



Environmental and Dietary Factors Contributing to the Rise of Childhood Leukemia

Collaborative on Health and the Environment

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Environmental Health Sciences



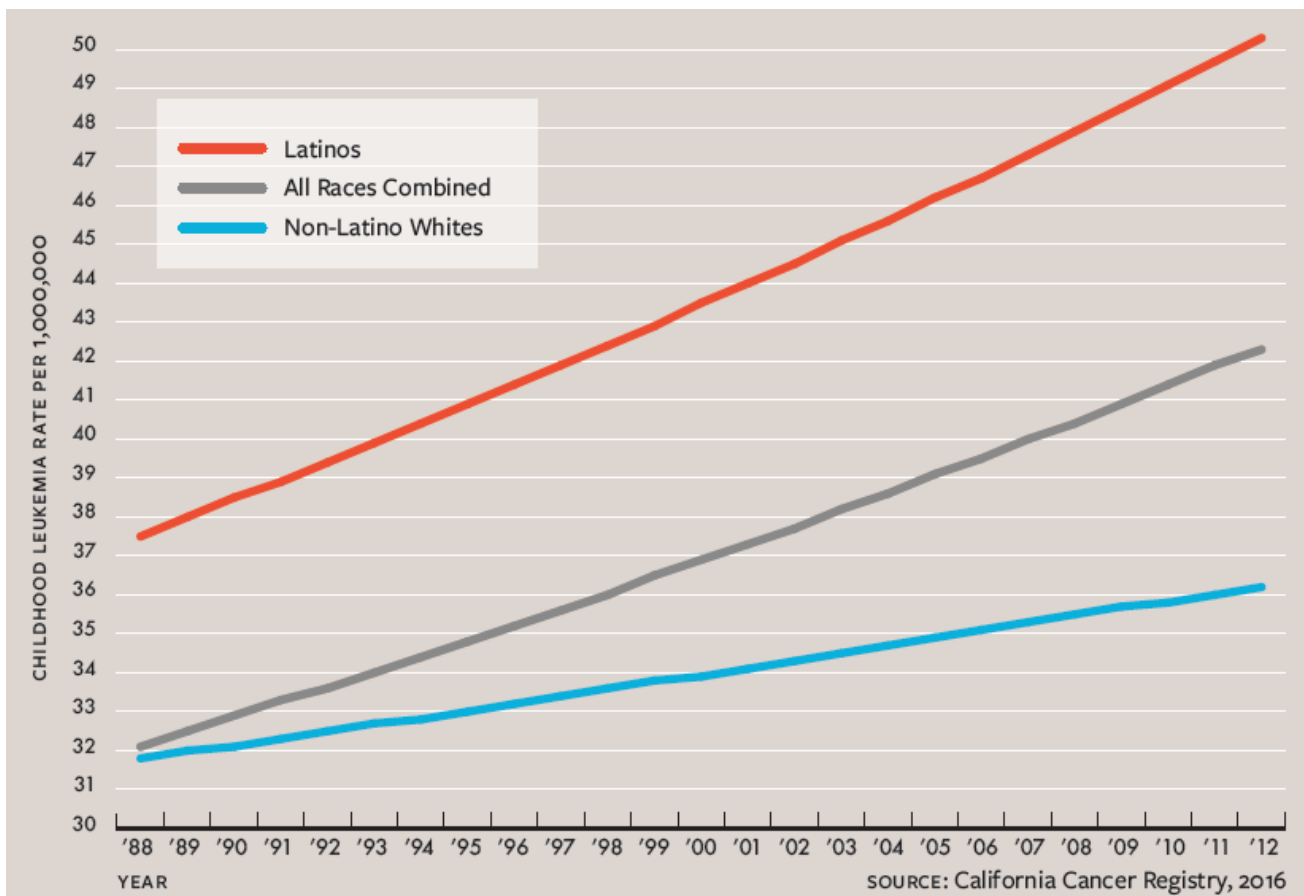
Childhood Leukemia

- First cancer in children
- 3,800 diagnosed per year in the U.S.
- Second cause of death in children
- Lifelong complications in survivors



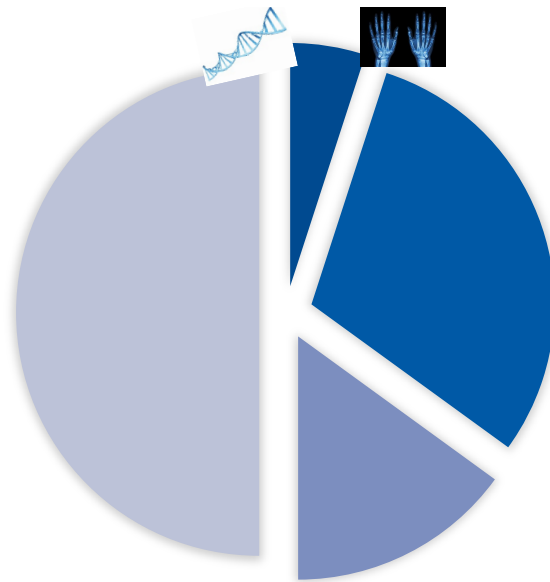
Incidence of Childhood Leukemia in California

