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CROP PROTECTION: NEW STRATEGIES FOR SUSTAINABLE DEVELOPMENT

Does area deprivation modify the association between exposure to a nitrate and low-dose atrazine metabolite mixture in drinking water and small for gestational age? A historic cohort study

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Abstract Birth weight may be influenced by environmental and socio-economic factors that could interact. The main objective of our research was to investigate whether area deprivation may modify the association between drinking water exposure to a mixture of atrazine metabolites and nitrates during the second trimester of pregnancy and prevalence of small for gestational age (SGA) neonates. We conducted a historic cohort study in Deux-Sèvres, France between 2005 and 2010, using birth records, population census and regularly performed drinking water withdrawals at community water systems. Exposure to an atrazine metabolite/nitrate mixture in drinking water was divided into six classes according to the presence or absence of atrazine metabolites and to the terciles of nitrate concentrations in each trimester of pregnancy. We used a logistic regression to model the association between SGA and mixture exposure at the second trimester while taking into account the area deprivation measured by the Townsend index as an effect modifier and controlling for the usual confounders. We included 10,784 woman–neonate couples. The risk of SGA when exposed to second tercile of nitrate without atrazine metabolites was significantly greater in women living in less deprived areas (OR=2.99; 95 % CI (1.14, 7.89)), whereas it was not significant in moderately and more deprived areas. One of the arguments used to explain this result is the presence of competing risk factors in poorer districts.

Keywords Small for gestational age · Endocrine disruptor · Atrazine metabolites · Nitrates · Mixture · Drinking water · Area deprivation · Townsend index

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Introduction

The consequences of low birth weight are important in both the short and the long term. In the short term, low birth weight increases the risks of child mortality, respiratory distress, and neonatal infection (McIntire et al. 1999). In the long term, those born with low birth weight more often suffer from hypertension, diabetes, or coronary heart disease than those who had normal birth weight (Barker 2004). Many individual factors that influence birth weight have been highlighted, including constitutional and medical factors, obstetric history, behaviors, and socio-economic and environmental factors (Kramer 1987; Miranda et al. 2009). Moreover, living in a disadvantaged neighborhood increases the risk of low birth weight independently of these different individual factors (Metcalfe et al. 2011).

Among the environmental factors, exposure to a number of substances in drinking water can affect birth weight. In 2009,

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an American study found a significant association between exposure of pregnant women to high levels of the thiazine-class pesticide atrazine in drinking water, and prevalence of small for gestational age (SGA) (Ochoa-Acuña et al. 2009). In addition, a Canadian study showed a dose–response relationship between drinking water nitrate level and risk of intrauterine growth restriction (Bukowski et al. 2001). A French study investigated the effect of a mixture of nitrate and atrazine metabolites in drinking water on pregnancy outcomes (Migeot et al. 2013). It showed, in the absence of atrazine metabolites, an increased risk of SGA when the pregnant women in second trimester were exposed to moderate doses of nitrates compared to low doses. The increased risk was neither found in the presence of atrazine metabolites nor in high doses of nitrates. The study took into account the individual socio-economic status, but not standard of living in the areas where they resided and factors which could influence the relationship between exposure and pregnancy outcome. In fact, the relationship between environmental and socio-economic factors in a given geographical area is particularly complex.

On one hand, people with low socio-economic status may be more exposed to certain pollutants than those with high socio-economic status. This has been demonstrated in USA with regard to nitrate contamination of drinking water, which was found to be higher in areas with a large proportion of people from Latin America than in areas where this proportion was lower (Balazs et al. 2011). In Spain, a cohort study of 257 women who had given birth in a hospital of Granada showed that concentrations of some pesticides (e.g., hexachlorobenzene) in the placenta were lower when the socio-economic level of women was high (Freire et al. 2011). However, another study conducted in Spain in 2010 on a cohort of 2,081 pregnant women found only weak links between exposure to multiple pollutants and social class, with some exposures (polychlorinated biphenyls, hexachlorobenzene and mercury) being more frequent in relatively favored women (Vrijheid et al. 2010).

On the other hand, people with a low socio-economic level may be more sensitive to certain types of pollution, as was the case in a Korean study that showed an effect of air pollution in the second trimester of pregnancy on the prevalence of prematurity only among women living in areas where the average income was low, whereas no effect was observed among women living in areas where the average income was intermediate or high (Yi et al. 2010). Another study in USA focused on the role of individual and contextual socio-economic factors in the relationship between traffic pollution and birth weight. In the census district studied by the authors, they found the protective effect of distance from major highways or access to open or recreational space to be greater in the more advantaged (Zeka et al. 2008).To explain this fact, some authors have underlined what they term the “social stress” of disadvantaged people, which could be responsible for the heightened sensitivity to pollutants (Gee and Payne-Sturges 2004). In France as well, disparities in exposure to outdoor air pollutants have been studied. A relationship between high levels of nitrogen dioxide and social disadvantages was demonstrated in Strasbourg (Havard et al. 2009). To our knowledge, no such study has been conducted on water quality.

