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1 **Air pollution modeling and exposure assessment during pregnancy in the French**
2 **Longitudinal Study of Children (ELFE)**

3 Emmanuel Riviere^a, Julien Bernard^a, Agnès Hulin^b, Jonathan Virga^c, Fabrice Dugay^d, Marie-
4 Aline Charles^{e,f}, Marie Cheminat^e, Jérôme Cortinovis^g, François Ducroz^h, Anne Laborieⁱ, Laure
5 Malherbe^j, Damien Piga^c, Elsa Real^l, Pierre-Yves Robic^k, Cecile Zaros^e, Emie Seyve^l, Johanna
6 Lepeule^l

7

8 ^aATMO Grand Est, France

9 ^bATMO Nouvelle-Aquitaine, France

10 ^cATMO Sud, France

11 ^dAIRPARIF, France

12 ^eIned-Inserm-EFS joint unit Elfe, Paris, France

13 ^fInserm Univ Paris Descartes, U1153 CRESS, Paris, France

14 ^gATMO Normandie, France

15 ^hAIR Pays-de-la-Loire, France

16 ⁱATMO France, France

17 ^jNational Institute for industrial Environment and Risks (INERIS), Verneuil en Halatte, France

18 ^kATMO Occitanie, France

19 ^lUniv. Grenoble Alpes, Inserm, CNRS, IAB, 38000 Grenoble, France

20

21

22 Correspondence to Johanna LEPEULE, Johanna.lepeule@univ-grenoble-alpes.fr

23 Phone : +33 476 549 466

24 Team of Environmental Epidemiology Applied to Reproduction and Respiratory Health

25 Inserm U1209 / CNRS UMR 5309 / Univ. Grenoble Alpes joint research center

26 Institute for Advanced Biosciences

27 Site Santé, Allée des Alpes, 38700 La tronche, France

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29

30

31 **Abstract**

32 We developed a nation-wide exposure model to NO₂, PM₁₀ and PM_{2.5} at a fine spatial and
33 temporal resolution for France in order to study air pollutants exposure during pregnancy for the
34 French Longitudinal Study of Children (ELFE).

35 The exposure to air pollutants was estimated daily for years 2010 and 2011 by combining three
36 simulation models at the national and regional scale (CHIMERE) and at the local urban scale
37 (ADMS-Urban or SIRANE). The spatial resolution was 4 km for the national scale model, 3 to 4
38 km for regional models and from 10 to 200 meters for urban-scale models. We developed a
39 confidence index (from 0 to 10) based on the target plot to identify the best model to estimate
40 exposure for a given address, year and pollutant. Air pollution exposure during pregnancy was
41 then estimated using each modeling scale for the 17,427 women participating in the ELFE cohort.
42 We described the exposure of the women during different time windows of pregnancy using each
43 of the three models and using the most suitable model as estimated by the confidence index.

44 The exposure estimates obtained from the three models were quite similar and highly correlated
45 (spearman correlation between 0.64 and 0.96), especially for the national and regional models.
46 For NO₂ and PM₁₀ predicted by the urban models, the minimum values were lower and the
47 maximum values and the variability were higher, compared to the regional and national models.
48 The averaged confidence indexes were comprised between 5.6 and 8 depending on the pollutant,
49 year and exposure model considered. The best confidence index was observed for urban
50 modeling (10) and the lowest for the regional modeling (0). In average during pregnancy, using
51 the most suitable model, women were exposed to 21 µg/m³ for NO₂, 16 µg/m³ for PM_{2.5} and 24
52 µg/m³ for PM₁₀.

53 To our knowledge, this is the first study combining three modeling tools available at different
54 scales to estimate NO₂, PM₁₀ and PM_{2.5} concentrations at a fine spatial and temporal resolution
55 over a large geographical area. The confidence index provides guidance in the choice of the
56 exposure model. These exposure estimates will be used to investigate potential effects of air
57 pollutants on the pregnant woman health and on health of the fetus and development of the child.

58

59 **Keywords**

60 Cohort, air pollution, dispersion modeling, exposure assessment, pregnancy

61

62 **1. Introduction**

63 A large body of literature has been published in the last 20 years about the relationship between
64 maternal exposure to air pollutants and pregnancy outcomes, including pre-eclampsia, fetal
65 growth, and gestational duration (Pedersen et al., 2013; 2014; Shah et al., 2011). The contribution
66 of maternal exposure to air pollutants to child's respiratory health (Korten et al., 2017), metabolic
67 diseases (Lavigne et al., 2016), or neurodevelopmental disorders (Clifford et al., 2016; Xu et al.,
68 2016) is an area of growing interest. Yet, little is known about the lasting influences of in utero
69 exposure to air pollutants on child health.

70 Air quality monitoring stations provide a high temporal resolution, usually hourly or daily
71 measures, but their spatial resolution is poor due to the low density of monitors for a usually large
72 area of study. Thus using air quality monitors for exposure assessment is subject to measurement
73 error. The last 10 years have seen a rapid development of air quality modeling (Oliveri Conti et
74 al., 2017). Models with fine spatial resolution have been implemented including dispersion
75 models or land-use regressions, the most used in epidemiological studies, sometimes combined
76 with geostatistical techniques. Most often, these models are developed for a few cities and focus
77 on the most urbanized areas (Eeftens et al., 2012; Sellier et al., 2014). Annual estimates are
78 usually provided (Eeftens et al., 2012), although some models may produce sub-annual
79 predictions (Sellier et al., 2014).

80 As part of a study on the effects of early exposure to air pollutants on pregnancy outcomes and
81 child's health (the PATer project "*Pollution Atmosphérique sur le territoire français: modélisation et effets sanitaires*") in the ELFE cohort (The French Longitudinal Study of
82 Children) (Vandentorren et al., 2009), we aimed to develop a nation-wide exposure model to
83 NO₂, PM₁₀ and PM_{2.5}, with daily estimates in 2010 and 2011 (the time period covering the
84 pregnancies of the ELFE cohort women) and a fine spatial resolution for France. We describe the
85 development of air quality models at the national, regional and local scale, and the development
86 of a confidence index based on the target plot (Thunis et al., 2013), which was used to identify
87 the best model for a given address, year and pollutant. The exposure of the women participating
88 in the ELFE cohort are described for each modeling scale and for the best model as estimated by
89 the confidence index. A specific challenge of the project was to bring together about 25
90 organizations able to produce air quality data from numerical simulations on a large number of
91 urban areas of metropolitan France, but also at regional and national scale.
92

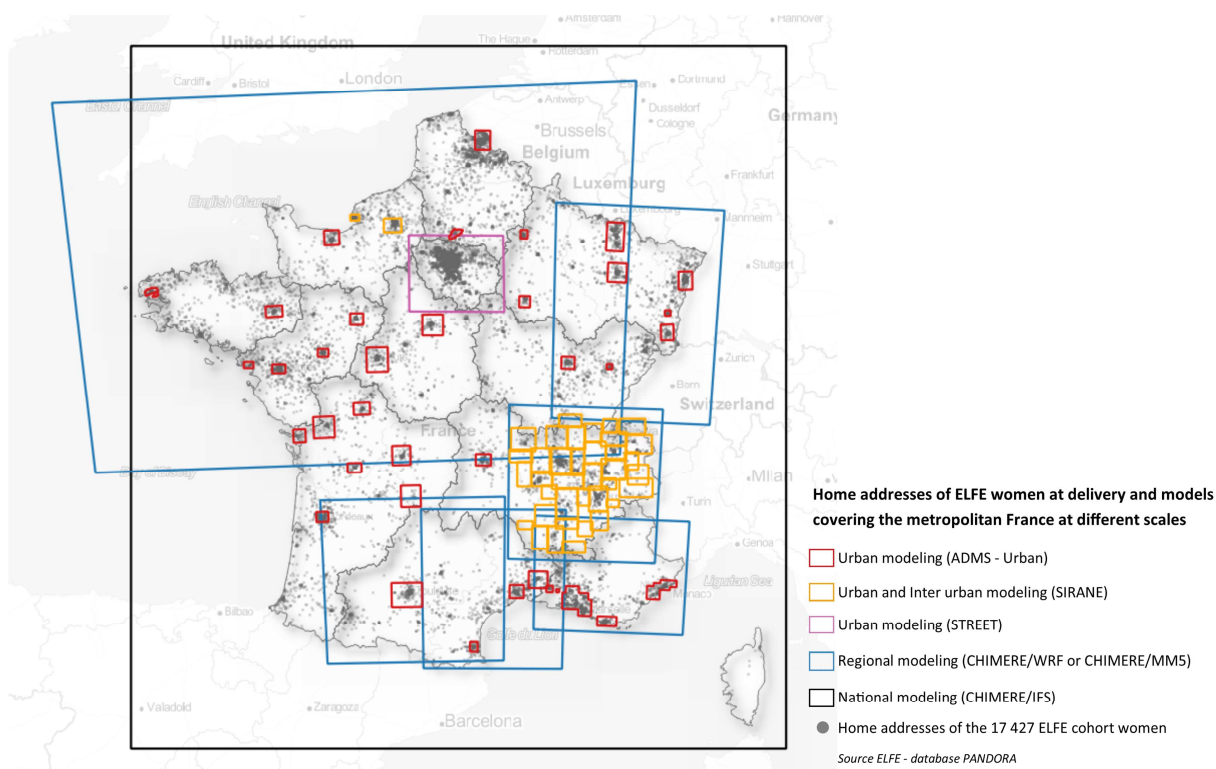
93

94 **2. Methods**

95 **2.1. Population studied**

96 The French Longitudinal Study of Children (ELFE, <https://www.elfe-france.fr/en/>) is a
97 prospective birth cohort recruited in 2011 and designed to collect data on the health and
98 development of children, their family, socio-cultural, nutritional and environmental factors from
99 conception to 20 years of age. Women giving birth in one of the 344 randomly selected maternity
100 wards (out of 540) in metropolitan France during the 4 enrollment periods (April 1st -4th; June
101 27th-July 4th; September 27th-October 4th; November 28th-December 5th) were invited to
102 participate. Multiple births of three children or more, very preterm births (before 33 weeks of
103 gestation), mothers under age 18, mothers who did not read French, Arabic, Turkish or English,
104 mothers unable to give informed consent, or who planned to move abroad within three years were
105 not eligible. Finally, 18 329 children and their mothers were included. Home addresses of the
106 women during pregnancy and of the children after birth were collected and geocoded, but for 902
107 women, geocoded address was not available. Therefore our analysis included 17 427 women for
108 whom at least one geocoded address during pregnancy was available (Figure 1). All participating
109 women gave informed consent to participate in the study. The ELFE study was approved by the
110 relevant ethical committees (CNIL, Commission nationale de l'informatique et des libertés;
111 CCTIRS, Comité Consultatif sur le traitement de l'Information en matière de Recherche dans le
112 domaine de la Santé; CNIS, Conseil National de l'Information Statistique).

