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ORIGINAL ARTICLE

Assessment of residential environmental exposure to pesticides from agricultural fields in the Netherlands

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We developed a spatio-temporal model for the Netherlands to estimate environmental exposure to individual agricultural pesticides at the residential address for application in a national case–control study on Parkinson's disease (PD). Data on agricultural land use and pesticide use were combined to estimate environmental exposure to pesticides for the period 1961 onwards. Distance categories of 0–50 m, >50–100 m, >100–500 m and >500–1000 m around residences were considered. For illustration purposes, exposure was estimated for the control population ($n = 607$) in the PD case–control study. In a small validation effort, model estimates were compared with pesticide measurements in air and precipitation collected at 17 stations in 2000–2001. Estimated exposure prevalence was higher for pesticides used on commonly cultivated (rotating) crops than for pesticides used on fruit and bulbs only. Prevalence increased with increasing distance considered. Moderate-to-high correlations were observed between model estimates (>100–500 m and >500–1000 m) and environmental pesticide concentrations measured in 2000–2001. Environmental exposure to individual pesticides can be estimated using relevant spatial and temporal data sets on agricultural land use and pesticide use. Our approach seems to result in accurate estimates of average environmental exposure, although it remains to be investigated to what extent this reflect personal exposure to agricultural pesticides.

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INTRODUCTION

Pesticides are extensively used in agriculture and a wide range of active ingredients and product formulations have been marketed over the past decades. Exposure to pesticides has been associated with different health effects, including cancer, respiratory health and neurodegenerative diseases, such as Parkinson's disease (PD).[1–3] Traditionally, research has focused on pesticide exposure among agricultural workers. However, as pesticides can move from their intended application sites during and after agricultural application, also the general population in surrounding residential areas may be exposed to these pesticides.

Emission from agricultural pesticide applications can occur as primary spray drift of droplets during application, as secondary drift via volatilization of pesticide residues from crops or soil or as wind erosion of soil particles.[4] Depending on factors such as the application technique, the formulation used and environmental conditions, more than half of the applied dosage can be lost to air due to drift and volatilization, during and after application.[5,6] Primary drift of pesticides typically occurs over short distances (<100 m) and the highest concentrations are measured within the first few meters from treated fields.[7,8] The maximum distance at which pesticides have been detected following ground applications can be >100 m however.[9,10] Air monitoring results indicate increased environmental pesticide concentrations following agricultural pesticide applications and decreasing concentrations with increasing distance from the treated fields.[11] Also, pesticide concentrations measured in residential house dust samples have been associated with residential proximity to crops treated with pesticides.[12,13] Ward et al. [14] and Gunier et al.[15] found the crop area present within 750 m and 1250 m buffers around the home, respectively, to be predictive for pesticide concentrations in house dust.

Individuals living in the vicinity of agricultural fields treated with pesticides may potentially be exposed to these pesticides, either via inhalation of pesticides in air, dermal contact with pesticides in air or precipitation, treated crops, soil or dust or via ingestion of contaminated food or drinking water.[4,16,17] Pesticide exposure levels originating from the environment are considered to be low, but the number of people potentially exposed could be high, including potentially sensitive groups in the population (e.g., children and elderly). Exposure assessment for pesticides is challenging, especially for environmental exposure, where people are generally unaware of the pesticides applied in the vicinity of their residences. Individual (personal) measurements are neither feasible in large epidemiological studies nor available back in time. Past exposures or cumulative exposures, however, may be most relevant for diseases with a long latency or induction period or increased susceptibility during specific time windows in life.

Geographic information systems (GIS) have been increasingly used to assess environmental exposure to pesticides. The first studies making use of GIS calculated relatively simple spatial exposure proxies, such as proximity to agricultural crops[18] or the

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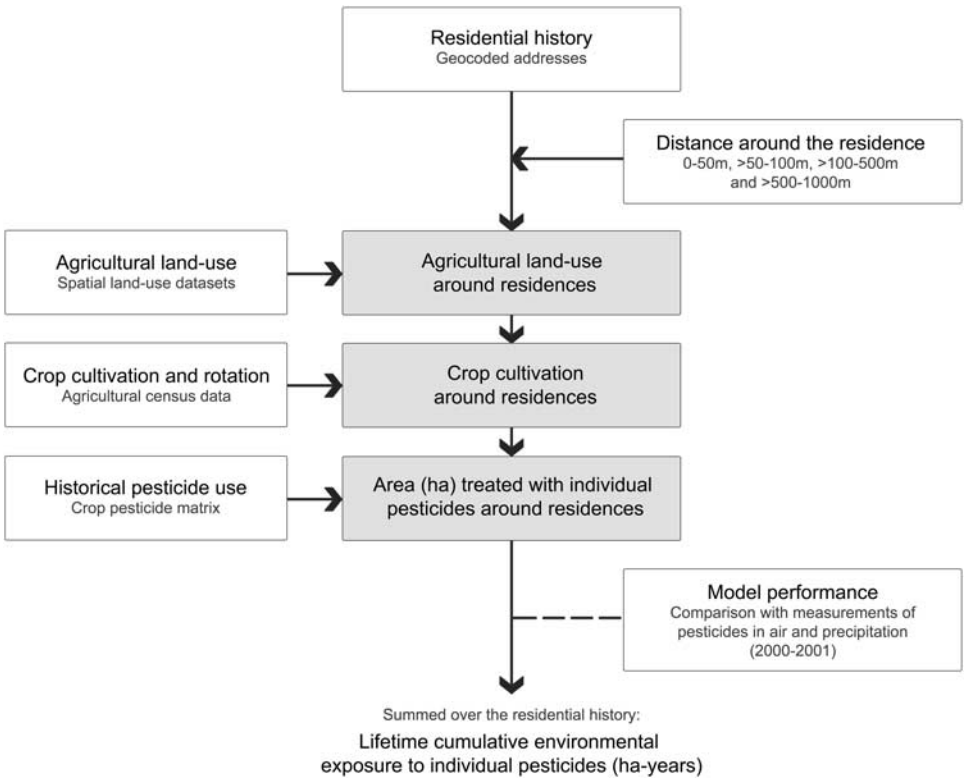

Figure 1. Overview of the modeling steps in the assessment of environmental pesticide exposure.

