Testimony of: Cassandra J. Clark, Ph.D.

Thank you for the invitation to speak with you all today. I am honored to be able to present our study entitled "Unconventional oil and gas development exposure and risk of childhood acute lymphoblastic leukemia: A case-control study in Pennsylvania, 2009-2017." This peer-reviewed work was published in *Environmental Health Perspectives* and reflects years of effort from a team of talented researchers from diverse disciplines. My goal today is to provide you with the context and information needed to interpret the results of this study, to discuss some of the broader public health implications of this work, and to be available for any questions you may have on these topics. I will begin by briefly providing context and rationale for the study before highlighting some of the most relevant results and discussing their broader implications for the deliberations at hand.

Introduction. The focus of this study, childhood acute lymphoblastic leukemia (or ALL), is a cancer of the blood that arises in the immune cells [1]. ALL is the most common type of cancer in children aged 0-14 years, representing nearly 80% of childhood leukemia cases and 20-30% of all childhood cancer cases [1-3]. ALL is most common in children aged 2-4 years [1, 4], and thus the early-life environment is thought to be an important time for potential exposures. Despite a decrease in the incidence of cancer overall in the United States, the incidence of childhood ALL has continued to increase, underscoring the need for primary prevention of the exposures that cause this disease.

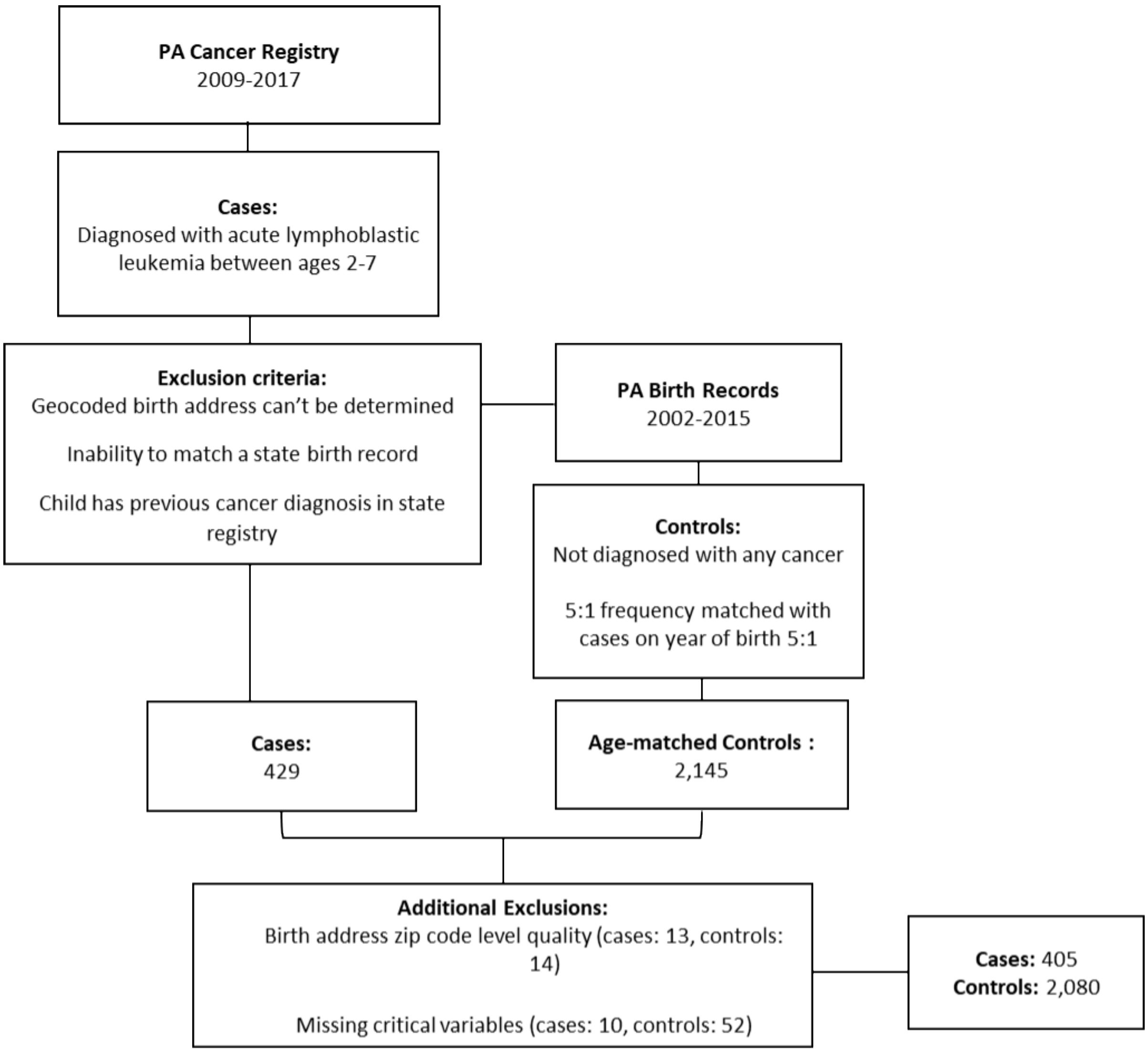
The development of childhood ALL is thought to be attributable to both genetic susceptibility and environmental exposures [5-7]. The current evidence and the early age of peak ALL incidence suggest that early-life exposure to environmental chemicals may contribute to the development of leukemia, particularly chemicals that are toxic to the blood, damage DNA, or interfere with the immune system [2, 8]. To date, ALL has been linked to several environmental and chemical exposures, including ionizing or diagnostic radiation [9, 10], radon [11], air pollution [12-16], pesticides [17-21], polybrominated diphenyl ethers [22], and benzene [14, 23-27]. Multiple risk factors mentioned here are associated with unconventional oil and gas development (UOGD). Several of the hundreds of chemicals have reportedly used in UOGD injection water or detected in wastewater have been associated with leukemia, and many more have not undergone any health risk assessments at all [28]. In addition to water pollution, studies of UOGD-related air emissions have measured several carcinogens, including radioactivity, particulate matter, and volatile organic compounds (e.g., benzene) [29-32]. The potential for children living near UOGD to be exposed to chemical carcinogens and radiological contaminants is a major public health concern.