113



114
 115 *Figure 1: Home addresses of ELFE pregnant women at delivery and models covering the*
 116 *metropolitan France at different scales*

117
 118 **2.2. Study area**

119 We studied the metropolitan area of France (excluding Corsica island), which represents about
 120 551,695 km² with a population of 65,058,000.

121
 122 **2.3. Modeling strategy**

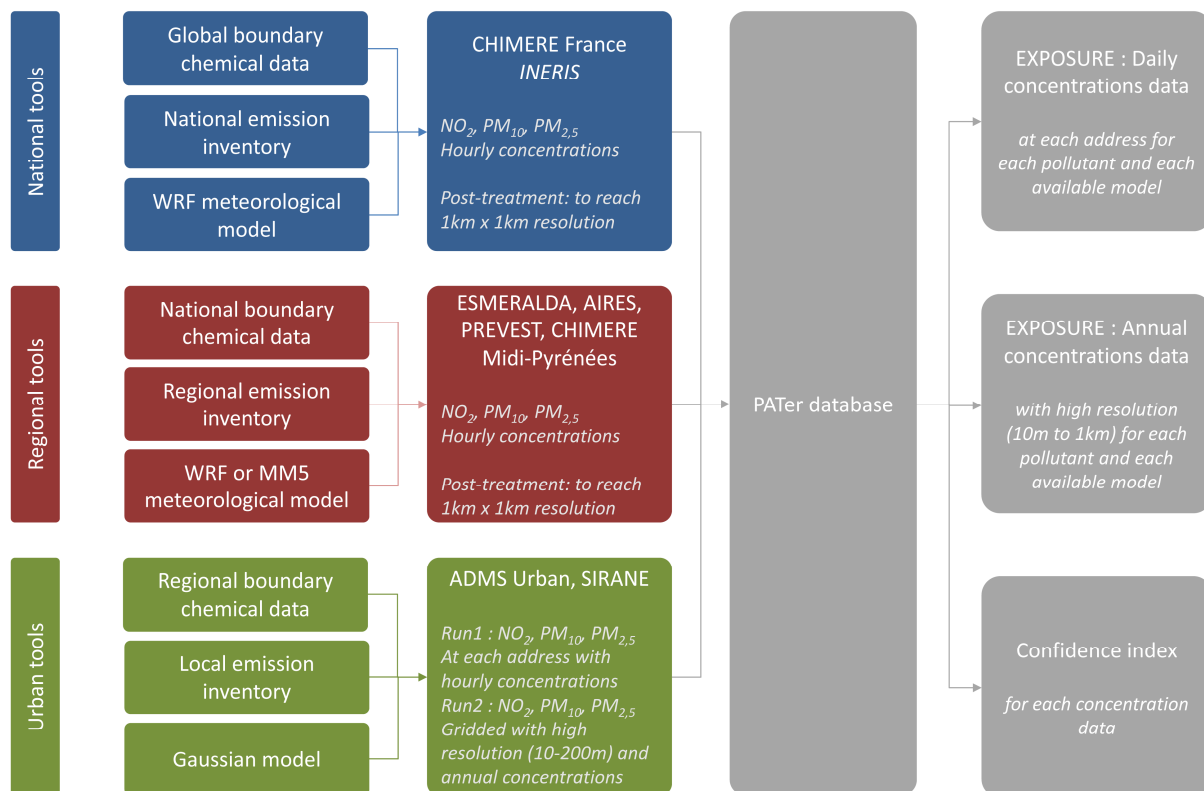
123 The characterization of exposure to air pollution is based on three simulation models at the
 124 national, regional and local scale (Figure 1). The national CHIMERE chemistry-transport model
 125 (Mailler et al., 2017; Menut et al., 2013; Valari et al., 2011) is used to estimate air pollution
 126 levels for the metropolitan France, with a resolution of 4 km x 4 km. This model has long been
 127 run and evaluated in France as the main component of the national air quality forecasting and
 128 monitoring system PREV’AIR (Honoré et al., 2008). It is also implemented across several
 129 regional areas with resolution of 3 km x 3 km or 4 km x 4 km, depending on the regional area. In
 130 urban areas, air pollution levels are estimated by urban-scale models which are currently
 131 implemented on most agglomerations >250,000 inhabitants (20 out of 24), but also in smaller

132 agglomerations (23 out of 31 agglomerations with more than 100,000 inhabitants), with a very
133 high spatial resolution from ten to two hundred meters. The quasi-Gaussian Atmospheric
134 Dispersion Modeling System (ADMS) Urban (Cambridge Environmental Research Consultants,
135 Cambridge, United Kingdom (Carruthers et al., 2000a)) or the SIRANE model (Soulhac et al.,
136 2017; 2011; 2012b) are widely used in France as part of or to supplement the regulatory
137 monitoring of air quality. The use of ADMS-urban and SIRANE is supported by validation
138 studies ((Carruthers et al., 2000b; Stocker et al., 2012), for ADMS-Urban,
139 <https://www.cerc.co.uk/environmental-software/model-validation.html>, Soulhac et al., 2017 for
140 SIRANE) and comparison studies (inter-model and inter-laboratory comparisons) organized by
141 the national reference laboratory (Wroblewski et al. 2009 ; Malherbe et al., 2010 ; Tognet et al.,
142 2016).

143

144 **2.3.1. Input data**

145 Three types of input data were used. National and local emission inventories came from the
146 European Monitoring and Evaluation Program emission cadaster
147 (<http://www.emep.int/index.html>) (Figure 2). The local inventories are mainly based on the
148 national coordination pole guidebook to ensure methodological consistency across local
149 inventories (Pôle national de coordination des inventaires territoriaux, 2012). Meteorological data
150 were provided by the Integrated Forecast System (IFS) data re-analyzed for the national model,
151 coupling with the MM5 model for the great north-west zone. For regional modeling tools, NCEP
152 FNL Operational Global Analysis data were used with the WRF or MM5 model. For urban tools,
153 observed data were provided by Meteo-France. Boundary conditions were collected from a
154 European dataset provided by CHIMERE France – European scale for the national model and
155 from the measurement network observations (background monitors) for urban-scale models.



156

157 *Figure 2: Diagram of the modeling strategy*

158

159 2.3.2. Computations

160 Simulation runs were performed on the national, regional and urban scales to predict
 161 concentrations of nitrogen dioxide (NO_2), particulate matter (PM_{10} and $PM_{2.5}$), ozone (O_3), sulfur
 162 dioxide (SO_2) and benzene (C_6H_6) for years 2010 and 2011.

163 On national and regional scales, hourly simulations were performed on regular grids of 3 to 4 km
 164 resolution. In a second stage, statistical or geostatistical approaches were applied to refine the
 165 modeling results and produce the most realistic concentration fields. On the national scale, model
 166 outputs and measurements from the permanent monitoring network were thus combined by
 167 external drift kriging (Malherbe 2009; Benmerad et al., 2017). In addition for NO_2 , NO_x
 168 emission data from the national emission inventory were introduced as an auxiliary variable into
 169 the kriging to better account for concentration gradients in the vicinity of emission sources. An
 170 estimation grid mesh of 1 km was used for NO_2 and PM_{10} pollutants (and by homogeneity $PM_{2.5}$)
 171 considering the resolution of NO_x emission data and the spatial density of measurements in some
 172 urban areas whereas the initial grid resolution of 4 km was kept for ozone due to its more

173 regional nature. Kriging-based or optimal interpolation methods were also applied on the regional
174 scale to combine model outputs and observation data. In some regions, a mesh refinement
175 technique was implemented to improve the accuracy of the modeling results and increase the
176 resolution of the calculation efficiently. It interpolates the result of a pollutant concentration
177 calculation on a finer mesh based on physical and physiographic principles governing the spatial
178 differentiation of concentrations. This method makes it possible to highlight the concentration
179 gradients near the sources of emissions. In concrete terms, the technique is based on the
180 interpolation of a 3D field of a coarse mesh grid on a fine mesh grid, based on topology data and
181 emissions (at a 1 x 1 km resolution).

182 On the urban scale, because of the high volume of data and the high computation time that is
183 needed for generating hourly predictions, two types of outputs were considered: the first one
184 consisted in hourly predictions of pollutant concentrations at each of the 17,427 addresses of the
185 ELFE cohort for the specific needs of the project; the second one consisted in annual average
186 predictions of pollutants concentrations on a grid, allowing reuse of data for other
187 epidemiological studies. Depending on the characteristics and configuration of the modeling
188 tools, different simulation grids were defined: usually a regular grid for SIRANE and an irregular
189 one, sparse in background areas and denser close to roads and emission sources for ADMS
190 Urban. In that second case annual modeling results were interpolated on a fine regular grid using
191 interpolation techniques (Beauchamp et al., 2014).

192 The final spatial resolution of the concentration maps after post-processing is 1 to 4 km for the
193 national scale model, 1 km for regional models and 10 to 200 meters for urban-scale models for
194 annual concentrations.

