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Monitoring of prenatal exposure to organic and inorganic contaminants using meconium from an Eastern Canada cohort.

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Abstract

Evaluating *in utero* exposure to inorganic and multiclass organic contaminants is critical to better evaluate potential harmful effects on prenatal and postnatal development. The analysis of meconium, the first bowel discharge of the newborn, has been proposed as a non-invasive way to assess cumulative prenatal exposure. The aim of this study was to implement an analytical method for quantifying 72 targeted organic compounds, including pesticides, pharmaceutical compounds and daily life xenobiotics, in meconium in addition to selected elements (17 elements). We report initial monitoring results based on the analysis of 396 meconium samples from an Eastern Canada cohort (Quebec, Canada). Element contents in meconium were analyzed by mass spectrometry after digestion in nitric acid and peroxide. Targeted organic compounds were extracted and purified from meconium samples by a solid-liquid extraction followed by a dispersive-SPE purification before tandem mass spectrometry analysis. Concentrations of targeted elements were within the range of concentration reported in European and US studies but were lower than concentrations found in a developing country cohort (i.e., Pb, Cd). Out of the 72 targeted organic compounds, 31 were detected at least once and 30 were quantified. Compounds with the highest frequency of detection were caffeine, detected in all samples (from 2.80 to 6186 ng g⁻¹), followed by acetaminophen detected in 53% of the samples (up to ~402 µg g⁻¹) and methyl paraben detected in 20% of the samples (up to ~10 µg g⁻¹). Pesticides were detected in low frequencies (< 2%) and low concentration (< 35 ng g⁻¹). Results show that meconium can be used to monitor prenatal exposure of foetus to a wide array of inorganic and organic contaminants.

Keywords

Prenatal exposure; Organic contaminants; Inorganic contaminants; Meconium

Introduction

Exposure to inorganic contaminants (e.g., heavy metals) has been a major concern to environmental and human health since the second half of the 20th century. In the last few decades, the development and progresses in mass spectrometry lead to the identification of countless organic contaminants of anthropogenic origin in all compartments of the environment (Alder et al., 2006). The transfer of these contaminants of emerging concern has been reported in many biota, such as plants (Gonza et al., 2005), insects (Haroune et al., 2015), marine mammals (Tanabe et al., 1982), and humans (Bolognesi, 2003; Chevrier et al., 2008; Waliszewski and Aguirre, 1998). Because many xenobiotics can pass the placenta barrier, human foetuses can be exposed to many contaminants (i.e. organic and inorganic) with potential effects on pre and postnatal development that are still vastly unknown (Haram-Mourabet et al., 1998; Koren et al., 1998; Ostrea et al., 2002; Syme et al., 2004). For instance, the intensive use of nonsteroidal anti-inflammatory drugs (e.g. ibuprofen) during pregnancy has been linked to pulmonary hypertension in newborns, miscarriage and other health issues (Alano et al., 2001; Li et al., 2003; Østensen, 1998; Sharon et al., 2014). Prenatal exposure to pesticides has been reported to be related to thyroid, neurodevelopmental disorders, and birth defects, as well as higher risks of leukemia (Chevrier et al., 2008; Infante-Rivard et al., 1999; Nurminen, 1996). Better evaluating foetus exposure to xenobiotics is an important but highly challenging task.

Xenobiotics can be analysed in cord blood (Woollen, 1993), but this only provides a snapshot of foetus exposure to xenobiotics. The analysis of meconium, the first bowel discharge of the newborn, has been proposed as a non-invasive way to monitor cumulative *in-utero* exposure to contaminants (Gareri et al., 2006). Meconium is accumulated from the 12th-16th week following pregnancy and is released in the first 48 hours after birth (Ostrea et al., 1993). Meconium can thus potentially record foetus exposure to xenobiotics for up to 6–7 months (2/3 of pregnancy). Meconium is a complex matrix composed of water, lipids, mucopolysaccharides, proteins, bile acids, organic and inorganic salts, epithelial cells, sterols, blood substances, amniotic fluid residues, enzymes and bacteria (Ardissone et al., 2014; Rapoport and Buchanan, 1950; Tsatsakis et al., 2009). It has been successfully used to monitor foetal exposure to illicit drugs and selected organic (i.e., nicotine, pesticides, persistent organic pollutants) and inorganic (i.e., heavy metals) contaminants (Gray et al., 2008; Hamzaoglu et al., 2014; Jeong et al., 2016; Moore et al., 1998). However, the effect of xenobiotic exposure on biota often result from interactions between contaminants in complex mixture (Relyea, 2009). Thus, the monitoring of many organic contaminants from various chemical families and origins (e.g., antibiotics, pesticides, personal care products) is needed to better evaluate foetus exposure to xenobiotics. The aim of the study was to optimised an analytical method for the analysis of multi-class organic compounds (72 compounds) in meconium and report initial monitoring results for these compounds in addition to selected elements (17 elements). This UPLC-MS/MS method allowed the quantification of a large variety of polar ($\log_{\text{kow}} = -1,49$) and non-polar ($\log_{\text{kow}} = 7,43$) organic compounds from one single injection. We report initial monitoring results based on the analysis of 396 meconium samples from an Eastern Canada cohort (Quebec, Canada).

