

1 **Organophosphate metabolite concentrations in maternal urine**  
2 **during pregnancy**

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14 **Abstract**

15

16 The burden of organophosphate (OP) pesticides in pregnant women from Tarragona (n = 157),  
17 a Mediterranean area of intense agricultural activity, has been assessed from the study of  
18 hydroxylated organic metabolites in urine samples in the three trimesters of pregnancy. 2-  
19 Diethylamino-6-methylpyrimidin-4-ol (DEAMPY), a metabolite of pirimiphos, was the compound  
20 found in higher concentration, medians 0.66-2.8 µg/g creatinine. 4-Nitrophenol (PNP), a  
21 metabolite of parathion, medians 0.24-0.41 µg/g creatinine, was the second most abundant  
22 compound. 2-Isopropyl-6-methyl-4-pyrimidol (IMPY), a metabolite of diazinon, was also present  
23 but in lower concentrations. Except for DEAMPY, the concentrations found in this cohort were  
24 lower than those reported in studies from other countries.

25 Intraclass correlation coefficients (ICCs) were calculated for the compounds found in  
26 more than the 35% of the samples, the reliability between trimesters was poor (<0.40) to fair  
27 (0.40-0.60). Statistically significant differences were observed for the creatinine adjusted  
28 concentrations of the most abundant OP metabolites in these trimesters when examined with  
29 the Wilcoxon signed rank test for paired data.

30 In general, no association was found between urinary OP metabolites and most  
31 demographic and lifestyle predictors. However, a positive significant association was observed  
32 for women with vegetarian diet and for women of higher economic status and eventual  
33 consumption of organic food which showed higher PNP concentrations. These results suggest  
34 that higher fruit and vegetable consumption may involve higher OP pesticide ingestion but the  
35 overall association was weak.

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37

38 **Keywords:** Organophosphorus pesticides, Pyrethroids, Human Biomonitoring, Pregnant  
39 Women, Agriculture.

40

41 **1. Introduction**

42

43 Human exposure to organophosphate (OP) pesticides is common as consequence of their wide  
44 use to control insects in agriculture, commercial buildings, gardens and indoor and outdoor  
45 domestic environments. These pesticides have been found in different matrices, such as dietary  
46 products, water, outdoor and indoor air and house dust (Mercier et al., 2011, Banerjee et al.,  
47 2012; Coscollà et al., 2017; Gibbs et al., 2017; Sousa et al., 2018; Tang et al., 2018). Thus, people  
48 can be exposed to OP pesticides as consequence of domestic use, proximity to spraying areas or  
49 consumption of contaminated drinks and food (Becker et al., 2006; McKone et al., 2007).  
50 Because of their extensive use and potential toxicity, there is concern on the potential negative  
51 effects of these compounds in the environment and human health (Barr, 2008). Respiratory,  
52 digestive, reproductive and neurological problems, among others, have been related to OP  
53 pesticide ingestion or inhalation in humans (Ye et al., 2017; Arcury et al., 2016; Llop et al., 2017;  
54 Jokanovic, 2018; Liang et al., 2019).

55         When OP pesticides enter into the human body, they are metabolized and excreted  
56 through the urine, either in free form or bound to glucuronic acid or sulfates (Barr, 2008).  
57 Following a two-step metabolic pathway, they are transformed into a dialkylphosphate (DAP)  
58 and a hydroxylated organic moiety that is specific of each pesticide (Chambers and Russell,  
59 1995).

60         Tarragona is a Catalan province of intense agricultural activity and Reus, the city where  
61 the participating women were recruited, is located in an area of high olive oil, wine and hazelnut  
62 production (Tousa, 2018; Puig-Montserrat et al., 2017). The use of OP pesticides during the last  
63 decades might have had an impact on the population living in this area. In addition, there is  
64 increasing evidence of associations between prenatal exposure to OPs and deleterious effects  
65 on child neurodevelopment (Llop et al., 2017). The present study is therefore addressed to  
66 examine the burden of OP pesticides in pregnant women residing in this area by analysis of urine  
67 samples. Furthermore, in view of the metabolic changes undergone by mothers during  
68 pregnancy the study is also addressed to assess the variability of urinary OP pesticides during  
69 this period.

