Chapter 3
Health Effects of E-Cigarette Use Among U.S. Youth and Young Adults

Introduction

This chapter focuses on the short-term and potential long-term health effects related to the incidence and continued use of electronic cigarettes (e-cigarettes) by youth and young adults. The sharp increase in the prevalence of e-cigarette use among youth and young adults, especially from 2011 to 2015 (Centers for Disease Control and Prevention [CDC] 2015, 2016), highlights the compelling need to learn more about this evolving class of products. This chapter highlights the scientific literature that addresses potential adverse health effects caused by direct exposure to aerosolized nicotine, flavorants, chemicals, and other particulates of e-cigarettes; secondhand exposure to e-cigarette aerosol; and exposure to the surface-deposited aerosol contaminants. Literature regarding harmful consequences of close contact with malfunctioning e-cigarette devices and ingestion of the nicotine-containing liquids (e-liquids) are also explored. This chapter examines available data on e-cigarettes and youth, reviews established human and animal data on harmful developmental effects of nicotine (prenatal and adolescent), and reviews data on e-cigarettes among adults when data on youth are not available. Of note, given the relatively recent emergence of e-cigarettes, data are not yet available that address the long-term health effects of use or exposure over several years compared with nonuse or exposure to air free from secondhand tobacco smoke and aerosol from e-cigarettes; thus, the discussion is limited in that regard.

Conclusions from Previous Surgeon General's Reports

This chapter comprehensively reviews a new and emerging body of scientific evidence related to the use of e-cigarettes by youth and young adults. The enormous knowledge base on tobacco smoking and human health is also relevant to this discussion. That literature, which has been accumulating for more than 50 years, provides incontrovertible evidence that smoking is a cause of disease in almost every organ of the body (U.S. Department of Health and Human Services [USDHHS] 2004, 2014). Laboratory research has characterized the components of tobacco smoke and probed the mechanisms by which these constituents cause addiction and injury to cells, tissues, organs, and the developing fetus.

The evidence on the harmful consequences of nicotine exposure in conventional cigarettes, including addiction, and other adverse effects, is particularly relevant to e-cigarettes. Nicotine doses from e-cigarettes vary tremendously depending on characteristics of the user (experience with smoking conventional cigarettes or e-cigarettes), technical aspects of the e-cigarette, and levels of nicotine in the e-liquid. Although studies of nicotine doses in youth and young adults are lacking, studies of adults have found delivery of nicotine from e-cigarettes in doses ranging from negligible to as large as (Lopez et al. 2016; Vansickel and Eissenberg 2013; Spindle et al. 2015; St. Helen et al. 2016) or larger than (Ramôa et al. 2016) conventional cigarettes. Similarly, passive exposure to secondhand nicotine from e-cigarettes is just as large (Flouris et al. 2013) or lower than (Czogala et al. 2014) conventional cigarettes.

The findings of scientific research on smoking and involuntary exposure to tobacco smoke have been reviewed thoroughly in the 32 reports on smoking and health produced by the Surgeon General to date (there is one report on smokeless tobacco) (Table 3.1). The landmark first report was published in 1964 (U.S. Department of Health, Education, and Welfare [USDHEW] 1964), and the 50th-anniversary report, released in January 2014, comprehensively covered multiple aspects of cigarette smoking and health and lengthened the list of diseases caused by smoking and involuntary exposure to tobacco smoke (USDHHS 2014). Other Surgeon General's reports that are particularly relevant to the present report include reports on the health consequences of smoking and involuntary exposure to tobacco smoke (USDHHS 2004, 2006), on the mechanisms by which smoking causes disease (USDHHS 2010), and on the health consequences of smoking on youth and young adults (USDHHS 1994, 2012). The Surgeon General's reports on smoking and health have provided powerful conclusions on the dangers of nicotine. The 1988 report, released by Surgeon General C. Everett Koop, was the first to characterize smoking as addictive, and it identified nicotine as "…the drug in tobacco that causes addiction" (Appendix 3.1)[1] (USDHHS 1988, p. 9).

[1]All appendixes and appendix tables that are cross-referenced in this chapter are available only online at http://www.surgeongeneral.gov/library/reports/

Table 3.1 Relevant conclusions from previous Surgeon General's reports on smoking and health

Report	Year	Conclusions
The Health Consequences of Smoking: Nicotine Addiction (USDHHS 1988, p. 9)	1988	**Major Conclusions** 1. Cigarettes and other forms of tobacco are addicting. 2. Nicotine is the drug in tobacco that causes addiction. 3. The pharmacologic and behavioral processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine.
How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease (USDHHS 2010, p. 183)	2010	**Chapter 4. Nicotine Addiction: Past and Present** 1. Nicotine is the key chemical compound that causes and sustains the powerful addicting effects of commercial tobacco products. 2. The powerful addicting effects of commercial tobacco products are mediated by diverse actions of nicotine at multiple types of nicotinic receptors in the brain. 3. Evidence is suggestive that there may be psychosocial, biologic, and genetic determinants associated with different trajectories observed among population subgroups as they move from experimentation to heavy smoking. 4. Inherited genetic variation in genes such as *CYP2A6* contributes to the differing patterns of smoking behavior and smoking cessation. 5. Evidence is consistent that individual differences in smoking histories and severity of withdrawal symptoms are related to successful recovery from nicotine addiction.
Preventing Tobacco Use Among Youth and Young Adults (USDHHS 2012, pp. 8, 460)	2012	**Major Conclusions** 1. Cigarette smoking by youth and young adults has immediate adverse health consequences, including addiction, and accelerates the development of chronic diseases across the full life course. 2. Prevention efforts must focus on both adolescents and young adults because among adults who become daily smokers, nearly all first use of cigarettes occurs by 18 years of age (88%), with 99% of first use by 26 years of age. 3. Advertising and promotional activities by tobacco companies have been shown to cause the onset and continuation of smoking among adolescents and young adults. 4. After years of steady progress, declines in the use of tobacco by youth and young adults have slowed for cigarette smoking and stalled for smokeless tobacco use. 5. Coordinated, multicomponent interventions that combine mass media campaigns, price increases including those that result from tax increases, school-based policies and programs, and statewide or community-wide changes in smokefree policies and norms are effective in reducing the initiation, prevalence, and intensity of smoking among youth and young adults. **Chapter 4. Social, Environmental, Cognitive, and Genetic Influences on the Use of Tobacco Among Youth** 1. Given their developmental stage, adolescents and young adults are uniquely susceptible to social and environmental influences to use tobacco. 2. Socioeconomic factors and educational attainment influence the development of youth smoking behavior. The adolescents most likely to begin to use tobacco and progress to regular use are those who have lower academic achievement. 3. The evidence is sufficient to conclude that there is a causal relationship between peer group social influences and the initiation and maintenance of smoking behaviors during adolescence. 4. Affective processes play an important role in youth smoking behavior, with a strong association between youth smoking and negative affect. 5. The evidence is suggestive that tobacco use is a heritable trait, more so for regular use than for onset. The expression of genetic risk for smoking among young people may be moderated by small-group and larger social-environmental factors.

Table 3.1 Continued

Report	Year	Conclusions
The Health Consequences of Smoking—50 Years of Progress (USDHHS 2014, p. 126)	2014	**Chapter 5: Nicotine** 1. The evidence is sufficient to infer that at high-enough doses nicotine has acute toxicity. 2. The evidence is sufficient to infer that nicotine activates multiple biological pathways through which smoking increases risk for disease. 3. The evidence is sufficient to infer that nicotine exposure during fetal development, a critical window for brain development, has lasting adverse consequences for brain development. 4. The evidence is sufficient to infer that nicotine adversely affects maternal and fetal health during pregnancy, contributing to multiple adverse outcomes such as preterm delivery and stillbirth. 5. The evidence is suggestive that nicotine exposure during adolescence, a critical window for brain development, may have lasting adverse consequences for brain development. 6. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to nicotine and risk for cancer.

Note: USDHHS = U.S. Department of Health and Human Services.

Subsequent reports expanded on the conclusions in the 1988 report related to nicotine—reaffirming that nicotine causes addiction, describing nicotine's effects on key brain receptors (USDHHS 2010), and emphasizing that youth are more sensitive to nicotine than adults and can become dependent to nicotine much faster than adults (USDHHS 2012). This is of particular concern in the context of e-cigarettes because blood nicotine levels in e-cigarette users have been reported as being comparable to or higher than levels in smokers of conventional cigarettes (Lopez et al. 2016; Spindle et al. 2015), and serum cotinine (a nicotine metabolite) levels have been reported as being equal to that found in conventional cigarette users (Etter 2016; Marsot and Simon 2016). Because of their sensitivity to nicotine and subsequent addiction, about 3 out of 14 young smokers end up smoking into adulthood, even if they intend to quit after a few years; among youth who continue to smoke as adults, one-half will die prematurely from smoking (Peto et al. 1994; CDC 1996; Hahn et al. 2002; Doll et al. 2004). Surgeon General's reports have also emphasized the critical role of environmental determinants of tobacco use, including the causal roles of the tobacco industry's advertising and promotional activities and of the peer social environment (USDHHS 2012).

The 2014 Surgeon General's report included a chapter that addressed the numerous adverse consequences of nicotine other than addiction (USDHHS 2014). The review documented the broad biological activity of nicotine, which can activate multiple biological pathways, and the adverse effects of nicotine exposure during pregnancy on fetal development and during adolescence on brain development. Of concern with regard to current trends in e-cigarette use among youth and young adults, the evidence suggests that exposure to nicotine during this period of life may have lasting deleterious consequences for brain development, including detrimental effects on cognition (USDHHS 2014).

Finally, the aerosol from e-cigarettes may include other components that have been addressed in previous Surgeon General's reports, such as tobacco-specific nitrosamines (TSNAs), acrolein, and formaldehyde (USDHEW 1979; USDHHS 2010). Aerosols generated with vaporizers contain up to 31 compounds, including nicotine, nicotyrine, formaldehyde, acetaldehyde glycidol, acrolein, acetol, and diacetyl (Sleiman et al. 2016). Glycidol is a probable carcinogen not previously identified in the vapor, and acrolein is a powerful irritant (Sleiman et al. 2016). Although these constituents have been identified in e-cigarette aerosol, current evidence is unclear on whether typical user dosages achieve levels as high as conventional cigarettes, or at harmful or potentially harmful levels. More information will be available in the coming years as e-cigarette manufacturers begin reporting harmful or potential harmful constituents in compliance with the Tobacco Control Act.