Material and methods

Chemicals and reagents

Methanol (MeOH), acetonitrile (MeCN), ethyl acetate (AcOEt), formic acid (FA), and nitric acid (HNO₃) were all analytical grade and were purchased from Fisher Scientific (Ottawa, ON, Canada). All reagents, (including C18 powder) and chemical standards, supplied as solids (purity > 95%), were purchased from Sigma Aldrich (Saint-Louis, MO, USA).

Meconium sampling

Meconium samples were provided by the GESTE (GESTation and the Environment,) cohort and were collected in the Sherbrooke area (Eastern Townships, Quebec, Canada) between 2008 and 2009. More information on the GESTE cohort can be found in Laue et al. 2018 and the GESTE website <https://www.maelstrom-research.org/mica/individual-study/geste#/>. Meconium samples were collected directly from the diaper with a wooden spatula, placed in a glass container (20 mL) and stored (within 10 minutes) at –80°C until analysis.

Multielement analysis

Three mineralisation methods were tested for meconium mineralisation in nitric acid (optima); a microwave digester (CEM, MarsXpress) and a DigiPrepJr digester (SCP science), with and without peroxide addition (Sup. Info. Table S1). The three methods provided similar results. The microwave digestion offered slightly higher digestion performances. However, the DigiPrepJr digester with H₂O₂ addition was selected because it allows using smaller digestion tubes (15 mL as compared to the 50 mL microwave digestion vessels) greatly facilitating the handling of small biomass samples (~25 mg of dried meconium) digested in small volume of acid (few mL of HNO₃).

Thus, 25 mg of oven dried meconium (24 h at 70°C) was weighted in a 15 mL polypropylene tube and 1 mL of HNO₃ (trace metal grade, Fisher Scientific) was added to each tube. Then samples were mineralised using a DigiPrepJr digester (SCP science); ramp from room temperature to 45°C in 15 min, hold for 15 min then cool down to room temperature. Another 1 mL of HNO₃ and 0.2 mL of H₂O₂ were added before further mineralisation; ramping from room temperature to 45°C in 15 min, hold for 45 min, rising to 65°C in 15 min, hold for 60 min and cooled down to room temperature for a total run time of 2 hours and 15 min. Samples were then adjusted to 10 mL with milli-Q water. A 2 mL aliquot was withdrawn, diluted to 10 mL with milli-Q water in a 15 mL polypropylene tube. 200 µL of internal standards (⁴⁵Sc, ¹⁰³Rh and ¹⁵⁷Gd) were added before analysis by inductively coupled plasma mass spectrometer ICP-MS (X-Series II, Thermo Scientific), using an argon plasma torch as previously described (Darnajoux et al., 2015). The elements analysed were: ²³Na, ²⁴Mg, ²⁷Al, ³¹P, ³⁹K, ⁴⁴Ca, ⁵¹V, ⁵²Cr, ⁵⁵Mn, ⁵⁷Fe, ⁵⁹Co, ⁶⁰Ni, ⁶⁵Cu, ⁶⁶Zn, ⁷⁵As, ¹¹¹Cd, and ²⁰⁸Pb (Table 1). Matrix effects (ME) were assessed by comparing expected and measured element concentrations in spiked samples (0 ppb, 5 ppb, 50 ppb and 500 ppb). It was expressed as follow:

$$ME = \frac{\text{Concentration in spiked sample} - \text{concentration in blank}}{\text{theoretical concentration}}$$

The limit of quantification (LOQ) was determined as being 10 times the standard deviation of a blank sample.

Targeted organic compounds analysis

The LC-MS/MS method was based on a method previously developed for the analysis of 54 pesticides in swallow boluses (Haroune et al., 2015). The method was upgraded to allow the analysis of 18 additional compounds, including pharmaceuticals, and other daily life xenobiotics (e.g., plasticizer, stimulant, personal care products) (Table 2).

Glassware passivation.

To prevent sorption of target organic compounds on glassware, all glassware was deactivated using 5% (v/v) dimethyldichlorosilane in toluene. Glassware was soaked for 1 h then rinsed with two volumes of toluene and then three volumes of MeOH and water until reaching a neutral pH.

Preparation of organic compounds stock and working solutions.

Individual stock solutions ($1000 \mu\text{g mL}^{-1}$) were prepared by accurately weighting 10 mg of the individual analytical standard in 10 mL of MeOH in 10 mL deactivated volumetric flask. Some standards were diluted in acidified MeOH (0.1% of formic acid) depending on their solubility in MeOH. All stock solutions were stored at -20°C in the dark and renewed every 6 months and brought to room temperature before use. Intermediate solutions ($10 \mu\text{g mL}^{-1}$), containing the 72 selected organic compounds, were prepared by diluting individual stock solutions 100 folds with MeOH (1 mL of each individual stock solutions in 100 mL). These solutions were stored at 4°C in the dark and were renewed monthly. Working solutions were prepared for every experiment by diluting to the appropriate concentration the intermediate solutions.