crop area cultivated in the vicinity of the residence.[14] A Belgian study developed indicators of environmental pesticide exposure for use in a bladder cancer study, based on available agricultural land-use data (only for the year 2002) and data on pesticide use at the functional group level (e.g., herbicides).[19] When trying to investigate the (causal) association between health effects and specific chemical agents, such broad exposure groups or exposure proxies are of limited interest, and more studies now focus on exposure to individual pesticides or pesticide chemical groups.[20,21] Several studies in the United States have combined spatial data on the location of residences relative to crop cultivation, with information from the California Pesticide Use Reporting (CPUR),[22,23] or historical records of large-scale public pest control applications and meteorology[24] to investigate the association between potential environmental pesticide exposure and adverse health effects. Few countries have publicly accessible databases with similar detail to the CPUR. The spatial land-use data underlying these US exposure assessments have a relatively low resolution (0.81 ha), however. As drift of pesticides is most substantial in the direct vicinity of the field, high-resolution data on agricultural fields is warranted to study the effect of proximity to fields and exposure intensity over short distances. The availability of databases on agricultural land-use and pesticide-use records can differ substantially between countries. In the Netherlands, high-resolution multi-date land-use data sets have been created,[25] but no accessible central registration of pesticide applications is available. Therefore, historical information on crop-specific pesticide use has been collected previously,[26] in order to estimate environmental exposure to agricultural pesticides in the Netherlands.

The current work is part of a large PD case–control study in the Netherlands,[27] which investigates the association between both occupational[28] and environmental exposure to specific pesticides and the risk of PD. Here we present a spatio-temporal model to estimate past and current environmental exposure to individual agricultural pesticides, based on geocoded residential histories. This paper describes the model development and provides examples of the resulting exposure estimates, using data from the PD case–control study. Furthermore, in a small validation effort, model estimates of environmental pesticide exposure are compared with pesticide concentrations measured in air and precipitation in 2000–2001.

MATERIALS AND METHODS

In summary, multi-date data sets on agricultural land use, data from national agricultural censuses and expert-derived data on crop-specific pesticide use were combined to estimate potential environmental exposure to individual agricultural pesticides at the residential addresses of the study participants (Figure 1).

Residential History

This work is part of a national hospital-based case–control study on PD.[27] Cases and controls were enrolled at five neurological hospital departments across the Netherlands and matched based on hospital, sex, age and visiting date (within 3 years). A complete residential history was collected from participants, including all residential addresses the participant had ever lived, for at least 1 year. Addresses were geocoded by linking the postal code, street name and house number to the building coordinate in the Dutch cadastral key registry of buildings and addresses (BAG),[29] which is a point located within the polygon of the building outline (i.e., within the outside walls). If there was no match with a building coordinate for a specific address, the address was geocoded to the midpoint of the corresponding 6-digit, 5-digit or 4-digit postal code area.

Agricultural Land Use

For this study, we obtained data from spatial land-use data sets of the Netherlands available for the years 1960, 1970, 1980 and 1990 (HGN)[30] and 1986, 1992, 1995, 1999, 2003 and 2007 (LGN).[25] These data sets consist of

Figure 2. Example of the land-use data sets used in this study, left: LGN4 (1999), right: HGN1960.

raster cells of 25×25 m^2 (0.06 ha), with a code linking to the dominant land-use class in the cell. The LGN data sets (LGN1–LGN6) were based on satellite imagery from 1986, 1992/1994, 1995/1997, 1999/2000, 2003/2004 and 2007/2008, respectively, and incorporated other relevant spatial data sets available at the time of the development. The LGN data sets provide information on the cultivation of a number of specific crops, although the amount of detail can differ between the different editions (Supplementary Table S1). Crop classification was based on the Normalised Difference Vegetation Index and the procedures followed have previously been described.[25,31] For each LGN data set, accuracy of crop classification was investigated using external data sets (e.g., field measurements, regional census data) and estimated to be around 70–80% overall (Supplementary Table S1). The LGN1 (1986) data set was not used in the current study, as this was considered an experimental data set with limited accuracy.[31]

The historical land-use data sets (HGN) were based on topographical maps of the Netherlands[30] and do not provide information on specific crops but distinguish two agricultural classes: 'arable and bare land' and greenhouses. Figure 2 illustrates the difference in thematic detail between LGN and HGN data sets.

For the purpose of this study, six main agricultural crops were considered (i.e., potatoes, cereals, beets, maize, fruit orchards and bulbs) from the five LGN data sets and the class 'arable and bare land' from the four HGN data sets. These six crops have been accounting for roughly 80% of the cultivated arable land in the Netherlands over the past decades.[32] Information on greenhouses and 'other crops' was not used, as no data on historical pesticide use were collected for these two classes.[26]

For each geocoded residential address, the area (ha) of crops was extracted from the land-use data set(s) corresponding to the time period covered by the address (Supplementary Table S1). This crop area was extracted using four, *a priori* defined, distance categories around the address: 0–50 m, >50–100 m, >100–500 m, and >500–1000 m, corresponding to an total surface area of 0.8 ha, 2.4 ha, 76.2 ha and 238.0 ha, respectively. The lowest cutoffs were set at 50 m and 100 m, covering potential primary drift.[6–8] Furthermore, 500 m and 1000 m were included as cutoffs also to enable comparison with other epidemiological studies investigating environmental pesticide exposure and PD risk.[21] If the total surface area of a crop in one of the distance categories was <312.5 m^2 (0.03 ha), corresponding to half of a raster cell, this was considered negligible and set to zero.

Crop Cultivation

The Dutch agricultural census is held annually by Statistics Netherlands (CBS) and provides information on the total surface area of crops for different administrative divisions, such as provinces ($n=12$) or agricultural regions ($n=66$), which are more or less homogeneous areas as far as soil type and agricultural land use are concerned.[32] As the LGN data sets pertain to individual points in time, assumptions were made on the likely rotation of crops during the period in between data sets. Crops that were considered to be part of regular annual rotation schemes (i.e., potatoes, cereals and beets) were grouped into a class 'rotating crops'. For each agricultural region, the proportion of potatoes, cereals and beets cultivated was extracted from census data and averaged over the years assigned to each land-use data set (Supplementary Table S1). When one of these crops contributed <10% to the total surface area of 'rotating crops' in an agricultural region, it was considered negligible and set to zero. This regional crop 'probability' was used to estimate the average area of potatoes, beets and cereals from the area of rotating crops extracted from the LGN data sets for each distance category around the address per agricultural region and time period. Orchards are regarded as stable crops over several decades, and the location of bulbs and maize was also considered to be stable in between the LGN data sets, owing to highly localized cultivation (bulbs) and substantial monoculture (maize).