Health Effects of E-Cigarette Use

The potential adverse health effects for youth who inhale e-cigarette aerosol include those on the body from acute administration of nicotine, flavorants, chemicals, other particulates, and additional effects, such as (1) nicotine addiction; (2) developmental effects on the brain from nicotine exposure, which may have implications for cognition, attention, and mood; (3) e-cigarette influence initiating or supporting the use of conventional cigarettes and dual use of conventional cigarettes and e-cigarettes; (4) e-cigarette influence on subsequent illicit drug use; (5) e-cigarette effects on psychosocial health, particularly among youth with one or more comorbid mental health disorders; and (6) battery explosion and accidental overdose of nicotine.

Effects of Aerosol Inhalation by the E-Cigarette User

Determining the potential health effects of inhaling e-cigarette aerosol is challenging due to the number of possible combinations of customizable options (Seidenberg et al. 2016), including battery power, nicotine concentration, e-liquids (Goniewicz et al. 2015; Buettner-Schmidt et al. 2016), and use behaviors and puff topography (Dawkins et al. 2016; Lopez et al. 2016). The amount of nicotine, flavorants, and other e-liquid constituents in e-cigarettes available for consumers to purchase varies widely, and the aerosolized constituents delivered vary by the type and voltage of the e-cigarette device being used (Cobb et al. 2015). Studies of commercial products have shown that e-liquids can contain as little as 0 milligrams/milliliter (mg/mL) to as much as 36.6 mg/mL of nicotine (Goniewicz et al. 2015); can be mislabeled (Peace et al. 2016); can vary by propylene glycol (PG)/vegetable glycerin (VG) ratio; and can contain one or more of several thousand available flavorants (Zhu et al. 2014b). Some liquids intended for use in e-cigarettes contain adulterants not named on ingredient lists (Varlet et al. 2015), and under at least some user conditions, the aerosolization process, which involves heating, produces additional toxicants that may present health risks (Talih et al. 2015). The sections that follow comprehensively cover the effects of inhaling aerosolized nicotine and then consider what is known about solvents (i.e., PG and VG, flavorants, and other chemicals) added to e-cigarettes, adulterants in e-liquids formed in the nicotine extraction process (e.g., *N*-nitrosonornicotine), and toxicants formed during the heating and aerosolization process (e.g., acrolein and formaldehyde) (Sleiman et al. 2016).

Dose and Effects of Inhaling Aerosolized Nicotine

Nicotine addiction via e-cigarette use is a primary public health concern due to the exponential growth in e-cigarette use among youth. The potential for widespread nicotine addiction among youth is high, as are the harmful consequences of nicotine on fetal development and the developing adolescent brain (USDHHS 2014). Nicotine, a psychomotor stimulant drug, is the primary psychoactive and addictive constituent in the smoke of conventional cigarettes and an important determinant in maintaining smoking dependence (e.g., USDHHS 2014). E-liquids typically contain nicotine, although in more widely variable concentrations than those found in conventional cigarettes (Trehy et al. 2011; Cameron et al. 2014; Cheng 2014; Goniewicz et al. 2015; Marsot and Simon 2016). The concentration of liquid nicotine is only one factor that influences the amount of aerosolized nicotine available for inhalation (Lopez et al. 2016); other factors include the power of the device being used (e.g., battery voltage, heater resistance) and user behavior (e.g., puff duration, interpuff interval) (Shihadeh and Eissenberg 2015; Talih et al. 2016; Etter 2016). The interplay of these factors may help to explain the variability in plasma nicotine concentration when adults use e-cigarettes under controlled conditions which can be higher (Ramôa et al. 2016), lower (Bullen et al. 2010; Vansickel et al. 2010, 2012; Farsalinos et al. 2014b; Nides et al. 2014; Oncken et al. 2015; Yan and D'Ruiz 2015), or similar to those obtained by smoking conventional cigarettes (Vansickel and Eissenberg 2013; Spindle et al. 2015; St. Helen et al. 2016; see Figure 3.1). Generalization across studies is difficult due to variations in devices, e-liquids, and e-cigarette use behavior within the study sample. As demonstrated in Figure 3.1, in studies where a variety of products were used under similar laboratory conditions (i.e., blood sampling before and immediately after a 10-puff episode), there was wide variability in nicotine delivery between devices, with "cigalike" products (cigarette-like products) delivering less nicotine than "tank" products (Farsalinos et al. 2014b; Yan and D'Ruiz 2015), and low-resistance, dual-coil "cartomizer" products having the capacity to deliver less or more nicotine than a conventional cigarette, depending on the concentration of liquid nicotine (Ramôa et al. 2016).

When the device type and liquid dose were held constant in a controlled session in one study, plasma nicotine concentrations (in this case in nanograms [ng]/mL) varied considerably across participants (0.8 to 8.5 ng/mL) (Nides et al. 2014). This variation was likely attributable to the manner in which the users puffed when using

e-cigarettes, or that person's "puff topography," which includes the number of puffs, the intake volume and duration, the interpuff interval, and the flow rate (Zacny and Stitzer 1988; Blank et al. 2009).

Available data suggest that puff durations among adult cigarette smokers who are new e-cigarette users are comparable to those observed with conventional cigarettes (at least about 2 seconds [sec]) (Farsalinos et al. 2013b; Hua et al. 2013; Norton et al. 2014). However, puff durations during e-cigarette use among experienced e-cigarette users may be twice as long (~4 sec) (Farsalinos et al. 2013b; Hua et al. 2013; Spindle et al. 2015) as puff duration during conventional cigarette use. Puff duration is directly related to the nicotine content of the e-cigarette aerosol (i.e., the yield or dose) (Talih et al. 2016), suggesting that smokers of conventional cigarettes who switch to e-cigarettes may increase the duration of their puffs when using the new product in an attempt to extract more nicotine. Research also suggests that cigarette smokers may learn to alter other aspects of their puffing behavior when using an e-cigarette (Spindle et al. 2015). Relative to smokers of conventional cigarettes (Kleykamp et al. 2008), experienced e-cigarette users were found to have puff volumes that were significantly higher (101.4 mL vs. 51.3 mL) and puff flow rates that were significantly lower (24.2 mL/sec vs. 37.9 mL/sec) (Spindle et al. 2015). In a different study, adult cigarette smokers who had never used e-cigarettes but switched to e-cigarettes showed significantly increased puff durations and decreased puff flow rates within 1 week (Lee et al. 2015). Elsewhere, adult cigarette smokers given an e-cigarette appeared to show an enhanced ability to extract nicotine from their device after 4 weeks of use (Hajek et al. 2015). Thus, the health effects of aerosolized nicotine in e-cigarette users may depend on a variety of factors, including the e-liquid used, the user's behavior, and the user's experience with the product.

Aerosolized Nicotine and Cardiovascular Function

Smoking is a major cause of death from cardiovascular disease (USDHHS 2014), and exposure to nicotine has been identified as a potential initiating factor in the atherogenic process (Lee et al. 2011; Santanam et al. 2012; Benowitz and Burbank 2016). Acute administration of nicotine causes a variety of well-characterized, dose- and route-dependent effects in adults, including cardiovascular effects, such as increases in heart rate and blood pressure (BP) and greater cardiac output, leading to an increase in myocardial oxygen demand (Rosenberg et al. 1980; USDHHS 2014). Reports from cell biology and animal studies have established biologic plausibility between nicotine alone and negative cardiovascular effects (Hanna 2006; Santanam et al. 2012). These studies have shown that nicotine induces the production of various inflammatory mediators involved with atherosclerotic pathogenesis (Lau and Baldus 2006), and that at the cellular level, nicotine induces C-reactive protein (CRP) expression in macrophages that contribute pro-inflammatory and pro-atherosclerotic effects (Mao et al. 2012).

Long-term studies on the safety of nicotine-only exposure (e.g., as with using e-cigarettes rather than smoking conventional cigarettes) among youth have not been conducted, and little is known about the cardiovascular effects of e-cigarette use among adults. However, when e-cigarettes are accompanied by a measurable increase in plasma nicotine concentration, it increases heart rate (Vansickel et al. 2012; Vansickel and Eissenberg 2013; Nides et al. 2014; Yan and D'Ruiz 2015), and diastolic BP rises.

Given the paucity of long-term data on the impact of e-cigarette smoking in relation to cardiovascular disease, other nicotine products offer a useful analogy. A meta-analysis reported that replacing the consumption of conventional cigarettes with nicotine replacement therapy (NRT) reduces cardiovascular risk among former smokers without significant adverse consequences (compared with current smokers) (Greenland et al. 1998; Moore et al. 2009). However, most NRT use is temporary (<26 months), and the adverse consequences of longer term NRT therapy are unknown.

Elsewhere, investigators examined the relationship between the use of Swedish-type moist snuff (or "snus"), which contains high levels of nicotine and low levels of TSNAs, and the incidence of acute myocardial infarction among men with a mean age of 35 years who had never smoked cigarettes. The researchers, who pooled data from eight prospective cohort studies, found no support for any association between the use of snus and the development of acute myocardial infarction (Hansson et al. 2012), regardless of timing, intensity, duration, or period of use among the men who were followed for 4–29 years.

In summary, despite overwhelming epidemiologic evidence linking the use of conventional cigarettes with cardiovascular disease, the precise components of cigarette smoke responsible for this relationship and the mechanisms by which they exert their effects have not yet been fully explained (Hanna 2006). For e-cigarettes, biological data support a potential association with cardiovascular disease, and short-term use of these products is accompanied by a measurable increase in plasma nicotine concentrations in adults as well as increases in heart rate and blood pressure. Much more research is needed, but the limited data available suggest the typical cardiovascular effects exerted by nicotine are also exerted by e-cigarettes (Benowitz and Burbank 2016; Bhatnagar 2016).

Aerosolized Nicotine and Dependence

Although a great deal is known about self-administration of nicotine and the development of nicotine dependence among adults (USDHHS 2014) and youth (Colby et al. 2000; USDHHS 2012; O'Loughlin et al. 2014; Yuan et al. 2015), more research is needed on nicotine dependence in youth and young adults as a result of using e-cigarettes. Nicotine dependence, also referred to as nicotine addiction (USDHHS 2010) or tobacco use disorder (American Psychiatric Association [APA] 2013), is defined as a neurobiological adaptation to repeated drug exposure that is manifested behaviorally by highly controlled or compulsive use; psychoactive effects such as tolerance, physical dependence, and pleasant effect; and nicotine-reinforced behavior, including an inability to quit despite harmful effects, a desire to quit, and repeated cessation attempts (USDHHS 1988; APA 2013). In tobacco-dependent users of conventional cigarettes, a predictable consequence of short-term abstinence (e.g., for more than a few hours) is the onset of withdrawal symptoms indicated by self-reported behavioral, cognitive, and physiological symptoms and by clinical signs (USDHHS 2010). Subjective withdrawal symptoms are manifested by affective disturbance, including irritability and anger, anxiety, and depressed mood. The behavioral symptoms include restlessness, sleep disturbance, and increased appetite. Cognitive disturbances usually center on difficulty in concentrating (USDHHS 2010).