Sample preparation.

We optimised the solid-liquid extraction step and the purification step for all 72 compounds. For the solid-liquid extraction step, we tested three solvents; MeOH, ACN, and AcOE. MeOH provided the best overall recovery for analytes in solvent (data not shown), but AcOEt achieved better recovery on spiked meconium samples (Sup. Info. Fig. S1). The better performances (% of recovery) of AcOEt on meconium samples are likely explained by the reduced amount of undesired co-extracts in the final extract as compared to MeOH and ACN, resulting in fewer interferences during analysis (Sup. Info. Fig. S2). MgSO_4 was used as extraction salt, as previously described (Haroune et al., 2015), without further optimisation. For the purification step, several SPE stationary phases were tested under different elution conditions to optimise recovery (Sep-Pack C18 and Oasis HLB; data not shown), but the best overall recovery performances were achieved with a dispersive SPE (d-SPE, see method section for details).

Briefly, around 150 mg of meconium was weighted in a 15 mL polypropylene tube (Falcon, BD). After addition of 5 mL of AcOEt, the tube was thoroughly mixed by hand then placed in an ultrasonic bath at room temperature for 15 min. 400 mg of MgSO_4 was added and samples were vortexed for 1 min then centrifuged at 4500 RPM for 15 min. Supernatants

were collected, transferred to a 15 mL tube and evaporated to dryness under a constant stream of dinitrogen in a sand bath at 40°C. 1 mL of ACN was then added and samples were placed in an ultrasonic bath for 1 min and vortexed for 30 sec. A dispersive SPE was performed by adding 150 mg of MgSO₄ and 50 mg of C18 in each tube which were then vortexed for 30 sec and centrifuged at 4500 RPM for 15 min. Supernatants were collected, transferred to a 15 mL tube and evaporated to dryness under a constant stream of dinitrogen in a sand bath at 40°C. Finally, samples were reconstituted in 1 mL of MeOH/H₂O (50:50, v/v), filtered on PTFE 0,2 µm filter before analysis by UPLC-MS/MS.

UPLC-MS/MS parameters.

Multiresidues analyses were performed on an UPLC Acquity (Waters Corporation, Milford, MA, USA) equipped with a HSS-T3 column (100 mm x 2.1 mm, 1.8 µm with a 0.2 µm fritted pre-filter from Waters Corporation, Milford, MA, USA) coupled with a tandem mass spectrometer XEVO TQ (Waters Corporation, Milford, MA, USA). The flow rate was 0.4 mL.min⁻¹, the column temperature was set at 40°C and the injection volume was 5 µL. Mobile phases were H₂O with 0.2% formic acid (A) and a mixture of MeOH-ACN (80:20, v/v) with 0.2 % formic acid (B). The gradient started with 5% of eluent B for 1 min, increased to 80% in 5 min, increased to 90% in 1 min, hold for 2 min and then back to 5% in 1 min. The equilibration time was 3 min for a total run time of 12 min. The analyses were performed using an electrospray ionisation (ESI) source in positive mode in multiple-reaction-monitoring (MRM). Analysis parameters were obtained by direct infusion of the analytical standards at 1 µg mL⁻¹ in MeOH as follows: desolvation gas flow (N₂) at 800 L h⁻¹; cone gas flow (N₂) at 50 L h⁻¹; collision gas flow (Ar) at 0.22 mL min⁻¹; capillary voltage 2.5 kV; source temperature 150°C, and desolvation temperature 550°C.

For each compound two product ions (transitions) were used for quantification (the most abundant) and qualification (the second most abundant). The data obtained were processed using MassLynx 4.1 (Waters Corporation). A list of the compounds and the optimised MS parameters are presented in Table 2.

Recoveries were obtained by extraction of 5 replicates of meconium samples spiked with standards of the 72 targeted organic compounds at a final concentration of 100 ng g⁻¹. Matrix effects (ME) were assessed by comparing the peak area measured for each compound in solvent against the peak area in an extracted sample of unspiked meconium. It was expressed as follow:

$$ME = \frac{\text{Area of the spiked extract}}{\text{Area of the spiked solvent}} - 1$$

The limit of detection (LOD) and quantification (LOQ) were determined as being three and ten times the standard error of the calibration curve ranging from 0.1 ng mL⁻¹ to 100 ng mL⁻¹ for UPLC-MS/MS analysis. LOD and LOQ were determined as follow:

LOD = $b_0 + 3 \times S(b_0)/b_1$ and LOQ = $b_0 + 10 \times S(b_0)/b_1$, where $S(b_0)$ is the standard deviation of the blank, b_0 the mean signal of the blank and b_1 the mean signal of the compound.