The main objective of our research was to explore the role of area deprivation in the relationship between exposure to a mixture of nitrate and atrazine metabolites in drinking water during the second trimester of pregnancy and the prevalence of SGA children between 2005 and 2010 in the department of Deux-Sèvres (France).

Method

A historic cohort study was carried out in Deux-Sèvres between 2005 and 2010. Deux-Sèvres is a district of the Poitou-Charentes region in western France with an area of 5,999 km^2. Its population (362,944 inhabitants in 2007) resides in 305 municipalities. Agricultural activity is paramount and essentially involves livestock, predominantly sheep and goats, along with cereal production. This study was based on birth records, population census, and regularly performed drinking water withdrawals at community water systems (CWS).

Individual data

Birth records came from the district office of maternal and childhood protection, via the mandatory infant health certificates completed by the hospital prior to an infant's discharge; all births are included. The available information indicates sex, weight at birth, gestational age (number of weeks of amenorrhea, reported by obstetrical staff at birth), age of mother, number of previous pregnancies, compliance of pregnancy follow-up, smoking or absence of smoking during pregnancy, parental occupations, single-parent family, medical history of SGA in siblings, gestational diabetes, and place of residence at birth. Validation of the data drawn from birth records was carried out according to a methodology approved by the Research, Study, Evaluation and Statistics Directorate (French Ministry of Social Affairs and Health) (Collet and Vilain 2010). According to ethical rules, we identified all live births in Deux-Sèvres from January 1, 2005 through December 31, 2010 of neonates whose mothers lived in the district at the time of birth and whose birth certificates had been recorded (n=24,316). We excluded from our analysis the non-environmental causes known to induce low birth weight or SGA such as multiple births, early deaths (before birth record completion), and newborns with congenital malformations. Births by cesarean section were likewise excluded because cesarean indications may be associated with risk of SGA. We defined SGA status as birth weight below the tenth percentile for sex and gestational age, based on the population growth curves obtained from 100,176 births in different French regions between 1984 and 1988 (Mamelle et al. 1996). The cut-off values used to define SGA are presented in Appendix 1 (see electronic supplementary material).

Area-level data

Area-level socio-economic status was characterized by the census-based Townsend index, which reflects material deprivation (Townsend et al. 1988). The geographical units used were IRISs (regrouped statistical information blocks) as defined by the French National Institute for Statistics and Economic Studies (INSEE), an IRIS representing the smallest geographical census unit available in France. The regional capital and other major towns are divided into several IRIS units, and small towns form a single IRIS. Each IRIS includes approximately 2,000 individuals with relatively homogeneous social characteristics. In 2007, Deux-Sèvres counted 305 municipalities and 362 IRISs.

The Townsend index is the sum of four aggregate variables related to socio-economic context of IRIS (unemployment, non-car ownership, non-home ownership, and household overcrowding). The higher the index, the more the IRIS is considered to be deprived. The data needed for its construction were drawn from the population census carried out by the INSEE in 2007. The mothers' addresses were geocoded at the IRIS level through a correlation map effective in 1999 (INSEE 1999). The map was provided by the Maurice Halbwachs Center, which collects surveys and databases following agreements with the INSEE, several ministerial statistical services, and other public institutions (http://www.cmh.ens.fr/). Births that could not be located in an IRIS unit because they occurred in a municipality of which the configuration had changed since 1999 or on account of an incomplete address were excluded from the analysis.

Exposure

The measurements of atrazine metabolites (desethylatrazine, 2-hydroxyatrazine, atrazine) and nitrates in drinking water came from samples routinely taken at the CWSs between April 1, 2004 and December 31, 2010 by a laboratory accredited by the Regional Health Agency. The exposure of each pregnant woman was defined by assessing samples drawn from the CWS supplying her municipality of residence during the second trimester of pregnancy, according to a method described elsewhere (Migeot et al. 2013). Mixture exposure was defined by a combination of the two variables (atrazine metabolites and nitrates), resulting in six classes (unexposed to atrazine metabolites but exposed to the first tercile of mean nitrate concentrations, unexposed to atrazine metabolites but exposed to the second tercile of mean nitrate concentrations, unexposed to atrazine metabolites but exposed to the third tercile of mean nitrate concentrations, exposed to atrazine metabolites and to the first tercile of mean nitrate concentrations, exposed to atrazine metabolites and to the second tercile of mean nitrate concentrations, exposed to atrazine metabolites and to the third tercile of mean nitrate concentrations). Women residing in municipalities supplied by several CWSs, women who were exposed to other pesticides in drinking water, or who had undergone no measurement of nitrate and/or atrazine metabolites during the second trimester of pregnancy were excluded from the study.