Methods. We conducted an analysis to identify potential associations between early life exposure to UOGD and ALL risk. Our population of children included all children diagnosed with ALL between the ages of 2-7[1] years in PA from 2009-2017[2] (n=429), each matched by birth

[1] We selected the age range of 2-7 years because it includes the peak age of ALL incidence in the U.S [4] and excludes infant leukemia (diagnosis between the ages of 0-1), which tends to have different causes.
[2] We selected the years of diagnosis (2009-2017) to ensure there was opportunity for exposure after drilling commenced in the state and to include a latency period of at least one year to provide time for the development of disease.

year with five control children with no diagnosis of cancer (n=2,145). Figure 1 in the provided handout is a flow chart depicting the data acquisition process and inclusion decisions made. After exclusions for geocode quality and missingness for important variables, we included 405 cases and 2,080 controls in our final analyses (Figure 1).

Figure 1. Data sources and selection process for Pennsylvania cases and controls (2009-2017).



Exposure Assessment. We used oil and gas well permit and production report datasets from the PA Department of Environmental Protection's Office of Oil and Gas Management [37] to construct a dataset of location, permit, and production data for UOG wells that were either drilled or producing in PA from 2001-2015. We then used maternal residential address at birth to assign exposures using a surrogate of oil and gas exposure, an inverse distance-squared weighted well count.[3] This metric assumes that exposure potential decreases significantly with increasing distance between the home and the well. We calculated this metric at buffer sizes of 2, 5, and 10 km around the maternal residence for two exposure windows: (i) three months prior to conception to one year prior to diagnosis, called the "primary window," and (ii) three months prior to conception to birth, called the "perinatal window."

