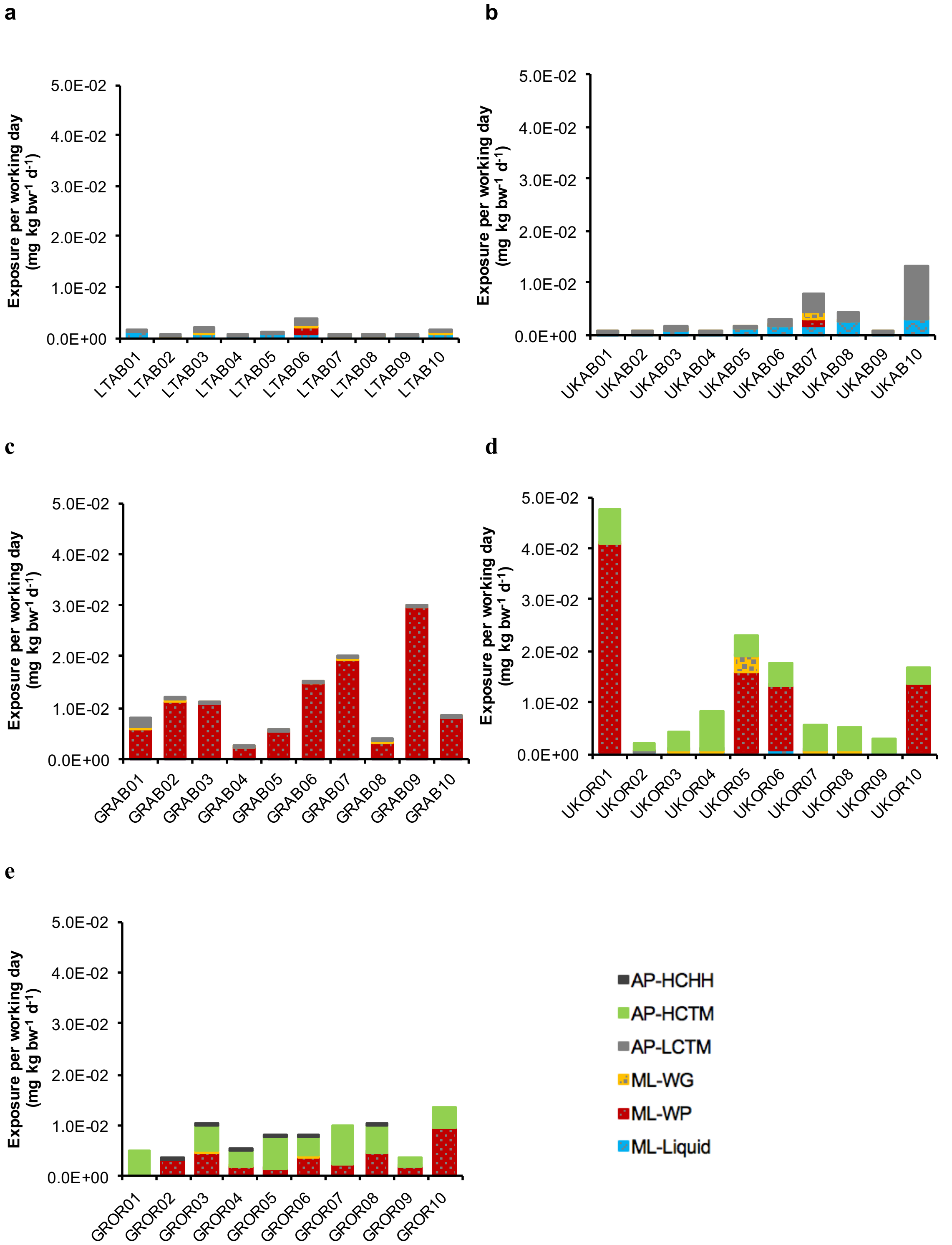


Figure A2- 1. Estimated daily exposures for the 10 professional operators from the arable systems of Lithuania (a), the UK (b), Greece (c), and the orchard systems of the UK (d) and Greece (e) during applications (AP) and mixing/loading (ML) of pesticides with different application methods and formulation types. Values are calculated based on the respective total number of working days.

Appendix 3 Supplementary Chapter 4

Table A3- 1. Classification of 48 pesticide active substances with known or possible endocrine activity by pesticide type, chemical group, and approval status in the EU. All information sourced from the Pesticide Properties Database (PPDB, 2018).

Active substances	Pesticide type	Substance group	Endocrine disrupting classification	Status of use
2,4-D	Herbicide	Alkylchlorophenoxy	Possibly	Approved
Amitrole	Herbicide	Triazole	Possibly	Not approved
Beta-cyfluthrin	Insecticide	Pyrethroid	Possibly	Approved
Bifenthrin	Insecticide	Pyrethroid	Yes	Approved
Bromoxynil	Herbicide	Hydroxybenzonitrile	Yes	Approved
Bupirimate	Fungicide	Pyrimidinol	Possibly	Approved
Captan	Fungicide	Phthalimide	Possibly	Approved
Carbendazim	Fungicide	Benzimidazole	Possibly	Not approved
Chlorothalonil	Fungicide	Chloronitrile	Possibly	Approved
Chlorpyrifos	Insecticide	Organophosphate	Possibly	Approved
Chlorpyrifos-methyl	Insecticide	Organophosphate	Possibly	Approved
Copper oxychloride	Fungicide	Inorganic compound	Possibly	Approved
Cypermethrin (alpha-/zeta-cypermethrin)	Insecticide	Pyrethroid	Possibly	Approved
Cyproconazole	Fungicide	Triazole	Possibly	Approved
Deltamethrin	Insecticide	Pyrethroid	Yes	Approved
Difenoconazole	Fungicide	Triazole	Possibly (based on open literature; Teng et al., 2018)	Approved

Epoxiconazole	Fungicide	Triazole	Possibly	Approved
Esfenvalerate	Insecticide	Pyrethroid	Possibly	Approved
Fenbuconazole	Fungicide	Triazole	Possibly	Approved
Fenoxycarb	Insecticide	Carbamate	Yes	Approved
Fluazinam	Fungicide	Phenylpyridinamine	Possibly	Approved
Flusilazole	Fungicide	Triazole	Possibly	Not approved
Glyphosate	Herbicide	Phosphonoglycine	Possibly	Approved
Indoxacarb	Insecticide	Oxadiazine	Possibly	Approved
Ioxynil	Herbicide	Hydroxybenzonitrile	Yes	Not approved
Linuron	Herbicide	Urea	Possibly	Approved
Mancozeb	Fungicide	Carbamate	Possibly	Approved
Maneb	Fungicide	Carbamate	Possibly	Approved
Metconazole	Fungicide	Triazole	Possibly (based on open literature; Marx-Stoelting et al., 2014)	Approved
Methoxyfenozide	Insecticide	Diacylhydrazine	Possibly	Approved
Metiram	Fungicide	Carbamate	Possibly	Approved
Metribuzin	Herbicide	Triazinone	Possibly	Approved
Myclobutanil	Fungicide	Triazole	Possibly	Approved
Paclobutrazol	Fungicide	Triazole	Possibly (based on open literature; Andersen et al., 2002)	Approved
Penconazole	Fungicide	Triazole	Possibly	Approved
Pendimethalin	Herbicide	Dinitroaniline	Possibly	Approved
Picloram	Herbicide	Pyridine compound	Yes	Approved
Prochloraz	Fungicide	Imidazole	Possibly	Approved
Propamocarb (hydrochloride)	Fungicide	Carbamate	Possibly	Approved

Propiconazole	Fungicide	Triazole	Possibly	Approved
Pyrimethanil	Fungicide	Anilinopyrimidine	Possibly	Approved
Pyriproxyfen	Insecticide	Unclassified	Possibly	Approved
S-metolachlor	Herbicide	Chloroacetamide	Possibly	Approved
Tau-fluvalinate	Insecticide	Synthetic pyrethroid	Yes	Approved
Tebuconazole	Fungicide	Triazole	Possibly (based on open literature; Lv et al., 2017)	Approved
Triadimenol	Fungicide	Triazole	Yes	Approved
Tribenuron-methyl	Herbicide	Sulfonylurea	Possibly	Approved
Ziram	Fungicide	Carbamate	Possibly	Approved

Table A3- 2. List of pesticide co-formulants used in the UK orchard system that were identified as having potential endocrine activity based on the Hazardous Substances Data Bank (HSDB) of the TOXNET database and the Pesticide Property Database (PPDB, 2018).

Chemical name	CAS No.	Potential ED effect(s)
1-methoxy-2-propanol	107-98-2	Mild damage to the liver and adrenal glands were observed in laboratory rats following repeated exposure to high vapour levels.
1,2-propanediol/propane-1,2-diol/propylene glycol	57-55-6	Seizures developed in an 11-year old boy with multiple endocrine problems and systemic candidiasis who ingested a medication containing propylene glycol. Endocrine modulation: did not cause any significant changes in adrenal steroidogenesis in the rat; spleen weights were increased in the treatment groups in acute exposure.
1,2,4-trimethylbenzene	95-63-6	Rat (4-week): observations in high dose group (2.0g/kg) included enlarged adrenals (only 2 doses tested; low dose: 0.5 g/kg diet).
2-ethylhexan-1-ol	104-76-7	Rat (11-day): absolute spleen weights of both sexes were reduced at 1000 mg/kg bw/d; decreased absolute spleen and adrenal weights at 1500 mg/kg bw/d.
3-pyridinecarboxamide, 2-chloro-N-(4'-chloro(1,1'-biphenyl)2-yl)-	188425-85-6	Induction of liver microsomal enzyme system resulting in increased glucuronidation of thyroxine, resulting in an increase in TSH secretion as a compensatory response of the physiological negative feedback system; increased TSH resulted in increased thyroid weight.
4,4’-methylenediphenyl diisocyanate/diphenylmethane-4,4’-diisocyanat	101-68-8	Repeated doses for 5 days in corn oil produced slight spleen enlargement in rats.
Amines, tallow alkyl, ethoxylated/polyetoxylated N-tallow alkyltrimethylenedi-amine/tallowalkylamineethoxylate	61791-26-2	Polyethoxylated tallow amine: decrease of aromatase activity, a key enzyme in the balance of sex hormones (Defarge et al. 2016).

Ammonium sulphate/sulfate	7783-20-2	Rat (1-year): absolute spleen weights were decreased in high dose males.
Citric acid	77-92-9	Rat (6-week): slight degeneration of the thymus gland and spleen.
Cumene	98-82-8	Rat (2-week inhalation): For females in the two highest dose groups, the relative and absolute adrenal weights were increased significantly over control values.
Ethylene glycol	107-21-1	Target organ cellular damage is seen in the kidney, brain, myocardium, pancreas, and blood vessel walls.
Hydrocarbon, C9, aromatics	N/A	Polycyclic aromatic hydrocarbons (PAHs): Endocrine modulation: PAHs exhibited either weakly estrogenic or antiestrogenic responses.
Hydrocarbon, C10, aromatics, <1% naphthalene	N/A	
Hydrocarbons, C11-C14, n-alkanes, isoalkanes, cyclics <2% aromatic	N/A	
Lignin, alkali, reaction products with sodium bisulfite and formaldehyde/Lignosulfonic acid, sodium salt/sodium ligninsulfonate	8061-51-6	When given to rats in drinking-water 16-week; spleen changes.
Naphtha/petroleum distillates	64742-94-5	Rat (7/8-week developmental/reproductive toxicity, f/m): increased spleen weights in parental females at 7500 ppm.
Naphthalene	91-20-3	Mice (14- and 90-day): Females had decreased spleen at the high dose, 267 mg/kg and 133 mg/kg, respectively. Mice (14- and 90-day): Females had decreased spleen at the high dose, 267 mg/kg and 133 mg/kg, respectively.
N-methyl-2-pyrrolidone/methyl pyrrolidone	872-50-4	Subchronic exposure of rats had atrophy of lymphoid tissue in the spleen and thymus.
Nonylphenol ethoxylated/polyethylene glycol nonylphenyl ether	9016-45-9	Nonylphenol: discovered to have estrogenic activity.
Talc	14807-96-6	There was clear evidence of carcinogenic activity of talc in female F344/N rats based on increased incidences of alveolar/bronchiolar adenomas and carcinomas of the lung and benign or malignant pheochromocytomas of the

		adrenal gland.
Cyprodinil	121552-61-2	Cyprodinil acts as an aryl hydrocarbon receptor activator, a potential endocrine disrupter, and an extracellular signal-regulated kinase disrupter. Weak androgen receptor binding was shown for cyprodinil.
Dicamba	1918-00-9	Rat (115-118 weeks): adrenal enlargement was increased at >/= 250 ppm in both sexes.
Diquat (diquat dibromide)	2764-72-9	Diquat dibromide (1-year): reductions in adrenal and epididymal weights were noted in males.
Fludioxonil	131341-86-1	Endocrine modulation: fludioxonil showed endocrine disruptor activity as antiandrogens in an androgen receptor reporter assay in engineered human breast cancer cells.
Fumaric acid	110-17-8	Rabbit (17-29 weeks): by the end of the test period, gonadotropic activity of the serum, as well as estrogenic activity was detected. Chromophobe cells were increased in the pituitary.
Metribuzin	21087-64-9	Metribuzin shows effects in single high doses corresponding to a depression of the CNS system. With repeated high doses, it effects the thyroid and stimulates the metabolizing enzymes of the liver.
Pyraclostrobin	175013-18-0	Subchronic or prechronic exposure/ Mice, in a 90-day feeding study, also showed thickening of the duodenal mucosa together with erosion or ulcers in the glandular stomach and a decrease in lipid vacuolization in the adrenal cortex. Females were more sensitive than males with adrenal effects occurring at 50 ppm (12.9 mg/kg/day).

Table A3- 3. Summary of toxicological data for 48 active substances with known or possible endocrine activity.