Similarly, the HGN data sets did not distinguish individual crops and therefore census data were used to estimate the area of crops (i.e. potatoes, cereals, beets, maize) from the total area of 'arable and bare land' extracted from the HGN data sets. For 1960 and 1970, agricultural census data were available at province level only. Supported by agricultural census data,[32] fruit orchards and bulbs were considered traditionally stable, and their location in the LGN2 data set (1990) was deemed to be representative for the period 1961–1989.

Historical Pesticide Use

Data on past use of pesticides on potatoes, beets, cereals, maize, fruit orchards and bulbs in the Netherlands have previously been collected by expert assessment.[26] In brief, per crop, two agricultural experts individually rated the average annual probability (in percent) and frequency of use of authorized pesticides per 5-year time period between 1961 and 2005. The ratings of the two experts were averaged, and crop–pesticide matrices were created from this data, providing per crop, pesticide and time-period: (1) the average probability of use, corresponding to the percentage of farmers using the pesticide during a year and (2) the average frequency of use, expressed as the number of treatments during a year. Only those pesticides estimated to be ever used by >10% of farmers on one of the six selected crops were selected to exclude very low-level or uncertain use. In addition, we excluded ratings of pesticide use for seed treatment, given the anticipated low emission to air during this treatment. The resulting crop–pesticide matrices contained data on a total of 157 pesticides, covering the period 1961–2005. The last 5-year period in the matrices (2001–2005) was extended to 2011 taking into account withdrawals of pesticides from the market during this period, corresponding to the exposure period considered for the PD case–control study.

For the purpose of this study, we used the estimated probability and frequency of farmers applying a pesticide to a crop as the probability and frequency of the crop area being treated. Survey data from Statistics Netherlands (1995–2008) on self-reported pesticide use among farmers indicates that there is a high correlation between the percentage of farmers applying a pesticide to one of the crops selected for this study

and the percentage of crop area treated (Pearson's correlation coefficient 0.94–0.97).[33]

Environmental Pesticide Exposure

For each residential address, the estimated crop area present within the specified distances was multiplied with probability and frequency of pesticide use for all pesticides listed in the crop–pesticide matrix to estimate the total surface area (ha) likely treated with a pesticide during a specific year. This value was summed across the years and addresses in the participants' residential history to obtain an estimate of the participants' cumulative lifetime environmental exposure (ha-years).

Exposure Prevalence

A total of 607 control participants remained in the analytical data set used for the epidemiological analyses on environmental pesticide exposure and PD. For these participants, the presence of crops in each of the four distance categories around the residences was estimated, as well as environmental exposure to pesticides. Results for three pesticides (i.e., endosulfan, captan and paraquat) are shown in the main text to illustrate the effect of different 'pesticide-use scenarios' on the estimated exposure prevalence. Endosulfan and captan were rated to be only used on the (stable) crops fruit and bulbs, of which captan was used for a longer time period than endosulfan, and with a higher probability and frequency of use. Paraquat had also been used on potatoes (rotating crop), in addition to bulbs and orchards, for a substantial amount of time. The exposure period considered was 1961 until the year preceding the matched case diagnosis. This first year 1961 was chosen as it corresponds to the first available land-use data set (1960), the collected expert ratings on crop-specific pesticide use[26] and the implementation of pesticide legislation in the Netherlands in 1962.

Ever/never potential environmental exposure to the crops and pesticides was estimated for each distance category, as well as the participants' cumulative exposure (ha-years). In addition, heat maps were created for both crops and pesticides, visualizing the Spearman rank correlation coefficients between the cumulative environmental exposures estimated for the control participants using 0–100 m distance to limit the number of plots.

Model Performance

Between September 1999 and January 2002, a previous study has monitored pesticide concentrations in air and precipitation in the Netherlands. The sampling strategy and analytical procedures used have been described in detail elsewhere.[34,35] In brief, at 18 monitoring stations spread over country (Supplementary Figure S1), different pesticides ($n = 50$) and persistent pollutants were measured in precipitation and air samples repeatedly over 4-week periods and weekly at a subset of 3 stations. Precipitation was sampled for 4-week periods using wet-only samplers. Air measurements were conducted by drawing 600 m^3 air through samplers with polyurethane foam plugs and XAD adsorbent. Of the 50 pesticides investigated, 28 where registered for agricultural use at the time of the measurements ('current use'). The original monitoring study focused on atmospheric deposition in 50×50 km^2 areas and the stations were placed away from direct agricultural sources.[35] This data set is therefore not suitable to evaluate our model estimates based on crop cultivation in close proximity of the monitoring station (< 100 m) but can provide insight into the ability of the model to predict environmental pesticide exposure from agricultural pesticide applications at intermediate distances (> 100 m).

In the monitoring data set, all samples below the limit of detection (LOD) were set to zero. The average concentrations measured in air (ng/m^3) and precipitation (ng/l) were calculated for all pesticides per station over the complete monitoring years 2000 and 2001. Using our spatial model, cumulative environmental exposure to pesticides during the same period was estimated for the 17 monitoring stations (excluding 1 station located on a platform in the North Sea) based on crop cultivation within >100–500 m and >500–1000 m of the station.

Of the 28 'current-use' pesticides, 11 were frequently detected in air or precipitation, which was defined as being detected at $>20\%$ of the stations, with over 10% of samples at these stations being above LOD (either in air or precipitation). For these 11 pesticides, the Spearman rank correlation was used to compare the average pesticide concentrations in

Table 1. Estimated cumulative exposure of control participants in the case–control study ($n = 607$) to crop cultivation in the vicinity of the residential address.

Crop	*Distance from the residential address*			
	0–50 m	*>50–100 m*	*>100–500 m*	*>500–1000 m*
Orchards				
Ever exposed, *N* (%)	5 (0.8)	14 (2.3)	119 (19.6)	235 (38.7)
Ha-years, median (IQR)	1.6 (1.3–1.6)	1.4 (0.7–3.1)	12.2 (1.9–49.1)	13.8 (2.5–88.8)
Bulbs				
Ever exposed, *N* (%)	1 (0.2)	2 (0.3)	12 (2.0)	40 (6.6)
Ha-years, median (IQR)	0.45 (n.a.)	0.69 (0.16–1.2)	9.8 (3.6–35.2)	17.5 (2.5–23.3)
Maize				
Ever exposed, *N* (%)	222 (36.6)	348 (57.3)	532 (87.6)	559 (92.1)
Ha-years, median (IQR)	0.3 (0.1–0.9)	0.8 (0.2–2.4)	51.9 (21.2–122.0)	309.2 (123.1–663.7)
Potatoes				
Ever exposed, *N* (%)	361 (59.5)	467 (76.9)	598 (98.5)	602 (99.2)
Ha-years, median (IQR)	0.2 (0.1–0.5)	0.5 (0.2–1.0)	21.0 (8.3–43.2)	92.1 (52.8–150.3)
Beets				
Ever exposed, *N* (%)	251 (41.4)	375 (61.8)	594 (97.9)	605 (99.7)
Ha-years, median (IQR)	0.2 (0.1–0.4)	0.5 (0.2–1.0)	16.7 (5.4–37.1)	84.6 (44.3–153.8)
Cereals				
Ever exposed, *N* (%)	387 (63.8)	501 (82.5)	606 (99.8)	607 (100)
Ha-years, median (IQR)	0.8 (0.3–1.6)	2.0 (0.8–4.4)	91.7 (36.9–153.1)	376.6 (217.0–549.1)