Statistical analysis

We compared atrazine metabolites, nitrates, and mixture exposure according to the area deprivation characterized by Townsend index terciles through χ^2 tests. Multivariate logistic regression was used to model the relationship between SGA prevalence, mixture exposure, and area deprivation taking into account the individual characteristics found in birth certificates. Interactions between Townsend index terciles and each individual variable were investigated (Figueiras et al. 1998). The final model was selected after backward elimination. In order to take into account the two-level hierarchical structure of the data (women and IRIS) and possible intraclass correlation, we also attempted to apply a mixed model (Chaix and Chauvin 2002). There was no specific effect of belonging to a given IRIS on relative risk of SGA (inter-IRIS variance=0.087, p=0.25). The results of the logistic random effects model were similar to those of the logistic regression model and are not presented here.

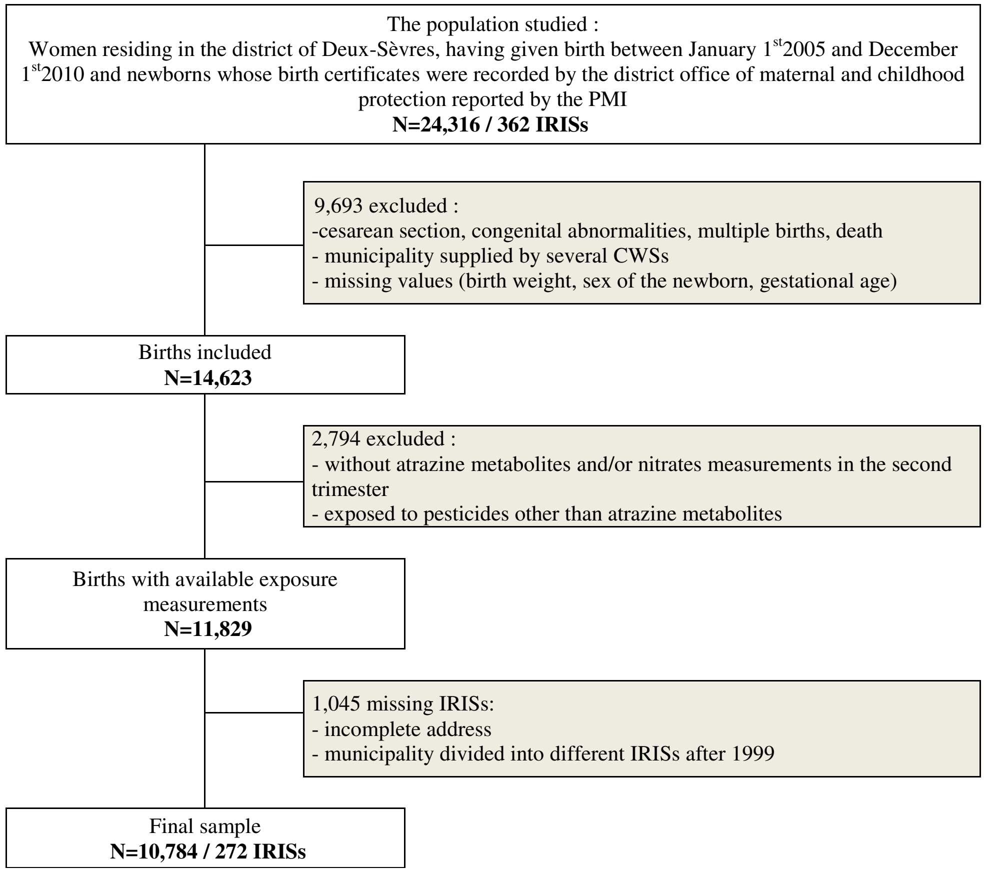
Analyses were performed using SAS version 9.3 (SAS institute Inc., NC, Cary); the significance level was set at 5 % for all analyses. Adequacy of the logistic model was checked by the Hosmer–Lemeshow test.

Results

Once the exclusion criteria defined above were taken into account, the sample included 10,784 women (Fig. 1), belonging to 272 IRIS units and supplied by 51 CWSs. Thirty percent of the 115 IRISs considered to be less deprived (tercile 1 of the Townsend index), 43 % of the 103 moderately deprived IRISs (tercile 2 of the Townsend index), and 20 % of the 54 most deprived IRISs (tercile 3 of the Townsend index) were located in rural areas.

