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Abstract

Background

Maternal occupational exposure to organic solvents during pregnancy has been associated with decreased visual function in offspring. Glycol ethers (GEs) belong to oxygenated solvents and are widely used both in occupational and domestic contexts.

Objectives

We aimed to assess associations between prenatal GEs exposure and contrast sensitivity in children.

Methods

Six GE alkoxy carboxylic acidic metabolites (methoxyacetic acid [MAA], ethoxyacetic acid [EAA], ethoxyethoxyacetic acid [EEAA], butoxyacetic acid [BAA], phenoxyacetic acid [PhAA], and 2-methoxypropionic acid [2-MPA]) were measured in first morning void urine samples collected from 220 early-pregnancy women, in the mother-child PELAGIE cohort (France). Trained investigators administered the Functional Acuity Contrast Test (FACT) to the 6-year-old children, providing scores for 5 spatial frequencies (1.5-18 cycles per degree (cpd)). We standardized biomarker urinary concentrations on urine sampling conditions. Values below the LOD were imputed based on log-normal distribution, generating five datasets for multiple imputation. Linear regression models were adjusted for potential confounders.

Results

GE metabolites were detected in 70-98% of maternal urine samples. Phenoxyacetic acid (PhAA) had the highest median concentration (0.33 mg/L), and 2-methoxypropionic acid (2-MPA) the lowest (0.01 mg/L). Children with higher prenatal PhAA concentrations had poorer FACT scores at various spatial frequencies (fourth vs. first quartile: β_{18cpd}= -0.90 (95% confidence interval CI =-1.64, -0.16), β_{12cpd}= -0.92 (95%CI =-1.55, -0.29) and $\beta_{1.5cpd}$= -0.69 (95%CI =-1.19, -0.20)). The 2-MPA log-scale concentration was negatively associated with the FACT score at the 3-cpd stimulus.

Discussion

PhAA is the metabolite of ethylene glycol monophenyl ether present in many cosmetics. 2-MPA is the metabolite of an isomer of propylene glycol methyl ether commonly present in household and industrial cleaning products. Although evidence of biological plausibility is lacking, the study suggests adverse impact of ubiquitous prenatal exposure to some GE on visual functioning among children.

Keywords: Children; Contrast sensitivity; Development; Vision, Glycol ethers, prenatal exposure

Introduction

Glycol ethers (GEs) are oxygenated solvents highly miscible in water and oils and widely used in various products in both occupational and domestic contexts, such as water-based paints, inks, glues, cleaning products, cosmetics, and pharmaceutical products. Over the past two decades, French and German measurements of urinary glycol ether metabolites have shown that the general population, including pregnant women, is ubiquitously exposed to these solvents (Ben-Brik et al. 2004; Fromme et al. 2013; Garlantézec et al. 2012; Nisse et al. 2017; Santé publique France 2019). This exposure is thought to occur mainly via the dermal route and inhalation (Institut national de la santé et de la recherche médicale (France) 1999; 2006).

There are more than 30 different GEs, derived from ethylene glycol (E series) or propylene glycol (P series). GEs of the E series and minor isomers of GEs of the P series contain a primary alcohol function that are rapidly metabolized into alkoxycarboxylic acids. Such metabolites are thought to be responsible for toxicity and are eliminated by urine, and may be used as biomarkers of exposure (Institut national de la santé et de la recherche médicale (France) 1999; 2006).

Case-control studies (Costa et al. 2012; Jiménez Barbosa, Boon, and Khuu 2015; Lacerda et al. 2012; Oliveira et al. 2018) have repeatedly reported that organic solvents in occupational contexts have adverse effects on human visual function, in particular, causing deficits in color vision and contrast sensitivity. The organic solvents most frequently mentioned have been carbon disulfide, trichloroethylene and tetrachloroethylene, styrene, toluene, and organic solvent mixtures (Fox 2015). Questions nonetheless remain about the pathogenesis of this visual loss associated with occupational exposure (Oliveira et al. 2018; Fox 2015). Costa *et al.* (Costa et al. 2012) listed some of the suggested causal mechanisms, including axonopathy of the visual pathway, disruption of photoreceptor function, and cortical (and/or retinal) changes in neurotransmitter systems such as glutamate, dopamine, and acetylcholine. Alterations in visual functioning, even subclinical, may have negative consequences on individuals' mental and physical health and social functioning (Fox 2015). A few other observational studies have shown associations between maternal occupational exposure to solvents during pregnancy and a decrease in their offspring's visual function, including contrast sensitivity (Till et al. 2005; 2001). The organic solvents in these studies have included ketones, aliphatic, halogenated, and

aromatic hydrocarbons, alcohols, glycols and ethers, but the multiple exposures and the small numbers of individuals involved have prevented researchers from isolating the individual contributions of each chemical.

Visual function is routinely evaluated by testing acuity, which measures the ability to recognize smaller and smaller stimuli at maximal contrast. This method may be insufficient however to reveal deficits of retinal and/or post-retinal processing caused by neural defects that might induce vision loss, even at low spatial resolution. More comprehensive information can be obtained by assessing visual function through contrast sensitivity, i.e., the ability to see a shape or pattern of decreasing contrast (light intensity) against a background (Cartier et al. 2018; Waksman and Brody 2007). Contrast sensitivity is thought to be mature at 6-7 years old (Ellemberg et al. 1999).