Active substance	Species / study	Doses	NO(A)EL/LO(A)EL (mg/kg bw/d)	LOAEL / effects	Toxicological database
2,4-D	Rat 90-day oral diet	0, 1, 15, 100, 300 mg/kg/d (average daily compound intake: 0.93, 13.98, 93.93, 278.39 mg/kg/d for males and 0.96, 14.39, 96.16, 293.42 mg/kg/d for females)	NOAEL: 15	LOAEL: 100 mg/kg/d based on the alterations in some hematology and clinical chemistry (decreased T_3 (females) and T_4 (both sexes)) parameters, and cataract formation in females.	EPA (EDSP Tier 1)
Amitrole	Rat 90-day oral	0, 2, 10, 50 ppm (0.11, 0.58, 2.85 mg/kg bw/d)	NOAEL: 0.11 (2 ppm)	LOAEL: 10 ppm equivalent to 0.58 mg/kg bw/d based on the thyroid effect.	EFSA (DAR)
Beta-cyfluthrin (cyfluthrin)	Rat 4-week gavage (once daily)	0, 5, 20, 80 mg/kg bw/d	NOEL: 20	Increased absolute and relative weights of the adrenal glands in female rats at the end of treatment at the highest dose.	TOXNET (HSDB)
Bifenthrin	Rat 28-day	0, 50, 100, 200, 300, 400 ppm (approximately 0, 4.4, 10.75, 21.9 and 34.5 mg/kg bw/d in males and 0, 5.4, 11, 21.6 and 32.6 mg/kg bw/d in females)	NOAEL: 21.9 (m) (200 ppm)	Based on significantly elevated adrenal weight and depressed testes weight and relative adrenal in males at 300 ppm group.	IPCS INCHEM (JMPR; ECHA, 2009)

Bromoxynil	Dog 13-week oral (7 days/week)	0, 0.43, 1.43, 7.14 mg/kg/d	NOEL: <0.43	Increased absolute and relative adrenal weights.	TOXNET (HSDB)
Bupirimate	Dog 90-day oral diet	0, 3, 15, 30, 600 mg/kg bw/d	NOAEL: 3	LOAEL: 15 mg/kg bw/d based on Increased thyroid weight.	EFSA (DAR)
Captan	Rat 2-year	0, 25, 100, 250 mg/kg/d	NOEL: 25	Increased relative organ weights of liver and thyroid/parathyroid (F) and kidney (m & f).	TOXNET (HSDB)
Carbendazim	Dog 13-week diet	0, 100, 300, 1000 ppm	NOAEL: 7.5 (300 ppm)	On the basis of minor changes in clinical chemistry and organ weights. There were slight increases in relative thyroid weight in the group at the highest dose.	IPCS INCHEM (JMPR)
Chlorothalonil	Dog 1-year	0, 160, 1280, 10240 ppm (0, 5.10, 43.26, 374 mg/kg/d in males and 0, 5.92, 45.30, 354 mg/kg/d in females)	NOAEL: 43.3/45.3 (m/f) (1280 ppm)	LOAEL: 10240 ppm based on a very slight hypertrophy of the cells in the zona fasciculate of the adrenal glands.	EPA (EDSP Tier 1)
Chlorpyrifos	Rat 13-week	-	NOAEL: 5	Increased fatty vacuolation of the adrenal zonal fasciculate and changes in haematological and clinical chemical parameters.	IPCS INCHEM (JMPR)
Chlorpyrifos-methyl	Rat 13-week	0, 0.1, 1, 10, 250 mg/kg bw/d	NOAEL: 1	On the basis of histological alterations detected in adrenals at 10 mg/kg bw/d.	IPCS INCHEM (JMPR)

Copper oxychloride (copper)	Rat 15-day	0, 1000, 2000, 4000, 8000, 16000 ppm (23, 44, 162, 196, 285 mg/kg bw/d in males and 23, 46, 92, 198, 324 mg/kg bw/d in females	NOAEL: 23 (1000 ppm)	A minimal to mild decrease in erythroid haematopoesis was seen in the spleens at ≥ 2000 ppm. (No guideline GLP with deviations of 15-day instead of 28-day).	ECHA (2013)
Cypermethrin (alpha-cypermethrin/zeta-cypermethrin)	Rat 15-day oral gavage	0, 6.25, 12.5, 25, 50 mg/kg/d	NOEL: 6.25	Damage to the seminiferous tubules and spermatids in studies reported as other scientifically relevant information (OSROI; Hu et al., 2011).	EPA (EDSP Tier 1)
Cyproconazole	Rat 90-day	5, 15, 300, 600 ppm (0.7, 2.2, 43.8, 88.8 mg/kg bw/d in males and 1.0, 3.2, 70.2, 128.2 mg/kg bw/d in females)	NOAEL: 0.7/1.0 (m/f) (5 ppm)	Increased relative adrenal weight in females at 15 ppm (2.2/3.2 mg/kg bw/d).	ECHA (2014)
Deltamethrin	Rat 65-day	1, 2 mg/kg w/d	LOEL: 1 (divided by 1000-factor for NOEL: 0.001)	Based on spermatogenesis, testosterone levels and pituitary weight *in vivo*.	EC (EDS)
Difenoconazole	Dog 6-month diet	0, 100, 1000, 3000, 6000 ppm (0, 3.6, 31.3, 96.6, 157.8 mg/kg/d in males and 0, 3.4, 34.8, 110.6, 203.7 mg/kg/d in females)	NOAEL: 31.3/34.8 (m/f) (1000 ppm)	Based on decreased prostate weight.	EFSA (DAR)
Epoxiconazole	Rat 13-week dietary	30, 90, 270, 800 ppm	NOAEL: 7/8 (m/f) (90 ppm)	Both absolute and relative adrenal weights were slightly reduced in all treated groups, but more clearly so at the upper two dose levels.	EFSA (DAR)

Esfenvalerate	Rat 90-day diet	0, 50, 150, 300 or 500 ppm	NOAEL: 7.5 (150 ppm)	On the basis of parenchymal-cell hypertrophy in the parotid salivary and pituitary glands in some rats at 300 ppm.	IPCS INCHEM (JMPR)
Fenbuconazole	Rat 3-month dietary	0, 20, 80, 400, 1600 ppm	NOAEL: 1.3 (20 ppm)	Hypertrophy of thyroid gland follicular cells at higher doses.	IPCS INCHEM (JMPR)
Fenoxycarb	Rat 3-month oral	0, 30, 150, 750, 3000 ppm	NOEL: 9.71/10.14 (m/f) (150 ppm)	Based on histological changes in thyroid.	TOXNET (HSDB)
Fluazinam	Rat 90-day oral	-	NOAEL: 4.1	LOAEL: 41 mg/kg bw/d. Effect on uterus weight may be indicative of endocrine disruption with no mechanistic evidence.	Ewence et al. (2013)
Flusilazole	Rat 2-year diet	0, 125, 375, or 750 ppm (0, 5.03, 14.8, 30.8 mg/kg bw/d for males and 0, 6.83, 20.5, 45.6 mg/kg bw/d for females)	NOAEL: 14.8	Increased incidence of testicular interstitial-cell (Leydig-cell) tumours in males at the highest dose.	IPCS INCHEM (JMPR)
Glyphosate	Dog 13-week oral	0, 30, 300, 1000 mg/kg bw/d	NOAEL: 300	LOAEL: 1000 mg/kg bw/d based on prostate and uterus atrophy.	ECHA (2016)
Indoxacarb	Rat 90-day	0, 10, 25 (females only), 50, 100, 200 (males only) (0, 0.62, 3.09, 6.01, 15 mg/kg/d for males and 0, 0.76, 2.13, 3.78, 8.94	NOEL: 0.62/<0.76 (m/f) (10 ppm)	Histologic effects in the spleen.	TOXNET (HSDB)

		mg/kg/d for females)			
Ioxynil	Rat 90-day oral	-	NOEL: 0.7 to 1.4	LOAEL: 10 mg/kg bw/d. There appears to be an increase in basal metabolism and an effect on the thyroid.	Ewence et al. (2013)
Linuron	Rat 2-year	-	NOEL: 6.25 (125 ppm)	Spleen and bone marrow changes indicative of haemolysis, increased mortality, growth retardation.	IRIS
Mancozeb	Rat 13-week oral	0, 30, 60, 125, 250, 1000 ppm	NOAEL: 7.4 (125 ppm)	Increased serum TSH and decreased T4 values at 250 ppm.	IPCS INCHEM (JMPR)
Maneb	Dog 13-week dietary	0, 100, 400, 1600 ppm	NOAEL: 3.7 (100 ppm)	Based on thyroid follicular cell hyperplasia at 400 ppm.	IPCS INCHEM (JMPR)
Metconazole	Mouse 90-day oral	0, 30, 300, 2000 ppm	NOAEL: 4.6 (30 ppm)	LOAEL: 50.5 mg/kg/d (300 ppm) based on increased spleen weight and spleen lymphoid hyperplasia.	EFSA (DAR)
Methoxyfenozide	Rat 2-week diet	250, 1000, 5000, 20000 mg/kg diet	NOAEL: 24 (250 mg/kg diet)	On the basis of follicular cell hypertrophy and/or hyperplasia of the thyroid in both sexes at 1000 mg/kg (equal to 98 mg/kg bw/d).	IPCS INCHEM (JMPR)
Metiram	Rat 13-week dietary	0, 50, 100, 300, 900 (equal to 0, 3, 6, 20, 61 mg/kg bw/d for males and 0, 4, 8, 24, 76 mg/kg bw/d for females)	NOAEL: 6 (100 ppm)	Decreased serum T4 levels and increased thyroid weights at dietary levels of 300 and 900 ppm.	IPCS INCHEM (JMPR)

Metribuzin	Rat 9-week oral	0, 35, 100, 300, 900 ppm	NOAEL: ≤ 2.41 (≤ 35 ppm)	LOAEL: ≥ 35 ppm: effects on thyroid gland and liver.	EFSA (DAR)
Myclobutanil	Rat 13-week diet	0, 100, 300, 3000 ppm (0, 6.2, 18.8, 192 mg/kg bw/d in males and 0, 6.9, 19.6, 225 mg/kg bw/d in females)	NOAEL: 18.8 (300 ppm)	Histomorphological alterations of the liver, kidney and adrenal glands at the highest dietary level of 3000 ppm.	IPCS INCHEM (JMPR)
Paclobutrazol	Dog 1-year	0, 15, 75, 300 mg/kg/d	NOAEL: 75	Based on the slight increase of adrenal weights in females at 300 mg/kg bw/d.	EFSA (DAR)
Penconazole	Rat 28-day gavage	0, 100, 500 mg/kg bw/d	NOAEL: < 100	Thyroids and adrenals (males) with histopathological findings at ≥ 100 mg/kg bw/d.	EFSA (DAR)
Pendimethalin	Rat 90-day oral	-	NOAEL: 41.3	Based on thyroid effects.	EFSA (DAR)
Picloram	Rat 90-day	-	NOEL: 50 (1000 ppm)	LEL: 150 mg/kg/d (3000 ppm) based on liver histopathology, necrosis, and bile duct proliferation.	IRIS
Prochloraz	Dog 13-week gastric intubation	1, 2.5, 7, 20 mg/kg bw/d	NOAEL: 2.5	On the basis of effects on prostate and testes weights at the next highest dose.	IPCS INCHEM (JMPR)
Propamocarb hydrochloride	Rat 2-generation oral reproductive	-	NOAEL: 37.5 (parental & reproductive)	Some evidence of disruption of the male reproductive system (sperm concentration and count).	Ewence et al. (2013)

Propiconazole	Dog 1-year diet (short-term)	0, 50, 250, 1250 ppm	NOAEL: 7 (250 ppm)	Organ weights were not different than those of control animals except for significantly decreased relative pituitary weight in males of the highest dose group.	IPCS INCHEM (JMPR)
Pyrimethanil	Rat 90-day oral	-	NO(A)EL: 5.4	Follicular epithelial hypertrophy and pigment deposits in thyroid.	EFSA (DAR)
Pyriproxyfen	Rat 78-week diet	0, 120, 600, 3000 mg/kg food	NOAEL: 16.4/21.1 (m/f) (120 mg/kg food)	Increased severity of systemic amyloidosis was noted in several organs as the adrenal cortex, thyroid, heart, spleen, kidneys, liver, stomach, ovary, testes, etc.	EFSA (DAR)
S-metolachlor (metolachlor)	Rat Post-natal day 22 to 42 oral gavage	0, 300, 600 mg/kg/d	LO(A)EL: 300 (divided by 1000 for NO(A)EL: 0.3)	Based on a dose-related increase in serum T4 levels of 14% and 25% in the 300 and 600 mg/kg/d groups, respectively; the increase was significant ($p<0.05$) at 600 mg/kg/d only.	EPA (EDSP Tier 1)
Tau-fluvalinate	Dog 6-month	0, 2, 5, 15, 50 mg/kg/d	NOEL: 2	Decreased spleen weight.	TOXNET (HSDB)
Tebuconazole	Rat 90-day feeding	0, 100, 400, 1600 ppm	NOAEL: 9/11 (m/f) (100 ppm)	Histopathological changes (vacuoles) in the adrenal cortex.	EFSA (DAR)
Triadimenol	Mice 13-week	0, 160, 500, 1500, 4500 ppm (0, 25, 77, 235, 872 mg/kg/d in males and 0, 31,	NOAEL: 235/297 (m/f) (1500 ppm)	Reduced adrenal weights in the high-dose groups only in males and females.	ECHA (2011)

		94, 297, 797 mg/kg/d)			
Tribenuron-methyl	Rat 90-day oral	-	NOAEL: 7/8 (m/f)	LOAEL: 118/135 mg/kg/d (m/f). Increased relative brain, heart, liver, kidney, testes, and spleen weights.	TOXNET (HSDB)
Ziram	Rat 28-day oral	0, 100, 500, 2500, 5000 ppm (0, 10, 50, 250, 500 mg/kg bw/d)	NOAEL: 10 (100 ppm)	On the basis of growth retardation.	IPCS INCHEM (HSDB)

EC (EDS), European Commission Endocrine Disruptors Database; EFSA (DAR), EFSA Draft Risk Assessment Report and Assessment Report; EPA (EDSP Tier 1), EPA Endocrine Disruptor Screening Program Tier 1 screening determinations and associated data evaluation records; IPCS INCHEM (JMPR), Joint Meeting on Pesticide Residues of the International Programme on Chemical Safety; IRIS, Integrated Risk Information System; LO(A)EL, lowest observed (adverse) effect level; NO(A)EL, no observed (adverse) effect level; TOXNET (HSDB), Hazardous Substances Data Bank of Toxicology Data Network

