Prevalence of Selected Birth Defects, 2003–2014

Bladen, Brunswick, Cumberland, New Hanover and Pender Counties and North Carolina

Summary

What is the purpose of this report?

This report was created to address questions raised during the ongoing investigation of GenX and related compounds in and around the lower Cape Fear River. It describes the prevalence of selected birth defects in five counties and in North Carolina as a whole. Data were obtained from the NC Birth Defects Monitoring Program (NCBDMP). The NCBDMP collects information on all major birth defects diagnosed across the state but does not routinely collect information about potential environmental exposures.

What were the key findings?

- The prevalence of most types of birth defects examined in the five counties did not differ from statewide prevalence estimates.
- A higher prevalence of total brain defects was found in areas across North Carolina, including the five counties in this analysis. However, the higher prevalence of total brain defects was not limited to counties where GenX and other PFAS have been found in drinking water, nor was it confined to the lower Cape Fear region.
- The prevalence of neural tube defects and one specific type of cardiac defect were higher in one county each as compared to the state as a whole. However, county-level estimates were based on small numbers of cases and the prevalence varied widely from year to year.

What do these findings mean?

No conclusions can be drawn about the association between GenX or other exposures and the birth defects described in this report. This is because:

- NCBDMP data do not include information about causes of birth defects or associations with specific exposures.
- Birth defects can be due to a complex mix of genetic, medical, behavioral and environmental factors. These factors were not accounted for here and can contribute to geographic differences in the prevalence of birth defects.
- County prevalence estimates were compared to statewide prevalence estimates. Because the statewide estimate is an average, some counties will have a higher and some a lower prevalence. National estimates were not available for comparison.

Only a comprehensive research study can provide information about whether a specific exposure or factor might be associated with a specific type of birth defect.

What are the next steps?

NCBDMP will continue to monitor geographic variations in the occurrence of birth defects and is developing plans to specifically examine the occurrence of brain anomalies across the state. NCBDMP will also share these findings with partners who conduct research on potential causes of birth defects.

Background

This report describes the prevalence of selected birth defects in Bladen, Brunswick, Cumberland, New Hanover, and Pender counties and the state of North Carolina as a whole. The report was developed in response to questions raised during the ongoing investigation of GenX and related compounds detected in drinking water in and around the Cape Fear River. These compounds are part of a family of chemicals known as per- and polyfluoroalkyl substances (PFAS), some of which are associated with adverse health effects.

Data for this report were obtained from the NC Birth Defects Monitoring Program (NCBDMP), a statewide public health surveillance system. The NCBDMP captures information on all major birth defects diagnosed within the first year of life among live born infants, and birth defects diagnosed among fetal deaths and pregnancy terminations occurring among NC women.

NCBDMP staff publish information, and respond to questions and concerns about birth defects in North Carolina. NCBDMP also analyzes data to estimate the burden of birth defects in North Carolina to help focus resources and prevention activities in areas where they are most needed and partner with researchers to conduct birth defects research to identify causes of birth defects and prevention strategies.

Note: Only a comprehensive research study can provide information about whether a specific exposure is associated with an elevated prevalence of a specific birth defect. NCBDMP does not routinely collect detailed information about potential environmental exposures; therefore, no conclusions can be drawn from this report about the association between PFAS or other environmental exposures and the prevalence of birth defects.

Methods

Epidemiologists and toxicologists at the NC Division of Public Health reviewed the scientific literature for studies that have looked at the association between exposure to GenX or other PFAS and birth defects among animals and humans.

NCBDMP examined groups of birth defects that have been included in previous studies of PFAS exposure and for which associations with PFAS have been suggested in either animals or humans.

These include the following:

- Central nervous system defects
    - Neural tube defects
    - Brain defects (microcephaly, hydrocephaly, reduction defects)
- Orofacial clefts
- Cardiac defects
    - Conotruncal heart defects
    - Left and right ventricular outflow tract defects (LVOTO & RVOTO)
- Skeletal defects
    - Limb deficiency defects

These birth defects are serious and generally diagnosed at birth or within the first few months of life. Appendix A provides more details about the birth defects included. Detailed descriptions of each birth defect can be found here: https://www.cdc.gov/ncbddd/birthdefects/surveillancemanual/resource-library/glossary.html.

