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1 **Spatio-temporal assessment of pregnant women** 2 **exposure to chlorpyrifos at a regional scale**

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28 **Abstract**

29 **Background:** The aim of this study was to use an integrated exposure assessment approach,
30 combining spatio-temporal modeling of environmental exposure and fate of the chemical to
31 assess the exposure of vulnerable populations. In this study, chlorpyrifos exposure of pregnant
32 women in Picardy was evaluated at a regional scale during one year. This approach provided
33 a mapping of exposure indicators of pregnant women to chlorpyrifos over fine spatial and
34 temporal resolutions using a GIS environment.

35 **Methods:** Fate and transport models (emission, atmospheric dispersion, multimedia exposure,
36 PBPK) were combined with environmental databases in a GIS environment. Quantities spread
37 over agricultural fields were simulated and integrated into a modeling chain coupling models.
38 The fate and transport of chlorpyrifos was characterized by an atmospheric dispersion
39 statistical metamodel and the dynamiCROP model. Then, the multimedia model Modul'ERS
40 was used to predict chlorpyrifos daily exposure doses which were integrated in a PBPK model
41 to compute biomarker of exposure (TCPy urinary concentrations). For the concentration
42 predictions, two scenarios (lower bound and upper bound) were built.

43 **Results:** At fine spatio-temporal resolutions, the cartography of biomarkers in the lower bound
44 scenario clearly highlights agricultural areas. In these maps, some specific areas and hotspots
45 appear as potentially more exposed specifically in application period. Overall, predictions were
46 closed to biomonitoring data and ingestion route was the main contributor to chlorpyrifos
47 exposure.

48 **Conclusions:** This study demonstrated the feasibility of an integrated approach for the
49 evaluation of chlorpyrifos exposure which allows the comparison between modeled predictions
50 and biomonitoring data.

51 **Keywords:** Exposure Modeling, PBPK Modeling, Multi-media Studies, Pesticides, Geospatial
52 Analyses

53

54 **1. Introduction**

55 Amongst environmental stressors, chemical agents contribute to geographical environmental
56 health inequalities regarding human exposures [1]. Exposure to chemical agents is complex
57 to characterize due to the multiplicity of contamination sources and exposure pathways
58 (ingestion, inhalation, dermal contact). Pollutant transfer processes into environmental media
59 (air, soil, water) bring a spatial scope to exposure and involves territorial inequalities. Exposure
60 is also time-varying and has potential impacts on people health during lifetime, which is
61 included in the exposome concept [2]. In order to better understand the link between exposure
62 to chemicals with potential health effects, variation of the exposure can be grasped by
63 predicting representative internal doses and more specifically on target tissues of health effects
64 [3].

65 Simultaneously, the cross-analysis of environmental, exposure and human biomonitoring data
66 would enable to build a robust portrayal of the exposome, scalable on a large scale and at the
67 populational level [3]. Integration of such data into a Geographic Information System (GIS)
68 makes the link between source characterization and populational factors for a better
69 understanding of the exposure [4]. Environmental data integration is however made difficult by
70 the multitude of data produced according to specific objectives, with different levels of spatial
71 and temporal aggregation, and requires specific methods and tools [5]. Combination of
72 integrated environmental data with fate and transport modeling from the source to target
73 population provides exposure predictions comparable to measurements in spatially and
74 temporally consistent biological matrices. The comparisons of internal doses predictions with
75 biomonitoring measurements provide the information to evaluate the relevance of the modeling
76 approach.

77 Pesticides constitute a relevant application to use a spatialized and integrated exposure
78 assessment approach. Indeed, these substances, mainly used in agriculture for plant
79 protection, are transferred to air, soil and water after spreading [6]. The ubiquitous nature of
80 pesticides in the environment therefore constitutes a risk to human health [7]. Due to the
81 agricultural use of these products, rural populations living near crop fields where pesticides are
82 applied are likely to be more exposed [8]. The contamination of the atmospheric compartment
83 by pesticides is much less known than soil and water contaminations. Most epidemiological
84 studies start from the hypothesis that pesticide concentrations in air are higher near spreading
85 areas and decrease with the distance [9]. The estimation of pesticide atmospheric emissions
86 has long remained a blocking element for model implementation, due to the diversity of
87 application modes, the dependence of meteorological conditions and the lack of knowledge
88 about microphysics, depositions and remobilization processes. Thus, few studies use a spatial
89 modeling of pesticide atmospheric dispersion [9]. Advances in this field and the possibilities of
90 describing pesticide quantities on fine resolutions now allow the use of atmospheric models on
91 a local scale [10]. In France, there are databases on environmental quality (air, soil, water) and
92 human biomonitoring [11]. Several French studies (Elfe, Esteban) measured the level of
93 exposure to chemicals including pesticides [12]. However, such surveys of representative
94 samples are expensive and technically difficult to conduct in order to characterize the exposure
95 at fine spatial resolutions and on large-scale territories.

96 As an example of active pesticide, Chlorpyrifos (O,O-diethyl O-3,5,6-trichloro-2-pyridinyl-
97 phosphorothioate, CAS Registry No. 2921-88-2; CPF) belongs to the organophosphate class
98 (OP). Since its first use in 1965, it has become one of the most widely used pesticides in the
99 world and finds its main applications in agriculture and domestic use [13]. Human toxicological
100 effects of OP insecticides are associated with the inhibition of acetylcholinesterase (AChE) in
101 the brain and both central and peripheral nerve tissues [14]. Pregnant women are a vulnerable
102 population as associations with prenatal exposure to chlorpyrifos were observed in 3 and 7-
103 year-old children with an IQ and working memory abilities decrease [15, 16]. Recent national

104 studies and reports have shown general population exposure to chlorpyrifos and
105 organophosphate pesticides in France and OECD countries [17-22]. In the study of Béranger
106 et al. [22], TCPy, a metabolite of chlorpyrifos and a common biomarker of chlorpyrifos exposure
107 used in human biomonitoring, was among the molecules measured in hair with the highest
108 median concentrations, with value of 2.7 pg/mg of pregnant women hair.

109 In this context, this paper proposes to use an integrated exposure assessment approach,
110 combining spatio-temporal modeling of environmental exposure and fate of the chemical to
111 define relevant phenomena. The aim of this paper is to demonstrate the feasibility of our
112 integrated methodology for chlorpyrifos exposure assessment. This methodology combines
113 several transfer models with exposure models (multimedia, PBPK), integrates environmental
114 databases and accounts for the spatio-temporal variability of the exposure. This approach
115 provides a mapping of exposure indicators of pregnant women to chlorpyrifos over fine spatial
116 and temporal resolutions using a GIS environment.

117

118 **2. Materials and methods**

119 *2.1. Case study*

120 Chlorpyrifos exposure was assessed in 2013 over the Picardy region in northern France. It is
121 a moderately densely populated region, with an area of 19,399 km² and almost 2 million
122 inhabitants—3% of France's population. Picardy is a region of field crops which highly
123 consume pesticides [23]. Although chlorpyrifos has been progressively banned since 2013,
124 resulting in a 97% decrease in chlorpyrifos sales between 2013 and 2018, higher exposure to
125 this chemical has been observed in 2013 [24, 25]. According to the French National Bank of
126 Plant Protection Products Sales by Authorized Distributors (BNV-D), more than 12 tons of
127 chlorpyrifos have been sold in the region and spread over 1.3 million hectares of agricultural
128 land during this year, being used for cereal and vegetable crops, orchards and vineyards [25,
129 26].

130 Modeling of chlorpyrifos fate and transport between environmental compartments, exposure
131 media and population has required the integration of databases (Table S1) allowing the
132 characterization of pollutant sources in 2013 in Picardy such as the agricultural spreading [25],
133 the meteorological parameters [27] and the environmental concentrations of substances in
134 water and food products [28-30].

135 A deterministic approach integrating and coupling models with environmental data has been
136 developed and applied on this study (Fig. 1). The models have been adapted to allow the
137 integration of the output data of an upstream model as input data of the downstream model.
138 One model assessed ambient air concentrations and deposits (far-field) by considering
139 emission conditions either in gaseous or liquid aerosol phase and meteorological data (near-
140 field). Then, a multimedia model was used to predict pollutant transfers between each
141 environmental compartment (water, air, soil) to predict external exposure resulting from the
142 integration of all media concentrations [31-33]. In addition to this local exposure, the
143 contribution of other exposure sources, e.g. non-local food products, were also accounted.
144 Values of these exposures were then integrated in a PBPK model to predict internal exposure
145 to chlorpyrifos (Fig. 1).

146 Chlorpyrifos exposure was assessed over a weekly time step and a regular grid with a spatial
147 resolution of 4 km². The regular grid constituted a common spatial support on which all the
148 data were described. The following modeling approach therefore gave point estimates on grid
149 cell centroids.

