Childhood Leukemia: A Preventable Disease?

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(Comments do not represent state of California)

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Berkeley UNIVERSITY OF CALIFORNIA

Center for Integrative Research on Childhood Leukemia and the Environment

PEHSU Pediatric Environmental Health Specialty Units

No disclosures

Two Different Questions

- Why did this patient get this disease at this time?

- Or, Why does this population have a higher incidence?

Disease prevention and response after diagnosis is not just an individual responsibility. It belongs to the community as well.

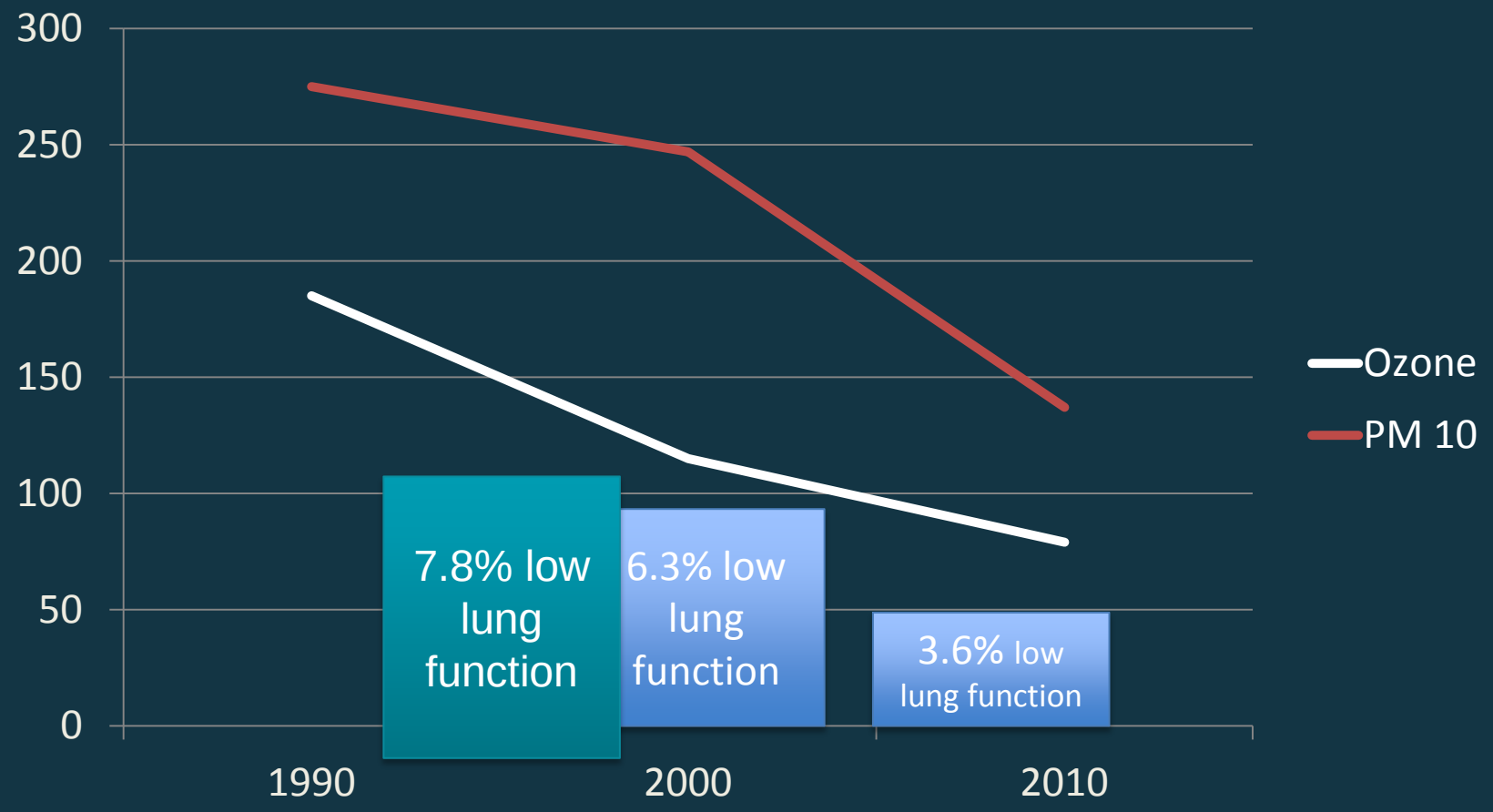
- North Karelia
  - In 35 years cardiac mortality decreased 85%

Creative commons: Strokin.Ru
http://commons.wikimedia.org/wiki/File:Kolin_finland.jpg

MaSii
http://commons.wikimedia.org/wiki/File:Juuankirkko.jpg

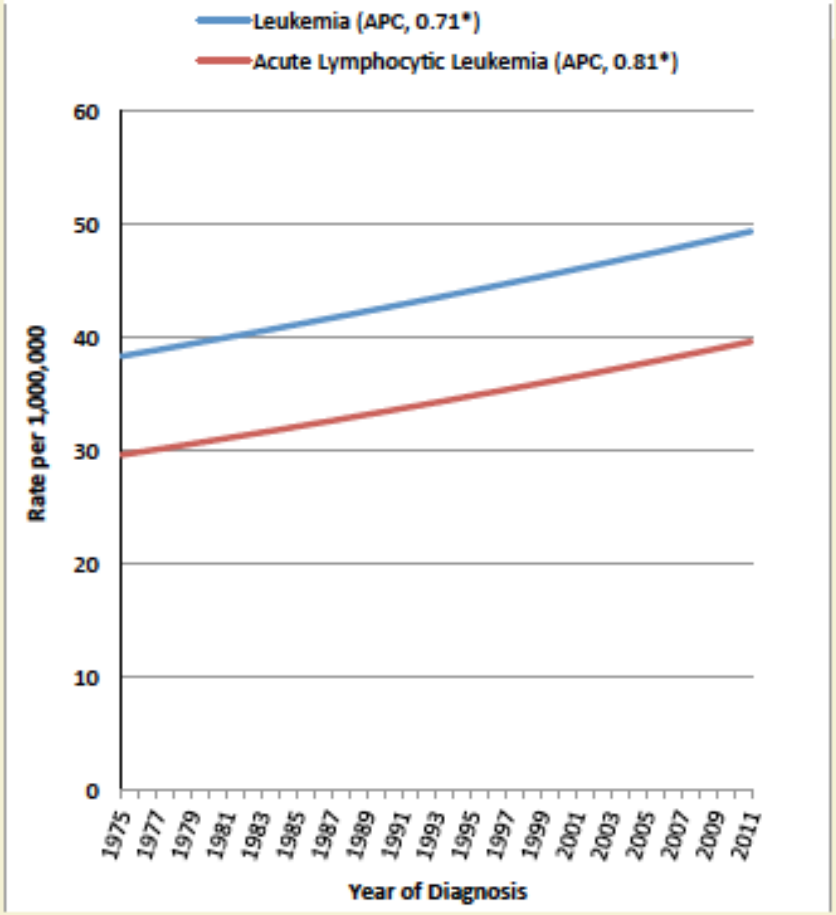
Puska P.. Prog Cardiovasc Dis. 2010; 53(1):15-20

Days exceeding CA standards for Ozone (1 hr) and PM10 (24 hr) (South Coast air basin Data California Air resources Board)



Gauderman WJ et al. N Engl J Med 2015;372:905-913 USC Children's Health Study

Trends in the Age-Adjusted Incidence Rate of Childhood Leukemia and Acute Lymphocytic Leukemia, Ages 0-14, SEER 9, 1975-2011



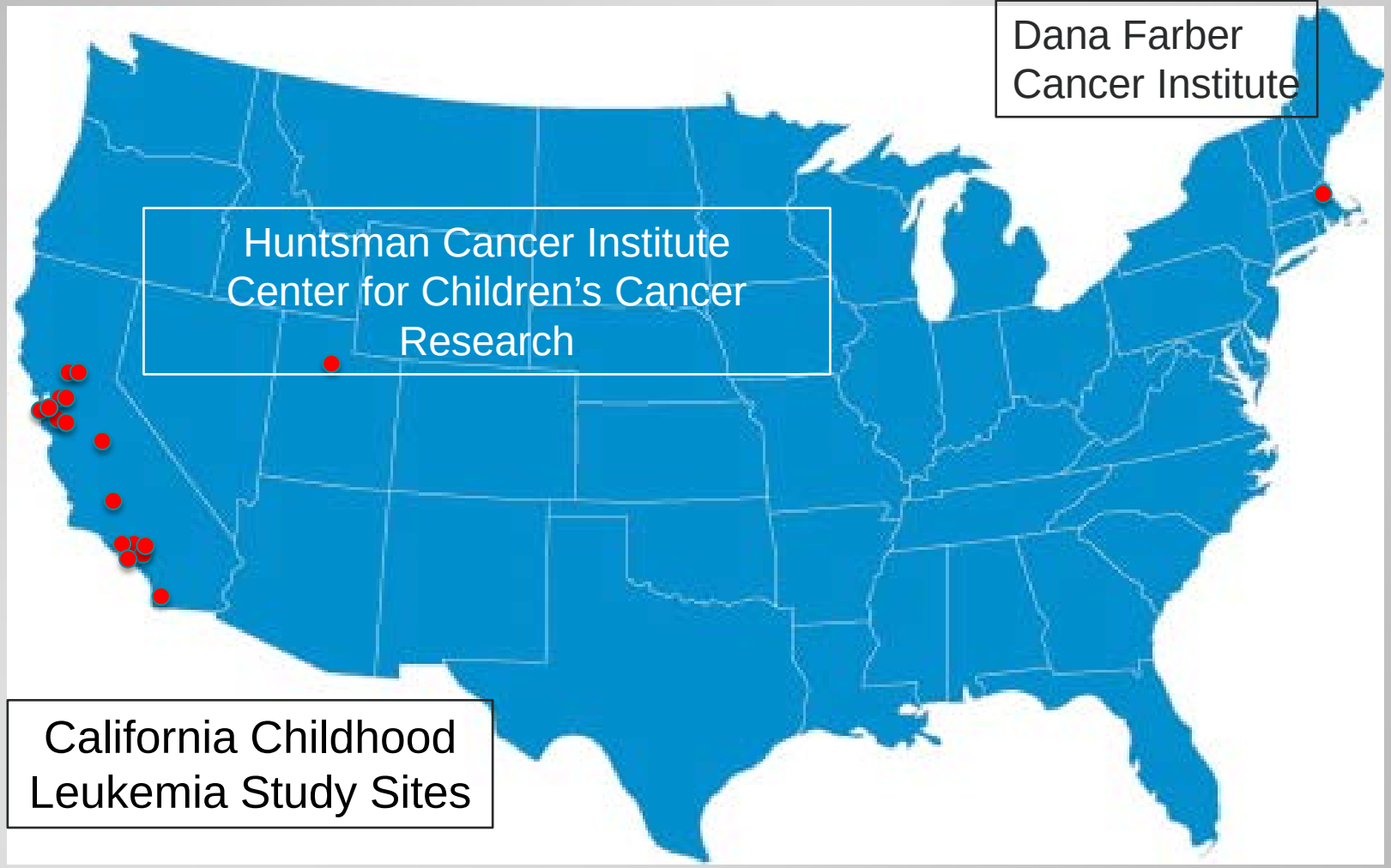
*The Annual Percent Change (APC) is significantly different from zero at alpha=0.5

