Costs of Environmental Health Conditions in California Children

Appendix B: Estimation of environmental attributable fractions for childhood asthma and select childhood cancers in California

California Environmental Health Tracking Program

June 2015

PUBLIC HEALTH INSTITUTE®

CALIFORNIA ENVIRONMENTAL HEALTH TRACKING PROGRAM

This publication was supported by the Cooperative Agreement Number 2 U38 EH000953-04, funded by the U.S. Centers for Disease Control and Prevention. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention or the U.S. Department of Health and Human Services.

Contents

Background

To generate estimates of the economic burden of environmentally related health conditions, the environmental attributable fraction (EAF) must be calculated for each condition. The EAF is defined as the "percentage of a particular disease category that would be eliminated if environmental risk factors were reduced to their lowest feasible levels."[1] In addition to aiding cost calculations, estimating the contribution of the environment to a particular health condition is important for understanding both the etiology of the disease and potential utility of various prevention strategies.

There have been previous efforts to estimate the EAF for use in cost calculations. In 2002, Landrigan et al. employed a Delphi method, convening a panel of content experts, to generate EAF estimates for several childhood illnesses in the United States including asthma, cancer, lead poisoning, and neurobehavioral disorders.[2] While these estimates have been used in many subsequent analyses, including in a 2011 analysis by Trasande et al., there is potential to update and quantify EAF estimates specifically for California.

Since 2002, new research has enabled the use of quantitative methods to estimate the EAF for childhood asthma and select childhood cancers. Additionally, California data can be applied to estimate the EAF for the state rather than the entire country. This is important because there are different levels of exposure to various hazards throughout the country. For example, less of the adult population in California smokes compared to other states, suggesting the potential for lower levels of exposure to secondhand smoke among children living in California.[3] However, many California cities consistently have the highest levels of ozone and airborne particulates in the country, so California children may have higher levels of ambient air pollution exposure compared to children in many other states.[4]

We did not attempt to quantify an EAF related to lead exposures or neurobehavioral disorders. Per other peer-reviewed studies, the EAF for childhood lead exposures was assumed to be 100%, as all lead exposures are attributable to the environment. There were insufficient data to quantify a California-specific EAF estimate related to neurobehavioral disorders, therefore the EAF estimated by Landrigan et al. of 10% (range 5 to 20%) using the Delphi method was used.

Environmental pollutants, narrowly defined, are the "chemical substances of human origin in environmental media — air, food, water, soil, the home, and the community."[2] The EAF calculations included indoor and outdoor pollutants that are potentially preventable through traditional public health prevention efforts. This definition also excludes the effects of individual behaviors related to diet, alcohol, personal tobacco use, other drugs of abuse, and other factors such as socioeconomic status. All of these factors are recognized as key components in the broadest definition of the environment (such as the built, economic, and social environments), but were considered outside the scope of this narrower assessment.

Calculating the environmental attributable fraction

The first step for estimating the proportion of childhood asthma and cancer in California due to the environment was to specifically define the health outcomes of interest. Childhood asthma was limited to "current asthma", defined as having ever been diagnosed with asthma and having had symptoms within the previous year. Childhood cancer was limited to those most commonly associated with environmental hazards: leukemia, lymphoma, and brain and other central nervous system (CNS) tumors (these three cancers also account for the majority of childhood cancer diagnoses). Then, indoor and outdoor hazards that had evidence of an association with asthma and/or one of the cancer types were identified by reviewing literature that summarizes the etiology of each condition. To be included in the calculations, each hazard must have fit within the definition of environmental pollutants and have sufficient exposure and risk data.

EAFs were calculated for each hazard-condition pair using data on (1) the increase in risk (expressed as the relative risk [RR]) of having the condition associated with each specific hazard and (2) the prevalence of the exposure to each hazard among children in California. **When sources in the scientific literature differed regarding either of these quantities, EAFs for each hazard-condition pair were presented as ranges of values bracketing the average among all the calculated values.** For each disease, the various hazard-specific EAFs were then combined to estimate the overall proportion of cases in California that were attributable to the environment. Because separate cancer types were included as part of the general term "cancer," type-specific estimates were combined with each other in an additional step.

Relative risk estimates

A literature search was conducted using PubMed and Google Scholar for meta-analyses and peer-reviewed studies that contained relative risk estimates describing associations of each condition in relation to each relevant hazard. The search terms were specific to each condition, defined age groups, and hazards. If risk ratios were not available, odds ratios were used as an approximation.

Estimates of prevalence of exposure to each hazard

Each risk estimate was paired with an estimate of the prevalence of hazard exposure among children in California. When available, estimates of exposure prevalence were obtained from California survey data and government agencies. Otherwise, estimates from national surveys or individual studies were generalized to the California population, as feasible.