150 *2.2. Input data*

151 *2.2.1. Agricultural data*

152 Annual quantities applied over agricultural fields in Picardy in 2013 were predicted with data
153 from the BNV-D [25]. Product sales extracted from this database were spatially distributed at
154 field resolution using a methodology built by French National Institute for Agriculture, Food,
155 and Environment (INRAE) according to the crop type and the postal code of the purchaser.

156 Based on agricultural spreading times data provided by departmental agricultural chambers,
157 quantities applied were predicted every three hours.

158 *2.2.2. Outdoor air*

159 Parameters including wind, temperature, precipitations, humidity and cloudiness available at a
160 3-hour frequency were extracted from the meteorological stations of Dieppe, Lille, Caen,
161 Rouen and Orly, these framing the target region and describing a representative climate of
162 northern France. Most notably for the atmospheric dispersion statistical model, the database
163 of the Synop Essential network of surface stations of the World Meteorological Organization
164 was used [27].

165 *2.2.3. Non-local food*

166 Concentrations of chlorpyrifos in non-local, i.e. commercial, food products came from French
167 Total Diet Study (EAT2) and European Food Safety Authority's measurement compilations [28,
168 29]. Quantification frequencies of chlorpyrifos in commercial food products were very low
169 (Table S2). Thus, two scenarios were determined to frame exposure to commercial products.
170 The lower bound scenario (LB) is a minimalist scenario for which the undetected values are
171 set to 0 and the values detected but not quantified are set to the limit of detection. The upper
172 bound scenario (UB) is a maximalist scenario for which the undetected values are set to the
173 limit of detection and the values detected but not quantified are set to the limit of quantification.
174 The values used in the upper bound scenario correspond to the maximum chlorpyrifos
175 concentrations measured in commercial food products.

176 *2.3. Fate and transport modeling approach*

177 *2.3.1. Air concentrations and atmospheric deposits*

178 Based on data from the BNV-D, departmental agricultural chambers and the simulations of the
179 quantities applied at a 3-hour step, the distributions on soil, plant and air (drift) in the first
180 minutes after spreading were predicted from PestLCI 2.0 [34] for each agricultural field in

181 Picardy concerned by chlorpyrifos use. Emission fluxes from soil and plant volatilization were
182 predicted with dynamiCROP [31, 32]. Air drift for this short period, as well as emission fluxes,
183 then fed the atmospheric dispersion model described below.

184 The large number of parcels, their heterogeneous boundaries and the strong temporal
185 variability of emissions have driven the modeling approach towards a machine learning
186 approach and the development of a statistical metamodel. A database resulting from ADMS
187 (Numtech, version 5.2) simulations, including gaseous and liquid aerosol deposits on ground
188 and air concentrations, was thus constituted based on emissions of one basic parcel (100 per
189 100 m) and meteorological parameters observed at surface stations [27]. Additional
190 meteorological parameters such as the Monin-Obukhov length and the boundary layer height
191 were calculated and enrich the description of each calculation result so that they can be used
192 as explanatory variables for the learning of the statistical model. The size of aerosols
193 considered for modeling liquid phase drift was set at the lowest value found in the literature
194 [35], i.e., a minimum particle size of 50 μm , in order to give preference to a major atmospheric
195 transport approach. Once the metamodel was calibrated, it was applied on all parcels and
196 provided atmospheric deposits and concentrations of chlorpyrifos either in the gaseous and
197 liquid aerosol phase at a 3-hourly interval. The phase of the substance was assumed not to
198 evolve after emission and considered as a passive tracker.

199 *2.3.2. Multimedia exposure model*

200 Multimedia exposure modeling follows a mass balance approach and is based on the
201 resolution of differential equations with first-rate kinetics. The modeling has been performed
202 with two multimedia models, dynamiCROP [31, 32] for the assessment of environmental
203 transfers, and Modul'ERS [33] to predict chlorpyrifos daily exposure doses from environmental
204 compartments (water, air, soil and food).

205 Contamination of local food products cultivated in vegetable gardens was predicted from
206 atmospheric deposits on plant and root uptake from soil. Four crops corresponding to the main

207 food products consumed [36] were studied: apple, lettuce, potato and tomato. For each crop,
208 one plant model was used to integrate transfer specificities (leaf, fruit, root, tuber). Transfers
209 between plant, air and soil were predicted from the dynamiCROP model which was conveyed
210 to Python language to reduce large computing times generated by Excel and MATLAB ® [31].
211 Chlorpyrifos concentrations were predicted at harvest time. Lettuce being a crop harvested all
212 year round, all concentrations predicted each week of the year were weighted according to a
213 probability of harvesting based on the evolution of the leaf area index (LAI).

214 One model was provided for each crop studied (apple, lettuce, potato, tomato) according to
215 their specificities. In each model, plant biomass and LAI were the main time-varying
216 parameters. The calculation method of these parameters was redefined from the initial model.
217 They were weekly estimated to consider temporal variations. The calculation method of all
218 other parameters directly depending on plant biomass and LAI, i.e., plant compartment
219 biomasses, volumes and areas, part of the deposits reaching compartments, transfer
220 coefficients and flow rates, was thus temporally adjusted. Finally, chlorpyrifos concentrations
221 were computed using time-varied biomass values and transfer coefficients.

222 A percentage of self-consumption was defined from INSEE data [36]. It corresponds to the
223 proportion of home-grown food products consumed (i.e. apple, lettuce, potato and tomato) in
224 total food consumption per person. Four categories were defined, based on the number of
225 inhabitants per urban unit (1) commune with less than 2,000 inhabitants (rural areas) (2)
226 between 2,000 and 10,000 (3) between 10,000 and 100,000 (4) with more than 100,000 (Fig.
227 S1).

228 Consumption of commercial food products was predicted using concentrations measurements
229 from French and European studies (Table S3) and mean dietary beverage products
230 consumption from the SISE-Eaux database [30].

231 Aggregated multimedia exposure was then assessed from ingestion and inhalation pathways.
 232 Inhalation pathway was given as the sum of chlorpyrifos concentrations (C_{inh} , $\text{mg}\cdot\text{m}^{-3}$) in its
 233 liquid (C_{par}) and gaseous (C_{gas}) phase:

$$234 \quad C_{inh} = C_{par} + C_{gas} \quad (\text{Eq. 1})$$

235 Ingestion pathway was predicted considering weight, quantities of food products ingested,
 236 water consumption [30], soil ingestion [37] and a self-consumption factor characterizing local
 237 food products ingestion. Intake from food products, water and soil, i.e. daily ingested doses
 238 (D_{ing} , $\text{mg}\cdot\text{kg}\ \text{bw}^{-1}\cdot\text{d}^{-1}$) were given from Eq. 2:

$$239 \quad D_{ing} = I_{com,food} + I_{veg} + I_{soil} + I_{H2O} \quad (\text{Eq. 2})$$

240 where $I_{com,food}$, I_{veg} , I_{soil} and I_{H2O} are intakes from commercial food products, local and
 241 commercial vegetables, soil and water.

242 2.3.3. Toxicokinetic modeling and internal exposure

243 To model the pharmacokinetics behavior of chlorpyrifos and its two metabolites: chlorpyrifos-
 244 oxon (O,O-diethyl O-3,5,6-trichloro-2-pyridyl; CPF-oxon) and trichloropyridinol (3,5,6-trichloro-
 245 2-pyridinol; TCPy), we used a PBPK/PD model developed by Poet et al. [38]. The model
 246 structure includes 10 tissue compartments for chlorpyrifos, 6 for chlorpyrifos-oxon and one
 247 urinary compartment for TCPy. This model considers changes in physiology, metabolism and
 248 sensitivity to toxicity over life-stages from childhood to adulthood and multi-route exposure
 249 [38]. It includes also physiological and metabolic changes that occur with pregnancy (increase
 250 in cardiac output, blood volume, fat mass). Three compartments (uterus, placenta, fetus) and
 251 their respective diffusion coefficients are included to describe the pregnancy [38]. The
 252 PBPK/PD model simulates the organ and blood concentrations of chlorpyrifos and chlorpyrifos-
 253 oxon as well as the urinary excretion of TCPy. The model, initially built with acsIXtreme (Aegis
 254 Technologies), was converted to C-based GNU software MCSim [39].

255 *2.4. Statistical analysis*

256 In order to construct the exposure maps from spatialized databases, several statistical
257 methods were used to specifically address environmental, behavioral or populational
258 databases to increase their representativeness regarding the objectives of the exposure
259 characterization. Data processing methods were adapted from the GIS-based modeling
260 platform PLAINE (“Environmental INequalities Analysis PLaform”) [40]. Statistical and
261 geoprocessing methods interfaced in a GIS were particularly used to bypass the issues
262 generated by data gaps and predict exposure indicators on the areas of interest.