Abbreviations: Ha-years, hectare-years; IQR, interquartile range. Median ha-years and IQR are calculated for the exposed subjects. Surface area of the 0–50 m, >50–100 m, >100–500 m and >500–1000 m buffers: 0.8 ha, 2.4 ha, 76.2 ha and 238.0 ha, respectively. The number of exposure-years varies between the participants, depending on their age and the year of diagnosis of their matched case.

air and precipitation with the model estimates of environmental pesticide exposure at the station during 2000–2001 (ha-years).

For the remaining 17 'current-use' pesticides, there were only few measurements above LOD or the pesticide was not included in our model (e.g., general use for public weed control), preventing a quantitative comparison. To provide some insight into the model performance for these less detected pesticides, environmental exposure (yes/no) to all 28 'current-use' pesticides was estimated for the 17 monitoring stations using the model and compared with being detected above LOD (yes/no) in any of the air or precipitation samples per station in 2000–2001. The percentage of raw agreement was calculated, as well as the sensitivity and specificity of the modeled presence of exposure.

Furthermore, correlations between the measured pesticide concentrations and chemical properties (i.e., vapor pressure, Henry's law constant)[4] and application volume[33] were investigated using the Spearman rank correlation for the 11 frequently detected pesticides to investigate the effect of these factors on potential pesticide emission to the environment.

RESULTS

Geocoding of Addresses

A total of 2942 addresses were collected from the control population (n = 607) in the PD case–control study, from 1961 onward. Of these addresses, 2433 (82.7%) could be matched to BAG building coordinates, 169 (5.7%) to the 6-digit postal code coordinate, 207 (7.0%) to the 5-digit postal code coordinate, 39 (1.3%) to the 4-digit postal code coordinate and 94 addresses (3.2%) could not be geocoded. When expressing these numbers as the percentage of lifetime geocoded for the control population (n = 28865 years), 91.8% was geocoded with building coordinates, 4.1% with the 6-digit postal code, 2.6% with the 5-digit postal code, 0.4% with the 4-digit postal code and 1.2% could not be geocoded or was missing in the residential history.

Exposure Prevalence

Only few control participants from the case–control study (n = 607) ever lived within 50 m from orchards (0.8%) or bulb fields (0.2%), while for maize, potatoes, beets and cereals, this ranged between 37% and 64% (Table 1). Exposure prevalence increased with increasing distance, approaching 100% for being ever exposed to maize, potatoes, beets and cereals, in the two largest distance categories. There was substantial overlap between the area of potatoes, beets, cereals and maize cultivated in the vicinity of the residences. This was also reflected in the moderate-to-high correlation coefficients between the estimated cumulative crop area, for example, R_s 0.87 between potatoes and cereals in 0–100 m (Supplementary Figure S2). Estimated environmental exposure to the three selected pesticides is shown in Table 2. Only few participants were classified as ever exposed to endosulfan. Exposure to captan was slightly more prevalent, and the estimated cumulative environmental exposure was high compared with endosulfan, due to its higher probability and frequency of use. Over 90% of the control population was considered ever exposed to paraquat in >100–500 m or >500–1000 m distance, but the estimated cumulative ha-years were relatively low. Considering all pesticides present in the crop–pesticide matrices (n = 157), the median Spearman rank correlation coefficient between estimated cumulative exposures in 0–100 m was 0.14 (interquartile range (IQR) 0.00–0.45). Within herbicides, the median correlation coefficient was 0.20 (IQR 0.05–0.42), 0.14 (IQR 0.00–0.53) for fungicides, 0.30 (IQR 0.00–0.61) for insecticides and 0.42 (IQR −0.02–0.82) for other pesticides (e.g., nematicides and acracides) (Supplementary Figure S3).

Model vs Measurements

The monitoring study included only two stations located within 100 m of agricultural crops and therefore only model estimates based on crop cultivation within >100–500 m and >500–1000 m of the station were generated. The model did not estimate environmental pesticide exposure at monitoring stations without any relevant crops cultivated within the specified distance categories (Supplementary Table S2). The percentage of samples above LOD varied between the 28 'current-use' pesticides, ranging from 0% to 96% in air and from 0% to 81% in precipitation. Overall, pesticides were more likely to be detected in precipitation than in air samples, and the Spearman rank correlation between pesticide concentrations in air and precipitation ranged between −0.46 and 0.89 (Supplementary Table S2). Relatively poor agreement was found between the modeled presence of environmental exposure at the monitoring station (yes/no) and the pesticide being detected above LOD (Supplementary Table S3). For the subset of 11 more frequently detected pesticides (Table 3), the estimated environmental pesticide exposure showed an overall moderate-to-high positive correlation with the average concentrations measured in air and precipitation (Table 4). For 9 out of the 11 pesticides (i.e., MCPA, chlorpropham, chlorothalonil, ethofumesate, metolachlor, kresoxim-methyl, procymidone, tolclofos-methyl, vinclozolin), significant. significant correlations

Table 2. Estimated cumulative environmental exposure of control participants in the case–control study (n = 607) to three selected pesticides, potentially applied to crops in the vicinity of the residential address.