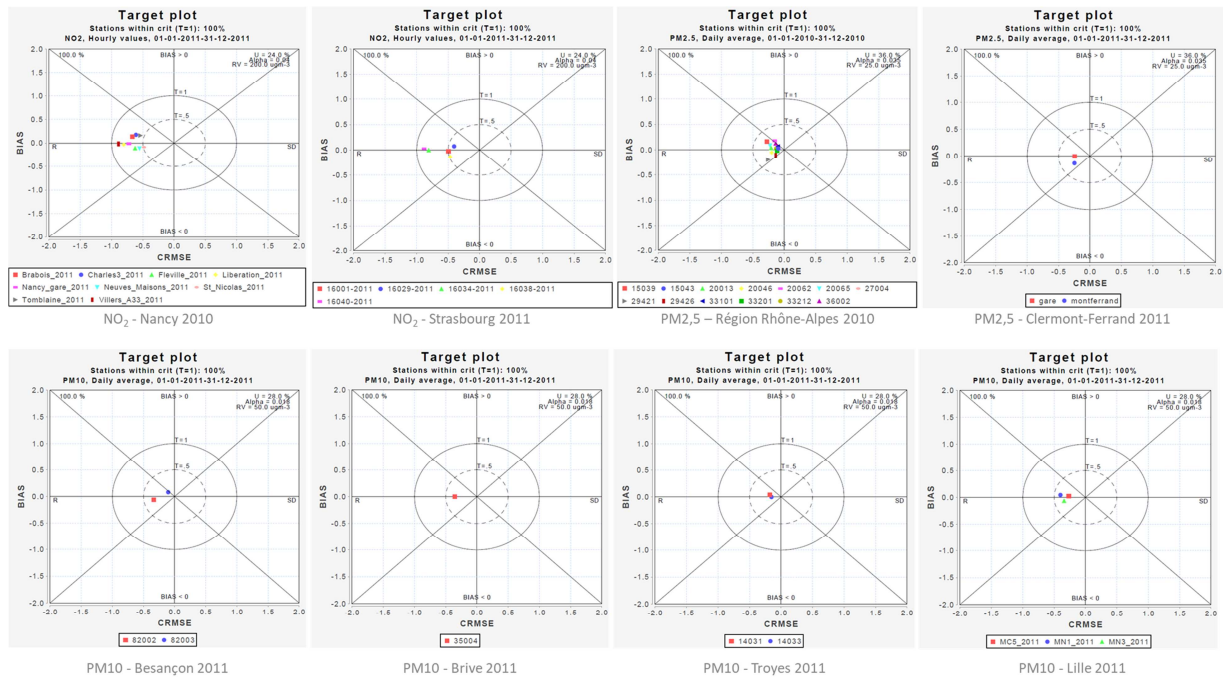
195

196 **2.3.3. Validation and indicators of quality of the models**

197 Validation of the models was performed by comparing the predicted concentrations to the
198 concentrations measured by the network of permanent air quality monitors using the Delta Tool
199 methodology (Pernigotti et al., 2013; Thunis et al., 2013; Thunis and Cuvelier, 2016; Thunis et
200 al., 2012). This method has been developed by the European Joint Research Center (JRC) within
201 FAIRMODE (<http://fairmode.jrc.ec.europa.eu>) to perform diagnostics of air quality and
202 meteorological model performances. Model performance assessment includes in particular the so-
203 called Target Plot (Figure 3). This diagram is a representation of the Modeling Quality Indicator

204 (MQI), a statistical indicator which describes the discrepancy between modeling results and
205 measurements, taking the measurement uncertainty into account. The MQI combines different
206 statistical scores: CRMSE – Centered Root Mean Square Error, R – Correlation coefficient, SD –
207 Standard Deviation, NMB – Normalised Mean Bias (Figure 3). The modeling quality objective
208 (MQO) is the quality criterion associated to the MQI. It is considered as fulfilled if the MQI is
209 less than or equal to unity (points inside the circle of the Target Plot, Figure 3).

210 In the present project, the target plots were calculated for each of the three modeling scales using
211 daily averaged concentrations. Predicted concentrations of each model have been compared to all
212 the measurements of permanent monitors included in the modeled area. For the national and
213 regional models, which combine CHIMERE outputs with measurements from rural and urban
214 background monitors (see previous section), the target plots for background stations were
215 calculated using a leave-one-out cross validation approach so that the resulting estimates and the
216 measurements were independent and could be compared. For traffic stations (which are not used
217 in the kriging), the target plots were calculated by interpolating the model results at the
218 monitoring points. Higher MQI was logically obtained at those sites since the national and
219 regional models are not intended to finely reproduce traffic-related concentration levels. As for
220 the urban models, the performance of the modeling could not be as precisely characterized than
221 for the national and regional models since there is a lack of measurement stations in some urban
222 areas, with only one or two monitors for each pollutant. It can be observed that the points
223 representing the model performance at each station tend to be located on the left part of the
224 diagram (i.e. CRMSE error dominated by correlation, figure 3), which could be explained by a
225 very high dynamic of pollution levels not precisely taken into account by the emission inventory
226 at the point of the station.



227

228 *Figure 3: Example of target plots for urban models for different cities, years, and pollutants*

229

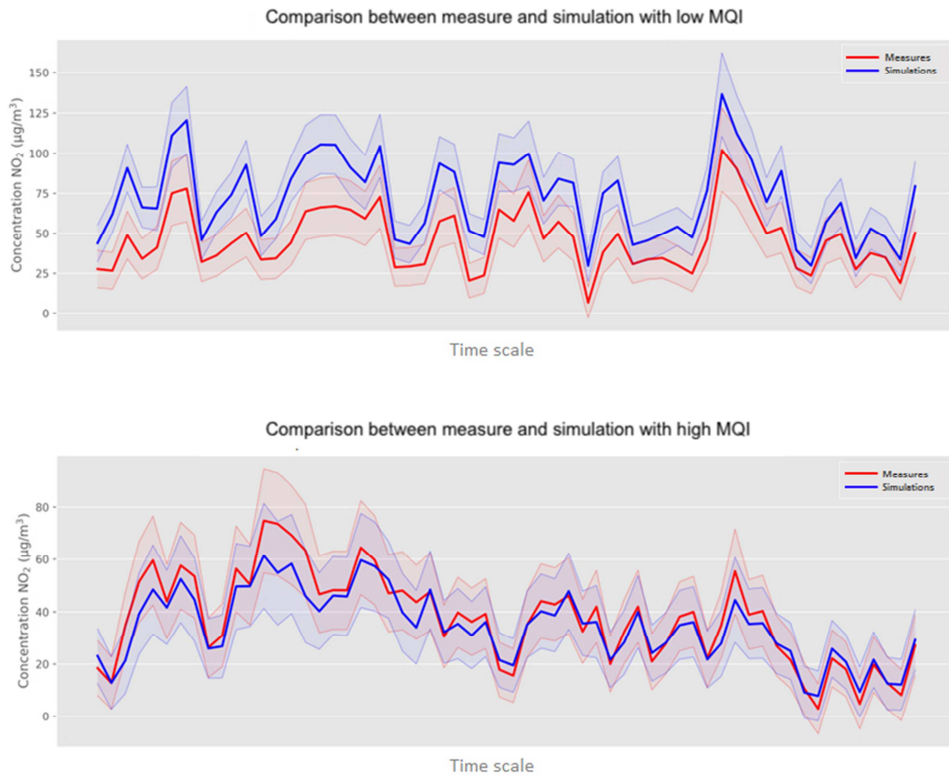
230 **2.4. Pregnancy exposures**

231 We estimated air pollutants exposure of pregnant women according to each of the three models
 232 (national, regional and urban scale) for short- and long-term time windows during pregnancy
 233 including: whole pregnancy, each trimester of pregnancy, each month, each week and the 30 last
 234 days of pregnancy. Therefore, for each woman and each time-window, up to three different
 235 concentrations were available from the national, regional and urban-scale models. Exposure for
 236 time windows with more than 25% of missing values was not estimated.

237

238 **2.5. Confidence index**

239 In order to help the epidemiologists to choose the most relevant exposure model, we calculated a
 240 confidence index (C) based on the Model Quality Index (MQI). The MQI provides insight into
 241 the quality of the model average performances (Thunis and Cuvelier, 2016). The MQI varies on a
 242 scale from 0 to infinite, between the origin of the Target Plot (0, 0) and the position of the
 243 measuring station for which concentrations have been calculated with the model (Figure 3). The
 244 closer the station's position is to the origin, the lower the MQI and the better the modeling are
 245 (Figure 4).