Calculations

Hazard exposures are quantified in different ways depending on the hazard itself and choices researchers make in how to measure them. In all, these variations resulted in three scenarios, each with slightly different formulas for EAF calculation (it should be kept in mind, however, that the concept of EAF was identical for all of these scenarios). The scenarios were:

I. Exposures were expressed as binary variables (exposed versus not exposed), and the exposure prevalence referred to the proportion of children exposed in the state overall.

II. Multiple categories of exposure were formulated (for example, high-medium-low-none). A different exposure prevalence was provided for each category (summing to 100%) to describe proportions of children in the state in each category of exposure.

III. Exposures were expressed as continuous variables (for example, the concentrations of pollutants in the air) instead of proportions of the population. Different sub-populations (in this example, counties)

had different pollutant concentrations, and the EAF would reflect the amount of disease that would be eliminated if every county's concentration were reduced to a uniform minimum level.

Scenario I: Let p be the proportion of children exposed (expressed as a fraction, so that — for example — the proportion of children not exposed is 1−p). Let RR be the risk of disease among exposed children relative to those that are not exposed. The EAF was therefore:[5,6,7]

$$EAF^{[I]} = \frac{p(RR-1)}{p(RR-1)+1}$$

Scenario II: Let p_0 be the proportion of children in the reference (lowest) exposure category and p_j be the proportion of children in each of J other categories for j = {1, 2, … , J}. Similarly, let RR_j be the risk of disease for children in category j relative to the baseline risk (that is, $RR_0 = 1$). Then:

$$EAF^{[II]} = \frac{\sum_{j=0}^{J} p_j(RR_j-1)}{\sum_{j=0}^{J} p_j RR_j}$$

The reader may note that, for the special case in which J=1, the formula for $EAF^{[II]}$ is equivalent to that for $EAF^{[I]}$.

Scenario III: Let RR be the relative risk per unit increase in the concentration of a pollutant. Then let c_k be the concentration of the pollutant in county k, and N_k be the number of children residing in county k, where k = {1, 2, … , K} for a total of K counties. Finally, let c_0 be the uniform minimum concentration that would be ideal to attain for all counties (which for rhetorical purposes is usually chosen to be greater than zero). Then:

$$EAF^{[III]} = \frac{\sum_{k=1}^{K} \frac{RR^{(c_k-c_0)}-1}{RR^{(c_k-c_0)}} N_k}{\sum_{k=1}^{K} N_k}$$

Combining EAFs from multiple hazards

A single condition may have multiple environmental hazards contributing to it, which raises the question of how to combine EAF estimates for multiple hazards. The answer hinges on the degree to which (1) hazard exposures were correlated among California children, and (2) whether exposure to multiple hazards increased risk beyond exposure to a single hazard. If children exposed to one hazard were also exposed to another (perfect correlation) and the effects were not additive, then the existence of multiple hazards would do little to increase the total EAF. If all hazards affect separate groups of children in the state (or if the effects of multiple hazards on a single child are additive), then the total EAF would be a multiplicative function of the individual hazard EAFs.

There was little information regarding the degrees of correlation or interaction among hazards, therefore a range of values was reported for each disease. The lower boundary of the range was calculated assuming perfect correlation and no additive effect, in which case the overall EAF was taken to be the summary EAF for the individual hazard with the largest EAF so that no attributable cases were double counted.

For the upper boundary of the range, all hazards were assumed to have independent and additive effects. In this case, all hazards were included in the overall calculation using a formula used by Steenland et al. and by Miettinen. Let EAF_h be the EAF for hazard h, where h = {1, 2, … , H}. Then:

$$EAF_{All\ hazards} = 1 - \left[\prod_{h=1}^{H} (1 - EAF_h)\right]$$

The midpoint between the upper and lower boundaries was employed as the single estimate of the EAF.

Combining EAFs for multiple cancer types

All cancer EAFs were calculated separately for leukemia, lymphoma, and brain/central nervous system cancers. Under the assumption that the number of children with more than one type of cancer is extremely small, these separate EAFs can then be combined in an additive fashion to arrive at an overall cancer EAF. Specifically, if N_t and EAF_t are the number of cases and EAF for each type of cancer t = {1, 2, 3}, then:

$$EAF_{cancer} = \frac{\sum_{t=1}^{3}(EAF_t)N_t}{\sum_{t=1}^{3} N_t}$$

Limitations

Calculations only included hazards that fell within the definition of environment and had (1) evidence of association with childhood disease and (2) available data on risk and prevalence associated with each hazard. This led to exclusion of some hazards that fell within the definition, but lacked adequate data. The definition of environment also excluded some physical substances, social and economic factors, and individual behaviors that are potentially important risk factors. These omissions may lead to an underestimation of the true environmental burden of childhood disease as it relates to the broader ecosystem of socioeconomic health determinants.

In addition, when calculating the overall EAF for each disease, the extent to which the exposures were correlated or additive was unknown. It is unlikely that relevant hazards would be entirely independent or entirely correlated, or would have effects that are entirely additive or non-additive; because reality is likely between these extremes, ranges of estimates are presented as described above.