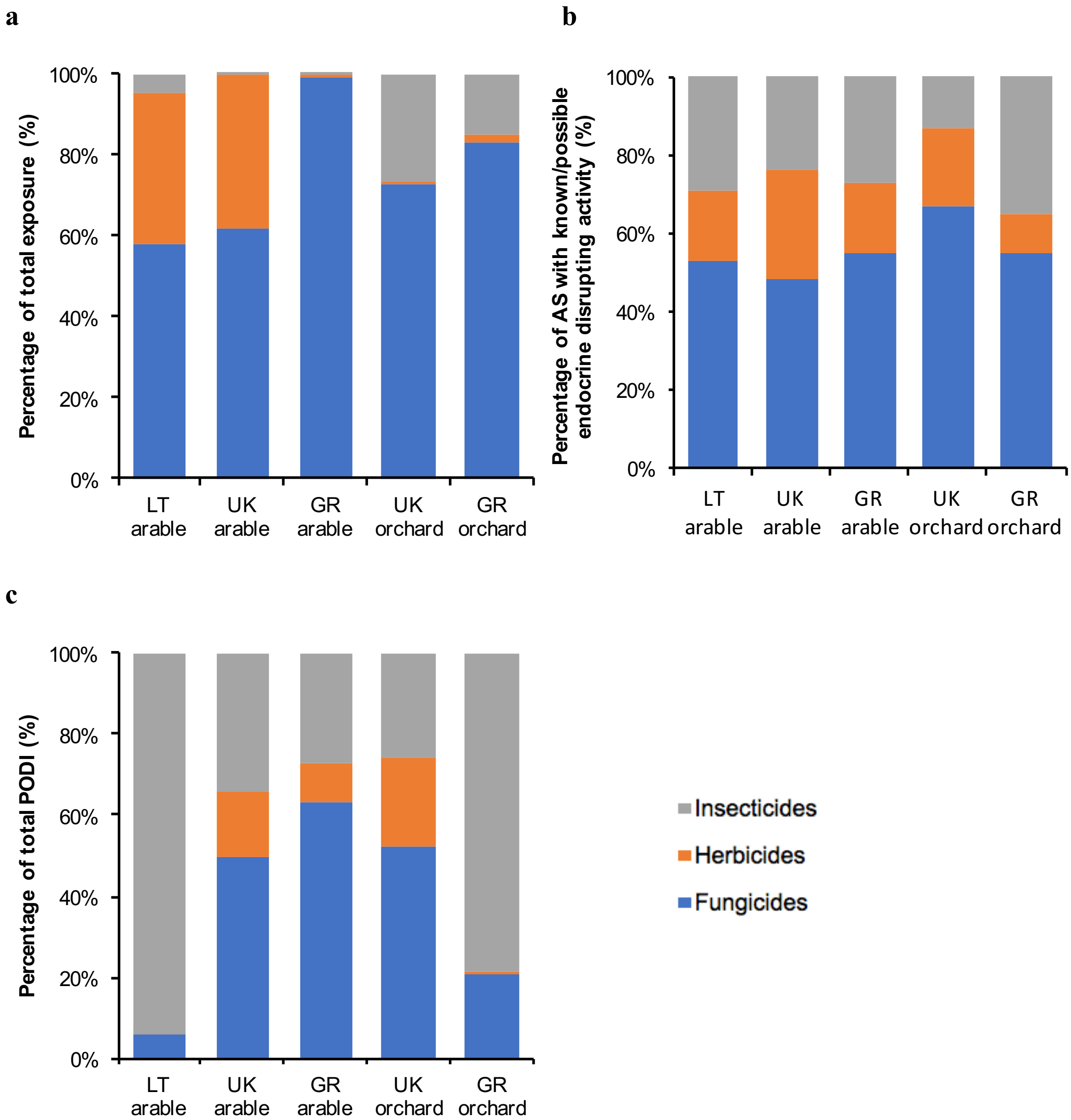


Figure A3- 1. Comparison of relative contributions of fungicides, insecticides and herbicides to the total use (a), total exposure (b) and total risk (c) associated with known/possible endocrine disrupting activity across the five cropping systems over the survey period.

Appendix 4 Model Evaluation

Introduction

After application of pesticides, volatilisation followed by transport in the vapour phase is a significant pathway for pesticides to enter into the environment (Bedos et al., 2002; Reichman et al., 2013). Quantification of these volatilised pesticides is important to have information on the state of their contamination in the atmosphere (Villiot et al., 2018). Models describing the volatility and potential fate of active substances are important tools in pesticide authorisation at the EU level, because they can cost-effectively supplement the limited number of field experiments (Kennedy et al., 2012; Houbraken et al., 2016). Nevertheless, the existing regulatory assessment models for pesticide vapour exposure were developed based on reasonable worst-case conditions at a maximum downwind distance of 10 m from the edge of the treated area; they provide a conservative first tier as set out in the guidance of EFSA (2014) and the Bystanders, Residents, Operators and WorkerS Exposure models (BROWSE model; van den Berg et al., 2016). Thus, a model was developed that allows the simulation of pesticide airborne concentration at different proximities from the treated field (Wong et al., 2017).

This work evaluates the performance of the model developed by Wong et al. (2017) in the simulation of airborne concentrations of pesticides at two selected distances downwind from the treated field (18 and 36 m), using a field dataset collected by the Swedish University of Agricultural Sciences between 2008 and 2010 (Karlsson and Arvidsson, 2015). On a daily basis, airborne concentrations of pesticides at a height of 1.0 m above ground were compared between the model outputs and the measurements. Results are analysed to determine any limitations of the model in the simulation of pesticide airborne concentrations under field conditions.

Methodology

Field data

We applied a dataset of pesticide applications and field observations collected by the Swedish University of Agricultural Sciences during the periods of summer (June/July) and autumn (September) for three years (2008-2010), with the purpose of understanding the volatilisation and dry deposition of pesticides under Swedish climatic conditions based at Funbo-Lovsta, Sweden (Karlsson and Arvidsson, 2015). The field experiment was a 54 m radius circular area with an untreated inner circular area of 18 m radius (where the air sampling and meteorological masts were located with 16 m in height for each); the remaining 36 m outer circle radius was treated with pesticides (Figure A4-1). This meant that the sampling equipment intercepted air flowing across the treated area independent of wind direction.

The treated area was cultivated with winter wheat/barley (crop heights ranged between 0.75 and 0.9 m) during summer and had no crop (bare soil) in autumn. The experiment was started during 2008 with a mixture of four pesticide active substances comprising pirimicarb (Pirimor), prosulfocarb (Boxer), fenpropimorph (Forbel), and pendimethalin (Stomp). Two further active substances, namely lindane and tolclofos-methyl (Rizolex), were added to the mixture during 2009-2010. Applied field doses ranged between 7.8 and 398 mg m^{-2} for individual active substances (Table A4-1).

In the field experiment, the airflow through the air sampling mast was measured by individual thermic mass flow meters at seven heights above ground comprising 0.25, 0.6, 1.0, 2.0, 4.0, 8.0, and 16.0 m, with sampling durations ranging between 24 and 232 h across seven sampling periods. At the same intervals, the meteorological masts measured a variety of weather variables including the wind speed, wind direction, solar radiation, air temperature, and relative humidity at the corresponding heights (Karlsson and Arvidsson, 2015). Here, the height of 1.0 m above ground was selected for all evaluation and results for the first day after application were considered to match the simulation output of the model.

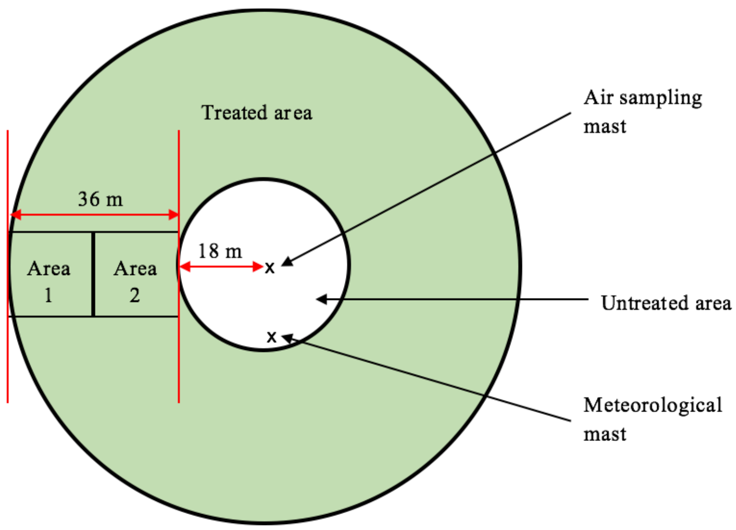


Figure A4- 1. Schematic of the layout of the field experiment (Karlsson and Arvidsson, 2015).

Table A4- 1. Applied field doses (mg m^{-2} of active substance) for six selected pesticide active substances during the periods of summer and autumn for the years 2008-2010.

Active substance	2008		2009		2010	
	June	Sept	July	Sept	July	Sept
Fenpropimorph	75	75	93.4	89.2	73.5	78.4
Lindane	N/A	N/A	10.0	9.5	7.8	8.4
Pendimethalin	160	160	199	19	15.7	16.7
Pirimicarb	15	15	18.7	89.2	14.7	78.4
Prosulfocarb	320	320	398	19	15.7	16.7
Tolclofos-methyl	N/A	N/A	31.1	29.8	24.5	26.1

Model description

The newly developed model is described by Wong et al. (2017). It combines algorithms taken from PEARL (Pesticide Emission Assessment at Regional and Local scales; van den Berg and Leistra, 2004), PELMO (Pesticide Leaching Model; Ferrari et al., 2005), and ISCST2 (Industrial Source Complex Short Term 2; US EPA, 1992a), to account for volatilisation and transport in air for pesticides with different properties and under varying field conditions (Wong et al., 2017).

Model set-up

Five pesticide active substances were simulated comprising fenpropimorph, lindane, pendimethalin, pirimicarb, and prosulfocarb. The five selected active substances were parameterised for their specific physicochemical properties based on the Pesticide Properties Database (PPDB, 2018); where, data for K_{oc} were missing, these were derived from the open literature (Table A4-2). When a crop is present, the model predicts volatilisation from both target plant surface (here 90% crop interception was assumed) and the exposed soil surface (10% by difference) at release heights of 0.75-0.9 and 0.1 m, respectively (Figure A4-2). Any differences between the winter wheat and barley crops were assumed to be negligible due to the short period of observation, and the small difference in crop interception factors and crop height (Houbraken et al., 2016).

The ISCST2 model requires that the area source must be a square, with recommendation of subdivision into smaller areas when the separation between the area and a receptor is less than the length of the side of the area source, X_o(US EPA, 1992a). Thus, the treated circular area with radius of 36 m was subdivided into two smaller areas each with X_o of 18 m at distances of 18 and 36 m from each edge to the air sampling mast (Figure A4-1). As the air sampling mast was surrounded by the treated area, the receptor was assumed to be always downwind of the emission source. Wind speeds and airborne concentrations measured at sub-daily resolution were averaged to derive daily values in order to match the resolution of model output (Table A4-3). An overall Pasquill stability B-class was assigned with a dimensionless default value of 0.07 for the rural wind profile exponent based on overall mean wind speed ≤3 m s^{-1} and mean solar radiation ≤640 W m^{-2} (US EPA, 1992a; Essa et al., 2006; Karlsson and Arvidsson, 2015). Where parameters were set to default values, these are listed in the supplementary information (Table A1-1; Wong et al., 2017).

Table A4- 2. Physicochemical properties for the five selected pesticide active substances (PPDB, 2018).

Active substance	Pesticide type	Molecular weight (g mol^{-1})	Vapour pressure at 25°C (mPa)	Henry's law constant at 20°C (dimensionless)	Koc (mL g^{-1})
Fenpropimorph	Fungicide	303.5	3.9	$5.5x10^{-5}$	2772[a]
Lindane	Insecticide	290.8	4.4	$6.1x10^{-5}$	1270
Pendimethalin	Herbicide	281.3	3.3	$1.5x10^{-3}$	17491
Pirimicarb	Insecticide	238.3	0.4	$1.4x10^{-7}$	290[b]
Prosulfocarb	Herbicide	251.4	0.8	$5.4x10^{-5}$	1367[c]

[a] EFSA (2008). Conclusion regarding the peer review of the pesticide risk assessment of the active substance: fenpropimorph. *EFSA Scientific Report*, 144, 1-89.

[b] MacBean, C. (2012). *A world compendium: the pesticide manual.* 6th edn. Hampshire: British Crop Production Council (BCPC).

[c] EFSA (2007). Conclusion regarding the peer review of the pesticide risk assessment of the active substance: prosulfocarb. *EFSA Scientific Report,* 111, 1-81.

Table A4- 3. Average values of wind speeds and air temperatures for 24 h after the application during the periods of summer and autumn for the three selected years.

	Average mean wind speed (m s^{-1})	Average mean air temperature (°C)	
Height above ground (m)	1.0 m	0.15 m (soil surface)	2.0 m (plant surface)
Summer			
2008	2.1	13.6	13.4
2009	1.3	15.2	15.1
2010	1.3	22.3	22.6
Autumn			
2008	0.8	7.7	N/R
2009	1.2	9.9	N/R
2010	1.5	12.9	N/R

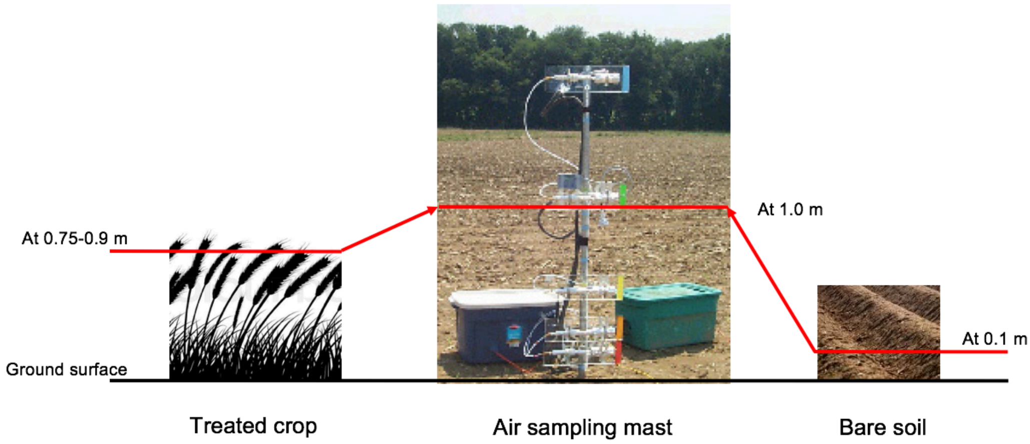


Figure A4- 2. Illustration of the model set-up for the simulation of pesticide airborne concentration at a downwind distanced of air sampling mast (source: Google image).

Model evaluation

To compare between the model outputs and the observed concentrations at 1.0 m above ground on a daily basis, the measured mean values during different sampling periods and durations were averaged on a 24 h basis. Derwent et al. (2010) considers that an urban air quality model is acceptable when more than half of the model outputs lie within a factor of 2 of the observations; here the factor was modified to up to 10 to allow for uncertainties introduced by many other variables that were not parameterised in the model, e.g., the effects of adjuvants and formulations, competing factors, and agricultural practices under actual field conditions.