Pesticide	*Distance from the residential address*			
	0–50 m	*>50–100 m*	*>100–500 m*	*>500–1000 m*
Endosulfan				
Ever exposed, *N* (%)	3 (0.5)	9 (1.5)	79 (13.0)	148 (24.4)
Ha-years, median (IQR)	1.6 (0.6–1.6)	2.2 (0.8–2.4)	8.6 (2.3–39.1)	26.2 (5.0–119.6)
Captan				
Ever exposed, *N* (%)	6 (1.0)	16 (2.6)	126 (20.8)	255 (42.0)
Ha-years, median (IQR)	16.3 (0.5–18.0)	9.5 (3.6–29.9)	134.2 (17.3–561.9)	126.5 (16.1–824.1)
Paraquat				
Ever exposed, *N* (%)	206 (33.9)	321 (52.9)	563 (92.8)	596 (98.2)
Ha-years, median (IQR)	0.1 (<0.1–0.2)	0.2 (<0.1–0.4)	6.5 (2.2–19.2)	34.0 (15.4–110.4)

Abbreviations: Ha-years, hectare-years; IQR, interquartile range. Median ha-years and IQR are calculated for the exposed subjects. Surface area of the 0–50 m, >50–100 m, >100–500 m and >500–1000 m buffers: 0.8 ha, 2.4 ha, 76.2 ha and 238.0 ha, respectively. The number of exposure-years varies between the participants, depending on their age and the year of diagnosis of their matched case.

Table 3. Pesticides frequently detected in air and precipitation samples the Netherlands in 2000–2001, their estimated use on specific crops and the presence of these crops within 100–500 m and 500–1000 m of the monitoring stations.

Pesticide	*Air*			*Precipitation*			*Correlation air-precipitation samples* (R_s)[a]	*Model*		
	N *samples*	N *stations* > *LOD*	% *samples* > *LOD*	N *samples*	N *stations* > *LOD*	% *samples* > *LOD*		*Linked to crops*[b]	N *stations with crop (s) in 100–500 m*	N *stations with crop (s) in 500–1000 m*
Herbicides										
Chlorpropham	512	17	42.8%	440	17	73.9%	**0.82**	Bulbs	4	5
Ethofumesate	278	17	20.6%	266	16	18.1%	−0.04	Beets	7	10
MCPA	512	3	0.7%	440	17	38.6%	0.32	Orchards	3	2
Metolachlor	512	9	3.5%	440	17	14.3%	**0.58**	Maize	7	12
Terbuthylazine	278	10	7.0%	266	17	30.6%	0.43	Maize	7	12
Fungicides										
Chlorothalonil	278	17	30.4%	266	17	38.4%	0.07	Bulbs	4	5
Fluazinam	512	13	9.4%	440	17	14.1%	0.46	Potatoes, bulbs	9	12
Kresoxim-methyl	278	15	12.8%	266	17	36.2%	**0.68**	Bulbs, orchards	7	7
Procymidone	512	15	21.3%	440	17	32.7%	**0.89**	Bulbs	4	5
Tolclofos-methyl	512	11	13.6%	440	5	5.4%	**0.74**	Bulbs	4	5
Vinclozolin	278	17	37.1%	266	17	47.0%	**0.60**	Bulbs	4	5

Abbreviation: LOD, limit of detection. Bold type indicates < 0.05 significance. R_s, Spearman rank correlation coefficient. [a]Spearman rank correlation coefficient between the average pesticide concentration measured in air and precipitation per station ($n = 17$). [b]Crops these pesticides were used on by $> 10\%$ of farmers during the period 2000–2001 according to the crop–pesticide matrices.[26]

were found between one of the two model estimates and either the concentration in air or precipitation. The correlations presented are based on few points, which is also shown in the scatterplots of the modeled exposure estimates and measured pesticide concentrations (Supplementary Figures S4 and S5). There was no clear evidence that either the average applied dosage of the pesticide or the chemical properties of the pesticide (i.e., vapor pressure or Henry's law constant) were related to the percentage of samples above LOD or the average concentration measured in air or precipitation (Supplementary Tables S4 and S5).

DISCUSSION

We developed a spatio-temporal model to estimate potential environmental exposure to individual pesticides in the Netherlands within the framework of an ongoing case–control study on PD. Spatial data on agricultural land use was combined with census data on crop cultivation and expert-based estimates of pesticide use for six main crops in the Netherlands. Owing to the model input and design, cultivation of rotating, arable crops was assigned to most residences and environmental exposure to pesticides applied to any of these crops was highly prevalent among control participants in the case–control study. Relatively few participants lived in close proximity to bulb fields or fruit orchards, which are potentially the most interesting due to the high number and volumes of pesticides applied to these crops. We were only able to investigate the performance of our model for a limited number of pesticides ($n = 11$) and monitoring stations ($n = 17$), but moderate-to-high correlations were found between measured pesticide concentrations and environmental pesticide exposure estimates based on crop cultivation in $>$100–500 m and $>$500–1000 m around the stations.

The described model provides the opportunity to assess environmental exposure to specific pesticides dating back to 1961. For PD, little is known about the etiologically relevant time period of exposure, and disease risk could potentially be affected by long-term cumulative exposures or exposures at specific stages in life.[36] Furthermore, the model is not limited to a single distance around the home but provides exposure estimates based on four different distance categories, enabling us to investigate the effect of proximity to pesticide applications (assumed to be related to the intensity of exposure) in more detail. We developed crop–pesticide matrices listing 157 pesticides and expert-derived probability and frequency of use of these pesticides per crop and time period. This greatly improves over assigning crude pesticide exposure proxies (e.g., rural living, crop type) or using information on the registration of pesticides only, as the majority of registered pesticides will not have been used by all farmers on an annual basis.[26,37] Modeling environmental exposure based on residential histories and independent spatial and temporal data sets has the advantages of being independent of self-reported data, relatively low costs, high efficiency and feasibility of collecting and comparing large amounts of exposure data that cannot be actually measured in a large study population. The majority of addresses held by the control participants in the PD case–control study could be geocoded with a building coordinate (83%), which has a high precision, given that this coordinate lies within the building outline. This percentage corresponds to 92% of the total lifetime of the control population. Potential error in the residential location, due to assigning postal code coordinates, can be higher in rural than in urban areas, as postal codes cover a larger area in rural neighborhoods. However, the percentage of addresses geocoded with a postal code coordinate was lower in rural areas (10%) compared with highly urbanized areas (17%). Less than 1% of the total lifetime of control population was spent in rural areas and geocoded to postal code coordinates.

There are a number of assumptions underlying the model we have developed, for which some appear to be accurate, while for

Table 4. Correlation between average pesticide concentrations measured in air and precipitation and modeled exposure estimates, based on crop cultivation within a distance of >100–500 m and >500–1000 m around the monitoring stations.