More details of the limitations specific to each disease are discussed in the sections below.

Childhood asthma

Several indoor and outdoor environmental hazards have been associated with an increased risk for childhood asthma. Indoor environmental hazards include secondhand smoke (SHS), dampness and mold, dust mites, cockroach and mice allergens, pet dander, and chemicals used for cleaning.[8,9,10] Outdoor hazards include traffic and ambient air pollutants such as particulate matter, ozone (O3), and nitrogen dioxide.[11,12] Considering only outdoor, non-biologic, environmental hazards from sources amenable to abatement, Landrigan et al. estimated the EAF for childhood asthma in the U.S. to be 30% (range: 10-35%).[2]

For the purposes of this report, focus was on current asthma among children aged 0 to 17. Current asthma was defined as ever having received an asthma diagnosis and having reported asthma symptoms within the past year. Several potential hazards were excluded due to the lack of available data on the prevalence of exposure and/or the inability to prevent exposure with traditional public health prevention efforts.

Literature review

The literature search was conducted in PubMed using the search terms: asthma, child (age 0 to 17 years), and terms for each exposure including 'secondhand smoke', 'environmental tobacco smoke', 'mold', 'dampness', 'traffic pollution', 'particulate matter', and 'ozone'. Meta-analyses were included if studies focused on children and contained at least one study from the United States. Peer-reviewed publications were included if (1) they were not already included in a relevant me-

ta-analysis, (2) the study population included children under the age of 18, and (3) the study population was living in the United States. Seven meta-analyses and peer-reviewed studies were identified for the hazards of interest (Table 2): two on SHS, two on dampness and mold, one on traffic proximity, and two on $PM_{2.5}$ and ozone.

Exposure prevalence

California-specific data on exposure to SHS were from the California Health Interview Survey[12] and the American Housing Survey.[14] Estimates of prevalence of exposure to dampness and mold in the home were obtained from the American Housing Survey[14] and individual studies and meta-analyses.[15,16] The percent of the population of children living within various proximities to major roads was based on a study conducted in Southern California by McConnell et al.[17]

County data from the U.S. Environmental Protection Agency were used to estimate the number of children exposed to various levels of $PM_{2.5}$ and ozone.[18] In 2006, county annual average concentrations of $PM_{2.5}$ ranged from 5.19 $\mu g/m^3$ in Lake County to 20.85 $\mu g/m^3$ in Riverside County. Daily 8-hour maximum ozone levels for the ozone season for each county ranged from 0.030 ppm in Marin and San Francisco to 0.080 ppm in San Bernardino. The minimum concentrations (that is, concentrations for Lake and Marin Counties) were used as reference values for purposes of the EAF calculation.

Results

The combined-hazard EAF for current childhood asthma was between 20% and 41%, with 30% as a midpoint. Although using different methods and a more expansive definition of environment, this estimate is similar to Landrigan's estimate of 30% (Range 10-35%) for the United States. Table 2 display the full results of the literature search, the exposure prevalence estimates, and the hazard-specific EAFs.

Table 1. Hazards included in the EAF calculation for childhood asthma

Indoor hazards	Outdoor hazards
Secondhand smoke	Proximity to traffic
Dampness and/or mold	PM2.5
	Ozone

Limitations

These calculations only considered current, symptomatic asthma as an outcome. This limited the number of studies that could be included in the calculation, as many studies focus on incident asthma and exacerbations. The EAF may change if considering incident asthma or specific outcomes such as emergency room visits or hospitalizations. Additionally, the calculations only considered hazards that fell within the definition of environment and had (1) evidence of association with childhood asthma and (2) available data on risk and prevalence associated with each hazard. Therefore, exposure to pests (rodents, cockroaches), pet dander, dust mites, chemicals found in cleaning products/perfumes, wood burning, pollen, and extreme weather events were excluded. Inclusion of some or all of these factors may have led to a larger estimate for the childhood asthma EAF.

There were also limitations in the data available for prevalence of various hazard exposures. Household population data on exposure to dampness and mold in the home from the American Housing Survey were generalized to the population of children in California. Data on traffic proximity were from a Southern California study and generalized to the whole population of children in California. While this study included participants from thirteen communities in Southern California, it likely does not perfectly represent the entire state. For ambient air pollution, estimates relied on county data, which assume that all children in a county are exposed to similar concentrations of pollutants.

