Cotinine

Environmental tobacco smoke (ETS), commonly referred to as secondhand smoke, is a complex mixture of gases and particles and includes smoke from burning cigarettes, cigars, and pipe tobacco (sidestream smoke), as well as exhaled mainstream smoke.[1] There are at least 250 chemicals in ETS that are known to be toxic or carcinogenic, including acrolein, ammonia, benzene, carbon monoxide, formaldehyde, hydrogen cyanide, nicotine, nitrogen oxides, and sulfur dioxide.[1,2] In 1992, EPA classified ETS as a known human carcinogen.[3] Children can be exposed to ETS in their homes or in places where people are allowed to smoke, such as some restaurants in some locations throughout the United States.

According to the U.S. Surgeon General, there is no safe level of exposure to ETS, and breathing even a small amount can be harmful to human health.[1] The Surgeon General has concluded that exposure to ETS causes sudden infant death syndrome (SIDS), acute lower respiratory infection, ear problems, and more severe asthma in children. Smoking by parents causes respiratory symptoms and slows lung growth in their children.[1] Young children appear to be more susceptible to the respiratory effects of ETS than are older children.[3-5] It is also possible that early-life exposures to ETS may lead to adverse health effects in adulthood. Exposure to ETS in childhood has been reported to be associated with early emphysema in adulthood among nonsmokers.[6]

The exposure of a pregnant woman to ETS can also be harmful to her developing fetus. The Surgeon General has determined that exposure of pregnant women to ETS causes a small reduction in mean birth weight and the evidence is suggestive (but not sufficient to infer causation) of a relationship between maternal exposure to environmental tobacco smoke during pregnancy and preterm delivery.[1] In addition, the Surgeon General concluded the evidence is suggestive but not sufficient to infer a causal relationship between prenatal and postnatal exposure to ETS and childhood cancer.[1]

Exposure to ETS in the home is influenced by adult behaviors, including the decisions to smoke at home and to allow visitors to smoke inside the home. Children living in homes with smoking bans have significantly lower levels of cotinine (a biological marker of exposure to ETS) in urine than children living in homes without smoking bans.[7] Household smoking bans can significantly decrease children's exposures to ETS, but do not completely eliminate them.[8]

In recent years there has been a significant decline in children's exposures to ETS.[9] This reduction is in part attributable to a decline in the percentage of adults who smoke. In 2010, an estimated 19.3% of adults were current smokers, down from 24.7% in 1997.[10,11] In addition, the prevalence of smoke-free households increased from 43% of U.S. homes in 1992–1993 to 72% in 2003.[12] However, despite the increasing numbers of adults disallowing smoking in the home, approximately 34% of children live in a home with at least one smoker as of 2009.[13] The

enactment of smoking bans in restaurants, bars, and other public places has led to a decrease in ETS exposure for both children and adults.[14] Recent studies suggest that smoking bans can reduce the number of asthma-related emergency room visits and hospitalizations and reduce asthmatic symptoms, including persistent wheeze, wheeze-medication use, and chronic night cough in children.[15-18]

Cotinine is considered the best biomarker of exposure to tobacco smoke for both active smokers and those exposed to ETS.[19] The two indicators that follow use the best nationally representative data currently available on blood cotinine levels over time for women of child-bearing age and children. Indicator B4 presents median and 95th percentile blood serum levels of cotinine for children ages 3 to 17 years. Indicator B5 presents median and 95th percentile blood serum levels of cotinine for women ages 16 to 49 years. Both indicators have been updated since the publication of *America's Children and the Environment, Third Edition* (January 2013) to include data from 2011–2012.

Indicator B4: Cotinine in nonsmoking children ages 3 to 17 years: Median and 95th percentile concentrations in blood serum, 1988–2012

Indicator B5: Cotinine in nonsmoking women ages 16 to 49 years: Median and 95th percentile concentrations in blood serum, 1988–2012

About the Indicators: Indicators B4 and B5 present concentrations of cotinine in blood serum of U.S. children ages 3 to 17 years and women ages 16 to 49 years. Cotinine is a marker of exposure to environmental tobacco smoke (ETS). The data are from a national survey that collects blood specimens from a representative sample of the population every two years, and then measures the concentration of cotinine in the blood serum. Indicator B4 presents concentrations of cotinine in children's blood serum over time and Indicator B5 presents concentrations of cotinine in women's blood serum over time. The focus on both children and women of child-bearing age is based on concern for potential adverse effects in children exposed to ETS and in children born to women who have been exposed to ETS.