Source: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 9 Regs Research Data, Nov 2013 Sub (1973-2011) <Katrina/Rita Population Adjustment>

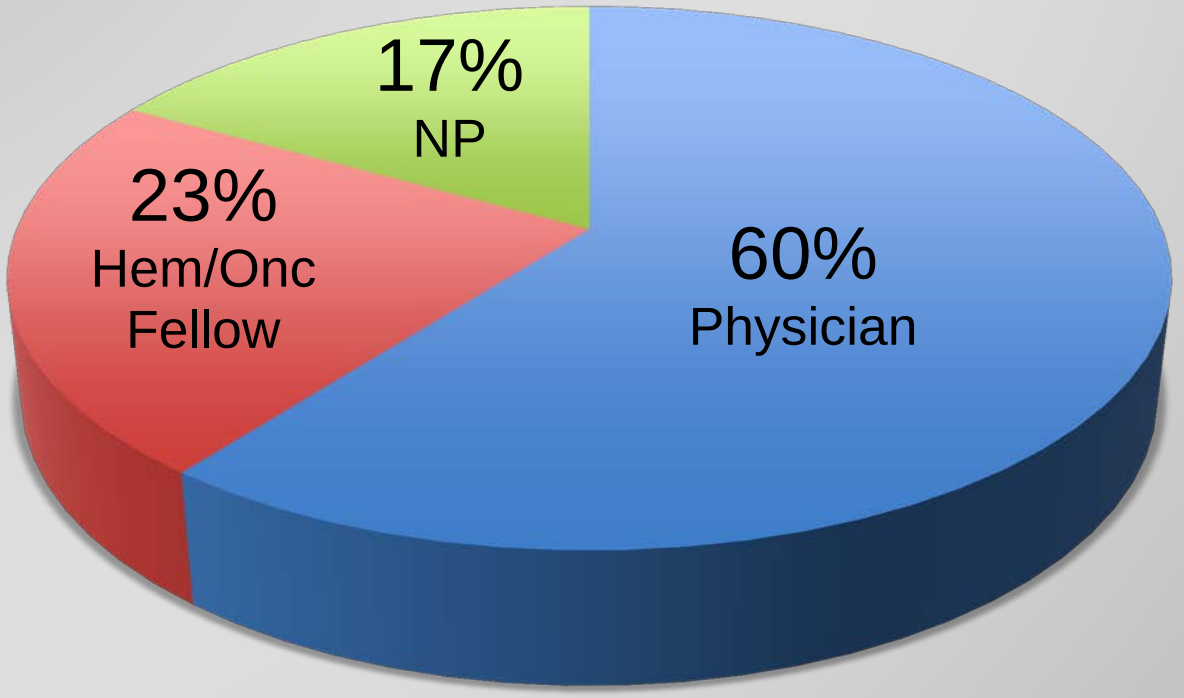
Graphic used with permission.

Story of Health
Used with permission

Participating Survey Networks

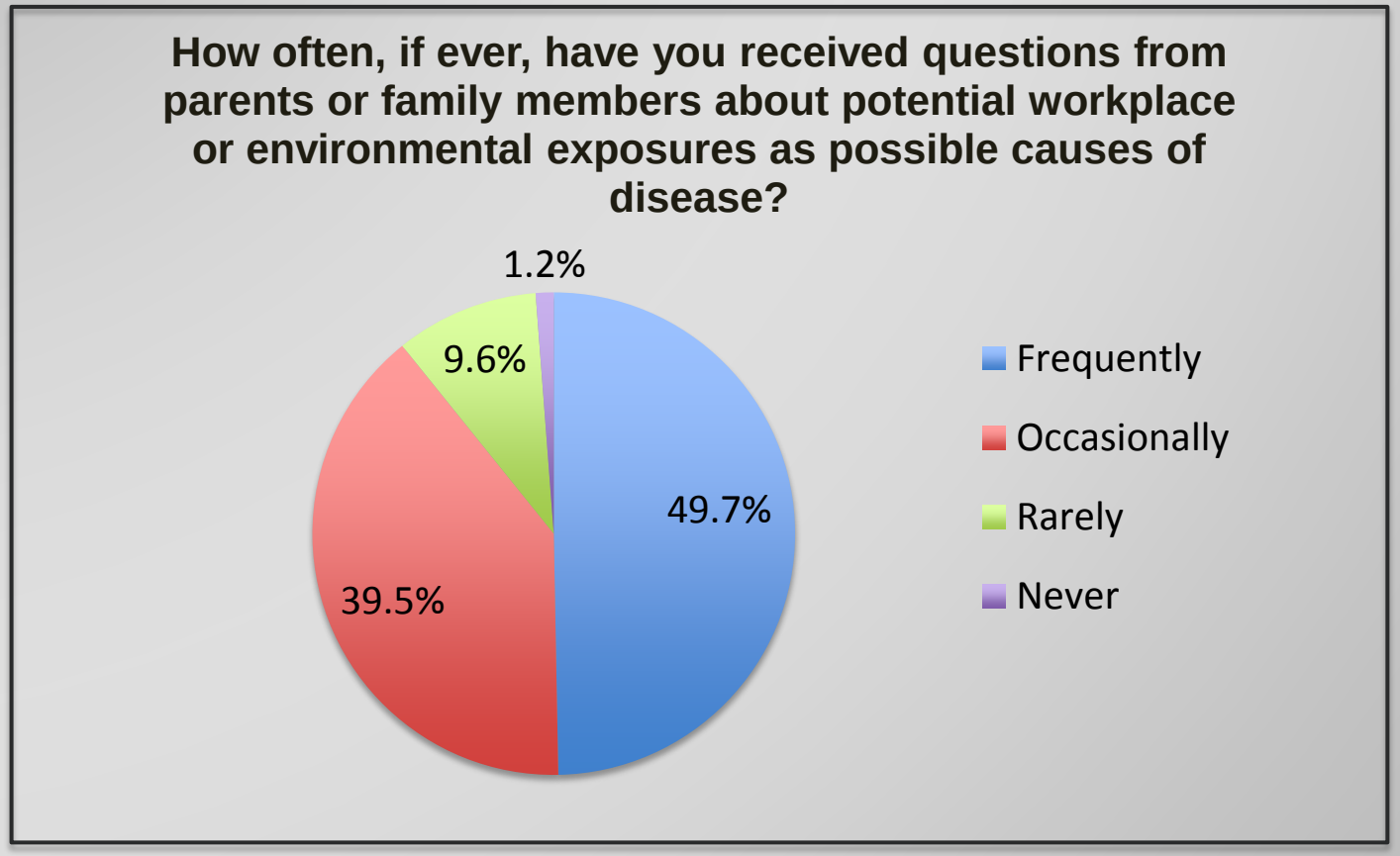


Survey Respondents
N = 191/427 (45% Response)

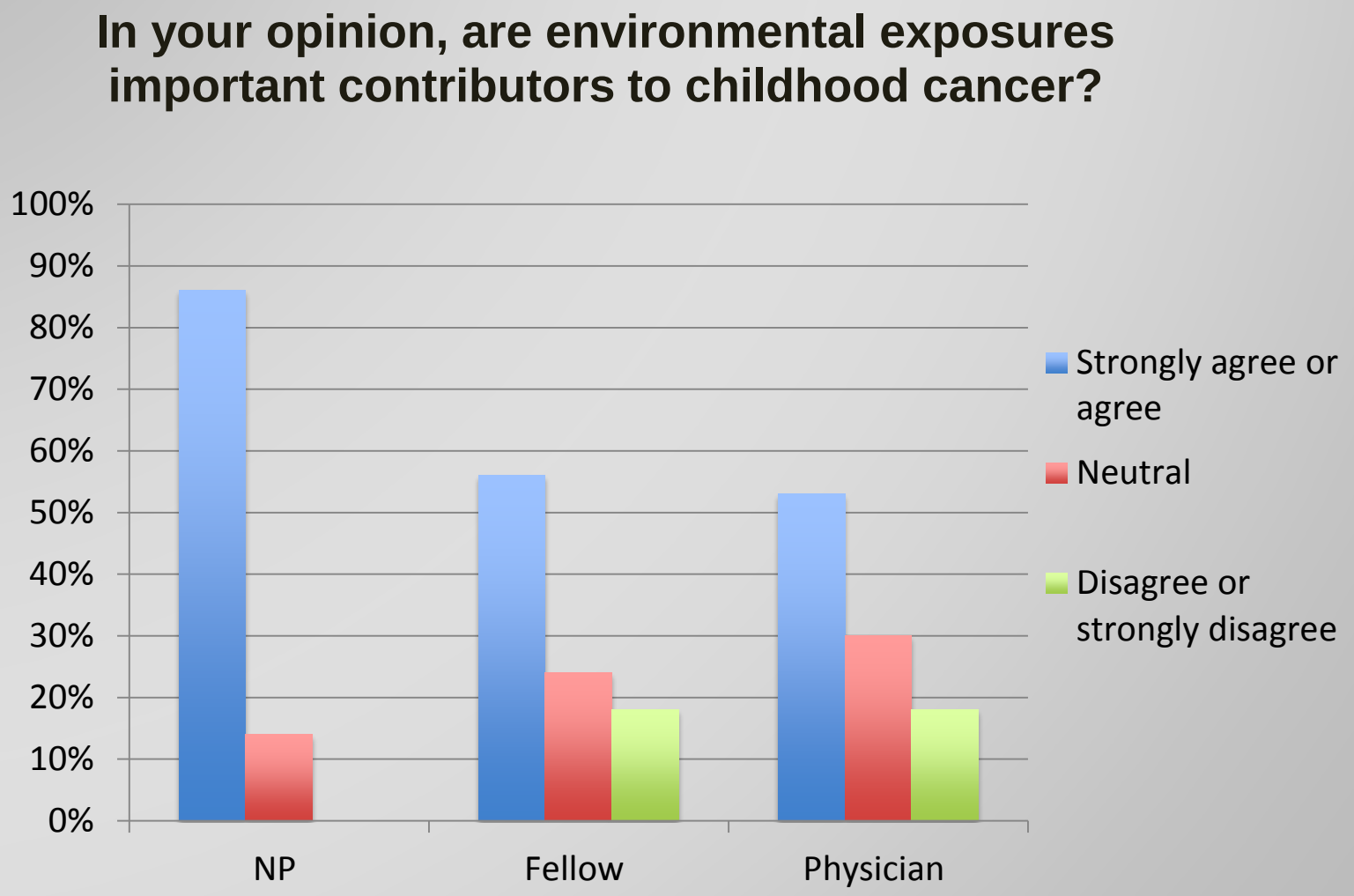


• 89% said they “frequently” or “occasionally” received questions from patients about potential environmental causes