35% increase in the past 40 Years



Known Risk Factors 25+ years ago

genetic syndromes & x-rays
accounted for <10% of all childhood leukemia

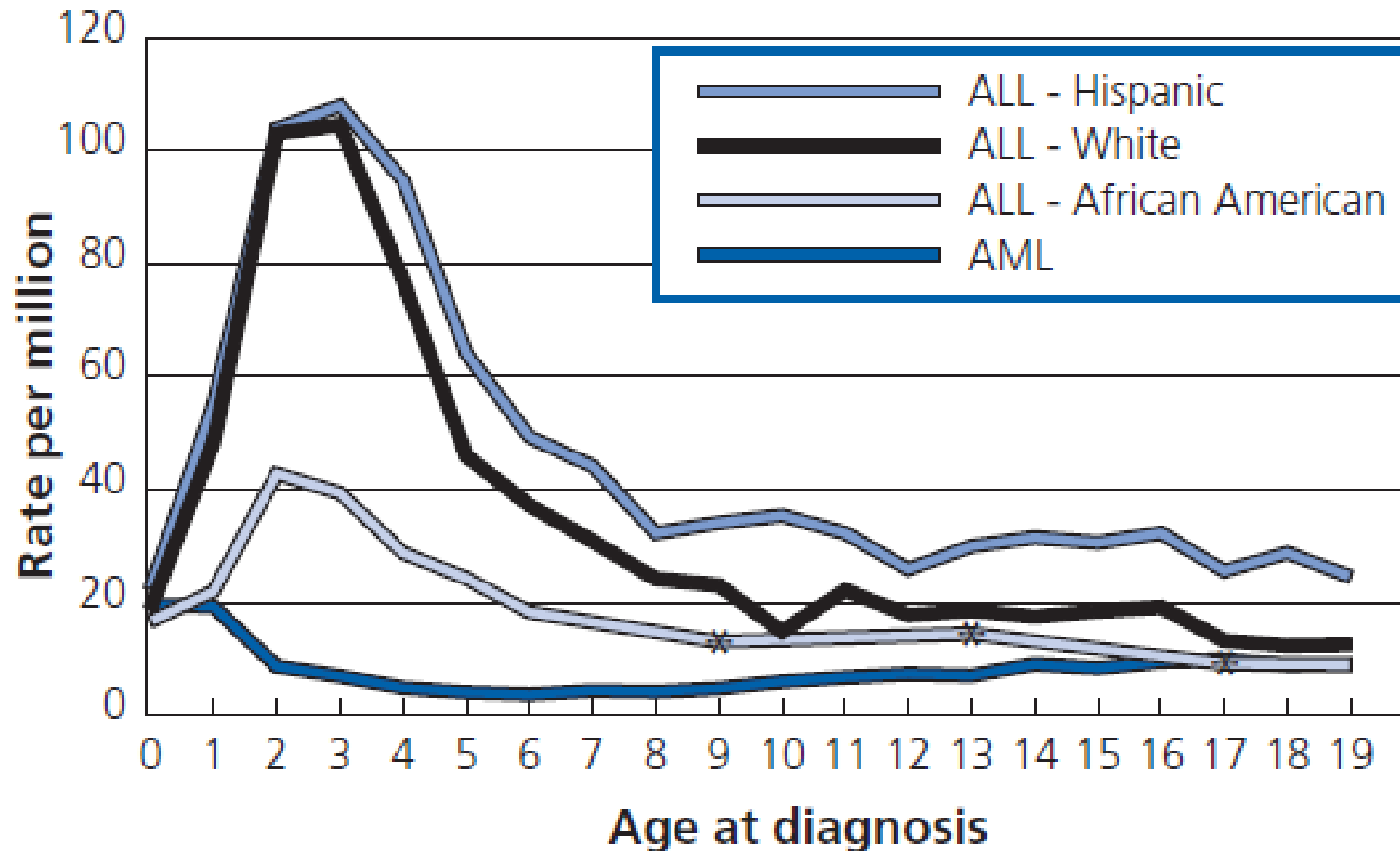


Factors under Investigation

- Immune regulation
 - Fetal growth
 - Environmental exposures
 - At home
 - Smoking
 - Paints
 - Solvents
 - Pesticides
 - At work for parents
 - Outdoor pollution
 - Diet (mother and child)
 - Ionizing and non-ionizing radiation
 - Genetic
- Many chemicals are known to cause cancer in adults