263 Since air inputs were the main environmental spatial determinant considered in the modeling,
264 a geostatistical analysis was conducted on atmospheric concentrations and deposits to assess
265 spatial autocorrelations. This analysis was conducted in order to better define a relevant grid
266 spatial resolution for reducing computation time and investigate the possibility to predict
267 exposure at a specific point (i.e. a located address of a cohort participant to compare with
268 measured biomarker) from initial grid calculation. This analysis consisted of studying the
269 sample 2D-variogram and testing the anisotropy [41]. The variogram computed the
270 dissimilarities between two-point values according to the distance between the points.
271 Anisotropy was tested to verify whether spatial variability trends of the phenomena changed
272 as a function of the direction [42]. These analyzes were carried out with R software and the
273 package “RGeostats” (<https://rgeostats.free.fr>).

274 **3. Results**

275 *3.1. Spreading times and implications in temporal variations of chlorpyrifos* 276 *presence*

277 Most of the applications occurred between the tenth and the nineteenth week of the year, i.e.
278 from mid-March to mid-May. The peak of applications was observed during April, between the

279 thirteenth and the sixteenth week of the year. At this time, the mean amount of chlorpyrifos
280 applied by parcel exceeded 50 kg, or 5.7 kg/ha (Fig. 2).

281 Following an application, air drifts occurred in a short time and were concentrated over a 36-
282 hour period. Volatilization rates, whether from soil or plant, extended over a longer period and
283 behaved on the same way. 95% of volatilization rates were concentrated over a 3-week period
284 (Fig. S2). The temporal evolutions of chlorpyrifos concentrations predicted in several
285 environmental matrices such as air and lettuce were similar to those of volatilization rates (Fig.
286 S3). For these two matrices, only 1% of initial concentrations remained after one month.
287 However, concentration decrease in soil was slower to the point that there was still a third of
288 chlorpyrifos after one month. It took about three months to drop below 5% of initial
289 concentrations (Fig. S3).

290 *3.2. Chlorpyrifos presence in environmental media and its spatialization*

291 *3.2.1. Atmospheric concentrations and deposits*

292 The annual mean of predicted air concentrations varied from 0 to 5.5×10^{-5} mg/m³ for the whole
293 region. The spatial distribution of concentrations was rather homogeneous over Picardy. The
294 main hotspots were located in the north-west of the region between Amiens and Abbeville, but
295 also in the southwest of Beauvais, south of Soissons and around Laon (Fig. S4A). Monthly
296 mean air concentrations during April varied from 0 to 7×10^{-4} mg/m³ over the Picardy region
297 and were up to 13 times higher than annual mean concentrations. Spatial distribution of air
298 concentrations in April was broadly the same as for the annual mean concentrations (Fig. S4B).
299 During the year, total atmospheric deposits per grid cell varied from 0 to 65 mg/year in Picardy.
300 Spatial distribution of deposits was fairly homogeneous over Picardy. Main hotspots were
301 located in the north-west of the region between Abbeville and Amiens as well as in the south-
302 east (Fig. S4C). In April, atmospheric deposits represented on average 75% of the annual
303 totals and rose up to 100% in some areas (Fig. S4D).

304 The spatial distribution of atmospheric concentrations and deposits both displayed the same
305 spatial structure and an anisotropy axis oriented from west southwest to east-northeast with a
306 65-degree angle to the North (Fig. S5). For both concentrations and deposits, the orthogonal
307 variograms displayed a little anisotropy since the anisotropy ratios, for the minor axis, were
308 0.819 for concentrations and 0.843 for depositions. Additionally, ranges (i.e. distances where
309 the model flattens out and where the autocorrelation between sample locations becomes
310 negligible) were also close, i.e. 66 km for the major axis and 55 km for the minor axis (Fig. S6A
311 and B).

312 *3.2.2. Local food products*

313 Local food products, i.e. vegetable gardens in the vicinity of crop fields, are indirectly
314 contaminated with chlorpyrifos deposits. Predicted concentrations in local-produced apples,
315 potatoes and tomatoes were comprised, for 95% of them, between 9.4×10^{-12} and 9.1×10^{-8}
316 mg/kg of fresh weight for apples, 2.4×10^{-11} and 2.3×10^{-7} mg/kg of fresh weight for potatoes,
317 7.5×10^{-11} and 6.9×10^{-7} mg/kg of fresh weight for tomatoes respectively. Local food
318 concentration predictions were less dispersed and rather centered around the median of the
319 two concentration scenarios based on commercial food products measured (Fig. S7). For
320 local-produced lettuces however, predictions were more centered around the maximum value
321 measured in commercial lettuces, which peaked at 1.1×10^{-2} mg/kg of fresh weight. Even 13%
322 of predictions exceeded this maximum measured value. This singularity trend came from the
323 cultivation of lettuce, which can be harvested throughout the year, while other crops are
324 harvested several months after the end of spreading.

325 *3.3. Chlorpyrifos external exposure*

326 Annual mean daily inhalation doses for pregnant women varied between 0 and 9.1×10^{-6}
327 mg/kg/d. The mean daily inhalation dose map clearly brought out rural areas with some
328 hotspots distributed all over Picardy. Urban areas (categories 3 and 4, Fig. S1) showed low to
329 medium inhalation doses, but the lowest doses were located in non-agricultural areas such as

330 forests and tidal marshes. Spatial variability was high, extending over 10 orders of magnitude
331 (Fig. 3A). Average daily inhalation doses during April varied between 0 and 1.2×10^{-4} mg/kg/d
332 and exceeded the annual doses by a ten-fold factor. However, the April daily inhalation doses
333 map presented the same spatial variability trend, i.e. hotspots in rural areas and lowest doses
334 in forests and tidal marshes, as the annual map (Fig. 3B).

335 Annual mean daily ingestion dose maps for the lower bound scenario varied by a hundred-fold
336 factor, between 1.6×10^{-7} and 4.5×10^{-5} mg/kg/d. There was no major difference—only 1.5% for
337 the lower bound hypothesis—between annual mean and April mean ingestion doses. As for the
338 inhalation, the lower bound scenario maps of daily exposure doses (Fig. 3C and D) brought
339 out rural areas with hotspots in northern and southeastern Picardy. In the upper bound case,
340 annual mean daily ingestion doses displayed a small variability across the entire area as the
341 range between the minimal and maximal values, respectively 2.9×10^{-4} and 3.4×10^{-4} mg/kg/d,
342 varied by 15%. There was no difference between annual mean and April mean ingestion
343 doses. The hotspots observed in the lower bound scenario maps were also observed in the
344 upper bound scenario maps although both were globally more homogeneous (Fig. 3E and F).

345 *3.4. Environmental inequality characterization*

346 Annual mean TCPy urinary concentrations for pregnant women, resulting from the aggregation
347 of inhalation and ingestion pathways, were comprised between 1.9×10^{-6} and 6.6×10^{-4} mg/L,
348 i.e. a 3-hundred factor, in the lower bound scenario. For the April predictions, the range of
349 values extended by a thousand-fold factor, between 2.3×10^{-6} and 2.5×10^{-3} mg/L. We observed
350 a significant difference of values between the entire year and April. Indeed, April predictions
351 were three to four times higher than annual predictions for the lower bound scenario (Fig. 4A
352 and B). With the upper bound scenario, the range of TCPy urinary concentrations varied by
353 18% for the annual mean and were comprised between 3.6×10^{-3} and 4.2×10^{-3} mg/L. For April,
354 the range of predictions varied by 60%, with concentrations comprised between 4.2×10^{-3} and
355 6.6×10^{-3} mg/L. April predictions exceeded by 19% the annual predictions (Fig. 4C and D).

356 The temporal evolution of TCPy urinary concentrations for pregnant women at the end of their
357 first trimester were commonly at a steady state but strongly varied during the spreading period
358 (Fig. S8). For the lower bound scenario, urinary TCPy concentrations began to increase in
359 March and reached a maximum in April (about 90% of the maximum urinary TCPy
360 concentrations). Then, the urinary TCPy concentrations decreased within six weeks and
361 returned to steady state (about 20% of the maximum urinary TCPy concentrations).

362 The analysis of pathways contributions to TCPy urinary concentrations showed that ingestion
363 was the prominent exposure pathway for both scenarios. It counted for 85 % of overall
364 exposure in the lower bound scenario and reached 99,5 % in the upper bound scenario (Fig.
365 5). For this pathway, contributions of local food and commercial food also differed significantly
366 between scenarios. While local food was the only contributor to the ingestion route in the lower
367 bound scenario, commercial food largely dominated in the upper bound scenario (accounting
368 for 99,2 % of total exposure against 0,3 % for local food). These observations only concerned
369 annual mean. Inhalation contribution fluctuated monthly and became substantial during
370 months where spreading was the highest. While inhalation contributed to 38 and 45% of overall
371 exposure in March and May, it became the major pathway in April (83%) when considering
372 lower bound case. Commercial food still dominated in the upper bound scenario even if
373 inhalation contribution reached 4% in April.