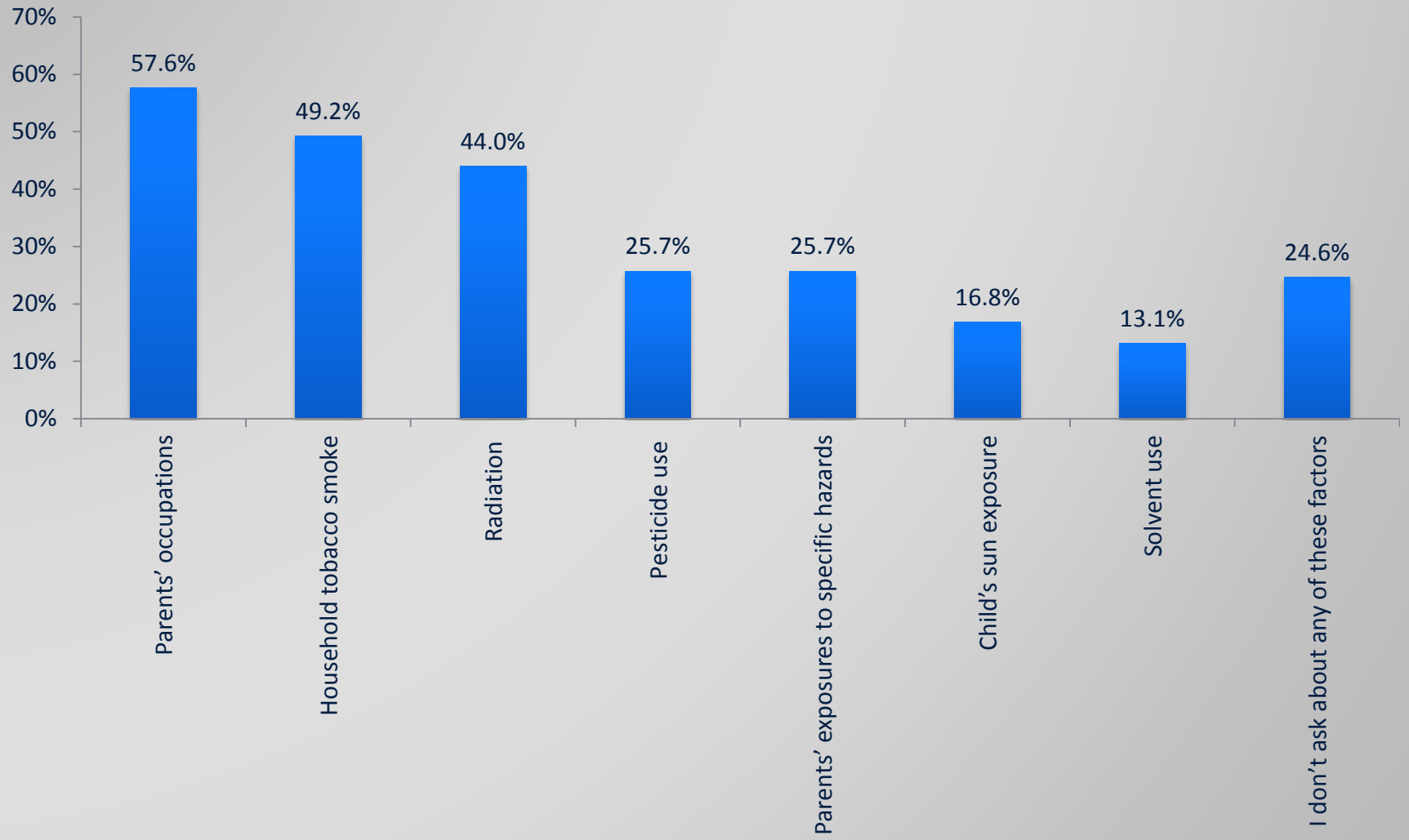
•Around half felt “somewhat uncomfortable” or “not at all comfortable” responding to these questions



Environmental Exposures as Contributors

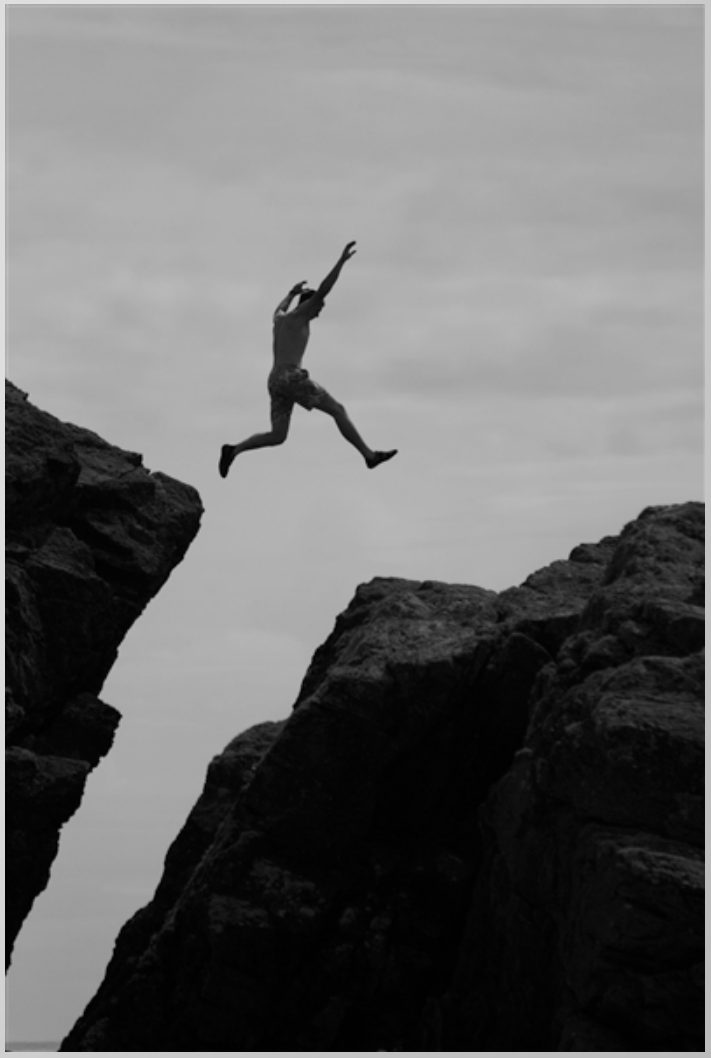


As part of your patient's history, do you collect information on potential exposures to any of the following external factors?



Knowledge Gap

- Only 6% had ever received training specifically for taking an environmental history
- 92% reported they would find it helpful to have more information about the association between childhood cancers and environmental exposures



Integrating Environmental Health

- Improved patient-provider communications
- Enhanced data collection
- Role of alert clinicians in informing research agendas

Causality vs. Association

Bradford Hill

- Strength
- Consistency
- Specificity
- Temporality
- Biologic gradient
- Plausibility
- Coherence
- Experiment and analogy

Hill AB. The environment and disease: association or causation? Proceedings of the Royal Society of Medicine. 1965;58:295–300

So! How is everybody today?

A Story of Health

Story of Health
with permission

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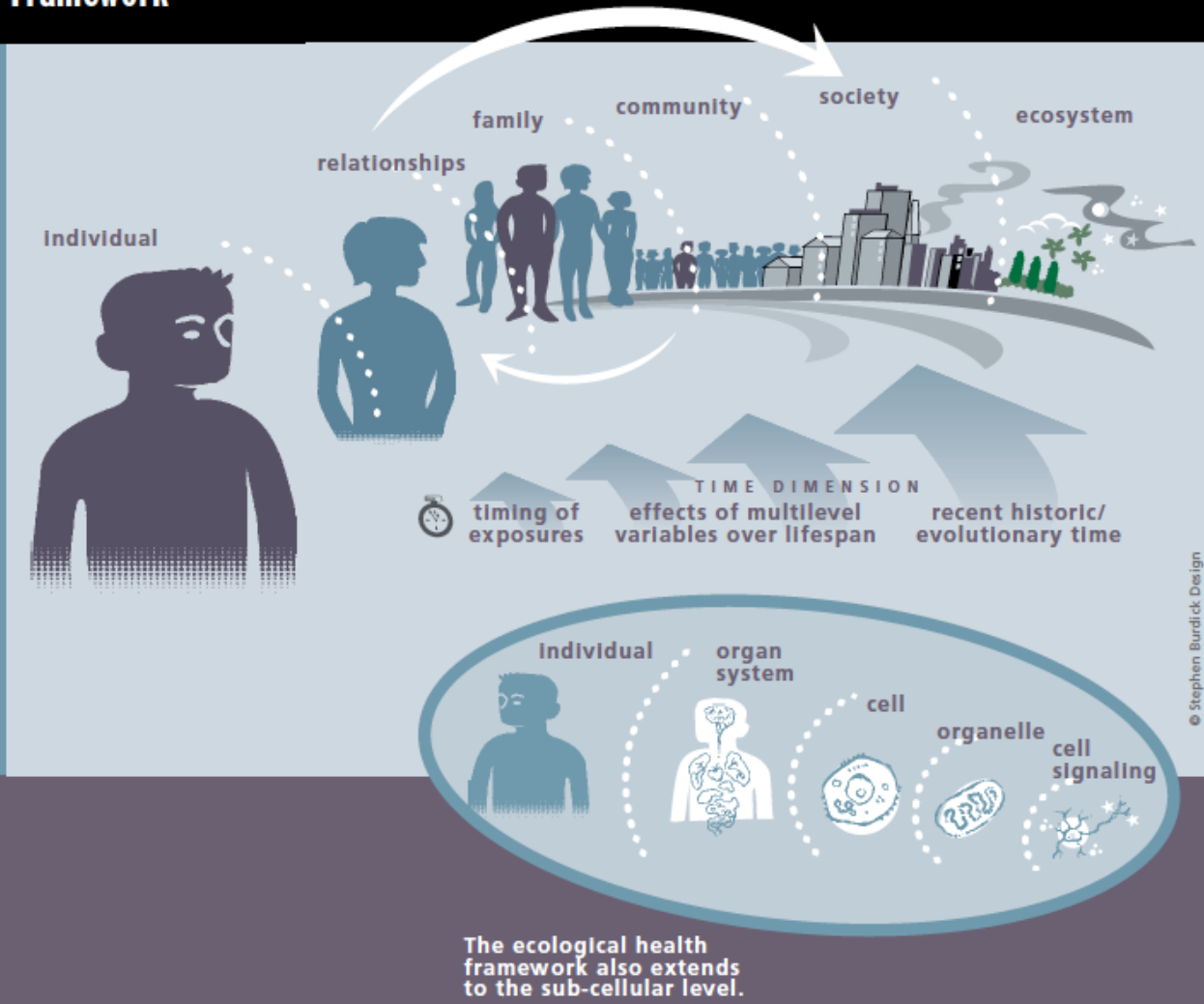
INTRODUCTION Ecological Health Framework

The ecological framework can include multiple levels from sub-cellular to societal.

It is not hierarchical in the sense that one level is more important than another, but rather in the sense that individual biology is progressively nested within the person, family, community, society and ecosystem.

The interactions and feedback loops within, across, and among these levels are complex and variable. They exert their influences on health across time.



The ecological health framework also extends to the sub-cellular level.

Story of Health with permission graphic: Burdick Design

A Story of Health

Help Page | Reunion Home | Asthma | Cancer (Childhood Leukemia) | Learning/ Developmental Disabilities | Diabetes | Infertility | Cognitive Decline | References | Go Back ←

A FAMILY REUNION Six Stories

This page is your portal to six stories of health.

It is recommended that you read through the introduction first and then choose stories in the order you wish.

Health professionals can receive CE credits for completing *A Story of Health*. Click here for more details.

Choose stories in the order you wish. Select a disease term to highlight the affected person. Click the arrow button to read his or her fictional story of health.