NHANES

The National Health and Nutrition Examination Survey (NHANES) provides nationally representative biomonitoring data for cotinine. NHANES is designed to assess the health and nutritional status of the civilian noninstitutionalized U.S. population and is conducted by the National Center for Health Statistics, part of the Centers for Disease Control and Prevention (CDC). Interviews and physical examinations are conducted with approximately 10,000 people in each two-year survey cycle. CDC's National Center for Environmental Health measures concentrations of environmental chemicals in blood and urine samples collected from NHANES participants. Summaries of the measured values for more than 200 chemicals are provided in the *Fourth National Report on Human Exposure to Environmental Chemicals*.[19]

Environmental Tobacco Smoke (ETS) and Cotinine

Indicators B4 and B5 present blood serum levels of cotinine as a marker of exposure to ETS. Nicotine is a distinctive component of tobacco that is found in large amounts in tobacco smoke, including ETS. Once nicotine enters the body, it is rapidly broken down in a matter of a few hours into other chemicals. Cotinine is a primary breakdown product of nicotine, and has a longer half-life. This characteristic makes cotinine a better indicator than nicotine of an individual's exposure to ETS.[20-22]

Measurement of cotinine in blood serum is a marker for exposure to ETS in the previous few days.[23] Some studies have shown that, given the same exposure to tobacco smoke, cotinine levels may differ by race/ethnicity and sex, and there may be genetic differences in the rate at which cotinine is removed from the body.[1,24-28]

These indicators present cotinine levels for non-tobacco-users only. Children and women who were active smokers, as indicated by a relatively high serum cotinine level, were excluded from these statistics. For these analyses, individuals with a serum cotinine level greater than 10 nanograms of cotinine per milliliter of serum (ng/mL) are considered active smokers, and all individuals with cotinine levels below 10 ng/mL are considered nonsmokers.[19] Active smokers will almost always have serum cotinine levels above 10 ng/mL, and sometimes those levels will be higher than 500 ng/mL.[19,29] Nonsmokers who are exposed to typical levels of ETS have serum cotinine levels of less than 1 ng/mL, whereas those nonsmokers with heavy exposure to ETS will have serum cotinine levels between 1 and 10 ng/mL.[19]

Concentrations of cotinine in blood serum have been measured in all NHANES participants ages 4 years and older for the 1988–1991 and 1991–1994 survey cycles, and then for ages 3 years and older beginning with the 1999–2000 survey cycle.

For 2011–2012, NHANES collected cotinine biomonitoring data for 6,108 nonsmoking individuals ages 3 years and older, including 2,126 children ages 3 to 17 years and 1,277 women ages 16 to 49 years. Cotinine was detected in about 60% of all nonsmoking individuals sampled. The frequency of cotinine detection was 65% in children ages 3 to 17 years and 62% in women ages 16 to 49 years.[i] The median blood serum cotinine level for all nonsmoking NHANES participants in 2011–2012 was 0.02 ng/mL and the 95th percentile was 1.3 ng/mL.

Birth Rate Adjustment

Indicator B5 uses measurements of cotinine in blood serum of women ages 16 to 49 years to represent the distribution of ETS exposures to women who are pregnant or may become pregnant. For example, in 2003–2004, women aged 27 years had a 12% annual probability of giving birth, and women aged 37 years had a 4% annual probability of giving birth.[30] A birth rate-adjusted distribution of women's cotinine levels is used in calculating this indicator,[ii] meaning that the data are weighted using the age-specific probability of a woman giving birth.[31]

Data Presented in the Indicators

Indicator B4 presents median and 95th percentile concentrations of cotinine in blood serum over time as a marker of exposure to ETS among non-smoking children ages 3 to 17 years, using NHANES data from 1988–2012.

[i] The percentage for women ages 16 to 49 years is calculated with the birth rate adjustment described below.
[ii] There may be multiple ways to implement an adjustment to the data that accounts for birth rates by age. The National Center for Health Statistics has not fully evaluated the method used in ACE, or any other method intended to accomplish the same purpose, and has not used any such method in its publications. NCHS and EPA are working together to further evaluate the birth rate adjustment method used in ACE and alternative methods.

