

# UC Berkeley

## UC Berkeley Previously Published Works

### Title

Childhood Leukemia: A Preventable Disease

### Permalink

<https://escholarship.org/uc/item/2kh7p6tp>

### Journal

Pediatrics, 138(Supplement 1)

### ISSN

0031-4005

### Authors

Metayer, Catherine

Dahl, Gary

Wiemels, Joe

et al.

### Publication Date

2016-11-01

### DOI

10.1542/peds.2015-4268h

Peer reviewed

# Childhood Leukemia: A Preventable Disease

Catherine Metayer, MD, PhD,<sup>a</sup> Gary Dahl, MD,<sup>b</sup> Joe Wiemels, PhD,<sup>c</sup> Mark Miller, MD, MPH<sup>d</sup>

abstract

In contrast to most pediatric cancers, there is a growing body of literature, nationally and internationally, that has implicated the role of several environmental indoor and outdoor hazards in the etiology of childhood leukemia. For example, exposures to solvents, traffic, pesticides, and tobacco smoke have consistently demonstrated positive associations with the risk of developing childhood leukemia. Intake of vitamins and folate supplementation during the preconception period or pregnancy has been demonstrated to have a protective effect. Despite the strength of these findings, the dissemination of this knowledge to clinicians has been limited. Some children may be more vulnerable than others as documented by the high and increasing incidence of childhood leukemia in Hispanics. To protect children's health, it is prudent to establish programs to alter exposure to those factors with well-established associations with leukemia risk rather than to suspend judgment until no uncertainty remains. This is particularly true because other serious health outcomes (both negative and positive) have been associated with the same exposures. We draw from historical examples to put in perspective the arguments of association versus causation, as well as to discuss benefits versus risks of immediate and long-term preventive actions.

Leukemia is the most common cancer in children. Treatment of childhood leukemia has undergone dramatic change in the last 50 years. Today, ~90% of children are cured of this once nearly uniformly fatal disease. Sadly, accompanying this miraculous advance in treatment, the incidence of



<sup>a</sup>School of Public Health, University of California, Berkeley, Berkeley, California; <sup>b</sup>School of Medicine, Stanford University, Stanford, California; and <sup>c</sup>Department of Epidemiology and Biostatistics, and <sup>d</sup>Western States Pediatric Environmental Health Specialty Unit, University of California, San Francisco, San Francisco, California

Dr Metayer conceptualized the manuscript, reviewed the literature, and codrafted the initial manuscript; Drs Dahl and Wiemels critically reviewed the manuscript; Dr Miller participated in the concept of the manuscript, reviewed the literature, and codrafted the initial manuscript; and all authors approved the final manuscript as submitted.

**DOI:** 10.1542/peds.2015-4268H

Accepted for publication Feb 16, 2016

Address correspondence to Catherine Metayer, School of Public Health, University of California, Berkeley, 1995 University Ave, Ste 460, Berkeley, CA 94704. E-mail: cmetayer@berkeley.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2016 by the American Academy of Pediatrics

**FINANCIAL DISCLOSURE:** The authors have indicated they have no financial relationships relevant to this article to disclose.

**FUNDING:** Research reported in this publication was supported by the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health under awards P01ES018172 and P50ES018172 (the content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health), and by agreement RD83451101 and RD83615901 awarded by the US Environmental Protection Agency (EPA) to Dr Metayer (it has not been formally reviewed by EPA). The views expressed in this document are solely those of Drs Metayer, Dahl, Wiemels, and Miller, and do not necessarily reflect those of the EPA. Dr Miller was also supported by cooperative agreement award 1 U61TS000237-02 from the Agency for Toxic Substances and Disease Registry (ATSDR). Its contents are the responsibility of the authors and do not necessarily represent the official views of the ATSDR. The US EPA supported the Pediatric Environment Health Specialty Unit by providing partial funding to ATSDR under interagency agreement DW-75-92301301. EPA, NIEHS, and ATSDR do not endorse the purchase of any commercial products or services mentioned in this publication. Funded by the National Institutes of Health (NIH).

**POTENTIAL CONFLICT OF INTEREST:** The authors have indicated they have no potential conflicts of interest to disclose.

childhood leukemia (age 0–14 years) in the United States has increased an average of 0.7% per year since 1975<sup>1</sup>; taking into account the annual percent change during the 35 years between 1975 and 2012, the overall percent change was estimated to be 33% for acute lymphoblastic leukemia (ALL) and 42% for acute myeloid leukemia (AML).<sup>2</sup> Moreover, Hispanic children in the United States experience a higher incidence rate (and increase in rate) of childhood ALL compared with non-Hispanics.<sup>3,4</sup> The side effects of treatment (both short- and long-term), secondary cancers, and the emotional and financial costs to children and families are all reasons that we should not settle for improved medical care, but also focus on primary prevention of this disease.

The steady increase in incidence is a strong indicator that the origins of childhood leukemia are influenced not only by genetics. Studies support that environmental chemical exposures and altered patterns of infection during early development may play an important role.<sup>5</sup> Despite these observations, only a small fraction of National Institutes of Health funding goes to support studies of etiologic factors related to the development of childhood leukemias, with most targeting diagnosis and treatment advances.

To date, there are no prevention programs for childhood leukemia that we have been able to identify. The US Centers for Disease Control and Prevention has been exploring the possibility of primary prevention of childhood cancer (see other papers in this supplement). This lack of public health prevention activities is likely owing in part to a lack of consensus about whether the level of evidence warrants a causative determination. This conclusion is supported by statements from professional societies that we do not know the cause of most childhood leukemia and that children who get

leukemia are not exposed to any known risk factors.<sup>6</sup>

The level of evidence necessary to determine causation and whether something needs a causative label for preventive actions to be undertaken has historically been viewed in different ways. The European community recognizes a precautionary principle, which provides justification for public policy actions in situations of uncertainty to reduce health threats.<sup>7</sup> In the United States, proof of harm is more stringently required under the regulatory rubric.

In clinical medicine, the dependence on guidance resulting from systematic reviews (eg, Cochrane, GRADE) has become the gold standard. In environmental health, the current schema of systematic reviews has been recognized as at times problematic for the protection of public health.<sup>8</sup> Human studies of environmental exposures are almost exclusively limited to observational studies, a category given a low quality of evidence rating. At times, the necessary studies may be considered unethical and so may never be done despite substantial evidence of harm. Adaptation of systematic reviews are being developed to respond to the needs of environmental health.<sup>9,10</sup>

In a survey conducted among health professionals providing care to children with leukemia,<sup>11</sup> clinicians indicated that although they believe that environmental exposures are significant risk factors, they felt uncomfortable addressing these issues with patients. Pediatric oncologists are provided little training about environmental health, but overwhelmingly indicate an interest in learning more about the evolving science on environmental causes of childhood cancer.