We excluded from this analysis infants with chromosomal anomalies (e.g., Down syndrome and other trisomies, 22q11.2 deletion syndrome) because chromosomal anomalies are associated with a higher risk of the birth defects listed above.

Using NCBDMP data, we estimated the prevalence and 95% confidence intervals (CIs) for each of the above birth defects separately for Bladen, Brunswick, Cumberland, New Hanover, and Pender counties and for North Carolina statewide during 2003–2014. These counties were included because at least some area within each county has had evidence of drinking water contamination with GenX. This period was chosen because it is the most recent period for which consistent and comparable county-level data were collected across North Carolina. Because individual types of birth defects are rare, we estimated prevalence for the entire 12-year period.

In this analysis, the prevalence is a measure of how common the birth defect is in the population during the 12-year period. CIs are provided to illustrate how precise an estimate is; the wider the CI, the less precise the estimate and the more the estimate could vary. To determine if a prevalence estimate was higher or lower than the state estimate, we looked at the width of the CIs and considered whether county-specific and statewide CIs overlapped. If county and state CIs did not overlap, estimates were considered different.

To provide context for the county-specific results for brain defects, we also estimated the prevalence of brain defects throughout North Carolina.

Results

A review of epidemiologic and toxicological studies identified no definitive links between exposure to PFAS and birth defects in humans. Some studies in mammals have reported weak associations between PFAS exposure and birth defects; however, these studies have important limitations. A summary of the literature review (including notes regarding these limitations) and a list of citations are provided in Appendix B.

Table 1 shows the prevalence estimates for selected birth defects in each of the five counties and for the state of North Carolina. Comparisons of county and state rates for groups of birth defects examined are described below.

Central nervous system defects

- The prevalence of neural tube defects in Bladen County was higher than the statewide prevalence; however, the Bladen County estimate was based on small numbers and the prevalence varied widely from year to year.
- The prevalence of total brain defects varied substantially across the state with a higher prevalence of total brain defects in numerous counties across North Carolina, including the five counties in this analysis. Within the five counties, compared to the state, different types of brain defects were elevated in different counties: Brain reduction defect prevalence was higher in Bladen, Brunswick and Cumberland counties, while microcephaly and hydrocephaly were more prevalent in New Hanover County. The higher prevalence of these birth defects was not confined to the lower Cape Fear region.

Orofacial clefts

- The prevalence estimates of orofacial clefts did not differ in any of the five counties compared to the statewide prevalence.

Cardiac defects & Skeletal anomalies

- Overall, the prevalence of skeletal and cardiac defects did not differ from the statewide prevalence, except for the prevalence of RVOTO lesions in Brunswick County, which was higher than the statewide prevalence but based on small numbers resulting in prevalence estimates that varied widely from year to year.

Conclusions

The prevalence of most types of birth defects in these five counties did not differ from statewide prevalence estimates consistently across all counties. The prevalence of some central nervous system and cardiac defects were higher in one or more of the five counties examined compared with the state, but were based on small numbers that caused the estimates to vary widely from year to year. For reasons that are not well understood, the prevalence of brain anomalies varied substantially across North Carolina and higher prevalence was not limited to the lower Cape Fear region.

There are several important factors that need to be considered in interpreting the results reported here. Although major birth defects are relatively common (occurring in 1 in every 33 infants nationally),[2] the individual types of birth defects included in this report are rare. Small numbers of cases result in prevalence estimates that can vary widely over time and therefore can be difficult to interpret. We attempted to estimate more stable rates by combining specific birth defects into categories based on similar developmental pathways.[3] However, some of these categories still had small numbers of birth defects.

Because of the small numbers of birth defects, as well as differences in NCBDMP data collection prior to 2003, we were not able to determine whether the prevalence of these birth defects may have changed over time. As NCBDMP continues to track the occurrence of birth defects, the program will be able to better determine if there have been changes in their occurrence over time.