Asthma | Cancer | Learning/ Developmental Disabilities | Diabetes | Infertility | Cognitive Decline

Story of Health with permission

Stephen is a 3-year-old boy who lives with his parents David and Tricia in a suburb in Connecticut.

He is an only child, and his parents spend as much time as they can with him even though they manage a successful plant nursery and garden center.

He spends four days a week at child care and is with his parents the other three days, sometimes at their house and sometimes at the garden center.

Stephen had been an active toddler, but during the past month, Tricia noticed that Stephen was not as lively and energetic as usual. His child care providers also mentioned this.

When he became listless and started to run a fever, Tricia became concerned. She took Stephen to see his pediatrician, Dr. Jones.

(*a fictional case)

Story of Health with permission

CHILDHOOD LEUKEMIA Stephen's Story

After talking with Tricia and examining Stephen, Dr. Jones was also concerned. She confirmed that Stephen appeared ill and that the cause could be a number of things. She said she needed laboratory tests to make an accurate diagnosis.

Dr. Jones ordered blood tests that could be done at the local hospital and called to make an appointment for Stephen to get his blood drawn that same day.

Tricia was upset and called her husband David with the news. She started to ask a lot of questions. Dr. Jones tried to calm her and said she would call her as soon as she had the results.

Tricia brought Stephen to the hospital laboratory for the tests and went home very worried.

Story of Health with permission

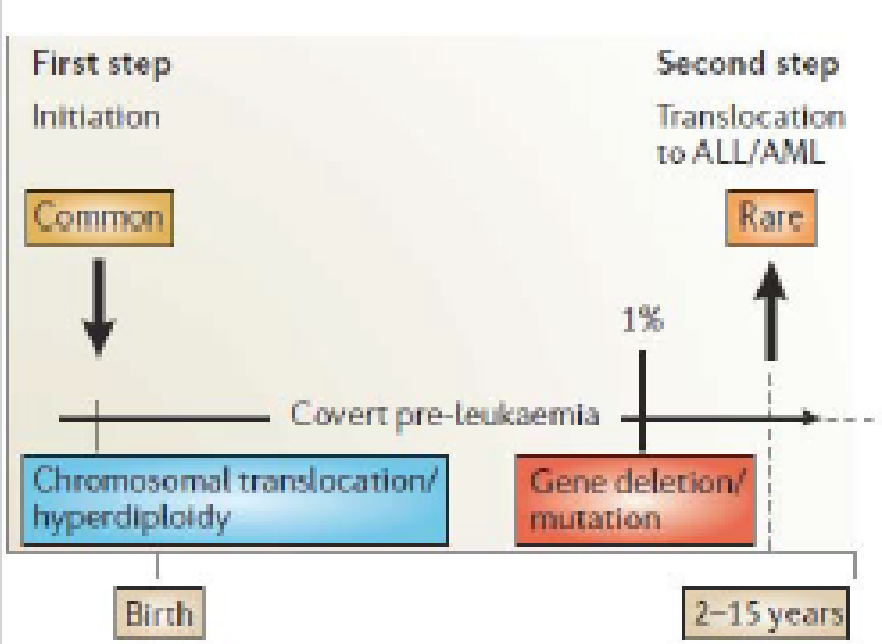
Story of Health: Paintings by Susan Macfarlane used with permission

Changes to DNA that cause leukemia:

Two-Hit Model Hypothesis

Childhood leukemia results from more than one insult to DNA

Researchers consider cancer to often be a result of more than one temporal event. For childhood ALL and AML, there are two exposure windows: one prenatal (before conception or in utero), when leukemia is commonly initiated through chromosomal rearrangements, and a second, postnatal window that is linked to the emergence of overt disease through secondary genetic changes.



This model is supported by evidence that the genetic changes are far more frequent than the actual disease. This suggests that initiation of leukemia may be a common event, but the second "hit" that transitions to ALL or AML is rare (Greaves, 2006).

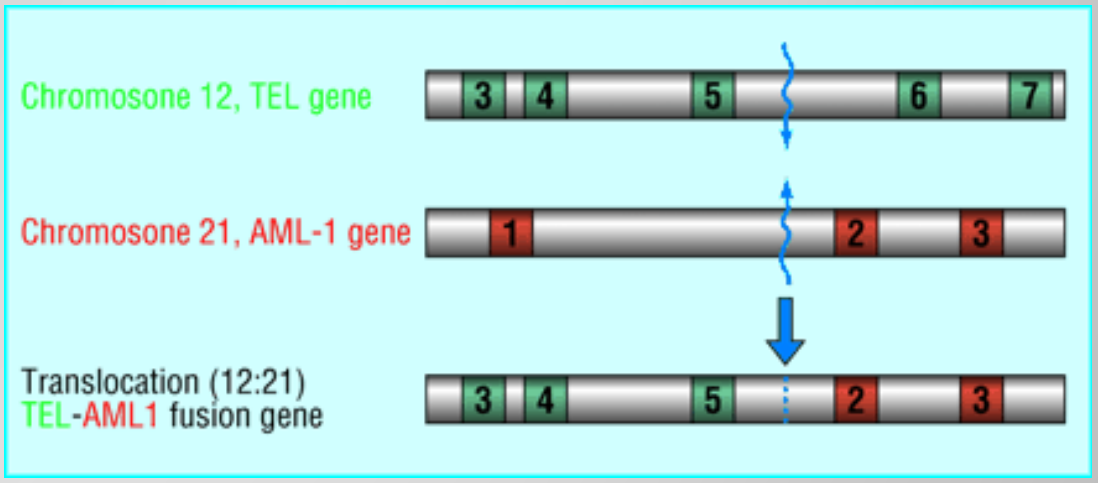
Note: 1% refers to an estimated frequency of transition between covert pre-leukemia and overt clinical leukemia. Infant ALL and AML (<1 year of age) has a much-abbreviated natural history in which all the necessary genetic events are thought to occur prenatally.

Greaves, 2006, graphic used with permission.

Leukemia Result of Hyperdiploidy or Translocations

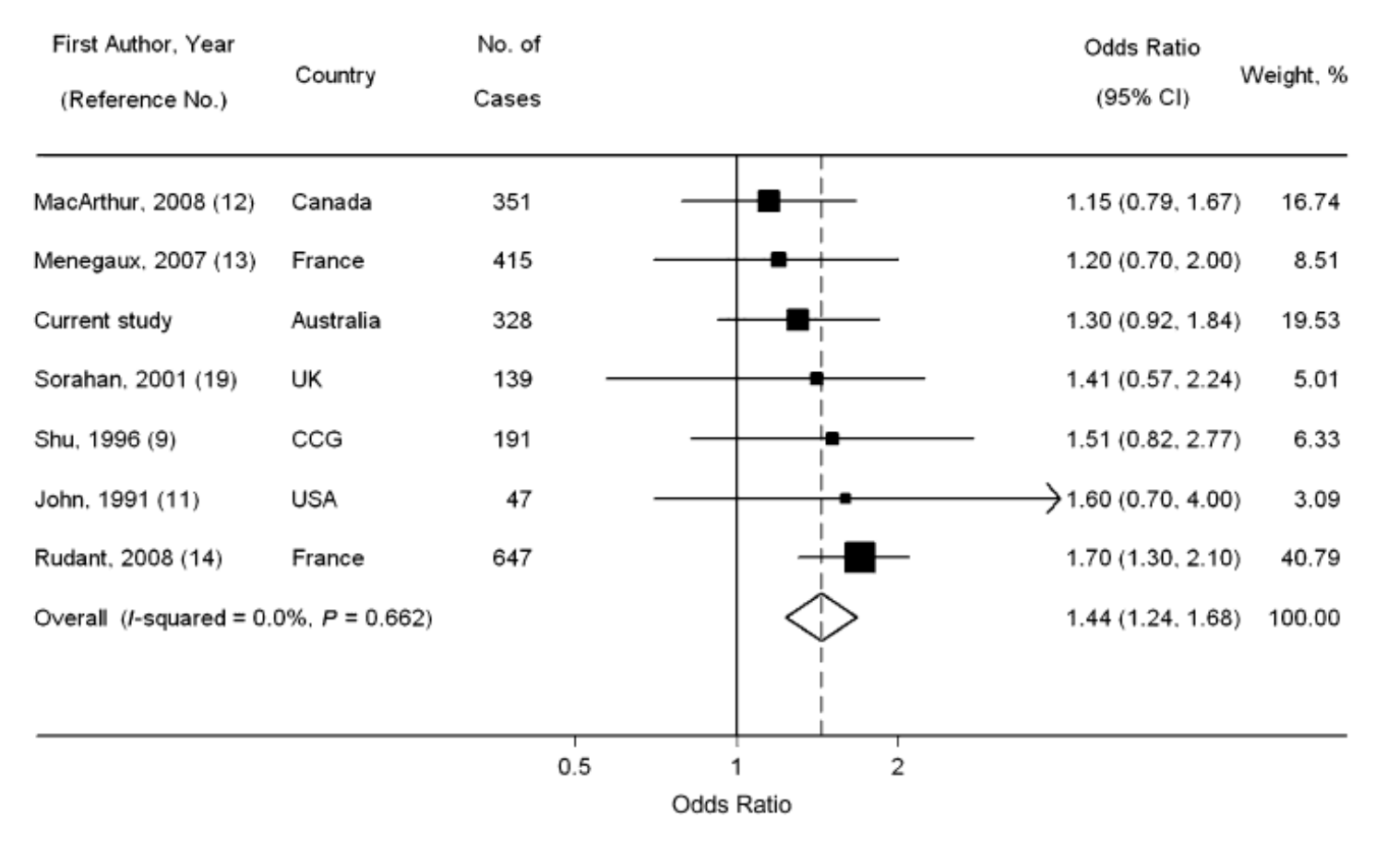
Translocations Associated with ALL: *TEL-AML1* Gene Fusion

Common genetic event in ALL:
there is a shift of genes between chromosome 12 and 21.



- Occurs in approximately 20-25% of patients with ALL with peak incidence between ages 2 – 5 years.
- Strong evidence that this occurs *in utero.*
- Frequency of this translocation at birth is 100-fold greater than the risk of developing the corresponding leukemia.

Meta-analysis Paternal Smoking around Conception (> 20cpd vs. none)



Milne et al., Am J Epidemiology 2012

Critical Periods of Exposure to Tobacco Smoke and Risk of Childhood B-cell ALL

Mother smoked before birth	Child exposed to passive smoking	Number of cases (n=689)	Number of controls (n=975)	OR (95% CI)
No	No	527	777	Reference
No	Yes	9	21	0.59 (0.22-1.28)
Yes	No	63	67	1.14 (0.80-1.79)
Yes	Yes	85	96	1.05 (0.74-1.51)

The odds ratios are derived from logistic regression, adjusted for age, sex, race/ethnicity, household income, and paternal smoking.