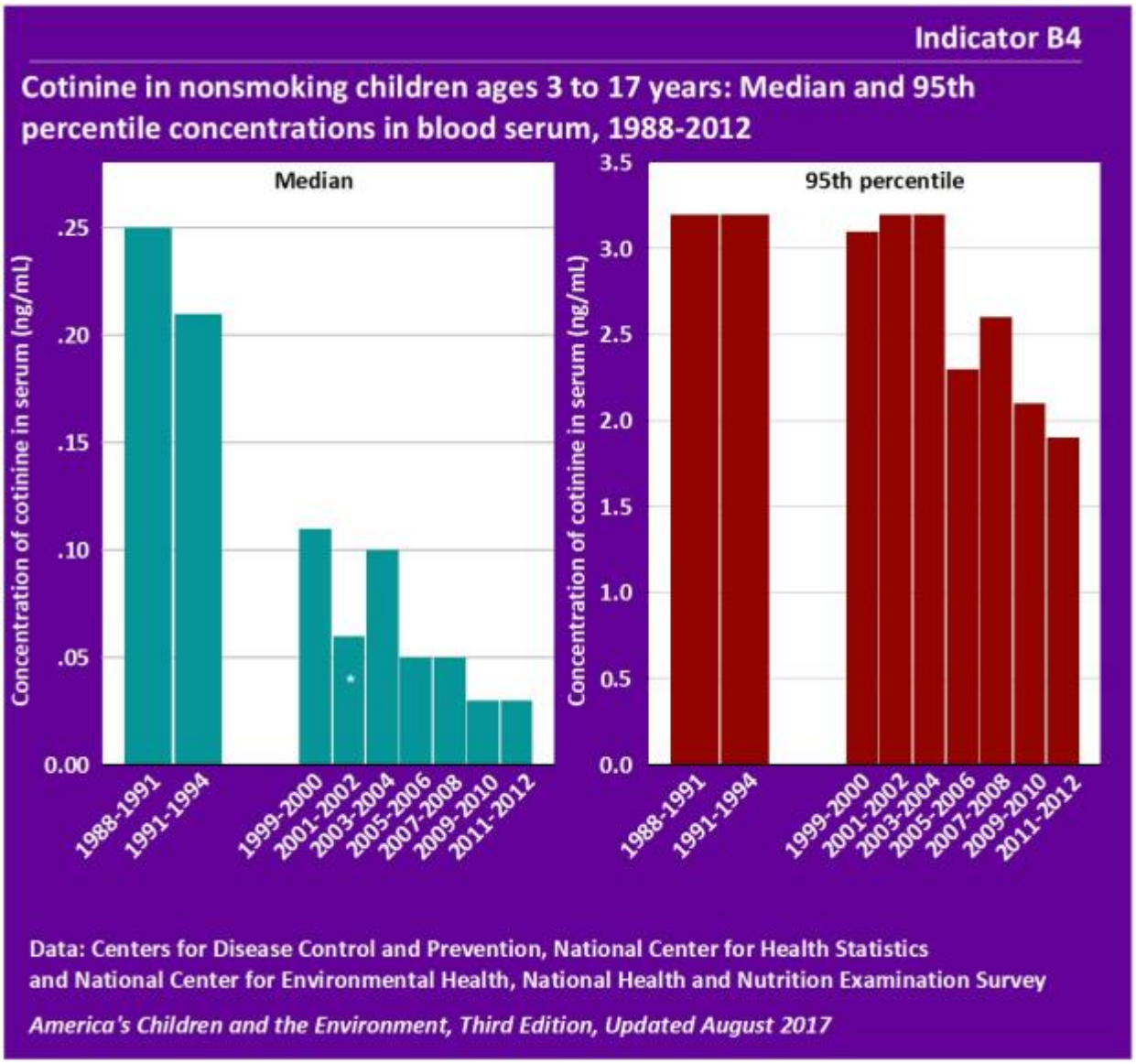
Indicator B5 presents median and 95th percentile concentrations of cotinine in blood serum over time as a marker of exposure to ETS among non-smoking women ages 16 to 49 years, using NHANES data from 1988–2012.

Although the sensitivity of measurement techniques has improved over the years spanned by Indicators B4 and B5, allowing increased detection of lower serum cotinine levels over time, these improvements do not affect the comparability of the median or 95th percentiles over time since the majority of children and women have had detectable levels of cotinine in each NHANES cycle.

Additional information showing how median and 95th percentile blood serum levels of cotinine vary by race/ethnicity, family income, and age for children ages 3 to 17 years is presented in the supplemental data tables for these indicators. Data tables also show how median and 95th percentile blood serum levels of cotinine vary by race/ethnicity and family income for women ages 16 to 49 years.

NHANES does not provide cotinine measurements for children under the age of 3 years (or under age 4 years prior to 1999), who may be especially sensitive to the effects of ETS exposure.