Results and discussion

Methods performances

The parameters of the elemental analysis method for the 17 selected elements are presented in Table 1. The repeatability was $< |10\%|$ and the matrix effect $< |15\%|$ for all elements. The limit of quantification (LOQ) ranged from 0.001 ppb (e.g., ^{111}Cd) to 39.70 ppb (^{39}K). The analytical performances of the LC-MS/MS method for the 72 selected organic compounds are presented in Table 3. For most compounds (64/72) recoveries are superior to 70% and only 8 have a recovery ranging from 30% to 70% with a minimum recovery of 30% (Diazinon). All analytes have a residual standard deviation (RSD) $< 30\%$. The matrix effects ranged from -49% for Phosmet to $+18\%$ for Ofloxacin. For most tested compounds (60 out of 72), the matrix effect was low ($\text{ME} < |10\%|$). Three compounds (atenolol, spinosad A and ofloxacin) were affected by moderate signal amplification ($10\% < \text{ME} < 18\%$), and 9 compounds by signal suppression ($-15\% < \text{ME} < -10\%$). Stronger signal suppression ($\text{ME} < -10\%$) was observed for analytes with retention time between 5.2 min (Carbaryl) and 7.63 min (Permethrin), which correspond to the highest intensity of undesired co-extracts from the matrix (Sup. Info. Fig. S2). The repeatability and matrix effect were $< |30\%|$ for all compounds except phosmet ($\text{ME} = -49\%$) (Table 3). The limits of detection (LOD) and quantification (LOQ) ranged from 0.1 to 0.2 ng mL^{-1} (i.e., thiabendazole) to 4 to 11 ng mL^{-1} (i.e., Ifosfamide). For compounds analysed in other studies, the recovery rates reported here are similar to those reported previously. However, our method achieved better limits of quantification and a wider range of targeted analytes (Berton et al., 2014; Meyer-Monath et al., 2014; Ostrea et al., 2002).

Initial monitoring results from the GESTE cohort

Elements contents in meconium—Among the 396 samples analysed by UPLC-MS/MS, 371 contained enough meconium biomass to perform a multielemental analysis by ICP-MS. Data for the 17 elements analysed are presented in Table 4. The range of concentrations measured in this study is wider than previously reported in meconium samples from the US and the Philippines (Haram-Mourabet et al., 1998; Ostrea et al., 2002), except for Cd and Pb for which the maximal concentrations are much lower. This wider range of concentrations for several elements is likely explained by the significantly higher number of samples analysed in this study (e.g., 371 vs 34 samples (Haram-Mourabet et al., 1998)). The use of a softer mineralisation procedure by Haram-Mourabet et al 1998 than the one used in this study could also contribute to explain these differences as the authors reported the presence of insoluble residues after mineralisation that were removed by filtration prior analysis. The high level of Pb reported in the Philippines was attributed to leaded gasoline and proximity of the hospital in which children were born to a lead battery recycling plant (Ostrea et al., 2002). Leaded gasoline has been banned in Canada for decades and no important Pb emitting industries are present in the studied region. Unlike many countries in Asia, the use of leaded paint has also been banned in North America and Europe, significantly reducing exposure to lead. Unsurprisingly, lead concentrations in meconium samples from the Canadian cohort are very low, as compared to the Philippines (Ostrea et al., 2002). The content of Cd was also markedly higher in the studies from the Philippines than our samples from eastern Canada, which might relate to low tobacco

smoking in Canada as compared to the Philippines, as well as looser regulations on heavy metals use and disposal.

The high levels of Ca found in our cohort (up to 26,000 ppm) could reflect the geology of the region, where the GESTE cohort is located (Estrie, Quebec, Canada), dominated by limestone rocks. Many households use personal artesian well for their water supply. Water consumption, as well as natural aerosols (soil particles), are thus a likely source of high Ca in the studied region and could explain the wider range of Ca concentration found in meconium as compared to meconium samples from other regions (e.g, New-York, USA, Haram-Mourabet et al., 1998).

Targeted organic compounds in meconium—Out of the 72 targeted analytes, only 10 have already been studied in meconium (Berton et al., 2014; Meyer-Monath et al., 2014; Ostrea et al., 2002). Among the 72 compounds analysed, 31 were detected, at least once, and 30 were quantified (Table 5). Caffeine was detected in all meconium samples, reflecting the omnipresence of this molecule in our daily life. This is consistent with another report of high frequency of caffeine detection in meconium from western populations (90%, Poland, (Baranowski et al., 1998)). While, the effect of in utero exposure to caffeine on foetus remain unclear (Fang et al., 2016; Klebanoff and Keim, 2015), the omnipresence of caffeine in meconium samples from our cohort at concentrations up to 6186 ng g⁻¹ calls for more research on the pre and postnatal effects of this molecule on infant development. Acetaminophen was the second most frequently detected compound (from 1µg g⁻¹, up to 403 µg g⁻¹), with roughly 53% of the 396 samples containing acetaminophen. Acetaminophen has been detected in high frequency in another study on amniotic fluid (20%, Italy, (Burrai et al., 2015)). This high frequency of detection is not surprising considering that acetaminophen is one of the rare painkillers considered safe during pregnancy. The use of acetaminophen during pregnancy has been associated with abnormal fetal neurodevelopment and other disorders (Arendrup et al., 2017; Laue et al., 2018; Thiele et al., 2013). Whether or not this association reflects direct effects of the molecule on foetal development or confounded effects from other unmeasured factors linked to the intake of acetaminophen remains to be fully studied (Stergiakouli et al., 2016). Nonetheless, our data show that most fetuses (> 50%) are exposed to this compound during gestation.