Age at Diagnosis

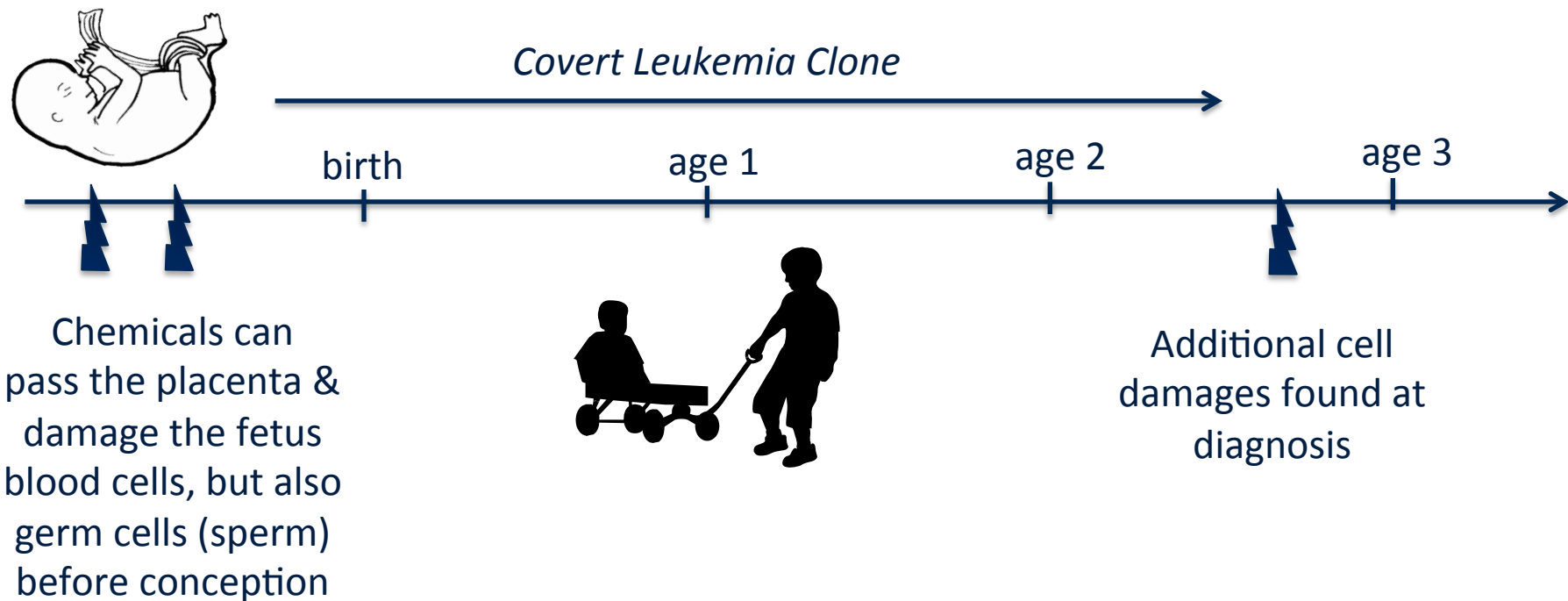


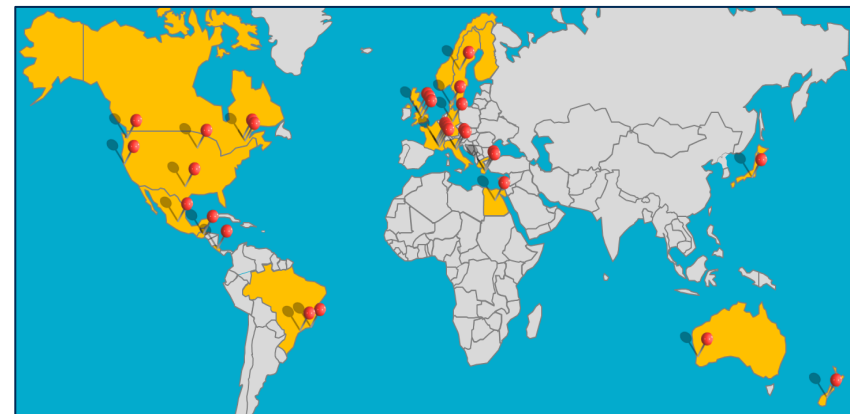
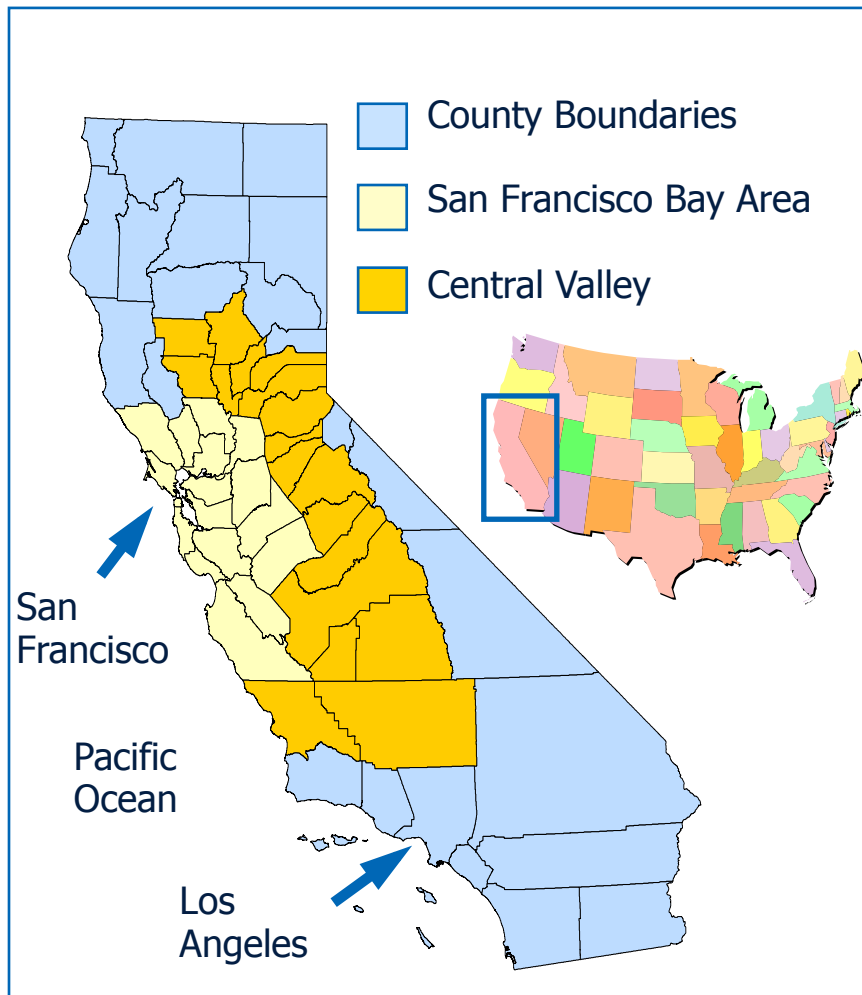
Natural History of Leukemia

INITIATING EVENTS
BEFORE BIRTH

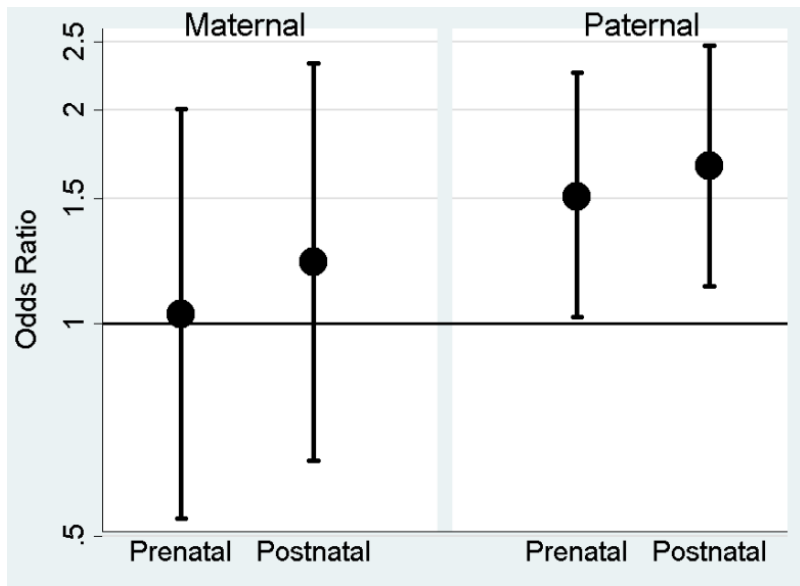
PROMOTING EVENTS
AFTER BIRTH

LEUKEMIA
DIAGNOSIS





Occupational Exposures to Pesticides and Childhood Acute Lymphoblastic Leukemia (ALL)



