International Journal of Hygiene and Environmental Health xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh

Perfluorooctanoic acid and low birth weight: Estimates of US attributable burden and economic costs from 2003 through 2014

Julia Malits[a], Jan Blustein[b], Leonardo Trasande[a,c,d,e,*], Teresa M. Attina[a]

[a] Department of Pediatrics, NYU School of Medicine, 403 E 34th St, New York, NY 10016
[b] Department of Health Policy, Medicine, and Population Health, NYU School of Medicine; NYU Wagner School of Public Service, New York, NY
[c] Departments of Environmental Medicine and Population Health, NYU School of Medicine, New York, NY
[d] NYU Wagner School of Public Service, 295 Lafayette Street New York, NY, 10012
[e] NYU College of Public Health, 726 Broadway New York, NY, 10012

ARTICLE INFO

Keywords:
Low birth weight
PFOA exposure
NHANES
Economic costs

ABSTRACT

Background and objective: *In utero* exposure to perfluorooctanoic acid (PFOA) has been associated with decreases in birth weight. We aimed to estimate the proportion of PFOA-attributable low birth weight (LBW) births and associated costs in the US from 2003 to 2014, a period during which there were industry-initiated and regulatory activities aimed at reducing exposure.

Methods: Serum PFOA levels among women 18–49 years were obtained from the National Health and Nutrition Examination Survey (NHANES) for 2003–2014; birth weight distributions were obtained from the Vital Statistics Natality Birth Data. The exposure-response relationship identified in a previous *meta*-analysis (18.9 g decrease in birth weight per 1 ng/mL of PFOA) was applied to quantify PFOA-attributable LBW (reference level of 3.1 ng/mL for our base case, 1 and 3.9 ng/mL for sensitivity analyses). Hospitalization costs and lost economic productivity were also estimated.

Results: Serum PFOA levels remained approximately constant from 2003–2004 (median: 3.3 ng/mL) to 2007–2008 (3.5 ng/mL), and declined from 2009–2010 (2.8 ng/mL) to 2013–2014 (1.6 ng/mL). In 2003–2004, an estimated 12,764 LBW cases (4% of total for those years) were potentially preventable if PFOA exposure were reduced to the base case reference level (10,203 cases in 2009–2010 and 1,491 in 2013–2014). The total cost of PFOA-attributable LBW for 2003 through 2014 was estimated at $13.7 billion, with $2.97 billion in 2003–2004, $2.4 billion in 2009–2010 and $347 million in 2013–2014.

Conclusions: Serum PFOA levels began to decline in women of childbearing age in 2009–2010. Declines were of a magnitude expected to meaningfully reduce the estimated incidence of PFOA-attributable LBW and associated costs.

1. Introduction

Birth weight is a widely recognized predictor of short and long-term health outcomes. Among other adverse birth outcomes, low birth weight (LBW, < 2,500 g) remains a serious public health issue. In 2015, 8.1% of births were LBW (CDC, 2015) with its associated comorbidities, such as subnormal growth and neurodevelopmental complications (Hack et al., 1995). LBW is also associated with substantial medical care costs and lost economic productivity (Russell et al., 2007).

Perfluorooctanoic acid (PFOA) is one of the most widely utilized chemicals in the class of long chain perfluorinated compounds (PFCs). PFOA, along with other PFCs, is a man-made chemical that has been used in various industrial and chemical processes worldwide for approximately sixty years (Lindstrom et al., 2011; Lien et al., 2013). PFOA serves as an intermediate in the manufacture of fluoroelastomers and fluoropolymers (Apelberg et al., 2007), and has traditionally been incorporated into many consumer products such as Teflon™ coatings (Fenton et al., 2009), contaminated drinking water, food packaging, electronics, textiles, nonstick cookware, and carpets (Post et al., 2012; Inoue et al., 2004; Holzer et al., 2008; Arbuckle et al., 2013).