374

375 **4. Discussion**

376 In this study, we performed an integrated and spatialized exposure assessment approach
377 applied for a pesticide at a regional scale. The coupling of models and the integration of
378 environmental data in a GIS environment provides a detailed mapping of chlorpyrifos
379 exposure. These maps provide insights for the identification of potentially more exposed areas
380 and populations. The cartography of TCPy urinary concentrations in the lower bound scenario
381 clearly highlights agricultural areas. In these maps, some specific areas and hotspots appear

382 as potentially more exposed specifically in application period. For both scenarios, the different
383 dietary behaviors between rural and urban areas reflect higher chlorpyrifos levels among the
384 rural areas. These results are consistent with previous biomonitoring studies which have also
385 found higher levels of urinary metabolite concentrations in rural populations than in urban
386 populations or the general population [8, 43-45].

387 The comparison between internal dose predictions and measurements from biomonitoring
388 studies allows to appreciate the quality of predicted values. Predictions were compared with
389 data from North American cohorts measured over similar periods but not with French
390 campaigns such as ELFE or ENNS because the TCPy was not retained in these studies [17,
391 18]. Moreover, a regional cohort, "MecoExpo", was constituted to estimate prenatal exposure
392 but the analyzes did not allow to find traces of chlorpyrifos or its metabolites. Comparisons of
393 TCPy urinary concentrations predictions with biomonitoring campaigns are shown in Table 1.
394 Overall, the distribution of predictions lies in the range of the distributions of the measurements
395 regardless of the period of the year. However, biomarker measurements consider all sources
396 and exposure pathways at the individual level. Combined with questionnaires providing
397 information on lifestyle habits, biomarker measurements and predictions of modeled internal
398 concentrations allow to provide environmental contributions to distinguish behavioral and
399 professional factors in the context of explanatory analyzes of impregnation.

400 In this study, we considered that TCPy urinary concentrations were only due to the
401 metabolization of chlorpyrifos in human body. However, populations are directly exposed to
402 chlorpyrifos-oxon and TCPy in the environment [48]. The presence of chlorpyrifos-oxon and
403 TCPy in the environment could occur from the degradation of chlorpyrifos by biotic
404 (microorganisms) and abiotic (photolysis, hydrolysis) processes [13]. It is then necessary to
405 improve the consideration of degradation phenomena of chlorpyrifos in the environment
406 especially as degradation is the main factor explaining mass evolution of pesticides [31].

407 Concerning the contributions to TCPy urinary levels, ingestion of commercial food is the most
408 contributive pathway for the upper bound scenario. This finding is consistent with previous

409 studies which found ingestion as the prominent residential exposure pathway [49, 50].
410 However, many uncertainties emerge from commercial food products data. Indeed, there are
411 a high number of concentrations below detection and quantification limits within food
412 databases. This led to a dual scenarization (lower and upper bound) of the exposure
413 assessment which probably gives extreme estimates. In view of this, the integration of
414 additional data, measured or modeled, would improve exposure predictions. Also, several
415 statistical methods would allow to process data for which the majority of samples are below
416 the limits of detection and quantification [51, 52]. Moreover, probabilistic approaches such as
417 Monte Carlo methods could propagate uncertainties over the entire computation chain. If we
418 consider that ingestion of commercial food products contributes to more than 99% of
419 aggregated exposure in the upper bound scenario, the influence of the atmospheric part is
420 therefore marginal. Conversely, the lower bound scenario does not consider the ingestion of
421 commercial food products and we only observe the contribution of the atmospheric part, i.e.
422 ingestion of local food products and inhalation. Actual chlorpyrifos exposure probably lies
423 between the two scenarios.

424 Exposure to chlorpyrifos can also result from exposure to other environmental media such as
425 indoor air or home dust [49]. Our predictions do not consider indoor exposures derived from a
426 former or current domestic use or medium contamination by outdoor sources. This source is
427 potentially non-negligible as chlorpyrifos can stay many months after use [14]. In the same
428 way, dermal pathway was not considered because it does not contribute significantly to overall
429 exposure [53, 54], especially since dermal absorption is less than 3% [55, 56]. However, it
430 could be incorporated into residential exposure assessment if contamination of indoor
431 environments is considered as a source of exposure. It could also become a non-negligible
432 exposure pathway in the case of agricultural workers using pesticides.

433 To improve this approach and regarding the computation time, it is necessary to address the
434 relevance of the spatial and temporal resolutions of analysis to obtain the best compromise
435 between predictions and computation times. In our study, seasonality of spreading plays a

436 major role in the variability of exposure and contamination of environmental media over time,
437 unlike diet whose contribution to overall exposure remains the same throughout the year.
438 Following spreading, chlorpyrifos persists a few weeks to a few months in environmental
439 media. In our study we demonstrated that the variation in TCPy urinary concentrations was
440 greater during the three months of spreading. For both environmental media and humans,
441 chlorpyrifos levels do not return to their previous state until one month after spreading. This
442 analysis shows that it would be better to use a variable temporal resolution, focusing most of
443 the predictions during the exposure window between mid-March and mid-June. Additionally,
444 we chose a regular geographic grid cell to assess populational exposure regardless of their
445 remoteness to agricultural areas. To obtain a grid resolution more representative of
446 populational exposure at an individual level, we used geostatistical methods and the variogram
447 analysis of chlorpyrifos atmospheric concentrations and deposition. This additional analysis
448 makes it possible to apprehend spatial autocorrelation structures of these phenomena. From
449 the analysis of the variogram models, we could define optimized spatial entities able to capture
450 relevant individual and aggregated environmental and population information.

451

452 **5. Conclusion**

453 This study demonstrated the feasibility of an integrated approach for the evaluation of exposure
454 to chlorpyrifos across the Picardy region. The use of this approach and the choice of fine
455 spatio-temporal resolutions would allow researchers to improve exposure assessment
456 methods. Both measurement and modeling approaches allow to assess the exposure of the
457 populations considered with their own limits and uncertainties. The intersection of these
458 complementary approaches improves the efficiency of decision-support tools to reduce the
459 health and environmental impacts associated with exposure. Population stratification in the
460 sampling plan based on exposure predictions can help reducing the number of samples in
461 biomonitoring campaigns by selecting more contrasting individual profiles in terms of exposure.

462 Likewise, predicting the evolution of biomarkers as a function of exposure makes it possible to
463 guide biomonitoring studies in order to identify key moments for sampling as well as to target
464 specific areas and moments in the year.

465 Beyond the uncertainties generated by data and models, the cartography of chlorpyrifos
466 exposure helps decision-makers to identify potentially more exposed areas and populations
467 and guide exposure reduction policies. To improve the approach, localized and regional
468 biomonitoring campaigns should be conducted to compare them with exposure predictions.
469 The analysis of spatio-temporal resolutions will also allow to extend the methodology on larger
470 territories and other substances. Before that, a next step will be to refine this approach by
471 integrating new datasets, other exposure pathways (indoor environments) and by using a
472 probabilistic method based on Monte Carlo analysis. The representativeness of measurement
473 data will also be improved by using advanced statistical methods to reconstruct censored data.
474 The use of a probabilistic method will allow to consider uncertainties and to propagate them
475 throughout the computing chain.

476

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483 **Conflict of Interest**

484 The authors declare that they have no conflicting interests.

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488 plan context.

489

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652

653 Figure legends

654 Table 1 – Comparisons of TCPy urinary concentrations (mg/L) predicted with measurements from biomonitoring campaigns.

655 Figure 1 – Conceptual scheme of the modeling approach used in this study. Environmental data (blue) are integrated into models (green) which
656 characterize the transfers of chlorpyrifos from the source to the contamination of the target populations. Output data generated by these models
657 (white) are themselves integrated as input data of the following model. At the end of the modeling chain are predicted the external and internal
658 exposure doses (yellow).

659 Figure 2 – Seasonality of chlorpyrifos spreading in Picardy. Red symbols are the mean and the 95 % confidence interval of the quantities applied
660 on each agricultural field. Note that the application period is very short and that the peak is reached during early spring.

661 Figure 3 – Mapping of daily exposure doses for the inhalation and ingestion pathways for pregnant women in Picardy. A) Mean annual daily inhalation
662 doses; B) Mean daily inhalation doses during April; C) Mean annual daily ingestion doses (lower bound); D) Mean daily ingestion doses during April
663 (lower bound); E) Mean daily ingestion doses (upper bound); F) Mean daily ingestion doses during April (upper bound). There is a seasonal difference
664 between annual and April mean inhalation doses but not for ingestion doses. For these, only the difference between the scenarios is notable.

665 Figure 4 – Mapping of urinary concentrations of TCPy for pregnant women in Picardy. A) Mean annual urinary concentrations (lower bound); B)
666 Mean urinary concentrations during April (lower bound); C) Mean annual urinary concentrations (upper bound); D) Mean urinary concentrations
667 during April (upper bound). These maps result from the aggregation of the ingestion and inhalation exposure pathways for each scenario. For the
668 lower bound scenario, there is a difference in urinary concentrations between the year and April. This case is however not found in the upper bound
669 scenario.