70

71 **2. Methods**

72

73 *2.1. Population and study design*

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75 The study population comprises a cohort (EXHES-Spain cohort) of pregnant women (n = 54) that  
76 were recruited during their first prenatal visit to the University Hospital "Sant Joan de Reus"  
77 (Reus, Catalonia, Spain) as part of the European HEALS project (recruitment started in March  
78 2016 and ended in October 2017). Urine samples were collected in the first (n = 53), second (n  
79 = 54) and third trimester (n = 50) of pregnancy of each women. The inclusion criteria were as  
80 follows: older than 16 years, intention to deliver at the reference hospital, and lack of language  
81 communication problems.

82 Dietary habits were assessed using a food frequency questionnaire (FFQ;  
83 servings/week). The different food items were classified in eight general food groups: a) Grains  
84 and grain-based products (cereals, pasta, and bread); b) Milk and dairy products (milk, yogurt,  
85 hard cheese and fresh cheese), c) Meat and meat products (chicken, turkey, beef, pork, lamb  
86 and minced meat), d) Fish and other seafood (white fish, blue fish and seafood), e) Fruits and  
87 vegetables (salad, green beans, Swiss chard, spinach, garnish vegetables, potatoes, and fruits),  
88 f) Legumes (lentils, chickpeas, and white beans), g) Ready to eat (pre-cooked and canned food)  
89 and h) Water. In addition, questions potentially relevant to exposure to endocrine disruptors  
90 were asked: type and frequency of water consumption (bottled water or tap water), organic  
91 food consumption, heating and use of plastic microwave food containers and consumption of  
92 plastic packaged food or canned food. In addition, at 20th gestation week a personal care  
93 products (PCPs) frequency questionnaire was filled in a face-to-face interview. Different PCPs  
94 were included in the questionnaire: a) makeup (face cream, eyeshadow and liquid foundation),  
95 b) lipstick, c) body lotion, d) shampoo, e) shower gel, f) hair conditioner, g) toothpaste, h)  
96 deodorant and i) spray perfume.

97 The questionnaires also included requests on the general characteristics of the study  
98 population, such as maternal age at delivery, twin pregnancy, maternal body mass index (BMI),  
99 maternal education, social economic status, country of origin, and marital status. In addition, a  
100 set of questions targeting to know other sources of potential exposure to pollutants were  
101 included, such as maternal smoking, lifestyle, hours spend outdoors and indoors, place of living  
102 and environment and occupational risks, among others.

103 The study was approved by the Ethical Committee of the Clinical Research of the  
104 University Hospital "Sant Joan de Reus". Written informed consent was obtained from the  
105 participants. The information was obtained from questionnaires administered during  
106 recruitment.

107

108 *2.2. Sample preparation and instrumental analysis*

109

110 Sample preparation and the procedures of analysis have been described elsewhere (Garí et al,  
111 2018). Briefly, centrifuged and filtered urine samples were introduced into 10-mL centrifuge  
112 tubes together with a mixture of isotopically labelled internal standards for hydrolysis with  
113  $\beta$ -glucuronidase. The hydrolysed samples were cleaned up by solid-phase extraction using  
114 cartridges preconditioned with a mixture of (1:3) MeOH:acetone followed by a solution of acetic  
115 acid 1% in H<sub>2</sub>O. The OP metabolites were eluted with a mixture of (1:3) MeOH:acetone. The  
116 collected extracts were reduced to near dryness with a gentle N<sub>2</sub> stream and transferred to  
117 chromatographic vials with (1:3) MeOH:H<sub>2</sub>O.

118 Identification and quantification of six specific organophosphate metabolites, DEAMPY,  
119 IMPY, MDA, PNP, CMHC, TCPY (Table 1), was carried out using an Ultra-Performance Liquid  
120 Chromatography (UPLC Acquity H-Class, Waters, Milford, MA, USA) equipped with an  
121 electrospray ionization interface. The chromatographic separation was performed on a Betasil  
122 C<sub>18</sub> column.