Among the 10,784 woman–neonate couples, the average number of nitrates measurements during the second trimester was 14±11. Almost all of the women (except for three) were exposed to nitrates above the limit of quantification. Limits of nitrate concentration terciles were 0 to 15.70 mg/L for the first tercile, 15.72 to 27.25 mg/L for the second tercile, and 27.26 to 63.30 mg/L for the third tercile.

Fig. 1 Flow chart of the population studied, Deux-Sèvres, France



Seventy-five percent of the women had one sample with a pesticide measurement during the second trimester of pregnancy, 23 % had two samples, and 2 % had three samples. Among them, 74 % had not been exposed to atrazine metabolites, 26 % had been exposed to one atrazine metabolite, and less than 1 % to two different atrazine metabolites. Among the positive samples, 64 % contained 2-hydroxyatrazine (average 0.03±0.01 mg/L) and 36 % desethylatrazine (average 0.03±0.02 mg/L); less than 1 % contained atrazine (average 0.04±0.02 mg/L). Exposure varied according to IRIS deprivation (Table 1). Women living in the most advantaged IRISs were more often exposed to atrazine metabolites and third tercile of nitrates in the second trimester of pregnancy than those living in deprived and moderate IRISs. Women living in the most deprived IRISs were more frequently exposed to the second tercile of nitrate without atrazine metabolites.

Of the 10,784 births analyzed, 914 (8.5 %) were SGA. Mean birth weight was 3,304±462 g, and the mean gestational age was 39±1 weeks. Population characteristics, mean birth weight, and risk of SGA according to these characteristics are presented in Table 2. Before proceeding to adjustments on the available confounders, exposure to the second tercile of nitrates without atrazine metabolites versus the first tercile of nitrates without atrazine metabolites and residing in an IRIS of the third tercile of Townsend index were associated with an increased risk of SGA.

In the least deprived IRISs, 6 % of the neonates were SGA when women were exposed to the first tertile of nitrate without atrazine metabolites, and 10 % when they were exposed to second tertile of nitrate without atrazine metabolites. In moderate IRISs, this prevalence was respectively 8 and 8 %. In disadvantaged IRISs, it was 8 and 11 % (Table 3).

Multivariate analysis found a significant interaction between IRIS deprivation characterized by Townsend index terciles and mixture exposure (p=0.002, see Table 4 and Fig. 2). In the least deprived IRISs, the mixture exposure was associated with SGA ($p<10^{-3}$), with a significantly increased risk for women exposed to the second tercile of nitrates without atrazine metabolites (OR=2.99, 95 % CI=(1.14, 7.89)) and a non-significant increased risk for those exposed to the second tercile of nitrates in the presence of atrazine metabolites (OR=3.46, 95 % CI=(0.96, 12.39)). In the moderate and most deprived IRISs, the exposure mixture was not associated with SGA (p=0.741 and p=0.434, respectively).

Discussion

In this study, we have found that the socio-economic context of the places where pregnant women live indeed has an effect on the association between exposure to a mixture of nitrates and atrazine metabolites in drinking water during the second

Table 1 Exposure to atrazine metabolites, nitrates, and mixture in drinking water during the second trimester of pregnancy by Townsend index for the IRIS

	Townsend index			*p*
	Terciles 1 (least deprived) *n* (%)	Terciles 2 *n* (%)	Tercile 3 (most deprived) *n* (%)	
Atrazine metabolites exposure				$<10^{-3}$
No	2,411 (67.1)	2,625 (73.2)	2,899 (80.5)	
Yes	1,182 (32.9)	963 (26.8)	704 (19.5)	
Nitrates exposure				$<10^{-3}$
Tercile 1 (0 to 15.70 mg/L)	1,179 (32,8)	1,379 (38.4)	1,037 (28.8)	
Tercile 2 (15.72 to 27.25 mg/L)	921 (25,6)	1,074 (29.9)	1,600 (44.4)	
Tercile 3 (27.26 to 63.30 mg/L)	1,493 (41,6)	1,135 (31.6)	966 (26.8)	
Atrazine metabolites and nitrates mixture exposure				$<10^{-3}$
Atrazine metabolites: no, nitrates: tercile 1	578 (16.1)	727 (20.3)	603 (16.7)	
Atrazine metabolites: no, nitrates: tercile 2	814 (22.7)	954 (26.6)	1,412 (39.2)	
Atrazine metabolites: no, nitrates: tercile 3	1,019 (28.4)	944 (26.3)	884 (24.5)	
Atrazine metabolites: yes, nitrates: tercile 1	601 (16.7)	652 (18.2)	434 (12.1)	
Atrazine metabolites: yes, nitrates: tercile 2	107 (3.0)	120 (3.3)	188 (5.2)	
Atrazine metabolites: yes, nitrates: tercile 3	474 (13.2)	191 (5.3)	82 (2.3)	

Deux-Sèvres, France, 2005–2010; n=10,784

trimester of pregnancy and prevalence of SGA neonates. The risk of SGA associated with exposure to the second tercile of nitrates without atrazine metabolites was significant only in women residing in the most advantaged IRISs.