Table 2. Data inputs and hazard-specific EAF estimates for childhood asthma

Categorical exposure measures

Hazard definition	Effect size (RR or OR)		Exposure prevalence		Average hazard-specific EAF (%)
	Source	Estimate (95%-confidence interval)	Source	Estimate	
Secondhand smoke					
Household secondhand smoke	Vork 2007[19]	1.25 (1.21, 1.30)	CHIS 2009[13]	0.031	1.2 Range: 0.6–1.8
Current smoker in home	Pattenden 2006[20]	1.20 (1.06, 1.35)	AHS 2011[14]	0.087	
Dampness and mold					
Mold	Antova 2008[21]	1.43 (1.20, 1.51)	Spengler 1994[15]	0.313	10.9 Range: 5.3–19.9
Dampness, mold, or mold odor	Fisk 2007[22]	1.53 (1.39, 1.68)	AHS 2011[14]	0.129	
			Mudarri 2011[16]	0.470	
Distance from major road					
> 300 meters	McConnell 2006[17]	1.00	McConnell 2006[17]	0.434	12.2
150–300 meters		1.04 (0.82, 1.33)		0.252	
75–150 meters		1.33 (1.02, 1.72)		0.164	
< 75 meters		1.50 (1.16, 1.95)		0.150	

Continuous exposure measures

Hazard definition	Effect size (RR or OR)		Reference concentration		Average hazard-specific EAF (%)
	Source	Estimate (95%-confidence interval)	Source	Estimate	
$PM_{2.5}$					
per 5 µg/m³ increase	Akinbami 2010[23]	1.02 (0.97, 1.06)	U.S. EPA[18]	5.19 µg/m³	5.2 Range: 3.6-6.8
per 10 µg/m³ increase	Gasana 2012[24]	1.06 (0.93, 1.21)			
Ozone (O_3)					
per 5 ppb increase	Akinbami 2010[23]	1.08 (1.02, 1.14)	U.S. EPA[18]	30 ppb	19.7 Range: 0-39.4
per 10 µg/m³ increase	Gasana 2012[24]	1.00 (0.94, 1.08)			

Childhood cancer

A combination of many factors may play a role in the development of childhood cancer, including genetics, environment, and parental exposures. Associations have been observed between childhood cancers and many environmental factors, including indoor radon; diagnostic X-rays and CT scans during gestations or childhood; house paint, glue, and solvent exposures; high levels of nitrate in drinking water; secondhand smoke; residence on a farm; exposure to pesticides; living near high voltage electric power lines; air pollution; and parental occupational exposures.[25,26,27] Due to the nature of childhood cancer, it is important to consider exposure to these hazards at various times in development — from parental exposure at the time of conception to childhood exposure before the time of diagnosis. By consulting a panel of experts, Landrigan et al. estimated the EAF for childhood cancer in the U.S. to be 5% (range: 2–10%), however the authors suggested that this was a very conservative estimate due to the lack of sufficient evidence available.

For the purposes of this report, focus was on the three most common childhood cancers: leukemia, lymphoma, and brain and other central nervous system (CNS) tumors. Childhood cancers were restricted to children age 0 through 14 years, because this is how childhood cancers are often reported by many cancer registries, and cancer types among children 0–14 tend to be different than the cancer types among older patients, and therefore receive different treatment regimens. The National Cancer Institute, for example, distinguishes childhood cancers as those occurring among children 0–14 years, and adolescent and young adult cancers as those in patients age 15–39 years (www.cancer.gov/cancertopics/factsheet/Sites-Types/childhood). Due to different disease etiologies and associations with various hazards, each of the cancer types is considered separately before estimating a combined EAF for childhood cancer overall.

Table 3. Hazards included in the EAF calculation for childhood cancer and timing of exposure

Hazard	Timing of exposure
Indoor radon	Childhood
Secondhand smoke	In-utero
Solvents	In-utero and/or childhood
Parental occupational pesticides	Periconception
Residential pesticides	In-utero and/or childhood
Traffic pollution	In-utero
Parental occupational traffic pollution	Periconception

Environmental hazards that were associated with at least one of the cancer types were classified into seven categories reflecting different hazard types and exposure timing (Table 3). EAFs were calculated for single hazards using data on (1) the increase in risk of each type of childhood cancer associated with the hazard and (2) the prevalence of the exposure to the hazard among children ages 0–14 in California or among parents during conception or pregnancy. Although there has been some research on associations with childhood cancer, exposure to electric power lines and nitrates in drinking water were excluded because of insufficient exposure data. In addition, diagnostic X-ray and CT scans were excluded from analysis because they are less subject to reduction through conventional public health practice (as these are core tools in clinical health).

Literature review

A literature search on risk factors for the three most common types of childhood cancer was completed using PubMed and Google Scholar, and the key words for childhood cancer, epidemiology, and each hazard. Peer-reviewed individual studies and meta-analyses were included

if the study population included children ages 0 to 14. Unlike the literature search for asthma, there were no geographic requirements for study inclusion. Relevant studies were examined to obtain the relative risk (RR) for childhood cancer associated with a given hazard. If risk ratios were not available, odds ratios were used as an approximation. The literature search for estimates of the risk associated with the seven categories of environmental hazards resulted in 14 studies and meta-analyses; 13 studies included childhood leukemia as an outcome, two studies included lymphoma, and three studies included brain and other CNS tumors (Table 4).