Analysis. We calculated odds ratios (OR), which are a representation of the risk of developing ALL given the exposure level considered, and their corresponding confidence intervals (95% CI), which represent the range in which the odds ratio could feasibly fall given other factors such as sample size. We adjusted our results for both individual- and area-level factors in multivariable logistic regression models.[4]

Results and Discussion. We observed elevated risk of developing ALL for children living within 2, 5, and 10 km of UOGD during the prenatal period and in early life (Figure 2). The odds of developing ALL were nearly 2 times higher in children with at least one UOG well within 2 km of their birth residence during early life compared to those with no UOG wells. This effect was statistically significant (OR: 1.98, 95% CI: 1.06-3.69). The size of the effect that we observed decreased across the larger 5 km[5] and 10 km[6] buffer sizes, but remained elevated, indicating consistently increased risk associated with exposure to UOGD within 10 km.

When we considered just the perinatal exposure period, the risk estimates were larger in magnitude by 20-40% than the estimate for the corresponding buffer size using the full primary period of pre-conception to 1 year prior to ALL diagnosis. This indicates that exposure during pregnancy may be particularly important. Children with mothers living within 2 km of UOGD during pregnancy had nearly 3 times the odds of developing ALL as compared to children with no UOG wells nearby (OR: 2.80, 95% CI: 1.11-7.05); this was also a statistically significant effect. The risk of developing ALL remained similarly elevated (at about 1.5 times the odds) for children born in homes with UOG wells within 5 and 10 km. Consistently, adjusting these models for additional variables resulted in little to no attenuation of the observed effect. In summary, we found that Pennsylvania children born or living near UOGD in early life had up to 2-3 times the odds of developing ALL as compared to children not living near UOGD.

---

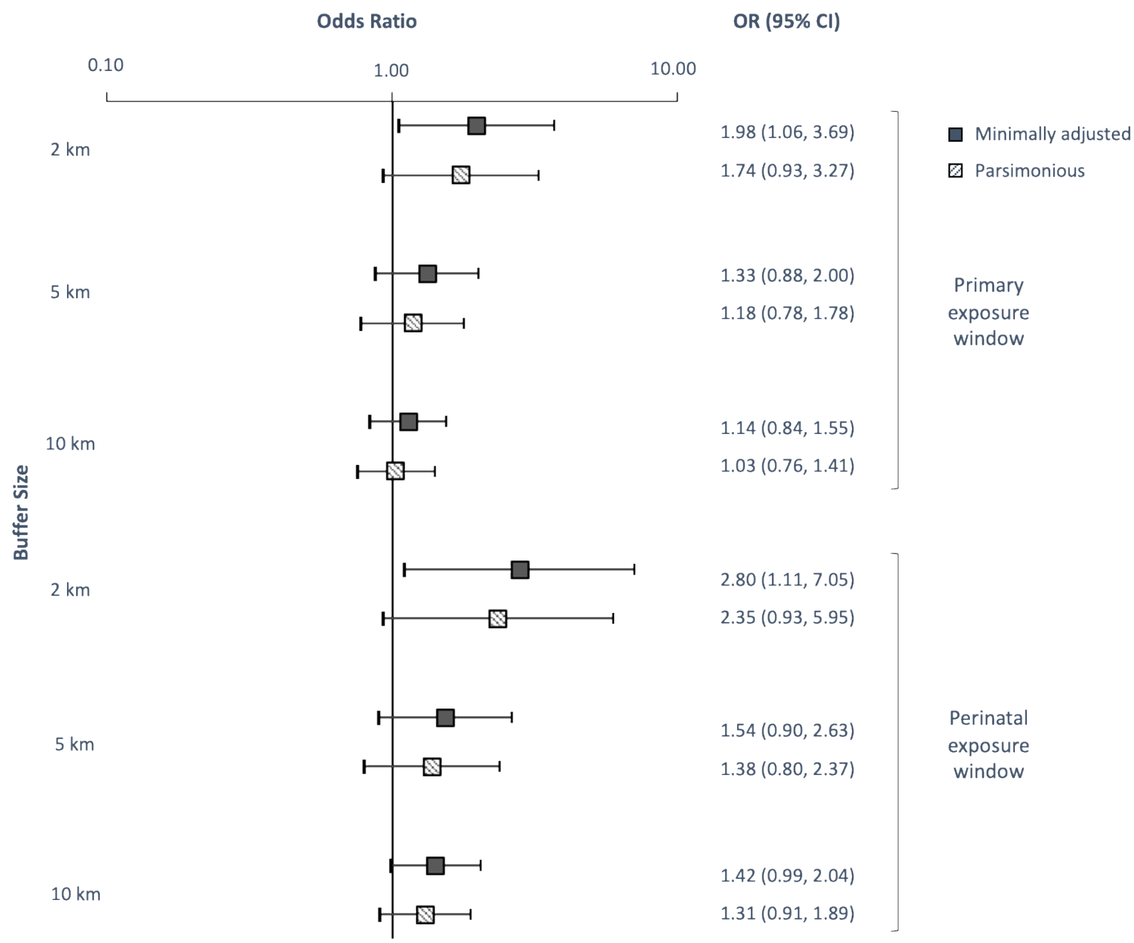
[3] Represented by $\sum_{i=1}^{n} \frac{1}{d_i^2}$ for all UOG wells within a buffer zone, where (*d*) is distance between the i^{th} UOG well and a residence.