In agreement with the descriptions in the literature, we have found nitrate exposure to be associated with heightened risk of SGA (Bukowski et al. 2001). In our study, the increased risk of SGA associated with exposure to the second tercile of nitrates was not observed in the presence of atrazine metabolites, whereas several epidemiological studies have found an association to exist between exposure during pregnancy to atrazine in drinking water or the presence of urinary atrazine biomarkers and risk of SGA (Ochoa-Acuña et al. 2009; Chevrier et al. 2011). However, unlike the findings of our study, these results did not specifically involve the second trimester of pregnancy. There indeed exist critical periods in embryonic and fetal development during which the effect of exposure to certain substances can differ (Sheehan et al. 1999). This phenomenon may also be related to the fact that the interaction between substances present in the environment may be synergistic or antagonistic according to their doses and modes of action (Silins and Högberg 2011).

Since the women residing in the most disadvantaged IRISs were the ones most exposed to the second tercile of nitrates and the least exposed to atrazine metabolites, we could have put forward the hypothesis that the socio-economic IRIS levels were sources of confusion with regard to the relation found between exposure and risk of SGA. However, our analysis rather tends to show that socio-economic context could constitute a factor modifying the effects of the former.

To our knowledge, no study has dealt at any length on how the effect of water pollution can be modified by socio-economic factors. On the other hand, several studies have dealt with possible modification of the effect of air pollution on pregnancy outcomes (Généreux et al. 2008; Ponce et al. 2005; Yi et al. 2010). Two of the studies suggest a heightened effect of pollution when the overall socio-economic context is unfavorable (Ponce et al. 2005; Yi et al. 2010). On the contrary, one of the studies concludes that the effect of pollution is more pronounced in the event of a favorable socio-economic context (Généreux et al. 2008). This phenomenon may possibly be explained by the existence of other risk factors, which are most often present in the deprived segments of the population and constitute competing risks with regard to pollutant exposure, thereby diminishing the effect of the latter (Charafeddine and Boden 2008; Gouveia and Fletcher 2000). The deteriorating health of the most disadvantaged persons are likely to be associated with other types of risk factors (especially behavioral), while the most advantaged persons, who are relatively protected from these kinds of risk factors, may nonetheless be more vulnerable to pollution (Charafeddine and Boden 2008). A sizable number of SGA risk factors are indeed known to be more frequent in deprived neighborhoods, as was shown in a study carried out in the Netherlands in which the differences in occurrence of unfavorable pregnancy outcomes (such as intrauterine growth restriction) between socio-economically favored and disfavored neighborhoods were wholly attributed to individual factors such as ethnic origin, low revenue, body mass index <20, tobacco use,

Table 2 Birth weight and prevalence of small for gestational age babies according to population and IRIS characteristics