Methyl paraben was detected in roughly 20% of the samples. Methyl paraben has been found in high concentrations (up to 1800 ppm) in several hygiene products, including baby wipes (Stone, 2014). Thus, the contamination of meconium by methyl paraben post-delivery can not be ruled out. The other 27 detected compounds were present at low concentration and/or low frequencies, with 11 compounds only detected once. The most frequently detected pesticide (Fenofibrate) was only quantified in ten samples. Similar low detection frequency and concentration of pesticides in meconium was reported in France (Berton et al., 2014). In contrast, a study from the Philippines (Ostrea et al., 2002), reported much higher concentrations and higher frequency of detection for pesticides (up to 53% of samples contained Malathion against 1.2% in the French cohort (Berton et al., 2014) and 0,3% in the Canadian cohort (this work) (Table 5). A recent meta analysis on the global occurrence of anti-infectives contaminants in surface waters concluded that surface waters of low income countries are more contaminated than those of high income countries (Segura et

al., 2015). The higher concentration of pesticides in meconium from the Philippines cohort, as compared to the European and Canadian cohorts, likely reflect similar socioeconomic discrepancies. Philippines is a more rural society than France and Canada, where the population might be in more direct contact with pesticides. Differences in the kind of pesticides applied locally could also explained differences in exposure. The tighter regulation for pesticides use in Europe and Canada, as compared to Philippines, could also explained the reduced exposure of French and Canadian foetuses to pesticides. The effect of regulation on exposure might be accentuated by the fact that a decade separates results from the French and Canadian cohorts (meconium samples collected around 2010) and the Filipino cohort (meconium samples collected in early 2000'). Nonetheless, this suggests that foetuses in some developing countries, where the use of pesticides is raising and remains poorly regulated, might have a higher risk of *in utero* exposure to pesticides, as well as other organic contaminants, than foetuses in western countries.

Many organic contaminants and pharmaceuticals can be partially or totally metabolised (Woollen, 1993), generating by-products that are not detected by classical targeted analytical approaches, such as the one use here. Further studies, using untargeted approaches are required to draw a more comprehensive picture of *in utero* exposure to organic contaminants. Nonetheless, our study confirms that the analysis of meconium is a promising non-invasive approach to monitor exposure to inorganic and organic contaminants.

Conclusion

We optimised a simple method that allows the monitoring of 72 organic compounds from various chemical families and 17 elements in meconium allowing a wider survey of *in utero* exposure to organic contaminant than previously reported (Berton et al., 2014; Jeong et al., 2016; Meyer-Monath et al., 2015; Ostrea et al., 2006). The analysis of 396 samples showed that caffeine and acetaminophen are the two most often detected organic xenobiotics in meconium. However, foetuses are exposed to a variety of many other organic compounds, with 31 organic contaminants detected at least once in meconium samples. The potential effect of these exposures on newborn development will be the subject of subsequent studies, as part of the GESTE research program. We recently reported results on the association between acetaminophen contents in meconium and childhood neurocognitive development (Laue et al., 2018). A preliminary comparison of our data with previous studies suggests that foetuses in developing countries are more likely to be exposed to organic (i.e., pesticides) and inorganic (i.e., Pb, Cd) contaminants than foetuses in developed countries. This likely result from differences in lifestyle (urban versus rural) as well as environmental regulations between developing and western countries.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

ICP-MS acquisition parameters and instrumental limits of quantification.

Elements	Acquisition time (ms)	LOD (ppb)	LOQ (ppb)	Inter-day Variation (%)	Matrix effect (%)
²³ Na	5	17,110	26,370	0.9	n.d.
²⁴ Mg	10	0,462	0,767	−12	4
²⁷ Al	50	0,731	1,144	0	4
³¹ P	30	8,297	9,611	−5.3	5
³⁹ K	10	37,020	39,700	−7.8	n.d.
⁴⁴ Ca	50	18,630	34,020	−16	−2
⁵¹ V	20	0,001	0,002	0	5
⁵² Cr	10	0,008	0,400	−33	4
⁵⁵ Mn	5	0,006	0,012	−11	3
⁵⁷ Fe	50	0,696	0,828	−14	3
⁵⁹ Co	50	0,001	0,001	−7.2	4
⁶⁰ Ni	50	0,0126	0,018	−30	5
⁶⁵ Cu	10	0,585	1,230	−6.8	3
⁶⁶ Zn	10	1,316	2,195	−9.5	−3
⁷⁵ As	50	0,050	0,200	0	1
¹¹¹ Cd	30	0,001	0,001	0	−7
²⁰⁸ Pb	5	0,004	0,009	0	−15

(n.d.: not determined).