Exposure prevalence

County radon levels were used to estimate childhood exposure to various categories of indoor radon.[28] Estimates of parental smoking during pregnancy were from the National Center for Health Statistics[29] and the California Health Interview Survey.[30] For solvents and hydrocarbons, data were obtained from studies based in other areas of the United States.[31,32,33] California data from the American Community Survey were used to estimate parental occupational exposures to pesticides and air pollutants, as well as farm residence.[34,35] Data on specific residential pesticide exposure from a statewide study in California;[36] exposure to herbicides, insecticides, and general pesticides were estimated from the Northern California Childhood Leukemia Study.[37] Carbon monoxide data were from a statewide study by Heck et al.,[38] while county data from the U.S. Environmental Protection Agency were paired with 2010 Census data to estimate the number of children exposed to various levels of $PM_{2.5}$ in the state.[18]

Results

Individual EAFs for childhood leukemia, lymphoma, and brain or other CNS cancers were estimated to be 20.8% (Range 11.7–29.9%), 16.1% (Range 15–17.2%), and 2.0% (Range: 1.7–2.2%), respectively. Combining the type-specific EAFs according to the occurrence of each type in the population, an estimated 14.8% (Range: 9.4–20.7%) of childhood cancer cases were attributable to the environment. The California estimate is slightly higher than Landrigan et al.'s estimate of 5% (Range: 2–10%). This may be due to a more inclusive definition of environment, increased data allowing for consideration of more hazards, different levels of exposure to hazards in California, or the self-described conservative nature of Landrigan et al.'s initial estimate. Tables 4 through 6 display the results of the literature search, the exposure prevalence estimates, and the hazard-specific EAFs.

Limitations

These calculations did not account for all cancers potentially related to environmental exposures. While leukemia, lymphoma, and brain and other CNS tumors account for the majority of childhood cancers, other cancers are likely to have different etiologies and risk factors and therefore a different proportion of cases are attributable to the environment. Additionally, the focus was on childhood cancer and calculations did not account for any onset of cancer at age 15 or later that may be related to exposures in-utero or childhood.

There are some hazards, including electromagnetic fields and nitrates in drinking water that have been linked to various childhood cancers, but are lacking data to estimate the prevalence of these exposures in California or the United States. Although they are important risk factors for childhood cancer, exposure to CT Scans and X-rays in-utero and childhood were excluded from the calculations because they did not fit within the definition of environmental pollutant. If additional environmental hazards were included, the resulting EAF estimate would be larger.

There were limitations in the data available for estimates of exposure prevalence to hazards. For indoor radon and air pollution, estimates relied on county level data that were applied to the number of children living in a county. This assumes that all children in a county had the same level of exposure. For exposure to solvents, California specific data were not available and estimates were used from individual studies based in the United States. To estimate exposures to pesticides or occupational hazards occurring near the time of conception or in utero, Census industrial and occupational data from the adult population in California were generalized to apply to adults near the time of conception or pregnancy. This assumes that adults that are near the time of conceiving have similar occupational patterns as those in the general workforce.

Table 4. Data inputs and hazard-specific EAF estimates for childhood leukemia

Hazard definition	Categorical exposure measures: Effect size (RR or OR) Source	Effect size (RR or OR) Estimate (95%-confidence interval)	Exposure prevalence Source	Exposure prevalence Estimate	Average hazard-specific EAF (%)
Indoor radon, childhood					
in 5 years before diagnosis					11.7 Range: 8.7–14.7
<37 Bq/m^3	Lubin 1998[39]	1.00	Air Chek, Inc.[28]	0.222	
37–73 Bq/m^3		1.30 (0.9, 1.8)		0.408	
74–147 Bq/m^3		0.91 (0.6, 1.3)		0.359	
≥148 Bq/m^3		1.44 (0.9, 2.3)		0.011	
in 5 years before diagnosis					
<37 Bq/m^3	Steinbuch 1999[40]	1.00	Air Chek, Inc.[28]	0.222	
37–100 Bq/m^3		1.22 (0.7, 2.1)		0.725	
>100 Bq/m^3		1.25 (0.6, 2.7)		0.053	
Tobacco smoke, In-utero					
Maternal smoking during pregnancy	Boffetta 2000[41]	1.10 (1.03, 1.19)	NCHS 2011[29]	0.020	0.2
Solvents & hydrocarbons					
Parental exposure to solvents around pregnancy	Shu 1999[31]	1.30 (1.0, 1.7)	Shu 1999[31]	0.060	2.0 Range: 0.7–4.2
Parental exposure to plastics around pregnancy		2.30 (1.2, 4.4)		0.010	
Father's exposure to inhaled particulate hydrocarbons during periconception	McKinney 2003[32]	1.48 (1.19, 1.84)	McKinney 2003[32]		
Mother lived in homes painted excessively (>4 rooms) in year before childs birth		1.70 (1.1, 2.7)	Freedman 2001[33]	0.063	
Model building in home (>4 times/month) during childhood	Freedman 2001[33]	1.90 (0.7, 5.8)		0.008	
Artwork using solvents in home (>4 times/month) during childhood		4.10 (1.1, 5.1)		0.005	
Parental occupational pesticide, in-utero					
Paternal/maternal occupational exposure to agriculture/farming	Van Maele-Fabry 2010[42]	1.37 (0.97, 1.93)	ACS 2012[34]	0.013	0.9