Model simulation of pesticide volatilisation

Figure A4-3 shows that simulated losses of pesticide via volatilisation from treated surfaces was larger during summer (6-92% of total applied doses) than during autumn (0.04-12%). Overall, the volatilisation increased from 2008 to 2010 by 14-39% of applied dose during summer and up to 5% of applied dose during autumn. During the summer, active substances fenpropimorph, lindane, and pendimethalin had relatively larger estimated volatilisation (>50% of total applied doses) compared to pirimicarb and prosulfocarb (<40%; Figure A4-3a). During the autumn, pendimethalin had largest estimated volatilisation (7-12% of total applied doses), intermediate for lindane (5-7%), prosulfocarb (3-5%) and fenpropimorph (2-3%), and least for pirimicarb (0.04-0.1%; Figure A4-3b).

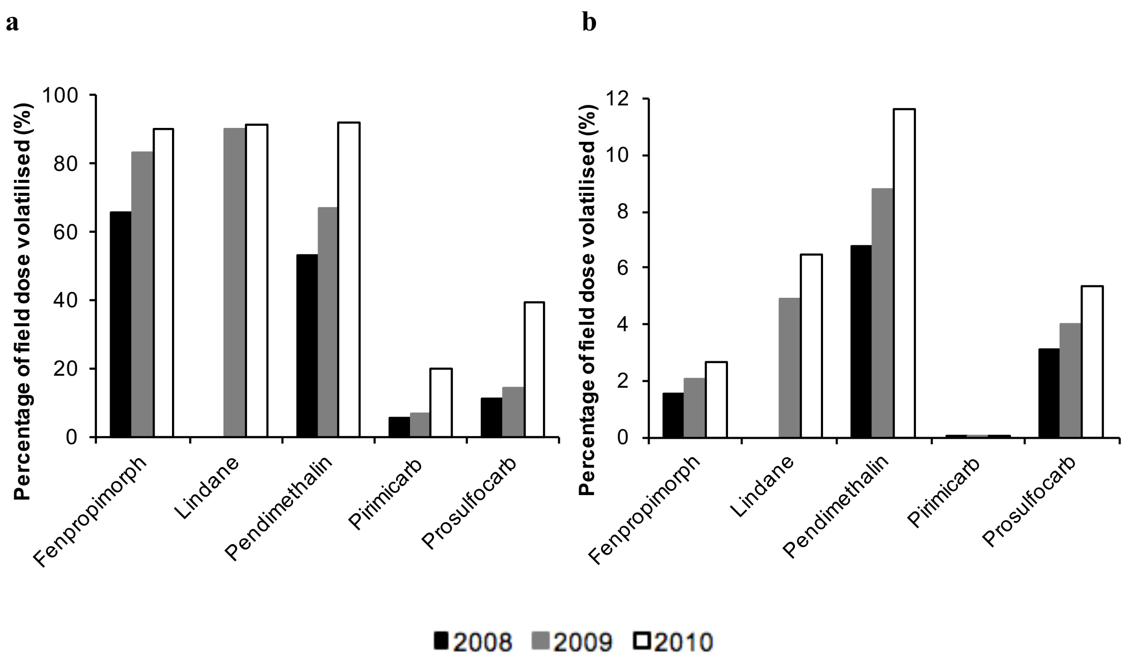


Figure A4- 3. Model simulation for volatilisation of the five pesticide active substances following applications in summer (a) and autumn (b) for the years 2008-2010.

Model output of pesticide airborne concentration

Figure A4-4 shows that model outputs were generally larger than the observed concentrations in air for fenpropimorph (2220-5450 and 36-1120 ng m^{-3}, respectively), pendimethalin (990-9380 and 441-2380 ng m^{-3}, respectively) and lindane (486-634 and 163-209 ng m^{-3} respectively) during the periods of summer with highest outputs in 2009. The reverse was true for prosulfocarb (425-4060 and 568-5190 ng m^{-3}, respectively) and there was no consistent pattern for pirimicarb (Figure A4-4d). Overall, the model simulated largest airborne concentrations for pendimethalin and fenpropimorph (9380 and 5450 ng m^{-3}, respectively; Figures A4-4b and A4-4a) in 2009 while prosulfocarb had the largest observed concentrations for the years 2008 and 2009 (2750 and 5190 ng m^{-3}, respectively; Figure A4-4e).

Figure A4-5 shows the model outputs were larger than the observed concentrations during autumn for pendimethalin (149-1520 and 5.7-515 ng m^{-3}, respectively) and fenpropimorph (162-171 and 1.3-129 ng m^{-3}, respectively) whilst the reverse was true for lindane (42-44 and 73-112 ng m^{-3}, respectively) and there was no consistent pattern for pirimicarb and prosulfocarb (Figures A4-5d and A4-5e). Overall, the model simulated largest airborne concentrations for pendimethalin and fenpropimorph for all three years (Figures A4-5b and A4-5a) while the largest observed concentration was prosulfocarb in 2008 (2570 ng m^{-3}; Figure A4-5e).

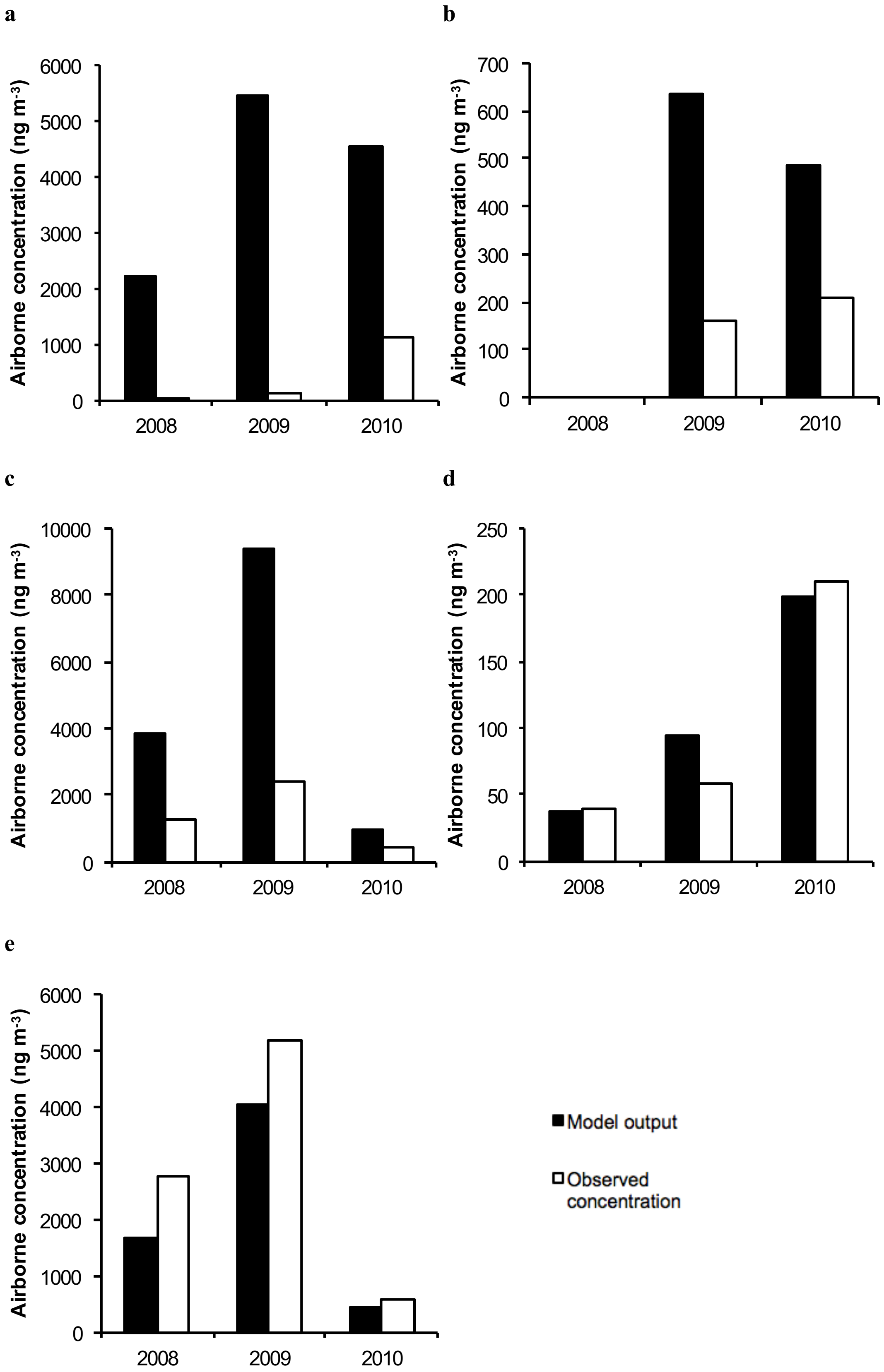


Figure A4- 4. Comparison between model outputs and observed concentration for active substances fenpropimorph (a), lindane (b), pendimethalin (c), pirimicarb (d), and prosulfocarb (e) during the survey periods of summer over the years 2008-2010.

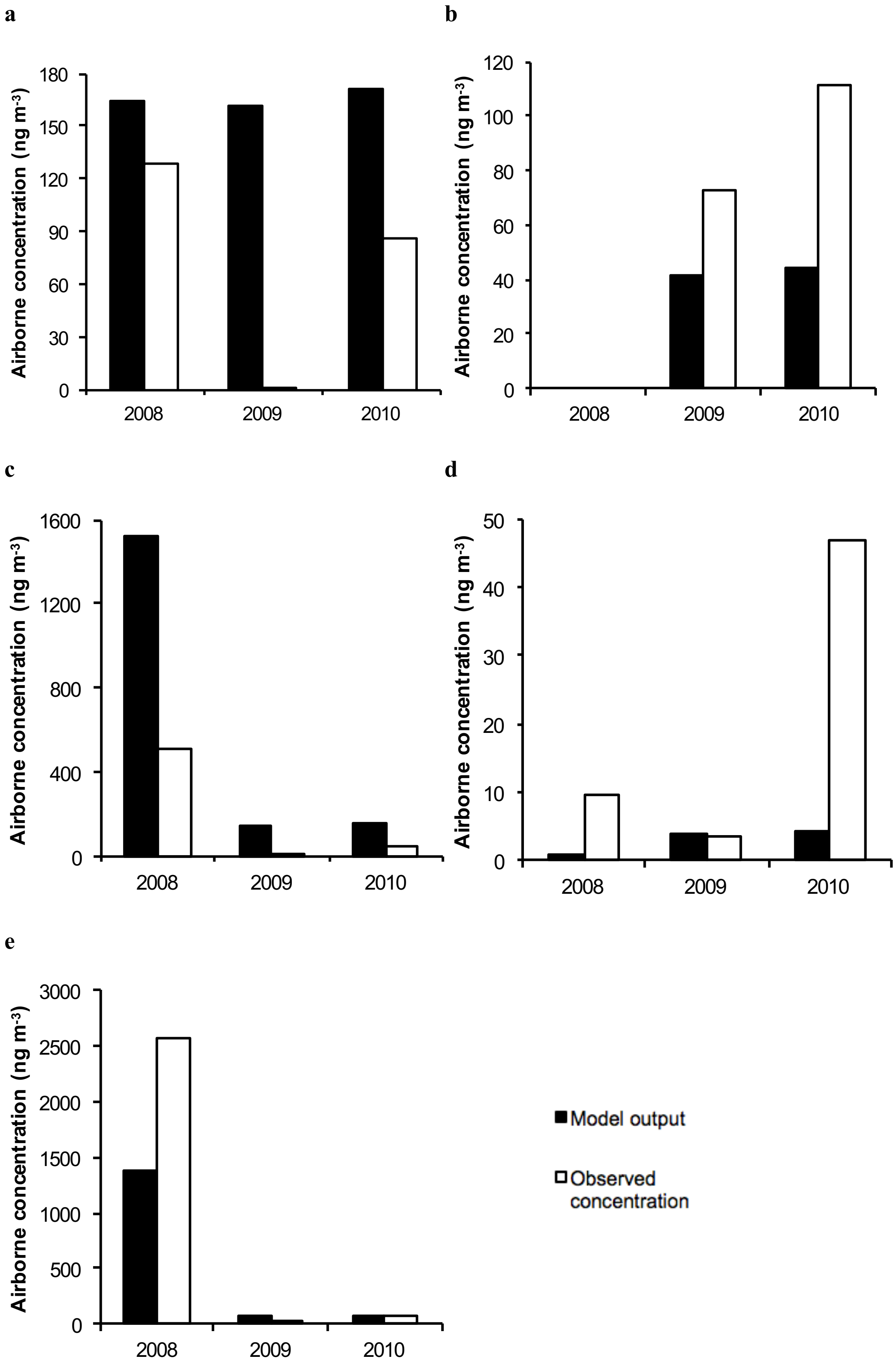


Figure A4- 5. Comparison between model simulation and observed concentration for active substances fenpropimorph (a), lindane (b), pendimethalin (c), pirimicarb (d), and prosulfocarb (e) during the survey periods of autumn over the years 2008-2010.

Model evaluation

Table A4-4 shows that most of the model outputs were within a factor of ten of the observed concentrations during both summer and autumn over the three years (average of ca. 86% of total model outputs; Table A4-5). Overall, two active substances had factors of difference that exceeded the 10-factor, namely fenpropimorph during summer 2008 and 2009 (at maximum 61- and 40-factor of difference, respectively) and autumn 2009 (26-factor), and pendimethalin during autumn 2009 (26-factor). Table A4-5 shows that ca. 86% and 79% of the model outputs were within a factor of 5 for the summer and autumn, respectively.

Figure A4-6 shows a linear relationship for prosulfocarb and pirimicarb during summer with the model outputs generally lying within or close to the one-to-one line. Pendimethalin was also a linear relationship, but with model outputs consistently over-estimated. The other two active substances for summer and all autumn simulations had no linear relationship identified. Overall, the correlation coefficients of the scatter plots indicate relatively poor correlations between the model outputs and observations during the periods of summer and autumn with R^2 values of 0.21 and 0.59, respectively (Figure A4-6).

Table A4- 4. Comparison between the model outputs and observed concentrations based on the factor of difference for the five selected pesticide active substances during the periods of summer and autumn for the three years 2008-2010.

	Factor of difference between model and observation (M_i/O_i)				
	Fenpropimorph	Lindane	Pendimethalin	Pirimicarb	Prosulfocarb
Summer					
2008	61.4	N/A	3.0	1.0	0.6
2009	40.4	3.9	3.9	1.6	0.8
2010	4.0	2.3	2.2	1.0	0.7
Autumn					
2008	1.3	N/A	2.9	0.1	0.5
2009	126.4	0.6	26.0	1.1	6.1
2010	2.0	0.4	3.3	0.1	1.1

Table A4- 5. Cumulative frequency of total number of model outputs within a factor of 2, 5 and 10 of the observed concentrations.