Metayer C et al. CEBP, 2013

Critical Periods of Exposure to Tobacco Smoke and Risk of Childhood B-cell ALL

Father smoked before birth	Child exposed to passive smoking	Number of cases (n=689)	Number of controls (n=975)	OR (95% CI)
No	No	444	670	Reference
No	Yes	90	127	0.94 (0.69-1.27)
Yes	No	44	74	0.90 (0.57-1.41)
Yes	**Yes**	**104**	**88**	**1.60 (1.07-2.38)***

The odds ratios are derived from logistic regression, adjusted for age, sex, race/ethnicity, household income, and maternal smoking.
*p-value for interaction<0.05

Metayer C et al. CEBP, 2013

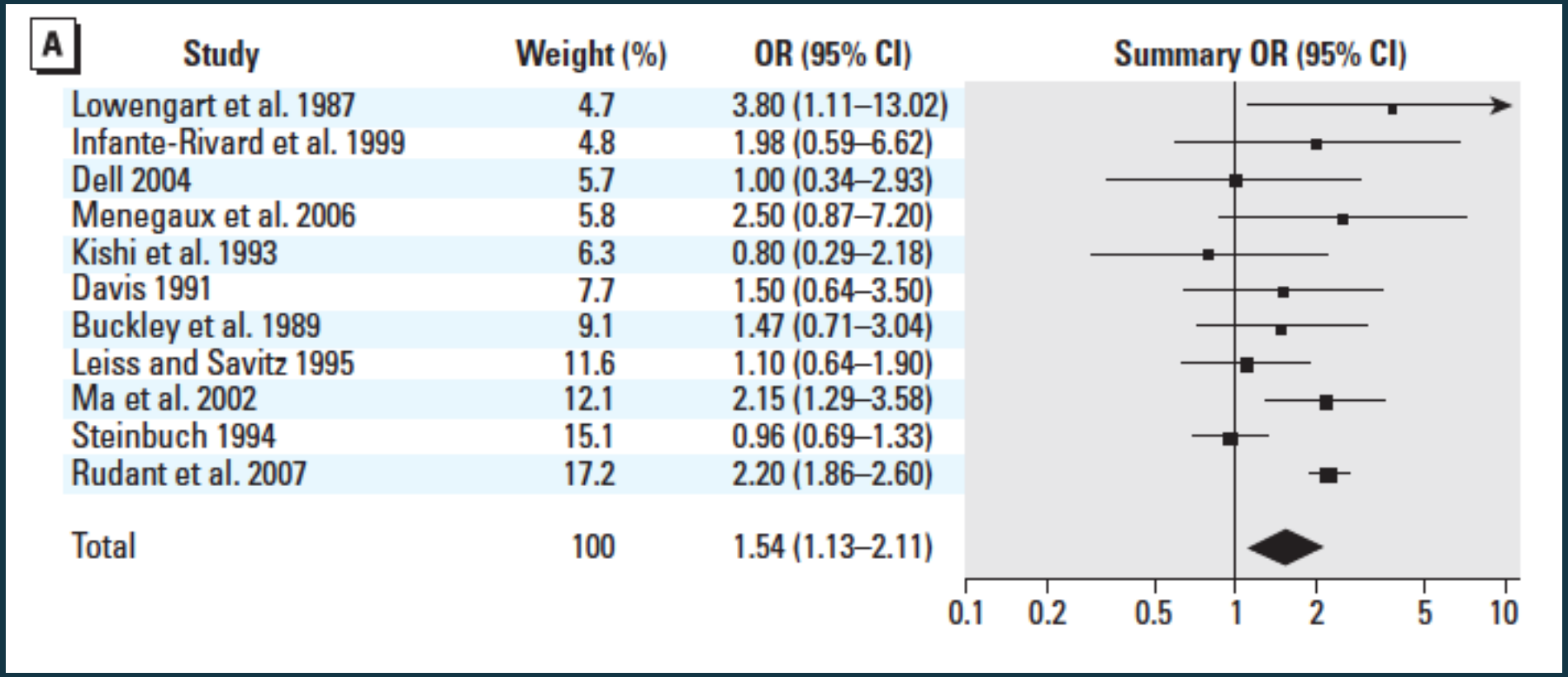
Joint Effect of Paternal Smoking and Risk of Childhood B-cell ALL with t(12;21)

Father smoked before birth	Child exposed to passive smoking	Number of cases (n=130)	Number of controls (n=975)	OR (95% CI)
No	No	82	670	Reference
No	Yes	12	127	0.69 (0.36-1.40)
Yes	No	8	74	0.85 (0.37-1.96)
Yes	**Yes**	**26**	**88**	**2.08 (1.04-4.16)***

The odds ratios are derived from logistic regression, adjusted for age, sex, race/ethnicity and household income.
*p-value for interaction<0.01