Categorical exposure measures					
	Effect size (RR or OR)		Exposure prevalence		Average hazard-specific EAF (%)
Hazard definition	Source	Estimate (95%-confidence interval)	Source	Estimate	
Residential pesticides, in-utero or childhood					
Metam sodium used within half mile of residence at time of birth					
<1 lb/mi^2		1.00		0.980	
1-208 lbs/mi^2		0.83 (0.36, 1.91)		0.011	
209-8254 lbs/mi^2	Reynolds 2005[36]	2.05 (1.01, 4.17)	Reynolds 2005[36]	0.009	
Dicofol used within half mile of residence at time of birth					
<1 lb/mi^2		1.00		0.970	
1-9 lbs/mi^2		0.75 (0.36, 1.55)		0.016	10.5 Range: 0.8–19.8
10-454 lbs/mi^2		1.83 (1.05, 3.22)		0.016	
Residential exposure to pesticides during or after pregnancy	Van Maele-Fabry 2011[43]	1.74 (1.37, 2.21)		0.285	
Outdoor herbicides during pregnancy		1.84 (1.32, 2.57)		0.190	
Insecticides used in home for cockroaches, ants, flies, bees, wasps during pregnancy	Infante-Rivard 1999[44]	1.79 (1.34, 2.40)	Guha 2013*[37]	0.313	
Insecticides used in home for cockroaches, ants, flies, bees, wasps during childhood		1.38 (1.07, 1.77)		0.313	
Outdoor herbicides during childhood		1.41 (1.06, 1.86)		0.266	
Parental occupational traffic pollution, periconception					
Father's occupation as driver during periconception	McKinney 2003[32]	1.36 (1.10, 1.68)	ACS 2012[34]	0.032	1.1
Residential traffic pollution, in-utero					
Carbon monoxide from traffic					
Quartile 1		1.00		0.250	
Quartile 2	Heck 2013[38]	1.07 (0.90, 1.27)	Heck 2013[38]	0.250	9.2 Range: 7.6–10.7
Quartile 3		1.14 (0.96, 1.35)		0.250	
Quartile 4		1.12 (0.94, 1.34)		0.250	

Continuous exposure measures				
	Effect size (RR or OR)		Reference concentration	
Hazard definition	Source	Estimate (95%-confidence interval)	Source	Estimate
$PM_{2.5}$ per 7.84 µg/m^3 increase, in-utero	Heck 2013[38]	1.1 (0.92, 1.30)	U.S. EPA[18]	N/A

*Guha 2013 provides several estimates for exposure to pesticides in pregnancy and early childhood from the Northern California Childhood Leukemia Study. For some exposures, there are multiple estimates of the prevalence of exposure. Therefore the most conservative estimate was used for the EAF calculation, explaining why multiple hazards may have the same exposure prevalence.

Table 5. Data inputs and hazard-specific EAF estimates for childhood lymphomas

	Effect size (RR or OR)		Exposure prevalence		Average hazard-specific EAF (%)
Hazard definition	Source	Estimate (95%-confidence interval)	Source	Estimate	
Tobacco smoke, In-utero					
Maternal smoking during pregnancy	Boffetta 2000[41]	1.10 (1.03, 1.19)	NCHS 2011[29]	0.020	0.2
Parental occupational pesticides, in-utero					
Maternal occupational exposure around pregnancy	Meinert 2000[45]	4.10 (1.1, 16)	ACS 2012[34]	0.008	2.4
Residential pesticides, in-utero or childhood					
Residential use by professional pest controllers between the year of birth and the date of diagnosis	Meinert 2000[45]	2.60 (1.2, 5.7)	Guha 2013[37]	0.110	15.0

Table 6. Data inputs and hazard-specific EAF estimates for childhood brain and other CNS tumors

	Effect size (RR or OR)		Exposure prevalence		Average hazard-specific EAF (%)
Hazard definition	Source	Estimate (95%-confidence interval)	Source	Estimate	
Tobacco smoke, In-utero					
Maternal Smoking during pregnancy	Boffetta 2000[41]	1.10 (1.03, 1.19)	NCHS 2011[29]	0.020	1.7 Range: 0.2–3.3
Paternal smoking during pregnancy		1.22 (1.05, 1.40)	CHIS 2011–12[30]	0.154	
Parental occupational pesticides, in-utero					
Parental occupational exposure to pesticides (meta-analysis of case-control studies)	Van Maele-Fabry 2013[46]	1.30 (1.11, 1.53)	ACS 2012[34]	0.013	0.5 Range: 0.4–0.7
Parental occupational exposure to pesticides (meta-analysis of cohort studies)		1.53 (1.20, 1.95)		0.013	
Residential pesticides, in-utero or childhood					
Farm residence during childhood	Efird 2003[47]	1.30 (1.0, 1.7)	Census 2000	0.003	0.1

Endnotes

1 Smith KR, Orvalin CF, Kjellstrom T. 1999. *How much global ill health is attributable to environmental factors?* Epidemiology. 10:573-584.