123 Synthetic urine was used for blanks, quality control materials and calibration curves.  
124 Accuracies were assessed at low and high and concentration levels. Calibration curves were  
125 prepared by adding 25  $\mu$ l of standard solutions at concentrations ranging from 2.5 to 800 ppb  
126 into synthetic urine. Quantification was performed by isotopically-labelled internal standards  
127 (Garí et al., 2018). Since 2016, this methodology is externally checked by participation in rounds  
128 of the German External Quality Assessment Scheme (G-Equas), which includes the  
129 organophosphate metabolites PNP and TCPY.

130

### 131 2.3. Data analysis

132

133 Data analysis and graphics were performed using the statistical software R (R Development Core  
134 Team, 2018). Statistics was focused on the metabolites found above limit of detection in more  
135 than 35% of the samples: DEAMPY, IMPY and PNP. One-half of the limits of detection were  
136 assigned to non-detected values. Geometric means and 95% confidence intervals, as well as the  
137 medians, were used for the descriptive analysis (Table 4).

138 The compound concentrations were transformed into natural logarithms for  
139 normalization before calculation of intraclass correlation coefficients (ICCs) and multivariate  
140 regression models.

141 To assess variability in urinary concentrations over the three trimesters, ICCs were  
142 calculated only for the analytes detected in at least 35% of the samples. For each compound the  
143 reliability was characterized as poor (ICC < 0.40), fair (0.40  $\leq$  ICC < 0.60), good (0.60  $\leq$  ICC < 0.75)  
144 and excellent ( $\geq$  0.75) (Rosner, 2011).

145 Regression analyses were performed to explore associations between the individual log  
146 transformed concentrations of OP pesticides metabolites and several demographic and lifestyle  
147 predictors.

148

### 149 **3. Results and discussion**

150

#### 151 *3.1. Socio-demographic characteristics*

152

153 Table 2 summarizes the descriptive characteristics of the women included in the study. The  
154 average age of the participating women was 33.9 years, ranging between 26 and 45 years.  
155 Twenty-seven of the women had healthy weight, twenty-five were overweight or obese and  
156 only two were underweight.

157 Most women were predominantly employed, 44 worked indoor and 2 outdoor. Thirty-  
158 two of them were transported to work by car. Thirty-one of the women had a median economic  
159 status and 21 of them had university studies. Nearly all women had most omnivorous diet, 41  
160 of them never or hardly ever bought organic food, and most of them drank bottled water (40).

161

#### 162 *3.2. Concentrations of urinary organophosphate metabolites*

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164 Descriptive statistics of the urinary concentrations of the analysed metabolites are summarized  
165 in Table 3. The detection frequencies of each compound ranged from below limit of detection  
166 (<LOD) to 79% in the first trimester, <LOD-80% in the second and <LOD-98% in the third. The  
167 most frequently detected compound in all cases was DEAMPY, the pirimiphos metabolite,  
168 followed by PNP and IMPY, parathion and diazinon metabolites, respectively. TCPY, the  
169 chlorpyrifos metabolite, was found at extremely low detection frequency.

170 In all three trimesters the metabolite found in highest concentration was DEAMPY,  
171 medians 2.6, 1.4 and 4.0 ng/g creatinine, for the first, second and third trimester, respectively.  
172 The second most abundant was PNP, again in the three trimesters, medians 0.75, 0.56 and 0.47  
173 ng/g creatinine, and in the case of third most abundant, IMPY, the medians were below limit of  
174 detection. The occurrence of parathion and diazinon metabolites is unexpected as the use of  
175 this pesticide in Europe is not approved (European Commission, 2001). However, the detection  
176 frequencies for malathion and chlorpyrifos metabolites, both approved for use, are very low.