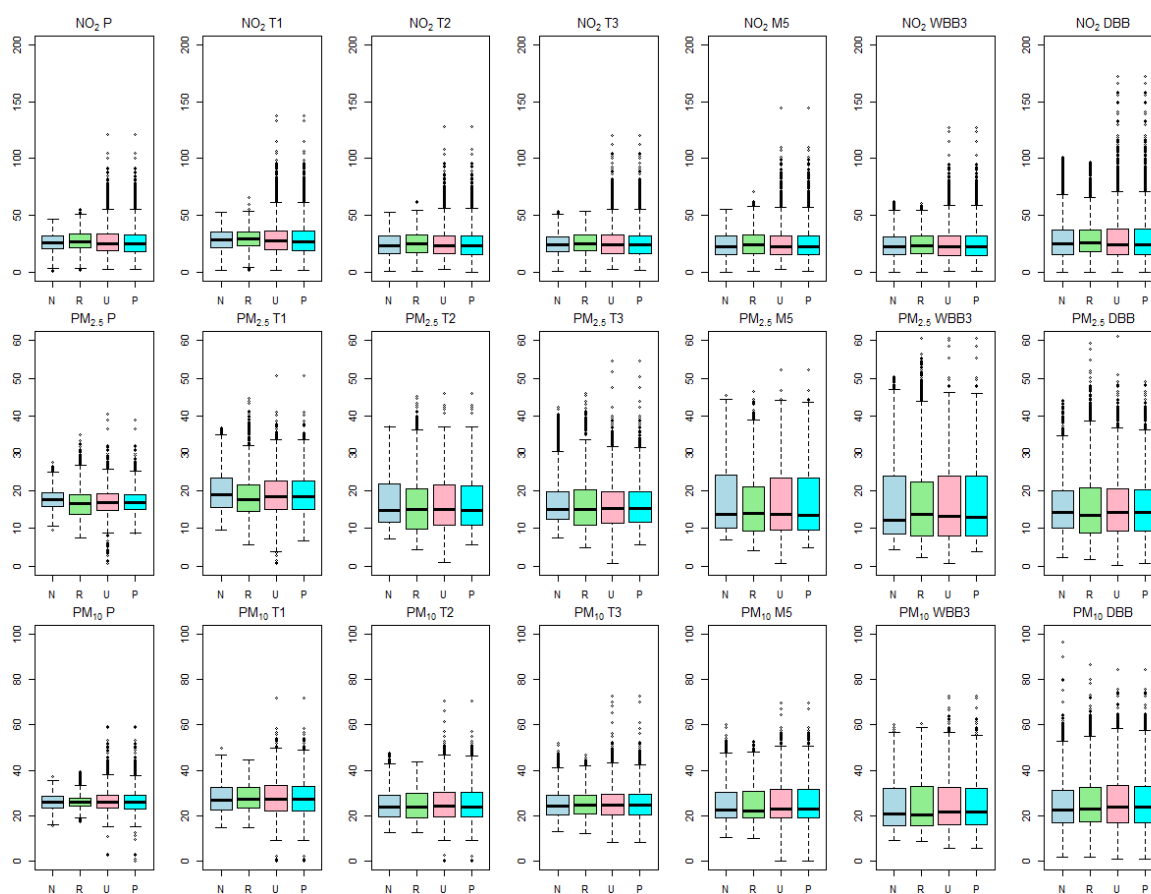
246
 247 *Figure 4: Comparison between measurements from a station and predictions from a model for a*
 248 *high and low Model Quality Index (MQI).*

249
 250 For proper comparisons of the quality of the estimates from the three models, the statistics
 251 compared across models should be on the same scale. Therefore, we calculated a Confidence
 252 index (C), which converts the result of the MQI (from 0 to infinite) to a value between 0 and 10
 253 using the following equation: $C = -6 \times MQI + 10$ (1)
 254 with 10 being the best C (reached when the MQI is 0) indicating a perfect modeling result. On
 255 the contrary, for a MQI of 1 the C will be 4. A C with a value of 0 (bad confidence) will be
 256 reached for a MQI of about 1.67.

257 For the urban scale models, model performance was assumed to be homogeneous according to
 258 the type of location (i.e. background or traffic). The MQI was calculated for each measurement
 259 station and was then averaged separately for background and traffic stations, leading to two types
 260 of confidence index (C) depending on distance to traffic. A woman located close to traffic (i.e. in
 261 a 200 m buffer around motorway type roads, or in a 150 m buffer around a main link road, or in a
 262 100 m buffer around a regional link road) was assigned the average confidence index calculated

263 for near traffic monitors, whereas in other locations she was assigned the average confidence
264 index calculated for background monitors. For the national and regional scale models, model
265 performance was assumed to be more variable across the modeling domain. The MQI was
266 calculated for each monitor as described in section 2.3.3. The MQI and the corresponding
267 confidence index at each background (resp. near-traffic) address of the ELFE cohort women were
268 then calculated by interpolating the MQI of all the available background (resp. traffic)
269 measurement monitors using the inverse-distance weighting method between the address of the
270 woman and the location of the monitors.

271
272 Since the spatial coverage of monitors is limited (497 monitors for NO₂ (297 background, 200
273 traffic), 390 for PM₁₀ (223 background, 167 traffic) and 106 for PM_{2.5} (64 background, 42
274 traffic)), the Target Plot, MQI and C calculated do not account for the high spatial variability of
275 air pollutants concentrations (especially for NO₂) and therefore for the potential variability of
276 model performances. This high spatial variability in concentrations captured by urban-scale
277 models (Figure 5) is a major asset of these models when one is interested in the local variations
278 of exposure. This is illustrated in Supplemental Figure S1, which shows that smoothing
279 concentrations on a kilometer grid obviously leads to a decrease in the accuracy of the
280 concentrations near the main roads, better represented on a metric grid. Indeed, in the urban
281 modeling tools, road emissions are precisely entered into the model while they are diluted on
282 meshes of several square kilometers in the national and regional models. In our study, among the
283 17,427 addresses, 33% were located close to traffic. The urban models allow to account for the
284 variability of concentrations near traffic. They are implemented with final spatial resolutions
285 ranging from 10 (near sources) to 200 meters and are more adapted to the complexity of air
286 pollutants sources in the cities than the regional or national models. Therefore, if an urban model
287 exists, this one will be favored compared to the other scales, irrespectively of the confidence
288 index, to provide the value of exposure of the ELFE women during pregnancy.



289
 290 P: Pregnancy, T1: trimester 1, T2: trimester 2, T3: trimester 3, M5: month 5, WBB3: 3rd
 291 before birth, DBB: day before birth, N: National model, R: Regional model, U: Urban model, P:
 292 PATer estimate (i.e. the most suitable model: the urban model if there is one, the model which
 293 has the highest confidence index among the regional and national model).

294
 295 *Figure 5: Distribution of exposures during pregnancy as estimated by each of the 3 models and*
 296 *by the final PATer most suitable estimate, for all women covered by the 3 models*

298 2.6. Statistical analyses

299 Coverage of the study area was heterogeneous for O₃, SO₂ and C₆H₆. We therefore focused our
 300 analyses on NO₂, PM_{2.5} and PM₁₀. We described pregnant women's exposures and their
 301 confidence index using each of the three models (national, regional and urban-scale) for the
 302 following time windows: pregnancy, each trimester of pregnancy, fifth month of pregnancy, third
 303 week before birth and day before birth. Then, for the sub-sample of women covered by the 3

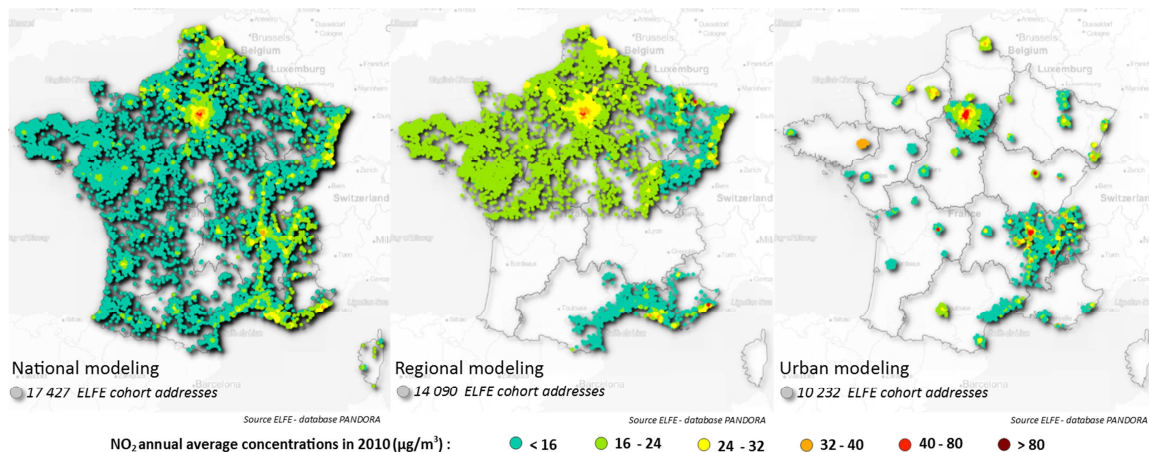
304 models, we compared their exposures and confidence indexes as estimated by the 3 models and
 305 the final exposures as estimated by the most suitable model (i.e. the urban model if there is one,
 306 the model which has the highest confidence index among the regional and national model). For
 307 simplicity, this final exposure is hereinafter called the PATer (from the name of the project)
 308 estimate. Spearman correlation coefficients between the 3 models and the PATer estimates were
 309 calculated.

310

311 3. Results

312 3.1. Pregnancy exposures as estimated by each of the 3 models

313 NO₂ exposures during pregnancy as estimated by the national, regional and urban models are
 314 represented in figure 6. Depending on the exposure model used, women in the ELFE cohort were
 315 exposed on average during pregnancy between 20 and 26 µg/m³ for NO₂, 16 and 17 for µg/m³ for
 316 PM_{2.5} and 24 and 25 µg/m³ for PM₁₀ (Table 1). These average values were quite similar for
 317 exposure during the other time windows studied.



