Results by Chemical Group

Tobacco Smoke

Cotinine

CAS No. 486-56-6

General Information

Tobacco use is the most important preventable cause of premature morbidity and mortality in the United States. The consequences of smoking and of using smokeless tobacco products are well known and include an increased risk for cancer, emphysema, cardiovascular disease, and possibly other disorders.

Inhalation of tobacco smoke is the main source of nicotine exposure for the general population. Cigarettes contain about 1.5% nicotine by weight (Kozlowski et al., 1998), producing roughly 1-2 mg of bioavailable nicotine per cigarette (Institute of Medicine, 2001). Nicotine can also be absorbed from the gastrointestinal tract and skin as a result of chewing tobacco or chewing gum or using skin patches that contain nicotine. Workers who harvest tobacco can be exposed to nicotine and intoxicated as a result of the transdermal absorption of nicotine contained in the plant. Some other plants also contain nicotine in smaller amounts. Nicotine has been used previously as an insecticide and is still available for that purpose in its sulfate and alkaloid forms.

Up to 92% of the nicotine delivered in smoke is absorbed from the lungs into the blood stream (Armitage et al., 1975; Iwase et al., 1991). Air concentrations of nicotine in public spaces where smoking is allowed are about 1-10 µg/m^3. Once absorbed, nicotine has a half-life in blood plasma of several hours (Benowitz, 1996). Cotinine is a metabolite of nicotine and is currently regarded as the best biomarker in active smokers and in nonsmokers exposed to environmental tobacco smoke (ETS). Measuring cotinine is preferred over measuring

Table 32. Cotinine

Geometric mean and selected percentiles of serum concentrations (in ng/mL) for the non-smoking U.S. population aged 3 years and older, National Health and Nutrition Examination Survey, 1999-2002.

	Survey years	Geometric mean (95% conf. interval)	Selected percentiles (95% confidence interval)				Sample size
			50th	75th	90th	95th	
Total, age 3 and older	99-00	*	**.059** (<LOD-.070)	**.236** (.190-.300)	**1.02** (.750-1.25)	**1.96** (1.60-2.62)	5999
	01-02	**.062** (.050-.077)	†	**.163** (.123-.224)	**.932** (.737-1.17)	**2.19** (1.83-2.44)	6813
Age group							
3-11 years	99-00	*	**.109** (.063-.180)	**.500** (.259-1.09)	**1.88** (.997-3.44)	**3.37** (1.42-4.79)	1174
	01-02	**.110** (.076-.160)	**.071** (<LOD-.124)	**.570** (.306-1.01)	**2.23** (1.60-2.78)	**3.21** (2.53-4.01)	1414
12-19 years	99-00	*	**.107** (.080-.160)	**.540** (.428-.660)	**1.65** (1.48-1.92)	**2.56** (2.09-3.39)	1773
	01-02	**.086** (.059-.126)	**.051** (<LOD-.109)	**.352** (.189-.580)	**1.53** (1.09-2.12)	**3.12** (2.47-3.99)	1902
20 years and older	99-00	*	**< LOD**	**.167** (.140-.193)	**.630** (.530-.810)	**1.48** (1.28-1.66)	3052
	01-02	**.052** (<LOD-.063)	†	**.113** (.090-.150)	**.623** (.465-.770)	**1.38** (1.11-1.84)	3497
Gender							
Males	99-00	*	**.080** (.059-.109)	**.302** (.220-.394)	**1.20** (.950-1.49)	**2.39** (1.66-3.22)	2789
	01-02	**.075** (.059-.095)	†	**.230** (.165-.316)	**1.17** (.932-1.42)	**2.44** (2.23-2.97)	3149
Females	99-00	*	**< LOD**	**.179** (.148-.220)	**.850** (.597-1.14)	**1.85** (1.33-2.45)	3210
	01-02	**.053** (<LOD-.066)	†	**.123** (.092-.180)	**.711** (.537-.990)	**1.76** (1.32-2.16)	3664
Race/ethnicity							
Mexican Americans	99-00	*	**< LOD**	**.138** (.110-.176)	**.506** (.370-.726)	**1.21** (.900-1.70)	2241
	01-02	**.060** (<LOD-.084)	†	**.157** (.080-.308)	**.727** (.452-1.19)	**2.11** (1.14-2.98)	1877
Non-Hispanic blacks	99-00	*	**.131** (.111-.150)	**.505** (.400-.625)	**1.43** (1.18-1.75)	**2.34** (1.84-3.50)	1333
	01-02	**.164** (.136-.197)	**.132** (.106-.161)	**.570** (.436-.760)	**1.77** (1.54-2.01)	**3.12** (2.47-4.25)	1599
Non-Hispanic whites	99-00	*	**.050** (<LOD-.070)	**.210** (.150-.310)	**.950** (.621-1.40)	**1.92** (1.48-3.02)	1950
	01-02	**.052** (<LOD-.068)	†	**.119** (.087-.180)	**.800** (.571-1.11)	**1.88** (1.49-2.30)	2845

< LOD means less than the limit of detection, which may vary for some chemicals by year and by individual sample. See Appendix A for LODs.

* Not calculated. Proportion of results below limit of detection was too high to provide a valid result.