Table 2.

List of the 72 selected organic compounds and the optimized parameters of the MS/MS. CT: cone tension, CE: collision tension.

Analytes	Precursor ions		Fragment ion 1 : quantification		Fragment ion 2 : qualification	
	(m/z)	CT (V)	(m/z)	CE (V)	(m/z)	CE (V)
1-naphthol *	145	24	127	16	117	16
Acetaminophen [§]	152	25	10	16	93	21
Acetamiprid	223	22	123	20	56	14
Aldicarb	191	10	116	5	89	23
Aldicarb-sulfone	223	20	86	14	148	8
Atenolol [§]	267	30	145	25	190	20
Atrazine	216	24	96	24	104	28
Azinphos-Methyl	318	10	132	14	125	18
Bendiocarb	224	14	167	16	109	8
Bentazone	239	34	132	24	197	20
Bezafibrate [§]	362	25	139	25	316	15
Boscalid	343	28	307	20	140	20
Caffeine *	195	32	138	18	110	22
Carbamazepin [§]	237	25	194	30	179	30
Carbaryl	202	14	145	10	127	26
Carbendazim	192	24	160	18	132	28
Carbofuran	222	18	165	22	123	12
Chlofenvinphos	359	18	154	12	99	30
Chlorotoluron	213	22	72	16	140	24
Chlorpyrifos	350	20	198	18	97	26
Chlotianidin	250	16	132	16	167	12
Coumaphos	363	30	227	26	307	18
Cyanazine	241	24	214	16	104	28
Cyclophosphamid [§]	261	35	140	20	106	20
Diazinon	305	20	169	20	153	20
Dicyclohexyl Phtalate *	331	13	149	25	167	12
Dimethoate	230	14	199	10	125	20
Dinotefuran	203	14	129	12	87	16
Diuron	233	18	72	18	160	26
Fenamiphos	304	25	217	25	231	18
Fenofibrate [§]	361	30	233	15	273	15
Fenthion	279	22	247	12	169	15
Fludioxonil	247	42	126	30	169	34
Hexazinon	253	22	271	16	71	30

Analytes	Precursor ions		Fragment ion 1 : quantification		Fragment ion 2 : qualification	
	(m/z)	CT (V)	(m/z)	CE (V)	(m/z)	CE (V)
Ibuprofen ^{\$}	207	15	161	10	119	20
Ifosfamide ^{\$}	261	30	92	25	154	20
Imazethapyr	290	32	177	26	246	18
Imidacloprid	256	20	209	18	175	14
Indometacine ^{\$}	358	25	139	20	174	10
Iprodione	330	16	245	14	162	30
Isoproturon	207	22	79	18	134	22
Ketoprofen ^{\$}	255	25	105	25	177	20
Kresoxim Methyl	314	10	267	6	206	6
Linuron	249	22	182	16	160	16
Malathion	331	14	127	20	99	12
Mefenamic Acid ^{\$}	242	20	224	15	180	40
Methibenzuron	222	16	165	16	150	32
Methyl Paraben	151	25	92	15	136	15
Metobromuron	259	20	170	18	148	16
Metolachlor	284	20	252	16	176	26
Metoxuron	229	22	72	16	156	24
Monolinuron	215	20	126	16	148	16
Naproxen ^{\$}	231	20	185	10	115	45
Nitenpyram	271	18	56	26	225	14
Ofloxacin ^{\$}	362	30	318	20	261	30
O-methoate	214	16	125	22	183	12
Parathion	292	18	236	14	94	38
Pendilethalin	282	12	212	10	194	18
Permethrin	408	12	183	8	355	16
Phosmet	318	14	160	14	133	38
Piperonil Butoxide ^{\$}	356	14	177	14	119	36
Pyraclostrobin	388	16	194	12	163	24
Pyrimethanil	200	36	110	24	82	24
Sebuthylazin	230	14	174	18	104	30
Simazin	202	26	132	18	124	18
Spinosad A	732	34	142	26	98	58
Terbuthylazin	230	22	174	16	96	26
Thiabendazole	202	42	175	24	131	32
Thiachloprid	253	28	126	20	186	14
Thiametoxam	292	16	211	12	181	24
Trifloxistrobin	409	20	186	48	145	18

Analytes	Precursor ions		Fragment ion 1 : quantification		Fragment ion 2 : qualification	
	(m/z)	CT (V)	(m/z)	CE (V)	(m/z)	CE (V)
Trimethoprim [§]	291	40	261	25	230	25

[§] pharmaceuticals,

^{*} daily life xenobiotics (plasticizer, stimulant, personal care products), all others are pesticides.

Table 3.

Parameters of the optimized LC-MS/MS method for the analysis of 72 targeted organic compounds in meconium (30 ng mL⁻¹ with n = 5).