Early studies of conventional cigarette smokers using e-cigarettes reported poor nicotine delivery with little to no increase in blood nicotine levels after puffing (Eissenberg 2010; Vansickel et al. 2010). Later studies reported that the effect on serum cotinine levels among new e-cigarette users can be similar to that generated by conventional cigarettes (Flouris et al. 2013; Lopez et al. 2016). Studies examining this discrepancy found that e-cigarette users require longer puffs to deliver equivalent nicotine doses (Lee et al. 2015), and within a week, inexperienced e-cigarette users adjust their puffing patterns after switching (Hua et al. 2013b; Lee et al. 2015; Talih et al. 2015).

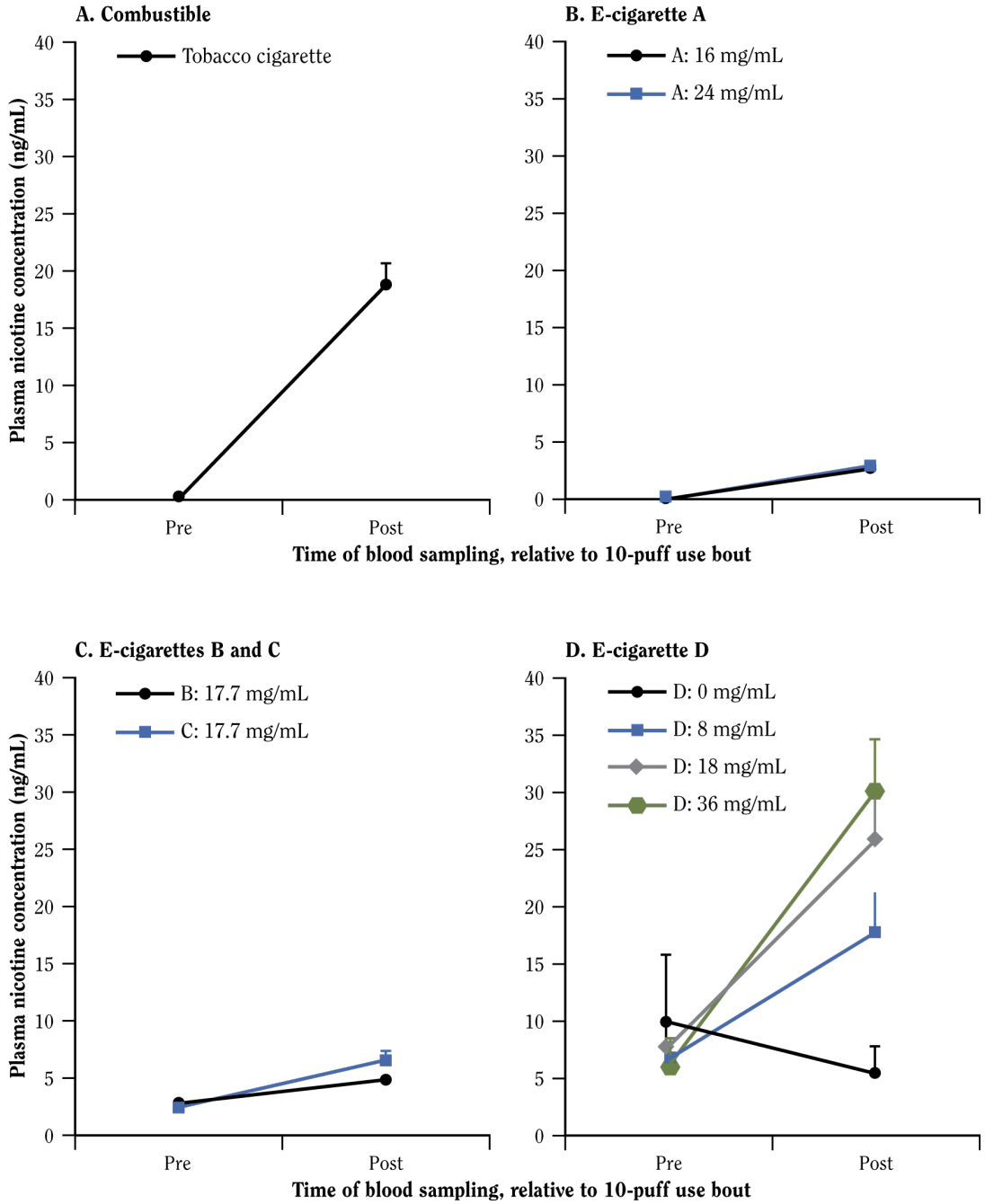
In more experienced e-cigarette users, blood nicotine levels appear to be influenced by puffing patterns, such as puff length. Volume and frequency and plasma nicotine levels ranging from 2.50 to 13.4 ng/mL have been observed after 10 puffs of an e-cigarette (Dawkins and Corcoran 2014). Dawkins and colleagues (2016) used 24 mg/mL nicotine strength liquid and observed high blood nicotine levels that were achieved very quickly, matching and even exceeding those reported in conventional cigarette smokers. St. Helen and colleagues (2016) conducted a similar study and reported that e-cigarettes can deliver levels of nicotine that are comparable to or higher than conventional cigarettes. Finally, Etter (2016) reported cotinine levels among experienced e-cigarette users similar to levels usually observed in conventional cigarette smokers. Figure 3.1 and Table A3.1-1 in Appendix 3.1 summarize studies on aerosolized nicotine from e-cigarettes and dependence using dependency criteria.

The ability of e-cigarettes to deliver comparable or higher amounts of nicotine compared to conventional cigarettes raises concerns about e-cigarette use generating nicotine dependence among young people (Dawkins et al. 2016; Etter 2016; St. Helen et al. 2016). The reported blood levels of nicotine, or cotinine, in e-cigarette users is likely to cause physiological changes in nicotinic acetylcholine receptors in the brain that would sustain nicotine addiction (Kandel and Kandel 2014; Yuan et al. 2015). This is particularly concerning for adolescents and young adults, given that early exposure to nicotine increases the severity of future nicotine dependence (St. Helen et al. 2016; USDHHS 2014).

Symptoms of nicotine dependence can occur soon after the initiation of conventional smoking, and even before established use, among adolescents and young adults (DiFranza et al. 2002; O'Loughlin et al. 2003; Dierker et al. 2007; Ramôa et al. 2016). Furthermore, some adolescents have reported nicotine dependence symptoms while using tobacco as little as 1–3 days per month (Rose et al. 2010). Using the National Comorbidity Survey-Adolescent dataset, Dierker and colleagues (2012) reported that nicotine dependence in adolescents was likely to occur within 1 year of the initiation of weekly or daily smoking, regardless of sociodemographic variables. Importantly, when smoking onset began at a younger age, the transition to weekly and daily smoking was more rapid, indicating a youthful neurobiological sensitivity to nicotine (Dierker et al. 2012). Zhan and colleagues (2012) found that symptoms of nicotine dependence could be detected among teenagers before they had smoked even 100 cigarettes.

Because few validated measures exist for assessing dependence on e-cigarette use, some researchers have adapted those originally developed to measure dependence in smokers of conventional cigarettes. Among adults, scores on these measures have been consistently lower in e-cigarette users than in smokers of conventional cigarettes (Farsalinos et al. 2013a; Etter and Eissenberg 2015; Foulds et al. 2015). Still, scores for e-cigarette dependence among former cigarette smokers were positively associated with the nicotine concentration of the e-cigarette liquid and the type of device used (Etter 2015; Etter and Eissenberg 2015; Foulds et al. 2015). Research in this area is challenging to interpret because measurement of youth e-cigarette dependence has not been standardized

Figure 3.1 Plasma nicotine concentration from different human laboratory studies and four different products with blood sampled before and immediately after a 10-puff bout with the products



Source: Vansickel et al. (2010); Farsalinos et al. (2014b); Yan and D'Ruiz (2015); and Ramôa et al. (2016).
Notes: Data for conventional cigarettes are from 32 tobacco cigarette smokers using their usual brand of cigarette (Vansickel et al. 2010). E-cigarette A is a cigalike called "blu" loaded with two different concentrations of liquid nicotine (16 or 24 mg/mL, both containing 20% propylene glycol and 50% vegetable glycerin). Data are from 23 smokers of tobacco cigarettes with 7 days of experience with the e-cigarette product (Yan and D'Ruiz 2015). E-cigarette B is a cigalike called "V2cigs", and E-cigarette C is a "tank" product called "EVIC" with an "Evod" heating element; both were loaded with an 18 mg/mL liquid containing 34% propylene glycol and 66% vegetable glycerin. Data are from 23 experienced users of e-cigarettes (Farsalinos et al. 2014b). E-cigarette D uses a 3.3-volt "Ego" battery fitted with a 1.5-Ohm dual coil cartomizer ("Smoktech") and filled with ~1 mL of a 70% propylene glycol, 30% vegetable glycerin liquid that varied by liquid nicotine concentration (0, 8, 18, or 36 mg/mL). Data are from 16 experienced users of e-cigarettes (Ramôa et al. 2016).

and there is a wide variation in device/e-liquid combinations, which allow for adjustable nicotine delivery among study participants. Regardless, among 766 adults, who were daily users of e-cigarettes (with nicotine) and who were either former cigarette smokers (83%) or current cigarette smokers (17%), 30.7% indicated that they would likely be unable to stop using e-cigarettes, 28.2% that they would find it "very difficult" or "impossible" to stop using e-cigarettes, and 27.5% that they were unable to stop e-cigarette use (Etter and Eissenberg 2015). However, it is important to note that e-cigarettes were less addictive than conventional cigarettes in this sample (Etter and Eissenberg 2015).

In summary, the addictive liability of e-cigarettes has the potential to be at least equivalent to that of conventional cigarettes, given nicotine dose levels produced by these products, particularly among experienced users operating new-generation devices (Ramôa et al. 2016). More generally, the delivery of nicotine in sufficient doses and blood concentration would be expected to produce and maintain dependence in e-cigarette users. Further work would be useful to determine the natural course and history of e-cigarette use among smokers of conventional cigarettes, former smokers, and never smokers and to more accurately determine the nicotine addiction liability of e-cigarette use. Unfortunately, these issues have not been explored in adolescents, although the prevalence of e-cigarette use has increased considerably in that population since 2011 (see Chapter 2).