In a previous study based on the French PELAGIE (*Perturbateurs endocriniens, Étude Longitudinale sur les Anomalies de la Grossesse, l'Infertilité et l'Enfance*) mother-child cohort, we observed an adverse association between maternal prenatal exposure to certain glycol ethers and some aspects of neuropsychological performance in 6-year-old children, including on tests involving visuo-spatial abilities (Béranger et al. 2016). In the present study, we aimed to examine in the same population the associations between prenatal exposure to glycol ethers, measured from maternal glycol ether metabolites in urine samples collected at the beginning of pregnancy, and their children's contrast sensitivity at 6 years of age.

Methods

The PELAGIE mother–child cohort included 3,421 pregnant women from Brittany, France, between 2002 and 2006. Women were recruited before the 19th week of gestation by their gynecologist, obstetrician, or ultrasonographer at their first prenatal visit (Garlantezec et al. 2009; Petit et al. 2012). A subcohort of 591 mother–child pairs was randomly selected from the live-born singleton children of study participants for a neuropsychological and visual function assessment at age 6 years (between 72 and 75 months of age). Among them, 20 were excluded for preterm birth before 35 weeks' gestation, neonatal respiratory distress or hospitalization, or Down syndrome; 125 could not be

reached by telephone; and 18 more were excluded because the child had previously undergone neuropsychological or behavioral tests (to avoid bias due to the learning effect). Among the 428 remaining families, 287 (67%) mothers agreed to participate with their child in the neuropsychological follow-up. At inclusion and at 6 years of age, women completed a self-administered questionnaire about their family, social and demographic characteristics, diet, lifestyle, and the child's health.

Contrast sensitivity measurement

The Functional Acuity Contrast Test (FACT® Stereo Optical Company, Inc.) was used to evaluate visual function. Easily administrated in children, it has been shown to be a valid measure over the age of 4 years (Ulrich and Palmowski-Wolfe 2019). This chart has five rows (A to E) of vertical gratings embedded in circular patches (1.7 degrees of visual angle), each with a specific spatial frequency, that is, 1.5 cycles per degree (cpd) in row A, 3 cpd in row B, 6 cpd in row C, 12 cpd in row D, and 18 cpd in row E. In each row, the grating contrast uniformly decreases in nine levels by 0.15 log10 units from high (left side) to low (right side) contrast levels (see Figure S1, Supplement Material, which illustrates spatial frequency change of stimulus (y axis) as a function of contrast (x axis) as used in the FACT). Assessments were conducted at home in daylight by one of two trained psychologists, blinded to the child's exposure status. Ambient light was measured just before the test with a digital light meter (Nicety LX 801). The child was asked to indicate the grating orientation (left, up or right) for each stimulus. The test was presented monocularly at a distance of 45 cm to the best eye (in the child's opinion). Children were instructed to use glasses during the test if they usually wore them. The scores, one per row or spatial frequency, were the last correct answer given, so that higher scores indicate better performance. This score was then transformed into contrast values and reported on a diagram to visualize the contrast sensitivity curve. The FACT was administered twice; the best answer was reported for each spatial frequency.

Glycol ether exposure measurement

At inclusion, each pregnant woman mailed a first morning void urine sample in a 10 mL test tube (95 × 16-mm polypropylene) to our laboratory. Samples were sent in an opaque, rigid box at ambient

temperature. Upon arrival, urine samples were frozen at –20°C until analysis. Six GEs alkoxycarboxylic acids metabolites, whose parent compounds and sources at the time of inclusion are summarized in Table 1, were measured: five alkoxy acetic acids from the E series (methoxyacetic acid [MAA], ethoxyacetic acid [EAA], ethoxyethoxyacetic acid [EEAA], butoxyacetic acid [BAA], phenoxyacetic acid [PhAA]), and one alkoxy propionic acid from the P series derivatives, (2-methoxypropionic acid [2-MPA]) (Ben-Brik et al. 2004; Fromme et al. 2013; Garlantézec et al. 2012; Institut national de la santé et de la recherche médicale (France) 1999).

A first set of samples (n=75; set 1) was analyzed at the Toxicology and Genopathy Laboratory at CHRU (Centre Hospitalier Régional Universitaire) Lille between 2004 and 2007 as part of previous analyses performed in a nested case-control study including 580 controls (Cordier et al. 2012). The limit of detection (LOD) was 0.05mg/L for all metabolites. A total of 205 samples (n=212; set 2; urinary sample was unavailable for 7 of them) were analyzed at the Institut Idhesa (Plouzané, Finistère, Brittany) in 2013. The LOD was then 0.003mg/L for all metabolites. Glycol ether metabolites were measured by gas chromatography coupled to mass spectrometry (Labat et al. 2008).The laboratory procedures for analysis of these glycol ether metabolites have been described elsewhere for sample sets 1 (Cordier et al. 2012) and 2 (Béranger et al. 2016).