Pesticide	*Air*		*Precipitation*	
	Model >100–500 m	*Model >500–1000 m*	*Model >100–500 m*	*Model >500–1000 m*
	R_s		R_s	
Herbicides				
Chlorpropham	**0.72**	**0.62**	**0.74**	**0.76**
Ethofumesate	0.21	0.16	0.48	**0.55**
MCPA	**0.58**	**0.73**	0.35	0.40
Metolachlor	**0.72**	**0.60**	**0.50**	**0.57**
Terbuthylazine	0.26	0.32	0.44	0.28
Fungicides				
Chlorothalonil	0.21	0.08	**0.57**	0.37
Fluazinam	0.25	0.22	0.06	−0.02
Kresoxim-methyl	0.47	0.20	**0.70**	0.41
Procymidone	**0.69**	**0.68**	**0.74**	**0.80**
Tolclofos-methyl	**0.75**	**0.62**	**0.92**	**0.82**
Vinclozolin	0.28	0.14	**0.62**	**0.51**

Modeled cumulative exposure estimates (ha-years) for the period 2000–2001 were compared with the average concentration of pesticides in air (ng/m^3) and precipitation (ng/l) per station; bold type indicates < 0.05 significance; R_s, Spearman rank correlation coefficient.

others their validity could not be assessed in the current study. Accuracy and resolution of the underlying data determines for a large extent the quality of the resulting exposure estimates. The LGN and HGN land-use data sets used in this study have their limitations, but overall they are assumed to provide an accurate overview of agricultural land use and crop cultivation in the Netherlands.[25,31] The resolution of these data sets (0.06 ha grid cells) is higher compared with, for example, the resolution of the land-use data used in several US studies investigating environmental pesticide exposure (0.81 ha).[22,23] In addition, multiple data sets were available for distinct points in time from 1960 onward, while many other studies had to rely on (recent) land-use data at one or two points in time.[19] However, as not each individual calendar year was covered, assumptions still had to be made on potential crop rotation in between the land-use data sets.

Census data on crop cultivation in agricultural regions was used to estimate the probability of individual (rotating) crops being cultivated in these regions during the periods allocated to each land-use data set. This will have resulted in some degree of misclassification during individual years, as an address with any rotating crop in its vicinity could be assigned a fraction of potatoes, cereals and beets and thereby some level of exposure to all pesticides associated with these crops. However, given the rotation of these crops over multiple consecutive years (e.g., one year potatoes, next year cereals), the estimated cumulative crop area will be close to the actual crop area cultivated during a period of several years and is considered to be an appropriate estimate of average crop cultivation and environmental pesticide exposure over time. For investigating the association with PD, we are most interested in long-term cumulative exposure or average exposure during specific periods in life. Exposure duration will be overestimated as these probabilities are assigned to each year, and exposure duration will therefore not be considered as exposure metric in this study. The majority of participants ever lived within vicinity of any rotating crop and was thereby assigned ever-exposure to paraquat, as this pesticide was reported to be used on potatoes for a substantial period of time. The estimated area treated could be low however, as only part of the rotating crop area was estimated to be potatoes, and again only a part of that area was likely to been treated with paraquat. This is reflected by the relatively low cumulative exposure (ha-years). As the historical data sets (HGN) before 1990 only distinguished 'arable and bare land' and the crop probabilities were derived at province level for 1970 and 1960 instead of the agricultural region, the potential for misclassification of crop cultivation might be greater further back in time. Since 2009, more detailed annual crop maps of the Netherlands are published with detailed information on the type of crop cultivated (e.g., individual cereal species instead of cereals as a group),[38] tackling the issue of crop rotation in between data sets. However, these recent crop maps were not used in the present study, as for the majority of the participants in the PD case–control study, the exposure period ended before 2009.

The use of specific pesticides on the selected crops has been estimated using ratings of agricultural experts, which have previously shown to be reliable and reasonably accurate, with a moderate-to-high correlation with self-reported pesticide use collected in farmer surveys.[26] We used the average-rated probability and frequency of use among farmers, as the percentage and frequency of crop area treated in the current study were supported by data from the aforementioned farmer surveys.[33] All average probability ratings $< 10\%$ were removed to exclude very low-level or uncertain use. However, exposure prevalence will have been overestimated, as even for a pesticide with a relatively low probability of use, a participant can be assigned a (low) environmental exposure. Some underestimation of exposure may occur as well as the model has been limited to six main crops, thereby discarding pesticide applications on other crops (e.g., open field crops or greenhouses) and non-agricultural applications, such as governmental weed or pest control in public green space, roads or railways. For example, the application of 2,4-D and dichlobenil for general weed control purposes is not accounted for in the model, resulting in a discrepancy with the monitoring data, in which these two pesticides were frequently detected. However, the crops selected do account for roughly 80% of the total Dutch agricultural surface area[32] and are among the highest in terms of pesticide-use volumes and diversity of products (i.e., bulbs and fruit orchards). An overall pesticide-use estimate was previously collected for each of the six crops, while, for example, specific types of cereals (e.g., wheat, barley) may be treated with different pesticides. Nonetheless, the overall pesticide-use estimates we collected have shown to correspond well to self-reported use from surveys, averaged over these crop types.[26] In California, US, self-reported information (e.g., date of application, pounds applied) on the use of several pesticides has been registered.[23] This type of detailed information was not available in the Netherlands for the current study and will be lacking in most other countries without validated, accessible registries. We have used average annual pesticide-use ratings, which we consider to be adequate for investigating PD and other long-latency diseases, in which the relevant exposure period may consist of several years or decades.

This exposure assessment assumes that pesticides applied to agricultural fields are being emitted into the environment and that the actual concentrations emitted depend on the distance to the field, as well as the total surface area treated. Emission of pesticides into the environment during and after application is supported by scientific literature.[4,5,17] Also, the monitoring data used for validation purposes in this study shows that a wide range of 'current-use', as well as banned, pesticides can be detected in air and precipitation.[34] Unfortunately, we could not investigate the effect of close proximity to crops and pesticide applications (primary drift) in this data set, as all monitoring stations were placed away from local agricultural sources where concentrations would be expected to be the highest. We did observe a moderate-to-high correlation between the surface area likely treated with a pesticide within >100–500 m or >500–1000 m of the monitoring station and the average concentrations measured in air or

precipitation in 2000–2001, which supports the assumption that pesticide emission (volatilization and dispersion) is related to the total crop area treated. For this comparison, we restricted to 'current-use' pesticides detected in >10% of the measurements and these were only herbicides and fungicides. No insecticides were detected at a sufficient level, which could indicate that the more infrequent use and lower volumes of these pesticides results in lower emissions. However, the monitoring data is no perfect gold standard for the current study. This data has been collected with a different study aim, and differences in the detection limits of the pesticides in air and precipitation complicate direct comparisons between pesticides and firm conclusions on their absence or presence in the environment. Of the pesticides for which a high correlation between the model and measurements was observed, the majority was used on bulbs or orchards, which are relatively localized, spatially stable crops. This suggests that misclassification error in model estimates might be higher for pesticides used mainly on rotating crops during short time windows.