177 Comparison of the results of the present cohort with those from other adult population  
178 studies show low values of all metabolites except for DEAMPY (Table 4). The high concentrations  
179 of DEAMPY in Tarragona are comparable with those from the rural population of Catalonia and

180 Atlanta. The median of this metabolite was lower in Galicia and Valencia (0.43 and 0.03 ng/mL,  
181 respectively). In this study it has not been possible to define the source of exposure of DEAMPY  
182 metabolite. However, Catalonia has high levels of cereals production and pirimiphos, the parent  
183 compound of DEAMPY, is used for the protection of stored grain.

184 The median concentration of PNP, 0.3 ng/ml, the second most abundant metabolite in  
185 our study, is similar to those found in Puerto Rico and US (NHANES), 0.5 ng/ml. This compound  
186 was found in much higher concentrations in urines of Catalonia, Galicia, Greece, Vietnam, China  
187 and some US sites, 1.6-5.0 ng/ml (Table 4). TCPY was not found in the cohort of Tarragona  
188 despite chlorpyrifos, the precursor pesticide, is largely applied in many world areas. Other  
189 studies performed in Spain, Valencia, Galicia and Catalonia showed higher concentrations of this  
190 metabolite (0.49, 2.4 and 0.93 ng/mL, respectively) than in Tarragona.

191 Due to lack of information on creatinine-adjusted levels in most literature data, crude  
192 concentrations have been used for the comparisons. Creatinine adjusted levels have been  
193 included when available (Table 4) showing that the differences between studies did not change  
194 significantly when using these values.

195

### 196 *3.3. Intraclass correlation coefficient*

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198 ICCs were calculated for the metabolites detected in at least 35% of the samples, DEAMPY, IMPY  
199 and PNP (Table 5). Both uncorrected and creatinine adjusted data were used, showing ICC  
200 ranges of 0.28-0.48 and 0.26-0.43, respectively. The differences between these two series of  
201 data were only significant for PNP ( $p < 0.05$ ). According to the observed coefficients, the  
202 reproducibility of the urinary OP metabolite concentration across these three trimesters ranged  
203 between poor for DEAMPY and non-adjusted PNP and fair for adjusted PNP and IMPY.

204 These observed ICCs are consistent with those reported in a study on urinary PNP from  
205 Puerto Rican women during pregnancy (Lewis et al., 2015) in which ICCs of 0.31 and 0.28 were  
206 observed for uncorrected and SG (specific gravity) adjusted levels, respectively. Other studies  
207 have assessed different time ranges. Thus, Cequier et al. (2017) and Egeghy et al. (2011) found  
208 moderate ICC values for all compounds, in a comparison of the diurnal variation. Studies  
209 encompassing longer time spans, e.g., 18 weeks (Spaan et al., 2015) or one year (Attfield et al.,  
210 2014), found OP metabolite ICCs ranging from 0.08 to 0.38. According to these ICC values,  
211 comparison of urinary metabolites between different time periods requires the analysis of more  
212 samples as longer is the time span considered.

213 Further insight into the homogeneity of the data was evaluated from the Wilcoxon  
214 signed rank test for paired data on the creatinine adjusted concentrations. Significant

215 differences were observed for the OP metabolites found in higher levels (Table 3). That is, in  
216 DEAMPY the values of the second trimester and in PNP the values of the third trimester were  
217 statistically significantly lower than the concentrations of the same metabolites in the other  
218 pregnancy periods (Table 3). These differences found between trimesters could be caused by  
219 metabolism variations or life-style changes during pregnancy. Pregnant women tend to raise  
220 their consumption of vegetables and fruits, increasing their potential exposure to OP pesticides.  
221 The values of the third trimester were highest for DEAMPY, the OP metabolite found in highest  
222 concentration.

223

#### 224 *3.4. Influence of demographic and lifestyle predictors on urinary OP metabolites*

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226 The number of statistically significant associations was low. No relationship was found between  
227 urinary OP metabolites and several demographic and lifestyle predictors, such as educational  
228 level, smoking during pregnancy, working indoor or outdoor, transport to work, type of water  
229 consumption or BMI. No significant association was found for DEAMPY concentrations, the  
230 major OP metabolite, and any of the socio-demographic and life-style predictors.