Statistical analyses

Maternal urinary concentrations and children's vision evaluations were available for 226 families (visual testing data were available for 78.7% of the home visits). Among them, six children were excluded: five children did not wear their glasses during the test, and one child had nystagmus. Analysis was performed with R software version 3.5.0 (R Core Team 2018) (NADA package for left-censored data analysis, mice and zelig packages to deal with multiple imputation, rms package to use restricted cubic splines).

Standardization and imputation of the urinary concentrations

As shown in previous analyses of other PELAGIE data (Cordier et al. 2012), certain sampling conditions can influence urinary concentrations of GEs metabolites. To limit the impact of between-subject variations due to sampling conditions, we standardized biomarker concentrations by a two-step method based on regression residuals (Mortamais et al. 2012). First, we estimated associations for each biomarker between its log-transformed concentration and sampling conditions [day of sampling (week or weekend), gestational age at collection, transportation time at room temperature before freezing, and duration of storage at -20°C before analysis] by separate tobit regression models, which take left-censored data into account (Helsel and Helsel 2012; Shoari and Dubé 2018; Lubin et al. 2004) (see Table S1, Supplement Material, which presents the relation between log-transformed GEs metabolite concentration and sampling collection characteristics). We also adjusted the models for maternal age, prepregnancy body mass index (BMI), parity, year of sampling, education, and active smoking before pregnancy. We then used the estimated regression coefficients (Table S1) to calculate for each subject the biomarker concentrations that would have been observed had all samples been collected under the same conditions (Mortamais et al. 2012).

Values below the LOD for standardized concentrations of these GEs metabolites were randomly imputed from a log-normal probability distribution, the parameters of which were estimated by a maximum-likelihood method (Jin et al. 2010). Imputation was implemented for each set, according to its LOD (0.05mg/L and 0.003mg/L respectively). Five datasets were generated for multiple imputation (Enders 2010).

Potential covariates

All models *a priori* included the following covariates: mother's urinary creatinine concentration (continuous, g/L), ambient light intensity (in lux units) at the time of testing, and the investigator who administered the FACT. With no other strong a priori knowledge on possible confounders, we also selected covariates using data-driven approach when association was observed with at least two urinary concentrations of the glycol ether metabolites and with two FACT spatial frequencies at $P < 0.2$

based on the relevant univariate analyses. We considered the following covariates: prepregnancy maternal BMI (<18.5 kg/m², 18.5-24.9 kg/m², 25.0-29.9 kg/m², ≥ 30.0 kg/m²), maternal education (≤ 12 years, > 12 years), maternal age at inclusion (continuous), sex, parity (0, ≥ 1), breastfeeding (none, ≤ 16, > 16 weeks), maternal tobacco consumption at the beginning of pregnancy (yes/no), habitual fish consumption before pregnancy (≤ 1, ≥ 2 times per week), place of residence of child at age 6 (urban, rural), siblings at age 6 (continuous), number of cigarettes smoked daily in the household at age 6 (0, ≤ 10, > 10), mother's verbal IQ, HOME score, duration of video gaming weekly (0, <1.5 h, ≥ 1.5 h), duration of television watching weekly (< 2h, 2.5–4.5 h,>4.5h), extracurricular sports activities (no, yes), child's sleep duration (< 10.5, 10.5–11 h, > 11h per day), and acid-leachable lead in floor dust (≤ 1, 1–3, > 3 µg/m²). There were few missing data for covariates. Simple imputation was used: ambient light with median (2% n=4), maternal prepregnancy BMI (1%) with the modal value of the distribution, time spent in front of TV or video games (4%) and sleeping duration (1%) with the nearest neighbor method.

Association between urinary concentrations of GE metabolites and FACT scores

For each GE metabolite, we constructed multivariable linear regression models to explore associations between maternal urinary concentrations and each of the children's 5 spatial frequency FACT scores. We applied Barnard and Rubin's pooling rules for multiple imputations with small samples (Barnard and Rubin 1999; Little and Rubin 1987).

Urinary concentrations were first categorized in quartiles. The linearity of the relations between these metabolite concentrations (in natural log-scale) and the FACT scores was assessed by using restricted cubic splines based on full multivariate models (Desquilbet and Mariotti 2010). We chose the 25th, 50th, and 75th percentiles as knots and rejected the assumption of linearity when the log-likelihood ratio test between the models with and without restricted cubic splines had a P-value < 0.05 (Meng and Rubin 1992). When linearity was not rejected, the final models included continuous GE urinary metabolite concentrations. Finally, in view of the weak correlation between the GEs metabolites (see Table S2, Supplement Material, showing correlation between log-transformed GE

metabolite maternal urinary concentrations), we did not mutually adjust for their multiple concentrations.

Sensitivity analysis

To explore the possible effects of standardizing the metabolite concentrations, we conducted a sensitivity analysis restricted on sample set 2, running models including the same covariates and crude concentrations of glycol ether urinary metabolites (no imputations, and concentrations categorized in quartiles), additionally adjusted for the sampling conditions and covariates included in the models that were adjusted in the first step of standardization. We compared the results of these models with those of the set 2 models that used the standardized concentrations of GEs urinary metabolites.