Effects of Nicotine in Youth Users

Nicotine is the prime psychoactive substance in conventional cigarettes (Yuan et al. 2015), and given that the developing adolescent brain is immature and vulnerable to neurobiological insults (Bernheim et al. 2013; Lydon et al. 2014), it is important to understand how nicotine delivered by e-cigarette use affects adolescent brain development and how responses to nicotine in adolescents differ from those seen in adults. Substantial evidence suggests that nicotine can negatively influence both adolescent and prenatal brain development (USDHHS 2014). For example, Weiss and colleagues (2008) reported a strong mechanistic link among early nicotine exposure (younger than 16 years of age), common genes related to the severity of nicotine addiction (CHRNA5-A3-B4 haplotypes), and adult nicotine addiction in three independent populations of European origins. Although much of the literature on nicotine addiction arises from studies of nicotine exposure among adults, and with combustible tobacco products (see Table A3.1-2 in Appendix 3.1), there is a growing body of biological mechanistic literature from animal studies that model the effects of nicotine in doses equivalent to those for humans (see Table A3.1-3 in Appendix 3.1). These animal and human studies, taken together with studies of rising e-cigarette prevalence in youth (see Chapter 2), point to an age-dependent susceptibility to nicotine as a neurobiological insult.

Limited direct human experimental data exist on the effects of nicotine exposure from e-cigarettes on the developing adolescent brain, but experimental laboratory data have been found to be relevant in animal models to contextualize effects in humans (Stevens and Vaccarino 2015). Even if the full complexity of human brain development and behavioral function during adolescence cannot be completely modeled in other species, the similarities across adolescents of different species support the use of animal models of adolescence when examining neural and environmental contributors to adolescent-characteristic functioning (Spear 2010).

Animal studies provide an effective method to examine the persistent effects of prenatal, child, and adolescent nicotine exposure, in addition to human epidemiologic data. When considering an epidemiologic causal argument of exposure (risk factor) to health outcome (disease), one should note that animal models lend biological plausibility when experimentation with humans is not possible (or ethical) (Rothman et al. 2008). Furthermore, animal studies offer significant advantages compared to human studies—with the ability to control for many confounding factors, to limit nicotine exposure to differing levels of physical and neural development—and are pivotal for understanding the neural substrates associated with adolescence. The validity of any causal argument when examining animal models requires careful consideration, and yet in combination with epidemiologic data—such as prevalence, incidence, and strength of association between exposure and outcome—a causal argument can be constructed with literature from animal models representing biologic plausibility. Using a variety of study designs and research paradigms including humans and animals, research in this area provides evidence for neuroteratogenic and neurotoxic effects on the developing adolescent brain (Lydon et al. 2014; England et al. 2015).

The brain undergoes significant neurobiological development during adolescence and young adulthood, which are critical periods of sensitivity to neurobiological insults (such as nicotine) and experience-induced plasticity (Spear 2000; Dahl 2004; Gulley and Juraska 2013). Although maturation occurs in different regions of the brain at different rates, a similar progression occurs in all areas characterized by a rapid formation of synaptic connections in early childhood, followed by a loss of redundant or unnecessary synapses (called pruning) and the formation of myelin. Myelination is the process by which a fatty layer, called myelin, accumulates around

nerve cells (neurons). Because of myelin, nerve cells can transmit information faster, allowing for more complex brain processes. Pruning allows for more focused concentration, and myelination allows for faster electrical and neural signaling; both allow for more efficient cognitive processing. During adolescence and into young adulthood, myelination occurs rapidly in the frontal lobe, a place in the brain that controls executive functioning, reasoning, decision-making skills, self-discipline, and impulse control. Plasticity refers to the current understanding that the brain continues to change throughout life, not only because of normal, maturational neural growth and development but also because of changes in environmental neurobiological exposures (such as nicotine), injuries, behaviors, thinking, and emotions (Mills and Tamnes 2014).

Across species, and in humans, adolescence is a key period of increased plasticity and rapid growth of brain circuits that regulate social, emotional, and motivational processes and decision making (Spear 2000, 2011; Nelson et al. 2005; Ernst and Fudge 2009; Counotte et al. 2011). The prefrontal cortex, which is involved in higher level regulatory control of complex behaviors (such as planning, impulse control, and working memory), continues normal structural and functional development into young adulthood, to about 25 years of age (Giedd and Rapoport 2010; Somerville and Casey 2010). Because of the immaturity and rapid growth of the prefrontal cortex, adolescents and young adults normally exhibit moody, risk-taking, and unpredictable impulsive behaviors. The combination of delayed maturation of frontal cognitive control and increased reactivity of subcortical reward-related and emotion-processing systems may lead to increased risk-taking behavior and a greater susceptibility to initiating substance use and the development of dependence (Steinberg 2008; Ernst and Fudge 2009; Counotte et al. 2011; Spear 2011). Thus, myelination is vitally important to the healthy functioning of the central nervous system, and any exposure that significantly interferes with the myelination process can cause mild-to-severe cognitive and learning problems (Brady et al. 2012).

Brain development in juvenile rodents has been reported to display patterns that resemble those of human beings, suggesting that the rodent model might be relevant to studying the neurobiological underpinnings of brain maturation in teenagers (Spear 2000). Studies across species have revealed unique characteristics of adolescent nonhuman brain structure, mechanisms, and function that provide biological plausibility to the hypothesis that human adolescents are particularly vulnerable to nicotine uptake (O'Loughlin et al. 2015; Yuan et al. 2015). There is evidence for rapid growth of gray matter, followed by activity-dependent synaptic pruning (the process of synapse elimination that occurs between early childhood and the onset of puberty) and increasing myelination throughout the brain (Casey et al. 2005; Lenroot and Giedd 2006; Giedd and Rapoport 2010; Counotte et al. 2011).

Nicotine has more significant and durable damaging effects on adolescent brains compared to adult brains, the former suffering more harmful effects. Preclinical animal studies have shown that in rodent models, nicotinic acetylcholine receptor (nAChR) signaling is still actively changing during adolescence, with higher expression and functional activity of nAChRs in the forebrain of adolescent rodents compared to their adult counterparts (Britton et al. 2007; Kota et al. 2007; Doura et al. 2008). Furthermore, in rodent models, nicotine actually enhances neuronal activity in several reward-related regions and does so more robustly in adolescents than in adults (Schochet et al. 2005; Shram et al. 2007; Dao et al. 2011). This increased sensitivity to nicotine in the reward pathways of adolescent rats is associated with enhanced behavioral responses, such as strengthening the stimulus-response reward for administration of nicotine. In conditioned place-preference tests—where reward is measured by the amount of time animals spend in an environment where they receive nicotine compared to an environment where nicotine is not administered—adolescent rodents have shown an increased sensitivity to the rewarding effects of nicotine at very low doses (0.03 mg/kg) (Vastola et al. 2002; Belluzzi et al. 2004; Brielmaier et al. 2007; Kota et al. 2007; Natarajan et al. 2011) and exhibited a unique vulnerability to oral self-administration during the early-adolescent period (Adriani et al. 2002). Adolescent rodents also have shown higher levels of nicotine self-administration than adults (Levin et al. 2003; Chen et al. 2007; Natividad et al. 2013), decreased sensitivity to the aversive effects of nicotine (Adriani et al. 2002; Shram et al. 2006; Torres et al. 2008), and less prominent withdrawal symptoms following chronic nicotine exposure (O'Dell et al. 2006). This characteristic in rodent models of increased positive and decreased negative short-term effects of nicotine during adolescence (versus adulthood) highlights the possibility that human adolescents might be particularly vulnerable to developing dependency to and continuing to use e-cigarettes. These biological mechanisms are of great public health importance as exposure to nicotine grows among nonsmoking youth through the increasing prevalence of e-cigarette use.

Beyond their unique vulnerability to nicotine use, and thus smoking uptake, human adolescents may be particularly vulnerable to the detrimental consequences of nicotine exposure, including an increase in drug-seeking behaviors (Kandel and Kandel 2014), deficits in attention and cognition, and mood disorders (Yuan et al. 2015). In

animal models, chronic nicotine exposure during adolescence has been shown to produce long-lasting, unique effects that are not observed in mature adult animals. Moreover, animal models have provided substantial evidence that the limbic system—which controls cognition, emotion, and drug-reward—is actively maturing during adolescence and during this age is vulnerable to long-term modification by nicotine.

Reward-Seeking Behaviors. A very strong argument can be made about the association between adolescent exposure to nicotine by smoking conventional cigarettes and the subsequent onset of using other dependence-producing substances. Strong, temporal, and dose-dependent associations have been reported (Isensee et al. 2003; John et al. 2004b; Bronisch et al. 2008; Kandel and Kandel 2015), and a plausible biological mechanism (via rodent and human modeling) suggests that long-term changes in the neural reward system take place as a result of adolescent smoking (Lewinsohn et al. 1999; Huang et al. 2013; Kandel and Kandel 2014). Adolescent smokers of conventional cigarettes have disproportionately high rates of comorbid substance abuse (Kandel et al. 1992; Lai et al. 2000; Hanna et al. 2001), and longitudinal studies have suggested that early adolescent smoking may be a starting point or "gateway" for substance abuse later in life (Kandel et al. 1992; Lewinsohn et al. 1999; Wagner and Anthony 2002; Brook et al. 2007), with this effect more likely for persons with attention deficit hyperactivity disorder (ADHD) (Biederman et al. 2006; Wilens et al. 2008). Although factors such as genetic comorbidity, innate propensity for risk taking, and social influences may underlie these findings (Lindsay and Rainey 1997; Smith et al. 2015), both human neuroimaging and animal studies suggest a neurobiological mechanism also plays a role. In addition, behavioral studies in adolescent and young adult smokers have revealed an increased propensity for risk taking, both generally and in the presence of peers, and neuroimaging studies have shown altered frontal neural activation during a risk-taking task as compared with nonsmokers (Lejuez et al. 2005; Cavalca et al. 2013; Galvan et al. 2013). Rubinstein and colleagues (2011b) used neuroimaging to show decreased brain response to a natural reinforcer (pleasurable food cues) in adolescent light smokers (1–5 cigarettes per day), with their results highlighting the possibility of neural alterations consistent with nicotine dependence and altered brain response to reward even in adolescent low-level smokers.