The county prevalence estimates reported here were compared to the statewide prevalence estimates. Because the state estimate is an average, by definition some counties will have a higher and some a lower prevalence than the state. National estimates for most categories of birth defects we examined are not available for comparison because different states vary in how they collect data on birth defects. Prevalence estimates of microcephaly and hydrocephaly from other states are available and ranged between 2 and 12 per 10,000 live births;[1] most of the county estimates reported here fall within or close to this range. Prevalence of reduction defects is not available from other states.

NCBDMP does not include all births occurring at federal or military facilities, such as Womack Army Medical Center in Cumberland County. Infants born at military facilities are only included if transferred to a non-military hospital for care. This might result in an underestimate of the prevalence of certain birth defects in Cumberland County.

Birth defects can be due to many recognized and unrecognized factors. Some recognized risk factors include inadequate folate intake and other dietary deficiencies, hypertension, diabetes,

obesity, infections, certain medications, smoking, alcohol use, maternal age, and genetic factors, as well as certain environmental exposures. These factors were not accounted for in this analysis and can contribute to geographic variation in the prevalence of birth defects.

While NCBDMP does not routinely collect information about potential environmental exposures, NC DHHS was able to use the registry's data to describe the prevalence of birth defects in five counties during 2003–2014. Moving forward, NCBDMP is developing plans to examine the occurrence of brain anomalies across North Carolina and will continue to monitor geographic variations in the occurrence of birth defects throughout the state.

References

1. National Birth Defects Prevention Network (2013) Major birth defects data from population-based birth defects surveillance programs in the United States, 2006-2010. Birth Defects Res A Clin Mol Teratol 97:S1-S172.
2. CDC. Centers for Disease Control and Prevention (2008) Update on overall prevalence of major birth defects–Atlanta, Georgia, 1978-2005. MMWR 57(1):1-5.
3. Botto LD, Lin AE, Riehle-Colarusso T, Malik S, Correa A (2007) Seeking causes: Classifying and evaluating congenital heart defects in etiologic studies. Birth Defects Res A Clin Mol Teratol 79:714–27.

Where Can I Learn More?

For more information about the North Carolina Birth Defects Monitoring Program, visit http://www.schs.state.nc.us/units/bdmp/. For more information about per- and polyfluoroalkyl substances (PFAS) and the GenX response, visit https://epi.publichealth.nc.gov/oee/a_z/pfas.html.

Who Can I Contact if I Have Questions?

- For questions about your health, we recommend that you contact your healthcare provider.
- For questions about this report or about GenX and your health, please contact the Occupational and Environmental Epidemiology Branch at (919) 707-5900.

Table 1. Number of Cases, Prevalence[1], and 95% Confidence Intervals[2] for Selected Birth Defects in North Carolina, Bladen, Brunswick, Cumberland, New Hanover, and Pender Counties, North Carolina Residents, 2003–2014.