670 Figure 5 – Mean contributions of exposure pathways to aggregated TCPy urinary concentrations for the lower bound (A) and upper bound (B)
671 scenarios. For both scenarios, ingestion is the major exposure pathway.

672 Tables

	Population	Period	P10	P25	Percentile		P90	P95
					P50	P75		
	Lower bound (year)		2.70e ⁻³	5.40e ⁻³	1.07e ⁻²	2.18e ⁻²	4.25e ⁻²	6.82e ⁻²
	Lower bound (April)		5.76e ⁻³	1.86e ⁻²	4.28e ⁻²	9.23e ⁻²	0.18	0.28
	Upper bound (year)		3.56	3.56	3.57	3.58	3.60	3.63
	Upper bound (April)		4.17	4.18	4.21	4.25	4.34	4.44
	Non-farmworkers women (Hispanic)	2013	–	1.3	2.6	3.7	4.2	–
	NHANES (2019) [20]	2009 – 2010	–	–	0.34	1.88	3.22	4.40
	Health Canada (2017) [19]	2014 – 2015	0.31	–	1.10	–	5.20	7.80
	Pregnant women (Afro-American and Dominican)	2001 – 2004	<0.26	<0.26	<0.26	1.02	3.30	4.80

673

Supplemental materials

Spatio-temporal assessment of pregnant women exposure to chlorpyrifos at a regional scale

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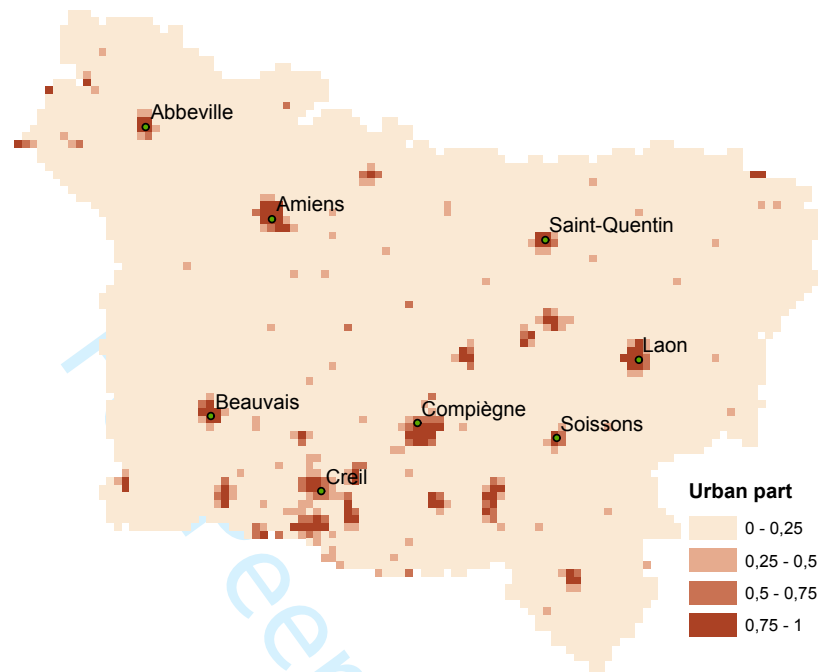


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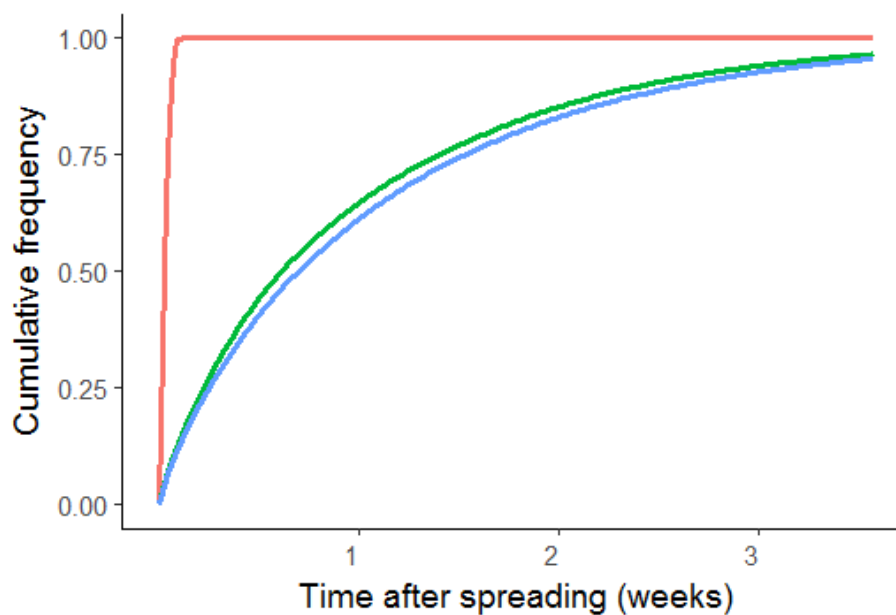


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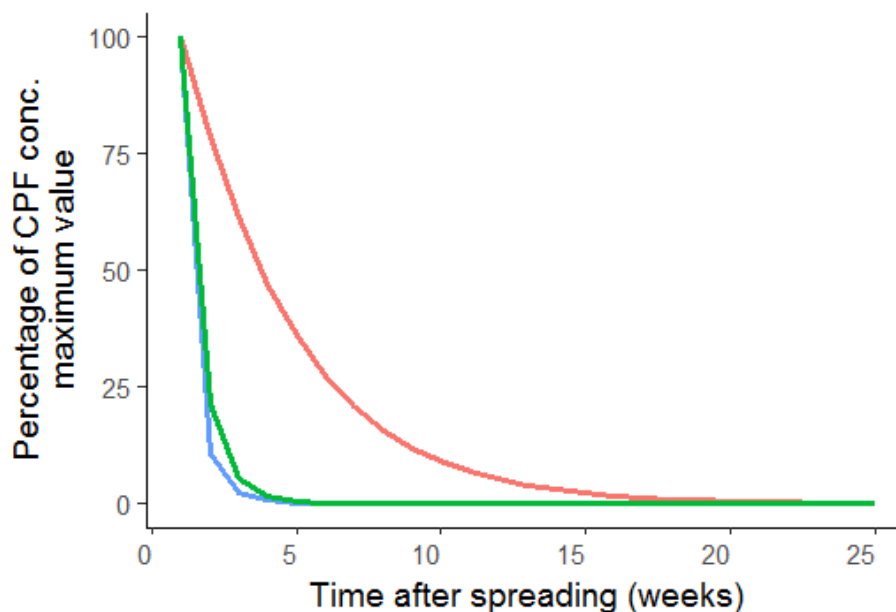


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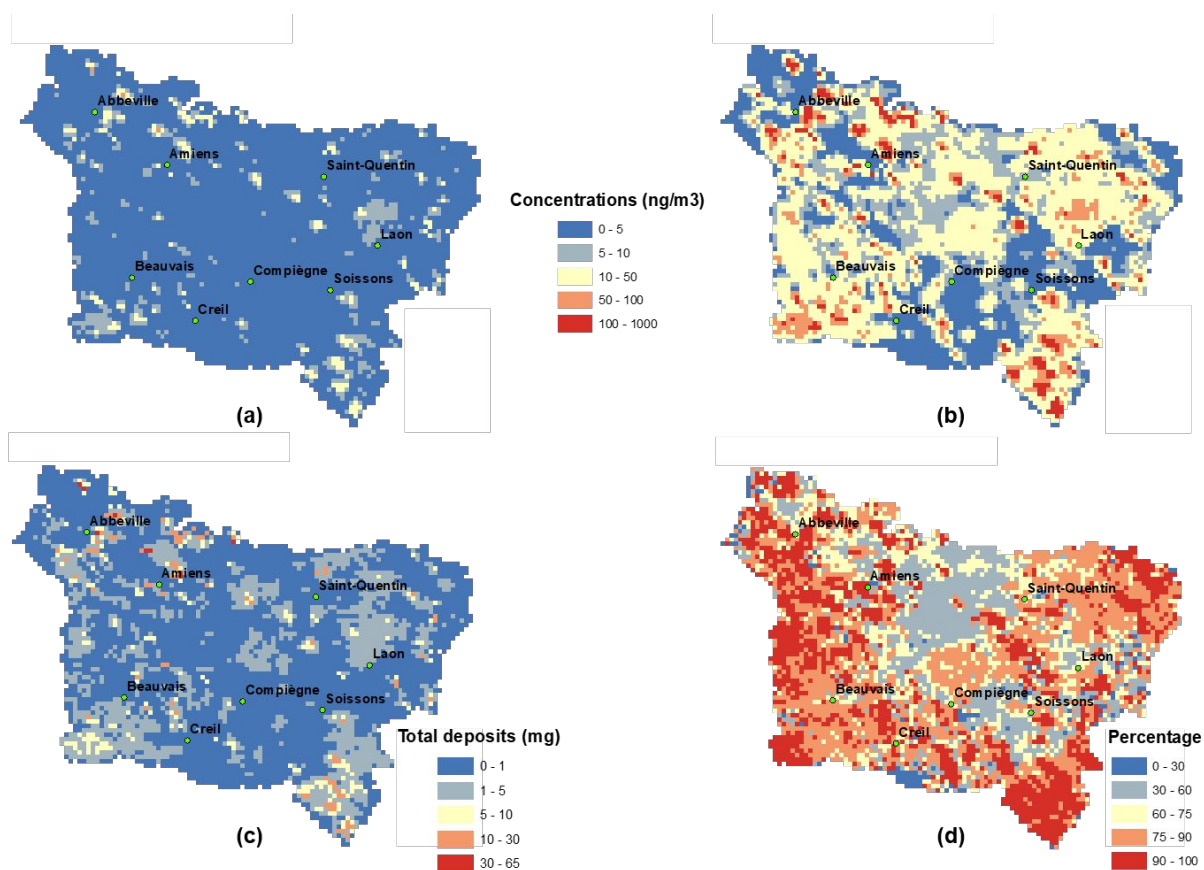