Nicotine exposure in rodents at an age of physical development corresponding to human adolescence has been found to increase the reinforcing effects of other drugs of abuse, including cocaine, methamphetamine, and alcohol, without having a major impact on responding for other rewards, thus providing further evidence in support of nicotine as an initiation toward other substance use and abuse (McQuown et al. 2007; Dao et al. 2011; Dickson et al. 2014; Pipkin et al. 2014; Kandel and Kandel 2014). In several rodent studies, treatment with very low doses of nicotine for a few days during early adolescence, but not in late adolescence or adulthood, produced lasting changes in D2 and D3 dopamine receptors and in the self-administration of other abused drugs (McQuown et al. 2007; Dao et al. 2011; Mojica et al. 2014). Nicotine exposure in adolescent rats also induced rapid and long-lasting dendritic remodeling in the nucleus accumbens shell, a critical component of reward learning and addiction, via a D1 dopamine receptor-mediated mechanism (Ehlinger et al. 2016). This persistent form of nicotine-induced neuroplasticity has the potential to alter synaptic connectivity within reward-processing centers and enhance the addictive effects of drugs of abuse.

Attention and Cognition. Both cognitive improvements (Jasinska et al. 2014) and cognitive deficits (Hall et al. 2014) have been reported after nicotine exposure in healthy human adults, while smoking during adolescence impairs cognition and attention processes. Results of a genetically sensitive, longitudinal "concordant" and "discordant" twin study from the Netherlands Twin Registry indicated a larger increase in attention problems from adolescence to adulthood in twins who smoked than in their never-smoking co-twins (Treur et al. 2015). In another study, adolescent smokers were found to have chronic impairments in the accuracy of their working memory (e.g., in processing information from two sensory modalities simultaneously), which were more severe with an earlier age of onset of smoking (Jacobsen et al. 2005). Functional imaging studies have shown that 24-hour smoking abstinence in adolescent smokers causes acute impairments of verbal memory and working memory, along with chronic decrements in cognitive performance (Jacobsen et al. 2007a). In another study, adolescent users of conventional cigarettes showed decreased prefrontal cortex activation (versus never smokers) during attention tasks, and duration of smoking (in years) was directly correlated with the extent of reduction in prefrontal cortical activity (Musso et al. 2007).

Thus, longitudinal and imaging studies in humans provide support for the hypothesis that adolescent use of conventional cigarettes has both acute and long-term effects on attention and memory. Although nicotine exposure cannot be cited as the sole cause of cognitive defects (or even one of several combined effects in humans), other studies have shown that adolescent nicotine exposure in rats induces lasting synaptic changes in the prefrontal cortical regions critical for normal attention, memory, and cognition that likely underlie observed impairments in attentional and cognitive function (Bergstrom et al. 2008). Adolescent nicotine exposure in rats has induced impairments in

stimulus-response-discrimination-learning processes but not in abstract rule-learning processes, which are dependent on dissociable cognitive systems, thus showing the selective effects of nicotine (Pickens et al. 2013). In addition, adolescent, but not postadolescent, treatment of rats with nicotine resulted in diminished attention span and enhanced impulsivity in adulthood (Counotte et al. 2009, 2011). The biological causes of these cognitive disturbances (reduced attention span and impulse control) were associated with reduced regulation of prefrontal cortex excitatory synapses function in metabotropic glutamate receptor 2 (mGluR2) (Counotte et al. 2011; Goriounova and Mansvelder 2012). In addition, hippocampal function, which is critical for memory, was altered in adult mice by nicotine exposure during adolescence. Contextual fear conditioning—a hippocampus-dependent task in which animals learn and remember to associate a fearful stimulus (e.g., a foot shock) with a particular context—was disrupted in adult mice that had been treated during adolescence with chronic nicotine but not following chronic treatment with nicotine in adulthood (Portugal et al. 2012). Rodent studies have implications for human adolescents, suggesting that exposure to tobacco during youth may lead to long-lasting changes in behavioral and neuronal plasticity into adulthood.

Mood Disorders. Adolescents with symptoms of mental health disorders (e.g., anxiety, aggressive and disruptive behaviors, mood disorders) are at increased risk for initiation of conventional cigarette use and long-term nicotine dependence compared with those without such disorders (Gehricke et al. 2007; Morris et al. 2011). Although this risk may reflect a common genetic predisposition, or the use of nicotine to self-medicate in the hope of improving mental health symptoms, the question arises of whether the smoking of conventional cigarettes by adolescents contributes to the development of mood disorders. A meta-analysis of existing studies showed consistent evidence that both tobacco use and dependence on tobacco products among adolescents indeed increased their risk of anxiety disorders (Moylan et al. 2012). Other studies have shown that an early onset of smoking is associated with a shorter time to first onset of an anxiety disorder (Jamal et al. 2011), and there is a positive association between adolescent smoking, particularly through a nicotine pathway, and anxiety in early adulthood (Moylan et al. 2013). Bidirectional relationships between adolescent smoking and disruptive disorders (e.g., ADHD; oppositional defiant disorder [ODD] [Griesler et al. 2011]) as well as depression (Tjora et al. 2014) also have been reported, while a longitudinal birth cohort found evidence to support a causal relationship between teen smoking and onset of depression (Boden et al. 2010). Although these findings are complex and warrant further study using comparisons of genetic polymorphisms associated with smoking or twin and sibling discordant/concordant studies (Munafo and Araya 2010; Leventhal and Zvolensky 2015), they do suggest that nicotine exposure during adolescence could contribute to long-term mental health disorders.

Findings of animal studies support the theory that adolescent nicotine exposure results in long-term alterations in emotional response, specifically enhanced anxiety and fear (Slawecki et al. 2003; Smith et al. 2006), and in persistent alterations in serotonin systems involved in mediating mood disorders by reprogramming the future response of 5-HT systems to nicotine (Slotkin and Seidler 2009). Even a single day of nicotine treatment in adolescent rats can enhance sensitivity to aversive stimuli later in life and result in a depression-like state in adulthood that is normalized by treatment with nicotine or antidepressants (Iniguez et al. 2009).

In summary, given the existing evidence from human and animal studies of the detrimental impact of nicotine exposure on adolescent brain development, the use of e-cigarettes by youth should be avoided and actively discouraged. Both preadolescence and adolescence are developmental periods associated with increased vulnerability to nicotine addiction, and exposure to nicotine during these periods may lead to long-lasting changes in behavioral and neuronal plasticity. Studies reveal that for most tobacco users, initial use begins before 18 years of age. Moreover, in some adolescents, symptoms of nicotine dependence can develop after exposure to very low levels of nicotine—less than 100 cigarettes. Cross-species studies have identified characteristics of the adolescent brain that may render it vulnerable at this age to nicotine uptake in the form of equivalent doses via nonsmoking administration mechanisms. In addition, animal models of nicotine exposure in adolescence reveal neural and behavioral alterations consistent with an increased likelihood of future nicotine use, increased activation of reward pathways and, unlike in adult animals, decreased aversive effects. Regarding e-cigarettes, data demonstrate adolescent use of these devices is associated with use of tobacco, alcohol, and other drugs (Dutra and Glantz 2014; Kristjansson et al. 2015; Wills et al. 2015a, b; Schneider and Diehl 2016). Finally, animal and human studies suggest a bidirectional relationship between the smoking of conventional cigarettes and exposure to nicotine during adolescence and factors related to disruptive disorders, such as ADHD and ODD that impair academic performance, as well as to depression. Because the adolescent brain is still developing, nicotine use during adolescence can disrupt the formation of brain circuits that control attention, learning, and susceptibility to addiction. Further research is warranted to more fully understand the effects of e-cigarette use on youth.

Nicotine Exposure from Maternal Nicotine Consumption: Prenatal and Postnatal Health Outcomes

Prenatal nicotine exposure through maternal cigarette use during pregnancy is one of the most widespread perinatal insults in the world (Levin and Slotkin 1998; Xiao et al. 2008; USDHHS 2014). Despite medical and societal sanctions and ongoing public health campaigns, the prevalence of maternal cigarette use during pregnancy in the United States was estimated to be 11–15% in 2013 (Tong et al. 2013). Smoking rates were even higher among women who were poor, young, or less educated, with rates as high as 25–30%, indicating that infants born to mothers who are poor have disproportionately higher exposure to nicotine (Dietz et al. 2011; Hamilton et al. 2012; Tong et al. 2013). Despite these adverse consequences, an estimated one-half of pregnant smokers continue to smoke into the third trimester (Osterman et al. 2013; Tong et al. 2013).

Because adults who use e-cigarettes can achieve plasma nicotine concentrations similar to those found among smokers of equivalent amounts of conventional cigarettes (Vansickel et al. 2010; Lopez et al. 2016; St. Helen et al. 2016), it is important that research continues in this area. Nicotine has been shown to cross the placenta and has been found in placental tissue as early as 7 weeks of embryonic gestation, and nicotine concentrations are higher in fetal fluids than in maternal fluids (Luck et al. 1985; Jauniaux et al. 1999). nAChRs are widely distributed in the fetal brain. As has been clearly demonstrated in animal models, acetylcholine acts on nAChRs to modulate functional connections during critical periods of development when regions are most sensitive to environmental input (Dwyer et al. 2008). When nicotine in the maternal bloodstream crosses the placental barrier, it binds to these receptors (Pentel et al. 2006; Wong et al. 2015), and in rodents this can result in long-term changes in neural structure and function. Results from animal studies show consistent associations between prenatal nicotine exposure and upregulation of nAChRs associated with disruption of fetal brain cell replication and differentiation (Slotkin 1998). Highlighting the role of nicotine in the effects of maternal smoking during pregnancy, nAChRs have been shown to be present in the human embryonic brain from 5 weeks of gestation (Hellstrom-Lindahl et al. 1998), and their normal maturation is altered in a region- and receptor subtype-dependent fashion by maternal cigarette smoking during pregnancy (Falk et al. 2005; Duncan et al. 2008). In those brainstem nuclei important for arousal, prenatal nicotine exposure decreases [^{3}H]-nicotine binding (Duncan et al. 2008) and prevents normal age-related increases in $\alpha 4$ and $\alpha 7$ mRNA (Falk et al. 2005).

Prenatal nicotine exposure also has been associated with dysregulation of catecholaminergic, serotonergic, and other neurotransmitter systems. In addition, animal work suggests significant adverse effects of nicotine alone at levels commensurate with exposure to secondhand smoke (10-fold below those seen in active smokers), and that the non-nicotine components of tobacco smoke can exacerbate nicotine's teratogenic effects (Slotkin et al. 2015). Offermann (2015) concluded that e-cigarettes emit many harmful chemicals into the air and that indirect exposure to nicotine exceeded exposure-level standards for noncarcinogenic health effects established by the California Environmental Protection Agency. No safe level of prenatal nicotine exposure has been established (England et al. 2015).