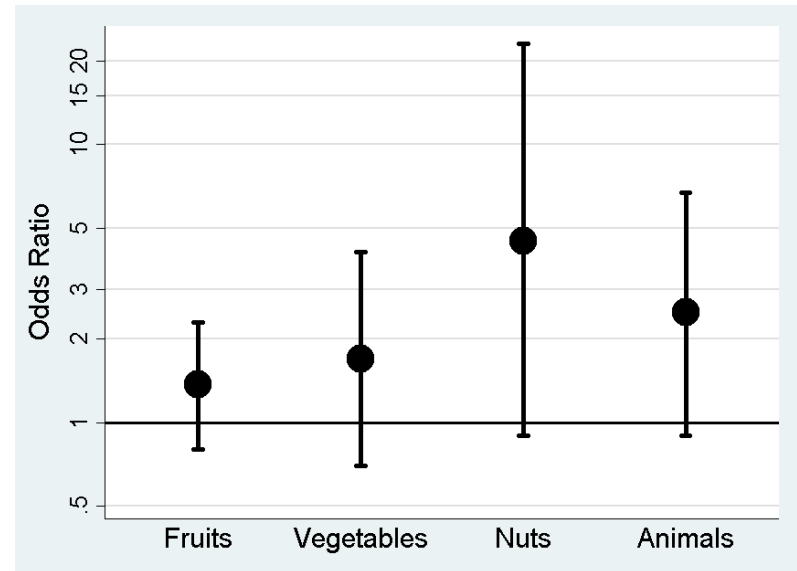
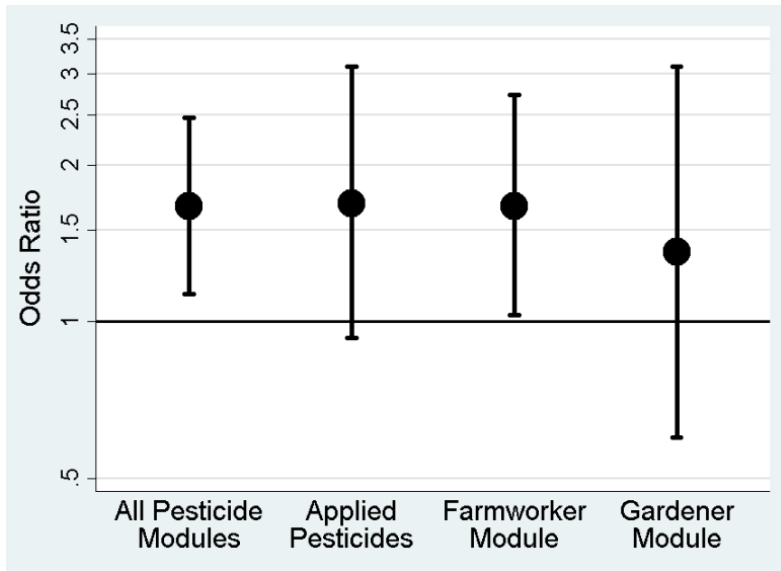
Adjusted for child's sex, age, ethnicity, mother's race and household income

Gunier, Env Research, 2017

- Pooled original data for ~8,000 cases and ~14,000 controls
- Maternal exposure – pregnancy
OR=1.01 (0.78-1.30)
- Paternal exposure – periconception
OR=1.20 (1.06-1.38)

Bailey, Int J Cancer, 2014

Routes of Pesticide Exposure



Mother Jones and the Foundation for National Progress Photographer Matt Black

Home Use of Any Pesticides



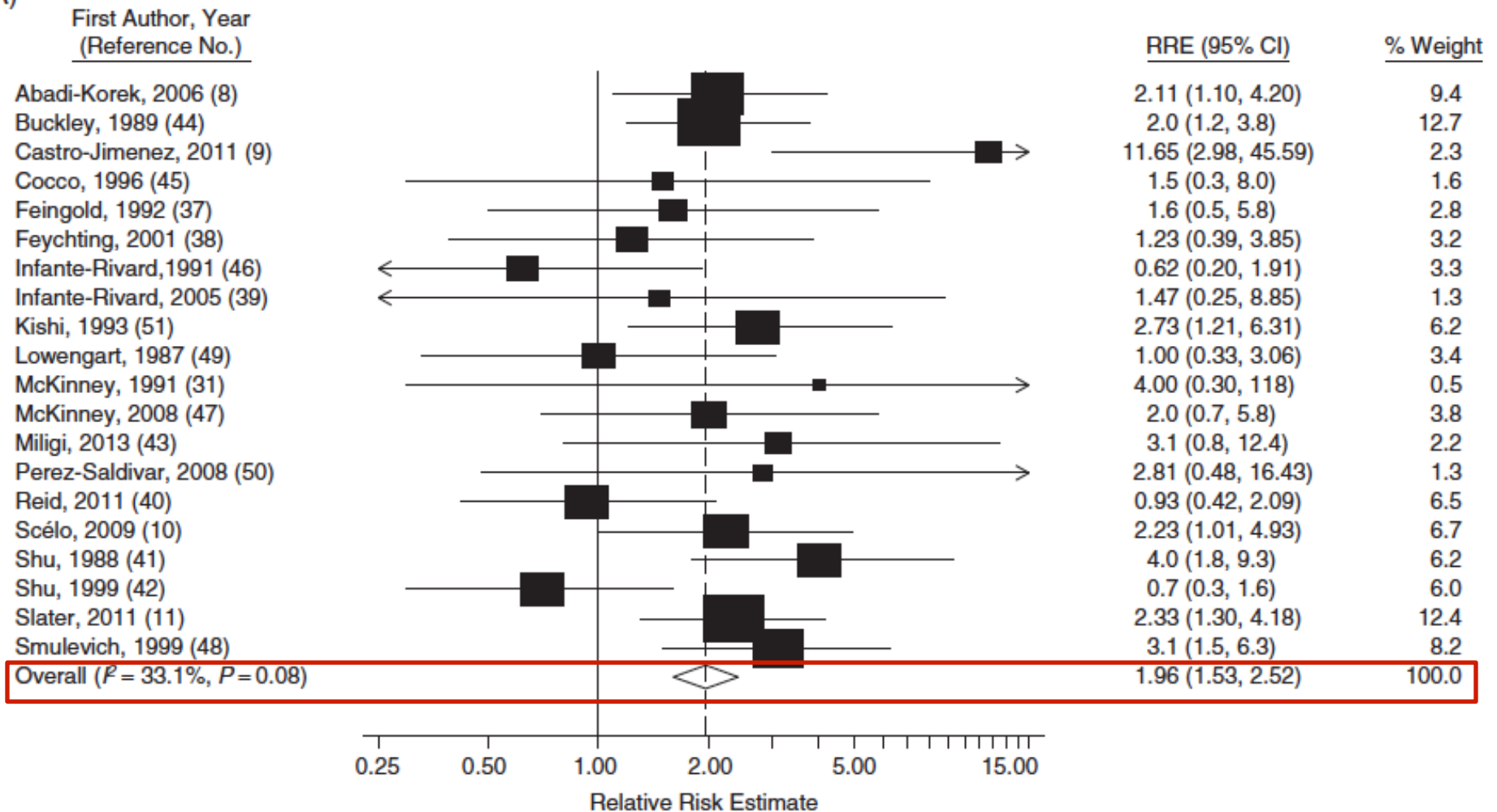
Time period	Acute Lymphoblastic Leukemia (ALL)		Acute Myeloid Leukemia (AML)	
	# Cases	OR (95% CI)	# Cases	OR (95% CI)
Before conception	2785	1.4 (1.2,1.5)	173	1.5 (1.0, 2.2)
During pregnancy	5055	1.4 (1.3, 1.5)	345	1.5 (1.2, 2.0)
After birth	4162	1.4 (1.2, 1.5)	198	1.1 (0.8, 1.5)

Adjusted for age, sex, birth year group, ethnicity, highest level of education either parent +/-birth order.