[4] The variables considered were birth year, maternal race, maternal participation in a food stamp program, sex, delivery route, birth weight, and percent cropland within 500 m of the residence.

[5] OR: 1.33, 95% CI: 0.88-2.00

[6] OR: 1.14, 95% CI: 0.84-1.55

Figure 2. Plots of the risk of childhood acute lymphoblastic leukemia (odds ratios and 95% confidence intervals) by buffer size, assessed with the *aggregate metric* for the primary and perinatal exposure windows.



The aggregate metric refers to inverse distance-squared well counts. Odds ratios and 95% confidence intervals calculated using unconditional logistic regression. Minimally adjusted: adjusted for year of birth only; Parsimonious: adjusted for year of birth, maternal race, and WIC. OR: Odds Ratio; 95% CI: Confidence Interval.

When interpreting science, it is critically important to be aware of both the strengths and limitations of the approaches employed. Our study has several notable strengths. At the time of publication, it was the largest study to date investigating UOGD with ALL or any childhood cancer and the first case-control study to focus exclusively on UOGD exposure. We controlled our models for multiple known risk factors for ALL and examined the impact of several competing environmental exposures. We assessed UOGD exposure at multiple buffer sizes informed by the epidemiologic and environmental literature and during multiple exposure windows thought to be important in the development of ALL, and our results were highly consistent across models.

Our study also has a few important limitations. Principally, though we designed a statewide study, UOGD is confined to the extent of the shale and drilling is not performed in urbanized metropolitan centers. Therefore, most of our study population was unexposed. Low exposure prevalence may reduce model stability and the overall precision of risk estimates. However, we would expect this to have reduced the size of any observed relationships, as the incidence for cancer with non-modifiable risk factors tends to be higher in urban areas [38], and urban dwelling individuals are more likely to be exposed to known risk factors for ALL, such as air pollution [39, 40]. ALL is also a rare disease, and as such our sample size, though the largest study of ALL and UOGD to date, restricts the types of analyses that we can perform.

In summary, our study suggests that children living near UOGD have increased odds of developing leukemia. These results, when considered alongside a large body of peer-reviewed evidence demonstrating that exposure to UOGD is associated with adverse health effects in children [41-43], have significant implications for the creation of health-protective policies like the one being discussed. The current setback distance in PA is 152 m (500 ft), which was extended from 61 m (200 ft) in 2012 [44]. We observed elevated odds of cancer associated with UOG activity within 2 km (more than 6,560 ft), which far exceeds any existing setback distance. Further, although effect sizes diminished with increasing buffer size, the odds of developing ALL were still elevated for children living within 5 and 10 km of UOGD. Our results in the context of the broader environmental and epidemiologic literature suggest that existing setback distances are insufficiently public health protective, particularly for vulnerable populations like children, and should be revisited and informed by more recent data.

Thank you for your time and attention, and I would be happy to take any questions at this time.