Ethics statements

All adult participants provided written informed consent. Children provided verbal and witnessed assent. The French Consulting Committee for the Treatment of Information in Medical Research (no. 09.485) and the French National Commission for the Confidentiality of Computerized Data (no. 909347) approved this study.

Results

Mean maternal age at inclusion was 30 years old, nearly 60% were multiparous, 75% had a normal prepregnancy BMI, 65% had a maternal education level exceeding 12 years, and 75% reported they were nonsmokers (Table 2). When the child in the study was 6 years old, most families (56%) had 2 children, and no one smoked cigarettes in 60% of the homes. Mean birth weight was 3400g, 67% were breastfed (52% of them for more than 16 weeks), and 53% were girls. Half of the children spent more than 5 hours a week in front of the television.

As expected, the highest mean ± SD FACT scores were those corresponding to lower spatial frequencies: 6.3 ± 1.3 for 1.5 cpd and 6.4 ± 1.5 for 3 cpd (Table 3). Mean FACT scores then decreased for higher spatial frequencies; with the lowest mean score for the 18 cpd frequency (2.4 ± 2.1). FACT scores for each spatial frequency were normally distributed. Mean scores were all correlated, with higher correlations for adjacent spatial frequencies and for the highest spatial frequencies (data not shown). Scores for boys and girls did not differ for spatial frequencies from 1.5 to 12 cpd, but boys had better scores at the highest spatial frequency (18 cpd: 2.7 vs. 2.1 respectively, *P*=0.04).

The two sample sets, with different LODs, differed for their proportions of left-censored data: from 7% for PhAA to 96% for 2-MPA for set 1 and from 0.5% for PhAA to 10% for EEAA for set 2 (see Table S3, Supplement Material, which shows the distribution of GE metabolites maternal urinary concentration according to sample set). PhAA was the most frequently detected glycol ether metabolite in our study in both sample sets and the one with the highest standardized median concentration (0.33 mg/L). The other median glycol ether metabolite standardized concentrations ranged from 0.01 mg/L for EAA, EEAA and 2-MPA to 0.04 mg/L for MAA and 0.10 mg/L for BAA. The median concentrations of BAA diverged: 0.1 mg/L in set 1 and 0.04 mg/L in set 2. After standardization of the glycol ether metabolite concentrations, BAA had the highest median concentration variation (+112%), and EAA and PhAA showed the lowest variations (Table 4, and Figure S2, Supplement Material, which gives the cumulative distributions of the measured and standardized concentrations of GE metabolites in urine samples).

FACT scores showed no association with maternal urinary concentrations of MAA, EAA, EEAA, and BAA, in either the crude (see Table S4, Supplement Material, which gives the crude associations between concentrations of glycol ether metabolite in mothers' prenatal urine samples and FACT scores of their 6-year-old children) or adjusted analyses (Table 5). FACT scores decreased as maternal prenatal urinary PhAA concentrations were increasing (using continuous exposure variable (mg/L, log-scale: β=-0.08 (95%CI= -0.18, 0.02) for 1.5 cpd; β=-0.13 (95%CI=-0.26, 0.001) at 12 cpd; and β=-0.17 (95%CI= -0.33, -0.02) at 18 cpd). These associations were the strongest at the highest spatial frequencies but also existed at the lowest spatial frequency (e.g. Fourth vs first quartile: β=-

0.69 (95%CI= -1.19, -0.20) for 1.5 cpd; β=-0.92 (95%CI= -1.55, -0.29) for 12 cpd; and β=-0.90 (95%CI= -1.64, -0.16) for 18 cpd). The crude analyses yielded similar conclusions (see Table S4, Supplement Material). The maternal prenatal urinary 2-MPA concentration was also associated with the FACT score at the 3 cpd stimulus when treated as continuous exposure variable: β=-0.29 (95%CI= -0.54, -0.04), but the other spatial frequencies showed no associations.

The sensitivity analyses produced similar conclusions for MAA, EAA, EEAA, BAA, and PhAA. Associations at the 3 cpd stimulus for urinary 2-MPA concentrations appeared stronger with the non-standardized concentrations (see Table S5, Supplement Material, which presents the associations between crude concentrations of glycol ether metabolite in mothers' prenatal urine samples and FACT scores of their 6-year-old children for sample set 2 (N=165)).

Discussion

Our results showed that higher maternal prenatal urinary concentrations of PhAA were associated with lower contrast sensitivity FACT scores in children at age 6. These associations were the strongest for the lowest (1.5 cpd) and two highest spatial frequencies (12 and 18 cpd). A decrease in the contrast sensitivity score was also associated with a higher maternal prenatal urinary concentration of 2-MPA, but only at the 3 cpd stimulus.