Source: Bailey et al, IJE, 2015

Sources of Benzene at Work and Home and Childhood Leukemia

A)



Air Pollution and Childhood Leukemia

Boothe et al / Am J Prev Med 2014;46(4):413-422

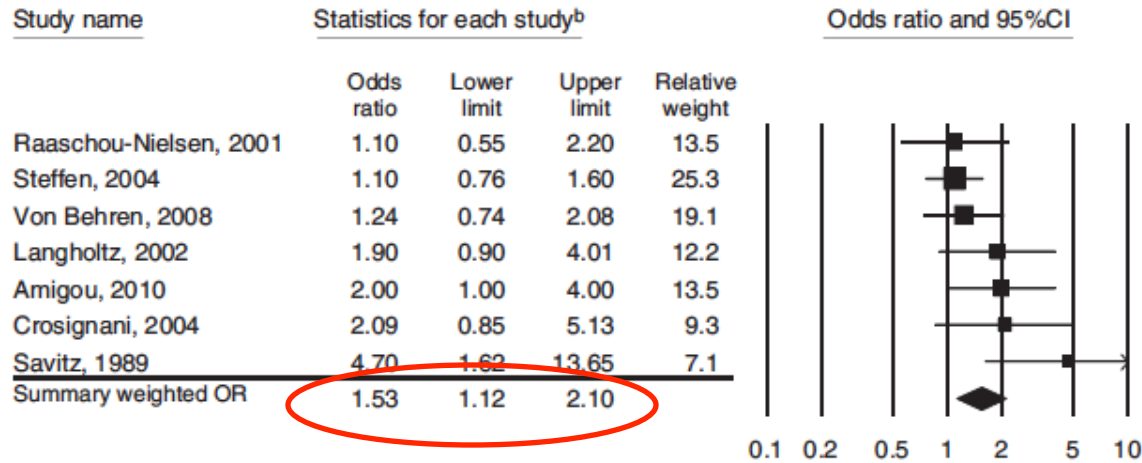
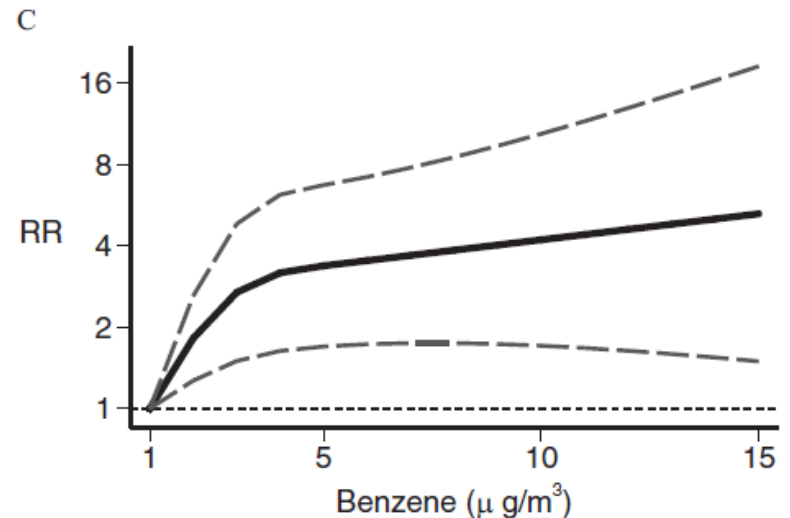


Figure 1. Forest plot of case-control studies examining the association between residential traffic exposure assessed during the postnatal period^a and childhood leukemia, and the random effects weighted summary OR and 95% CI

Childhood acute myeloid leukemia →

Fillippini, EHP 2019



Paternal Exposures to Organic Compounds at Work & Childhood ALL---Latino Fathers



Expert exposure assessment	Cases	Controls	OR*	95% CI
Any organic compounds	107	102	1.72	(1.22-2.44)
-- Benzene	30	20	2.03	(1.11-3.70)
-- Chlorinated hydrocarbons	31	17	2.53	(1.36-4.71)
Combustion exhausts	64	56	1.70	(1.16-2.57)

* OR adjusted for child's age at diagnosis/reference date, sex, maternal race, and household annual income

Metayer, Env Research (2016)