One final assumption is that the transport and presence of pesticides in the environment results in contamination of the residential area, which will eventually lead to personal exposure of the general population. The lack of proper model validation is one of the main critiques on geographical modeling of environmental exposure in epidemiological studies.[39] Unfortunately, extensive measurements of the residential environment or biomarkers reflecting of personal pesticide exposure (back in time) were not available for our study. Previous research has indicated a relation between the distance to the nearest field or crop acreage and the concentrations of pesticides in residences.[12–15] Few consistent findings have emerged, however, when comparing measured pesticide concentrations or modeled exposure estimates to biomarkers of pesticide exposure. Urinary DMTP concentrations were reported to decrease with increasing distance from agricultural fields,[12] but Krieger et al.[40] found a poor correlation between biomarkers for organophosphate pesticides and pesticide concentrations in house dust. Ritz and Costello[41] observed a small correlation between DDE and pesticide exposure estimates generated by applying a geographic model. Biomarkers have their limitations too, as for most pesticides no biomarkers for distant past exposure exist due to short half-lives in the body or low (metabolite) concentrations or they are not specific for exposure to individual pesticides. Measurements in and around the residential address, combined with personal exposure measurements, would be required to determine how well the environmental pesticide exposure estimates generated using our model reflect personal exposure.

Despite the limitations described, most of the assumptions underlying our model appear to be appropriate and are supported by previous research. The high correlations between some pesticide exposures, resulting from crop assignment based on regional probabilities and the potential use of several pesticides on the same crop(s) during the same time period(s), need to be taken into account when designing and interpreting subsequent epidemiological analyses. Although co-occurring exposures to pesticides (and other potential risk factors) are a given in many agricultural settings,[42] this might limit our ability to investigate the individual association with PD for some highly correlated pesticides.

CONCLUSION

We developed a spatio-temporal model to estimate lifetime environmental exposure to individual agricultural pesticides in the Netherlands based on residential histories. Such a model has great advantages in terms of efficiency and the ability to estimate environmental exposures for any etiologic period of interest, as far as the available input data allows. The assumptions underlying our country-specific model appear to be appropriate, and estimates of environmental pesticide exposure showed moderate-to-high correlations with measured pesticide concentrations in 2000–2001. To what extent these environmental exposure estimates reflect personal exposure levels remains to be investigated. Our method can be applied to evaluate potential associations between environmental exposure to pesticides and different (long-latency) diseases of interest, although not for all pesticides will it be feasible to make inferences on their individual effects due to high correlations with other pesticide exposures.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1 van der Mark M, Brouwer M, Kromhout H, Nijssen P, Huss A, Vermeulen R. Is pesticide use related to Parkinson disease? Some clues to heterogeneity in study results. *Environ Health Perspect* 2012; **120**: 340–347.
2 Hoppin JA. Pesticides and respiratory health: where do we go from here? *Occup Environ Med* 2014; **71**: 80–81.
3 Weichenthal S, Moase C, Chan P. A review of pesticide exposure and cancer incidence in the agricultural health study cohort. *Environ Health Perspect* 2010; **118**: 1117–1125.
4 Kubiak R, Burkle L, Cousins I, Hourdakis A, Jarvis T, Jene B *et al. Pesticides in air: considerations for exposure assessment*. Report of the FOCUS Working Group on Pesticides in Air, EC Document Reference SANCO/10553/2006, Rev 2 June 2008, 327 pp. http://esdac.jrc.ec.europa.eu/public_path/projects_data/focus/air/docs/FOCUS_AIR_GROUP_REPORT-FINAL.pdf.
5 Van Den Berg F, Kubiak R, Benjey WG, Majewski MS, Yates SR, Reeves GL *et al.* Emission of pesticides into the air. *Water Air Soil Pollut* 1999; **115**: 195–218.
6 Ravier I, Haouisee E, Clément M, Seux R, Briand O. Field experiments for the evaluation of pesticide spray-drift on arable crops. *Pest Manage Sci* 2005; **61**: 728–736.
7 Rautmann D, Streloke M, Winkler R. New basic drift values in the authorization procedure for plant protection products. Workshop on Risk Assessment and Risk Mitigation Measures in the Context of the Authorization of Plant Protection Products (WORMM) 27-29 September 1999. Biologischen Bundesanstalt für Land- und Forstwirtschaft: Berlin, Germany, 2001, pp 133–141. URL report: http://pub.jki.bund.de/index.php/MittBBA/article/download/736/671.
8 Wolters A, Linnemann V, van de Zande JC, Vereecken H. Field experiment on spray drift: Deposition and airborne drift during application to a winter wheat crop. *Sci Total Environ* 2008; **405**: 269–277.
9 Siebers J, Binner R, Wittich K. Investigation on downwind short-range transport of pesticides after application in agricultural crops. *Chemosphere* 2003; **51**: 397–407.
10 Carlsen SCK, Spliid NH, Svensmark B. Drift of 10 herbicides after tractor spray application. 2. Primary drift (droplet drift). *Chemosphere* 2006; **64**: 778–786.
11 Garron CA, Davis KC, Ernst WR. Near-field air concentrations of pesticides in potato agriculture in Prince Edward Island. *Pest Manag Sci* 2009; **65**: 688–696.
12 Coronado GD, Holte S, Vigoren E, Griffith WC, Barr DB, Faustman E *et al.* Organophosphate pesticide exposure and residential proximity to nearby fields: evidence for the drift pathway. *Occup Environ Med* 2011; **53**: 884–891.
13 Fenske RA, Lu C, Barr D, Needham L. Children's exposure to chlorpyrifos and parathion in an agricultural community in central Washington State. *Environ Health Perspect* 2002; **110**: 549–553.
14 Ward MH, Lubin J, Giglierano J, Colt JS, Wolter C, Bekiroglu N *et al.* Proximity to crops and residential to agricultural herbicides in Iowa. *Environ Health Perspect* 2006; **114**: 893–897.
15 Gunier RB, Ward MH, Airola M, Bell EM, Colt J, Nishioka M *et al.* Determinants of agricultural pesticide concentrations in carpet dust. *Environ Health Perspect* 2011; **119**: 970–976.
16 Wilson NK, Strauss WJ, Iroz-Elardo N, Chuang JC. Exposures of preschool children to chlorpyrifos, diazinon, pentachlorophenol, and 2,4-dichlorophenoxyacetic acid over 3 years from 2003 to 2005: a longitudinal model. *J Expos Sci Environ Epidemiol* 2010; **20**: 546–558.
17 Royal Commission on Environmental Pollution. *Crop Spraying and the Health of Residents and Bystanders*. RCEP: London, UK, 2005, 176 pp.