2 Landrigan PJ, Schechter CB, Lipton JM, Fahs MC, Schwartz J. 2002. *Environmental pollutants and disease in American children: estimates of morbidity, mortality, and costs for lead poisoning, asthma, cancer, and developmental disabilities.* Environmental Health Perspectives. 110(7):721-728.

3 Centers for Disease Control and Prevention. Smoking and Tobacco Use: State Highlights at www.cdc.gov/tobacco/data_statistics/state_data/state_highlights/2010/states/california/index.htm, accessed May 25, 2014.

4 American Lung Association. 2013. State of the Air 2013 at www.stateoftheair.org/2013/assets/ala-sota-2013.pdf, accessed May 25, 2014.

5 Levin ML. 1953. *The occurrence of lung cancer in man.* Acta Unio Int Contra Cancrum. 9(3):531-41.

6 Miettinen OS. 1974. *Proportion of disease caused or prevented by a given exposure, trait or intervention.* American Journal of Epidemiology. 99(5):325-32.

7 Kleinbaum DG, Kupper LL, Morgenstern H. 1982. *Epidemiologic Research: Principles and Quantitative Methods.* Belmont, CA: Lifetime Learning Publications.

8 Etzel RA. 2003. *How environmental exposures influence the development and exacerbation of asthma.* Pediatrics. 112(1 Pt 2):233-9.

9 Heinrich J. 2011. *Influence of indoor factors in dwellings on the development of childhood asthma.* International Journal of Hygiene and Environmental Health. 214(1):1-25.

10 Herzog R, Cunningham-Rundles S. 2011. *Pediatric asthma: natural history, assessment, and treatment.* Mount Sinai Journal of Medicine. 78(5):645-60.

11 Diette GB, McCormack MC, Hansel NN, Breysse PN, Matsui EC. 2008. *Environmental issues in managing asthma.* Respiratory Care. 53(5):602-15; discussion 616-7.

12 Clark NA, Demers PA, Karr CJ, Koehoorn M, Lencar C, Tamburic L, et al. *Effect of early life exposure to air pollution on development of childhood asthma.* Environ Health Perspect 2010;118(2):284-90.

13 California Health Interview Survey. CHIS 2009. Los Angeles, CA: UCLA Center for Health Policy Research at www.askchis.com/, accessed September 25, 2013.

14 U.S. Census Bureau. American Housing Survey 2011. Health and Safety Characteristics Table S-01-AO-M using American FactFinder at http://factfinder2.census.gov, accessed September 25, 2013.

15 Spengler J, Neas L, Nakai S, et al. 1994. *Respiratory Symptoms and Housing Characteristics.* Indoor Air. 4:72-82.

16 Mudarri D, Fisk WJ. 2007. *Public health and economic impact of dampness and mold.* Indoor Air. 17(3):226-35.

17 McConnell R, Berhane K, Yao L, et al. 2006. *Traffic, susceptibility, and childhood asthma.* Environmental Health Perspectives. 114(5):766-72.

18 U.S. EPA Air Explorer, 2006. Accessed on 12/15/2013 at: www.cehtp.org/p/air_query

19 Vork KL, Broadwin RL, Blaisdell RJ. 2007. *Developing asthma in childhood from exposure to secondhand tobacco smoke: insights from a meta-regression.* Environmental Health Perspectives. 115(10):1394-400.

20 Pattenden S, Antova T, Neuberger M, et al. 2006. *Parental smoking and children's respiratory health: independent effects of prenatal and postnatal exposure.* Tobacco Control. 15(4):294-301.

21 Antova T, Pattenden S, Brunekreef B, et al. 2008. *Exposure to indoor mould and children's respiratory health in the PATY study.* Journal of Epidemiology & Community Health. 62(8):708-14.

22 Fisk WJ, Lei-Gomez Q, Mendell MJ. 2007. *Meta-analyses of the associations of respiratory health effects with dampness and mold in homes.* Indoor Air. 17(4):284-96.

23 Akinbami LJ, Lynch CD, Parker JD, Woodruff TJ. 2010. *The association between childhood asthma prevalence and monitored air pollutants in metropolitan areas, United States, 2001-2004.* Environmental Research. 110(3):294-301.

24 Gasana J, Dillikar D, Mendy A, Forno E, Ramos Vieira E. 2012. *Motor vehicle air pollution and asthma in children: a meta-analysis.* Environmental Research. 117:36-45.