Home Use of Paints & Childhood ALL

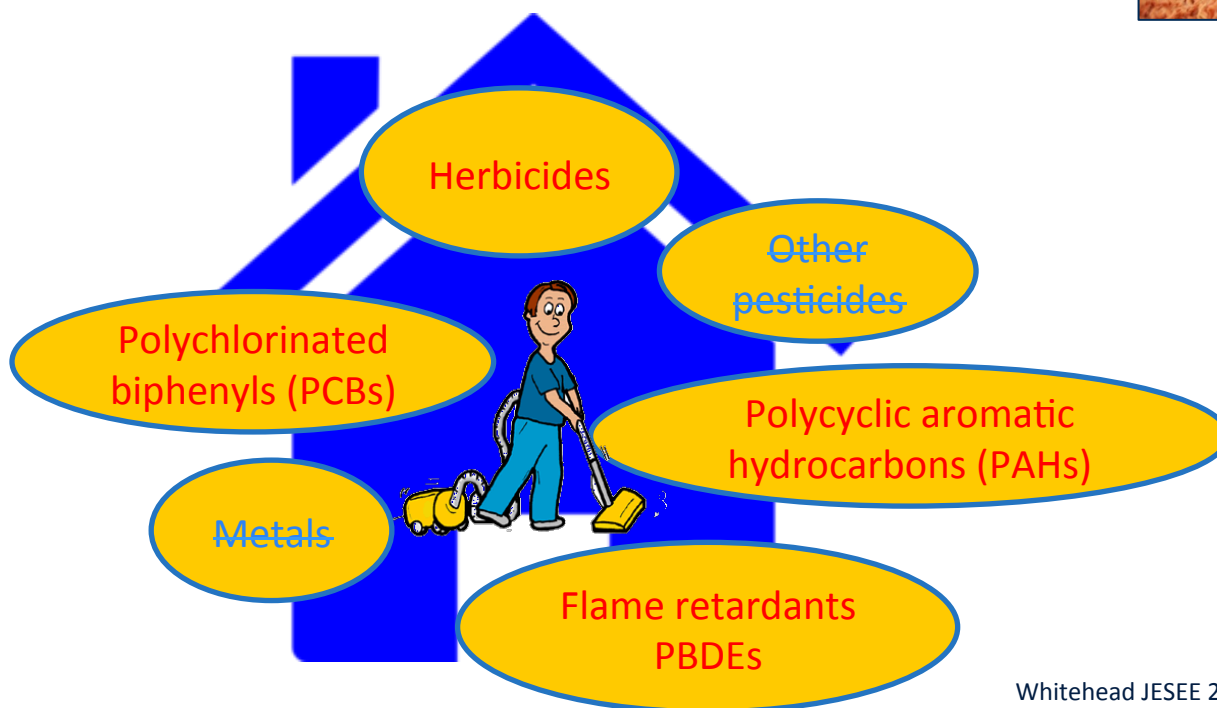


Time window	Exposure	# Cases	OR*	95% CI
Before conception	Any paints	3,000	1.42	(0.92-2.19)
	Water-based paints	1,146	0.87	(0.72-1.04)
	Oil-based paints	1,146	1.27	(1.03-1.57)
	Professional	608	1.53	(1.03-2.26)
Pregnancy	Any paints	1,962	3.91	(1.54-9.90)
	Water-based paints	1,387	0.96	(0.80-1.15)
	Oil-based paints	1,387	1.22	(0.98-1.53)
	Professional	1,305	1.66	(1.21-2.28)
After birth	Any paints	35	1.12	(1.07-1.39)
	Water-based paints	1,157	1.01	(0.83-1.23)
	Oil-based paints	1,157	1.17	(0.94-1.45)
	Professional	928	1.46	(1.18-1.80)

* OR adjusted for child's age at diagnosis/reference date, sex, maternal race, and household annual income

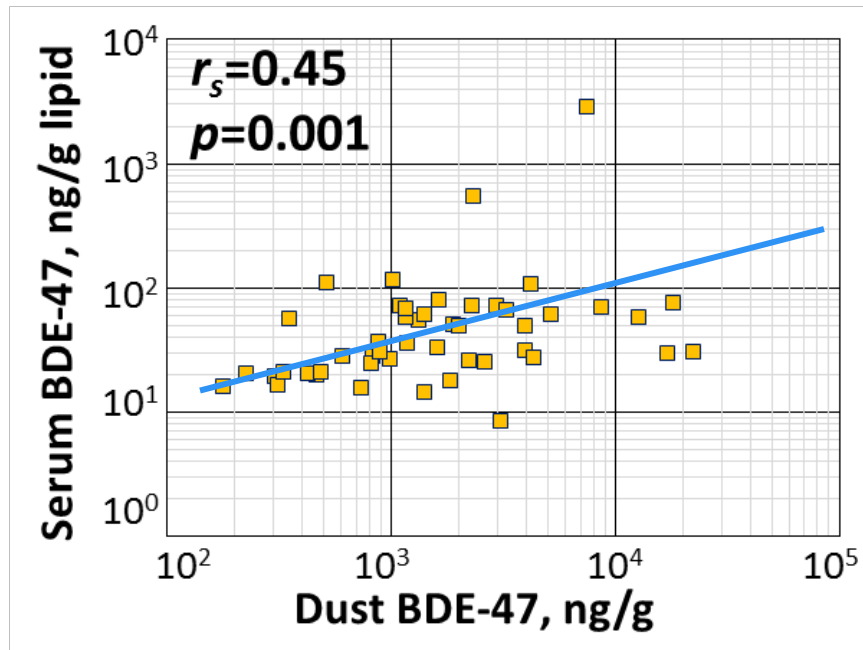
Chemicals in Home Dust

- Dust is a reservoir of persistent chemicals
- Young children are exposed via hand-to-mouth and skin contact
- Measured 50+ chemicals ~ 500 homes