Airborne nicotine exposure through secondhand aerosol from e-cigarettes has been observed, as has salivary cotinine concentrations of nonsmokers in the homes of e-cigarette users (Ballbe et al. 2014; Czogala et al. 2014). Ballbe and colleagues (2014) reported the geometric means of airborne nicotine were 0.74 µg/m3 in the homes of smokers, 0.13 µg/m3 in the homes of e-cigarette users, and 0.02 µg/m3 in the homes of nonsmoking controls. While airborne nicotine exposure from combustible cigarette smoke was 5.7 (Ballbe et al. 2014) to 10 times higher (Czogala et al. 2014) than e-cigarette aerosol, one study reported only a twofold increase in salivary cotinine (0.38 ng/ml in the homes of smokers versus 0.19 ng/ml in the homes of e-cigarette users) (Ballbe et al. 2014), and another study found that exposure to cigarette smoke and exposure to e-cigarette aerosol had similar effects on the serum cotinine levels of bystanders (Flouris et al. 2013). Thus, the passive exposure to nicotine from e-cigarette smoking has been reported to be just as large (Flouris et al. 2013; Grana et al. 2013) or lower than (Czogala et al. 2014) conventional cigarettes, but exposure to nicotine from e-cigarette smoking is not negligible and is higher than in nonsmoking environments. This evidence suggests the importance of avoiding secondhand exposure of e-cigarette vapor and secondhand smoke during pregnancy (Flouris et al. 2013; Grana et al. 2013; Czogala et al. 2014).

Of the components of tobacco smoke, nicotine has been cited as the most important toxicant in terms of interfering with fetal development. Because of the health risks to the developing fetus associated with nicotine exposure during pregnancy, the U.S. Food and Drug Administration (FDA) (2015) recommends that pregnant women seek medical approval before using NRT, and the American College of Obstetricians and Gynecologists (2011) recommends consideration of NRT only if a woman fails behavioral interventions to quit smoking conventional cigarettes and has discussed the potential harms

and benefits of NRT with her physician. NRT is most often used during pregnancy as a last resort to avoid exposing the fetus to the other toxic ingredients found in conventional tobacco smoke (Fiore et al. 2008). A Cochrane Database systematic review concluded that both the effectiveness and safety of NRT during pregnancy are unclear (Coleman et al. 2012). Table A3.1-4 in Appendix 3.1 presents a summary of studies in humans on the effects of tobacco exposure on fetal brain development.

Even with a firm understanding of the negative health consequences of nicotine on the developing fetus (Fiore et al. 2008; USDHHS 2014; Ekblad et al. 2015), little is known about the prevalence of e-cigarette use among pregnant women or the direct harmful effects on their fetus by other toxicants delivered by the aerosol from e-cigarettes (England et al. 2015; Suter et al. 2015). In one of the few studies identified, a survey of 316 pregnant women in a Maryland clinic found that the majority had heard of e-cigarettes, 13% had ever used them, and 0.6% were current daily users (Mark et al. 2015). These findings are of concern because the dose of nicotine delivered by e-cigarettes can be as high or higher than that delivered by conventional cigarettes. Therefore, plasma nicotine concentrations delivered while using e-cigarettes have the potential to harm the developing fetus. Furthermore, in 2013 in the United States, there were 26.5 births for every 1,000 adolescent females (15–19 years of age), or 273,105 babies born to females in this age group (Hamilton et al. 2013). Currently, the rate of e-cigarette use among pregnant adolescents is unknown, but the effects of nicotine and the potential for harm by other e-cigarette toxicants indicate that the use of e-cigarettes is a fetal risk factor among pregnant adolescent girls.

As outlined below, the specific effects of nicotine on prenatal development and postnatal outcomes include sudden infant death syndrome (SIDS) and may include altered development of the corpus callosum, deficits in auditory processing, and alterations in appetitive behavior, attention, and cognition.

SIDS. SIDS is the sudden and unexplained death of an infant younger than 1 year of age (Krous 2014). Maternal smoking and infant exposure to secondhand smoke have been causally associated with SIDS, with 20–29% of deaths from SIDS attributable to maternal smoking of conventional cigarettes during pregnancy (Dietz et al. 2010; Zhang and Wang 2013; USDHHS 2014). Prenatal exposure to cigarettes and to smokeless tobacco have been associated with increased risk for apnea events, which have been linked to increased risk for SIDS (Gunnerbeck et al. 2011; Zhang and Wang 2013; Inamdar et al. 2015).

Although the mechanistic pathways underlying SIDS remain largely unknown, nicotine has effects on pathways that could be related to SIDS and is related to known risk factors, particularly lung and respiratory development (England et al. 2015; Holbrook 2016; Spindel and McEvoy 2016). Evidence from animal models supports the hypothesis that prenatal nicotine exposure alters both fetal autonomic function and arousal, which could increase the risk of SIDS (Slotkin 1998; Task Force on Sudden Infant Death Syndrome and Moon 2011). In humans, a dose–response relationship between cotinine (the major nicotine metabolite) and altered arousal patterns has been shown in preterm infants (Richardson et al. 2009), and this relationship is suggestive of nicotine's role in arousal deficits that could be linked to SIDS. There is widespread distribution of nAChRs in the brainstem nuclei in both humans and animals that control cardiopulmonary integration and arousal in the newborn (Dwyer et al. 2008). In some animal studies, prenatal exposure to nicotine has increased mortality in newborns that were exposed to reduced oxygen (Slotkin et al. 1995; Fewell and Smith 1998). Prenatal exposure to nicotine is also associated with altered serotonin signaling in the brainstem in the rat model, leading to an exaggerated trigeminocardiac reflex and resulting in bradycardia, hypotension, and apnea (Gorini et al. 2013).

Altered Development of the Corpus Callosum. The corpus callosum, the largest white matter structure in the brain, facilitates communication between the left and right cerebral hemispheres. Several human studies have revealed alterations in the structure of the corpus callosum in offspring following their exposure to maternal cigarette use during pregnancy (Jacobsen et al. 2007b; Paus et al. 2008). In animal models, prenatal exposure to nicotine has been shown to result in widespread alterations in gene expression in the brains of adolescent offspring (Cao et al. 2011, 2013; Wei et al. 2011). In particular, the expression of a number of genes involved in myelination—the formation of white matter via the addition of protective myelin sheaths to axons—is altered in a sex-dependent manner, with upregulation in males and downregulation in females (Cao et al. 2013). Such changes in the expression profiles of myelin-related genes may influence the structure and function of white matter, and both hypermyelination and hypomyelination have been associated with cognitive deficits (Quaranta et al. 2002; Sokolov 2007).

Deficits in Auditory Processing. A number of human studies, using a variety of methods, have investigated the effects of maternal cigarette smoking during pregnancy on auditory processing from the fetal period through childhood (Jacobson and Morehouse 1984; Kristjansson et al. 1989; McCartney et al. 1994; Franco et al. 1999; Leech et al. 1999; Cowperthwaite et al. 2007). Deficits in auditory processing in fetuses are of concern because they affect later language development (Kisilevsky

and Davies 2007; Kisilevsky et al. 2014). Various studies in infants have investigated the brain's physiological activity response to auditory stimuli (the cochlea translates sound into nerve impulses to be sent to the brain), neuroelectric activity of the auditory nerve, and cochlear response (Key et al. 2007; Korres et al. 2007; Kable et al. 2009; Peck et al. 2010; Katbamna et al. 2013). Key and colleagues (2007) reported prenatal exposure to cigarette use (compared with nonexposed infants) to be associated with alterations in hemispheric asymmetry and suboptimal brain activity related to speech processing in otherwise healthy newborns at least 2 days of age. Korres and associates (2007) found altered cochlear responses to auditory stimuli in newborns that were exposed to maternal cigarette smoking (n = 200) compared with those that were unexposed (n = 200), regardless of degree of cigarette exposure. Similar findings were reported by Durante and colleagues (2011) in two case-control studies.

Two additional studies investigated effects of maternal cigarette use during pregnancy on auditory brainstem responses in newborns (≤2 days old) (Peck et al. 2010) and infants (6 months old) (Kable et al. 2009). Both studies found greater neuroelectric response to sound stimuli, a phenomenon that may disrupt an infant's ability to encode auditory information, potentially leading to deficits in language development. Furthermore, both studies demonstrated dose–response relationships between altered auditory processing and maternal cotinine levels. Finally, in a study of a small sample of newborns that sought to understand the direct biological pathway, maternal smoking during pregnancy produced changes in newborn cochlear and auditory brainstem functions and changes in placental gene expression in genes that appear to modulate the motility of cochlear hair cells (Katbamna et al. 2013). Thus, all three studies indicate effects based on consumption of conventional cigarettes, and they highlight the possibility of a mediating role of maternal nicotine use in altered infant auditory processing, although further work must rule out confounding effects and effect modification by other constituents (e.g., arsenic, benzene, and cadmium).

A study using functional magnetic resonance imaging (fMRI) in older offspring exposed to tobacco in utero assessed response to auditory and visual attention tasks in adolescent smokers (Jacobsen et al. 2007a). Teens whose mothers smoked during pregnancy exhibited decreased accuracy in the tasks, with greater activation of both the temporal lobe and the occipital lobe, regions of the brain that are critical for auditory and visual processing. Additive effects of maternal cigarette use during pregnancy and of adolescent smoking on activation of the temporal and occipital lobes also emerged, indicative of reduced coordination among brain regions during auditory attention tasks.

Animal studies have shown that nAChRs play a critical developmental role in establishing synaptic connections between sensory thalamic afferents and those cortical targets that are necessary for normal sensory processing (Table A3.1-5 in Appendix 3.1). Brief nicotine exposure during this critical postnatal period of sensory cortex development disrupts glutamate transmission (Aramakis et al. 2000) and eliminates nAChR regulation of signal processing in the adult auditory cortex, inhibiting normal auditory learning (Liang et al. 2006). Animals that are prenatally exposed to nicotine also exhibit deficits in cognitive processing in response to an auditory cue, which appears to be mediated by a loss of function of the nAChR β2 subunit (Liang et al. 2006; Horst et al. 2012).

Appetitive and Consummatory Behaviors. Clinical studies and animal studies have linked prenatal exposure to nicotine to subsequent appetitive behaviors (an active searching process that is performed consciously) and consummatory behaviors (such as ingestion of food or drugs) in offspring. Associations have been demonstrated in humans between maternal cigarette use during pregnancy and risk to the child of smoking uptake/nicotine dependence, drug abuse, and obesity; parallel relationships have been shown in animal models between prenatal exposure to nicotine and similar appetitive behaviors of offspring.