References

1. Pui, C.-H., *Acute Lymphoblastic Leukemia*, in *Encyclopedia of Cancer*, M. Schwab, Editor. 2011, Springer Berlin Heidelberg: Berlin, Heidelberg. p. 23-26.
2. Eden, T., *Aetiology of childhood leukaemia.* Cancer Treat Rev, 2010. **36**(4): p. 286-97.
3. Siegel, D.A., et al., *Rates and Trends of Pediatric Acute Lymphoblastic Leukemia - United States, 2001-2014.* MMWR. Morbidity and mortality weekly report, 2017. **66**(36): p. 950-954.
4. Rossig, C. and H. Juergens, *Aetiology of childhood acute leukaemias: current status of knowledge.* Radiat Prot Dosimetry, 2008. **132**(2): p. 114-8.
5. Hunger, S.P. and C.G. Mullighan, *Acute Lymphoblastic Leukemia in Children.* 2015. **373**(16): p. 1541-1552.
6. Greaves, M., *Infection, immune responses and the aetiology of childhood leukaemia.* Nature Reviews Cancer, 2006. **6**(3): p. 193-203.
7. Greaves, M.F., et al., *Leukemia in twins: lessons in natural history.* Blood, 2003. **102**(7): p. 2321-33.
8. Buffler, P.A., et al., *Environmental and genetic risk factors for childhood leukemia: appraising the evidence.* Cancer Invest, 2005. **23**(1): p. 60-75.
9. Bailey, H.D., et al., *Exposure to Diagnostic Radiological Procedures and the Risk of Childhood Acute Lymphoblastic Leukemia.* 2010. **19**(11): p. 2897-2909.
10. Bartley, K., et al., *Diagnostic X-rays and risk of childhood leukaemia.* International journal of epidemiology, 2010. **39**(6): p. 1628-1637.
11. Tong, J., et al., *Environmental radon exposure and childhood leukemia.* Journal of Toxicology and Environmental Health - Part B: Critical Reviews, 2012. **15**(5): p. 332-347.
12. Ghosh, J.K., et al., *Prenatal exposure to traffic-related air pollution and risk of early childhood cancers.* Am J Epidemiol, 2013. **178**(8): p. 1233-9.
13. Filippini, T., et al., *Association between Outdoor Air Pollution and Childhood Leukemia: A Systematic Review and Dose-Response Meta-Analysis.* Environmental health perspectives, 2019. **127**(4): p. 46002-46002.
14. Heck, J.E., et al., *Risk of leukemia in relation to exposure to ambient air toxics in pregnancy and early childhood.* Int J Hyg Environ Health, 2014. **217**(6): p. 662-8.
15. Heck, J.E., et al., *Childhood cancer and traffic-related air pollution exposure in pregnancy and early life.* Environ Health Perspect, 2013. **121**(11-12): p. 1385-91.
16. Symanski, E., et al., *Air toxics and early childhood acute lymphocytic leukemia in Texas, a population based case control study.* Environ Health, 2016. **15**(1): p. 70.
17. Bailey, H.D., et al., *Home pesticide exposures and risk of childhood leukemia: Findings from the childhood leukemia international consortium.* Int J Cancer, 2015. **137**(11): p. 2644-63.
18. Park, A.S., et al., *Prenatal pesticide exposure and childhood leukemia - A California statewide case-control study.* International journal of hygiene and environmental health, 2020. **226**: p. 113486-113486.
19. Wigle, D.T., M.C. Turner, and D. Krewski, *A systematic review and meta-analysis of childhood leukemia and parental occupational pesticide exposure.* Environmental health perspectives, 2009. **117**(10): p. 1505-1513.
20. Gunier, R.B., et al., *A task-based assessment of parental occupational exposure to pesticides and childhood acute lymphoblastic leukemia.* Environ Res, 2017. **156**: p. 57-62.
21. Ma, X., et al., *Critical windows of exposure to household pesticides and risk of childhood leukemia.* Environmental health perspectives, 2002. **110**(9): p. 955-960.
22. Ward, M.H., et al., *Residential levels of polybrominated diphenyl ethers and risk of childhood acute lymphoblastic leukemia in California.* Environmental health perspectives, 2014. **122**(10): p. 1110-1116.
23. Smith, M.T., *The mechanism of benzene-induced leukemia: a hypothesis and speculations on the causes of leukemia.* Environmental Health Perspectives, 1996. **104**(suppl 6): p. 1219-1225.
24. Heck, J.E., et al., *Parental occupational exposure to benzene and the risk of childhood and adolescent acute lymphoblastic leukaemia: a population-based study.* Occupational and environmental medicine, 2019. **76**(8): p. 527-529.
25. Snyder, R., *Leukemia and Benzene.* International Journal of Environmental Research and Public Health, 2012. **9**(8).
26. Savitz, D.A. and K.W. Andrews, *Review of epidemiologic evidence on benzene and lymphatic and hematopoietic cancers.* 1997. **31**(3): p. 287-295.
27. Zhou, Y., et al., *Maternal Benzene Exposure during Pregnancy and Risk of Childhood Acute Lymphoblastic Leukemia: A Meta-Analysis of Epidemiologic Studies.* PLoS ONE, 2014. **9**(10): p. e110466.