Please see the Introduction to the Biomonitoring section for an explanation of the terms "median" and "95th percentile," a description of the race/ethnicity and income groups used in the ACE3 biomonitoring indicators, and information on the statistical significance testing applied to these indicators.

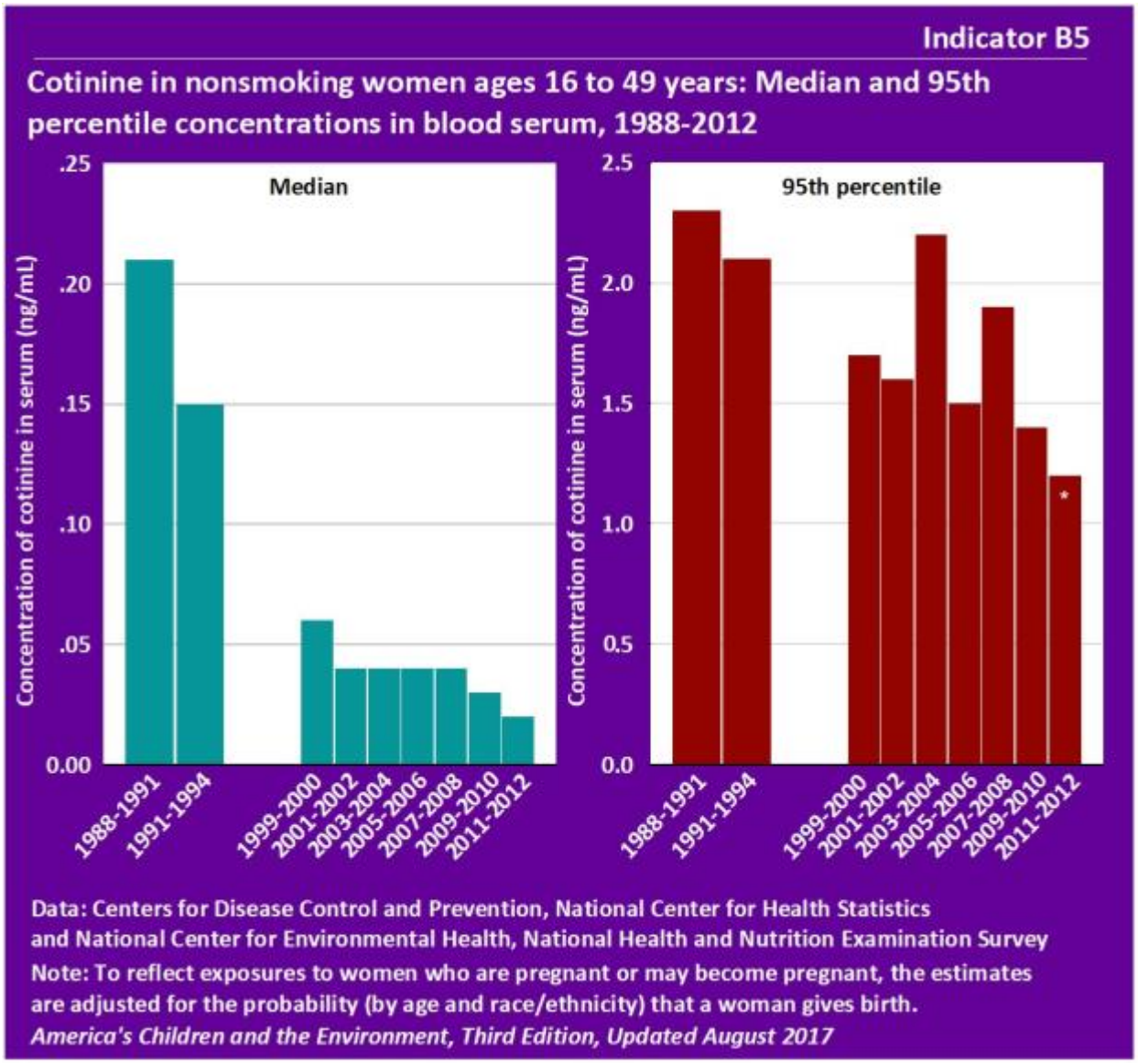


*The estimate should be interpreted with caution because the standard error of the estimate is relatively large: the relative standard error, RSE, is at least 30% but is less than 40% (RSE = standard error divided by the estimate), or the RSE may be underestimated.

Data characterization

- Data for this indicator are obtained from an ongoing continuous survey conducted by the National Center for Health Statistics.
- Survey data are representative of the U.S. civilian noninstitutionalized population.
- Cotinine is measured in blood samples obtained from individual survey participants.