The history of environmental health is rife with examples of “late-learned lessons”. These are chemicals with early warning signs

of health impacts that took many years and often decades to prove conclusively the hazard, during which time they continued to be used and in some cases accumulated in the environment.<sup>12</sup> Well-known examples include PCBs, DDT, lead, and tobacco smoke.

An example of medicine taking timely action based on limited evidence suggesting likely harm but without determination of causation is sudden infant death syndrome (SIDS). In 1992, an American Academy of Pediatrics (AAP) policy statement suggested that infants be placed to sleep on their backs or sides rather than prone, despite the lack of prospective randomized clinical trials. Some had argued for these trials and better understanding of mechanisms of action before undertaking any intervention, but the AAP launched the “Back to Sleep” campaign to discourage prone sleeping in 1994. By 2000, the US mortality for SIDS had dropped to 50% of the 1990 rates. A 2011 AAP policy statement included recommendations for a suite of other sleep-related interventions based on findings of varying scientific rigor.<sup>13</sup> Three levels of recommendations were outlined based on the strength of evidence conforming to the US Preventive Services Task Force protocols. The strongest, level A, is based on: “Recommendations are based on good and consistent scientific evidence (ie, there are consistent findings from at least 2 well-designed, well-conducted case-control studies, a systematic review, or a meta-analysis). There is high certainty that the net benefit is substantial, and the conclusion is unlikely to be strongly affected by the results of future studies”. Several of the exposures related to childhood leukemia would by this standard, be considered level A. There are many similarities between SIDS and childhood leukemia, including being rare diseases, difficult to study, not

conducive to randomized control studies, but with many studies consistently finding significant associations with a variety of risk factors. Thus, there is precedent for taking preventive measures in light of less than full agreement that causation has been proven.

Many of the risk factors for childhood leukemia in the following review result from widespread exposures of parents before and during pregnancy, as well as to their children after birth. Even though these exposures individually represent relatively modest risk, because they are common, a significant portion of the disease burden may be attributable to them. Thus, a concerted public health effort to reduce exposure has the potential to reduce the overall rate significantly.

### CURRENT KNOWLEDGE ON “ACTIONABLE” RISK FACTORS OF CHILDHOOD LEUKEMIA

Many epidemiologic studies of childhood leukemia have been conducted in the United States and worldwide during the last decades, with a common goal of identifying pre- and postnatal risk factors that are related to the parents' and child's environment broadly defined, such as smoking, alcohol use, diet, and chemical exposures at (and near) home and workplaces. Some of those factors have already been classified as possible, probable, or definite carcinogens to humans based on reviews of human and nonhuman studies by the International Agency for Research on Cancer<sup>14</sup> and the Environmental Protection Agency.<sup>15</sup> Although those reviews are often limited in scope and largely for adult cancers, the weight of evidence for carcinogenicity, when available, should also strengthen the case for childhood leukemia. Another prominent hypothesis in the etiology of childhood leukemia, specifically ALL, is that aberrant priming of

the child's immune system in response to allergies and infections may lead to leukemic clones and subsequent overt leukemia. Several of the chemicals or mixtures described below are known to alter immune function, providing additional rationale for a possible impact of certain chemicals on the development of childhood ALL.

Because of the rarity of the disease, our current knowledge on candidate risk factors for childhood leukemia is mostly derived from case-control studies and with various degrees of validation between independent studies. More recently, meta-analyses of published results and pooled analyses of original data from studies participating in the Childhood Leukemia International Consortium<sup>16–21</sup> have been conducted in an attempt to comprehend the extended body of literature and data, providing an overall direction and magnitude of the associations between several environmental factors and childhood leukemia, while accounting for study heterogeneity. Combining data also allows analysis of rarer subtypes of childhood leukemia, such as AML, and quantification of leukemia risk in understudied and vulnerable populations as defined, for example, by racial/ethnic background. Cohort studies of childhood leukemia are less frequent and often limited by small sample sizes even in the context of collaborative efforts, such as the International Childhood Cancer Cohort Consortium.<sup>22,23</sup> Nonetheless, cohort studies can be valuable in confirming temporality of events.

Few studies have used environmental sampling<sup>24,25</sup> and biomarkers<sup>26–29</sup> to better characterize chemical exposures, which could provide powerful insights to better understand the continuum between routes of exposure, chemical body burden, and risk of childhood leukemia. Several studies have

reported that genes in xenobiotic pathways, such as *CYP2E1*, *GSTM1*, *NQO1*, *NAT2*, and *MDR1*, influence the risk of childhood leukemia alone or in combination with chemical exposures.<sup>30</sup> Here, we provide examples of risk factors for childhood leukemia with strong levels of evidence to date, and for which preventive measures can be implemented at the individual level through information to families and health care providers or, at the population-level, leveraging existing programs and resources.

### Pesticides

Opportunities for a child's (and fetus') exposure to pesticides are ubiquitous and include residential use, migration from nearby agricultural areas, and parental workplaces. Use of pesticides in and around the home is of particular interest because of young children's hand and mouth contact with surfaces potentially contaminated by persistent pollutants, including pesticides. Certain organochlorine compounds, such as those banned in the 1970s (eg, DDT) have been found to persist many years in home carpet dust,<sup>24,31</sup> therefore presenting an opportunity for long-term exposure. Recent pooled analyses from the Childhood Leukemia International Consortium, including up to 13 studies worldwide and representing up to ~10 000 leukemia cases, reported elevated risks of childhood ALL and AML with home use of pesticides before and after birth (Table 1).<sup>19</sup> Maternal occupational exposure to pesticides also increased the risk of childhood AML, whereas preconception paternal exposure slightly increased the risk of childhood ALL.<sup>17</sup> These findings are derived, for the most part, from other meta-analyses of published data.<sup>32–34</sup>

Childhood leukemia studies using dust samples and geographic information systems to assess indoor and outdoor pesticide exposure have