28. Elliott, E.G., et al., *Unconventional oil and gas development and risk of childhood leukemia: Assessing the evidence.* Science of The Total Environment, 2017. **576**: p. 138-147.
29. Macey, G.P., et al., *Air concentrations of volatile compounds near oil and gas production: a community-based exploratory study.* Environmental Health, 2014. **13**(1): p. 82.
30. McKenzie, L.M., et al., *Human health risk assessment of air emissions from development of unconventional natural gas resources.* Science of The Total Environment, 2012. **424**: p. 79-87.
31. Goetz, J.D., et al., *Atmospheric Emission Characterization of Marcellus Shale Natural Gas Development Sites.* Environmental Science & Technology, 2015. **49**(11): p. 7012-7020.
32. Li, L., et al., *Unconventional oil and gas development and ambient particle radioactivity.* Nature Communications, 2020. **11**(1): p. 5002.
33. Barrington-Trimis, J.L., et al., *Trends in childhood leukemia incidence over two decades from 1992 to 2013.* International journal of cancer, 2017. **140**(5): p. 1000-1008.
34. Doerrenberg, M., et al., *T-cell acute lymphoblastic leukemia in infants has distinct genetic and epigenetic features compared to childhood cases.* Genes Chromosomes Cancer, 2017. **56**(2): p. 159-167.
35. Wiemels, J., *Chromosomal translocations in childhood leukemia: natural history, mechanisms, and epidemiology.* J Natl Cancer Inst Monogr, 2008(39): p. 87-90.
36. Howard, J., *Minimum Latency and Types or Categories of Cancer*, World Trade Center Health Program, Editor. 2012.
37. Pennsylvania Department of Environmental Protection. *Oil and Gas Reports*. 2022 [cited 2022 January 10]; Available from: https://www.dep.pa.gov/DataandTools/Reports/Oil%20and%20Gas%20Reports/Pages/default.aspx.
38. Zahnd, W.E., et al., *Rural–Urban Differences in Cancer Incidence and Trends in the United States.* 2018. **27**(11): p. 1265-1274.
39. Clark, L.P., D.B. Millet, and J.D. Marshall, *National Patterns in Environmental Injustice and Inequality: Outdoor NO2 Air Pollution in the United States.* PLOS ONE, 2014. **9**(4): p. e94431.
40. Brønnum-Hansen, H., et al., *Assessment of impact of traffic-related air pollution on morbidity and mortality in Copenhagen Municipality and the health gain of reduced exposure.* Environment International, 2018. **121**: p. 973-980.
41. Deziel, N.C., et al., *Assessing Exposure to Unconventional Oil and Gas Development: Strengths, Challenges, and Implications for Epidemiologic Research.* Curr Environ Health Rep, 2022.
42. Deziel, N.C., *Invited Perspective: Oil and Gas Development and Adverse Birth Outcomes: What More Do We Need to Know?* 2021. **129**(7): p. 071301.
43. Shonkoff, S.B.C., et al., *RE: Response to CalGEM Questions for the California Oil and Gas Public Health Rulemaking Scientific Advisory Panel*, California Department of Conservation, Editor. 2021.
44. Pennsylvania Department of Environmental Protection. *Act 13 of 2012*. 2012 [cited 2020 June 15]; Available from: https://www.dep.pa.gov/Business/Energy/OilandGasPrograms/Act13/Pages/default.aspx.