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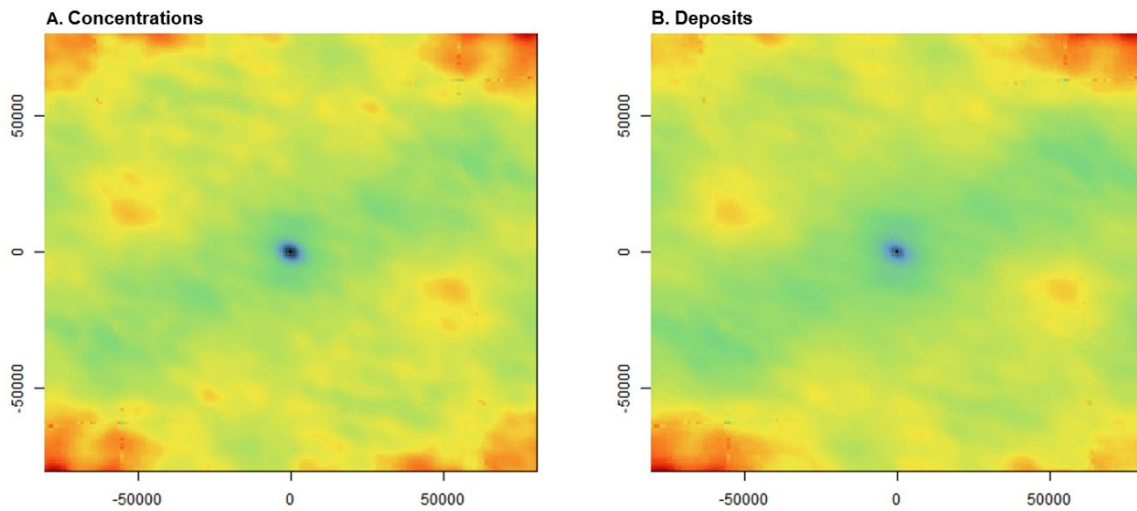


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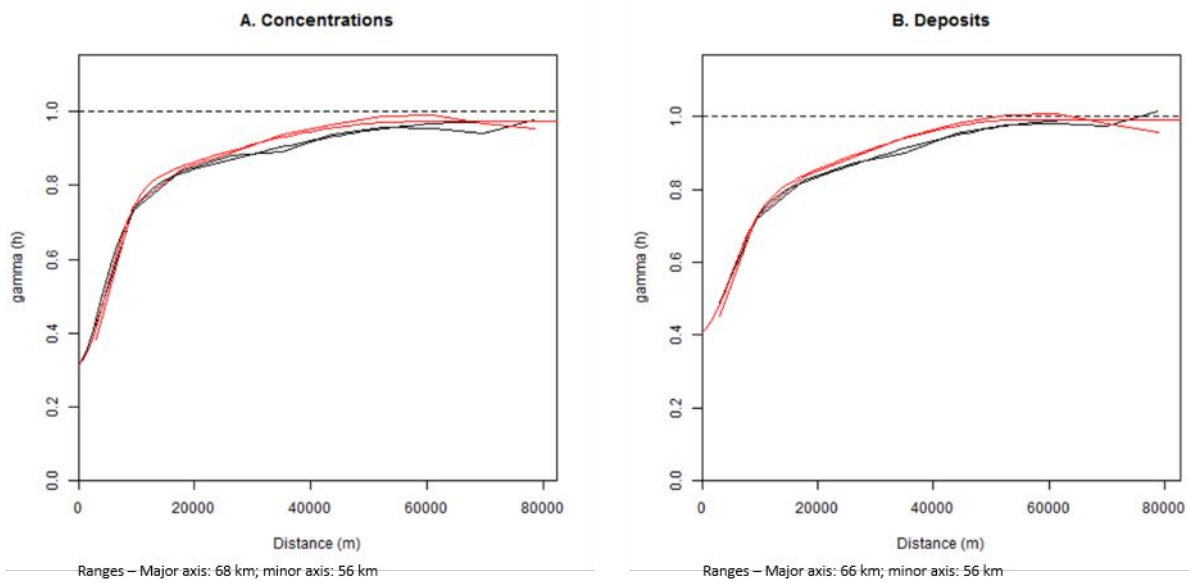


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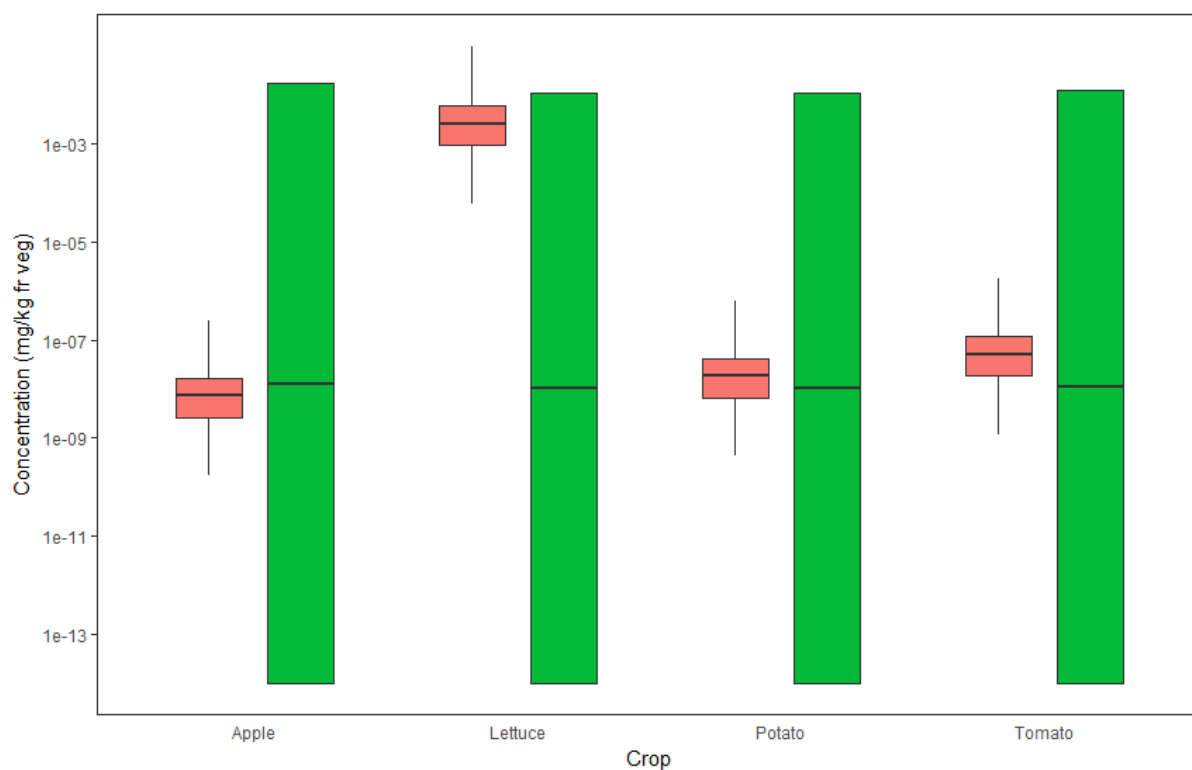