318
 319 *Figure 6: Annual averaged NO₂ concentrations in 2010 for the addresses of the ELFE population*
 320 *where a national, regional or urban model existed.*

321

322

Pollutant Exposure window	National modeling									Regional modeling									Urban modeling								
	n	mean	sd	Percentiles					n	mean	sd	Percentiles					n	mean	sd	Percentiles							
				5	25	50	75	95				5	25	50	75	95				5	25	50	75	95			
NO ₂																											
P	15909	20.2	9.0	7.7	12.9	19.0	26.5	36.6	12571	22.9	8.3	9.4	17.5	21.9	28.2	38.3	8942	26.2	12.6	9.2	17.4	24.4	32.8	50.1			
T1	15744	22.3	10.5	7.4	14.1	20.9	29.1	41.7	12467	25.1	9.3	9.9	18.9	24.5	31.5	41.6	8828	28.1	14.3	8.7	18.2	26.3	35.7	55.1			
T2	16173	19.1	10.6	5.6	10.8	16.9	25.5	40.0	12773	21.8	10.0	6.8	14.3	21.0	28.7	40.7	9156	24.9	13.6	7.6	15.0	22.7	31.8	51.1			
T3	16805	19.0	10.2	5.8	11.0	17.0	25.2	39.3	13263	21.6	9.5	7.0	15.0	20.1	27.9	39.8	9626	25.3	13.3	7.7	15.7	23.4	32.0	50.5			
M5	16260	19.1	11.3	5.3	10.2	16.6	25.5	42.0	12847	21.6	10.5	6.5	13.6	20.0	28.9	41.3	9228	24.7	14.3	7.1	14.4	22.0	31.9	52.5			
WBB3	17307	18.7	11.1	4.5	10.1	16.6	25.4	39.7	13667	21.0	10.4	5.3	13.0	20.0	27.8	39.6	9945	24.4	14.4	6.5	13.9	21.6	32.0	51.6			
DBB	17375	20.7	15.0	4.7	9.7	16.6	27.6	49.9	13720	23.7	14.6	5.6	14.0	20.5	30.1	52.3	10074	27.6	18.9	5.7	14.1	23.2	36.6	64.4			
PM _{2.5}																											
P	15909	17.2	2.9	12.7	15.2	16.9	19.0	22.6	12978	15.8	4.6	9.0	12.2	15.8	18.7	23.3	8281	16.2	3.9	9.4	14.0	16.3	18.7	22.0			
T1	15744	18.9	5.6	10.9	14.6	18.1	22.4	29.2	12869	17.4	6.3	7.8	13.0	16.7	21.1	28.9	8298	18.0	5.9	9.5	13.9	17.6	21.7	28.3			
T2	16173	16.5	6.5	8.9	11.4	14.5	20.8	29.2	13183	15.0	7.0	5.9	9.3	14.1	19.0	28.0	8526	15.7	6.8	7.2	10.2	14.1	20.4	27.9			
T3	16805	16.1	5.8	9.5	12.0	14.5	19.2	28.0	13687	14.8	6.4	6.7	9.7	13.9	18.5	26.8	9017	15.3	6.2	7.3	10.6	14.2	18.9	27.1			
M5	16260	17.0	8.4	8.7	10.3	13.6	22.6	33.5	13257	15.1	8.0	6.1	8.5	13.2	19.5	31.3	8567	16.0	8.3	7.1	9.5	13.0	21.9	32.2			
WBB3	17307	16.4	9.9	6.7	8.3	11.8	23.0	35.2	14101	14.9	10.0	4.0	7.1	12.2	20.6	34.8	9399	15.0	8.9	5.6	7.8	11.6	21.4	31.9			
DBB	17375	15.3	7.0	6.5	10.1	14.2	19.4	28.4	14154	14.3	8.4	4.7	7.8	12.2	18.7	30.5	9571	14.9	7.7	5.1	8.8	13.6	19.4	28.8			
PM ₁₀																											
P	15909	24.5	3.4	19.3	21.9	24.1	26.8	30.5	12978	25.1	3.3	19.8	22.7	25.1	27.3	30.4	8878	25.0	5.6	15.5	21.7	24.8	28.3	34.1			
T1	15744	26.0	6.2	17.4	21.1	25.0	30.2	37.3	12869	26.6	6.0	17.3	21.9	26.2	30.9	37.2	8736	26.5	7.7	15.5	20.7	25.6	31.8	39.8			
T2	16173	23.6	6.9	15.0	18.3	22.0	27.9	37.0	13183	24.2	6.7	15.2	18.7	23.1	28.5	37.1	9079	24.2	8.0	13.6	18.5	22.7	29.2	39.0			
T3	16805	23.6	6.2	15.5	19.0	22.1	27.3	36.1	13687	24.2	6.1	15.8	19.7	23.2	27.9	36.3	9545	24.0	7.6	12.9	18.8	23.2	28.5	38.1			
M5	16260	23.9	8.8	14.1	17.5	20.8	29.1	41.6	13257	24.4	8.3	14.8	18.4	21.4	29.5	40.9	9148	24.4	9.4	12.3	17.8	21.8	30.0	42.9			
WBB3	17307	23.0	10.3	11.7	14.7	19.3	30.1	42.7	14101	23.5	10.2	12.5	15.0	19.5	31.3	42.6	9862	22.8	10.2	10.5	15.2	19.4	30.3	41.9			
DBB	17375	23.3	9.7	10.5	16.4	21.6	28.7	42.1	14154	23.7	10.3	10.2	16.6	21.2	29.4	43.8	9991	24.0	11.3	8.8	15.5	21.9	31.2	45.3			

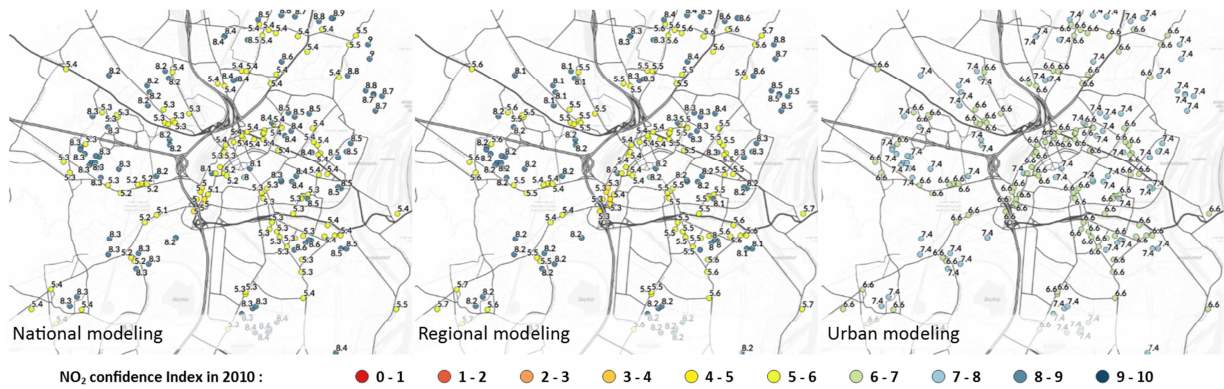
323 P: Pregnancy, T1: trimester 1, T2: trimester 2, T3: trimester 3, M5: month 5, WBB3: 3rd week before birth , DBB: day before birth, n:

324 sample size; p25, p50, p75, p95: percentiles 25, 50, 75, 95;

325 *Table 1: Averaged exposures during pregnancy as estimated for each of the 3 models*

326 **3.2. Confidence index of estimated exposures and comparison across the 3 models**

327 The confidence indexes were calculated for each address of the cohort, each pollutant and each
328 year. The figure 7 presents the results of these calculations for NO₂ in 2010 in the Strasbourg
329 metropolitan area.



330
331 *Figure 7: NO₂ estimated confidence indexes for women of the ELFE cohort living in the*
332 *Strasbourg agglomeration area in 2010*

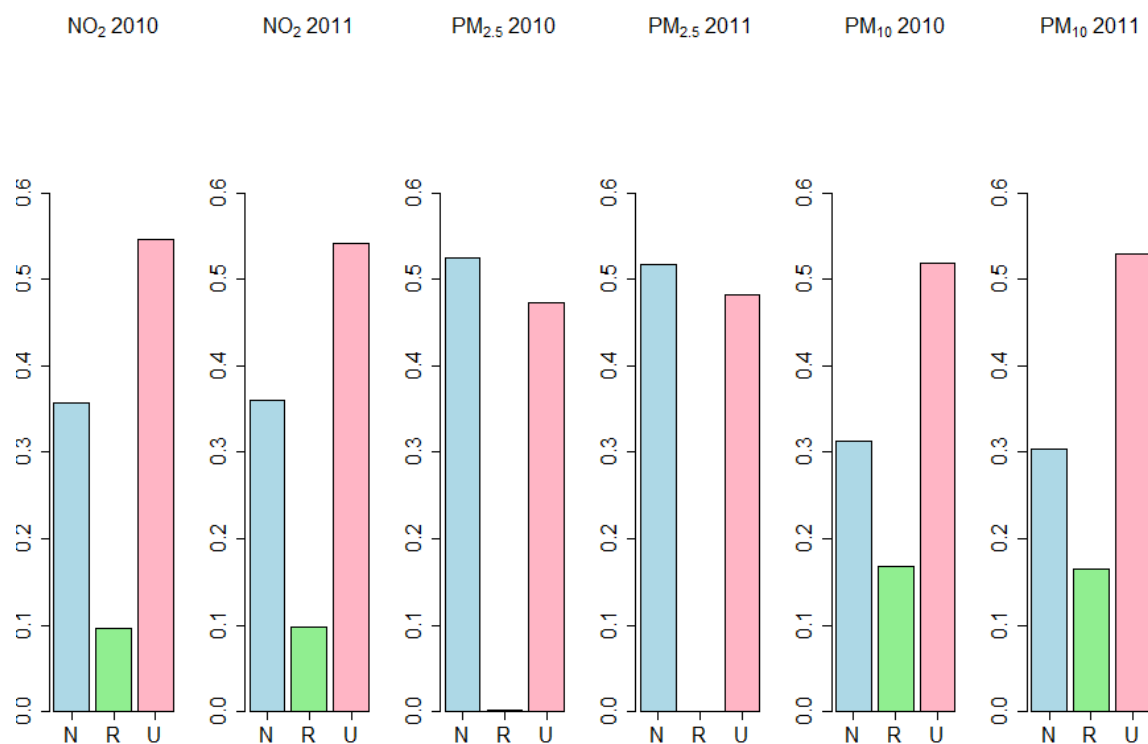
333
334 We compared the confidence indexes for women covered by the 3 models (Table 2). With the
335 exception of PM_{2.5} and NO₂ estimated by the regional models, the averaged confidence indexes
336 were about 7.5 depending on the pollutant, year and exposure model considered (Table 2). For
337 NO₂ and PM_{2.5}, the lowest C was observed for the regional modeling (0 for both pollutants) and
338 the highest C was observed for the national modeling for NO₂ (9.3) and for the urban modeling
339 for PM_{2.5} (9.3). For PM₁₀, the urban modeling showed the lowest (1.5) and highest C (10).
340 Estimated confidence indexes were quite stable between 2010 and 2011. For NO₂ confidence
341 indexes, 10% of women had differences greater than 1 across the 3 models. For both PM_{2.5} and
342 PM₁₀ confidence indexes, 10% of women had differences greater than 1 for the national modeling
343 compared to the regional modeling. As for the urban modeling, 30% of women for PM_{2.5} (20%
344 for PM₁₀) had differences in confidence indexes greater than 1 compared to the regional
345 modeling. The PATer final exposure of the women was mostly estimated from the urban model
346 for NO₂ and PM₁₀ and from the national model for PM_{2.5} (Figure 8). PM_{2.5} estimates from the
347 regional model showed in average the lowest confidence indexes (Table 2) and the regional
348 model was almost never chosen to represent the PATer final PM_{2.5} exposure estimate (Figure 8).