	IRIS	Women	Birth weight (g)		Small for gestational age				
			Mean	SD	*n*	%	OR	95 % CI	*p*
Area variables									
Townsend indices									$<10^{-3}$
Tercile 1 (less deprived)	115	3,593	3,319	452	261	7	1		
Tercile 2	103	3,588	3,311	462	294	8	1.14	0.96, 1.36	
Tercile 3 (more deprived)	54	3,603	3,282	470	359	10	1.41	1.20, 1.67	
Rural residence									0.462
No	128	7,447	3,301	462	641	9	1		
Yes	144	3,337	3,310	461	273	8	0.95	0.82, 1.10	
Individual variables									
Atrazine metabolite and nitrate mixture exposure during second trimester									0.004
Atrazine metabolites: no and nitrates: tercile 1		1,908	3,308	446	144	8	1		
Atrazine metabolites: no and nitrates: tercile 2		3,180	3,295	473	320	10	1.37	1.11, 1.68	
Atrazine metabolites: no and nitrates: tercile 3		2,847	3,308	462	237	8	1.11	0.90, 1.38	
Atrazine metabolites: yes and nitrates: tercile 1		1,687	3,288	459	133	8	1.05	0.82, 1.34	
Atrazine metabolites: yes and nitrates: tercile 2		415	3,338	444	30	7	0.96	0.63, 1.44	
Atrazine metabolites: yes and nitrates: tercile 3		747	3,334	470	50	7	0.88	0.63, 1.23	
Maternal age (years)									0.027
<20		275	3,209	458	35	13	1.58	1.10, 2.27	
20 to 34		8,421	3,297	457	711	8	1		
>34		2,068	3,344	479	163	8	0.93	0.78, 1.11	
Single-parent family									$<10^{-3}$
No		10,228	3,311	461	837	8	1		
Yes		556	3,168	453	77	14	1.80	1.40, 2.32	
Primiparity									$<10^{-3}$
No		6,004	3,359	464	426	7	1		
Yes		4,299	3,229	448	448	10	1.52	1.33, 1.75	
History of low birth weight									$<10^{-3}$
No		6,227	3,279	451	561	9	1		
Yes		217	2,987	510	40	18	2.28	1.60, 3.25	
Antenatal care									0.392
In conformity		8,142	3,315	456	674	8	1		
Not in conformity		311	3,141	510	30	10	1.18	0.81, 1.74	
Smoking during pregnancy									$<10^{-3}$
None		3,989	3,358	457	262	7	1		
1 to 10 cigarettes per day		828	3,122	458	134	16	2.75	2.20, 3.43	
>10 cigarettes per day		160	3,103	519	33	21	3.70	2.47, 5.53	
Household occupation[a]									$<10^{-3}$
Advantaged		2,138	3,351	453	129	6	1		
Moderately advantaged		7,016	3,307	459	584	8	1.41	1.16, 1.72	
Disadvantaged		1,585	3,230	475	198	12	2.22	1.76, 2.80	

Univariate analysis, Deux-Sèvres, France, 2005–2010

[a] More advantageous occupation of either of the parents: advantaged household (managers or executives), moderately advantaged household (self-employed, employees, and farmers), disadvantaged household (workers and unemployed)

nulliparity, relative youth, and unmarried status in disadvantaged persons (Timmermans et al. 2011).

In this study, we were informed of the participants' socio-professional categories, which are good indicators

Table 3 Birth weight and small for gestational age neonates according to exposure during second trimester of pregnancy to atrazine metabolite and nitrate mixture in drinking water, in the different terciles of Townsend index

	Townsend tercile 1 (least deprived)					Townsend tercile 2					Townsend tercile 3 (most deprived)				
	N	BW (g)		SGA		*N*	BW (g)		SGA		*N*	BW (g)		SGA	
		Mean	SD	*n*	%		Mean	SD	*n*	%		Mean	SD	*n*	%
Drinking water exposure to atrazine metabolite and nitrate mixture during second trimester															
Atrazine metabolites: no, nitrates: tercile 1	578	3,317	459	35	6	727	3,317	448	60	8	603	3,289	429	49	8
Atrazine metabolites: no, nitrates: tercile 2	814	3,305	462	84	10	954	3,306	460	79	8	1,412	3,283	487	157	11
Atrazine metabolites: no, nitrates: tercile 3	1,019	3,332	440	63	6	944	3,319	476	82	9	884	3,268	469	92	10
Atrazine metabolites: yes, nitrates: tercile 1	601	3,317	442	38	6	652	3,279	467	51	8	434	3,261	468	44	10
Atrazine metabolites: yes, nitrates: tercile 2	107	3,292	455	8	7	120	3,375	404	8	7	188	3,340	(460)	14	7
Atrazine metabolites: yes, nitrates: tercile 3	474	3,328	467	33	7	191	3,354	472	14	7	82	3,326	(491)	3	4

Deux-Sèvres, France, 2005–2010

for measurement of their social status (Ribet et al. 2007), and we availed ourselves of the Townsend index so as to assess the socio-economic levels associated with the context, which need to be taken into account in studies focusing upon the health of mother and child (Culhane and Elo 2005). Indeed, context is a multidimensional notion that cannot be satisfactorily apprehended through the individual variables alone (Braveman et al. 2005). The use of this type of indicator, which is constructed from aggregated data, nevertheless generally requires multi-level analytical methods through which correlations between individuals belonging to the same geographical entity can be persuasively accounted for (Chaix and Chauvin 2002). Since any heterogeneity between the IRISs with regard to SGA presence did not exists in our study, we had no need to implement the aforementioned methods. The lack of variability between the different IRIS units included in our study may be explained by the relatively low number of participants in each one. Were the same type of study to be performed on a larger, regional or inter-regional sample, it would undoubtedly improve the exploration of the effect of residential context on the risk of SGA.