Compound	Recovery (%)	RSD (%)	RT (min)	Matrix effects (%)	LOD (ng g ⁻¹)	LOQ (ng g ⁻¹)
1-naphthol	95	24	5.27	-3	0.10	0.2
Acetaminophen	104	15	2.78	0	2.00	5.6
Acetamiprid	90	20	4.25	-3	0.20	0.4
Aldicarb	74	15	4.76	-11	5.00	2.0
Aldicarb-sulfone	99	20	3.19	-1	0.40	0.9
Atenolol	44	18	2.66	10	0.20	0.3
Atrazine	91	20	5.55	-1	0.10	0.2
Azinphos-Methyl	93	21	5.8	-6	1.00	5.0
Bendiocarb	90	20	5.1	-1	0.20	0.4
Bentazone	102	26	5.27	5	0.20	0.5
Bezafibrate	84	20	5.9	-5	0.20	0.4
Boscalid	90	21	6.01	-13	0.10	0.4
Caffeine	109	20	3.48	-2	0.20	0.4
Carbamazepin	88	20	5.3	-1	0.30	0.6
Carbaryl	95	22	5.27	-10	0.10	0.3
Carbendazim	95	21	3.15	-1	0.10	0.3
Carbofuran	93	22	5.17	-5	0.10	0.3
Chlofenvinphos	92	19	6.41	-4	0.10	0.3
Chlorotoluron	99	20	5.45	0	0.10	0.3
Chlorpyrifos	78	22	6.82	-9	0.10	0.2
Chlotianidin	90	19	3.99	1	0.20	0.4
Coumaphos	112	23	6.42	3	0.10	0.3
Cyanazine	77	18	4.99	-2	0.10	0.2
Cyclophosphamid	82	19	4.74	-2	0.20	0.5
Diazinon	30	8	6.44	-5	0.10	0.3
Dicyclohexyl Phthalate	85	21	7.15	-3	0.05	0.1
Dimethoate	92	20	4.22	-3	0.20	0.4
Dinotefuran	94	20	2.99	-2	0.20	0.4
Diuron	95	24	5.61	-2	0.10	0.2
Fenamiphos	87	22	6.28	-4	0.20	0.3
Fenofibrate	102	24	6.76	-5	0.10	0.2
Fenthion	81	23	6.36	-12	0.10	0.4
Fludioxonil	136	27	5.89	-1	0.20	0.6
Hexazinon	84	18	5.11	1	0.10	0.2
Ibuprofen	69	20	6.35	-28	2.00	5.0
Ifosfamide	69	20	4.73	-11	4.00	11.0
Imazethapyr	78	21	4.94	-5	0.10	0.2

Compound	Recovery (%)	RSD (%)	RT (min)	Matrix effects (%)	LOD (ng g ⁻¹)	LOQ (ng g ⁻¹)
Imidacloprid	89	20	3.99	-7	0.10	0.2
Indometacine	94	21	6.31	-13	0.10	0.3
Iprodione	75	26	6.26	1	1.00	5.0
Isoproturon	98	22	5.58	-1	0.10	0.5
Ketoprofen	88	18	5.73	-4	0.10	0.2
Kresoxim Methyl	73	23	6.33	2	0.20	0.5
Linuron	87	24	5.9	-8	0.20	0.5
Malathion	95	23	6.08	-2	0.10	0.2
Mefenamic Acid	78	22	6.51	-11	0.10	0.2
Methibenzuron	88	19	5.47	-2	0.10	0.2
Methyl Paraben	91	22	4.54	-5	5.00	10.0
Metobromuron	96	23	5.51	3	0.10	0.3
Metolachlor	80	20	6.33	-9	0.10	0.2
Metoxuron	98	22	4.78	0	0.20	0.4
Monolinuron	93	24	5.38	0	0.10	0.2
Naproxen	81	19	5.81	-1	0.10	0.5
Nitenpyram	86	19	3.2	1	0.20	0.5
Ofloxacin	59	19	3.46	18	0.40	0.2
O-methoate	88	19	2.77	0	0.20	0.5
Parathion	74	20	6.32	-8	0.10	0.3
Pendilethalin	84	22	6.87	-6	0.10	0.3
Permethrin	67	19	7.63	-11	0.50	1.0
Phosmet	97	24	5.83	-49	1.00	5.0
Piperonil Butoxide	87	22	6.79	-3	0.05	0.1
Pyraclostrobin	87	20	6.43	-12	0.10	0.2
Pyrimethanil	92	20	5.37	-1	0.10	0.2
Sebuthylazin	79	21	5.89	-3	0.10	0.2
Simazin	89	19	5.1	-4	0.20	0.3
Spinosad A	45	8	6.09	15	0.10	0.2
Terbuthylazin	80	20	6	-3	0.10	0.2
Thiabendazole	90	20	3.41	1	0.10	0.2
Thiachloprid	93	21	4.54	-1	0.10	0.3
Thiametoxam	88	18	3.58	-8	0.20	0.3
Trifloxistrobin	44	14	6.5	-6	0.10	0.3
Trimethoprim	74	17	3.3	9	0.10	0.3

Table 4.