PhAA is the acidic metabolite of ethylene glycol monophenyl ether (EGPhE or 2-phenoxyethanol CAS no.: 122-99-6 and EC / List no.: 204-589-7), a GE present in some professional (as anesthetic in aquaculture) and pharmaceutical products (as antimicrobial in vaccines) and in a large variety of consumer products such as antimicrobial in cosmetic and care products, perfumes, deodorants, or slimming textiles, with a maximal authorized proportion of EGPhE at 1% (Agence française de sécurité sanitaire de l'environnement et du travail (Afsset) 2008). A study by the French drug and health products agency (ANSM) (Agence nationale de sécurité du médicament et des produits de santé (ANSM) 2012) showed that most of cosmetics tested (39 out of 43 products) contained two or more preservative agents: the largest common association was between EGPhE and parabens (methyl- ethyl- propyl- butyl- paraben) (33 products), but other associations are likely to occur (EGPhE and

benzoate sodium or methyldibromoglutaronitrile). Furthermore, the European committee on consumer safety (Scientific Commitee on Consumer Safety (SCCS) 2016) reported the presence of EGPhE in some cleaning agents and in some exotic fruits (this last natural source was considered negligible). PhAA is also itself used as a flavoring agent in food (WHO 2003).

PhAA was the most frequently detected GE acidic metabolite in our study in both sample sets and with the highest median standardized concentration (0.33 mg/L). This level is similar to those published in another French study of exposure in 2014-2016; where PhAA was quantified most often among 8 GE urinary metabolites and with the highest median concentration (respectively 0.22 mg/L in adults and 0.46 mg/L in children) (Santé publique France 2019). A study among adults in northern France (2008-2010) reached similar conclusions, while reporting higher median levels of PhAA concentrations in urine (0.70 mg/L) (Nisse et al. 2017), as did a study in the German general population (respectively, 0.80 mg/L) (Fromme et al. 2013).

2-MPA is the acidic metabolite of 1-propylene glycol-2-methyl ether (1PG2ME 2-methoxy-1-propanol CAS no.: 1589-47-5 and EC / List no.: 216-455-5), a minor β isomer of the technical-grade propylene glycol methyl ether (PGME) or its acetate. GEs from the P series are mainly produced as compounds with a secondary alcohol and are metabolised via O-demethylation and oxidation to carbon dioxide. Their inability to forming alkoxy carboxylic acids is the most likely reason for their low toxicity when compared to GEs from the E series (Multigner et al. 2005). 1PG2ME, together with its acetate, is classified as category 1B reprotoxicant by the classification, labeling and packaging regulation (CLP) in the European Union. In their commercial forms, technical grade PGME and its acetate currently contain less than 0.5% β isomer. PGME is widely used and is present in paints, varnishes, inks, coating products, in household and industrial washing and cleaning products, and in biocidal and pharmaceuticals products (Agence française de sécurité sanitaire de l'environnement et du travail (Afsset) 2008; European Chemical Agency 2020). This may explain why, despite low concentrations of the minor β isomer in commercial preparation, 2-MPA was detected in 71% of urine samples in our study, with a median standardized concentration of 0.01 mg/L. A French study reported a similar median urinary concentration of 2-MPA among adults (0.01 mg/L) and children (0.02 mg/L) (Santé publique France 2019).

Evidence from observational studies suggests that maternal prenatal exposure to organic solvents can adversely affect the visual functioning of offspring. Getz *et al*. have reported that prenatal exposure to tetrachloroethylene from tap water is related to contrast sensitivity and color vision impairments (Getz et al. 2012). Till *et al. .*described defective color vision and loss of contrast sensitivity and graphomotor ability among 32 children aged from 3 to 7 years whose mothers were occupationally exposed to organic solvents during pregnancy (Till et al. 2001). In 2005, the same research team used visual evoked potentials to demonstrate decreased contrast sensitivity for low and medium spatial frequencies (i.e., <10 cpd) in 21 12-month-old children whose mothers had been occupationally exposed to organic solvents (aliphatic and/or aromatic hydrocarbons (n=9), alcohols (n=3), multiple solvents (n=6), and perchloroethylene (n=3)) during pregnancy (Till et al. 2005).There is a lack of animal toxicological studies on glycol ethers. Only very few possible mechanisms by which glycol ethers might impair visual function have been suggested (Boyes et al. 2016; Pomierny et al. 2013).

It is generally agreed that deficits in contrast sensitivity for low and medium frequencies are mainly due to post retinal neurologic processes, while impairments for higher frequencies (i.e., detailed and fine spatial vision) are more likely associated with optic anomalies (Waksman and Brody 2007). Our finding that PhAA affected the entire spatial frequency range and not only high spatial frequencies thus suggests the involvement of brain processes. Other studies have also shown that losses all along the spatial frequency spectrum, although often more pronounced at high frequencies, are associated with exposure to organic solvents (Costa et al. 2012; Jiménez Barbosa, Boon, and Khuu 2015; Oliveira et al. 2018; Getz et al. 2012; Schreiber et al. 2002). As suggested by Costa *et al*., general contrast sensitivity loss can occur because the liposolubility of solvents suggests nonselective, widespread neural alterations at all levels of the central nervous system (Costa et al. 2012).