**TABLE 1** Selected Meta- and Pooled Analyses of Pesticide Exposure and Risk of Childhood Leukemia Subtypes

| Source                          | Source of Exposure        | Period of Exposure  | ALL         |                  | ANLL/AML    |                  |
|---------------------------------|---------------------------|---------------------|-------------|------------------|-------------|------------------|
|                                 |                           |                     | No. Studies | OR (95% CI)      | No. Studies | OR (95% CI)      |
| Van Maele-Fabry, 2011 (32) (MP) | Residential (insecticide) | Ever                | 5           | 2.11 (1.80–2.48) | 3           | 2.30 (1.53–3.45) |
|                                 |                           | Pregnancy           | 4           | 2.22 (1.87–2.64) | 2           | 3.13 (1.45–6.75) |
|                                 |                           | After birth         | 2           | 1.78 (1.12–2.84) | n/a         | n/a              |
| Bailey, 2015 (19) (PO)          | Residential               | Preconception       | 12          | 1.39 (1.25–1.55) | 9           | 1.49 (1.02–2.16) |
|                                 |                           | Pregnancy           | 12          | 1.43 (1.32–1.54) | 9           | 1.55 (1.21–1.99) |
|                                 |                           | After birth         | 12          | 1.36 (1.23–1.51) | 9           | 1.08 (0.76–1.53) |
| Van Maele-Fabry, 2010 (33) (MP) | Maternal occupation       | Ever                | 4           | 1.34 (0.70–2.59) | 2           | 2.68 (1.06–6.78) |
|                                 |                           | Paternal occupation | 3           | 1.09 (0.75–1.60) | 2           | 0.73 (0.19–2.76) |
| Bailey, 2014 (17) (PO)          | Maternal occupation       | Pregnancy           | 12          | 1.01 (0.78–1.30) | 5           | 1.94 (1.19–3.18) |
|                                 | Paternal occupation       | Preconception       | 12          | 1.20 (1.06–1.38) | 8           | 0.91 (0.66–1.24) |
| Bailey, 2014 (17) (MO + MP)     | Maternal occupation       | Pregnancy           | n/a         | n/a              | 9           | 3.30 (2.15–5.06) |
|                                 | Paternal occupation       | Preconception       | 14          | 1.23 (0.99–1.53) | n/a         | n/a              |

ANLL, acute nonlymphoblastic leukemia; CI, confidence interval; MO, meta-analysis of original data; MP, meta-analysis of published data; OR, odds ratio; n/a, not available; PO, pooled analysis of original data.

reported associations with specific types of pesticides based on target pest, phytochemical characteristics, or carcinogenicity.<sup>35,36</sup> Additional support for a causal link between pesticide exposure and childhood leukemia comes from adult studies, such as the Agricultural Health Study, a prospective cohort of pesticide applicators, reporting increased risks of hematopoietic tumors, including leukemia, with 12 agricultural pesticides registered in the United States/Canada.<sup>37</sup> Preliminary Agricultural Health Study analyses also suggested an overall increase of cancers in the offspring of fathers exposed to 3 out of the 16 pesticides evaluated, an observation that will be important to reproduce.<sup>38</sup>

Several pesticides commonly used in and around residences have been classified as possible human carcinogens (eg, tetramethrin, piperonyl butoxide, trifluralin) or probable/likely human carcinogens (eg, propoxur, permethrin, carbaryl).<sup>15</sup> Many other chemicals, however, have not been assessed for human carcinogenicity. Recent in vitro laboratory studies have shown that pesticides, such as organophosphates, carbamates, and pyrethroids, can induce increased DNA damage in human peripheral lymphocytes.<sup>39,40</sup> Certain pesticides,

such as DDT, pyrethroids, and chlorinated pesticides, can also dysregulate the immune system, a key pathway in the development of childhood ALL.<sup>41,42</sup> Most toxicologic studies of pesticides have focused on active ingredients; however, the so-called inert ingredients added to enhance pesticide activity may have significant toxicological properties, as shown for glyphosate.<sup>43</sup>

### Tobacco Smoking

Tobacco smoking contains at least 60 known human or animal carcinogenic compounds, such as benzene, formaldehyde, 1,3 butadiene, and polycyclic aromatic hydrocarbons, and is responsible for ~20% of all adult cancers, including AML.<sup>44</sup> Tobacco-based products affect both germ and somatic cells<sup>45</sup> or may act through other mechanisms, such as DNA methylation.<sup>46,47</sup> Because many carcinogens are known to cross the placenta, early case-control studies of childhood leukemia, mostly ALL, have focused on in utero exposure to maternal smoking. However, results from most individual studies and meta-analyses have been surprisingly negative (Table 2),<sup>48–50</sup> raising possible methodologic issues, such as selection and recall biases or presence of competitive risks (eg, fetal loss). Also, studies taking into

account genetic polymorphisms in metabolic pathways reported that *CYP1A1* variants and a *GSTM1* deletion may modify the effect of in utero exposure to tobacco smoking.<sup>30,51</sup>

Although the debate is still open regarding the impact of maternal smoking on the risk of childhood leukemia, stronger evidence is accumulating for the role of paternal smoking as reported in several individual studies and meta-analyses of ALL.<sup>48,50,52,53</sup> In a study examining the effect of paternal smoking by period of exposure, elevated risks of childhood ALL were observed only when fathers reported smoking both before and after birth (and not those smoking only before birth or only after birth),<sup>54</sup> suggesting that pre- and postnatal cellular insults were necessary steps, consistent with the 2-hit model of leukemogenesis.<sup>55,56</sup>

Molecular epidemiologic studies have provided important insights for understanding the etiology of specific subtypes of adult AML, such as those harboring chromosome translocation t(8;21).<sup>57</sup> Likewise, childhood leukemia studies have revealed subtype-specific associations between tobacco smoking,<sup>54</sup> as well as between exposure to paints/solvents, and ALL with t(12;21)<sup>16,58</sup> and AML with structural abnormalities.<sup>58</sup> Although

**TABLE 2** Selected Meta-analyses of Published Data of Tobacco Smoking and Risk of Childhood ALL

| Source                    | Source of Exposure                       | Period of Exposure | No. Studies | OR (95% CI)      |
|---------------------------|--|--------------------|-------------|------------------|
| Liu, 2011 (52)            | Paternal (yes/no)                        | Preconception      | 13          | 1.25 (1.08–1.46) |
|                           | Paternal (highest exposure index)        | Preconception      | 10          | 1.38 (1.11–1.72) |
|                           | Paternal (yes/no)                        | Pregnancy          | 8           | 1.24 (1.07–1.43) |
|                           | Paternal (highest exposure index)        | Pregnancy          | 4           | 1.28 (0.93–1.76) |
|                           | Paternal (yes/no)                        | After birth        | 7           | 1.24 (0.96–1.60) |
|                           | Paternal (highest exposure index)        | After birth        | 6           | 1.33 (1.00–1.78) |
| Milne, 2012 (53)          | Paternal (yes/no)                        | Preconception      | 10          | 1.15 (1.06–1.24) |
|                           | Paternal ( $\geq 20$ cigs/day versus no) | Preconception      | 7           | 1.44 (1.24–1.68) |
| Klimentopoulou, 2012 (49) | Maternal (yes/no)                        | Pregnancy          | 20          | 1.03 (0.95–1.12) |

CI, confidence interval; OR, odds ratio.