231 Regression analysis showed a positive significant association ( $p < 0.05$ ) between women  
232 with vegetarian diet and higher IMPY concentrations (diazinon metabolite; Table 6). This  
233 association has also been observed in other studies (Aprea et al., 1999 and Berman et al., 2016)  
234 and is consistent with the use of OP pesticides for plant protection against insects in agriculture.

235 A positive significant association ( $p > 0.01$ ) and borderline significance ( $0.05 < p < 0.1$ )  
236 between PNP and DEAMPY concentrations and eventual consumers of organic food was also  
237 observed. Other studies, encompassing children or adults, found associations between organic  
238 food consumption and OP pesticide exposure markers, either specific organic moieties or DAPs  
239 (Curl et al., 2003; Lu et al., 2006; Lu et al., 2008; Oates et al., 2014 and Berman et al., 2016).  
240 Tarragona results may be explained by higher consumption of organic food among vegetarians  
241 or vegans (Baudry, 2016). However, the association is not very significant because it is not  
242 observed in the mothers who consumed organic food very often (Table 6). In any case, the  
243 positive statistically significant association between concentrations for this pesticide and  
244 women in higher economic status ( $p < 0.05$ ; Table 6) is consistent with the previous associations  
245 as people of higher income tend to have greater awareness of the need of good nutrition and  
246 consume more fruits and vegetables (Kamphuis et al., 2006). Associations between higher  
247 urinary concentrations of OP metabolites, DAPs in this case, in the higher income class have also  
248 been observed in Canada (Socolof et al., 2016).

249 In addition, borderline significance ( $0.05 < p < 0.1$ ) for some of the studied characteristics  
250 has been found. Overweight women had higher DEAMPY concentrations and those who drank  
251 water from both bottle and tap had higher levels of PNP (Table 6).

252

### 253 *3.5. Strengths and limitations*

254 The present study of OPs in pregnant women uses a robust analytical methodology (Garí et al.  
255 2018). OPs have been analysed in the three trimesters of pregnancy, which is rather unusual,  
256 allowing us to assess the variability during this period. The main shortcoming of the study is the  
257 small sample size.

258

## 259 **4. Conclusions**

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261 Comparison of the concentrations of urinary OP metabolites in the pregnant women from the  
262 Tarragona area with those reported in previous studies show low values except for DEAMPY, the  
263 pirimifos metabolite, the most abundant of this cohort. TCPY, the metabolite of chlorpyrifos,  
264 was not observed in nearly all cases despite this OP pesticide is still allowed for use. Moderate  
265 variability in the three trimesters of pregnancy was assessed by ICC calculation of almost all OP  
266 pesticides. Statistically significant differences were observed for the creatinine adjusted  
267 concentrations of the most abundant OP metabolites in these trimesters when examined with  
268 the Wilcoxon signed rank test for paired data. Accordingly, more than one spot of urine sample  
269 may be needed to characterize exposures over pregnancy.

270 In general, no association was found between urinary OP metabolites and most  
271 demographic and lifestyle predictors. However, a positive significant association was observed  
272 for women with vegetarian diet and for women of higher economic status and eventual  
273 consumption of organic food, which showed higher PNP concentrations. These results broadly  
274 indicate that higher fruit and vegetable consumption may involve higher OP pesticide ingestion  
275 but the overall association is weak.

276

## 277 **Acknowledgements**

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279 This paper was supported by funding from the European Union projects: HEALS (FP7-ENV-2013-  
280 603946), Neurosome (H2020-MSCA-ITN-2017 SEP-210411486) and EDC-MET (H2020-  
281 HEALTH/0490-825762). J. Rovira received funds from Health Department of Catalonia  
282 Government through "Pla Estratègic de Recerca i Innovació en salut" (PERIS 2016-2020).

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**Table 1.** Metabolite's acronyms and principal uses of the pesticides analysed.