	Summer		Autumn	
Factor of difference	Total number	Cumulative frequency (%)	Total number	Cumulative frequency (%)
$0 < M_i/O_i \leq 2$	6	42.9	9	64.3
$2 < M_i/O_i \leq 5$	6	85.8	2	78.6
$5 < M_i/O_i \leq 10$	0	85.8	1	85.7
$M_i/O_i > 10$	2	100	2	100

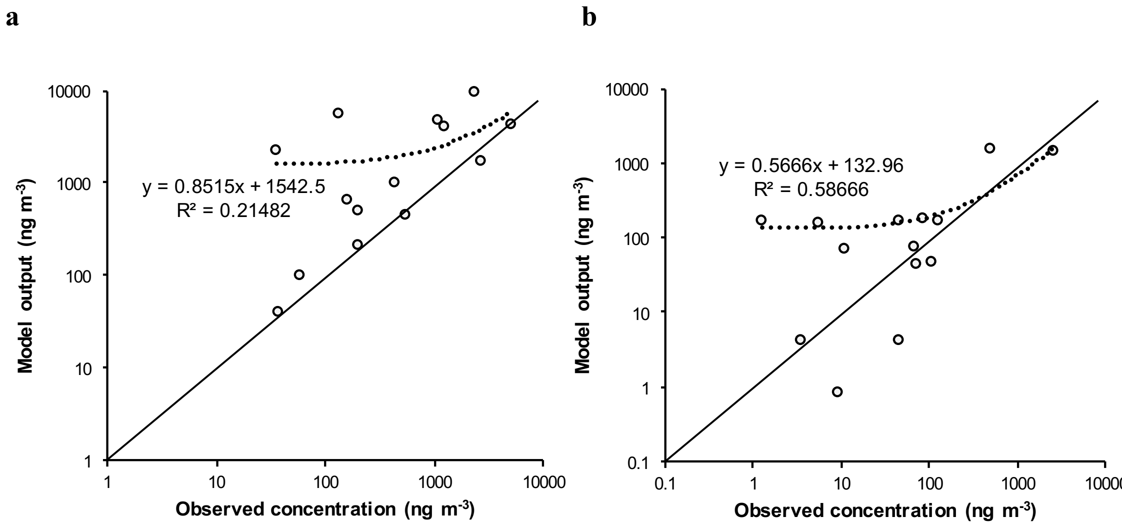


Figure A4- 6. Scatter plots of the model outputs vs observed concentrations for five selected active substances with the one-to-one line during the periods of summer (a) and autumn (b) of the years 2008-2010. Each dot represents predicted average daily concentration at 1.0 m above the ground.

Discussion

Overall, initial evaluation indicates that model outputs for concentrations of pesticides in air matched field observations to within an order of magnitude in most cases (Table A4-4). There was ca. 86% of model outputs lying within a factor of ten of the observations during the periods of summer and autumn between 2008 and 2010 (Table A4-5). On the other hand, the correlation coefficients of the scatter plots indicate relatively poor correlations between the model outputs and observations during the periods of summer and autumn (R^2 of 0.21 and 0.59, respectively; Figure A4-6), indicating more processes and factors would need to be considered as further discussed below.

For the summer, the model simulated relatively larger pesticide volatilisation from the plant surface than from the exposed soil surface (5.7-90% and 0.01-2.2% of applied doses, respectively), with the vapour pressure as the indicator for the volatilisation from the plant surface. There were some large variations in field application rates across the study period, including a drastic decrease of prosulfocarb from 398 mg m^{-2} in summer 2009 to only 15.7 mg m^{-2} in the following year (Table A4-1). Figure A4-3a indicates an overall increasing trend of volatilisation for the five active substances over the three years, mainly due to increased air temperatures on treated surfaces by ca. 2°C and 10°C from 2008 to 2009 and to 2010, respectively (Table A4-3). This is solely based on the assumption that all applied doses were available for the volatilisation, whilst 20-30% of pesticide may not reach the target site during an application (Villiot et al., 2018).

Figure A4-4 indicates correct order-of-magnitude with higher measured concentrations corresponding to higher simulated concentrations for three active substances pendimethalin, pirimicarb, and prosulfocarb, whilst no association was found for fenpropimorph and lindane. This may indicate that other processes not parameterised by the vapour pressure determine the volatilisation. This includes the assumption that there are no other dissipation pathways and formulation effects on the plant surface, inaccuracies in the value of (mixture) vapour pressures, and the possibility that the model algorithms are not completely correct (Houbraken et al. 2016). Ellis et al. (2017) proposed that improvement to the PEARL model should include descriptions of formulation attributes and leaf wetness during application. For instance, the volatilisation of up to 90% of pure fenpropimorph and lindane in 48 h was subjected to reductions of up to 80% through addition of adjuvants (Houbraken et al., 2015). Besides, the fraction of pesticide available for volatilisation is still not well quantified due to the difficulties to describe the competing processes occurring at the leaf surface including photo-degradation and rain wash-off (Lichiheb et al., 2016), and foliar absorption that is known to be enhanced by high humidity (Farha et al., 2016).

For the bare soil surface during the periods of autumn, the dimensionless Henry's law constant is the indicator for pesticide volatilisation with largest simulated volatilisation of applied doses for pendimethalin and least for pirimicarb (6.7-11.6% and 0.04-0.1% of applied doses, respectively; Figure A4-3b). Meanwhile, inaccuracy in the values of Henry's law constant remains a major issue, particularly for low-volatility chemicals due to difficulties in its determination (Chao et al., 2017). What is more, the Henry's law constant alone may not explain the under- and over-estimated airborne concentrations for pirimicarb in 2010 and fenpropimorph in 2009 with factors of difference of 0.1 and 126, respectively (Table A4-4). This indicates that other influential factors have not been factored into the simulation of pesticide volatilisation from the soil surface.

Numerous studies proposed soil moisture content as an important factor for the volatilisation of pesticides from bare soil, whereby a moist surface can increase the volatilisation (Gish et al., 2009; Reichman et al., 2013; Karlsson and Arvidsson, 2015). Therefore, the observed concentrations in 2009 would be expected to be generally smaller than those for 2010 owing to smaller soil moisture content in 2009 (17-18% and 27% of the mass of the dry soil for 2009 and 2010, respectively; Karlsson and Arvidsson, 2015). Furthermore, it was less humid in 2009 with an overall average humidity of around 70% compared to both 2008 and 2010 with overall averages around 87% (Karlsson and Arvidsson, 2015). Schneider et al. (2013) in their study on the effect of humidity on volatilisation from bare soil proposed that an increase in the relative humidity in the adjacent air from 60 to 85% resulted in up to 8 times greater volatilisation of the pesticides triallate and trifluralin.

The simplicity of the present model in simulating atmospheric transport of airborne pesticides does not take into account the dissipation of pesticides after entering into the atmosphere. Nevertheless, the residence time of airborne pesticides in the atmosphere can be affected by physical processes and/or chemical reactions including dry and wet deposition, photolysis, and oxidation (Villiot et al., 2018). For instance, the over-estimated simulation for fenpropimorph does not factor in its rapid degradation process in air with a half-life of 1h (Hassink et al., 2007); that may in turn be influenced by the relative humidity (Mattei et al., 2018). Moreover, Zivan et al. (2017) proposed that increased concentration of airborne spiroxamine from levels of tens of ng m^{-3} after six hours of application up to several hundred ng m^{-3} during night-time is likely attributable to the increased atmospheric stability. However, such effects of atmospheric stability are not reflected in the present simulation due to a lack of data on cloudiness to assign a relevant atmospheric stability class for the night time.

Much work is expended to improve the existing regulatory models to simulate accurately scenarios for human exposure to pesticides. All models have common limitations owing to data availability and the worst-case assumptions that are probably over-conservative for some pesticides (Ellis et al., 2017). Despite the inherent limitations, one major advantage of the present model is that it is possible to select any distance downwind from treated fields, rather than having a worst-case distance for volatilisation conditions at 10 m (van den Berg et al., 2016). More field measurements are needed to permit a better understanding of the volatilisation process, pesticide fate, and atmospheric dispersion for a range of active substances at different proximities. Improvement to the model can be made by incorporating more relevant processes and factors into the simulation.

Conclusion

Overall, the initial evaluation indicates the developed model for pesticide volatilisation and aerial dispersion is a promising starting point to measure the residential exposure to pesticide vapours at different proximities. Nevertheless, improvement to the model is necessary when additional data, enhanced scientific knowledge, and advanced model algorithms become available to quantify the amount of pesticide available for volatilisation after an application, and to describe the fate and atmospheric transportation of airborne pesticides after entering into the atmosphere.

Reference List

Abdul-Wahab, S. A. (2004). Evaluation of the industrial source complex short-term model: Dispersion over terrain. *Journal of the Air & Waste Management Association,* 54(4), 396-408.

Andersen, H. R., Vinggaard, A. M., Rasmussen, T. H., Gjermandsen, I. M. and Bonefeld-Jorgensen, E. C. (2002). Effects of currently used pesticides in assays for estrogenicity, androgenicity, and aromatase activity in vitro. *Toxicology and Applied Pharmacology,* 179(1), 1-12.

ATSDR (2005). Agency for Toxic Substances & Disease Registry. *Public Health Assessment Guidance Manual.* [Online]. Available at: file:///Users/Wong/Documents/1st%20paper%20-%20resident/trash/R/Exposure/ATSDR%20-%20Calculating%20Exposure%20Doses.webarchive [Assessed 20 April 2018].

Aprea, M. C. (2012). Environmental and biological monitoring in the estimation of absorbed doses of pesticides. *Toxicology Letters,* 210(2), 110-118.

Aprea, M. C., Bosi, A., Manara, M., Mazzocchi, B., Pompini, A., Sormani, F., Lunghini, L. and Sciarra, G. (2016). Assessment of exposure to pesticides during mixing/loading and spraying of tomatoes in the open field. *Journal of Occupational and Environmental Hygiene,* 13(6), 476-489.

Atabila, A., Phung, D. T., Hogarh, J. N., Osei-Fosu, P., Sadler, R., Connell, D. and Chu, C. (2017). Dermal exposure of applicators to chlorpyrifos on rice farms in Ghana. *Chemosphere,* 178, 350-358.

Balderacchi, M. and Trevisan, M. (2010). Comments on pesticide risk assessment by the revision of Directive EU 91/414. *Environmental Science and Pollution Research,* 17(3), 523-528.

Bang, D. Y., Kyung, M., Kim, M. J., Jung, B. Y., Cho, M. C., Choi, S. M., Kim, Y. W., Lim, S. K., Lim, D. S., Won, A. J., Kwack, S. J., Lee, Y., Kim, H. S. and Lee, B. M. (2012).

Human Risk Assessment of Endocrine-Disrupting Chemicals Derived from Plastic Food Containers. *Comprehensive Reviews in Food Science and Food Safety,* 11(5)**,** 453-470.

Barnett, E. A., Charlton, A. J. and Fletcher, M. R. (2007). Incidents of bee poisoning with pesticides in the United Kingdom, 1994-2003. *Pest Management Science,* 63(11)**,** 1051-1057.

Bedos, C., Cellier, P., Calvet, R., Barriuso, E. and Gabrielle, B. (2002). Mass transfer of pesticides into the atmosphere by volatilization from soils and plants: overview. *Agronomie,* 22(1)**,** 21-33.

Beronius, A. and Agerstrand, M. (2017). Making the most of expert judgement in hazard and risk assessment of chemicals. *Toxicology Research,* 6, 571.

BPDB (2017). *The Bio-Pesticide Database developed by the Agriculture & Environment Research Unit (AERY)*. University of Hertfordshire. [Online]. Available at: http://sitem.herts.ac.uk/aeru/bpdb/atoz.htm [Accessed 15 February 2017].

Briand, O., Bertrand, F., Seux, R. and Millet, M. (2002). Comparison of different sampling techniques for the evaluation of pesticide spray drift in apple orchards. *Science of the Total Environment,* 288(3)**,** 199-213.

Brouwer, M., Schinasi, L., Freeman, L. E. B., Baldi, I., Lebailly, P., Ferro, G., Nordby, K. C., Schuz, J., Leon, M. E. and Kromhout, H. (2016). Assessment of occupational exposure to pesticides in a pooled analysis of agricultural cohorts within the AGRICOH consortium. *Occupational and Environmental Medicine,* 73(6)**,** 359-367.

Bullock, W. H. and Ignacio, J. S. (2006). *A strategy for assessing and managing occupational exposures.* 3rd edn. Fairfax: AIHA Press.

Carlsen, S. C. K., Spliid, N. H. and Svensmark, B. (2006). Drift of 10 herbicides after tractor spray application. 1. Secondary drift (evaporation). *Chemosphere,* 64(5)**,** 787-794.

Carvalho, F. P. (2017). Pesticides, environment, and food safety. *Food and Energy Security,* 6(2)**,** 48-60.

Castilla, E. E., Lopez-Camelo, J. S., Carnpana, H. and Rittler, M. (2001). Epidemiological methods to assess the correlation between industrial contaminants and rates of congenital anomalies. *Mutation Research-Reviews in Mutation Research,* 489(2-3)**,** 123-145.

Castro, M. J. L., Ojeda, C. and Cirelli, A. F. (2014). Advances in surfactants for agrochemicals. *Environmental Chemistry Letters,* 12(1)**,** 85-95.

Cetin, B., Ozer, S., Sofuoglu, A. and Odabasi, M. (2006). Determination of Henry's law constants of organochlorine pesticides in deionized and saline water as a function of temperature. *Atmospheric Environment,* 40(24)**,** 4538-4546.

Chao, H. P., Lee, J. F. and Chiou, C. T. (2017). Determination of the Henry's law constants of low-volatility compounds via the measured air-phase transfer coefficients. *Water Research,* 120**,** 238-244.

Choi, H., Moon, J. K. and Kim, J. H. (2013). Assessment of the Exposure of Workers to the Insecticide Imidacloprid during Application on Various Field Crops by a Hand-Held Power Sprayer. *Journal of Agricultural and Food Chemistry,* 61(45)**,** 10642-10648.

Christiansen, S., Kortenkamp, A., Axelstad, M., Boberg, J., Scholze, M., Jacobsen, P. R., Faust, M., Lichtensteiger, W., Schlumpf, M., Burdorf, A. and Hass, U. (2012). Mixtures of endocrine disrupting contaminants modelled on human high end exposures: an exploratory study in rats. *International Journal of Andrology,* 35(3)**,** 303-316.

Colosio, C., Rubino, F. M., Alegakis. A., Ariano, E., Brambilla, G., Mandic-Rajcevic, S., Metruccio, F., Minoia, C., Moretto, A., Somaruga, C., Tsatsakis, A., Turci, R. and Vellere, F. (2012). Integration of biological monitoring, environmental monitoring and computational modelling into the interpretation of pesticide exposure data: Introduction to a proposed approach. *Toxicology Letters,* 213(1)**,** 49-56.