	North Carolina			Bladen County			Brunswick County			Cumberland County			New Hanover County			Pender County		
Phenotype	No.	Prevalence	95% CI	No.	Prevalence	95% CI	No.	Prevalence	95% CI	No.	Prevalence	95% CI	No.	Prevalence	95% CI	No.	Prevalence	95% CI
CNS[3] Defects																		
Neural Tube Defects	1,075	7.28	6.85, 7.73	9	18.60	8.51, 35.27	11	8.83	4.41, 15.79	58	8.55	6.49, 11.05	17	6.17	3.60, 9.88	-	-	-
Brain Defects	3,702	25.08	24.28, 25.90	20	41.32	25.26, 63.75	60	48.16	36.77, 61.95	220	32.42	28.28, 36.99	130	47.19	39.44, 56.01	32	47.44	32.47, 66.91
Microcephaly	707	4.79	4.44, 5.16	-	-	-	11	8.83	4.41, 15.79	30	4.42	2.98, 6.31	25	9.08	5.87, 13.39	8	11.86	5.12, 23.36
Hydrocephaly	1,274	8.63	8.16, 9.12	5	10.33	3.36, 24.09	17	13.65	7.95, 21.84	78	11.49	9.09, 14.34	43	15.61	11.30, 21.02	9	13.34	6.10, 25.31
Reduction Defects	1,050	7.11	6.69, 7.56	9	18.59	8.51, 35.27	19	15.25	9.18, 23.81	72	10.61	8.30, 13.36	26	9.44	6.17, 13.83	8	11.86	5.12, 23.36
Orofacial Clefts	1,970	13.34	12.76, 13.95	12	24.79	12.82, 43.27	26	20.87	13.64, 30.56	89	13.12	10.53, 16.14	44	15.97	11.61, 21.44	7	10.38	4.17, 21.37
Cardiac Defects																		
Conotruncal Defects	1,055	7.15	6.72, 7.59	-	-	-	10	8.03	3.85, 14.76	48	7.07	5.22, 9.38	12	4.36	2.25, 7.61	6	8.90	3.27, 19.35
LVOTO[4] Defects	1,059	7.17	6.75, 7.62	-	-	-	11	8.83	4.41, 15.79	42	6.19	4.46, 8.37	13	4.72	2.51, 8.07	-	-	-
RVOTO[5] Defects	1,733	11.74	11.19, 12.30	8	16.53	7.14, 32.54	26	20.87	13.64, 30.56	93	13.70	11.06, 16.79	41	14.88	10.68, 20.19	12	17.79	9.20, 31.06
Skeletal Defects																		
Limb Deficiency	642	4.35	4.02, 4.70	-	-	-	8	6.42	2.77, 12.65	22	3.24	2.03, 4.91	14	5.08	2.78, 8.53	5	7.41	2.41, 17.29

[1]number of cases per 10,000 live births; [2]95% confidence interval (CI) around prevalence estimate; CIs are provided to illustrate how precise an estimate is; the wider the CI, the less precise the estimate and the more the estimate could vary. CIs are based on exact binomial limits; [3]central nervous system; [4]left ventricular outflow tract obstruction; [5]right ventricular outflow tract obstruction;
- data for counts less than 5 are suppressed.

Notes:

- *Yellow shading indicates county-specific prevalence estimates that were considered different than the statewide prevalence estimates. Because the statewide estimates are averages, some counties will have higher and some lower prevalence. National estimates were not available for comparison.*
- *Birth defects can be due to a complex mix of genetic, medical, behavioral and environmental factors. These factors were not accounted for here and can contribute to geographic differences in the prevalence of birth defects.*

Appendix A
List of Birth Defects Included in this Report

For descriptions of each birth defect listed below, see:
https://www.cdc.gov/ncbddd/birthdefects/surveillancemanual/resource-library/glossary.html

Group	CDC/BPA Code
Neural Tube Defects	
Anencephaly and related defects	740.000-740.290
Spina bifida with and w/o hydrocephalus	741.000-741.990
Encephalocele	742.000-742.090
Brain Defects	
Microcephaly	742.100
Hydrocephaly w/o spina bifida	742.300-742.390
Reduction deformities	742.200-742.290
Other specified brain anomalies	742.400-742.486
Conotruncal Heart Defects	
Common truncus	745.000-745.010
Transposition of great arteries	745.100-745.120; 745.190
Tetralogy of Fallot	745.200-745.210; 747.310
Double-outlet right ventricle	745.130-745.150
Interrupted aortic arch- type B	747.216
Left Ventricular Outflow Tract Obstructive Defects	
Aortic valve stenosis (excl. supravalvular)	746.300
Coarctation of aorta	747.100-747.190
Hypoplastic left heart syndrome	746.700
Interrupted aortic arch- type A	747.215
Right Ventricular Outflow Tract Obstructive Defects	
Pulmonary valve stenosis and atresia	746.000-746.010
Tetralogy of Fallot	745.200-745.210; 747.310
Tricuspid atresia	746.100
Orofacial Clefts	
Cleft palate alone	749.000-749.090
Cleft lip alone	749.100-749.190
Cleft lip with cleft palate	749.200-749.290
Limb Deficiency Defects	
Reduction defects of upper limb, transverse & longitudinal	755.200-755.290
Reduction defects of lower limb, transverse & longitudinal	755.300-755.390