PFOA is highly soluble in water in its anionic form (USEPA, 2017a) with a half-life of approximately 3.5 years (Olsen et al., 2007). Widespread PFOA exposure has been detected in the blood of human populations worldwide (Bach et al., 2016; Calafat et al., 2007). Given PFOA's ubiquity in the environment and the numerous routes of human exposure, concerns have mounted in the past several decades about the

* Corresponding author at: Department of Pediatrics, NYU School of Medicine, 403 E 34th Street, New York, NY 10016.
E-mail addresses: julia.malits@nyumc.org (J. Malits), jan.blustein@nyu.edu (J. Blustein), leonardo.trasande@nyumc.org (L. Trasande), teresa.attina@nyumc.org (T.M. Attina).

https://doi.org/10.1016/j.ijheh.2017.11.004
Received 29 June 2017; Received in revised form 3 November 2017; Accepted 20 November 2017

risk of reductions in birth weight associated with exposure to PFOA among pregnant women (Apelberg et al., 2007). As such, the magnitude of the association between PFOA exposure among pregnant women and birth weight has been evaluated extensively. The evidence is not unequivocal: several studies support a significant association (Apelberg et al., 2007; Lenters et al., 2016; Lee et al., 2013), while others have yielded null results (Bach et al., 2016; Monroy et al., 2008).

However, the systematic review and *meta*-analysis performed by Johnson and colleagues (Johnson et al., 2014) has clearly synthesized the available evidence from nine human studies identifying a significant association between maternal serum or plasma PFOA levels and decrements in birth weight. Specifically, Johnson and colleagues found an 18.9 g (95% CI: −29.8, −7.9) decrease in birth weight per 1 ng/mL PFOA. Though reverse causation is a possible alternative explanation (i.e. mothers of LBW infants have reduced glomerular filtration rates and, therefore, have slower PFOA clearance), Johnson and colleagues (Johnson et al., 2014) found no compelling evidence within the literature to support reverse causation of this exposure-response relationship. Nonetheless, the possibility of reverse causation cannot be conclusively ruled out (Dhingra et al., 2017).

Further, studies have found that PFOA crosses the placental barrier and bioaccumulates in the serum of a fetus rather than in fat (Post et al., 2012; Midasch et al., 2007), and that concentrations of PFOA in maternal serum and infant cord blood are highly correlated (Fromme et al., 2010). A variety of mechanisms have been suggested to link prenatal PFOA exposure and reductions in birth weight, such as the possible influence of estrogen biosynthesis and/or interactions with estrogen receptors (Benninghoff et al., 2011).

The *meta*-analysis by Johnson and colleagues (Johnson et al., 2014) relied upon the Navigation Guide method in order to identify the exposure-response relationship between maternal serum or plasma PFOA levels and a decrease in birth weight. The Navigation Guide is a systematic methodology for synthesizing the available evidence, and was developed to reduce bias and maximize transparency in the evaluation of environmental health data. In particular, the method takes into account elements that are specific to environmental health assessments, including the major role played by observational studies instead of randomized controlled studies, which are not well-suited to evaluate environmental exposures (Woodruff and Sutton, 2014).

In recent years, some manufacturers have independently initiated programs to reduce PFOA exposure. Notably, 3M, one of the most prominent producers, discontinued the manufacture and use of long chain PFCs in 2002 (Policies and Reports, 2017). Thereafter, global emissions of PFOA were halved by 2004 (Prevedouros et al., 2006). In January 2006, the US EPA launched a Stewardship Program out of concern about the impact of PFOA on human health and the environment (USEPA, 2017b). In order to reduce the reliance of industrial and commercial processes on PFOA, the program mobilized eight leading PFC producers in the industry to voluntarily phase-out 95% of their PFOA use by 2010 and the remaining 5% by 2015. According to the final EPA progress report for 2015, all companies have successfully met the program goals (USEPA, 2015).