Cornelis, C., Schoeters, G., Kellen, E., Buntinx, F. and 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.

Coscolla, C., Colin, P., Yahyaoui, A., Petrique, O., Yusa, V., Mellouki, A. and Pastor, A. (2010). Occurrence of currently used pesticides in ambient air of Centre Region (France). *Atmospheric Environment,* 44(32)**,** 3915-3925.

Coscolla, C., Lopez, A., Yahyaoui, A., Colin, P., Robin, C., Poinsignon, Q. and Yusa, V. (2017). Human exposure and risk assessment to airborne pesticides in a rural French community. *Science of the Total Environment,* 584**,** 856-868.

Costa, C., Garcia-Leston, J., Costa, S., Coelho, P., Silva, S., Pingarilho, M., Valdiglesias, V., Mattei, F., Dall'Armi, V., Bonassi, S., Laffon, B., Snawder, J. and Teixeira, J. P. (2014). Is organic farming safer to farmers' health? A comparison between organic and traditional farming. *Toxicology Letters,* 230(2)**,** 166-176.

Cremonese, C., Piccoli, C., Pasqualotto, F., Clapauch, R., Koifman, R. J., Koifman, S. and Freire, C. (2017). Occupational exposure to pesticides, reproductive hormone levels and sperm quality in young Brazilian men. *Reproductive Toxicology,* 67**,** 174-185.

Cross, P. (2013). Pesticide hazard trends in orchard fruit production in Great Britain from 1992 to 2008: a time-series analysis. *Pest Management Science,* 69(6)**,** 768-774.

Cross, P. and Edwards-Jones, G. (2006). Variation in pesticide hazard from arable crop production in Great Britain from 1992 to 2002: Pesticide risk indices and policy analysis. *Crop Protection,* 25(10)**,** 1101-1108.

CTGB (2016). Board for the authorisation of plant protection products and biocides: Evaluation for the authorisation of plant protection products and biocides according to Regulation (EC) No 1107/2009. *Chapter 4 Human toxicology; mammalian toxicity dosser version 2.1*. [Online]. Available at: http://ctgb.nl/docs/default-source/gewas.-toetsingskader/evaluation-manual-v2.1/eu-part-v2.1/g-4-human-toxicology-dossier-eu-eu-2-1-alg.pdf?sfvrsn=2 [Accessed 12 April 2017].

Cunha, J. P., Chueca, P., Garcera, C. and Molto, E. (2012). Risk assessment of pesticide spray drift from citrus applications with air-blast sprayers in Spain. *Crop Protection,* 42**,** 116-123.

Damalas, C. A. and Abdollahzadeh, G. (2016). Farmers' use of personal protective equipment during handling of plant protection products: Determinants of implementation. *Science of the Total Environment,* 571**,** 730-736.

Damalas, C. A. and Koutroubas, S. D. (2016). Farmers' Exposure to Pesticides: Toxicity Types and Ways of Prevention. *Toxics,* 4(1)**,** 10.

Darbre, P. D. (2017). Endocrine disruptors and obesity. *Current Obesity Reports,* 6**,** 18-27.

Defarge, N., Takacs, E., Lozano, V. L., Mesnage, R., de Vendomois, J. S., Seralini, G. E. and Szekacs, A. (2016). Co-Formulants in Glyphosate-Based Herbicides Disrupt Aromatase Activity in Human Cells below Toxic Levels. *International Journal of Environmental Research and Public Health,* 13(3)**,** 17.

Den Hond, E., Tournaye, H., De Sutter, P., Ombelet, W., Baeyens, W., Covaci, A., Cox, B., Nawrot, T. S., Van Larebeke, N., D'Hooghe, T. (2015). Human exposure to endocrine disrupting chemicals and fertility: a case-control study in male subfertility patients. *Environmental International,* 84**,** 154-160.

Derwent, D., Fraser, A., Abbott, J., Jenkin, M., Willis, P. and Murrells, T. (2010). *Evaluating the performance of air quality models.* [Online]. Available at: https://uk-air.defra.gov.uk/assets/documents/reports/cat05/1006241607_100608_MIP_Final_Version.pdf [Assessed 13 March 2018].

ECHA (2009). *CLH report: proposal for harmonised classification and labelling – bifenthrin.* [Online]. Available at: https://echa.europa.eu/documents/10162/81b13962-33ca-4a28-81fa-69c3c0e11a0f [Assessed 6 October 2017].

ECHA (2011). *CLH report: proposal for harmonised classification and labelling – triadimenol.* [Online]. Available at: https://echa.europa.eu/documents/10162/13626/clh_triadimenol_en.pdf [Accessed 6 October 2017].

ECHA (2013). *CLH report: proposal for harmonised classification and labelling – tetracopper hexahydroxide sulphate (1) tetracopper hexahydroxide sulphate hydrate (2).* [Online]. Available at: https://echa.europa.eu/documents/10162/13626/clh_proposal_tribasic_copper_sulphate_en.pdf [Accessed 6 October 2017].

ECHA (2014). *CLH report: proposal for harmonised classification and labelling – cyproconazole.* Available at: https://echa.europa.eu/documents/10162/13626/clh_rep_ie_cyproconazole_dv003871-27_en.pdf [Accessed 6 October 2017].

ECHA (2016). *CLH report: proposal for harmonised classification and labelling – N-(phosphonomethyl)glycine; Glyphosate (ISO).* [Online]. Available at: https://echa.europa.eu/documents/10162/13626/clh_report_glyphosate_en.pdf [Accessed 6 October 2017].

EFSA (2010). Scientific opinion on preparation of a guidance document on pesticide exposure assessment for workers, operators, bystanders and residents. *EFSA Journal,* 8(2), 1501.

EFSA (2012). Guidance on dermal absorption EFSA panel on plant protection products and their residues (PPR). *EFSA Journal,* 10(4), 2665.

EFSA (2013a). Scientific opinion on the hazard assessment of endocrine disruptors: scientific criteria for identification of endocrine disruptors and appropriateness of existing test methods for assessing effects mediated by these substances on human health and the environment. *EFSA Journal,* 11(3), 3132.

EFSA (2013b). Scientific opinion on the identification of pesticides to be included in cumulative assessment groups on the basis of their toxicological profile. *EFSA Journal*, 11(7), 3293.

EFSA (2014). EFSA guidance on the assessment of exposure for operators, workers, residents and bystanders in risk assessment for plant protection product. *EFSA Journal,* 12(10), 3874.

EFSA (2018). Scientific risk assessment of pesticides in the European Union (EU): EFSA contribution to on-going reflections by the EC. *EFSA supporting publication,* 2018:EN-1367.

Ellis, M. C. B., de Zande, J. C. V., van den Berg, F., Kennedy, M. C., O'Sullivan, C. M., Jacobs, C. M., Fragkoulis, G., Spanoghe, P., Gerritsen-Ebben, R., Frewer, L. J. and 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.

Ellis, M. C. B., Underwood, B., Peirce, M. J., Walker, C. T. and Miller, P. C. H. (2010). Modelling the dispersion of volatilised pesticides in air after application for the assessment of resident and bystander exposure. *Biosystems Engineering,* 107(2)**,** 149-154.

Ellis, M. C. B., van den Berg, E., Kennedy, M., van de Zande, J., Fragkoulis, G., O'Sullivan, C., Jacobs, C. and Trevisan, M. (2013). *BROWSE: Deliverable 3.4. Work Package 3: models of exposure to agricultural pesticides for bystanders and residents.* Supported by the European Union 7th Framework Programme and coordinated by Fera. [Online]. Available at: https://secure.fera.defra.gov.uk/browse/index.cfm [Accessed 15 November 2016].

Ellis, M. C. B., van den Berg, F. R., Kennedy, M. et al. (2013). *Work Package 3: Appendix 5 - BROWSE_PEARL-OPS Parameterisation for the BROWSE Exposure Scenarios for Residents and Bystanders.* [Online]. Available at: https://secure.fera.defra.gov.uk/browse/software/ [Accessed 28 May 2017].

EPRS (2016). *Precision agriculture and the future of farming in Europe*. Scientific Foresight Unit, European Parliament. [Online]. Available at: http://www.europarl.europa.eu/RegData/etudes/STUD/2016/581892/EPRS_STU(2016)581892_EN.pdf [Assessed 12 April 2017].

Essa, K. S. M., Embaby, M. M., Kozae, A. M., Mubarak, F. and Kamel, I. (2006). *Estimation of seasonal atmospheric stability and mixing height by using different schemes.* VIII Radiation Physics & Protection Conference, 13-15 Novemer 2006. Egypt: Beni Sueif – Fayoum.

EU Commission (2009). *EU action on pesticides: "our food has become greener"* [factsheet]. In: Directorate-general for health and consumers (Hrsg.). European Commission, Brussels. [Online]. Available at: http://www.bezpecnostpotravin.cz/UserFiles/File/Kvasnickova/factsheet_pesticides_web.pdf [Accessed 2 February 2017].

EU Pesticide Database (2016). *European Commission - Plants.* [Online]. Available at: http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=activesubstance.selection&language=EN [Accessed 12 April 2017].

European Commission (2006). *Draft: guidance for the setting and application of acceptable operator exposure levels (AOELs).* Commission Working Document SANCO 7531 rev.10.

Eurostat (2008). *A common methodology for the collection of pesticide usage statistics within agriculture and horticulture 2008 edition*. Luxembourg: Office for Official Publications of the European Communities.

Ewence, A., Brescia, S., Johnson, I. and Rumsby, P. C. (2015). An approach to the identification and regulation of endocrine disrupting pesticides. *Food and Chemical Toxicology,* 78**,** 214-220.

Ewence, A., Rumsby, P. and Johnson, I. (2013). *Extended impact assessment study of the human health and environmental criteria for endocrine disrupting substances proposed by HSE*, CRD, Defra9088.02. Swindon: WRc plc.

Farha, W., Abd El-Aty, A. M., Rahman, M. M., Shin, H. C. and Shim, J. H. (2016). An overview on common aspects influencing the dissipation pattern of pesticides: a review. *Environmental Monitoring and Assessment,* 188(12)**,** 21.

Feigenbrugel, V., Le Calve, S. and Mirabel, P. (2004). Temperature dependence of Henry's law constants of metolachlor and diazinon. *Chemosphere,* 57(4)**,** 319-327.

Felsot, A. S., Unsworth, J. B., Linders. J. B. H. J., Roberts, G., Rautman, D., Harris, C. and Carazo, E. (2010). Agrochemical spray drift: assessment and mitigation – a review. *Journal of Environmental Science and Health Part B,* 46, 1-23.

Ferrari, F., Klein, M., Capri, E. and Trevisan, M. (2005). Prediction of pesticide volatilization with PELMO 3.31. *Chemosphere,* 60(5)**,** 705-713.

FOCUS (2000). *FOCUS groundwater scenarios in the EU review of active substances*. The report of the work of the Groundwater Scenarios Workgroup of FOCUS (FOrum for the coordination of pesticide fate models and their Use). Version 1. EC Document Reference SANCO/321/2000-rev.2, pp. 202.

FOCUS (2008). *Pesticides in air: considerations for exposure assessment.* Report of the FOCUS Working Group on Pesticides in Air (FOCUS Air Group), EC Document Reference SANCO/10553/2006-rev.2, pp. 7.

Fuhrman, V. F., Tal, A. and Arnon, S. (2015). Why endocrine disrupting chemicals (EDCs) challenge traditional risk assessment and how to respond. *Journal of Hazardous Materials,* 286**,** 589-611.

Galea, K. S., MacCalman, L., Jones, K., Cocker, J., Teedon, P., Cherrie, J. W. and van Tongeren, M. (2015). Comparison of residents' pesticide exposure with predictions obtained using the UK regulatory exposure assessment approach. *Regulatory Toxicology and Pharmacology,* 73(2)**,** 634-643.

Gao, B. B., Tao, C. J., Ye, J. M., Ning, J., Mei, X. D., Jiang, Z. F., Chen, S. and She, D. M. (2014). Measurement of operator exposure to chlorpyrifos. *Pest Management Science,* 70(4)**,** 636-641.

Garthwaite, D. G., Hudson, S., Barker, I., Parrish, G., Smith, L. and Pietravalle, S. (2012). *Pesticide Usage Survey Report 252: orchards in the United Kingdom 2012*. [Online]. Available at: https://secure.fera.defra.gov.uk/pusstats/surveys/documents/orchards2012V2.pdf [Accessed 15 November 2016].

Garthwaite, D., Sinclair, C., Glass, R., Pote, A., Trevisan, M., Sacchettini, G., Spanoghe, P., Ngoc, K. D., Fevery, D., Machera, K. et al. (2015). *External scientific report: collection of pesticide application data in view of performing Environmental Risk Assessments for pesticides. EFSA supporting publication*, 2015:EN-846.

Gemmill, A., Gunier, R. B., Bradman, A., Eskenazi, B. and Harley, K. G. (2013). Residential Proximity to Methyl Bromide Use and Birth Outcomes in an Agricultural Population in California. *Environmental Health Perspectives,*121(6)**,** 737-743.

Gish, T. J., Prueger, J. H., Kustas, W. P., Daughtry, C. S. T., McKee, L. G., Russ, A. and Hatfield, J. L. (2009). Soil Moisture and Metolachlor Volatilization Observations over Three Years. *Journal of Environmental Quality,* 38(5)**,** 1785-1795.

Gonzalez-Alzaga, B., Hernandez, A. F., Rodriguez-Barranco, M., Gomez, I., Aguilar-Garduno, C., Lopez-Flores, I., Parron, T. and Lacasana, M. (2015). Pre- and postnatal exposures to pesticides and neurodevelopmental effects in children living in agricultural communities from South-Eastern Spain. *Environment International,* 85**,** 229-237.

Green, J. M. and Beestman, G. B. (2007). Recently patented and commercialized formulation and adjuvant technology. *Crop Protection,* 26(3)**,** 320-327.

Groβkopf, C., Martin, S., Mielke, H. Westphal, D., Hamey, P., Bouneb, F., Rautmann, D., Erdtmann-Vourliotis, M., IVA Expert Committee for Operator Safety, ECPA Occupational and Bystander Exposure Expert Group, Tiramani, M., Gerritsen, R. and Spaan, S. (2013a). *Joint development of a new agricultural operator exposure model.* [Online]. Available at: http://www.bfr.bund.de/cm/350/joint-development-of-a-new-agricultural-operator-exposure-model.pdf [Accessed 12 April 2017].

Groβkopf, C., Mielke, H., Westphal, D., Erdtmann-Vourliotis, M., Hamey, P., Bouneb, F., Rautmann, D., Stauber, F., Wicke, H., Maasfeld, W., Salazar, J. D., Chester, G. and Martin, S. (2013b). A new model for the prediction of agricultural operator exposure during professional application of plant protection products in outdoor crops. *Journal Fur Verbraucherschutz Und Lebensmittelsicherheit-Journal of Consumer Protection and Food Safety,* 8(3)**,** 143-153.