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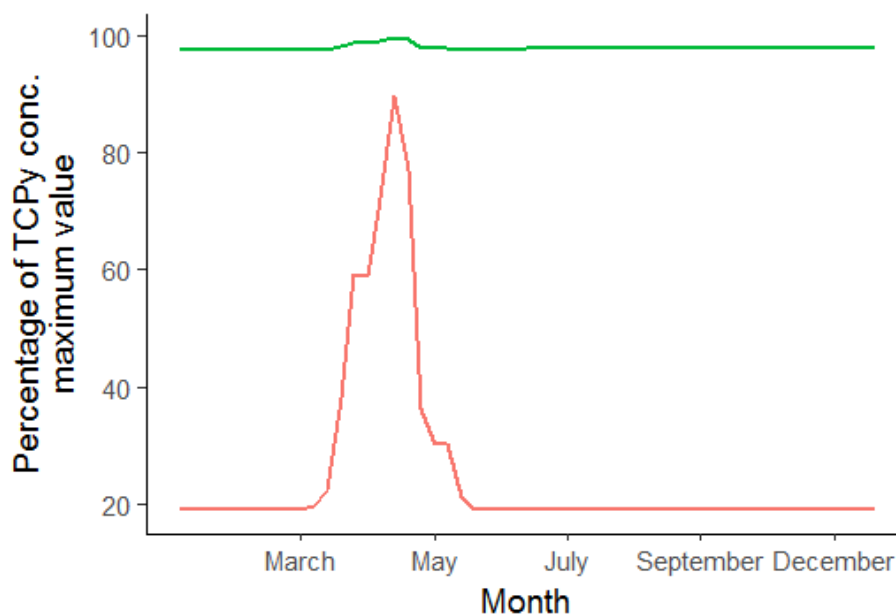


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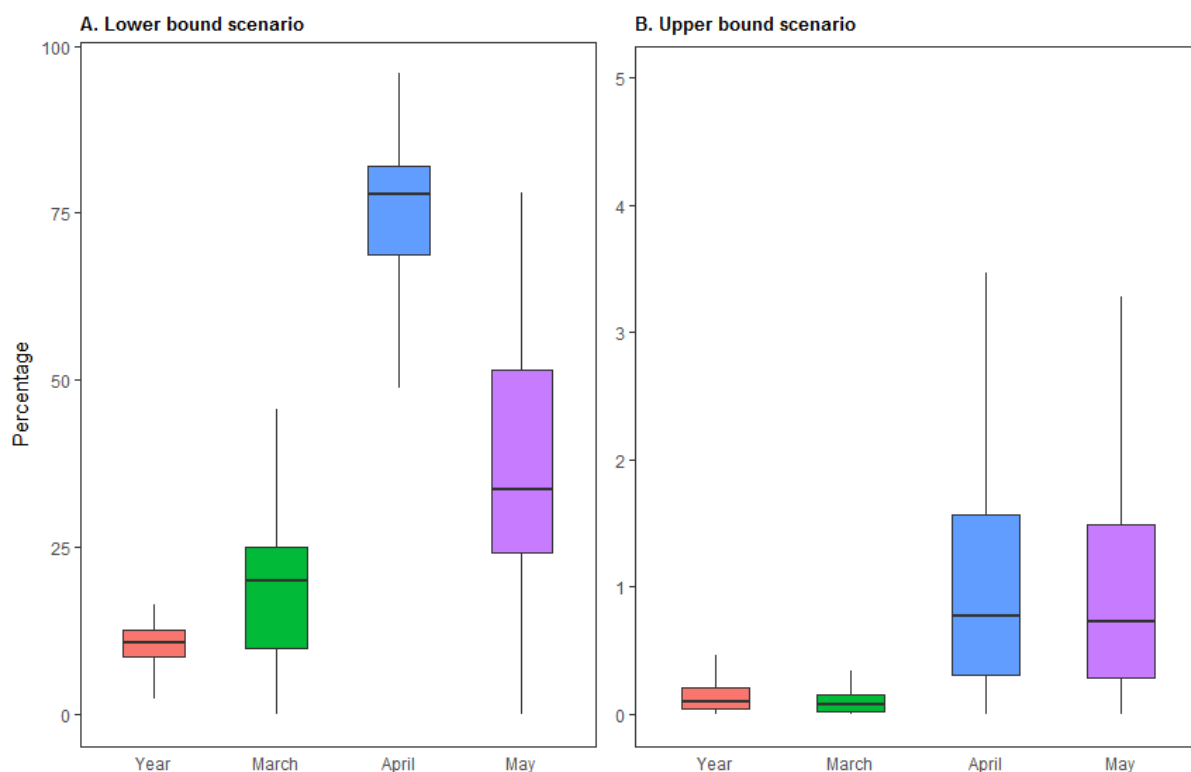


Figure S9 – Inhalation pathway contributions to overall TCPy concentrations. Comparisons between annual mean and monthly means for months which agricultural spreading are the highest.

Tables

Table S1 – Available data and use.

Variable	Data source and use
Plant protection product sales	National Bank of Plant Protection Products Sales by Authorized Distributors (BNV-D, 2020). To be used to predict annual quantities applied.
Spreading times	Departmental agricultural chambers (Chambres d'Agriculture Hauts-de-France, 2020). To be used to predict annual quantities applied.
Wind Temperature Precipitations Humidity Cloudiness	Synop Essential WMO (Synop Essentielles OMM, 2020). To be used to predict atmospheric dispersion.
Concentrations in commercial food products	French Total Diet Study (Leblanc et al., 2011) and EFSA (EFSA, 2015). To be used to predict dietary ingestion exposure.
Concentrations in tap water	SISE-Eaux (Davezac et al., 2008). To be used to predict water consumption exposure.

Table S2 – Quantification rates obtained from different food products in EAT2 and EFSA studies.

Study	Quantification rate
EAT2 (France)	1.1%
EFSA (EU)	7.3%

Table S3 – Concentration values used for commercial food products (mg/kg of fresh weight).

Food product	LOD	LOQ	Scenario	
			Lower bound	Upper bound
Apple	3e ⁻³	1.2e ⁻²	0	1.69e ⁻²
Lettuce	2.5e ⁻²	5e ⁻²	0	1.12e ⁻²
Potato	5e ⁻³ or 1e ⁻²	– ^a	0	5.6e ⁻³
Tomato	2.5e ⁻²	5e ⁻²	0	1.23e ⁻²
Other food products ^b	Between 1e ⁻³ and 2.5e ⁻²	Between 3e ⁻³ and 5e ⁻²	0	6.49e ⁻²

^aAll samples were below the limit of detection (LOD).

^bThe minimum limit of detection (LOD) was equal to 1e⁻³ mg/kg of fresh weight for meat, fish, seafood and dairy products. The maximum LOD was equal to 2.5e⁻² mg/kg of fresh weight for all vegetables excluding potatoes. The minimum limit of quantification (LOQ) was equal to 3e⁻³ mg/kg of fresh weight for merguez. The maximum LOQ was equal to 5e⁻² mg/kg of fresh weight for artichokes and turnips.

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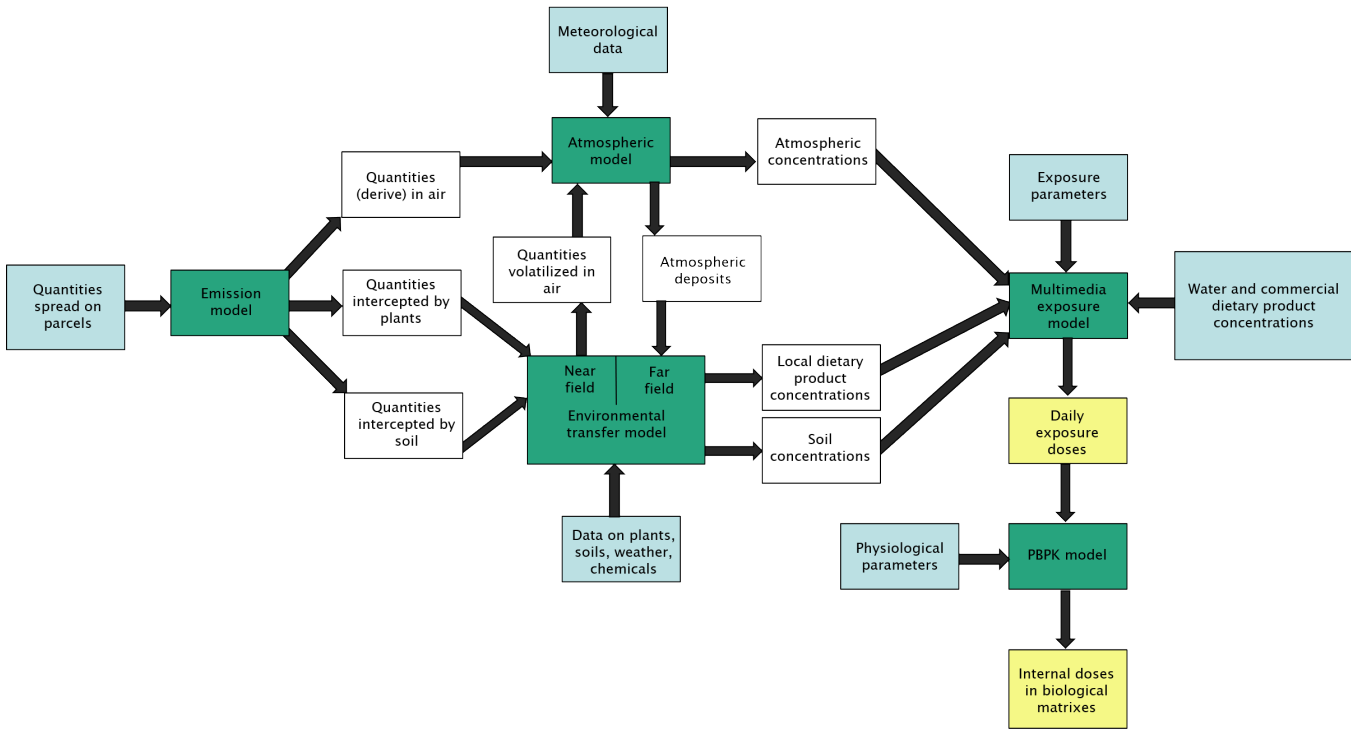
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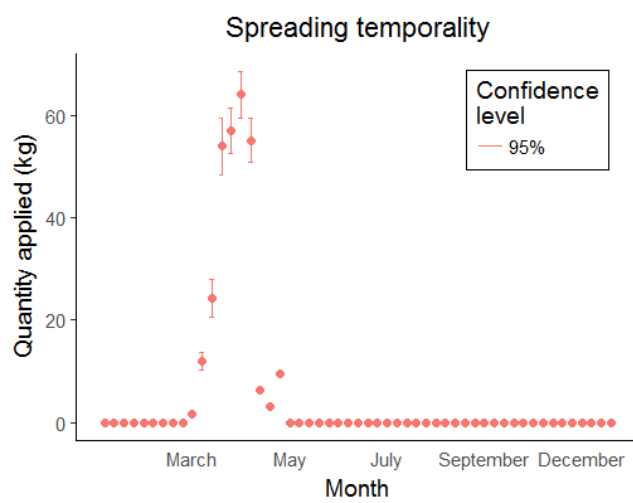
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Figure 2