Concentration of elements measured in meconium (n = 371) and comparison with the literature.

Element	Mean	Median	Range in this study (ppm)	Range in the literature (ppm)	Localisation
²³ Na	7590	7602	1100–15000	-	-
²⁴ Mg	2035	1920	150–6500	2350–3300	New-York, USA *
²⁷ Al	6.577	3.107	<LOQ-2.3	-	-
³¹ P	651.5	515.5	200–8000	110–170	New-York, USA *
³⁹ K	4951	4453	900–18000	-	-
⁴⁴ Ca	1412.4	936.8	100–26000	1600–3900	New-York, USA *
⁵¹ V	0.036	0.013	<LOQ	-	-
⁵² Cr	0.230	0.048	<LOQ –0.09	-	-
⁵⁵ Mn	18.02	14.31	1–100	9–35	New-York, USA *
⁵⁷ Fe	75.77	56.39	5–1100	47–115	New-York, USA *
⁵⁹ Co	0.061	0.056	0,01–0,17	-	-
⁶⁰ Ni	0.107	0.081	<LOQ-1.7	-	-
⁶⁵ Cu	78.17	67.18	15–250	90–154	New-York, USA *
⁶⁶ Zn	408.4	313.8	20–1500	156–365	New-York, USA *
⁷⁵ As	0.130	0.123	<LOQ-0.72	0.001–0.31	Manille, Philippine ^{\$}
¹¹¹ Cd	0.004	0.002	<LOQ-0,01	0,5–72	Manille, Philippine ^{\$}
²⁰⁸ Pb	1.830	0.022	<LOQ-0.35	8–600	Manille, Philippine ^{\$}

* Haram-Mourabet et al 1998,

^{\$} Ostrea et al 2002.

Table 5.

List of targeted organic compounds detected in meconium (n = 396) and comparison with the literature. * quantified only once, n.d. not detected.

Compound	Frequency (%)	Range (ng.g ⁻¹)	Mean (ng.g ⁻¹)	Frequency (%)	Mean (ng.g ⁻¹)	localisation
1-Naphthol	0.3	0.8	*	-	-	-
Acetaminophen	52.8	<LOD-402377	6981	20	0-1390	Italy [*] 77)
Acetamiprid	0.3	1.60	*	-	-	-
Azinphos-methyl	0.3	9.9	*	-	-	-
Boscalid	0.3	0,4	*	-	-	-
Caffeine	100.0	2.8-6186	645.1	90	10-45	Poland ^{**} 8)
Carbamazepin	0.5	<LOD-15983	7993	-	-	-
Carbaryl	0.3	2,3	*	-	-	-
Carbendazim	1.3	<LOD-0.7	0.6	-	-	-
Chlorpyrifos	0.0	n.d.		0 / 11	0 / 53.6	France ^{\$} / Philippines ^{&}
Clothianidine	0.5	<LOD-1.6	1.2	-	-	-
Diazinon	0.0	n.d.		3.5 / 34.3	0.3 / 226	France ^{\$} / Philippines ^{&}
Fenofibrate	2.5	<LOD-76	18	-	-	-
Fludioxonil	0.3	11	*	-	-	-
Hexazinone	0.8	<LOD-1.3	1.1	-	-	-
Ibuprofen	0.0	n.d.		22	703	Michigan US [#] (76)
Imazethapyr	0.8	<LOD-2.5	1.3	-	-	-
Indometacine	0.0	n.d.		7.9	4592	Michigan US [#] 76)
Isoproturon	1.5	<LOD-23	5.73	1.2	<LOQ	France ^{\$} (70)
Kresoxim-Methyl	1.5	<LOD-25	8.9	-	-	-
Linuron	0.5	<LOD-25	13	-	-	-
Malathion	0.3	<LOQ-<LOQ	<LOQ	1.2 / 53.0	<LOD / 71.7	France ^{\$} / Philippines ^{&}
Mefenamic acid	0.3	0.3	*	-	-	-
Methibenzuron	0.3	0.4	*	-	-	-
Methylparaben	19.9	<LOD-10415	1262	-	-	-
Metolachlor	0.5	<LOD-1.3	1.2	-	-	-
Naproxen	0.8	<LOD-9.4	4.04	19	435	Michigan US [#]
O-Methoate	1.8	<LOD-6.6	3.9	-	-	-
Parathion	0.8	<LOD-31	12.67	32	86	Philippines ^{&}
Pendimethalin	0.5	<LOD-1.1	1	-	-	-
Pyraclostrobin	1.5	<LOD-9.9	2.9	-	-	-
Pyrimethanil	0.8	<LOD-0.6	0.8	-	-	-
Thiabendazole	0.3	0.5	*	-	-	-
Thiamethoxam	1.0	<LOD-13	4.3	-	-	-
Trimethoprim	1.3	<LOD-0.8	0.5	-	-	-

* Burrai et al 2015,

** Baranowski et al 1998,

\$ Berton et al 2014,

& Ostrea 2002