25 Linet M, Wacholder S, Zahm SH. 2003. *Interpreting epidemiologic research: Lessons from studies of childhood cancer.* Pediatrics. 112 (1) 218-232.

26 McNally RJQ, Parker L. 2006. *Environmental factors and childhood acute leukemias and lymphomas.* Leukemia and Lymphoma. 47(4):583-598.

27 Ross J, Spector L. 2006. Cancers in Children. In Schottenfeld D and Fraumeni D. (Eds.), *Cancer Epidemiology and Prevention (*pp.1251-1268. Oxford University Press.

28 Air Chek, Inc. California Radon Information at http://ca-radon.info/, accessed January 23, 2014.

29 National Center for Health Statistics. NCHS 2011. Births to mothers who smoked during pregnancy at http://datacenter.kidscount.org/data/tables/13-births-to-mothers-who-smoked-during-pregnancy#, accessed March 13, 2014.

30 California Health Interview Survey. CHIS 2011-2012. Los Angeles, CA: UCLA Center for Health Policy Research at www.askchis.com/, accessed January 20, 2014.

31 Shu XO, Stewart P, Wen W, et al. 1999. *Parental occupational exposure to hydrocarbons and risk of acute lymphoblastic leukemia in offspring.* Cancer Epidemiology, Biomarkers & Prevention. 8:783-791.

32 McKinney PA, Fear NT, Stockton D. 2003. *Parental occupation at periconception: findings from the United Kingdom Childhood Cancer Study.* Occupational and Environmental Medicine. 60:901-909.

33 Freedman DM, Stewart P, Kleinerman RA, et al. 2001. *Household solvent exposures and childhood acute lymphoblastic leukemia.* American Journal of Public Health. 91(4):564-567.

34 U.S. Census Bureau. American Community Survey, 2012 5-year estimates. Table C24010 using American FactFinder at http://factfinder2.census.gov, accessed March 11, 2014.

35 U.S. Census Bureau. 110th Congressional District Summary File 2000. Table H005 using American FactFinder at http://factfinder2.census.gov, accessed March 11, 2014.

36 Reynolds P, Von Behren J, Gunier R, Goldberg DE, Harnly M, Hertz A. 2005. *Agricultural pesticide use and childhood cancer in California.* Epidemiology. 16(1):93-100.

37 Guha N, Ward MH, Gunier R, et al. 2013. *Characterization of Residential Pesticide Use and Chemical Formulations through Self-Report and Household Inventory: The Northern California Childhood Leukemia Study.* Environmental Health Perspectives 121(2):276-282.

38 Heck J, Wu J, Lombardi C, et al. 2013. *Childhood cancer and traffic related air pollution exposure in pregnancy and early life.* Environmental Health Perspectives. 121:1385-1391.

39 Lubin JH, Linet MS, Boice JD, et al. 1998. *Case-control study of childhood acute lymphoblastic leukemia and residential radon exposure.* Journal of the National Cancer Institute. 90(4):294-300.

40 Steinbuch M, Weinberg CR, Buckley JD, Robison LL, Sandler DP. 1999. *Indoor residential radon exposure and risk of childhood acute myeloid leukemia*. British Journal of Cancer. 81(5):900-906.

41 Boffetta P, Tredaniel J, Greco, A. 2000. *Risk of childhood cancer and adult lung cancer after childhood exposure to passive smoke: a meta-analysis*. Environmental Heath Perspectives. 108(1):73-82.

42 Van Maele-Fabry G, Lantin AC, Hoet P, Lison D. 2010. *Childhood leukemia and parental occupational exposure to pesticides; a systematic review and meta-analysis*. Cancer Causes and Control. 21:787-809.

43 Van Maele-Fabry G, Lantin AC, Hoet P, Lison D. 2011. *Residential exposure to pesticides and childhood leukemia: a systematic review and meta-analysis*. Environment International. 37(1):280-291.

44 Infante-Rivard C, Labuda D, Kranjinovic M, Sinnett D. 1999. *Risk of childhood leukemia associated with exposure to pesticides and with gene polymorphisms*. Epidemiology. 10(5):481-487.

45 Meinert R, Schuz J, Kaletsch U, Kaatsch P, Michaelis J. 2000. *Leukemia and Non-Hodgkin's Lymphoma in childhood and exposure to pesticides: results of a register-based case-control study in Germany*. American Journal of Epidemiology. 151(7):639-46.

46 Van Meale-Fabry G, Hoet P, Lison D. 2013. *Parental occupational exposure to pesticides as risk factor for brain tumors in children and young adults: A systematic review and meta-analysis*. Environment International. 56:19-21.

47 Efird JT, Holly EA, Preston-Martin S, et al. 2003. *Farm related exposures and childhood brain tumors in seven countries: results from the SEARCH International Brain Tumor Study*. Paediatric and Perinatal Epidemiology. 17(2):201-211.