**TABLE 3** Meta- and Pooled Analyses on Exposure to Paint, Solvents, and Petroleum Products and Risk of Childhood ALL

| Study                  | Source of Exposure               | Period of Exposure      | No. Studies | OR (95% CI)      |
|------------------------|----------------------------------|-------------------------|-------------|------------------|
| Zhou, 2014 (50) (MP)   | Solvents; any sources; maternal  | Pregnancy               | 7           | 1.25 (1.09–1.45) |
|                        | Petroleum, any sources; maternal | Pregnancy               | 7           | 1.42 (1.10–1.84) |
|                        | Paint; any sources; maternal     | Pregnancy               | 7           | 1.23 (1.02–1.42) |
| Bailey, 2015 (16) (PO) | Paint; residential; any users    | 12 mo before conception | 2           | 1.00 (0.86–1.17) |
|                        |                                  | 3 mo before conception  | 5           | 1.54 (1.28–1.85) |
|                        |                                  | Pregnancy               | 8           | 1.14 (1.04–1.25) |
|                        |                                  | After birth             | 4           | 1.22 (1.07–1.39) |
| Bailey, 2014 (18) (PO) | Paint; occupational; paternal    | 12 mo before conception | 12          | 0.93 (0.76–1.14) |
|                        | Paint; occupational; maternal    | Pregnancy               | 11          | 0.81 (0.39–1.68) |

CI, confidence interval; MP, meta-analysis of published data; OR, odds ratio; PO, pooled analysis of original data.

subgroup analyses suffer from small sample sizes, they provide insights in possible causal pathways that are specific to leukemia subtypes.

### Paints and Solvents

With few exceptions, case-control studies have reported increased risks of childhood ALL and AML with exposure to paints and solvents at the home or workplace of the parents based on self-reports and/or expert exposure assessment. In an attempt to summarize the literature on maternal exposures during pregnancy to paints, solvents, and petroleum products from residential and occupational sources, a recent meta-analysis of published data reported 1.2- to 1.4-fold increased risks of childhood ALL associated with these exposures (Table 3).<sup>50</sup> A pooled analysis of original data reported elevated risks of childhood ALL and AML with use of paints at home,<sup>16</sup> but not at the workplace (Table 3).<sup>18</sup>

### Outdoor Air Pollution

Recent comprehensive reviews and meta-analyses reported a statistically

significant 1.2- to 1.5-fold increased risk of childhood leukemia associated with various markers of air pollution (eg, benzene, NO<sub>2</sub>, and proximity to traffic density), after accounting for study heterogeneity.<sup>59,60</sup> Associations were observed for ambient exposures early in life and, to a lesser extent, before birth. The independent contribution of particulate matter (PM<sub>10</sub>) has been suggested in the development of leukemia.<sup>61,62</sup> Studies of childhood brain tumors and other cancers also reported associations with ambient 3-butadiene, benzene, and particulate matter.<sup>62,63</sup>

Overall, the similarity between tobacco smoke, ambient air pollutants, and paints and solvents in terms of mixtures of carcinogenic compounds and consistent tendencies to increase the risk of childhood leukemia is noteworthy, despite differences in exposure assessment (self-reports versus geocoding) and source of study participants. This observation lends further support for the probable role of volatile and persistent organic

compounds in the development of the disease.

### Nutrition at Critical Periods of the Fetus and Child's Development

The importance of prenatal folic acid supplementation for preventing neural tube defects and other birth defects has been recognized for decades.<sup>64</sup> Folic acid and other B vitamins and nutrients involved in the 1-carbon metabolism also have anticancerous properties, mainly through their role on DNA synthesis and methylation. A pooled analyses of original data from 12 studies worldwide showed that prenatal intake of folic acid and other vitamins before conception and during pregnancy reduced the risk of childhood ALL and AML,<sup>21</sup> a finding confirmed by a recent study.<sup>65</sup> Maternal dietary intake of folic acid and B<sub>12</sub> vitamins have also been shown to reduce the risk of childhood ALL.<sup>66</sup> Similarly, the current literature generally suggests that a healthy maternal diet around the time of conception/early pregnancy and a child's diet during

the early years of life are protective. Reduced leukemia risks have been associated with consumption of fruits,<sup>67,68</sup> legumes,<sup>68,69</sup> proteins,<sup>68,70</sup> soybean,<sup>69</sup> and milk/dairy,<sup>70</sup> whereas increased risks were associated with consumption of added lipids<sup>70</sup> and cured/smoked meat or fish.<sup>69,71</sup>

It is well-documented that breastfeeding reduces the risk of childhood leukemia by ~10% overall and by 20% for women breastfeeding 6 months and longer.<sup>72,73</sup> Promoting breastfeeding during prenatal and postnatal visits is practical and cost-efficient. However, there was a suggestion that maternal smoking during breastfeeding was associated with a higher risk of leukemia.<sup>74,75</sup> Until more studies are available to assess beneficial versus harmful effects of breastfeeding with contaminated milk, it is prudent to encourage breastfeeding, but also reduce exposure to tobacco smoke and other chemicals during this critical time period.

## DISCUSSION

Although not flawless, observational and toxicological studies point to a strong basis for a causal association of small to moderate magnitude between several chemicals and childhood leukemia. Findings that derive mostly from individual case-control studies or pooled/meta-analyses may have inherent limitations owing to retrospective assessment of exposure, control selection, and study heterogeneity. However, prospective cohort study design is not easily applicable for studying childhood leukemia because of study size requirements, and may not be better than a case control study if exposure assessment is not as good or if the size limits the ability to look at subgroupings based on disease markers or classification or windows of exposure. Regardless of the approach, one could argue that a more complete evidence-based

assessment must be provided for every single compound. We are supportive of this approach, but this is time consuming and in some instances impossible to implement for newly registered products. Until additional information can strongly refute our current knowledge, measures are warranted for conceiving parents, childbearing mothers, and young children to avoid chemical exposures from various sources as we described.

Currently, there are no cancer prevention activities that we can identify directed at the primary prevention of childhood cancer. There are some programs aimed at reduction of childhood exposures for adult cancer prevention, such as tobacco use and sunburn prevention education. This is true despite accumulating evidence that a number of common exposures impact risk as reviewed above. Even a relatively modest increase in risk of a common exposure may result in a significant burden of disease.