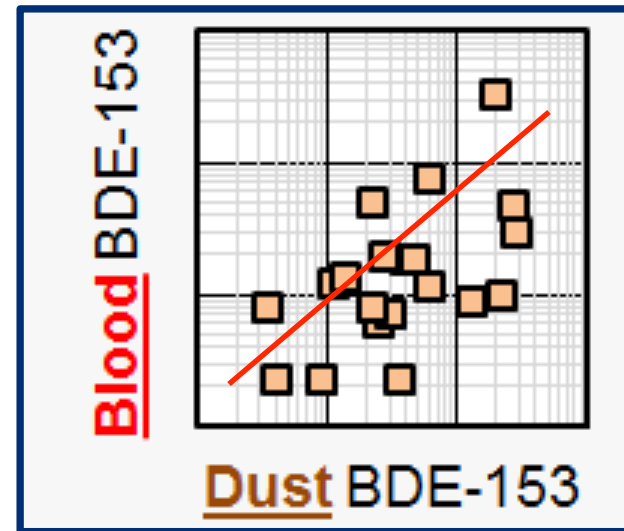


Chemicals Transmitted from Dust to Blood

Example with flame retardants - BDEs

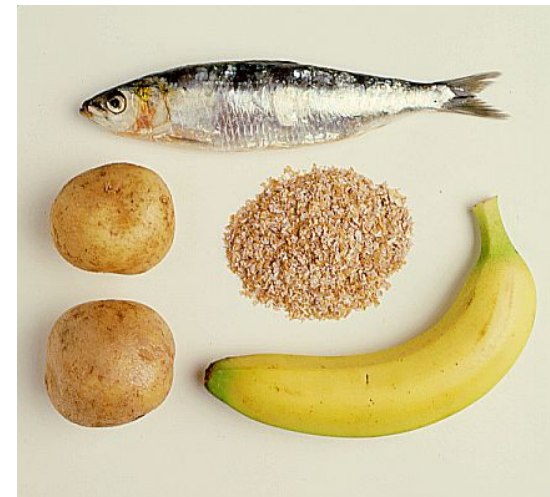
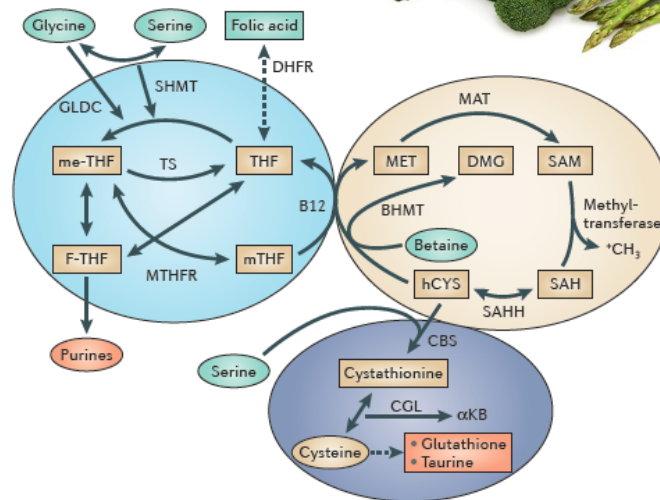


Mother



Child

Diet and Sources of One Carbon (Folate) Metabolism Nutrients



Prenatal Vitamin Supplementation and Childhood ALL



	Vitamins (Any Time)					Test for Interaction	Folic Acid (Any Time)					Test for Interaction
	No. Studies	No. Exposed		OR	(95% CI) ^a		No. Studies	No. Exposed		OR	(95% CI) ^a	
		Controls	Cases					Controls	Cases			
Parental education^c												
Overall ^b	12	6640	4336	0.85	(0.78–0.92)	<i>P</i> = 0.14 ^d	8	2164	1228	0.80	(0.71–0.89)	<i>P</i> = 0.01 ^d
None/Primary	12	873	447	0.72	(0.60–0.88)		8	352	132	0.47	(0.33–0.68)	
Secondary	12	2649	1879	0.78	(0.68–0.88)		8	660	410	0.73	(0.59–0.90)	
Tertiary	12	3118	2010	0.97	(0.86–1.09)		8	1152	686	0.96	(0.82–1.12)	

^aAdjusted for age, sex, ethnicity, parental education, and study. OR for parental education is adjusted for age, sex, ethnicity, and study

Prenatal B Vitamin Supplements & Childhood ALL by Mother's Ethnicity



Vitamin supplements before pregnancy	Hispanic mothers ^a 234 cases, 296 controls	White mothers ^a 265 cases, 374 controls
None	(Ref)	(Ref)
Moderate intake	1.12 (0.44-2.84)	1.25 (0.75-2.07)
High intake	0.36 (0.17-0.74)	0.76 (0.50-1.16)

Conditional logistic models adjusted for father's education, mother's education, household income, maternal age at child's birth, and nutrient intake from food. N= number of discordant pairs/triplets

*For folic acid, moderate intake is >0 & <600 µg and high intake is ≥600 µg. For vitamins B12, B6, and riboflavin, moderate intake is >0 & <5 µg B12 and <1.5 mg B6 and riboflavin, and high intake is ≥5 µg B12 and ≥1.5 mg B6 and riboflavin.

Singer, Cancer Causes and Control, 2016

Peri-conception Maternal Diet Healthy Eating Index (HEI) 2010



Modified HEI-2010	ALL 638 cases, 843 controls		AML 96 cases, 125 controls	
	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Continuous score ^a	0.88 (0.78-0.98)	0.02	0.76 (0.54-1.13)	0.19
Q1 (<12.5)	(Ref)		(Ref)	
Q2 (12.5-16)	0.71 (0.51-1.00)	0.06	0.65 (0.25-1.69)	0.43
Q3 (16-20)	0.73 (0.54-1.01)	0.06	0.60 (0.21-1.68)	0.26
Q4 (>20)	0.66 (0.47-0.93)	0.01	0.42 (0.15-1.15)	0.14

*Models adjusted for mother's ethnicity, father's education, mother's education, household income, maternal age at child's birth, and vitamin supplement use.

^a ORs reflect a 5 point increase in HEI-2010 score.

Breastfeeding and Childhood ALL

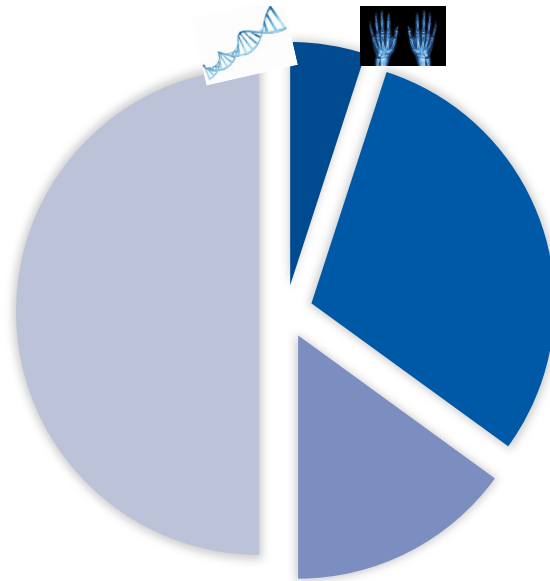


	No. of Studies	ALL		Controls		OR ^a	95% CI
		No.	%	No.	%		
Breastfeeding	11	7,399		11,181			
No		2,696	36.4	3,798	34.0	1.00	Referent
Yes		4,639	62.7	7,264	65.0	0.95	0.89, 1.02
Missing		64	0.9	119	1.0		
<6 months		2,899	39.2	4,324	38.7	1.01	0.94, 1.08
≥6 months		1,717	23.2	2,892	25.9	0.86	0.79, 0.94
Missing		87	1.2	167	1.5		
Breastfeeding duration							
1 month or less		1,318	17.8	1,896	17.0	1.06	0.97, 1.16
2–4 months		1,284	17.4	1,894	16.9	0.99	0.90, 1.08
5–7 months		793	10.7	1,303	11.7	0.90	0.81, 1.01
8–10 months		439	5.9	831	7.4	0.78	0.69, 0.89
11–13 months		393	5.3	690	6.2	0.83	0.72, 0.96
14 months or more		389	5.3	602	5.4	0.92	0.79, 1.06
Missing		87	1.2	167	1.5		