The limitations of this study have partially to do with the choices of an exposure variable that does not necessarily reflect the actual exposure of pregnant women to a given mixture. More precisely, exposure depends on drinking water consumption patterns. In 2007, in the western part of France where the Deux-Sèvres district is located, the percentage of persons drinking tap water alone was estimated at 20 % and the percentage of people drinking tap water and bottled water at 41 %, while the remaining 38 % only drank bottled water, with no significant difference between men and women (Menard et al. 2008). In USA (Colorado), Zender et al. (2001) found no significant difference in tap water consumption between 71 pregnant and 43 non-pregnant women: 75 vs. 72 %. We may consequently suppose that for the most part, the women participating in our study consumed tap water. In order to justify the hypothesis according to which the differences in exposure effect between the different IRIS categories are related to the different levels of water consumption according to socio-economic level, it would be necessary that the women living on the most advantaged IRISs consume more tap water than those residing in the moderately advantaged or disadvantaged IRISs. However, various studies suggest the opposite, which is to say that high revenue earners drink less tap water and are more inclined to drink bottled spring water (Forssén et al. 2007; Menard et al. 2008). This possible bias consequently fails to explain the reported results.

Another limitation of this study is that nitrate and pesticide exposure was measured with regard to drinking water alone; exposure through air or food could not be assessed. However, it has been demonstrated that atrazine metabolites are only rarely present in food and that their atmospheric concentration is usually less than 0.30 μg/m^3 (Registry 2003).

Moreover, the socio-demographic and sanitary data on mother–neonate couples were limited to the information available on the infants' health certificates. On the other hand, this means of collection presents the double advantage of being exhaustive (certificate issuance is mandatory in France), and of having undergone a quality control through which the procedures employed was validated. The only type of information that could not be used on account of excessive

Table 4 Association between exposure during second trimester of pregnancy to atrazine metabolite and nitrate mixture in drinking water and prevalence of small-for-gestational-age babies according to area level deprivation

	Small for gestational age (SGA)								
	Townsend tercile 1 (least deprived)			Townsend tercile 2			Townsend tercile 3 (most deprived)		
	OR	95 % CI	p	OR	95 % CI	p	OR	95 % CI	p
Drinking water exposure to atrazine metabolite and nitrate mixture during second trimester			$<10^{-3}$			0.741			0.434
Atrazine metabolites: no, nitrates: tercile 1	1			1			1		
Atrazine metabolites: no, nitrates: tercile 2	2.99	(1.14, 7.89)		1.30	(0.65, 2.61)		1.06	(0.60, 1.89)	
Atrazine metabolites: no, nitrates: tercile 3	0.82	(0.29, 2.31)		1.65	(0.85, 3.20)		1.21	(0.65, 2.25)	
Atrazine metabolites: yes, nitrates: tercile 1	0.78	(0.23, 2.67)		1.55	(0.71, 3.38)		1.42	(0.69, 2.93)	
Atrazine metabolites: yes, nitrates: tercile 2	3.46	(0.96, 12.39)		1.14	(0.38, 3.39)		0.79	(0.34, 1.82)	
Atrazine metabolites: yes, nitrates: tercile 3	1.18	(0.40, 3.51)		1.46	(0.58, 3.70)		0.22	(0.03, 1.75)	
Maternal age (years)			0.306			0.306			0.306
<20	1.25	(0.71, 2.20)		1.25	(0.71, 2.20)		1.25	(0.71, 2.20)	
20 to 34	1	–		1	–		1	–	
>34	1.24	(0.92, 1.67)		1.24	(0.92, 1.67)		1.24	(0.92, 1.67)	
History of low birth weight			$<10^{-3}$			$<10^{-3}$			$<10^{-3}$
No	1	–		1	–		1	–	
Yes	2.25	(1.48, 3.45)		2.25	(1.48, 3.45)		2.25	(1.48, 3.45)	
Smoking during pregnancy			$<10^{-3}$			$<10^{-3}$			$<10^{-3}$
None	1	–		1	–		1	–	
1 to 10 cigarettes per day	2.48	(1.89, 3.25)		2.48	(1.89, 3.25)		2.48	(1.89, 3.25)	
>10 cigarettes per day	2.79	(1.66, 4.70)		2.79	(1.66, 4.70)		2.79	(1.66, 4.70)	
Household occupation			0.059			0.059			0.059
Advantaged	1	–		1	–		1	–	
Moderately advantaged	1.63	(1.09, 2.45)		1.63	(1.09, 2.45)		1.63	(1.09, 2.45)	
Disadvantaged	1.61	(0.98, 2.65)		1.61	(0.98, 2.65)		1.61	(0.98, 2.65)	

Results of the logistic regression with an interaction between Townsend index tercile and exposure variable (p=0.002)