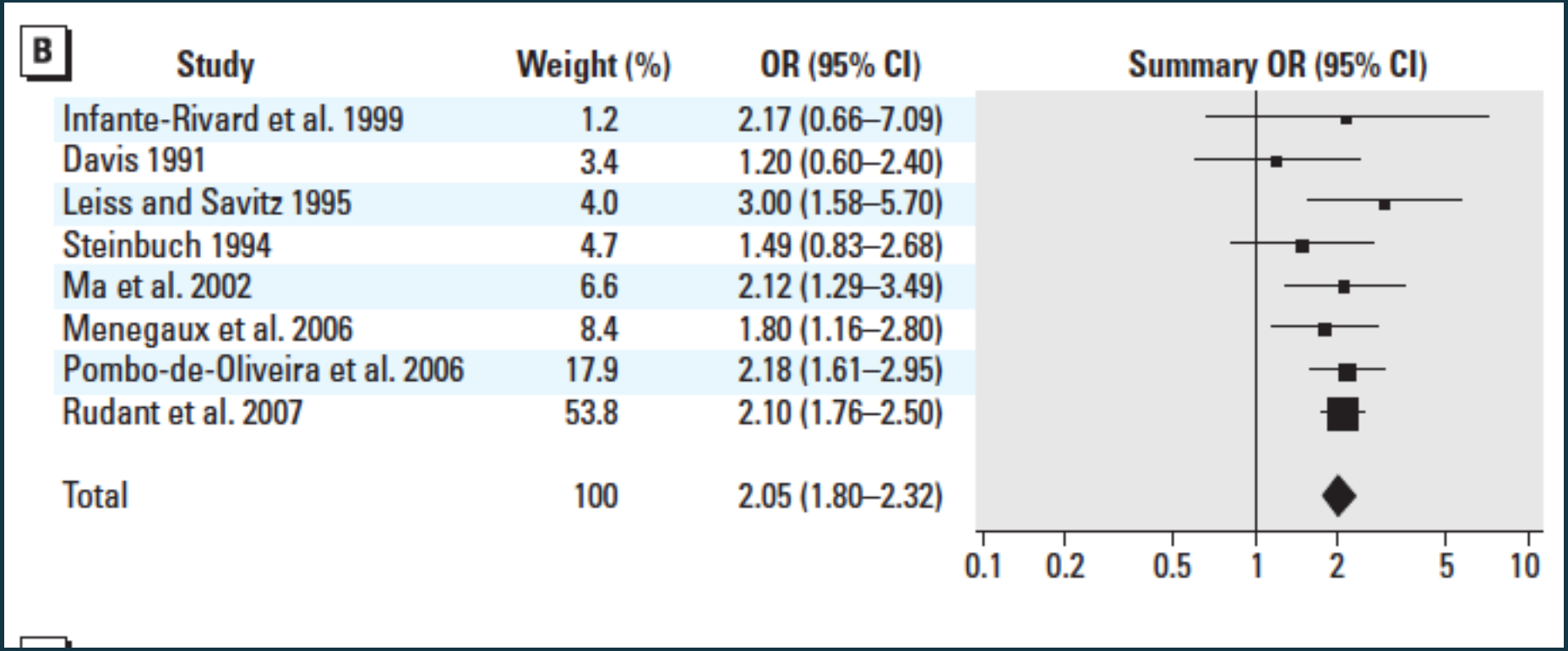
Metayer C et al. CEBP, 2013

Residential Pesticide (unspecified) During Pregnancy and Child ALL



Turner et al., Environmental Health Perspectives 2011

Residential Insecticide During Pregnancy and Child ALL

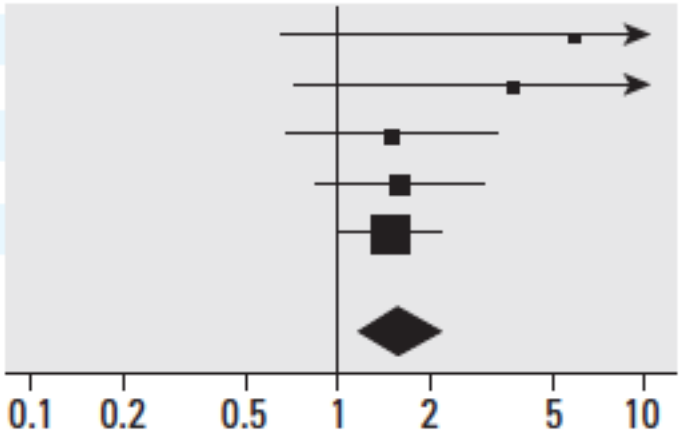


Turner et al., Environmental Health Perspectives 2011

ALL - Residential Herbicides During Pregnancy

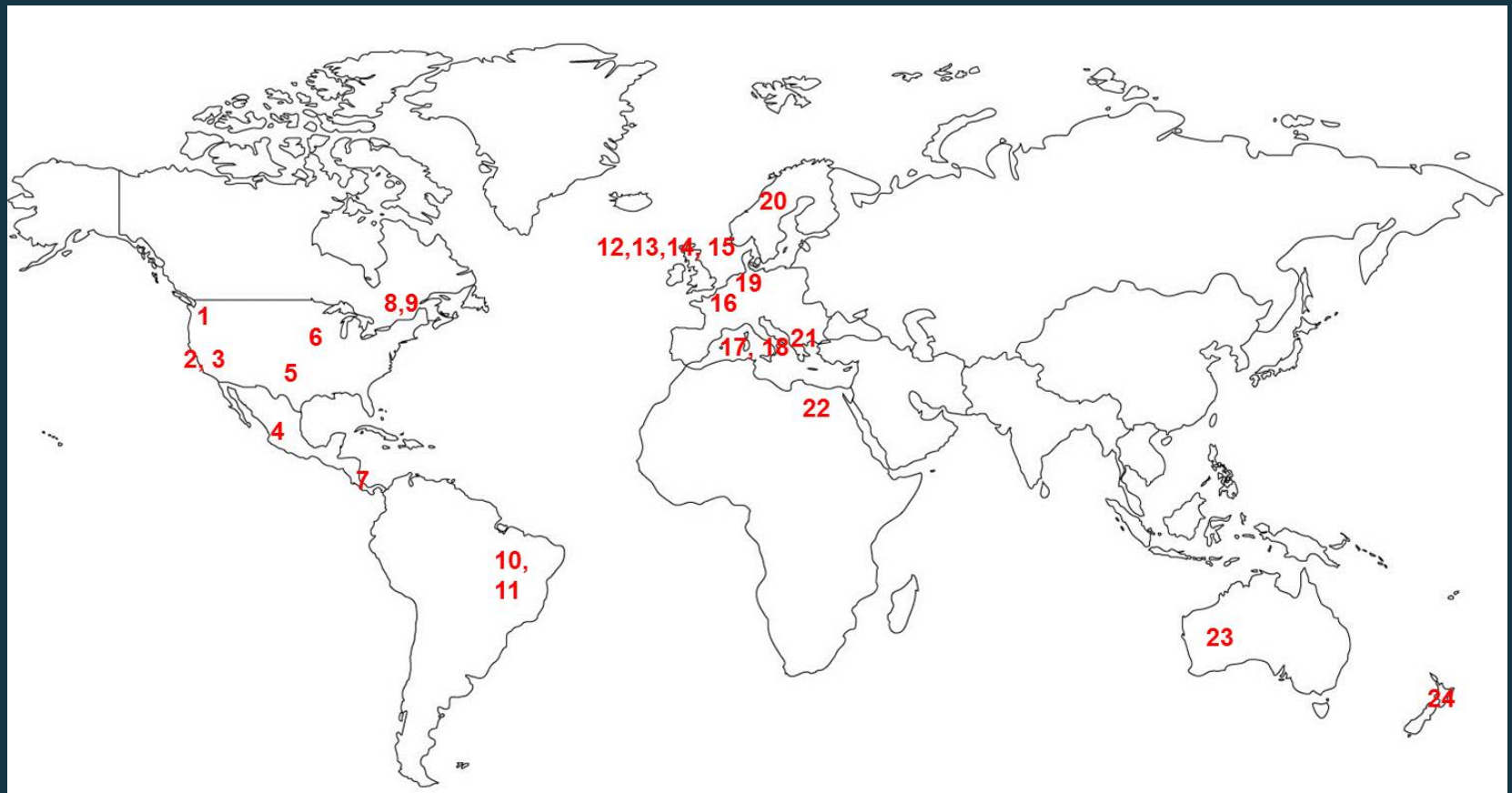
C

Study	Weight (%)	OR (95% CI)
Menegaux et al. 2006	1.8	5.90 (0.67–52.00)
Infante-Rivard et al. 1999	3.2	3.72 (0.73–19.06)
Davis 1991	13.9	1.50 (0.68–3.30)
Ma et al. 2002	22.1	1.60 (0.86–2.99)
Rudant et al. 2007	58.9	1.50 (1.02–2.20)
Total	100	1.61 (1.20–2.16)



Turner et al., Environmental Health Perspectives 2011

Childhood Leukemia International Consortium (23 studies)



Principal Investigators/designated co-investigators, study area (from left to right): 1) Beth Mueller, Parveen Bhatti, Washington State, USA; 2) Catherine Metayer, California State, USA; 3) Julia Heck, California State, USA; 4) Juan Manuel Mejía-Arangure, Mexico; 5) Michael Scheurer, Melissa Bondy, Texas State, USA; 6) Logan Spector, USA; 7) Patricia Monge, Costa Rica; 8) Claire Infante-Rivard, Quebec, Canada; 9) Daniel Sinnett, Quebec, Canada; 10) Maria Pombo-de-Oliveira, Sergio Koifman, Brazil; 11) Victor Wünsch Filho, Sao Paulo, Brazil; 12) Eve Roman, Tracy Lightfoot, UK; 13) Jill Birch, Malcolm Taylor, Pamela Thompson, Manchester, UK; 14) Michael Murphy, Kate O'Neill, UK; 15) Richard McNally, Newcastle, UK; 16) Jacqueline Clavel, France; 17) Corrado Magnani, Italy; 18) Marco Vinceti, Reggio Emilio, Italy; 19) Joachim Schüz, Peter Kaatsch, Germany; 20) Mats Heyman, NOPHO, Scandinavia; 21) Eleni Petridou, Nick Dissypris, Greece; 22) Sameera Ezzat, Egypt; 23) Elizabeth Milne, Bruce Armstrong, Australia; 24) John Dockerty, New Zealand.

Parental Occupational Exposure to Pesticides and Child Leukemia

	Mother during pregnancy					Father around conception				
Leukemia type	Study *N*	Total *N*; case/control	Summary OR (95% CI)[1,2]	I^2	Maximum percentage difference when individual studies removed in turn	Study *N*	Total *N*; case/control	Summary OR (95% CI)[1,2]	I^2	Maximum percentage difference when individual studies removed in turn
ALL	12	8236/14850	1.03 (0.77, 1.38)	11.2	8.4	12	8157/14201	1.22 (0.94, 1.58)	68.7	7.8
B Cell	12	6529/14850	1.04 (0.78, 1.38)	0.0	7.7	12	6449/14201	1.14 (0.85, 1.54)	71.4	10.1
T Cell	7[3]	526/10726	1.66 (0.88, 3.14)	0.0	25.8	10[3]	784/13681	1.86 (1.34, 2.58)	5.4	10.3
AML	5[3]	895/5428	2.69 (1.49, 4.86)	0.0	23.9	8[3]	1184/10863	1.12 (0.72, 1.70)	32.2	10.8

[1]The random effects model was used to calculate the summary OR.
[2]OR comparing Category 1 (High likelihood of pesticide exposure) to Reference Category 4 (No or minimal likelihood of pesticide exposure).
[3]Studies without any cases in Category 1 (High likelihood of pesticide exposure) were not included in the meta-analysis.

Bailey et al., International Journal of Cancer
4 APR 2014 DOI: 10.1002/ijc.28854
http://onlinelibrary.wiley.com/doi/10.1002/ijc.28854/full#ijc28854-fig-0002

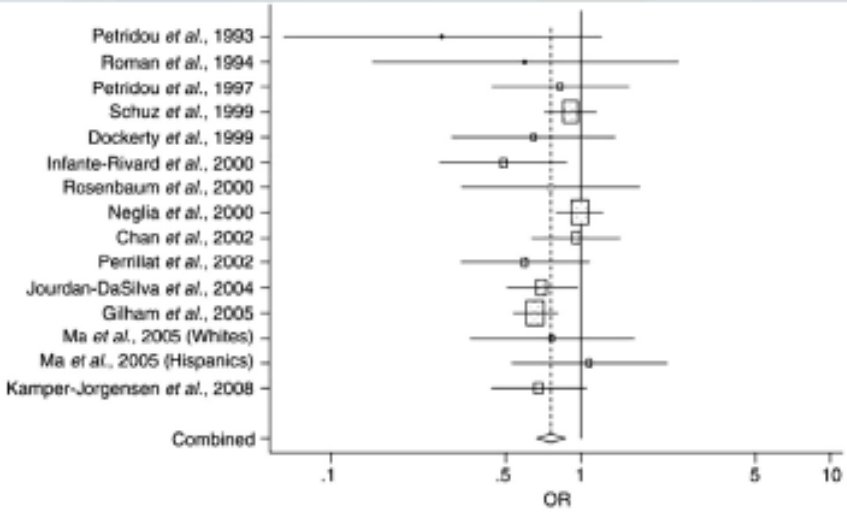
Infection as a protective factor

IMMUNE SYSTEM MODULATION:

Exposure to Common Childhood Infections May Modulate the Immune System and Reduce Leukemia Risk

One meta-analysis of 14 studies (shown below) indicates that day-care attendance is associated with a reduced risk of ALL (OR = 0.76) (Urayama et al., 2010). Day-care was used as a surrogate measure of exposure to common infections early in life. This reduced risk supports the hypothesis that common infections can be protective against exaggerated responses by the immune system that may be implicated in childhood leukemia.

Another study used month of birth, timing of birth in relation to cold and flu season, and birth order as markers of exposure to infections. They found an increased risk of developing leukemia in children born in the spring and summer and who experience cold and flu season at 9-12 months old (OR = 1.44) (Marcotte et al., 2014). This may indicate that early mild infections could be protective against leukemia.



Urayama et al, 2010.
Graphic used with permission.

Folate

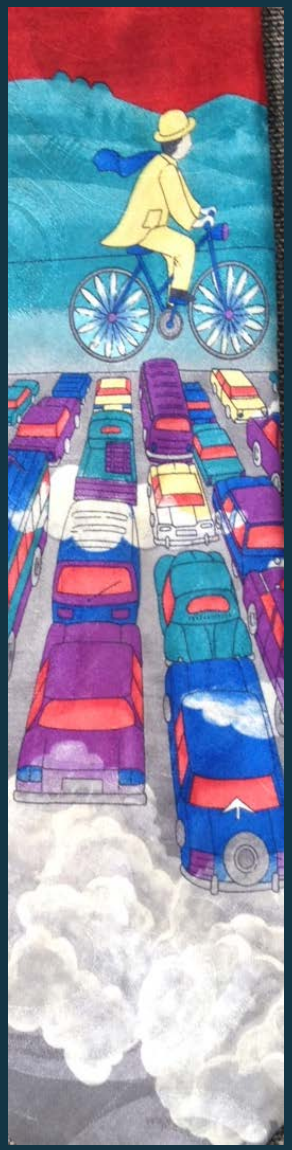
An analysis of data pooled from 12 studies of childhood leukemia from 10 countries found folate supplementation (or vitamins likely to contain folate) before or during pregnancy was associated with 15% (95% CI: 0.78-0.92) and 20% (95% CI: 0.71-0.89) reduction in risk.

Image: Story of Health

Metayer et. al. Epidemiology 2014

Traffic/Solvents

- CDC meta-analysis of 7 studies of children living near high trafficked roads had a 50% increase in risk for leukemia*
  - Benzene already a recognized risk for adult leukemia.
  - Chlorinated solvents associated in some studies



*Boothe et al. Am J Prev Medicine 2014

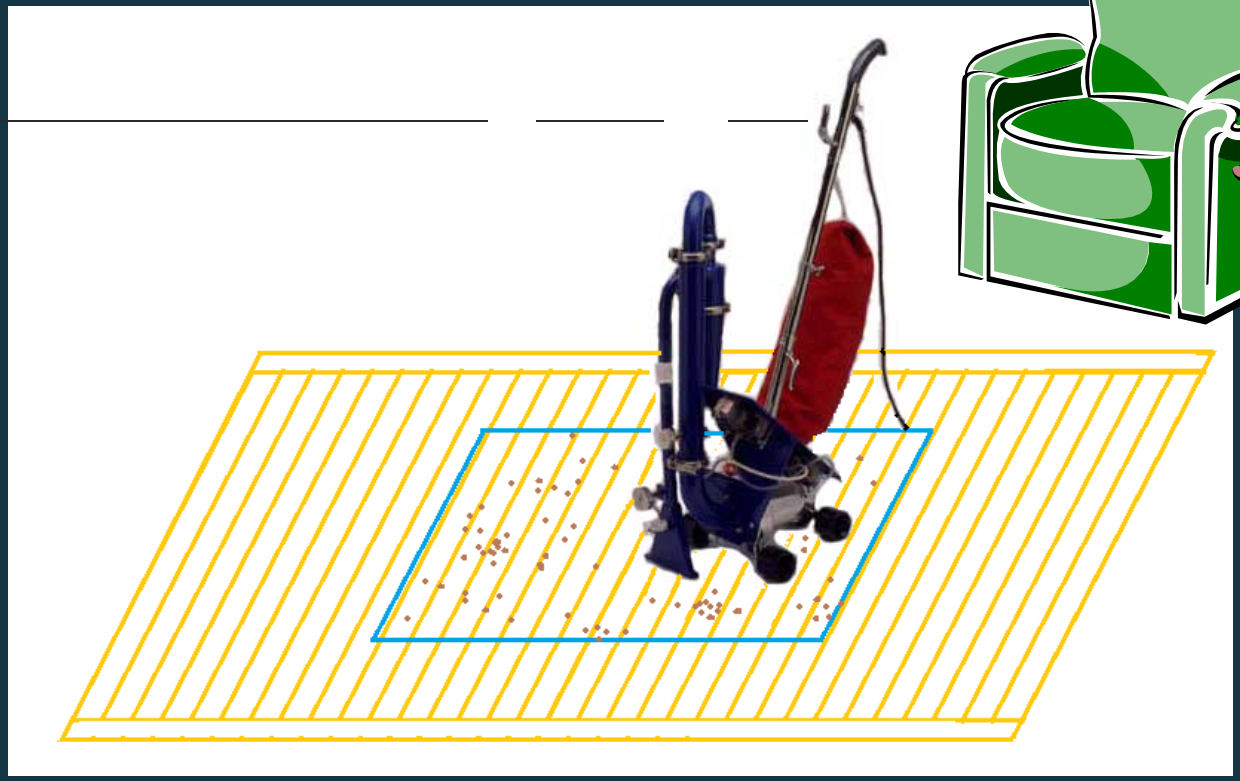
Home Use of Paint and Solvents (CCLS study)