Pollutant	Year	n	National modeling				Regional modeling				Urban modeling			
			mean	sd	min	max	mean	sd	min	max	mean	sd	min	max
NO ₂	2010	7817	7.2	1.9	3.0	9.2	6.9	2.0	0	9.2	7.2	0.9	4.2	8.8
	2011	7725	7.3	1.9	3.1	9.3	7.0	1.9	0	9.1	7.3	1.0	3.7	8.6
PM _{2.5}	2010	2330 ¹	7.5	0.5	6.9	8.9	5.9	2.1	0	8.3	8.0	0.3	7.1	9.2
	2011	2503 ¹	7.2	0.6	6.5	8.4	5.6	2.3	0	8.2	7.9	0.6	6.5	9.3
PM ₁₀	2010	7402	7.7	1.1	5.1	9.1	7.4	1.0	5.1	9.1	7.6	1.1	3.9	10
	2011	7616	7.7	0.9	5.0	9.1	7.4	1.0	4.1	8.8	7.8	0.9	1.5	10

350 ¹ the number of observations is lower for PM_{2.5} compared to PM₁₀ and NO₂ because there were
351 fewer monitoring stations measuring PM_{2.5}

352 *Table 2: Averaged confidence index by pollutant, year and type of modeling for all women*
353 *covered by the 3 models*

354



355

356 N: National model, R: Regional model, U: Urban model

357 *Figure 8: Sources of the PATer final exposure estimate by pollutant and year.*

358

359

360 **3.3. Comparison of pregnancy exposure estimates across the 3 models and with the final**
361 **PATer estimates**

362 Depending on the exposure window, between 6,406 and 7,515 women were covered by the three
363 exposure models and the final PATer estimates (Supplemental Table S1). Except PM_{2.5}
364 correlation during the whole pregnancy between the national and regional models, the three
365 models were highly correlated (correlation coefficients from 0.71 to 0.96, Supplemental Table
366 S2) for all pollutants and exposure windows. For the three pollutants, the exposure distributions
367 of the urban model and the PATer estimates were very similar as shown by statistics in
368 Supplemental Table S1 and by the very high correlation coefficients between exposures estimates
369 from these 2 models (i.e. between 0.95 and 0.99, Supplemental Table S2); this result was
370 expected because these statistics and correlation coefficients were calculated for women covered
371 by the 3 models, which restricts the sample mainly to women living in urban areas, and the final
372 PATer estimates gives priority to the urban model, which is therefore highly represented in this
373 sub-sample.

374 NO₂ exposures ($\mu\text{g}/\text{m}^3$) as estimated by the national and regional models were very close (p 5th,
375 50th, 95th during pregnancy 13, 26, 40 and 13, 27, 40, respectively), while the urban and PATer
376 estimates showed a higher variability (larger standard deviation) and a wider distribution (p 5th,
377 50th, 95th during pregnancy 11, 25, 50 for both models) compared to the national and regional
378 models (Figure 5 and Supplemental Table S1).

379 As for PM_{2.5} ($\mu\text{g}/\text{m}^3$), generally for the different time windows, the averages and standard
380 deviations of exposures were slightly higher and the distributions were shifted to the right for the
381 national model as compared to the regional, urban and PATer estimates. These results indicate
382 that exposures from the national model were slightly higher (p 5th, 50th, 95th for pregnancy 14, 18,
383 23) than those from the regional, urban and PATer estimates (p 5th, 50th, 95th for pregnancy
384 10,17, 22 for the regional and 12, 17, 22 for the urban and PATer estimates).

385 For PM₁₀ ($\mu\text{g}/\text{m}^3$), the exposure distribution of the women as estimated from the national and
386 regional models were very close (p 5th, 50th, 95th for pregnancy 21, 26, 31, and 22, 26, 31
387 respectively). As compared to the national and regional models, the urban model and PATer
388 estimates showed slightly higher standard deviations and medians as well as slightly wider
389 distributions for the different time windows investigated (p 5th, 50th, 95th for pregnancy 20, 26, 35
390 for both models).

391 Altogether, the urban and PATer estimates were finer and better captured the spatial variability
392 compared to the national and regional models, especially for NO₂ and PM₁₀. As expected, for the

393 3 pollutants and the 4 models, larger distribution of exposure was observed for shorter exposure
 394 time windows compared to longer time windows.

395
 396

397 **3.4. Pregnancy exposures as estimated by the final PATer most suitable estimate**

398 Exposures of the women as estimated by the urban model when there is one available or by the
 399 model with the highest confidence index from the regional and national models are described in
 400 table 3. In average during pregnancy, women were exposed to 21 $\mu\text{g}/\text{m}^3$ for NO_2 , 16 $\mu\text{g}/\text{m}^3$ for
 401 $\text{PM}_{2.5}$ and 24 $\mu\text{g}/\text{m}^3$ for PM_{10} . As shown in table 3, 90% of the estimated exposures had a
 402 confidence index comprised between 5.2 and 8.7 for NO_2 , 6.8 and 9.0 for $\text{PM}_{2.5}$, and 6.1 and 8.6
 403 for PM_{10} .

404

Pollutant	Exposure window	n	mean	sd	percentile				
					5	25	50	75	95
NO_2	Confidence index	17188	7.5	1.1	5.2	6.7	8.1	8.4	8.7
	Pregnancy	17188	20.9	11.8	6.9	12.2	18.5	26.5	44.0
	T1	15971	22.8	13.1	6.7	13.4	20.4	29.2	48.2
	T2	16445	19.9	12.7	5.2	10.6	17.0	26.2	44.1
	T3	16675	20.0	12.6	5.5	10.9	17.2	26.0	43.9
	M5	16104	19.9	13.1	5.0	10.2	16.8	26.3	44.9
	WBB3	16741	19.7	13.4	4.3	9.9	16.7	26.4	44.9
	DBB	16793	21.7	17.1	4.3	9.7	17.1	28.4	55.5
$\text{PM}_{2.5}$	Confidence index	17203	7.9	0.7	6.8	7.5	7.8	8.3	9.0
	Pregnancy	17203	16.2	3.7	10.4	14.0	16.1	18.5	22.3
	T1	16005	18.0	5.6	10.2	13.9	17.5	21.6	27.9
	T2	16469	15.6	6.3	8.0	10.5	14.0	19.9	27.3
	T3	16683	15.2	5.6	8.4	11.1	13.9	18.3	26.5
	M5	16124	16.0	7.9	7.9	9.9	13.1	21.1	31.6
	WBB3	16749	15.3	9.3	6.1	7.9	11.2	21.4	32.9
	DBB	16658	14.7	6.9	5.5	9.3	13.7	18.8	27.3
PM_{10}	Confidence index	17195	7.7	0.8	6.1	7.1	7.8	8.4	8.6
	Pregnancy	17195	23.8	4.9	16.7	20.9	23.4	26.7	32.0
	T1	15980	25.6	6.9	16.1	20.5	24.7	30.1	37.9
	T2	16456	23.2	7.2	14.2	17.8	21.6	27.7	37.1
	T3	16682	23.0	6.8	14.2	18.5	21.7	27.0	36.2
	M5	16114	23.4	8.7	13.2	17.3	20.6	28.6	41.0
	WBB3	16748	22.1	9.6	11.1	14.6	18.8	28.9	40.3
	DBB	16814	23.0	10.1	9.5	15.7	21.3	28.7	42.8

405 T1: trimester 1, T2: trimester 2, T3: trimester 3, M5: month 5, WBB3: 3rd week before birth ,
406 DBB: day before birth

407 *Table 3 : Averaged exposures and confidence indexes during pregnancy as estimated by the most*
408 *suitable model for pregnant women of the ELFE cohort*

409

410 **4. Discussion**

411 To our knowledge, this is the first study combining three modeling tools available at different
412 scales to estimate NO₂, PM₁₀ and PM_{2.5} concentrations at a fine spatial (down to 10 meters) and
413 temporal (hourly) resolution over a large geographical area (the French metropolitan area). We
414 further estimated a confidence index based on the target plot and Model Quality Indicator in
415 order to provide guidance in the choice of the exposure model, when several models are
416 available. Our results showed that the three models provided relatively similar exposure estimates
417 for the women of the ELFE cohort, allowing a combination of the three models. The urban-scale
418 model provides a finer spatial resolution compared to the national and regional models, which is
419 relevant in urban and peri-urban areas that are more densely populated and where local emissions
420 mainly originate from traffic and heating processes. We therefore chose to favor the urban-scale
421 model first, and to then use the confidence index to choose between the regional- and national-
422 scale models for women who were not covered by the urban-scale model. We finally used the
423 predicted concentrations of these models to evaluate the exposure during multiple time-windows
424 of 17,427 pregnant women participating to the ELFE cohort.