Each of the factors discussed in this paper that is associated with altered risk of childhood leukemia is also associated with altering the risk of other health outcomes in children. This should mitigate concerns that an error in attribution would result in unwarranted actions with potential negative impacts on health or increased financial burdens. In fact, many of these same exposures that are implicated in the risk for childhood leukemia have substantial documentation of their noncancer health impacts. Many already have clinical or public health recommendations that would result in exposure reductions if implemented whole-heartedly with coordinated funding and public health campaigns. Clinical recommendations and public health programs other than in tobacco control have had limited funding and penetration for these groups and exposures. Primary prevention

of childhood leukemia with its high visibility and public concern may become an important element in support and guidance for national programs, such as Healthy Homes (<http://www.cdc.gov/healthyhomes/>). Examples of the co-benefits with cancer and noncancer end points to be gained from coordinated programs for exposure reduction are noted below.

## Pesticides

Pesticide exposures have been implicated not only in childhood leukemia and brain tumors but also in risks for neurodevelopmental disorders, asthma, adult cancers, reproductive toxicity, and other health impacts.<sup>76-80</sup> Integrated pest management is an approach to minimizing pesticide use in residential, school, and agricultural settings and already recommended as the most sensible approach to pests by the US Environmental Protection Agency and university extension services. It integrates nonchemical methods with chemical controls only when necessary to provide the least toxic control of pests. Integrated pest management has proven to be cost effective and at times more effective at long-term control of pests while reducing pesticide exposure (including during pregnancy).<sup>81,82</sup>

## Tobacco Smoking

The health impacts of tobacco smoke during pregnancy and secondhand smoke in children, including SIDS, reduced fetal growth, neurodevelopmental, and respiratory outcomes, are well known and the focus of many public health campaigns.<sup>83,84</sup> Associations observed between tobacco smoke and childhood leukemia are complex, varying by leukemia subtype, period of exposure, intensity of exposure, and possible genetic susceptibility. Nonetheless, in light of the potent carcinogens contained in tobacco smoke, it is prudent to educate

parents about additional harmful effects of tobacco smoke. The association of preconception smoking in fathers with risk for childhood leukemia, however, is not well known and may be an effective additional deterrent to smoking for some.

### Folate Supplementation

As described earlier, a periconception diet rich in folate or folate supplementation as generally prescribed is associated with a reduction in childhood leukemia risk. Folate supplementation or a diet rich in folate before conception and early in pregnancy not only appears to be protective in the case of leukemia, but also reduces neural tube and other birth defects and may reduce the risk of developing autism.<sup>85,86</sup> Supplementation with folate is well accepted and recommended by the US Preventive Services Task Force,<sup>87</sup> the American College of Obstetrics and Gynecology,<sup>88</sup> and the American Academy of Family Practice.<sup>89</sup> Despite these recommendations, only 11% to 60% of women (depending on demographics) in the United States receive preconception supplementation.<sup>90</sup>

### Preconception Care

Although environmental health has been addressed by the AAP and others for some time, it is only recently that those involved in the care and support of women of childbearing age have begun to consider these factors in health promotion.<sup>91-93</sup> The current new emphasis on preconception care provides an ideal opportunity to begin providing information that will reinforce environmental health literacy and prevention activities within the context of an evolving program and standard of care.

### Breaking the Barrier of Inaction

The lack of public health campaigns specifically focused on primary prevention of childhood leukemia

may result from the absence of authoritative bodies determining exposure factors to be causative, despite steadily accumulating evidence that environmental exposures increase the risk of childhood leukemia. There will always be a measure of ambiguity in assessing risk. Assessment of the interaction of multiple exposures, impacts over the life course, and multiple outcomes associated with single chemical exposures are largely more a hope for the future than current reality.

The “Back to Sleep” campaign to reduce SIDS is an example of a successful public health measure saving many lives despite being adopted with less than uniform agreement on causation. Although the Surgeon General’s Report on Smoking and Health published in 1964 stopped short of finding that smoking caused cardiovascular disease, it concluded that, never the less, action was warranted: “Although the causative role of cigarette smoking in deaths from coronary disease is not proven, the Committee considers it more prudent from the public health viewpoint to assume that the established association has causative meaning than to suspend judgment until no uncertainty remains.”<sup>94</sup>

Because the activities suggested by research on risks for childhood leukemia largely reinforce programs already in existence by different public health entities (eg, tobacco cessation, healthy diet during pregnancy and folate supplementation, avoidance of exposure to volatile organic compounds, pesticides, and paints and solvents), environmental health agencies can partner to extend current programs with similar goals. Opportunities for innovative cross agency, multidisciplinary program development include:

- Adding risk reduction for childhood leukemia to

environmental health literacy education activities as appropriate for the general public.

- Inclusion of environmental health messaging in preconception and prenatal care and programs, such as “Text 4 Baby” and “Bright Futures”.
- Use of emerging systematic review methodologies to evaluate risk, as appropriate, with the goal of environmental health programs being recognized as evidence-based medicine.
- Development of programs to integrate environmental health education for nursing, physician, and allied health professionals (during schooling and postgraduate education) that include risk factors associated with childhood leukemia.
- Development of policy initiatives that would reduce exposure during prepregnancy, pregnancy, and early childhood to chemicals associated with childhood leukemia (and other negative outcomes).

### CONCLUSIONS

The published data available linking early life environmental exposures to childhood leukemia are more comprehensive than for most other cancers, adult or child. The link to several exposures is clear and consistent and there are now meta-analyses, pooled analyses, and systematic reviews published. Although there is hesitancy to determine causation based on case-control studies, prospective cohort study design also presents limitations. We have enough information now to begin to explore ways in which to reduce children’s exposures that have been consistently linked to increased risk for childhood leukemia. As in SIDS and other rare diseases, the impact of intervention can only really be



studied by widespread population adoption of prevention activity followed by evaluation of changes in incidence rates.