<b>Acronym</b>	<b>Analyte</b>	<b>Pesticide</b>	<b>Principal uses</b>	<b>Legal status<sup>1</sup></b>
DEAMPY	2-diethylamino-6-methylpyrimidin-4-ol	Pirimiphos		Approved <sup>2</sup>
IMPY	2-isopropyl-6-methyl-4-pyrimidol	Diazinon	All crops, specially fruits and citrus plantations and agricultural facilities	Not approved (2007/393)
MDA	Malathion dicarboxylic acid	Malathion		Approved
PNP	4-nitrophenol	Parathion		Not approved (01/520/EC)
TCPY	3,5,6-trichloro-2-pyridinol	Chlorpyriphos		Approved
CMHC	3-chloro-4-methyl-7-hydroxicoumarin	Coumaphos	Farm and domestic animals to control mite	Not approved <sup>3</sup>

<sup>1</sup>European Comission; <sup>2</sup>Pirimiphos-ethyl is not approved (2002/2076); <sup>3</sup>Never notified and authorised in EU.

**Table 2.** Demographics of the study population, pregnant women from Tarragona

	<b>Participants n</b>
<b>All women</b>	54
<b>Age (n=54)</b>	33.9±4.9
<b>Pre-pregnancy BMI<sup>a</sup> (n=54)</b>	
Underweight	2
Healthy weight	27
Overweight	15
Obese	10
<b>Economic status (n=54)</b>	
High	13
Median	31
Low	10
<b>Smoking (n=54)</b>	
Never	40
No (during pregnancy)	10
Yes (during pregnancy)	4
<b>Educational level (n=54)</b>	
Primary	15
Secondary	18
University	21
<b>Work (n=51)</b>	
Indoor	44
Outdoor	2
Does not work	5
<b>Transport to work (n=46)</b>	
Car	33
Walking	11
Bus	2
<b>Diet (n=54)</b>	
Omnivorous	52
Vegetarian	2
<b>Water (n=49)</b>	
Bottled	40
Tap	5
Both	4
<b>Organic food (n=51)</b>	
Never	29
Hardly ever	12
Sometimes	8
Very often	2

<sup>a</sup>Body mass index

**Table 3.** Creatinine adjusted ( $\mu\text{g}/\text{g}$  creatinine) and non-adjusted urinary levels ( $\text{ng}/\text{mL}$ ) of OPs metabolites in the first ( $n = 53$ ), second ( $n = 54$ ) and third trimester ( $n = 50$ ) of pregnancy. Full names of the metabolites in Table 1.

Metabolite	Creatinine adjusted results					Non-adjusted results			p-value <sup>4</sup>
	LOD <sup>1</sup> (ng/mL)	DF <sup>2</sup> (%)	GM (95% CI)	Median	Range	GM (95% CI)	Median	Range	
<b>1st Trimester n=53</b>									
DEAMPY	0.017	79	1.6 (0.76-3.3)	2.6	<LOD-84	0.82 (0.39-1.7)	1.8	<LOD-67	<b>0.023<sup>a</sup></b>
IMPY	0.014	38	0.049 (0.027-0.088)	<LOD	<LOD-58	0.025 (0.015-0.044)	<LOD	<LOD-11	0.67 <sup>a</sup>
MDA	0.069	6	<LOD	<LOD	<LOD-8.2	<LOD	<LOD	<LOD-12	
PNP	0.017	79	0.44 (0.25-0.78)	0.75	<LOD-9.0	0.23 (0.13-0.40)	0.41	<LOD-6.4	1.0 <sup>a</sup>
TCPY	0.02	4	<LOD	<LOD	<LOD-0.95	<LOD	<LOD	<LOD-0.15	
CMHC	0.026	0	<LOD	<LOD	-	<LOD	<LOD	-	
<b>2nd Trimester n=54</b>									
DEAMPY	0.017	80	0.89 (0.48-1.7)	1.4	<LOD-52	0.42 (0.21-0.83)	0.66	<LOD-133	<b>0.0094<sup>b</sup></b>
IMPY	0.014	41	0.066 (0.035-0.13)	<LOD	<LOD-36	0.031 (0.017-0.057)	<LOD	<LOD-31	0.98 <sup>b</sup>
MDA	0.069	2	<LOD	<LOD	<LOD-0.99	<LOD	<LOD	<LOD-0.39	
PNP	0.017	74	0.37 (0.20-0.69)	0.56	<LOD-9.1	0.17 (0.091-0.33)	0.24	<LOD-12	<b>0.050<sup>b</sup></b>
TCPY	0.02	0	<LOD	<LOD	-	<LOD	<LOD	-	
CMHC	0.026	0	<LOD	<LOD	-	<LOD	<LOD	-	
<b>3rd Trimester n=50</b>									
DEAMPY	0.017	98	4.3 (2.7-6.8)	4.0	<LOD-232	3.1 (1.8-5.2)	2.8	<LOD-179	0.82 <sup>c</sup>
IMPY	0.014	46	0.067 (0.035-0.13)	<LOD	<LOD-5.9	0.048 (0.025-0.093)	<LOD	<LOD-4.3	0.31 <sup>c</sup>
MDA	0.069	0	<LOD	<LOD	-	<LOD	<LOD	-	
PNP	0.017	78	0.26 (0.15-0.46)	0.47	<LOD-8.4	0.19 (0.10-0.34)	0.31	<LOD-6.4	<b>0.0032<sup>c</sup></b>
TCPY	0.02	0	<LOD	<LOD	-	<LOD	<LOD	-	
CMHC	0.026	0	<LOD	<LOD	-	<LOD	<LOD	-	