Parental use of tobacco is one of many well-known risk factors for offspring initiation of tobacco, progression to heavy use, and nicotine dependence. Tobacco use by parents influences their children through social, environmental, cognitive, and genetic mechanisms (USDHHS 2012). As a subset of these influences, mothers' use of tobacco during pregnancy has been studied as an independent risk factor and has been associated with offspring susceptibility, initiation, regular use, and dependence (Kandel et al. 1994; Griesler et al. 1998; Kandel and Udry 1999; Buka et al. 2003; Lieb et al. 2003; Oncken et al. 2004; Al Mamun et al. 2006; O'Callaghan et al. 2009; Tehranifar et al. 2009; Agrawal et al. 2010; Rydell et al. 2012; Weden and Miles 2012; Stroud et al. 2014; Shenassa et al. 2015). Wakschlag and colleagues (2010, 2011) suggest that maternal smoking during pregnancy has a teratologic effect with abnormalities stemming from the in utero environment which disrupt neural (Kandel et al. 1994; Jacobsen et al. 2006) and dopamine systems that promote sensitivity to nicotine dependence (Kandel et al. 1994; Selya et al. 2013). For example, nicotinic receptors of laboratory animals exposed to nicotine in utero are upregulated, suggesting a latent vulnerability to nicotine dependence among animals exposed to nicotine in utero (Slotkin et al. 2006, 2015).

At issue with all human studies investigating maternal use of tobacco during pregnancy and offspring use of tobacco is isolating the independent effect on the fetus in relation to the other social, environmental, and cognitive factors that also predict offspring tobacco use. After controlling for maternal smoking during the offspring's childhood, several studies have reported that maternal smoking during pregnancy is associated with higher nicotine dependence in offspring (Kardia et al. 2003; Lieb et al. 2003; Selya et al. 2013; Shenassa et al. 2015), increased or earlier smoking initiation, and heavier smoking among adolescent girls and adult offspring (Kandel et al. 1994; Cornelius et al. 2005). However, the association was attenuated and nonsignificant among several studies that controlled for a variety of environmental, social, and cognitive confounders between maternal cigarette use during pregnancy and initiation of offspring smoking (but not nicotine dependence) (Cornelius et al. 2005; Roberts et al. 2005; Munafo et al. 2006; Kandel et al. 2007; D'Onofrio et al. 2012; Rydell et al. 2014; Taylor et al. 2014), leaving speculation for the independent effect. In summary, evidence from animal models offers a biologic mechanism for, and human evidence is suggestive of, an association between maternal tobacco use during pregnancy with offspring smoking and nicotine dependence, but is insufficient to infer causation. Further research and longitudinal studies that examine these outcomes while assessing the full spectrum of environmental, social, and cognitive mediating pathways are needed to disentangle these issues.

A smaller set of literature has documented associations between maternal cigarette smoking during pregnancy and use of other substances by the child (Fergusson et al. 1998; Weissman et al. 1999; Porath and Fried 2005; Nomura et al. 2011). In utero exposure to nicotine also affects behavioral responses for drug rewards in both adolescent and adult experimental animals. Prenatal exposure to nicotine increases the preference of adolescents for a saccharin solution containing nicotine compared with saccharin alone (Klein et al. 2003), and it results in self-administration of nicotine either during acquisition of the task (Chistyakov et al. 2010) or after forced abstinence (Levin et al. 2006). Prenatal exposure to nicotine also increases subsequent oral intake of alcohol (Chang et al. 2013), and intravenous self-administration of both cocaine and methamphetamine is enhanced in a dose-dependent manner in adolescent rats (Franke et al. 2008) and adult rats (Lacy et al. 2014).

In contrast, in a study that used a discordant sibling pair design to reduce confounding by genetic and environmental factors, initial associations between prenatal smoking and alcohol use disorder were attenuated and were no longer statistically significant (D'Onofrio et al. 2012). In a large longitudinal study that spanned 40 years, Shenassa and colleagues (2015) found evidence to support effects on nicotine dependence among children of mothers who smoked during pregnancy, but no effects on their progression to marijuana dependence were observed. A possible explanation for these discordant findings is suggested by a study that found significant effects from prenatal smoking of conventional cigarettes on drug use among adolescents, but showed that these effects were restricted to a genetic subpopulation of carriers of a specific α6 nAChR gene (*rs2304297*) polymorphism (Lotfipour et al. 2010). In sum, a number of studies have documented associations between cigarette use by the mother during pregnancy and smoking initiation, heavy use, and nicotine dependence among her children, although control of confounding reduces this association. In addition, the literature is sparse and inconsistent regarding a connection between maternal cigarette use during pregnancy and the use of nontobacco substances by the child.

A large body of literature has demonstrated effects of maternal cigarette use during pregnancy on weight levels and obesity in childhood. For example, three meta-analytic reviews found a 47–64% increased risk of obesity in children following exposure to maternal cigarette smoking during pregnancy (Oken et al. 2008; Ino 2010; Weng et al. 2012; Behl et al. 2013). Additional systematic reviews (Bruin et al. 2010) and other studies (Harrod et al. 2015; La Merrill et al. 2015; Mourtakos et al. 2015; Bao et al. 2016) have all concluded that prenatal exposure to nicotine likely acts as a developmental obesogen in humans. However, unmeasured residual confounding or confounding by familial factors, which have not been fully explored, could attenuate the observed associations (Gilman et al. 2008; Iliadou et al. 2010). Animal studies support the epidemiologic literature suggesting a potentially causal relationship here by defining biologic pathways (Wong et al. 2015). Fetal and neonatal exposure to nicotine in rodents has resulted in neurochemical, neurobehavioral, and metabolic changes in the children that are consistent with obesity and type 2 diabetes (Williams and Kanagasabai 1984; Newman et al. 1999; Grove et al. 2001; Chen and Kelly 2005; Gao et al. 2005; Holloway et al. 2005).

In humans, studies involving structural MRI and fMRI have shown alterations in the size and sensitivity of brain reward centers in the teenage offspring of maternal smokers. Several of these studies revealed a thinning of the orbitofrontal cortex among persons who were prenatally exposed to maternal cigarette smoking, a thinning that was associated with drug use and experimentation during adolescence (Toro et al. 2008; Lotfipour et al. 2009); decreased amygdalar volume, which is associated

with increased fat intake (Haghighi et al. 2013); and altered response to reward anticipation in the ventral striatum, an area associated with risk taking and drug use (Muller et al. 2013). In addition, highlighting the role of altered nicotinic pathways in the disruption of neural circuits from prenatal tobacco exposure, changes in striatal volume, and a propensity for drug use in adolescent offspring have been linked to interactions between prenatal exposure to cigarette smoking and a polymorphism in the gene encoding the α6 nAChR (Lotfipour et al. 2010). Structural alterations in the orbital frontal cortex have also been shown to result from interactions between maternal cigarette smoking during pregnancy and polymorphisms of brain-derived neurotrophic factor, a growth factor that regulates growth and differentiation of new neurons and supports existing neurons (Lotfipour et al. 2009). Although these clinical findings are specific to conventional cigarettes, they converge with results of animal studies of the effects of prenatal nicotine on brain reward centers and thus highlight the potential pernicious effects of e-cigarettes in pregnant women.

Animal studies have shown that the dopamine system, which is critically involved in satisfaction-seeking or appetitive behaviors, is modulated by nAChRs from the fetal period to adulthood (Azam et al. 2007). Prenatal nicotine exposure alters dopamine's content, turnover, release, and receptor expression in forebrain regions, which are important for motor and cognitive functions (Navarro et al. 1988; Richardson and Tizabi 1994; Muneoka et al. 1999; Zhu et al. 2012) and for assigning motivational value to natural and drug rewards (Kohlmeier 2015; McNair and Kohlmeier 2015). Prenatal exposure to nicotine also modifies the structure of dendritic targets of dopamine innervations in the nucleus accumbens (a critical component of reward learning and addiction) (Mychasiuk et al. 2013) and alters neuronal signaling that affects dopamine function (Chang et al. 2013; Morgan et al. 2013).

Prenatal exposure to nicotine has been shown in a variety of animal studies to induce complex effects on behavioral response to natural rewards. Although adolescent offspring of nicotine-exposed mothers show an initial decrease in motivation to work for sucrose reward (Franke et al. 2008), they exhibit enhanced sensitivity to the rewarding effects as the task becomes harder (Lacy et al. 2012). Prenatal exposure to nicotine also results in enhanced intake of fatty foods, with no change in the intake of normal chow (Chang et al. 2013).

Attention and Cognition. Numerous human studies have investigated the effects of maternal cigarette use during pregnancy on disruptive behavior and attention deficits in the child. The 2014 Surgeon General's report included results of a systematic review of effects of maternal cigarette use during pregnancy on disruptive-behavior disorders—including ADHD, conduct disorder, and ODD—in offspring (USDHHS 2014). The evidence for effects of maternal cigarette use during pregnancy on disruptive-behavior disorders, and ADHD in particular, was suggestive but not sufficient to infer a causal relationship. Several systematic reviews using meta-analyses have found evidence for associations between exposure to maternal cigarette use during pregnancy and ADHD in offspring, including dose–response relationships between number of cigarettes smoked per day and ADHD symptoms (Linnet et al. 2003; Langley et al. 2005; Latimer et al. 2012; Massey et al. 2016). However, similar to effects on nicotine dependence and obesity in offspring, the possibility of unmeasured confounding remains (D'Onofrio et al. 2008; Thapar et al. 2009; Langley et al. 2012). Evidence for associations with maternal cigarette use during pregnancy is perhaps more consistent for offspring conduct disorders than it is for ADHD. In particular, although some studies that used a gene–environment interaction design or a propensity score-matching approach to exposure to control for confounding, they found no effect of maternal cigarette smoking during pregnancy on conduct disorders (D'Onofrio et al. 2008; Gilman et al. 2008; Boutwell and Beaver 2010; Lavigne et al. 2011). However, several other studies—including a meta-analytic review across three studies using "genetically sensitive"[2] research designs—have suggested a direct causal relationship between maternal smoking during pregnancy and conduct disorders in offspring (McCrory and Layte 2012; Gaysina et al. 2013; Kuja-Halkola et al. 2014; Estabrook et al. 2015; Paus and Pausova 2015).