Our aim for this analysis was to document changes in the concentration of serum PFOA among women of childbearing age during a period in which industry and regulatory activity was aimed at reducing exposure, and to estimate the magnitude of corresponding changes in the burden of LBW and associated economic costs.

2. Materials and methods

2.1. Data collection and measurements

Two distinct datasets were used for our analysis, which covered the years 2003–2014. The first was the U.S. National Health and Nutrition Examination Survey (NHANES), a continuous, multicomponent, nationally representative biennial survey of the noninstitutionalized US population administered by the National Centers for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC). We used serum PFOA levels (ng/mL) from women of childbearing age (18–49 years) who participated in the NHANES survey as an index of levels of *in utero* exposure to PFOA during the study years. Thus, our methodology was based on the assumption that NHANES participants were representative of women who gave birth during those years.

In NHANES, serum PFOA levels from 2003 to 2014 were measured by online solid phase extraction coupled with High Performance Liquid Chromatography-Tandem Mass Spectrometry. A more extensive methodological description is provided in the NHANES Laboratory Procedures Manual (NHANES, 2017).

Natality data from the National Vital Statistics System of the National Center for Health Statistics (CDC/NCHS, 2017) were used to extract birth weights during each of the calendar years included in this analysis.

2.2. Modeling PFOA-attributable changes in birth weight

Beginning with the CDC/NCHS natality dataset, we determined the actual mean birth weight (Table 1), number of total births, and actual number of LBW births for each year. We excluded non-singleton births. We removed 621,275 outliers (3 SD units above or below the mean birth weight) to avoid unduly impacting the mean birth weight for each year.

As illustrated in Table 1, Panel 1, for each year, we then developed groups defined by percentiles of levels of PFOA exposure (1st–9th, 10th–24th, 25th–49th, 50th–74th, 75th–89th, and 90th–99th). We calculated the number of LBW births that occurred during that year for each percentile group, using the CDC/NCHS natality data. We then assigned all of the LBW births in each group to the lowest PFOA exposure level in that group, using the NHANES data. For example, all births in the 1st − 9th percentile were assigned the mean NHANES PFOA serum level for the 1st percentile. The lowest grouping was assumed to have no actual exposure (e.g. no reductions in birth weight for 0.7 ng/mL of serum PFOA or less in 2003- 2004) and the other groups assumed to have exposure levels corresponding to the lower level.

We modeled PFOA-attributable changes in birthweight using a counterfactual approach, in which we assumed PFOA exposure was reduced to particular reference levels. Reference levels are the minimum level of PFOA exposure above which physiological effects in the fetus, such as birth weight, are assumed to be observable. We calculated the decrease in birthweight attributable to PFOA for each group's exposure level, using the exposure-response relationship of an 18.9 g decrease (95% CI: −29.8, −7.9) in birth weight per 1 ng/mL of PFOA exposure (Johnson et al., 2014), and three reference levels.

We reviewed the literature to determine an appropriate reference level that would not overestimate our findings, while also including appropriate sensitivity analyses. To select those reference levels, we qualitatively assessed the literature and based our choice on the distribution of PFOA levels measured across numerous studies. We employed a reference level of 3.1 ng/mL for the base case, which corresponds to the upper limit of the lowest tertile in the study by Maisonet and colleagues (Maisonet et al., 2012). As summarized in a systematic review (Bach et al., 2015), data are insufficient to determine a safe lower PFOA exposure level, but statistically significant associations have only been demonstrated when median serum or plasma levels during pregnancy were above approximately 3 ng/mL (Maisonet et al., 2012; Fei et al., 2007; Wu et al., 2012). However, one study with median levels above this level found no significant association (Darrow et al., 2013). The value of 3 ng/mL is similar to the present day average PFOA exposure in US women in the fertile age (Jain, 2013).

Along with the central estimate, in sensitivity analyses [SA], we applied alternative reference levels of 1 ng/mL and 3.9 ng/mL to provide a plausible range of uncertainty. We characterized 1 ng/mL as the high end reference level representing the lower limit of physiologically