425

426 Two main modeling tools were used for the urban-scale model: ADMS Urban (Carruthers et al.,
427 2000a) and SIRANE (Soulhac et al., 2017; 2011; 2012a). ADMS Urban accounts for linear
428 sources such as traffic, but also for many stationary sources like industrial or residential sources.
429 It also includes an intelligent gridding option, which provides high spatial resolution in the
430 vicinity of air pollution sources such as roads. SIRANE cannot include as many stationary
431 sources as ADMS-urban and its spatial resolution is identical throughout the simulated
432 geographical area. However, SIRANE works on a very high spatial resolution throughout the
433 Rhône-Alpes region, which therefore benefits from a very fine assessment of concentrations,
434 including in the interurban environment.

435

436 At the regional scale, a special feature of the modeling is the harmonized procedure used by all
437 regional platforms. This common approach included accounting for sharp specificities within
438 regions by using regional emission inventories (i.e. integration of spatialized and temporalized
439 local data) that are more precise compared to the national emission inventories; the use of models
440 in their configuration used in routine daily forecasting (CHIMERE, SIRANE, WRF or MM5) at 4
441 x 4 km or 3 x 3 km resolution and then refined at 1 x 1 km resolution; the application of a daily
442 or hourly kriging of the measurements over the whole 2010 and 2011 (rather than a yearly
443 kriging). These improvements led to better representation of local processes that influence
444 ambient pollutants concentrations. Comparing the confidence indexes between the national model
445 and the regional models requires some considerations: the national model integrates unified input
446 data as weather or emissions and operates a single configuration of model throughout the national
447 territory. Similarly, geostatic post-treatments are applied according to the same methodology
448 overall of this same territory. The regional model consists in an agglomeration of results from
449 several regional platforms. Each of these platforms delivers representative and coherent results
450 within its regional coverage, by managing its own modeling based on its knowledge and
451 experience on the models used, emissions and meteorological datasets used for modeling,
452 regional modeling calibration, local specificities, etc. The heterogeneity of the platforms used to
453 fuel the regional scale modeling can explain, at least partly, the overall poor performances and
454 lower confidence indexes of the regional model compared to the national (and urban) model, with
455 some regional models performing better than others.

456
457 The three models, national, regional and urban showed consistent distributions of exposure
458 estimates. The national and regional models were very close in terms of exposure estimates. The
459 urban models have a higher spatial resolution and showed a higher variability with a wider range
460 of exposure estimates, which is consistent with the stronger exposure contrasts observed in urban
461 and peri-urban areas compared to more rural areas. Further, the implementation of dedicated
462 validation methods such as the Delta tool, the target plot, the model quality indicator and the
463 confidence index substantiates the use of several exposure models. We showed that for the ELFE
464 cohort, the exposure estimates from the three models were close enough to be combined in order
465 to estimate air pollution exposure in this nation-wide population. The distributions of exposure to
466 the different air pollutants were very close across the three models and highly correlated. The

467 variability of the exposures was increased for predictions of the urban models compared to those
468 of the national and regional models; however, this is relevant as it reflects a real situation where
469 exposures are more contrasted in urban and peri-urban areas that are more densely populated and
470 where emissions due to traffic and heating are higher than in other areas. Since the ELFE cohort
471 is a representative sample of the French pregnant women, there is a priori no reason for the
472 combination of the three models to not be relevant for any other study. However, this would need
473 some validation by comparing the distribution of exposure estimate from the three models. In
474 ELFE, with the exception of NO₂, pregnancy exposure estimates were higher than air quality
475 values recommended by the WHO, respectively 40, 10 and 20 µg/m³ in annual average for NO₂,
476 PM_{2.5} and PM₁₀. In France, the limit values (according to the environmental code Article R221-1
477 Modified by the decree n°2010-1250 of October 21st, 2010-art.1) are 40, 25 and 40 µg/m³
478 respectively for NO₂, PM_{2.5} and PM₁₀ (PM_{2.5} only from 2015) in annual averages.

479
480 A previous national model for France developed for the GAZEL cohort, used the European
481 Monitoring and Evaluation Program (EMEP) emissions at a 50 x 50 km resolution and focused
482 on a 10 x 10 km CHIMERE grid with further improvements from specific recalculated data for
483 traffic and main industrial sources. After simulation, the exposure data were then refined to a 2 x
484 2 km resolution (Bentayeb et al., 2015). The “Pater model” represents a major improvement
485 compared to this previous approach. However, we acknowledge some limits of our approach.
486 One relates to the heterogeneity in the quality of predicted concentrations of the regional
487 platforms (see above), which decreases the overall performances of the regional scale model.
488 There was a restricted number (106) of PM_{2.5} monitors, which limited our ability to evaluate the
489 performances of the three models using the target plot and corresponding MQI and C. The “Pater
490 model” focus on years 2010 and 2011 in order to fit with the pregnancies of the women included
491 in the ELFE cohort; this work needs to be expanded in order to estimate exposure of the ELFE
492 children or to be used in other epidemiological studies that would have been conducted after
493 2011. The air pollutants exposure estimated for the women do not take into account the time
494 spent by pregnant women inside the buildings (housing, workplace) or during commuting. A
495 previous study performed in Grenoble, France, compared the exposure levels calculated from a
496 dispersion model with those accounting for indoor and commuting sources (Ouidir et al., 2015).
497 For NO₂ and PM_{2.5}, exposure assessed from a personal air sampler was poorly correlated with

498 exposure estimated from a model based on outdoor concentrations, suggesting that outdoor levels
499 do not reflect personal exposure. However, this result was based on a very small population (n=9)
500 and did not investigate the impact of measurement error on the association with the health
501 outcome.

502

503 **5. Conclusion**

504 This work is an important step towards the harmonization and combination of the different air
505 quality modeling tools used at different scales in France in order to promote a consistent
506 approach throughout the national territory. In the ELFE cohort, prenatal exposures to air
507 pollutants will be used to investigate their potential effects on the pregnant woman health, on the
508 fetal health, and on the child's neurodevelopment and respiratory health. In a broader perspective,
509 data from the PATer database can be used for other epidemiological studies as well as for health
510 impact studies. The next step of this project is to maintain and update the database for year 2012
511 and following years in order to estimate postnatal exposures to air pollutants for children of the
512 ELFE cohort and to allow more epidemiological studies conducted in 2010 and after to use these
513 exposure data.

514

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543

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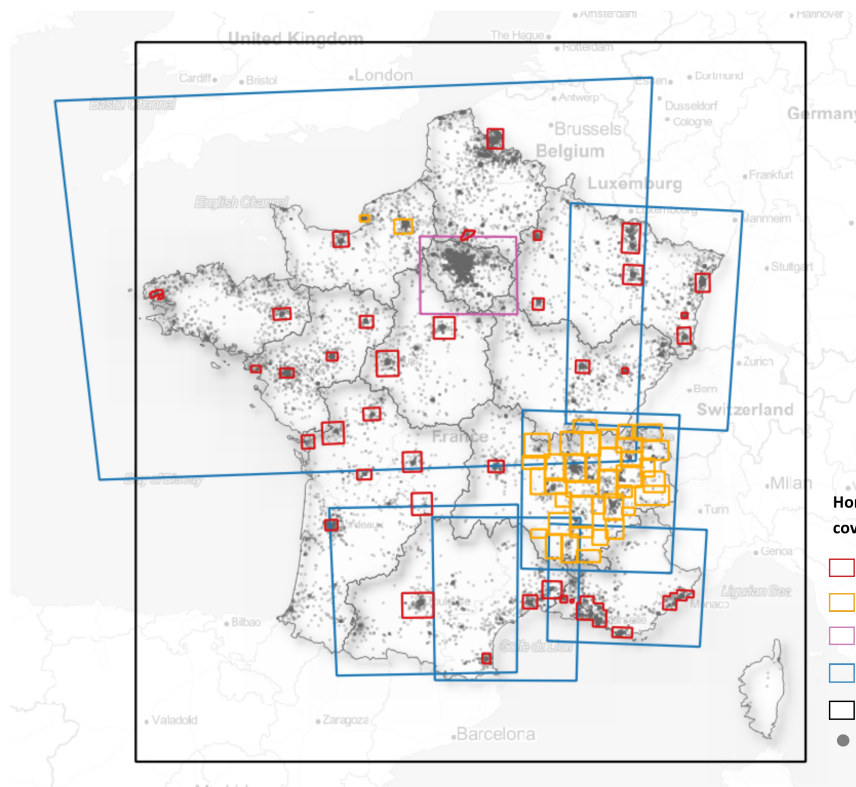
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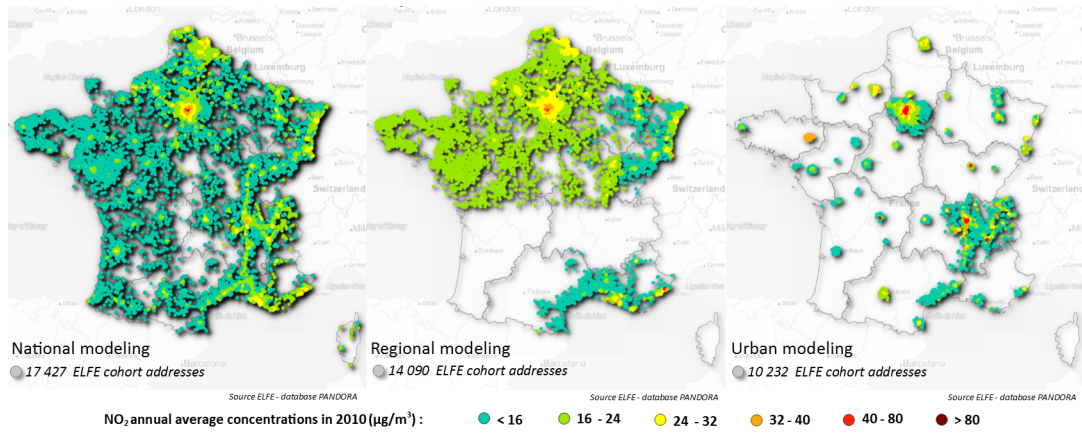
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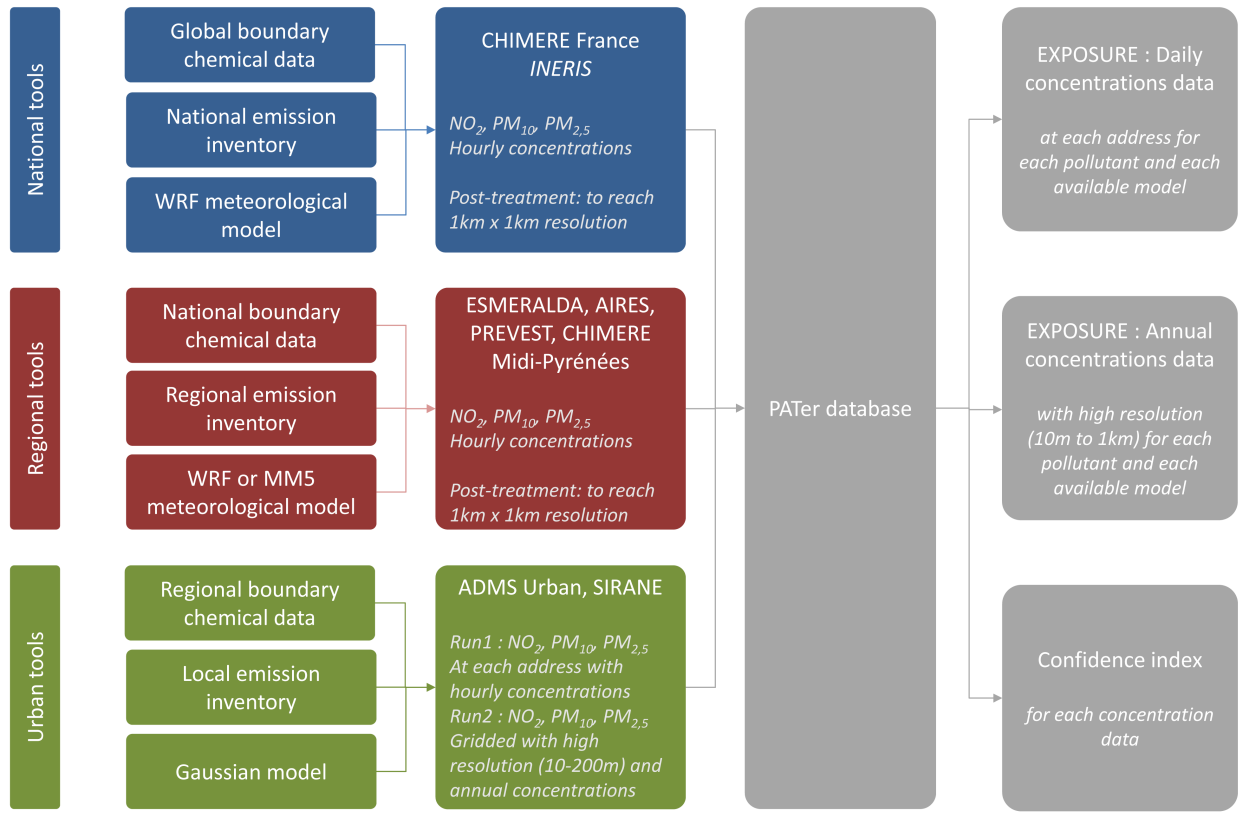