- 550 cases ALL, 100 cases AML
- Paint
  - ALL risk with OR 1.65 (1.26-2.15)
    - Higher with postnatal or frequent use
    - Restricted to 12 – 21 translocation OR 4.16 (1.66-10.4)
- Solvents
  - AML risk with solvent exposure OR 2.5 (1.19-5.42)
    - No increased risk for ALL
- Limited previous studies, some positive

Scelo et al., *Environ Health Perspect* 2009

Dust Samples from 500 Homes

- Initial method:
  - High volume small surface sampler (HVS3)
  - Interviewer collected dust from specific location



Courtesy T. Whitehead

Polychlorinated biphenyls (PCBs) in house dust (reservoir)

- Associated with non-Hodgkin's lymphoma in adults
- Case control 184 cases / 212 controls
- Any detection 2 fold risk (OR 1.97; 1.22 – 3.17)
- Highest vs. lowest quartile 3 fold (OR 2.78; 1.41-5.48)

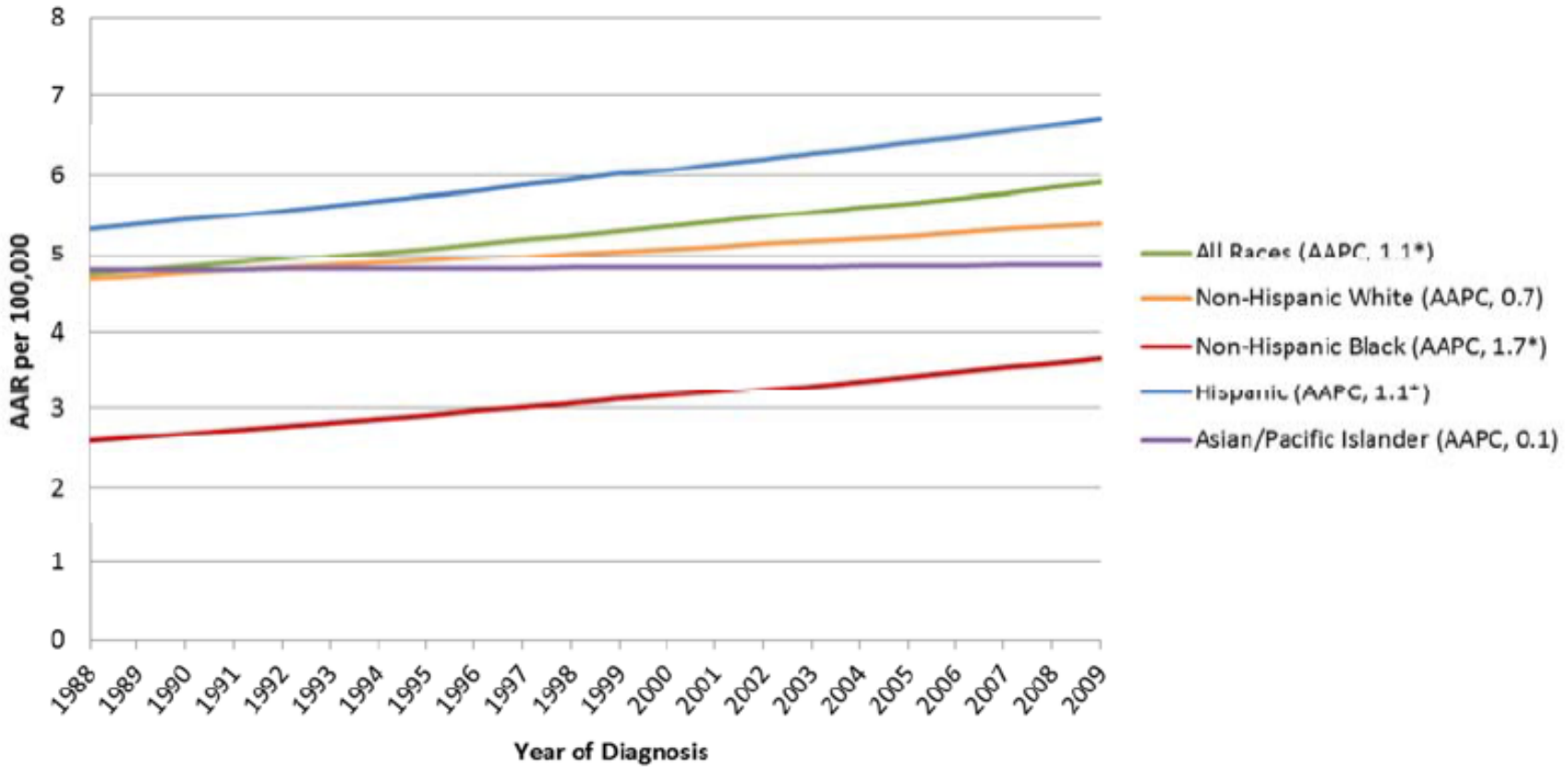
Ward et al., ***Environ Health Perspect*** **117:1007–1013 (2009). doi:10.1289/ehp.0900583 available via *http://dx.doi.org/***

PBDEs in house dust and ALL

- Structurally related to PCBs
- 167 cases 214 controls
- Highest tertile vs. non-detects (octa and nona)
  - BDE 196 OR 2.1 (95% CI 1.1 – 3.8)
  - BDE 202 OR 2.0 (1.1- 3.6)
  - BDE 207 OR 2.0 (1.0 – 3.8)
  - No excess risk with penta or deca the most common forms

Ward et al., Environmental Health Perspectives , Abstract from ISEE 2013

Trend in the Age-Adjusted Incidence Rate of Leukemia among Children Aged 0-14 years by Race/Ethnicity, CA, 1988-2009



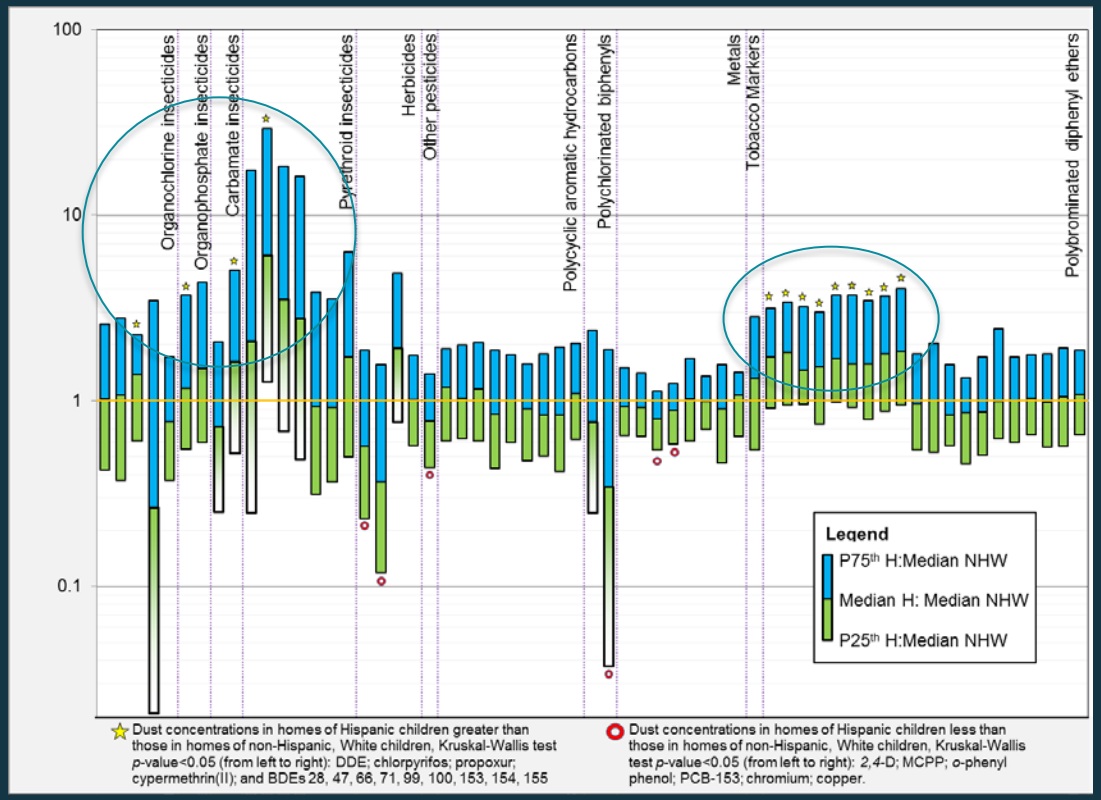
*The Average Annual Percent Change (AAPC) is significantly different from zero at alpah=0.05.
Source: California Cancer Registry, California Department of Public Health, Chronic Disease Surveillance and Research Branch. SEER*Stat Database: Incidence - California, February 2013 (1988-2010), 04/15/2013.

California Children's Environmental Health Program Report to the Legislature
http://coeh.berkeley.edu/ucpehsu/Articles/2014CAChildrensEnvHlthPrgReport.pdf

Household Dust

(583 homes 94 chemicals)

Several *pesticides* (DDE; chlorpyrifos; propoxur; cypermethrin) and *PBDEs* significantly higher in the homes of **Hispanic children vs. non-Hispanic Whites.**



Miller, Whitehead, et al., Poster ISEE 2013 Trends in Childhood Leukemia and Household Chemical Exposures by Ethnicity in California, EHP 2013

American Cancer Society

- **Can childhood leukemia be prevented?**

- Although the risk of many adult cancers can be reduced by lifestyle changes (such as quitting smoking), there is no known way to prevent most childhood cancers at this time. Most adults and children with leukemia have no known risk factors, so there is no sure way to prevent their leukemias from developing.[1]

http://www.cancer.org/cancer/leukemiainchildren/detailedguide/childhood-leukemia-prevention

Can we do primary prevention of cancer?

- SIDS
  - Many wanted to wait
  - Though studies supported a decreased risk they asked, “What is the mechanism?”