Hass, U., Boberg, J., Christiansen, S., Jacobsen, P. R., Vinggaard, A. M., Taxvig, C., Poulsen, M. E., Herrmann, S. S., Jensen, B. H., Petersen, A., Clemmensen, L. H. and Axelstad, M. (2012). Adverse effects on sexual development in rat offspring after low dose exposure to a mixture of endocrine disrupting pesticides. *Reproductive Toxicology,* 34(2)**,** 261-274.

Hassink, J., Platz, K., Stadler, R., Zangmeister, W., Fent, G., Mondel, M. and Kubiak, R. (2007). Comparison of wind tunnel and field experiments to measure potential deposition of fenpropimorph following volatilisation from treated crops. *Pest Management Science,* 63(2)**,** 171-179.

Hernandez, A. F. and Tsatsakis, A. M. (2017). Human exposure to chemical mixtures: Challenges for the integration of toxicology with epidemiology data in risk assessment. *Food and Chemical Toxicology,* 103**,** 188-193.

Herzfeld, D. (2017). *Private pesticide applicator safety education manual.* 19th edn. [Online]. University of Minnesota Extension. Available at: https://www.extension.umn.edu/agriculture/pesticide-safety/ppat_manual/Chapter%206.pdf [Accessed 20 April 2018].

Hofman, V. and Solseng, E. (2001). *Reducing spray drift.* North Dakota State University Extension Service. Publication AE-1210., North Dakota State University. [Online]. Available at: https://www.ag.ndsu.edu/publications/crops/reducingspray-drift/ae1210.pdf [Accessed 15 November 2016].

Hossain, F., Ali, O., D'Souza, U. J. A. and Naing, D. K. S. (2010). Effects of Pesticide Use on Semen Quality among Farmers in Rural Areas of Sabah, Malaysia. *Journal of Occupational Health,* 52(6)**,** 353-360.

Houbraken, M., van den Berg, F., Ellis, C. M. B., Dekeyser, D., Nuyttens, D., De Schampheleire, M. and Spanoghe, P. (2016). Volatilisation of pesticides under field conditions: inverse modelling and pesticide fate models. *Pest Management Science,* 72(7)**,** 1309-1321.

Hu, J. X., Li, Y. F., Li, J., Pan, C., He, Z., Dong, H. Y. and Xu, L. C. (2011). Toxic effects of cypermethrin on the male reproductive systems: with emphasis on the androgen receptor. *Journal of Applied Toxicology,* 33, 576-585.

Hvezdova, M., Kosubova, P., Kosikova, M., Scherr, K. E., Simek, Z., Brodsky, L., Sudoma, M., Skulcova, L., Sanka, M., Svobodova, M. et al. (2018). Currently and recently used pesticides in Central European arable soils. *Science of the Total Environment,* 613**,** 361-370.

HSE (2015). *Pesticide Incidents Report 2012/13*. [Online]. Available at: http://www.hse.gov.uk/agriculture/pdf/pir1213.pdf [Accessed 30 November 2016].

Jensen, P. K. and Spliid, N. H. (2003). *Deposition of pesticides on the soil surface.* Pesticide Research Nr. 65. Denmark: Danish Environmental Protection Agency.

Kabir, E. R., Rahman, M. S., Rahman, I. (2015). A review on endocrine disruptors and their possible impacts on human health. *Environmental Toxicology and Pharmacology,* 40**,** 241-258.

Kalliora, C., Mamoulakis, C., Vasilopoulos, E., Stamatiades, G. A., Kalafati, L., Barouni, R., Karakousi, T., Abdollahi, M. and Tsatsakis, A. (2018). Association of pesticide exposure with human congenital abnormalities. *Toxicology and Applied Pharmacology,* 346**,** 58-75.

Karabelas, A. J., Plakas, K. V., Solomou, E. S., Drossou, V. and Sarigiannis, D. A. (2009). Impact of European legislation on marketed pesticides - A view from the standpoint of health impact assessment studies. *Environment International,* 35(7)**,** 1096-1107.

Karlsson, S. and Arvidsson, T. (2015). *Volatilisation and dry deposition of pesticides under Scandinavian climatic conditions – a three-year field study at Lovsta (central Sweden).* SLU, Vatten och miljo: Rapport 2015:3. Uppsala: Swedish University of Agricultural Sciences.

Kegley, S. and Conlisk, E. (2010). *Pesticide risk mitigation engine. Inhalation risk index – white paper.* [Online]. Available at: https://pesticiderisk.org/materials/PRiME_Inhalation_Index_white_paper_092910.pdf [Accessed 28 May 2017].

Kienzler, A., Bopp, S. K., van der Linden, S., Berggren, E. and Worth, A. (2016). Regulatory assessment of chemical mixtures: Requirements, current approaches and future perspectives. *Regulatory Toxicology and Pharmacology,* 80**,** 321-334.

Kortenkamp, A., Faust, M., Scholze, M. and Backhaus, T. (2007). Low-Level Exposure to Multiple Chemicals: Reason for Human Health Concerns? *Environmental Health Perspectives,* 115**,** 106-114.

Kosikowska, M. and Biziuk, M. (2010). Review of the determination of pesticide residues in ambient air. *Trac-Trends in Analytical Chemistry,* 29(9)**,** 1064-1072.

Lammoglia, S. K., Kennedy, M. C., Barriuso, E., Alletto, L., Justes, E., Munier-Jolain, N. and Mamy, L. (2017). Assessing human health risks from pesticide use in conventional and innovative cropping systems with the BROWSE model. *Environment International,* 105**,** 66-78.

Leistra, M., van der Linden, A. M. A., Boesten, J. J. T. I., Tiktak, A. and van der Berg, F. (2001). *PEARL model for pesticide behaviour and emissions in soil-plant system;*

Description of the processes in FOCUS PEARL v 1.1.1. RIVM report 711401009/Alterra-rapport 013. Wageningen: Alterra.

Leistra, M. and Wolters, A. (2004). Computations on the volatilisation of the fungicide fenpropimorph from plants in a wind tunnel. *Water Air and Soil Pollution,* 157(1-4)**,** 133-148.

Leistra, M., Wolters, A. and van den Berg, F. (2008). Volatilisation and competing processes computed for a pesticide applied to plants in a wind tunnel system. *Pest Management Science,* 64(6)**,** 669-675.

Lewis, K. A., Tzilivakis, J., Warner, D. J. and Green, A. (2016). An international database for pesticide risk assessments and management. *Human and Ecological Risk Assessment,* 22(4)**,** 1050-1064.

Li, H. Z., Ma, H. Z., Lydy, M. J. and You, J. (2014). Occurrence, seasonal variation and inhalation exposure of atmospheric organophosphate and pyrethroid pesticides in an urban community in South China. *Chemosphere,* 95**,** 363-369.

Lichiheb, N., Personne, E., Bedos, C. and Barriuso, E. (2014). Adaptation of a resistive model to pesticide volatilization from plants at the field scale: Comparison with a dataset. *Atmospheric Environment,* 83**,** 260-268.

Lichiheb, N., Personne, E., Bedos, C., Van den Berg, F. and Barriuso, E. (2016). Implementation of the effects of physicochemical properties on the foliar penetration of pesticides and its potential for estimating pesticide volatilization from plants. *Science of the Total Environment,* 550**,** 1022-1031.

Lichtenberg, B., Mischke, U., Scherf, S., Rover, M. and Martin, S. (2015). Hazard and risk based allocation of safety instructions to operators handling pesticides. *Journal Fur Verbraucherschutz Und Lebensmittelsicherheit-Journal of Consumer Protection and Food Safety,* 10(4)**,** 373-384.

Liu, P., Song, X. X., Yuan, W. H., Wen, W. H., Wu, X. N., Li, J. and Chen, X. M. (2006). Effects of cypermethrin and methyl parathion mixtures on hormone levels and immune functions in Wistar rats. *Archives of Toxicology,*80(7)**,** 449-457.

Lundehn, J. R., Westphal, D., Kieczka, H., Krebs, B. et al. (1992). *Uniform principles for safeguarding the health of applicators of plant protection products.* Mitteilungen aus der Biologischen Bundesanstalt fur Land und Forstwirtschaft, Heft 277, Berlin, Germany, p. 277.

Lv, X., Pan, L. M., Wang, J. Y., Lu, L. P., Yan, W. L., Zhu, Y. Y., Xu, Y. W., Guo, M. and Zhuang, S. L. (2017). Effects of triazole fungicides on androgenic disruption and CYP3A4 enzyme activity. *Environmental Pollution,*222**,** 504-512.

MacFarlane, E., Carey, R., Keegel, T., El-Zaemay, S. and Fritschi, L. (2013). Dermal exposure associated with occupational end use of pesticides and the role of protective measures. *Safety and Health at Work,* 4(3), 136-141.

Mandic-Rajcevic, S., Rubino, F. M., Vianello, G., Fugnoli, L., Polledri, E., Mercadante, R., Moretto, A., Fustinoni, S. and Colosio, C. (2015). Dermal exposure and risk assessment of tebuconazole applicators in vineyards. *Medicina Del Lavoro,* 106(4)**,** 294-315.

Manibusan, M. K. and Touart, L. W. (2017). A comprehensive review of regulatory test methods for endocrine adverse health effects. *Critical Reviews in Toxicology,* 47(6)**,** 433-481.

Marrs, T. C. and Ballantyne, B. (2004). *Pesticide toxicology and international regulation.* West Sussex: John Wiley & Sons Ltd.

Martin, S., Westphal, D., Erdtmann-Vourliotis, M., Dechet, F., Schulze-Rosario, C., Stauber, F., Wicke, H. and Chester, G. (2008). Guidance for exposure and risk evaluation for bystanders and residents exposed to plant protection products during and after application. *Journal Fur Verbraucherschutz Und Lebensmittelsicherheit-Journal of Consumer Protection and Food Safety,* 3(3)**,** 272-281.

Marx-Stoelting, P., Niemann, L., Ritz, V., Ulbrich, B., Gall, A., Hirsch-Ernst, K. I., Pfeil, R. and Solecki, R. (2014). Assessment of three approaches for regulatory decision making on pesticides with endocrine disrupting properties. *Regulatory Toxicology and Pharmacology,* 70(3)**,** 590-604.

Marx-Stoelting, P., Pfeil, R. and Ritz, V. (2016). Science-based decision matrix for the identification of endocrine disruptors for regulatory purposes. *Journal Fur Verbraucherschutz Und Lebensmittelsicherheit-Journal of Consumer Protection and Food Safety,* 11(2)**,** 203-208.

Matthews, G. (2002). *Operator exposure to pesticides*. Pesticide Outlook 2002. [Online]. Available at: https://doi:10.1039/b211168n [Assessed 12 April 2017].

Mehrpour, O., Karrari, P., Zamani, N., Tsatsakis, A. M. and Abdollahi, M. (2014). Occupational exposure to pesticides and consequences on male semen and fertility: A review. *Toxicology Letters,* 230(2)**,** 146-156.

Melching-Kollmuss, S., Fussell, K. C., Schneider, S., Buesen, R., Groeters, S., Strauss, V. and van Ravenzwaay, B. (2017). Comparing effect levels of regulatory studies with endpoints derived in targeted anti-androgenic studies: example prochloraz. *Archives of Toxicology,* 91(1)**,** 143-162.

Mesnage, R., Phedonos, A., Biserni, M., Arno, M., Balu, S., Corton, J. C., Ugarte, R. and Antoniou, M. N. (2017). Evaluation of estrogen receptor alpha activation by glyphosate-based herbicide constituents. *Food and Chemical Toxicology,* 108**,** 30-42.

Met Office (2015). *UK climate: UK and regional series - rank ordered statistics.* [Online]. Available at: http://www.metoffice.gov.uk/climate/uk/summaries/datasets [Accessed 1 February 2017].

Moon, J. K., Park, S., Kim, E., Lee, H. and Kim, J. H. (2013). Risk Assessment of the Exposure of Insecticide Operators to Fenvalerate during Treatment in Apple Orchards. *Journal of Agricultural and Food Chemistry,* 61(2)**,** 307-311.

Mostafalou, S. and Abdollahi, M. (2013). Pesticides and human chronic diseases: Evidences, mechanisms, and perspectives. *Toxicology and Applied Pharmacology,* 268(2)**,** 157-177.

Mullin, C. A., Fine, J. D., Reynolds, R. D. and Frazier, M. T. (2016). Toxicological risks of agrochemical spray adjuvants: organosilicone surfactants may not be safe. *Frontiers in Public Health*, 4, 92.

Mulqueen, P. (2003). Recent advances in agrochemical formulation. *Advances in Colloid and Interface Science,*106**,** 83-107.

NASDA (2013). National Association of the State Departments of Agriculture Research Foundation. *Personal protective equipment for agricultural pesticide operators: policies, process, and standards/certifications required in the United States, European Union, and Brazil.* [Online]. Available at: https://s3.amazonaws.com/nasda2/media/Pages/PPEpoliciesMay2013.pdf?mtime=20171025135645 [Accessed 12 February 2017].

OECD (1997). *Guidance document for the conduct of studies of occupational exposure to pesticides during agricultural application*. Series on testing and assessment no. 9, Environment Directorate, OCDE/GD(97)148. Paris: Organisation for Economic Co-operation and Development.

OECD (2012). *Guidance document on standardised test guidelines for evaluating chemicals for endocrine disruption.* Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology. ENV/JM/MONO(2012)22. [Online]. Available at: http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono%282012%2922&doclanguage=en [Assessed 15 March 2018].

Olesen, M. H. and Jensen, P. K. (2013). External scientific report: collection and evaluation of relevant information on crop interception. *EFSA supporting publication*, 2013:EN-438.

Ogg, C. L., Hygnstrom, J. R., Bauer, E. C. and Hansen, P. J. (2012). *Managing the risk of pesticide poisoning and understanding the signs and symptoms.* Institute of Agriculture and Natural Resources, University of Nebraska-Lincoln Extension.

Panizzi, S., Suciu, N. A. and Trevisan, M. (2017). Combined ecotoxicological risk assessment in the frame of European authorization of pesticides. *Science of the Total Environment,* 580**,** 136-146.

PPDB (2017). *The Pesticide Properties Database (PPDB) developed by the Agriculture & Environment Research Unit (AERY), University of Hertfordshire*. Funded by UK national sources and the EU-funded Footprint Project (FP6-SSP-022704). [Online]. Available at: http://sitem.herts.ac.uk/aeru/ppdb/en/atoz.htm [Accessed 13 May 2017].