Appendix B
Literature Review

Summary: No birth defects have been definitively linked with PFAS exposure in humans. The existing epidemiologic and toxicologic literature about PFAS exposure and the occurrence of birth defects is limited and inconsistent. Below are citations to all studies reviewed for this report. Some of these studies have found weak associations with the following types of birth defects in either animals or humans: Central nervous system defects, orofacial clefts, cardiac defects, and skeletal abnormalities. Although weak associations have been found between PFAS exposure and these types of defects, limitations in the design of the available studies exist that make it challenging to determine whether a true association exists between PFAS exposure and birth defects in humans. It is unclear how conditions observed among laboratory animals may translate to humans. In epidemiologic studies of PFAS exposures in humans, limitations include an inability to accurately quantify PFAS exposure, reliance on unconfirmed reports rather than physician-confirmed birth defects, and combining of unrelated birth defects into one group.

Jiang Q, Lust RM, Strynar MJ, Dagnino S, DeWitt JC (2012) Perfluorooctanoic acid induces developmental cardiotoxicity in chicken embryos and hatchlings, Toxicol 293_97-106.

Lau C, Thibodeaux JR, Hanson RG, Narotsky MG, Rogers JM, Lindstrom AB, Strynar MJ (2006). Effects of perfluorooctanoic acid exposure during pregnancy in the mouse. Toxicol Sci 90:510–518.

Nolan LA, Nolan JM, Shofer FS, Rodway NV, Emmett EA (2010) Congenital anomalies, labor/delivery complications, maternal risk factors and their relationship with perfluorooctanoic acid (PFOA)-contaminated public drinking water. Reprod Toxicol 29:147-155.

Savitz DA, Stein CR, Bartell SM Elston B, Gong J, Shin HM et al. (2012a) Perfluorooctanoic acid exposure and pregnancy outcome in a highly exposed community. Epidemiol 23:386-392.

Savitz DA, Stein CR, Elston B, Wellenius GA, Bartell SM, Shin HM, Vieira VM Fletcher T (2012b) Relationship of perfluorooctanoic acid exposure to pregnancy outcome based on birth records in the mid-Ohio Valley. Environ Health Perspect 120:1201-1207.

Stein CR, Savitz DA, Dougan M (2009) Serum levels of perfluorooctanoic acid and perfluorooctane sulfonate and pregnancy outcome. Am J Epidemiol 170:837-846.

Stein CR, Savitz DA, Elston B, Thorpe PG, Gilboa SM (2014) Perfluorooctanoate exposure and major birth defects. Reprod Toxicol. 47:15-20.

Sun M, Arevalo E, Strynar M, Lindstrom A, Richardson M, Kearns B, Pickett A, Smith C, Knappe D (2016) Legacy and emerging perfluoroalkyl substances are important drinking water contaminants in the Cape Fear River Watershed of North Carolina. Environ Sci Technol Lett 3:415–419.

Thibodeaux JR, Hanson RG, Rogers JM, Grey BE, Barbee BD, Richards JH et al (2003) Exposure to perfluorooctane sulfonate during pregnancy in rat and mouse. I: maternal and prenatal evaluations. Toxocol Sci 74:369-381.

Wang Z, Cousins IT, Scheringer M, Hungerbuhler K (2013) Fluorinated alternatives to long-chain perfluoroalkyl carboxylic acids (PFCAs), perfluoroalkane sulfonic acids (PFSAs) and the potential precursors. Environ Int 60:242-248.

Yahia D, El-Nasser MA, Abedel-Latif M, Tsukuba C, Yoshida M, Sato I, Tsuda S (2010). Effects of perfluorooctanoic acid (PFOA) exposure to pregnant mice on reproduction. J Toxicol Sci 35:527-533.