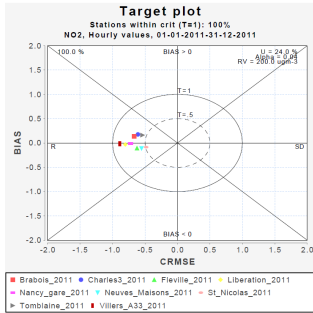
Home addresses of ELFE women at delivery and models covering the metropolitan France at different scales

- Urban modeling (ADMS - Urban)
- Urban and Inter urban modeling (SIRANE)
- Urban modeling (STREET)
- Regional modeling (CHIMERE/WRF or CHIMERE/MMS)
- National modeling (CHIMERE/IFS)
- Home addresses of the 17 427 ELFE cohort women

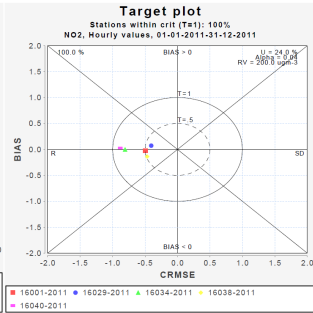
Source ELFE - database PANDORA



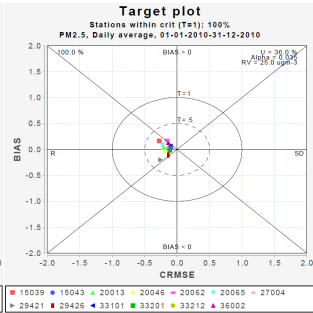




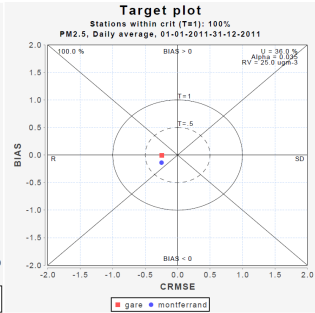
NO₂ - Nancy 2011



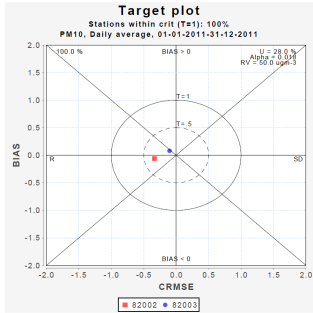
NO₂ - Strasbourg 2011



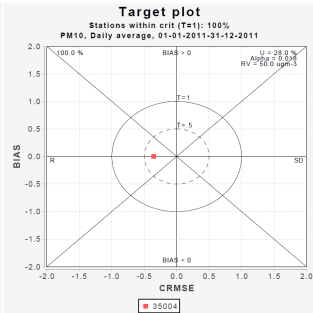
PM_{2.5} - Région Rhône-Alpes 2010



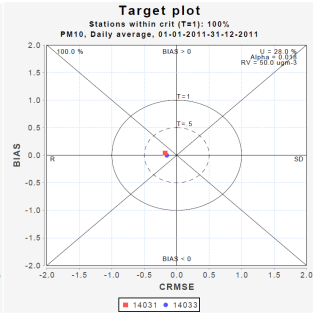
PM_{2.5} - Clermont-Ferrand 2011



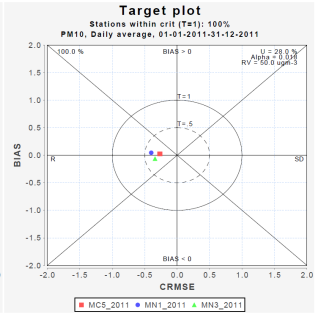
PM₁₀ - Besançon 2011



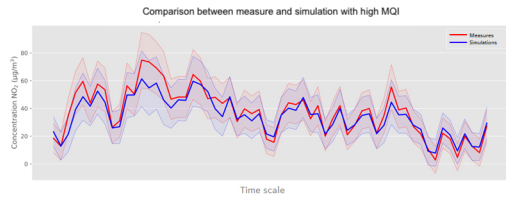
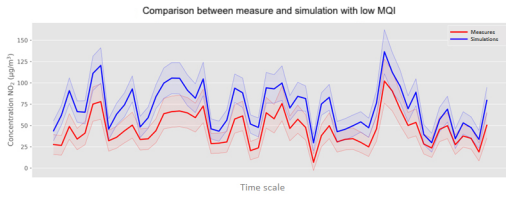
PM₁₀ - Brive 2011

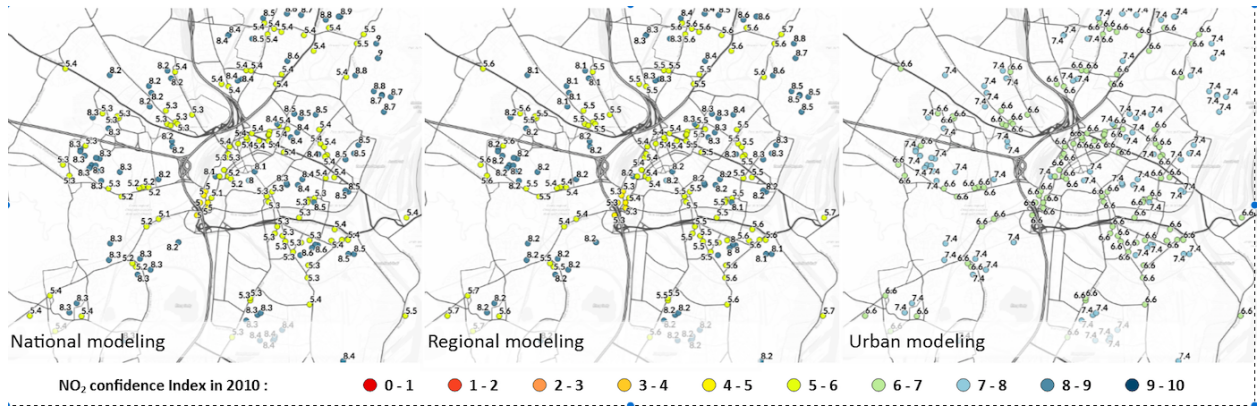


PM₁₀ - Troyes 2011



PM₁₀ - Lille 2011





Highlights

- NO₂, PM₁₀ and PM_{2.5} exposure during pregnancy for the ELFE mother-child cohort
- Fine spatial (10-200 meters at the urban scale) and temporal resolution for France
- Combination of three dispersion models at the national, regional, and local scale
- Confidence index to choose the best exposure model
- Mean pregnancy exposure was 21 µg/m³ for NO₂, 16 µg/m³ for PM_{2.5}, 24 µg/m³ for PM₁₀