PPDB (2018). *The Pesticide Properties Database (PPDB) developed by the Agriculture & Environment Research Unit (AERY).* University of Hertfordshire. Funded by UK national sources and the EU-funded Footprint Project (FP6-SSP-022704). [Online]. Available at: http://sitem.herts.ac.uk/aeru/ppdb/en/atoz.htm [Accessed 15 March 2018].

Ramaprasad, J., Tsai, M. Y., Fenske, R. A., Faustman, E. M., Griffith, W. C., Felsot, A. S., Elgethun, K., Weppner, S. and Yost, M. G. (2009). Children's inhalation exposure to methamidophos from sprayed potato fields in Washington State: Exploring the use of probabilistic modeling of meteorological data in exposure assessment. *Journal of Exposure Science and Environmental Epidemiology,* 19(6)**,** 613-623.

Randerson, D. (1984). *Atmospheric science and power production.* DOE/TIC-27601 (DE84005177). Technical information center, office of scientific and technical information, United States Department of Energy. [Online]. Available at: https://www.osti.gov/biblio/6503687/ [Assessed 15 November 2016].

Rautmann, D., Sreloke, M. and Winkler, R. (1999). *New basic drift values in the authorisation procedure for plant protection products*. Workshop on risk assessment and risk mitigation measures (WORMM), 27-29 September 1999, Germany, pp. 27-29.

Rieke, S., Heise, T., Schmidt, F., Haider, W., Bednarz, H., Niehaus, K., Mentz, A., Kalinowski, J., Hirsch-Ernst, K. I., Steinberg, P., Niemann, L. and Marx-Stoelting, P. (2017). Mixture effects of azole fungicides on the adrenal gland in a broad dose range. *Toxicology,* 385**,** 28-37.

Rizzati, V., Briand, O., Guillou, H. and Gamet-Payrastre, L. (2016). Effects of pesticide mixtures in human and animal models: An update of the recent literature. *Chemico-Biological Interactions,* 254**,** 231-246.

Rocheleau, C. M., Romitti, P. A. and Dennis, L. K. (2009). Pesticides and hypospadias: A meta-analysis. *Journal of Pediatric Urology,* 5(1)**,** 17-24.

Rudel, H. (1997). Volatilisation of pesticides from soil and plant surfaces. *Chemosphere,* 35(1-2)**,** 143-152.

Rushton, L. and Mann, V. (2008). *Estimating the prevalence and incidence of pesticide-related illness presented to general practitioners in Great Britain.* Research report RR608. [Online]. Available at: http://www.hse.gov.uk/research/rrpdf/rr608.pdf [Assessed 2 February 2017].

Sacchettini, G., Calliera, M., Marchis, A., Glass, R., Ellis, C. B., Machera, K., Gerritsen-Ebben, R., Spanoghe, P. and Capri, E. (2015). New risk indicator approach for Operators, Workers, Bystanders and Residents for a sustainable use of plant protection products. *Environmental Science and Pollution Research,* 22(22)**,** 17586-17595.

Salcedo, R., Vallet, A., Granell, R., Garcera, C., Molto, E. and Chueca, P. (2017). Eulerian-Lagrangian model of the behaviour of droplets produced by an air-assisted sprayer in a citrus orchard. *Biosystems Engineering,* 154**,** 76-91.

Salem, H. and Katz, S. A. (2006). *Inhalation toxicology. Chapter 1 – Inhalation risk assessment at the Environmental Protection Agency*. 2nd edn. Boca Raton: CRC Press.

Sarigiannis, D. A. and Hansen, U. (2012). Considering the cumulative risk of mixtures of chemicals - A challenge for policy makers. *Environmental Health,* 11**,** 12.

Sarigiannis, D. A., Kontoroupis, P., Solomou, E. S., Nikolaki, S. and Karabelas, A. J. (2013). Inventory of pesticide emissions into the air in Europe. *Atmospheric Environment,* 75**,** 6-14.

Shirangi, A., Nieuwenhuijsen, M., Vienneau, D. and Holman, C. D. J. (2011). Living near agricultural pesticide applications and the risk of adverse reproductive outcomes: a review of the literature. *Paediatric and Perinatal Epidemiology,* 25(2)**,** 172-191.

Sidorkiewicz, I., Zareba, K., Wolczynski, S. and Czerniecki, J. (2017). Endocrine-disrupting chemicals-Mechanisms of action on male reproductive system. *Toxicology and Industrial Health,* 33(7)**,** 601-609.

Skevas, T., Lansink, A. and Stefanou, S. E. (2013). Designing the emerging EU pesticide policy: A literature review. *Njas-Wageningen Journal of Life Sciences,* 64-65**,** 95-103.

Slama, R., Bourguignon, J. P., Demeneix, B., Ivell, R., Panzica, G., Kortenkamp, A. and Zoeller, R. T. (2016). Scientific Issues Relevant to Setting Regulatory Criteria to Identify

Endocrine-Disrupting Substances in the European Union. *Environmental Health Perspectives,* 124(10)**,** 1497-1503.

So, J., Ahn, J., Lee, T. H., Park, K. H., Paik, M. K., Jeong, M., Cho, M. H. and Jeong, S. H. (2014). Comparison of international guidelines of dermal absorption tests used in pesticides exposure assessment for operators. *Toxicological Research,* 30(4), 251-260.

Solecki, R., Kortenkamp, A., Bergman, A., Chahoud, I., Degen, G. H., Dietrich, D., Greim, H., Hakansson, H., Hass, U., Husoy, T. et al. (2017). Scientific principles for the identification of endocrine-disrupting chemicals: a consensus statement. *Archives of Toxicology,* 91(2)**,** 1001-1006.

Staudinger, J. and Roberts, P. V. (2001). A critical compilation of Henry's law constant temperature dependence relations for organic compounds in dilute aqueous solutions. *Chemosphere,* 44(4)**,** 561-576.

Stehle, S. and Schulz, R. (2015). Pesticide authorization in the EU-environment unprotected? *Environmental Science and Pollution Research,* 22(24)**,** 19632-19647.

Stein, B., Michalski, B., Martin, S., Pfeil, R., Ritz, V. and Solecki, R. (2014) Human health risk assessment from combined exposure in the framework of plant protection products and biocidal products*. Journal Fur Verbraucherschutz Und Lebensmittelsicherheit-Journal of Consumer Protection and Food Safety*, 9, 367-376.

Schrijver, R. (2016). *Precision agriculture and the future of farming in Europe.* Scientific Foresight Study IP/G/STOA/FWC/2013-1/Lot 7/SC5. Brussels, European Union.

Sutton, P., Perron, J., Giudice, L. C. and Woodruff, T. J. (2011). *Pesticides matter a primer for reproductive health physicians.* Program on Reproductive Health and the Environment, University of California, San Francisco. [Online]. Available at: https://prhe.ucsf.edu/sites/prhe.ucsf.edu/files/pesticidesmatter_whitepaper.pdf [Assessed 2 February 2017].

Teng, M. M., Qi, S. Z., Zhu, W. T., Wang, Y., Wang, D. Z., Dong, K. and Wang, C. J. (2018). Effects of the bioconcentration and parental transfer of environmentally relevant concentrations of difenoconazole on endocrine disruption in zebrafish (Danio rerio). *Environmental Pollution,* 233**,** 208-217.

Testai, E., Galli, C. L., Dekant, W., Marinovich, M., Piersma, A. H. and Sharpe, R. M. (2013). A plea for risk assessment of endocrine disrupting chemicals. *Toxicology,* 314(1)**,** 51-59.

Thomas, M. R. (1999). *Guidelines for the collection of pesticide usage statistics within agriculture and horticulture.* OECD, Eurostat. [Online]. Available at: http://www.oecd.org/chemicalsafety/pesticides-biocides/2078031.pdf [Accessed 2 February 2017].

Thomas, M. R. (2003). Pesticide usage in some vegetable crops in Great Britain: real on-farm applications. *Pest Management Science,* 59(5)**,** 591-596.

Thouvenin, I., Bouneb, F. and Mercier, T. (2016). Operator dermal exposure and individual protection provided by personal protective equipment during application using a backpack sprayer in vineyards. *Journal fur Verbraucherschutz und Lebensmittelsicherheit-Journal of Consumer Protection and Food Safety,* 11(4)**,** 325-336.

Toronto Public Health (2002). *Lawn and garden pesticides: a review of human exposure & health effects research.* Ontario: Health Promotion & Environmental Protection Office.

Tsakirakis, A. N., Kasiotis, K. M., Charistou, A. N., Arapaki, N., Tsatsakis, A., Tsakalof, A. and Machera, K. (2014). Dermal & inhalation exposure of operators during fungicide application in vineyards. Evaluation of coverall performance. *Science of the Total Environment,* 470**,** 282-289.

UK MAFF (1992). Scientific Subcommittee on Pesticides and British Agrochemicals Joint Medical Panel: *Estimation of exposure and absorption of pesticides by spray operators* (UK MAFF) 1986 and the Predictive Operator Exposure Model (POEM-UK MAFF).

US EPA (1992a). US Environmental Agency: *User's guide for the industrial source complex (ISC2) dispersion models. Volume II – description of model algorithms*. EPA-450/4-92-008b. North Carolina: Office of Air Quality Planning and Standards.

US EPA (1992b). US Environmental Agency: *Comparison of a revised area source algorithm for the industrial source complex short term model and wind tunnel data*. EPA-454/R-92-014. North Carolina: Office of Air Quality Planning and Standards.

US EPA (2009). US Environmental Agency: *Metabolically derived human ventilation rates: a revised approach based on oxygen consumption rates.* EPA/600/R-06/129F. Washington: Office of Research and Development.

Van de Zande, J. C., Ellis, M. C. B., Wenneker, M., Walklate, P. J. and Kennedy, M. (2014). Spray drift and bystander risk from fruit crop spraying. In conference "International advances in pesticide application, Oxford, UK, 8-10 January 2014". *Aspects of Applied Biology*, 122, 177-185.

van den Berg, F., Jacobs, C. M. J., Ellis, M. C. B., Spanoghe, P., Ngoc, K. D. and 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.

Van den Berg, F. and Leistra, M. (2004*). Improvement of the model concept for volatilisation of pesticides from soils and plant surfaces in PEARL. Description and user's guide for PEARL 2.1.1-C1.* [Online]. Available at: http://www.pearl.pesticidemodels.eu/pdf/focus_air_pearl.pdf [Assessed 15 November 2016].

Van Maele-Fabry, G., Lantin, A. C., Hoet, P. and Lison, D. (2011). Residential exposure to pesticides and childhood leukaemia: A systematic review and meta-analysis. *Environment International,* 37(1)**,** 280-291.

Vandenberg, L. N., Colborn, T., Hayes, T. B., Heindel, J. J., Jacobs, D. R., Lee, D. H., Shioda, T., Soto, A. M., vom Saal, F. S., Welshons, W. V., Zoeller, R. T. & Myers, J. P. (2012). Hormones and Endocrine-Disrupting Chemicals: Low-Dose Effects and Nonmonotonic Dose Responses. *Endocrine Reviews,* 33(3)**,** 378-455.

Villiot, A., Chretien, E., Drab-Sommesous, E., Riviere, E., Chakir, A. and 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**,** 82-91.

Weselak, M., Arbuckle, T. E. and Foster, W. (2007). Pesticide exposures and developmental outcomes: The epidemiological evidence. *Journal of Toxicology and Environmental Health-Part B-Critical Reviews,* 10(1-2)**,** 41-80.

WHO/IPCS (2002). *Global assessment of the state-of-the-science of endocrine disruptors.* [Online]. Available at: http://www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/ [Accessed 15 January 2018].

Wolterink, G., Ruggeri, L., Printemps, N., van Kesteren, P., Tosti, L., Gouze, M. E., Mahieu, K., Metruccio, F., Charles, S., van de Ven, B. et al. (2013). Toxicological data analysis to support grouping of pesticide active substances for cumulative risk assessment of effects on liver, on the nervous system and on reproduction and development. *EFSA Supporting Publications*, 2013:EN-392. [Online]. Available at: https://efsa.onlinelibrary.wiley.com/doi/abs/10.2903/sp.efsa.2013.EN-392 [Assessed 28 May 2017].

Wolters, A., Linnemann, V., Herbst, M., Klein, M., Schaffer, A. and Vereecken, H. (2003). Pesticide volatilization from soil: Lysimeter measurements versus predictions of European registration models. *Journal of Environmental Quality,* 32(4)**,** 1183-1193.

Wong, H. L., Garthwaite, D. G., Ramwell, C. T. and Brown, C. D. (2018). Assessment of exposure of professional agricultural operators to pesticides. *Science of the Total Environment,* 619**,** 874-882.

Woodruff, T. J., Kyle, A. D. and Bois, F. Y. (1994). EVALUATING HEALTH RISKS FROM OCCUPATIONAL EXPOSURE TO PESTICIDES AND THE REGULATORY RESPONSE. *Environmental Health Perspectives,*102(12)**,** 1088-1096.

Ye, M., Beach, J., Martin, J. W. and Senthilselvan, A. (2013). Occupational Pesticide Exposures and Respiratory Health. *International Journal of Environmental Research and Public Health,* 10(12)**,** 6442-6471.

Yusa, V., Coscolla, C. and Millet, M. (2014). New screening approach for risk assessment of pesticides in ambient air. *Atmospheric Environment,* 96**,** 322-330.

Yusoff, S. N. M., Kamari, A. and Aljafree, N. F. A. (2016). A review of materials used as carrier agents in pesticide formulations. *International Journal of Environmental Science and Technology,* 13(12)**,** 2977-2994.

Zhang, Z. L., Troldborg, M., Yates, K., Osprey, M., Kerr, C., Hallett, P. D., Baggaley, N., Rhind, S. M., Dawson, J. J. C. and Hough, R. L. (2016). Evaluation of spot and passive sampling for monitoring, flux estimation and risk assessment of pesticides within the constraints of a typical regulatory monitoring scheme. *Science of the Total Environment,* 569**,** 1369-1379.

Zhao, M. A., Yu, A. L., Zhu, Y. Z. and Kim, J. H. (2015). Potential Dermal Exposure to Flonicamid and Risk Assessment of Applicators During Treatment in Apple Orchards. *Journal of Occupational and Environmental Hygiene,* 12(8)**,** D147-D152.

Zhao, M. A., Yu, A. L., Zhu, Y. Z., Wu, S. Q. and Kim, J. H. (2016). Human exposure and risk assessment of chromafenozide during treatment in rice fields. *Human and Ecological Risk Assessment,* 22(1)**,** 116-125.

Zivan, O., Segal-Rosenheimer, M. and Dubowski, Y. (2016). Airborne organophosphate pesticides drift in Mediterranean climate: The importance of secondary drift. *Atmospheric Environment,* 127**,** 155-162.