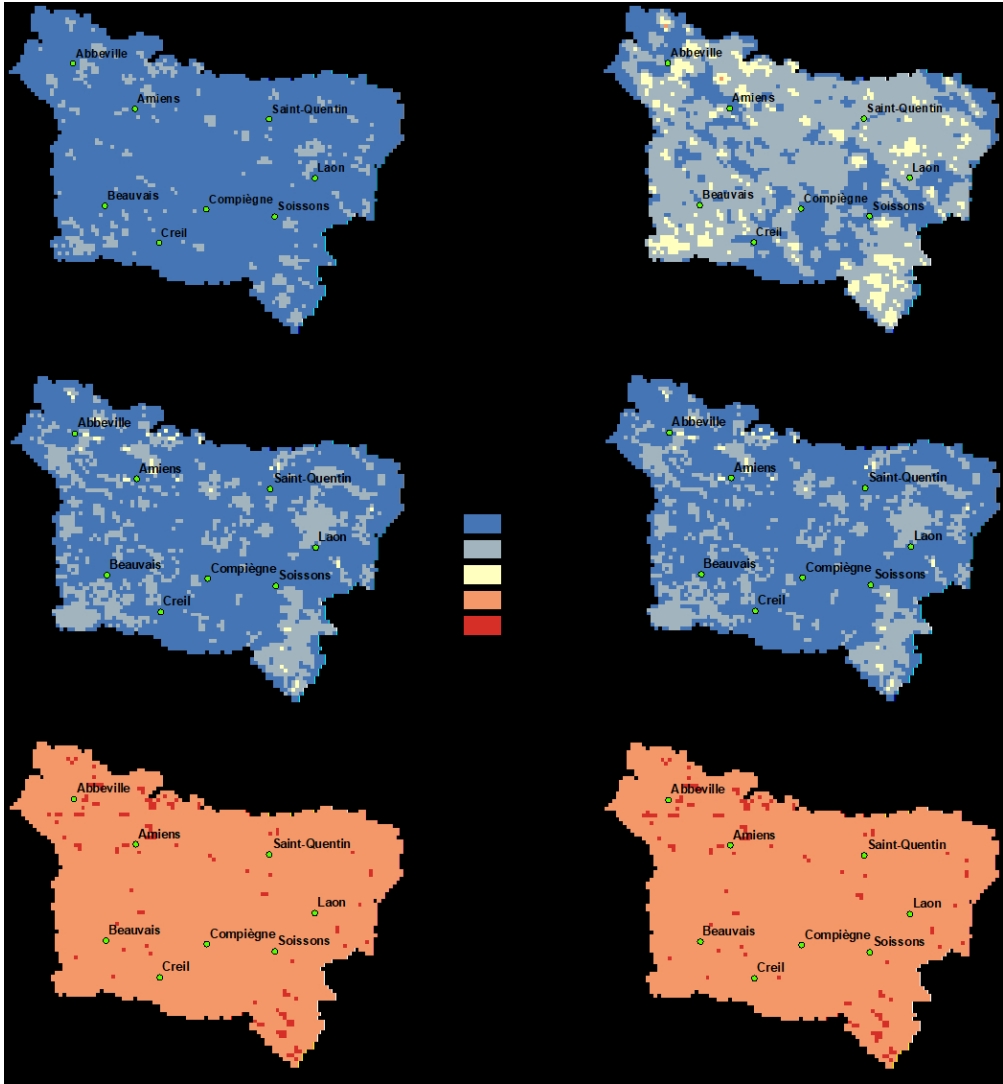


Figure 4

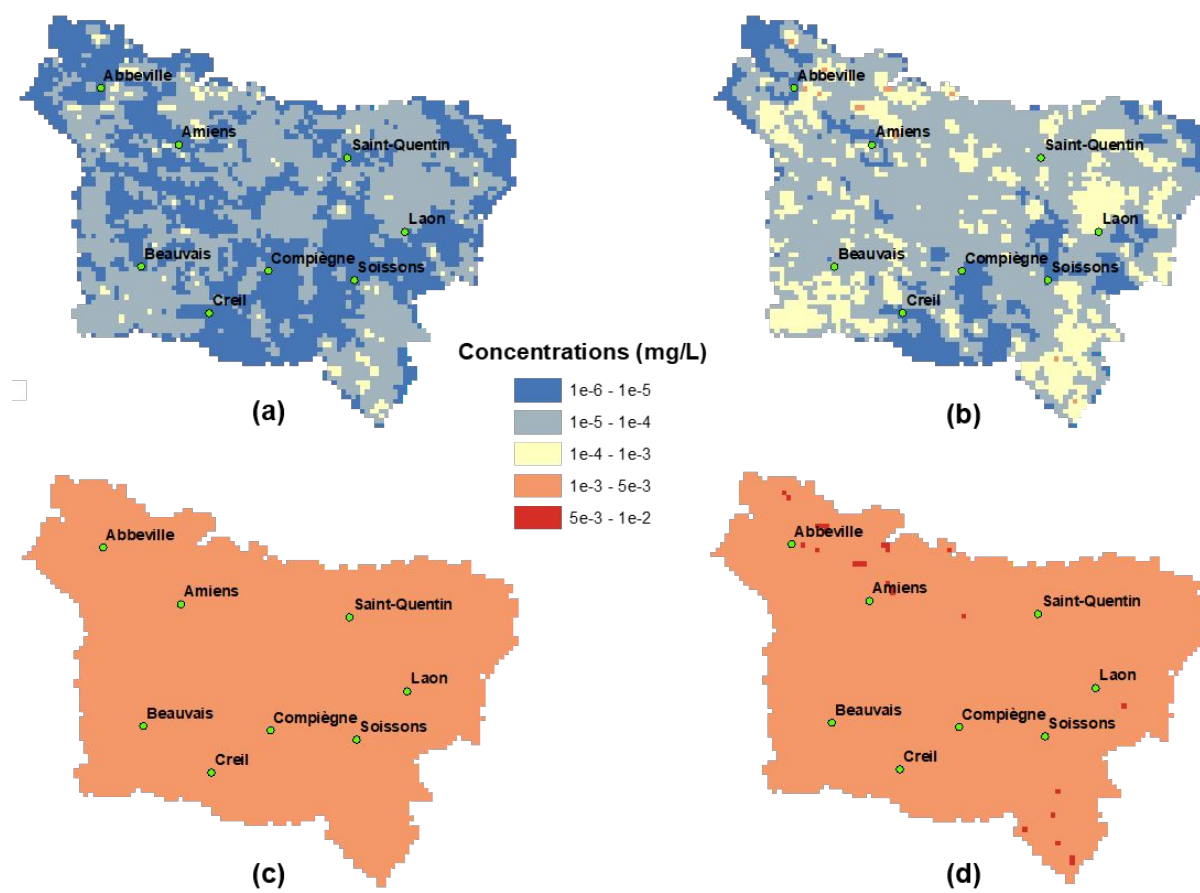


Figure 5