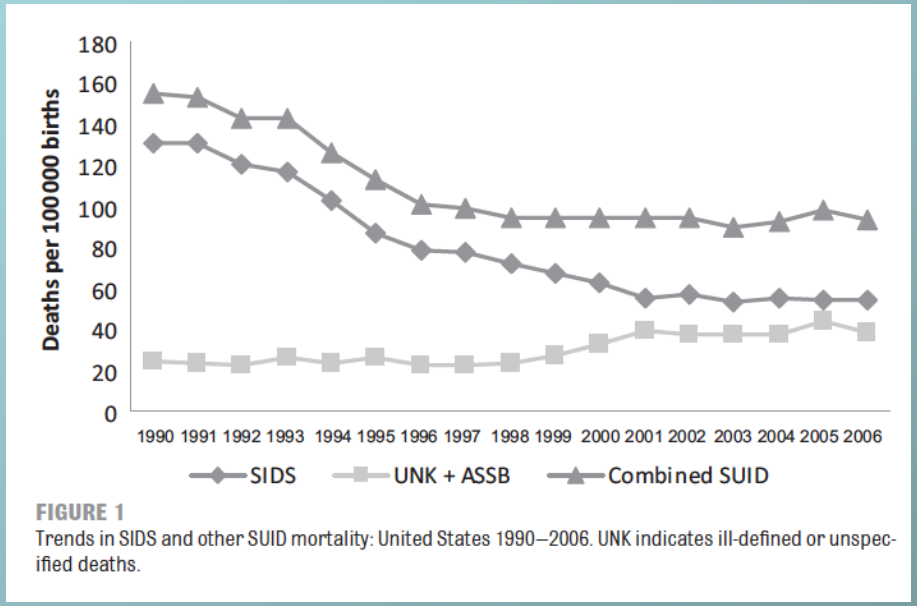


FIGURE 1
Trends in SIDS and other SUID mortality: United States 1990–2006. UNK indicates ill-defined or unspecified deaths.

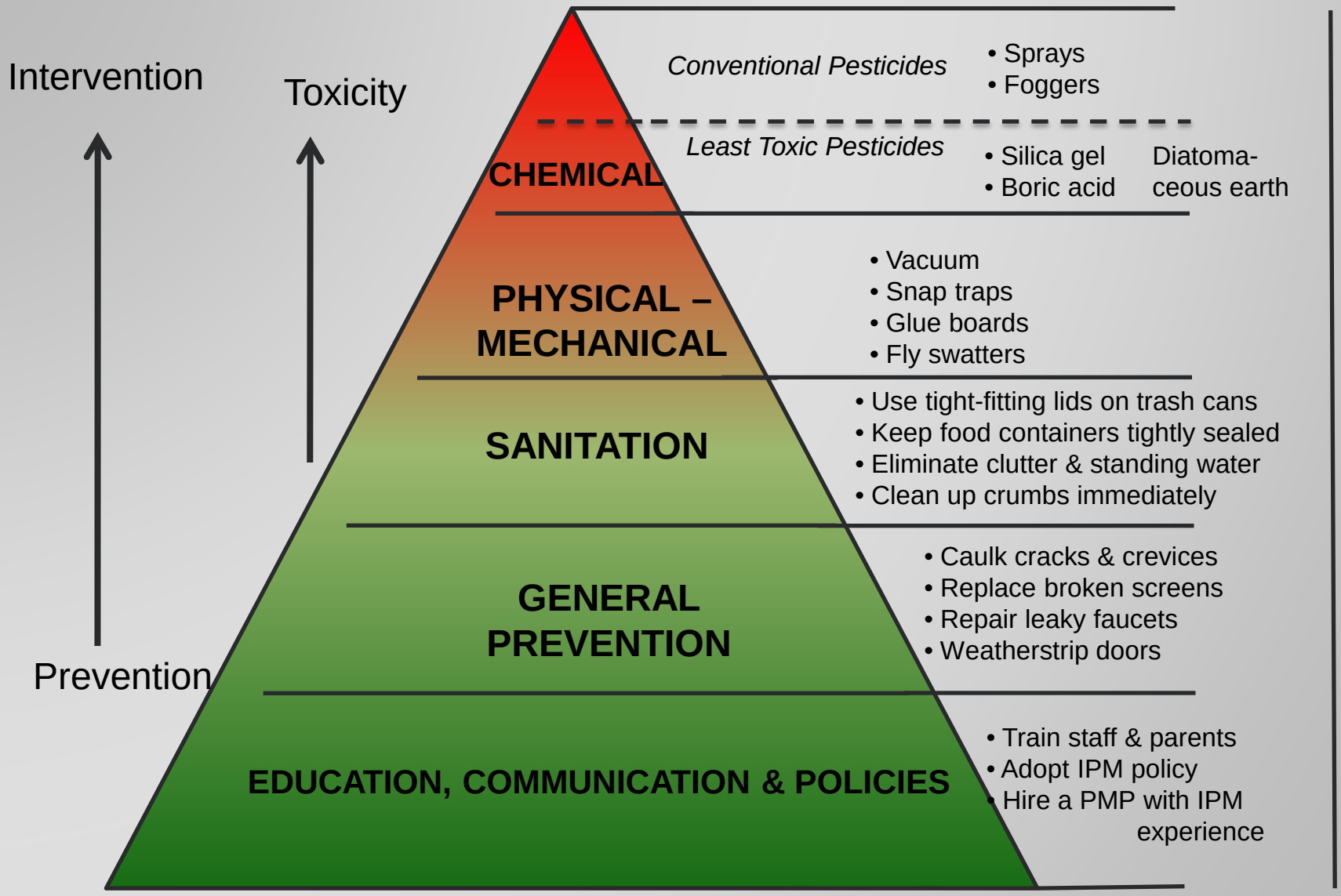
AAP technical report SIDS
Moon R. Pediatrics. 2011 Nov;128(5):1030-9. doi: 10.1542/peds.2011-2284

SIDS – A successful public health intervention

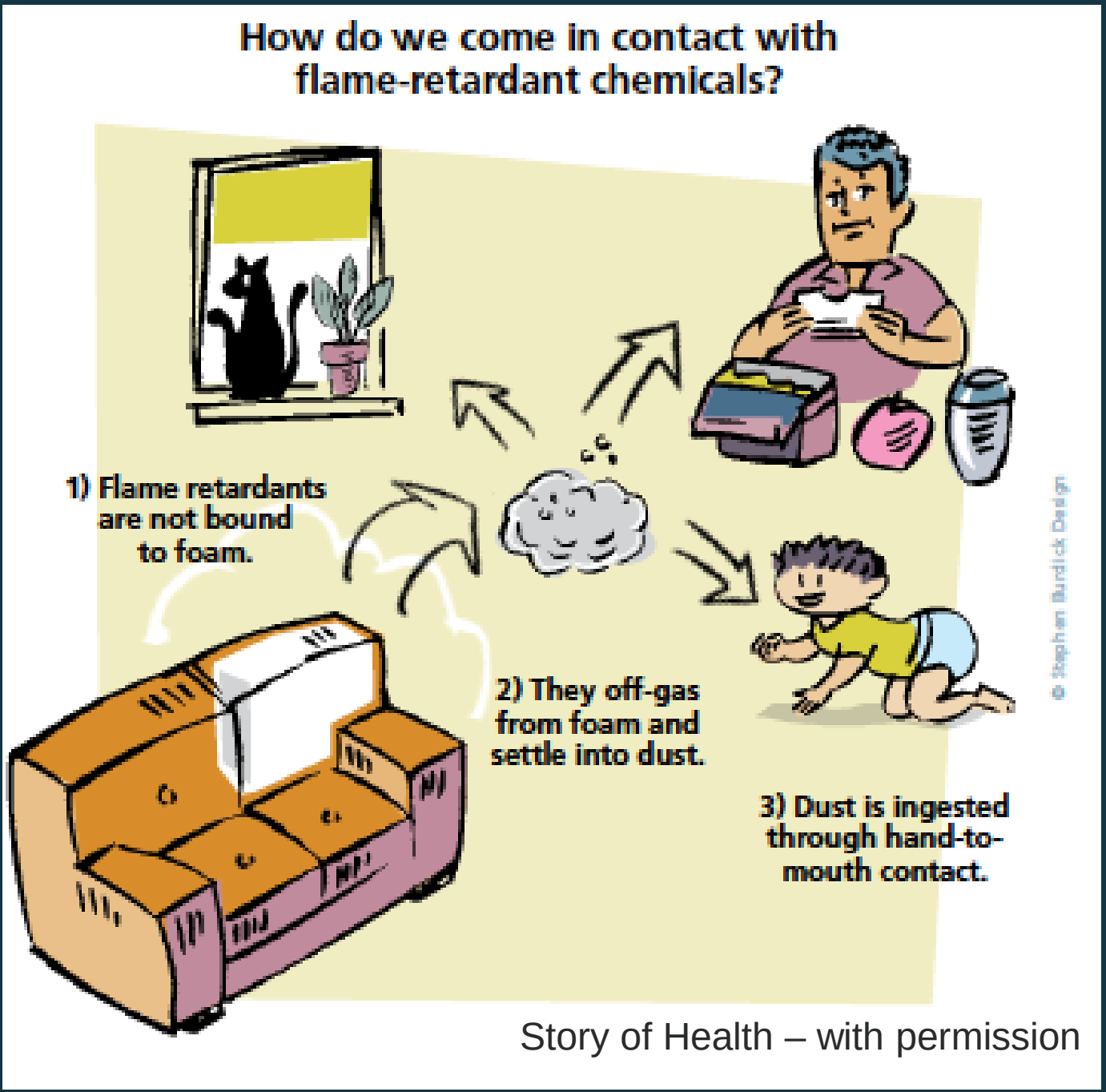
- Underlying issue and difficulties have some parallel with leukemia in children
  - Rare / difficult to study prospectively
  - Serious outcome
  - There is no consensus about mechanisms of causation
  - Individual studies showing association
  - There are a number of meta-analyses mostly identifying consistent patterns of risk
  - Intervention impact can only really be studied with widespread population adoption of prevention activity and then evaluate incidence rates.

We should be doing these things anyway

- Pesticides – asthma, neurodevelopmental disorders
- Tobacco – SIDS, asthma, LRI, preterm and low birth wt., lung and breast cancer
- Solvents – neurodevelopment, asthma, cancers
- Traffic – asthma, neurodevelopment (autism)
- Folate – neural tube, autism (<1/2 get)
- PCBs and PBDEs – cancer, endocrine disruption, neurodevelopment



Integrated Pest Management - IPM



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PRECONCEPTION AND HEALTHY CHILD DEVELOPMENT

Preconception care for women and men is important for lifetime health as well as healthy child development.

All women and men can benefit from healthy habits throughout life, whether or not they plan to have a baby one day. These include eating healthy food, getting regular exercise, avoiding toxic substances, and reducing excessive stress.

Even prior to conception some specific actions are important for prospective parents to take because they can influence birth outcomes. Maternal exposures to toxic chemicals before or around the time of conception can adversely affect the quality of eggs (ova) and newly-conceived embryos. But these exposures can be harmful to men's reproductive health as well. For example, a father's occupational exposure to pesticides has been associated with increased risk of some childhood cancers and birth defects in his offspring. (Roberts et al., 2012). Parents can also take home from the workplace toxicants like lead and pesticides on their clothing, resulting in direct exposures to other family members. (Gerson et al., 1996; Fenske et al., 2013)

Nutritionally, a prospective father's diet that is deficient in folate (a "B" vitamin) increases the risk of birth defects in his offspring. (Lambrot et al., 2013). Similarly, maternal folate supplements in the periconceptual period (~ 6 weeks before and after conception) are associated with decreased risk of having a child with an autism spectrum disorder. (Lyall, 2014)

Of course optimal nutrition and appropriate vitamin and mineral supplements throughout pregnancy are also important to help promote optimal fetal development.

More information: CDC's Preconception care for women and men

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