18 Royster MO, Hilborn ED, Barr D, Carty CL, Rhoney S, Walsh D. A pilot study of global positioning system/geographical information system measurement of residential proximity to agricultural fields and urinary organophosphate metabolite concentrations in toddlers. *J Expo Anal Environ Epidemiol* 2002; **12**: 433–440.
19 Cornelis C, Schoeters G, Kellen E, Buntinx F, Zeegers M. Development of a GIS-based indicator for environmental pesticide exposure and its application to a Belgian case-control study on bladder cancer. *Int J Hyg Environ Health* 2009; **212**: 172–185.
20 Costello S, Cockburn M, Bronstein J, Zhang X, Ritz B. Parkinson's disease and residential exposure to maneb and paraquat from agricultural applications in the central valley of California. *Am J Epidemiol* 2009; **169**: 919–926.
21 Wang A, Cockburn M, Ly TT, Bronstein JM, Ritz B. The association between ambient exposure to organophosphates and Parkinson's disease risk. *Occup Environ Med* 2014; **71**: 275–281.
22 Nuckols JR, Gunier RB, Riggs P, Miller R, Reynolds P, Ward MH. Linkage of the California Pesticide Use Reporting Database with spatial land use data for exposure assessment. *Environ Health Perspect* 2007; **115**: 684–689.
23 Rull RP, Ritz B. Historical pesticide exposure in California using pesticide use reports and land-use surveys: an assessment of misclassification error and bias. *Environ Health Perspect* 2003; **111**: 1582–1589.
24 Brody JG, Vorhees DJ, Melly SJ, Swedis SR, Drivas PJ, Rudel RA. Using GIS and historical records to reconstruct residential exposure to large-scale pesticide application. *J Expo Anal Environ Epidemiol* 2002; **12**: 64–80.
25 Hazeu GW, Bregt AK, de Wit AJW, Clevers JGW. A Dutch multi-date land use database: identification of real and methodological changes. *Int J Appl Earth Obs Geoinf* 2011; **13**: 682–689.
26 Brouwer M, Huss A, Vermeulen R, Nijssen PCG, De Snoo G, Kromhout H. Expert assessment of historical crop specific pesticide use in the Netherlands. *Occup Environ Med* 2014; **71**: 717–722.
27 van der Mark M, Nijssen PCG, Huss A, Mulleners WM, Sas GMG, van Laar T *et al.* A case-control study of the protective effect of alcohol, coffee, and cigarette consumption on parkinson disease risk: time-since-cessation modifies the effect of tobacco smoking. *PLoS ONE* 2014; **9**: e95297.
28 van der Mark M, Vermeulen R, Nijssen PCG, Mulleners WM, Sas AMG, van Laar T *et al*. Occupational exposure to pesticides and endotoxin and Parkinson disease in the Netherlands. *Occup Environ Med* 2014; **71**: 757–764.
29 Kadaster. Dutch cadastral key-registry of buildings and addresses (BAG), 2015. Available at https://data.overheid.nl/data/dataset/bag. Accessed June 2016.
30 Kramer H, van Dorland G. *Historisch grondgebruik Nederland 1990: een landelijke reconstructie van het grondgebruik rond 1990. Alterra-rapport 1327*. Alterra: Wageningen, The Netherlands, 2009, 58 pp.
31 De Wit AJW, Clevers JGPW. Efficiency and accuracy of per-field classification for operational crop mapping. *Int J Remote Sens* 2004; **25**: 4091–4112.
32 CBS, Statistics Netherlands. Landbouwtelling (Agricultural census statistics) 1960-2010. Available (in part) at http://statline.cbs.nl/Statweb/dome/?TH = 4220&LA = nl. Accessed December 2016.
33 CBS, Statistics Netherlands. Gebruik gewasbeschermingsmiddelen in de landbouw; werkzame stof, toepassing (Use of pesticides in agriculture; active ingredients, application), 1995, 1998, 2000, 2004 and 2008. Available at http://statline.cbs.nl/Statweb/selection/?DM = SLNL&PA = 37606&VW = T. Accessed December 2016.
34 Duyzer JH. Pesticide concentrations in air and precipitation in the Netherlands. *J Environ Monit* 2003; **5**: 77–80.
35 Duyzer JH, Vonk AW. *Atmospheric Deposition of Pesticides, PAHs and PCBs in the Netherlands (Translation of R2002/606). TNO Report R2003/255*. TNO: Apeldoorn, The Netherlands, 2003, 105 pp.
36 de Lau LM, Breteler MM. Epidemiology of Parkinson's disease. *Lancet Neurol* 2006; **5**: 525–535.
37 Blair A, Zahm SH. Patterns of pesticide use among farmers: implications for epidemiologic research. *Epidemiology* 1993; **4**: 55–62.
38 Dutch Ministry of Interior and Kingdom Relations. Dataportaal van de Nederlandse overheid—BRP Gewaspercelen, 2015; available at https://data.overheid.nl/data/dataset/basisregistratie-gewaspercelen-brp. Accessed June 2016.
39 Chang ET, Adami H, Bailey WH, Boffetta P, Krieger RI, Moolgavkar SH *et al*. Validity of geographically modeled environmental exposure estimates. *Crit Rev Toxicol* 2014; **44**: 450–466.
40 Krieger RI, Chen L, Ginevan M, Watkins D, Cochran RC, Driver JH *et al*. Implications of estimates of residential organophosphate exposure from dialkylphosphates (DAPs) and their relevance to risk. *Regul Toxicol Pharmacol* 2012; **64**: 263–266.
41 Ritz B, Costello S. Geographic model and biomarker-derived measures of pesticide exposure and Parkinson's disease. *Ann NY Acad Sci* 2006; **1076**: 378–387.
42 Kromhout H, Heederik D. Effects of errors in the measurement of agricultural exposures. *Scand J Work Environ Health* 2005; **31**(SUPPL. 1): 33–38.

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