Our study measured prenatal exposure to glycol ethers by assaying the concentrations of six metabolites in maternal urine samples. Use of a single urine sample might be a major limitation in case of higher within-subject variability compared to between-subject variability in urinary concentrations; however, there is yet no such available data for the GE urinary metabolites. The urinary measurement is currently considered appropriate for estimating internal exposure to glycol ethers due to occupational exposure (Fromme et al. 2013; Calafat et al. 2006; Laitinen and Pulkkinen

2005). The glycol ether metabolites we studied have short half-lives, from 7h for BAA to 70h for MAA (Agence française de sécurité sanitaire de l'environnement et du travail (Afsset) 2008). Glycol ethers metabolite measurements from first morning urine voids, as done in the present study, are thus likely to reflect at least in part exposure from the previous day. We thus expect that these measurements should partly reflect short-term but regular exposure such as that due to cosmetics and personal care products that are used daily, or cleaning products. We cannot rule out the possibility that exposure to one or more other chemicals including other organic solvents, which our study did not measure or consider, might have influenced our findings. Finally, chance findings cannot be ruled out for our result regarding 2-MPA.

This study underlines the possible adverse impact of ubiquitous exposure to certain glycol ethers during pregnancy on visual functioning among 6-year-old children. This conclusion is however still limited by the lack of evidence of possible underlying biological mechanisms that might explain these associations. Additional knowledge is also needed about the toxicokinetics of current-used GE and their urinary metabolites.

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Tables

Table 1: Major sources of the studied glycol ether alkoxycarboxylic acids during the PELAGIE mother-child cohort inclusion period (2002–2006, France)

Glycol ether	Major sources according to Agence française de sécurité sanitaire de l'environnement et du travail (Afsset) 2008	Alkoxycarboxylic acid (metabolite)
EGME	Aeronautic sector	MAA
EGDME	-	MAA
DEGME	Household (car) and industrial cleaning products / Gardening products	MAA
DEGDME	-	MAA
TEGME	Industrial cleaning products	MAA
TEGDME	Cleaning products	MAA
EGEE	Metal working sector / Rubber and plastics industry / Cleaning and printing	EAA
EGDEE; DEGDEE	-	EAA
DEGEE	Paints / Inks / Household products / Biocides / Restrained use for drugs and cosmetics	EAA; EEAA
TEGEE	Paints	EAA; EEAA
EGBE; DEGBE	Paints / Varnishes / Inks / Household and industrial cleaning products / Biocidal products / Cosmetics	BAA
TEGBE	Varnishes	BAA
EGPhE	Cosmetics	PhAA
PGME	Products for professional use (all sectors) / Domestic use (Varnished materials, household products)	2-MPA

Note : -: no use or very little identified in France during the inclusion period. EGME: ethylene glycol methylether; EGDME: ethylene glycol dimethylether; DEGME: diethylene glycol methylether; DEGDME: diethylene glycol dimethylether; TEGME: triethylene glycol methylether; TEGDME: triethylene glycol dimethylether; EGEE: ethylene glycol ethylether; EGDEE: ethylene glycol diethylether; DEGEE: diethylene glycol ethylether; DEGDEE: diethylene glycol diethylether; TEGEE: triethylene glycol ethylether; EGBE: ethylene glycol butylether; DEGBE: diethylene glycol butylether, TEGBE: triethylene glycol butylether, EGPhE: ethylene glycol phenylether; PGME: propylene glycol methylether; MAA: methoxyacetic acid; EAA: ethoxyacetic acid; EEAA: ethoxy-ethoxyacetic acid; BAA: 2-butoxyacetic acid; PhAA: phenoxy-acetic acid; 2-MPA: methoxy-proprionic acid

Table 2: Characteristics of the population (N=220)

Mothers and environment characteristics		N %	Mean ± SD	Median	Q1-Q3
Maternal age at inclusion (years)		220	30.4 +/- 4.2	30.5	27.2-33.2
Urine creatinine (mg/L)		220	1.1 ± 0.5	1.0	0.7-1.4
Education	<12 years	76 (34.5)			
	≥12 years	144 (65.5)			
Body mass index before pregnancy (kg/m²)		217	22.2 ± 3.4	21.7	19.9-23.4
	<18.5	19 (8.6)			
	18.5 – 24.9	163 (74.1)			
	25 – 29.9	27 (12.3)			
	≥ 30	8 (3.6)			
	Missing	3 (1.4)			
Tobacco use early pregnancy	No smoking	164 (74.5)			
	Smoking	56 (25.5)			
Fish consumption before pregnancy	<= 1 / week	157 (71.4)			
	>= 2 / week	63 (28.6)			
Parity at inclusion	No child	93 (42.3)			
	At least one child	127 (57.7)			
Mother WAIS Verbal IQ		220	92.7 ± 11.2	93.0	84.0-100.3
Siblings (at 6 years)	1	9 (4.1)			
	2	125 (56.8)			
	3	72 (32.7)			
	≥4	14 (6.4)			
Place of residence (at age 6)	Rural	124(56.4)			
	Urban	96 (43.6)			
Tobacco consumption in the households at age 6 years	None	128 (58.2)			
	≤ 10 cigarettes	44 (20.0)			
	> 10 cigarettes	48 (21.8)			
HOME score (at 6 years old)		220	46.1 ± 4.3	46	44-49
Acid-leachable lead in living room floor dust (tertiles)	0	88 (40.0)			
	1	67 (30.5)			
	2	65 (29.5)			
Childrencaracteristics		N (%)			
Sex	Boys	104 (47.3)			
	Girls	116 (52.7)			
Birth weight (g)		220	3418 ± 434	3370	3125-3748
Gestational age at birth (weeks)		220	39.6 ±1.2	40.0	39.0-40.3
Breast feeding (weeks)	None	72 (32.7)			
	≤16 weeks	71 (32.3)			
	>16 weeks	77 (35.0)			
Sleep duration (hours)		218	10.9 ± 0.4	11.0	10.5-11.3
	<10h30	60 (27.3)			
	10h30-11h	99 (45.0)			
	>11hres	61 (27.7)			
	Missing	2 (0.9)			
Time spent in front of video games (hours)		220	68.6 ± 106.1	30	0-90
	None	90 (40.9)			
	<1h30	70 (31.8)			
	>= 1h30	60 (27.3)			
Extra-curricular sport activity	No	65 (29.5)			
	Yes	155 (70.5)			
Time spent in front of TV (hours)		211	376.4 ± 226.0	325	220-500
	<2h30	74 (33.6)			
	2h30-4h30	67 (30.5)			
	>4h30	79 (35.9)			
FACT exam characteristics		N (%)			
Investigator	1	106 (48.2)			
	2	114 (51.8)			
Ambient light (LUX)		216 (98.2)	749.0 ± 1341.4	250.0	100.0-682.5