#### ABBREVIATIONS

AAP: American Academy of Pediatrics

ALL: acute lymphoblastic leukemia

AML: acute myeloid leukemia

SIDS: sudden infant death syndrome

#### REFERENCES

1. Howlader NNA, Krapcho M, Garshell J, et al, eds. *SEER Cancer Statistics Review, 1975–2010*. Bethesda, MD: National Cancer Institute; 2013
2. Howlader N, Noone A, Krapcho M, et al. *SEER Cancer Statistics Review, 1975–2012*. Bethesda, MD: National Cancer Institute, 2015
3. Barrington-Trimis JCM, Metayer C, Gauderman JW, Wiemels J, McKean-Cowdin R. Rising rates of acute lymphocytic leukemia in Hispanic Children: a review of trends in childhood leukemia incidence from 1992–2010. Paper presented at: American Association for Cancer Research; April 5–9, 2014; San Diego, CA
4. Ekanayake R, Miller M, Marty, M. *Report to the Legislature: Children's Environmental Health Program*. Sacramento, CA: Office of Environmental Health Hazard Assessment, California Environmental Protection Agency; 2014
5. Wiemels J. Perspectives on the causes of childhood leukemia. *Chem Biol Interact*. 2012;196(3):59–67
6. American Cancer Society. Can childhood leukemia be prevented? Available at: [www.cancer.org/cancer/leukemia/childhood/detailedguide/childhood-leukemia-prevention](http://www.cancer.org/cancer/leukemia/childhood/detailedguide/childhood-leukemia-prevention). Accessed May 26, 2016
7. Gee D. Establishing evidence for early action: the prevention of reproductive and developmental harm. *Basic Clin Pharmacol Toxicol*. 2008;102(2):257–266
8. Woodruff TJ, Sutton P; Navigation Guide Work Group. An evidence-based medicine methodology to bridge the gap between clinical and environmental health sciences. *Health Aff (Millwood)*. 2011;30(5):931–937
9. Woodruff TJ, Sutton P. The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. *Environ Health Perspect*. 2014;122(10):1007–1014
10. Rooney AA, Boyles AL, Wolfe MS, Bucher JR, Thayer KA. Systematic review and evidence integration for literature-based environmental health science assessments. *Environ Health Perspect*. 2014;122(7):711–718
11. Zachek CM, Miller MD, Hsu C, et al. Children's cancer and environmental exposures: professional attitudes and practices. *J Pediatr Hematol Oncol*. 2015;37(7):491–497
12. Harremoës P. *Late Lessons From Early Warnings: the Precautionary Principle 1896–2000*. Luxembourg: European Environment Agency; 2001
13. Moon RY; Task Force on Sudden Infant Death Syndrome. SIDS and other sleep-related infant deaths: expansion of recommendations for a safe infant sleeping environment. *Pediatrics*. 2011;128(5):1030–1039
14. Coglianò VJ, Baan R, Straif K, et al. Preventable exposures associated with human cancers. *J Natl Cancer Inst*. 2011;103(24):1827–1839
15. US Environmental Protection Agency. Chemicals evaluated for carcinogenic potential. Available at: [https://a816-healthpsi.nyc.gov/1137/pdf/carcclassJuly2004\\_1.pdf](https://a816-healthpsi.nyc.gov/1137/pdf/carcclassJuly2004_1.pdf). Accessed May 26, 2016
16. Bailey HD, Metayer C, Milne E, et al. Home paint exposures and risk of childhood acute lymphoblastic leukemia: findings from the Childhood Leukemia International Consortium. *Cancer Causes Control*. 2015;26(9):1257–1270
17. Bailey HD, Fritschi L, Infante-Rivard C, et al. Parental occupational pesticide exposure and the risk of childhood leukemia in the offspring: findings from the Childhood Leukemia International Consortium. *Int J Cancer*. 2014;135(9):2157–2172
18. Bailey HD, Fritschi L, Metayer C, et al. Parental occupational paint exposure and risk of childhood leukemia in the offspring: findings from the Childhood Leukemia International Consortium. *Cancer Causes Control*. 2014;25(10):1351–1367
19. Bailey HD, Infante-Rivard C, Metayer C, et al. Home pesticide exposures and risk of childhood leukemia: findings from the childhood leukemia international consortium. *Int J Cancer*. 2015;137(11):2644–2663
20. Metayer C, Milne E, Clavel J, et al. The Childhood Leukemia International Consortium. *Cancer Epidemiol*. 2013;37(3):336–347
21. Metayer C, Milne E, Dockerty JD, et al. Maternal supplementation with folic acid and other vitamins and risk of leukemia in offspring: a Childhood Leukemia International Consortium study. *Epidemiology*. 2014;25(6):811–822
22. Brown RC, Dwyer T, Kasten C, et al; International Childhood Cancer Cohort Consortium (I4C). Cohort profile: the International Childhood Cancer Cohort Consortium (I4C). *Int J Epidemiol*. 2007;36(4):724–730
23. Paltiel O, Tikellis G, Linet M, et al; International Childhood Cancer Cohort Consortium. Birthweight and childhood cancer: preliminary findings from the International Childhood Cancer Cohort Consortium (I4C). *Paediatr Perinat Epidemiol*. 2015;29(4):335–345
24. Whitehead TP, Metayer C, Ward MH, et al. Persistent organic pollutants in dust from older homes: learning from lead. *Am J Public Health*. 2014;104(7):1320–1326
25. Lagorio S, Ferrante D, Ranucci A, et al. Exposure to benzene and childhood leukaemia: a pilot case-control study. *BMJ Open*. 2013;3(2):e002275
26. Whitehead TP, Crispo Smith S, Park JS, Petreas MX, Rappaport SM, Metayer C. Concentrations of persistent organic pollutants in California children's whole blood and