- The median level of cotinine measured in blood serum of nonsmoking children ages 3 to 17 years dropped from 0.25 ng/mL in 1988–1991 (ages 4 to 17 years) to 0.03 ng/mL in 2011–2012, a decrease of 88%. This decreasing trend was statistically significant.
- Cotinine values at the 95th percentile decreased by 41% from 1988–1991 to 2011–2012. This trend was also statistically significant.
- Children at the 95th percentile of cotinine levels had much higher levels than those at the median. In 1988–1991, the 95th percentile cotinine level (3.2ng/mL) was 13 times the median level (0.25 ng/mL); in 2011–2012, the 95th percentile cotinine level (1.9 ng/mL) was 63 times the median level (0.03 ng/mL).
- In every time period measured, children at the 95th percentile had higher levels of cotinine in their blood than women at the 95th percentile. (Compare with Indicator B5.)
- Eighty-seven percent of nonsmoking children ages 4 to 17 years had detectable levels (at or above 0.05 ng/mL) of cotinine in 1988–1991. Thirty-seven percent of nonsmoking children ages 3 to 17 years had levels at or above 0.05 ng/mL of cotinine in 2011–2012, although improvements in laboratory methods made it possible to detect cotinine at lower concentrations starting with the 2001–2002 survey cycle. (Data not shown.)
- In 2009–2012, median concentrations of cotinine in blood for nonsmokers were approximately 0.11 ng/mL for Black non-Hispanic children, 0.03 ng/mL for White non-Hispanic children, and 0.02 ng/mL for Mexican-American children. The differences between these race/ethnicity groups were statistically significant after adjusting for age, sex, and income differences. (See Table B4a.)
- In 2009–2012, the median concentration of cotinine in blood serum for nonsmoking children living below the poverty level (0.09 ng/mL) was about 5 times the median for nonsmoking children living at or above the poverty level (0.02 ng/mL). The differences between income groups were statistically significant. (See Table B4a.)
- In 2009–2012, 95th percentile concentrations of cotinine in blood for nonsmokers were 2.3 ng/mL for White non-Hispanic children and 2.8 ng/mL for Black non-Hispanic children, while Mexican-American children had levels that were more than 3 times lower (0.6 ng/mL). (See Table B4b.)
  - The differences between levels for Mexican-American children and both White non-Hispanic and Black non-Hispanic children were statistically significant.
- For the years 2009–2012, median levels of cotinine in younger nonsmoking children ages 3 to 5 years and 6 to 10 years were 0.04 and 0.03 ng/mL, respectively, compared with 0.02 and 0.03 ng/mL in older nonsmoking children ages 11 to 15 years and 16 to 17 years, respectively. (See Table B4c.)
  - The differences between the levels for the four age groups were statistically significant.



*The estimate should be interpreted with caution because the standard error of the estimate is relatively large: the relative standard error, RSE, is at least 30% but is less than 40% (RSE = standard error divided by the estimate), or the RSE may be underestimated.

Data characterization

- Data for this indicator are obtained from an ongoing continuous survey conducted by the National Center for Health Statistics.
- Survey data are representative of the U.S. civilian noninstitutionalized population.
- Cotinine is measured in blood samples obtained from individual survey participants.

- The median level of cotinine measured in blood serum of nonsmoking women of child-bearing age dropped from 0.21 ng/mL in 1988–1991 to 0.02 ng/mL in 2011–2012, a decrease of 90%. This decreasing trend was statistically significant.
- Cotinine values at the 95th percentile decreased by 48% from 1988–1991 to 2011–2012. This trend was also statistically significant.
- Women at the 95th percentile cotinine levels had much higher levels than those at the median. In 1988–1991, the 95th percentile cotinine level (2.3 ng/mL) was 11 times the median level (0.21 ng/mL); in 2011–2012, the 95th percentile cotinine level (1.2 ng/mL) was 60 times the median level (0.02 ng/mL).
- In 2009–2012, median concentrations of cotinine in blood for nonsmoking women were approximately 0.08 ng/mL for Black non-Hispanic women and 0.02 ng/mL for White non-Hispanic women and Mexican-American women. (See Table B5a.)
  - The differences between Black non-Hispanic women and Mexican-American women and between Black non-Hispanic and White non-Hispanic women were not statistically significant.
- Cotinine values at the 95th percentile were five times higher for nonsmoking women living below the poverty level (4.0 ng/mL) than for nonsmoking women living at or above the poverty level (0.8 ng/mL) in 2009–2012. The differences between income groups were statistically significant. (See Table B5b.)

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