Note: SD: standard deviation.

Table 3: FACT Contrast sensitivity scores at age 6 years – The PELAGIE cohort.

	Min.	P25	Median	P75	Max.	Mean ± SD
1,5 cpd (line A)	3	5	6	7	9	6.29 ± 1.27
3 cpd (line B)	0	6	6	7	9	6.41 ± 1.54
6 cpd (line C)	0	5	6	7	9	5.63 ± 1.71
12 cpd (line D)	0	3	4	5	9	3.91 ± 1.77
18 cpd (line E)	0	1	2	4	9	2.41 ± 2.07

Note: SD: standard deviation. cpd : cycles per degree.

Table 4: Measured and standardized concentrations of glycol ethers metabolites in urine samples of 280 pregnant women randomly selected from the PELAGIE mother–child cohort

GE	N	% ≥ LOD	Measured concentrations					Standardized concentrations				
Metabolite			P5	P25	P50	P75	P95	P5	P25	P50	P75	P95
MAA mg/L	280	76.4%	0.003	0.026	0.049	0.090	0.182	0.003	0.018	0.037	0.068	0.158
EAA mg/L	280	70.4%	<LOD	0.010	0.016	0.027	0.061	0.003	0.009	0.014	0.025	0.053
EEAA mg/L	280	70.4%	<LOD	0.010	0.025	0.060	0.392	0.002	0.005	0.014	0.037	0.216
BAA mg/L	280	90.7%	0.006	0.026	0.049	0.085	0.180	0.014	0.049	0.105	0.168	0.288
PhAA mg/L	280	97.9%	0.039	0.156	0.390	1.202	22.045	0.034	0.127	0.336	1.200	15.566
2-MPA mg/L	280	71.4%	0.004	0.011	0.018	0.029	0.084	0.003	0.007	0.011	0.019	0.049

Note: GE: glycol ether, LOD: limit of detection. MMA: methoxyacetic acid, EAA: ethoxyacetic acid, EEAA: ethoxyethoxyacetic acid, BAA: butoxyacetic acid, PhAA: phenoxyacetic acid, 2-MPA: 2-methoxypropionic acid. LOD: 0.05mg/L (n=75) and 0.003mg/L (n=205) according to sample set.

Table 5: Associations between standardized concentrations of glycol ether metabolite in mothers' prenatal urine samples and FACT scores of their 6-year-old children – PELAGIE Cohort (N=220) – Adjusted linear regression models – Multiple imputation (m=5)