- residential dust. *Environ Sci Technol*. 2015;49(15):9331–9340
27. Whitehead TP, Crispo Smith S, Park JS, Petreas MX, Rappaport SM, Metayer C. Concentrations of persistent organic pollutants in California women's serum and residential dust. *Environ Res*. 2015;136:57–66
  28. Zhang Y, Gao Y, Shi R, et al. Household pesticide exposure and the risk of childhood acute leukemia in Shanghai, China. *Environ Sci Pollut Res Int*. 2015;22(15):11755–11763
  29. Chokkalingam AP, Chun DS, Noonan EJ, et al. Blood levels of folate at birth and risk of childhood leukemia. *Cancer Epidemiol Biomarkers Prev*. 2013;22(6):1088–1094
  30. Brisson GD, Alves LR, Pombo-de-Oliveira MS. Genetic susceptibility in childhood acute leukaemias: a systematic review. *Ecancermedicalscience*. 2015;9:539
  31. Colt JS, Lubin J, Camann D, et al. Comparison of pesticide levels in carpet dust and self-reported pest treatment practices in four US sites. *J Expo Anal Environ Epidemiol*. 2004;14(1):74–83
  32. Van Maele-Fabry G, Lantin AC, Hoet P, Lison D. Residential exposure to pesticides and childhood leukaemia: a systematic review and meta-analysis. *Environ Int*. 2011;37(1):280–291
  33. Van Maele-Fabry G, Lantin AC, Hoet P, Lison D. Childhood leukaemia and parental occupational exposure to pesticides: a systematic review and meta-analysis. *Cancer Causes Control*. 2010;21(6):787–809
  34. Chen M, Chang CH, Tao L, Lu C. Residential exposure to pesticide during childhood and childhood cancers: a meta-analysis. *Pediatrics*. 2015;136(4):719–729
  35. Metayer C, Colt JS, Buffler PA, et al. Exposure to herbicides in house dust and risk of childhood acute lymphoblastic leukemia. *J Expo Sci Environ Epidemiol*. 2013;23(4):363–370
  36. Rull RP, Gunier R, Von Behren J, et al. Residential proximity to agricultural pesticide applications and childhood acute lymphoblastic leukemia. *Environ Res*. 2009;109(7):891–899
  37. Weichenthal S, Moase C, Chan P. A review of pesticide exposure and cancer incidence in the Agricultural Health Study cohort. *Environ Health Perspect*. 2010;118(8):1117–1125
  38. Flower KB, Hoppin JA, Lynch CF, et al. Cancer risk and parental pesticide application in children of Agricultural Health Study participants. *Environ Health Perspect*. 2004;112(5):631–635
  39. Moretti M, Marcarelli M, Villarini M, Fatigoni C, Scassellati-Sforzolini G, Pasquini R. In vitro testing for genotoxicity of the herbicide terbutryn: cytogenetic and primary DNA damage. *Toxicol In Vitro*. 2002;16(1):81–88
  40. Undeğer U, Başaran N. Effects of pesticides on human peripheral lymphocytes in vitro: induction of DNA damage. *Arch Toxicol*. 2005;79(3):169–176
  41. Hoffman N, Tran V, Daniyan A, et al. Bifenthrin activates homotypic aggregation in human T-cell lines. *Med Sci Monit*. 2006;12(3):BR87–BR94
  42. Phillips TM. Assessing environmental exposure in children: immunotoxicology screening. *J Expo Anal Environ Epidemiol*. 2000;10(6 pt 2):769–775
  43. Richard S, Moslemi S, Sipahutar H, Benachour N, Seralini GE. Differential effects of glyphosate and roundup on human placental cells and aromatase. *Environ Health Perspect*. 2005;113(6):716–720
  44. Parkin DM. 2. Tobacco-attributable cancer burden in the UK in 2010. *Br J Cancer*. 2011;105(suppl 2):S6–S13
  45. Demarini DM. Declaring the existence of human germ-cell mutagens. *Environ Mol Mutagen*. 2012;53(3):166–172
  46. Marczylo EL, Amoako AA, Konje JC, Gant TW, Marczylo TH. Smoking induces differential miRNA expression in human spermatozoa: a potential transgenerational epigenetic concern? *Epigenetics*. 2012;7(5):432–439
  47. Köks G, Uudelepp ML, Limbach M, Peterson P, Reimann E, Köks S. Smoking-induced expression of the GPR15 gene indicates its potential role in chronic inflammatory pathologies. *Am J Pathol*. 2015;185(11):2898–2906
  48. Chang JS. Parental smoking and childhood leukemia. *Methods Mol Biol*. 2009;472:103–137
  49. Klimentopoulou A, Antonopoulos CN, Papadopoulou C, et al. Maternal smoking during pregnancy and risk for childhood leukemia: a nationwide case-control study in Greece and meta-analysis. *Pediatr Blood Cancer*. 2012;58(3):344–351
  50. Zhou Y, Zhang S, Li Z, 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):e110466
  51. Clavel J, Bellec S, Rebouissou S, et al. Childhood leukaemia, polymorphisms of metabolism enzyme genes, and interactions with maternal tobacco, coffee and alcohol consumption during pregnancy. *Eur J Cancer Prev*. 2005;14(6):531–540
  52. Liu R, Zhang L, McHale CM, Hammond SK. Paternal smoking and risk of childhood acute lymphoblastic leukemia: systematic review and meta-analysis. *J Oncol*. 2011;854584
  53. Milne E, Greenop KR, Scott RJ, et al. Parental prenatal smoking and risk of childhood acute lymphoblastic leukemia. *Am J Epidemiol*. 2012;175(1):43–53
  54. Metayer C, Zhang L, Wiemels JL, et al. Tobacco smoke exposure and the risk of childhood acute lymphoblastic and myeloid leukemias by cytogenetic subtype. *Cancer Epidemiol Biomarkers Prev*. 2013;22(9):1600–1611
  55. Greaves MF. Aetiology of acute leukaemia. *Lancet*. 1997;349(9048):344–349
  56. Wiemels JL, Cazzaniga G, Daniotti M, et al. Prenatal origin of acute lymphoblastic leukaemia in children. *Lancet*. 1999;354(9189):1499–1503
  57. Lichtman MA. Cigarette smoking, cytogenetic abnormalities, and acute myelogenous leukemia. *Leukemia*. 2007;21(6):1137–1140
  58. Scéolo G, Metayer C, Zhang L, et al. Household exposure to paint and petroleum solvents, chromosomal translocations, and the risk of childhood leukemia. *Environ Health Perspect*. 2009;117(1):133–139
  59. Boothe VL, Boehmer TK, Wendel AM, Yip FY. Residential traffic exposure and childhood leukemia: a systematic