Deux-Sèvres, France, 2005–2010, n=3,718

amounts of missing data pertained to alcohol consumption during pregnancies. It would also have been useful to have had information on the height and weight characteristics of the parents, which may influence the measurements of the

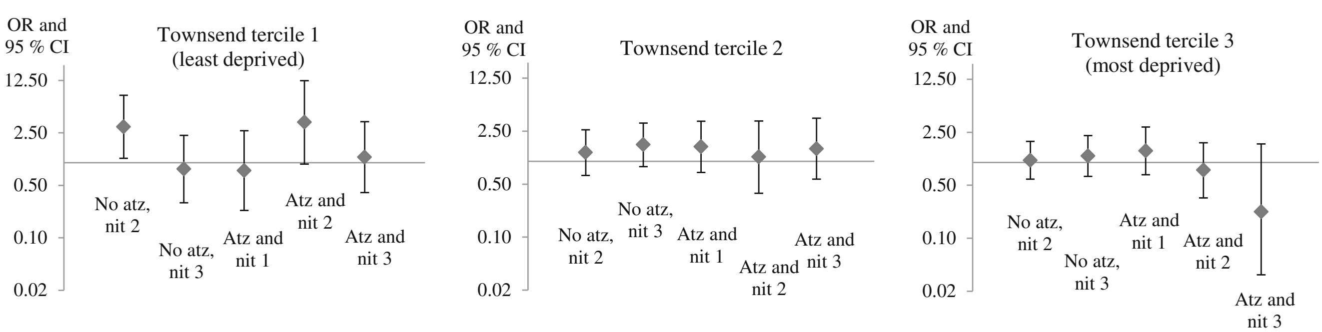


Fig. 2 Graphic representation of the association between exposure during second trimester of pregnancy to atrazine metabolite and nitrate mixture in drinking water and prevalence of small-for-gestational age (SGA) babies according to area level deprivation adjusted on maternal age, history of low birth weight, tobacco consumption, and household occupation. Results of the multivariable logistic regression with an interaction between Townsend index tercile and exposure variable (p=0.002). The *horizontal axis* represents value 1. Deux-Sèvres, France, 2005–2010, n=3,718

neonate (Albouy-Llaty et al. 2011). In addition, while the health certificates indicated the mother's home address at the time of childbirth, no facts were available with regard to the women's mobility during their pregnancies. According to the literature, moving during pregnancy is an infrequent occurrence involving only 9 % of the expectant women in Great Britain, and 17 % in USA (Chen et al. 2010; Fell et al. 2004; Hodgson et al. 2009); in most cases, the women having moved remain close to where they previously lived (Fell et al. 2004).

Finally, there could exist an IRIS classification bias related to the choice of the Townsend index as a means of characterizing the level of material deprivation. The percentage of households without a car, which is one of the four variables contributing to the index, is an indicator that may have different meanings in rural and urban environments. In rural areas, car ownership is a vital necessity in everyday activities. Yet, households of the same socio-economic level in rural and urban areas may be classified differently even though their only difference consists in this one indicator (Christie and Fone 2003). This factor may explain why exposure to atrazine metabolites and to the third tercile of nitrates is greater in the advantaged or moderately advantaged IRISs than in the disadvantaged IRISs, the latter being less frequently located in rural areas.

If we nevertheless chose to use the Townsend index for this study, it was because an association with low birth weight has already been shown to exist in several works (Bundred et al. 2003; Spencer et al. 1999). Moreover, a study carried out in 2003 tested the relationships between different indexes designed to measure contextual socio-economic level and prevalence of low birth weight, and came to the conclusion that the indexes measuring economic poverty, including the Townsend one, detected higher gradients than did those measuring educational level, professional category, or wealth (Krieger et al. 2003). The recently elaborated European Deprivation Index offers particularly interesting perspectives since it was built on theoretical premises likely to reflect individually experienced deprivation in a French context (Pornet et al. 2012).

Conclusion

The results of our study demonstrate an effect of socio-economic context on the relationship between exposure to a mixture of atrazine metabolites and nitrates in drinking water during the second trimester of pregnancy and SGA risk. The risk of SGA associated with exposure to medium-level doses of nitrates without atrazine metabolites increases significantly only in pregnant women residing in the least deprived neighborhoods. These results are in agreement with those of other published studies dealing with sensitivity to air pollution. Research needs to be pursued so as to better understand the mechanisms coming into play in the interaction between socio-economic, behavioral, and environmental factors with regard to states of health. Studies on the effects of different socio-economic contexts should be equipped with standardized measurement instruments adapted to local contexts and need to dispose of reliable data on large-scale samples.

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