	GEMetabolite	1.5 cpd (line A)	3 cpd (line B)	6 cpd (line C)	12 cpd (line D)	18 cpd (line E)
	Concentration mg/L (log-scale)	β (95%CI)	β (95%CI)	β (95%CI)	β (95%CI)	β (95%CI)
MAA	Q1	Ref.	Ref.	Ref.		Ref.
	Q2	-0.54 (-1.11, 0.04)	-0.27 (-0.96, 0.42)	-0.42 (-1.45, 0.61)	-0.49 (-1.38, 0.40)	-0.49 (-1.33, 0.35)
	Q3	-0.28 (-0.86, 0.31)	-0.17 (-0.82, 0.47)	0.06 (-0.63, 0.75)	-0.23 (-0.90, 0.44)	-0.16 (-0.91, 0.59)
	Q4	-0.27 (-0.81, 0.26)	-0.06 (-0.69, 0.56)	0.01 (-0.72, 0.73)	-0.17 (-0.86, 0.52)	0.14 (-0.62, 0.91)
	Continous (log)	NA	NA	NA	NA	NA
EAA	Q1	Ref.	Ref.	Ref.	Ref.	Ref.
	Q2	0.15 (-0.46, 0.76)	-0.17 (-0.93, 0.58)	-0.03 (-1.01, 0.95)	0.11 (-0.67, 0.90)	-0.20 (-1.11, 0.71)
	Q3	-0.03 (-0.63, 0.57)	0.02 (-0.65, 0.68)	-0.18 (-0.92, 0.57)	-0.44 (-1.20, 0.32)	-0.34 (-1.21, 0.54)
	Q4	-0.09 (-0.62, 0.45)	-0.15 (-0.87, 0.56)	0.11 (-0.62, 0.84)	0.40 (-0.29, 1.09)	0.03 (-0.80, 0.86)
	Continous (log)	-0.05 (-0.28, 0.17)	-0.09 (-0.36, 0.18)	-0.02 (-0.33, 0.28)	0.03 (-0.25, 0.31)	-0.07 (-0.39, 0.26)
EEAA	Q1	Ref.	Ref.	Ref.	Ref.	Ref.
	Q2	0.22 (-0.35, 0.78)	0.16 (-0.55, 0.87)	0.34 (-0.47, 1.16)	0.35 (-0.34, 1.04)	0.33 (-0.50, 1.16)
	Q3	0.04 (-0.50, 0.58)	0.05 (-0.61, 0.72)	0.26 (-0.40, 0.93)	0.47 (-0.18, 1.12)	0.05 (-0.74, 0.84)
	Q4	-0.05 (-0.59, 0.50)	-0.30 (-0.93, 0.34)	0.16 (-0.53, 0.85)	-0.28 (-0.94, 0.38)	-0.42 (-1.22, 0.38)
	Continous (log)	NA	NA	NA	NA	NA
BAA	Q1	Ref.	Ref.	Ref.	Ref.	Ref.
	Q2	0.33 (-0.16, 0.83)	0.16 (-0.43, 0.74)	0.38 (-0.24, 1.00)	0.40 (-0.24, 1.04)	0.36 (-0.39, 1.11)
	Q3	0.26 (-0.24, 0.76)	0.02 (-0.58, 0.62)	-0.25 (-0.89, 0.39)	0.05 (-0.59, 0.70)	0.69 (-0.07, 1.45)
	Q4	0.25 (-0.25, 0.75)	0.17 (-0.42, 0.77)	0.43 (-0.21, 1.06)	0.52 (-0.12, 1.17)	0.22 (-0.53, 0.98)
	Continous (log)	-0.04 (-0.16, 0.08)	-0.09 (-0.24, 0.05)	-0.08 (-0.22, 0.07)	-0.08 (-0.23, 0.07)	-0.15 (-0.32, 0.03)
PhAA	Q1	Ref.	Ref.	Ref.	Ref.	Ref.
	Q2	-0.41 (-0.90, 0.08)	-0.28 (-0.87, 0.30)	-0.15 (-0.79, 0.48)	**-0.67 (-1.29, -0.05)**	-0.31 (-1.04, 0.42)
	Q3	-0.38 (-0.88, 0.11)	-0.24 (-0.83, 0.35)	-0.26 (-0.90, 0.37)	**-0.64 (-1.27, -0.01)**	**-0.96 (-1.69, -0.22)**
	Q4	**-0.69 (-1.19, -0.20)**	-0.54 (-1.13, 0.05)	-0.29 (-0.93, 0.35)	**-0.92 (-1.55, -0.29)**	**-0.90 (-1.64, -0.16)**
	Continous (log)	-0.08 (-0.18, 0.02)	-0.07 (-0.19, 0.05)	-0.02 (-0.15, 0.11)	-0.13 (-0.26, 0.001)	**-0.17 (-0.33, -0.02)**
2-MPA	Q1	Ref.	Ref.	Ref.	Ref.	Ref.
	Q2	0.06 (-0.55, 0.67)	-0.55 (-1.26, 0.15)	-0.19 (-1.05, 0.67)	-0.18 (-0.88, 0.51)	0.17 (-0.65, 0.99)
	Q3	-0.34 (-0.89, 0.20)	-0.60 (-1.26, 0.06)	-0.41 (-1.28, 0.45)	-0.19 (-1.05, 0.67)	0.05 (-0.87, 0.98)
	Q4	-0.26 (-0.89, 0.36)	-0.56 (-1.19, 0.08)	0.01 (-0.74, 0.76)	0.00 (-0.70, 0.69)	0.21 (-0.64, 1.06)
	Continous (log)	-0.07 (-0.30, 0.15)	**-0.29 (-0.54, -0.04)**	-0.04 (-0.35, 0.26)	-0.02 (-0.29, 0.24)	-0.07 (-0.38, 0.23)

Note : GE : glycol ether, NA : not applicable, CI : confidence interval, cpd : cycles per degree, MMA: methoxyaceticacid, EAA: ethoxyaceticacid, EEAA: ethoxyethoxyaceticacid, BAA: butoxyaceticacid, PhAA: phenoxyaceticacid, 2-MPA: 2-methoxypropionic acid. Models were adjusted on creatinine level, ambient light, FACT investigator, maternal education, maternal pre-pregnancy BMI, number of cigarettes smoked daily at the child's home and child's extra-curicular sport activity. Bold: P < 0.05