- review and meta-analysis. *Am J Prev Med.* 2014;46(4):413–422
60. Filippini T, Heck JE, Malagoli C, Del Giovane C, Vinceti M. A review and meta-analysis of outdoor air pollution and risk of childhood leukemia. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev.* 2015;33(1):36–66
  61. Vinceti M, Rothman KJ, Crespi CM, et al. Leukemia risk in children exposed to benzene and PM10 from vehicular traffic: a case-control study in an Italian population. *Eur J Epidemiol.* 2012;27(10):781–790
  62. Knox EG. Childhood cancers and atmospheric carcinogens. *J Epidemiol Community Health.* 2005;59(2):101–105
  63. Danysh HE, Mitchell LE, Zhang K, Scheurer ME, Lupo PJ. Traffic-related air pollution and the incidence of childhood central nervous system tumors: Texas, 2001–2009. *Pediatr Blood Cancer.* 2015;62(9):1572–1578
  64. Blom HJ, Shaw GM, den Heijer M, Finnell RH. Neural tube defects and folate: case far from closed. *Nat Rev Neurosci.* 2006;7(9):724–731
  65. Ajrouche R, Rudant J, Orsi L, et al. Maternal reproductive history, fertility treatments and folic acid supplementation in the risk of childhood acute leukemia: the ESTELLE study. *Cancer Causes Control.* 2014;25(10):1283–1293
  66. Bailey HD, Miller M, Langridge A, et al. Maternal dietary intake of folate and vitamins B6 and B12 during pregnancy and the risk of childhood acute lymphoblastic leukemia. *Nutr Cancer.* 2012;64(7):1122–1130
  67. Kwan ML, Block G, Selvin S, Month S, Buffler PA. Food consumption by children and the risk of childhood acute leukemia. *Am J Epidemiol.* 2004;160(11):1098–1107
  68. Kwan ML, Jensen CD, Block G, Hudes ML, Chu LW, Buffler PA. Maternal diet and risk of childhood acute lymphoblastic leukemia. *Public Health Rep.* 2009;124(4):503–514
  69. Liu CY, Hsu YH, Wu MT, et al; Kaohsiung Leukemia Research Group. Cured meat, vegetables, and bean-curd foods in relation to childhood acute leukemia risk: a population based case-control study. *BMC Cancer.* 2009;9:15
  70. Diamantaras AA, Dessypris N, Sergeantanis TN, et al. Nutrition in early life and risk of childhood leukemia: a case-control study in Greece. *Cancer Causes Control.* 2013;24(1):117–124
  71. Peters JM, Preston-Martin S, London SJ, Bowman JD, Buckley JD, Thomas DC. Processed meats and risk of childhood leukemia (California, USA). *Cancer Causes Control.* 1994;5(2):195–202
  72. Rudant J, Lightfoot T, Urayama K, et al. Childhood acute lymphoblastic leukemia and indicators of early immune stimulation: a Childhood Leukemia International Consortium (CLIC) Study. *Am J Epidemiol.* 2015;181(8):549–562
  73. Amitay EL, Keinan-Boker L. Breastfeeding and childhood leukemia incidence: a meta-analysis and systematic review. *JAMA Pediatr.* 2015;169(6):e151025
  74. Ferreira JD, Couto AC, Pombo-de-Oliveira MS, Koifman S; Brazilian Collaborative Study Group of Infant Acute Leukemia. Pregnancy, maternal tobacco smoking, and early age leukemia in Brazil. *Front Oncol.* 2012;2:151
  75. Chang JS, Selvin S, Metayer C, Crouse V, Golembesky A, Buffler PA. Parental smoking and the risk of childhood leukemia. *Am J Epidemiol.* 2006;163(12):1091–1100
  76. Engel SM, Bradman A, Wolff MS, et al. Prenatal organophosphorus pesticide exposure and child neurodevelopment at 24 months: an analysis of four birth cohorts. *Environ Health Perspect.* 2016;124(6):822–830
  77. Harley KG, Huen K, Aguilar Schall R, et al. Association of organophosphate pesticide exposure and paraoxonase with birth outcome in Mexican-American women. *PLoS One.* 2011;6(8):e23923
  78. Rauh V, Arunajadai S, Horton M, et al. Seven-year neurodevelopmental scores and prenatal exposure to chlorpyrifos, a common agricultural pesticide. *Environ Health Perspect.* 2011;119(8):1196–1201
  79. Mamane A, Raheison C, Tessier JF, Baldi I, Bouvier G. Environmental exposure to pesticides and respiratory health. *Eur Respir Rev.* 2015;24(137):462–473
  80. Bassil KL, Vakli C, Sanborn M, Cole DC, Kaur JS, Kerr KJ. Cancer health effects of pesticides: systematic review. *Can Fam Physician.* 2007;53(10):1704–1711
  81. Williams MK, Barr DB, Camann DE, et al. An intervention to reduce residential insecticide exposure during pregnancy among an inner-city cohort. *Environ Health Perspect.* 2006;114(11):1684–1689
  82. Williams MK, Rundle A, Holmes D, et al. Changes in pest infestation levels, self-reported pesticide use, and permethrin exposure during pregnancy after the 2000–2001 U.S. Environmental Protection Agency restriction of organophosphates. *Environ Health Perspect.* 2008;116(12):1681–1688
  83. Health Effects of Environmental Tobacco Smoke. *Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant.* Sacramento, CA: Office of Environmental Health Hazard Assessment, California Environmental Protection Agency; 2005
  84. US Department of Health and Human Services. *The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General—Executive Summary.* Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2006
  85. Surén P, Roth C, Bresnahan M, et al. Association between maternal use of folic acid supplements and risk of autism spectrum disorders in children. *JAMA.* 2013;309(6):570–577
  86. Schmidt RJ, Tancredi DJ, Ozonoff S, et al. Maternal periconceptional folic acid intake and risk of autism spectrum disorders and developmental delay in the CHARGE (CHildhood Autism Risks from Genetics and Environment) case-control study. *Am J Clin Nutr.* 2012;96(1):80–89
  87. US Preventive Services Task Force. Folic acid for the prevention of neural tube defects: U.S. Preventive

- Services Task Force recommendation statement. *Ann Intern Med.* 2009;150(9):626–631
88. ACOG Committee on Practice Bulletins. ACOG practice bulletin. Clinical management guidelines for obstetrician-gynecologists. Number 44, July 2003. (Replaces Committee Opinion Number 252, March 2001). *Obstet Gynecol.* 2003;102(1):203–213
  89. American Academy of Family Practice. Clinical Preventive Service Recommendation. Neural tube defects, prevention, folic acid supplementation, women. Available at: [www.aafp.org/patient-care/clinical-recommendations/all/neural-tube-defects.html](http://www.aafp.org/patient-care/clinical-recommendations/all/neural-tube-defects.html). Accessed May 26, 2016
  90. Khodr ZG, Lupo PJ, Agopian AJ, et al. Preconceptional folic acid-containing supplement use in the National Birth Defects Prevention Study. *Birth Defects Res A Clin Mol Teratol.* 2014;100(6):472–482
  91. Di Renzo GC, Conry JA, Blake J, et al. International Federation of Gynecology and Obstetrics opinion on reproductive health impacts of exposure to toxic environmental chemicals. *Int J Gynaecol Obstet.* 2015;131(3):219–225
  92. Sutton P, Woodruff TJ, Perron J, et al. Toxic environmental chemicals: the role of reproductive health professionals in preventing harmful exposures. *Am J Obstet Gynecol.* 2012;207(3):164–173
  93. American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 575: Exposure to toxic environmental agents. *Obstet Gynecol.* 2013;122(4):931–935
  94. US Department of Health, Education, and Welfare. *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service.* Washington, DC: US Department of Health, Education, and Welfare, Public Health Service; 1964