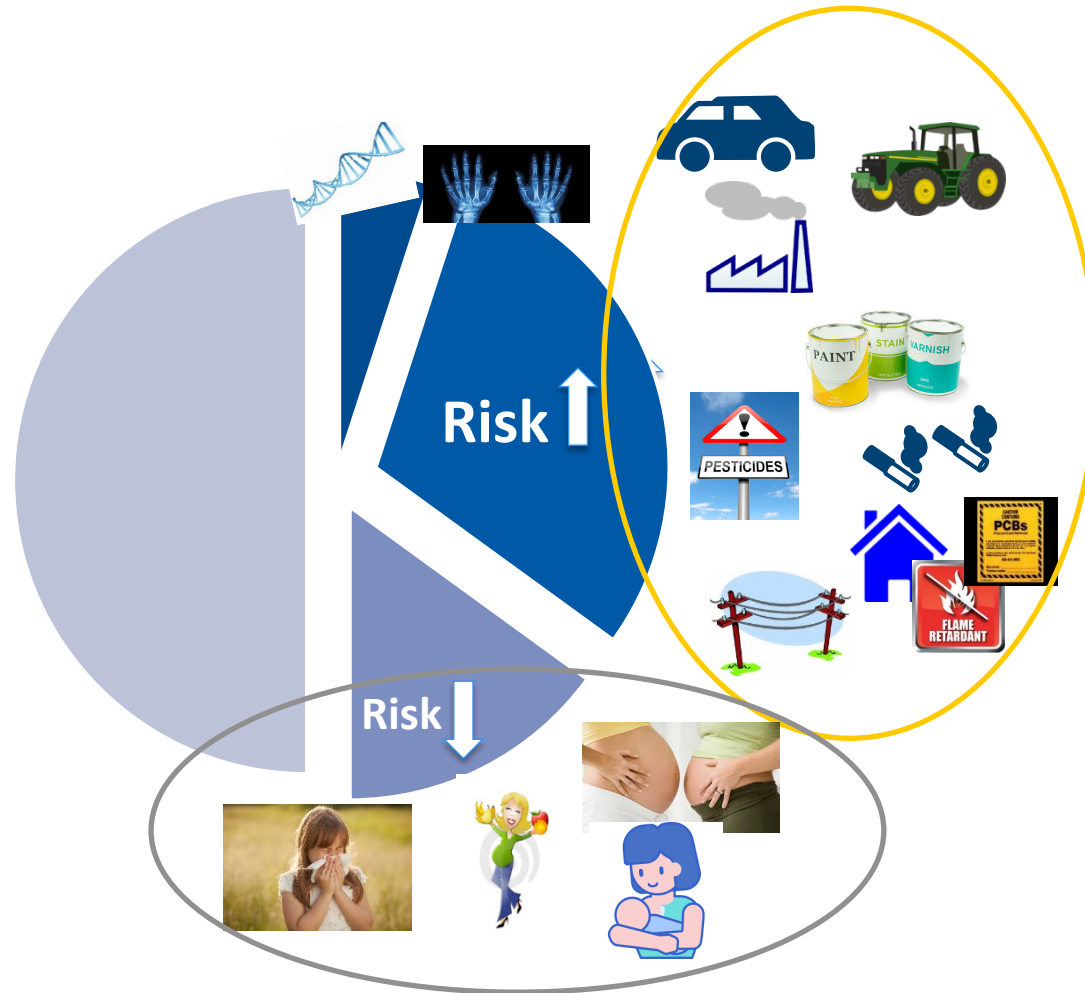
Rudant et al., AJE 2015

Known Risk Factors 25 years+ ago

genetic syndromes & x-rays
accounted for <10% of all childhood leukemia



Known Risk Factors Today



Whitehead, Curr Probl Pediatr Adolesc Health Care 2016; 46(10):317-352

Metayer, pediatrics. 2016; 138(Suppl 1): S45-S55

Concluding Remarks

- **POPULATION-BASED EPIDEMIOLOGIC STUDIES HAVE PROVIDED “ENOUGH” EVIDENCE TO START PREVENTION**
 - **Reduce** exposure to multiple harmful chemicals from multiple sources
 - **Increase** healthy diet during pregnancy and breastfeeding
- **WHAT WE HAVE NOT (FULLY) ADDRESSED**
 - **CUMULATIVE IMPACT** of those exposures, including social determinants
 - **CONTRIBUTION OF GENETIC** susceptibility
 - **MECHANISTIC PATHWAYS**
 - **ENVIRONMENTAL IMPACT IN CANCER SURVIVORS**

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Childhood Leukemia and Primary Prevention



Todd P. Whitehead, PhD,^{a,b} Catherine Metayer, MD, PhD,^{a,b}
 Joseph L. Wiemels, PhD,^{b,c} Amanda W. Singer, PhD,^a and Mark D. Miller, MD, MPH^{b,d}
Curr Probl Pediatr Adolesc Health Care 2016;46:317-352



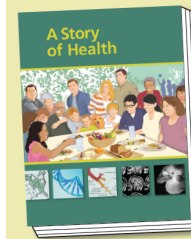
Childhood Leukemia: A Preventable Disease

Catherine Metayer, MD, PhD,^a Gary Dahl, MD,^b Joe Wiemels, PhD,^c Mark Miller, MD, MPH^d
 PEDIATRICS Volume 138, number s1, November 2016



About the eBook:

An interactive document with multiple chapters features prompts for embedded information and links to online resources.



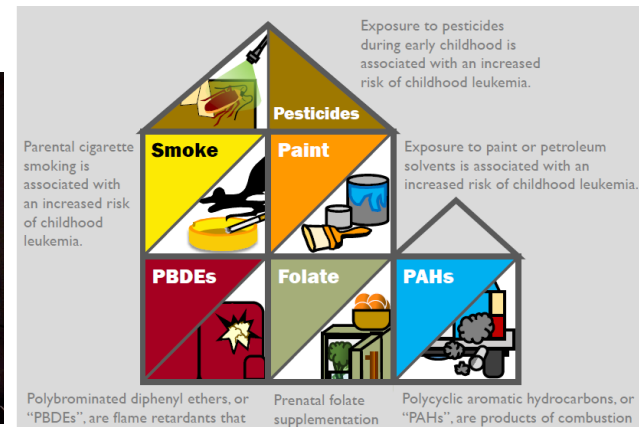
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Catherine Metayer has no financial relationships to disclose or conflicts of interest to resolve