<sup>1</sup>LOD: Limit of detection; <sup>2</sup>DF: Detection frequencies; <sup>3</sup>GM (95% CI): Geometric mean and 95% confidential interval; <sup>4</sup>p-values of the Wilcoxon signed rank test for paired data evaluating differences between trimesters, creatinine adjusted results were used (in bold, statistically significant differences). <sup>a</sup>First trimester vs. second trimester; <sup>b</sup>Second trimester vs. third trimester; <sup>c</sup>First trimester vs. third trimester.

**Table 4.** Comparison of the 50<sup>th</sup> percentile data (ng/mL) in mother’s urine samples from Tarragona with those of other similar studies. The results included in this Table are the arithmetic means of the medians of the three trimesters.

	<b>N</b>	<b>Population</b>	<b>Year</b>	<b>DEAMPY</b>	<b>IMPY</b>	<b>MDA</b>	<b>PNP</b>	<b>TCPY</b>	<b>Study</b>
<b>Tarragona (Spain)</b>	54	Women <sup>2</sup>	2016-2017	1.8 [1.4] (2.3)	<LOD <sup>1</sup> [0.06] (0.06)	<LOD	0.3 [0.2] (0.4)	<LOD	<i>Present study</i>
<b>Valencia (Spain)</b>	573	Women <sup>2</sup>	2003-2006	[0.03] (0.02)	[0.03] (0.02)		[0.04] (0.04)	[0.49] (0.57)	<i>Llop et al., 2017</i>
<b>Catalonia (Spain)</b>	42	General	2016	1.1	<LOD	<LOD	1.8	2.4	<i>Gari et al., 2018</i>
<b>Galicia (Spain)</b>	21	General	2016	0.43	<LOD	<LOD	1.0	0.93	<i>Gari et al., 2018</i>
<b>Greece</b>	40	General	2010-2014		0.3 [0.3] (0.3)	0.4 [0.4] (0.3)	1.6 [1.6] (1.2)	6.1 [5.5] (4.9)	<i>Li and Kannan, 2018</i>
<b>Queensland (Australia)</b>	200	Women	2012-2013		[0.34]	[0.81]	[1.3]	[17]	<i>Heffernan et al., 2016</i>
<b>US (NHANES)</b>	355	Women	2009-2010		<LOD	<LOD	0.5		<i>Lewis et al., 2015</i>
<b>Puerto Rico (US)</b>	152	Women <sup>2</sup>	2010-2012		<LOD	<LOD	0.5		<i>Lewis et al., 2015</i>
<b>Atlanta (US)</b>	55	General	2012	1.0	0.75	1.2	1.4	1.9	<i>Davis et al., 2013</i>
<b>Rotterdam (Netherlands)</b>	100	Women <sup>2</sup>	2002-2006					1.2	<i>Ye et al., 2008</i>
<b>China</b>	86	General	2010-2014		0.2 [0.2] (0.2)	0.6 [0.5] (0.6)	5.0 [5.0] (5.8)	3.4 [3.7] (4.2)	<i>Li and Kannan, 2018</i>
<b>Vietnam</b>	22	General	2010-2014		0.2 [0.2] (0.2)	0.4 [0.5] (0.4)	2.6 [2.6] (2.6)	9.3 [9.3] (8.3)	<i>Li and Kannan, 2018</i>