† 83% of measurements had a LOD of 0.015 ng/mL and 17% of measurements had a LOD of 0.050 ng/mL. See note in text.

nicotine because cotinine persists longer in the body (plasma half-life is about 16 hours) (Benowitz and Jacob, 1994). Cotinine can be measured in serum, urine, saliva, and hair. Nonsmokers exposed to typical levels of ETS have serum cotinine levels of less than 1 ng/mL, with heavy exposure to ETS producing levels in the 1-10 ng/mL range. Active smokers almost always have levels higher than 10 ng/mL and sometimes higher than 500 ng/mL.

Nicotine stimulates preganglionic cholinergic receptors within peripheral sympathetic autonomic ganglia and at cholinergic sites within the central nervous system. Nicotine indirectly causes a release of dopamine in the brain regions that control pleasure and motivation, a process leading to addiction. Acute tobacco or nicotine intoxication can produce dizziness, nausea, vomiting, diaphoresis, salivation, diarrhea, variable changes in blood pressure and heart rate, seizures, and death. Symptoms of nicotine withdrawal include irritability, craving, cognitive and sleep disturbances, and increased appetite.

Tobacco smoke is considered a human carcinogen by IARC and NTP. Lung cancer is the leading cancer-related killer of both men and women in the United States, and smoking is by far the leading cause of lung cancer. Persistent exposure to ETS is associated with an increased risk for lung cancer. More recently, coronary heart disease (Whincup et al., 2004) and prothrombotic risk factors (Bazzano et al., 2003) have been associated with ETS exposure. ETS may exacerbate asthma among susceptible children and increase the risk for lower respiratory-tract illnesses, such as bronchitis and pneumonia, among young children. Exposure to ETS has also been associated recently with decrements in pulmonary function in adults with asthma (Eisner, 2002). More information about the effects of smoking and nicotine can be found at: http://www.nida.nih.gov/researchreports/nicotine/nicotine.html.

Interpreting Levels of Serum Cotinine Reported in the Table

Serum cotinine levels were measured in a subsample of nonsmoking NHANES participants aged 3 years and older. Participants were selected within the specified age range to be a representative sample of the U.S. population. Nonsmoking is defined as a serum cotinine level of less than or equal to 10 ng/mL. Choosing a cutoff of 15 ng/mL makes little difference in the results. Serum cotinine has been measured in many studies of non-smoking populations, and such levels are similar or slightly higher than those reported here, depending on the degree of ETS exposure.

From 1988 through 1991, as part of NHANES III, CDC determined that the median level (50th percentile) of cotinine among nonsmokers in the United States was 0.20 ng/mL (Pirkle et al., 1996). Since that 1988-1991 survey period, median levels of cotinine (as measured in NHANES 1999-2002) have decreased 68% in children, 69% in adolescents, and about 75% in adults. This reduction in cotinine levels suggests a major reduction in exposure of the general U.S. population to ETS since the period 1988-1991.

Note: Results are reported as less than the limit of detection (LOD) if they are less than the LOD of the individual sample, which could be either 0.015 ng/mL or 0.050 ng/mL for the 2001-2002 subsample (more sensitive instrumentation was introduced during 2001-2002 analyses). The reporting requirement for a geometric mean is that 60% of the serum cotinine levels must be greater than or equal to the respective specimen-specific LOD. To calculate geometric means and percentiles, measurements below their LOD are assigned values of LOD/square root of 2.

The reporting requirement for percentiles is that they must be greater than the maximum LOD (i.e., greater than 0.050 ng/mL). This requirement avoids confusion in interpretation that could result if a percentile estimate was lower than one of the two LODs. These two reporting requirements (one for geometric means and one for percentiles) occasionally result in a geometric mean being reported with no estimate being reported for the 50th percentile (as is the case for cotinine). For completeness, we list here, for 2001-2002, the computed 50th percentiles (with 95% confidence limits), recognizing that these estimates are in between the two LODs; that is, between 0.015 ng/mL-0.050 ng/mL.

Age 3 years and older	0.035	(0.032-0.052)
Age 20 years and older	0.034	(0.024-0.038)
Males	0.045	(0.035-0.063)
Females	0.034	(0.023-0.038)
Mexican Americans	0.036	(0.025-0.060)
Non-Hispanic whites	0.034	(0.022-0.043)

Comparing Adjusted Geometric Means

Geometric mean levels of serum cotinine for the demographic groups in the NHANES 2001-2002 subsample were compared after adjusting for the covariates of age, race/ethnicity, and gender (data not

shown). Both groups aged 3-11 years and 12-19 years had higher adjusted geometric mean levels of cotinine than the group aged 20 years and older. Males had higher levels than females. Non-Hispanic whites and Mexican Americans both had lower levels than non-Hispanic blacks. Higher levels of cotinine have previously been reported for non-Hispanic blacks (Caraballo et al., 1998). It is unknown whether these age, gender, and race/ethnicity differences represent differences in exposure, pharmacokinetics, or the relationship of dose per body weight.

These serum cotinine data will help public health officials determine whether or not people have been exposed to higher levels of ETS than are found in the general population. These data will also help scientists plan and conduct research about exposure to ETS and health effects.

Results by Chemical Group

Polycyclic Aromatic Hydrocarbons