<sup>1</sup><LOD data below limit of detection; <sup>2</sup>Pregnant women. Geometric mean into [ ]. Geometric mean for the creatinine adjusted concentrations (ng/g creatinine) into ( ).

**Table 5.** Creatinine adjusted and non-adjusted interclass correlation coefficients (ICC, 95% CI) of urinary concentrations of OP pesticide metabolites in pregnant women from Tarragona.

OP metabolite	ICC (95% CI)			
	Creatinine adjusted		Non-adjusted	
<i>All participants (n=48)</i>				
DEAMPY	0.26 (-0.13-0.54)	Poor	0.32 (-0.024-0.58)	Poor
PNP	0.43 (0.088-0.66)	Fair	0.28 (-0.17-0.57)	Poor
IMPY	0.43 (0.082-0.66)	Fair	0.48 (0.16-0.69)	Fair

**Table 6.** Results of simple linear regression models with demographic and lifestyle predictors and urinary concentrations of organophosphate metabolites.

Variable	Categories <sup>1</sup>	<i>DEAMPY</i>		<i>PNP</i>		<i>IMPY</i>	
		$\beta^2$	<i>p-value</i>	$\beta^2$	<i>p-value</i>	$\beta^2$	<i>p-value</i>
Pre-pregnancy BMI	Underweight	Reference					
	Healthy weight	1.31	0.18	-0.11	0.91	-0.79	0.39
	Overweight	1.91	0.056	-0.88	0.34	-0.94	0.32
	Obese	1.37	0.18	0.090	0.93	-0.79	0.42
Diet	Omnivorous	Reference					
	Vegetarian	-0.49	0.61	-0.62	0.49	2.4	<b>0.012</b>
Organic food	Never	Reference					
	Hardly ever	0.083	0.86	0.41	0.34	-0.42	0.37
	Sometimes	1.01	0.072	1.3	<b>0.0098</b>	-0.14	0.80
	Very often	0.67	0.50	0.25	0.78	-0.47	0.63
Drink water	Bottled	Reference					
	Tap	-0.34	0.60	0.52	0.36	-0.94	0.15
	Both	0.76	0.29	1.2	0.060	-0.096	0.89
Economic status	High	Reference					
	Median	0.59	0.19	0.84	<b>0.045</b>	-0.48	0.26
	Low	0.96	0.10	0.68	0.20	-0.15	0.78
Educational level	Primary	Reference					
	Secondary	0.38	0.42	-0.71	0.1	-0.31	0.49
	University	0.045	0.92	-0.19	0.65	-0.46	0.29
Smoking	Never	Reference					
	No (during pregnancy)	-0.052	0.92	-0.21	0.64	0.41	0.37
	Yes (during pregnancy)	-0.10	0.89	-0.83	0.20	0.87	0.19
Work	Indoor	Reference					
	Outdoor	0.30	0.77	1.6	0.1	0.81	0.42
Transport to work	Car	Reference					
	Walking	0.25	0.59	-0.37	0.38	-0.17	0.70
	Bus	0.18	0.85	-0.08	0.93	-1.4	0.14

<sup>1</sup>Same categories as Table 1; <sup>2</sup> $\beta$  Coefficients of the simple regression models with non-standardized variables. In bold, statistically significant relations