To explore the potential role of nicotine exposure in these associations, a small number of studies have included a prospective measure of confirmed tobacco exposure, maternal cotinine levels, in addition to maternal report of smoking, to study relationships with disruptive behaviors among offspring (Wakschlag et al. 2011; O'Brien et al. 2013; Massey et al. 2016). Wakschlag and colleagues (2011) found associations between maternal cigarette smoking and aggression and noncompliance among offspring. Studies have also shown alterations in the structure and

[2]Genetically sensitive designs typically include monozygotic and dizygotic twins and a broader inclusion of sibling pairs, mother–child pairs, and grandparent–grandchild pairs. Genetically sensitive multigroup designs allow for simultaneous testing of additive and nonadditive genetic, common, and specific environmental effects, including cultural transmission and twin-specific environmental influences.

function of the orbital frontal cortex, a region important for emotional regulation and cognition, in relation to maternal cigarette smoking during pregnancy (Toro et al. 2008; Bennett et al. 2009). Consistent with animal models of altered dopamine regulation, two studies have shown interactions of maternal cigarette smoking during pregnancy with dopamine regulation genotype (DAT1) in influencing disruptive-behavior phenotypes in offspring (Wakschlag et al. 2011; O'Brien et al. 2013). In another study, Wakschlag and colleagues (2010) demonstrated a sex-dependent interaction of maternal smoking during pregnancy with monoamine oxidase A (MAOA) genotype, which is associated with the development of antisocial behavior. In this study, maternal smoking during pregnancy further increased the risk for conduct disorder. In sum, although issues of confounding remain, much evidence from human studies is suggestive of a causal association between maternal cigarette smoking during pregnancy and disruptive behaviors among offspring. This was confirmed by the 2014 Surgeon General's report on tobacco (USDHHS 2014). Since then, newer studies, controlling for personal and genetic confounders, have reported significant associations as well as nonsignificant, attenuated associations. Biologic evidence of nicotine-induced alterations in dopamine regulation also provides a possible mechanism for the role of nicotine in these outcomes.

Animal studies have shown that cholinergic modulation of prefrontal cortex function, via nAChRs, is essential for attention and cognition (Poorthuis and Mansvelder 2013; Proulx et al. 2014). Prenatal exposure to nicotine alters the morphology and nAChR functional response of prefrontal cortical neurons (Mychasiuk et al. 2013; Bailey et al. 2014). When tested as adolescents, animals that were exposed prenatally to nicotine show some behaviors characteristic of ADHD. For example, exposed offspring were found in two studies to show less impulse control and/or slower learning acquisition on two cognitive tests that tax attentional processes (Sorenson et al. 1991; Schneider et al. 2012). In addition, some studies have found hyperactivity in exposed offspring (Pauly et al. 2004; Schneider et al. 2012; Zhu et al. 2012), which was found in another study to be transmitted via maternal lineage from one generation to the next and to be ameliorated by methylphenidate treatment across all generations, showcasing the long-term impact of prenatal nicotine exposure (Zhu et al. 2014a). This transgenerational transmission of prenatal nicotine-induced hyperactivity must reflect long-term changes to the epigenome (Leslie 2013). Finally, emerging animal studies suggest that prenatal exposure to nicotine affects the proliferation and maturation of progenitor cells to glutamatergic neurons during neurodevelopment in the medial prefrontal cortex, resulting in behavioral impairments in attentional function and behavioral flexibility in adulthood (Aoyama et al. 2016; Poon and Leibowitz 2016; Powell et al. 2016).

Summary

Because of the rising prevalence of e-cigarette use, there is potential for widespread nicotine exposure to youth and young adults, resulting in nicotine addiction and related harmful consequences associated with exposure to nicotine. During pregnancy, there is neural sensitivity to the number and volume of substances, including nicotine, transported through the placenta. From prenatal development through adolescence and early adulthood, exposure to nicotine poses a serious threat, because these are critical times for brain development and brain plasticity. Furthermore, youth and young adults are more vulnerable than adults to the long-term consequences of nicotine exposure, including susceptibility to nicotine addiction and potentially reduced impulse control, deficits in attention and cognition, and mood disorders. An additional public health concern is exposure to e-cigarettes among persons who have never used conventional tobacco products. If the prevalence of e-cigarette use continues to rise among those who do not use conventional tobacco products, the harmful consequences of exposure to nicotine will rise accordingly.

The 2014 Surgeon General's report (USDHHS 2014) states there is sufficient evidence to infer that: (a) nicotine activates multiple biological pathways through which smoking increases risk for disease; (b) nicotine exposure during fetal development, a critical window for brain development, has lasting adverse consequences for brain development; (c) nicotine adversely affects maternal and fetal health during pregnancy, contributing to multiple adverse outcomes such as preterm delivery and stillbirth; and (d) nicotine exposure during adolescence, a critical window for brain development, may have lasting adverse consequences for brain development and cognition. The literature presented in this section attempts to differentiate the risks to fetal and child health associated with nicotine in tobacco versus nicotine alone or in e-cigarettes. Evidence is sufficient to conclude tobacco use increases the risk of SIDS (USDHHS 2014), but further research is necessary with regard to nicotine alone or nicotine in e-cigarettes. The review finds evidence that tobacco is associated with structural brain changes and alterations in cognition, attention, and appetitive behaviors in human offspring. Less well known is the role that nicotine plays in mediating these associations, although animal models provide support for a role for nicotine in these outcomes. nAChRs, the chief receptor targets for nicotine, are widely expressed in the fetal brain, and their normal functioning

is negatively affected by smoking and, in animals, by prenatal exposure to nicotine through experimental treatment. Furthermore, both human genetic studies and animal studies implicate a neurotoxic effect of fetal nicotine exposure. Pregnant women and women intending to become pregnant should be cautioned against using e-cigarettes to avoid unnecessary nicotine exposure to their baby.

Effects of the Inhalation of Aerosol Constituents Other than Nicotine

The scientific literature on the health effects of exposure to constituents other than nicotine in the e-cigarette aerosol is still developing. One study found that after 5 minutes of ad lib e-cigarette use, healthy adult cigarette smokers showed an increase in airway resistance, but no effect on other spirometry parameters such as forced vital capacity (FVC), forced expiratory volume in 1 second FEV1, and ratios of these values (FEV1/FVC) (Vardavas et al. 2012).

A noninvasive marker of airway inflammation is the fraction of exhaled nitric oxide (FeNO) (Taylor et al. 2006; Munakata 2012). NO is a gaseous molecule that produces vasodilation and bronchodilation (decreasing resistance in the respiratory airway and increasing airflow to the lungs). FeNO is reduced by acute and chronic cigarette smoking (resulting in poorer vasodilation and bronchodilation) and is increased among smokers following cessation (see Vleeming et al. 2002 for a review). Studies examining current adult cigarette smokers revealed a reduction in FeNO after use of an e-cigarette with and without nicotine (Vardavas et al. 2012; Marini et al. 2014; Ferrari et al. 2015). One study found that these reductions did not differ significantly between e-cigarettes containing nicotine and those without nicotine (Marini et al. 2014), suggesting non-nicotine factors mediated the effect.

However, a study of occasional smokers (<10 cigarettes per week), but non-e-cigarette users, found an increase in FeNO after use of an e-cigarette containing nicotine (Schober et al. 2014). Furthermore, this study found no statistical difference in FeNO after use of an e-cigarette not containing nicotine. This variation in findings suggests the impact of e-cigarette use on FeNO may vary based on smoking history, nicotine content of e-liquid, or other environmental or biological factors.

Limited studies have examined chronic exposure on the potential inhalation toxicity of PG and VG. Prior to e-cigarettes, consumer products containing these chemicals were almost exclusively liquids or creams, or the substance was contained in a matrix. Animal models have shown few toxicological effects resulting from nose-only exposure to VG aerosol, with the exception of minimal or mild squamous metaplasia in rats exposed to the highest concentration (0.662 mg glycerol) for 13 weeks (Anderson et al. 1950; Renne et al. 1992). Other inhalation studies testing PG in rats and monkeys did not observe treatment-related effects on respiratory physiology, clinical chemistry, hematology, gross pathology, or respiratory tract histology (Robertson et al. 1947). However, neither of these studies examined potential inhalation toxicity of PG and VG in humans using e-cigarette devices. In summary, other than nicotine, very little is known from human studies about the long-term health effects of inhaling PG and VG from e-cigarette aerosol, although adverse effects have been detected in animal models. Further investigation would improve our understanding of the effects of nicotine-related compounds, aerosolized solvents (PG and VG), aerosolized flavorants, aerosolized adulterants in e-liquids, and toxicants produced during the aerosolization process—or a combination of these chemicals.

Aerosolized Nicotine-Related Compounds

The nicotine used in e-liquids is extracted from tobacco. The extraction process may produce some potentially harmful tobacco-specific impurities, including minor alkaloids like nornicotine, anatabine, anabasine, myosmine, cotinine, nicotine-N-oxides (cis and trans isomers), β-nicotyrine, and β-nornicotyrine (Etter et al. 2013; Farsalinos et al. 2015a; Lisko et al. 2015; Oh and Shin 2015). The correlation between nicotine and the concentrations of minor alkaloids is much stronger in conventional tobacco products (Jacob et al. 1999) than in e-cigarettes (Lisko et al. 2015). While the cause of these differing concentrations of minor alkaloids is unknown, Lisko and colleagues (2015) speculated potential reasons may derive from the e-liquid extraction process (i.e., purification and manufacturing) used to obtain nicotine from tobacco, as well as poor quality control of e-liquid products.

The American E-Liquid Manufacturing Standards Association (2014), an industry group with no regulatory authority, has called for the use of U.S. Pharmacopeia (USP)-grade nicotine in its e-cigarette products. USP specifications for nicotine allow for a maximum of 0.5% (5 mg/g) of a single impurity and 1% (10 mg/g) of total impurities (U.S. Pharmacopeia n.d.). Although the health implications of nicotine-related impurities are not known, toxicology studies are needed to demonstrate the effects of high levels of these products.

Aerosolized Solvents

Although e-cigarettes produce PG aerosols at levels known to cause eye and respiratory irritation to both users and nonusers (Offermann 2015), only mild effects (e.g., upper respiratory irritation) have been described in humans exposed to PG mist for 1 minute (Wieslander et al. 2001), and little is known about long-term effects. Inhaling PG can increase the risk of developing asthma (Choi et al. 2010). Animal studies of PG and VG aerosolizing agents not produced by e-cigarettes concluded that these substances are relatively safe when inhaled by animals for up to 28 days (Werley et al. 2011) or 18 months (Robertson et al. 1947).

Particles emitted from e-cigarettes are assumed to be formed from supersaturated PG (i.e., concentration beyond the point of saturation) in e-liquids (Schripp et al. 2013). Several studies designed to characterize the aerosol generated by e-cigarettes examined the chemical composition of the particles and their concentrations as measured by their number and distribution by size (Trehy et al. 2011; Ingebrethsen et al. 2012; Schripp et al. 2013; Zhang et al. 2013; Fuoco et al. 2014; Ruprecht et al. 2014; Saffari et al. 2014 ; Mikheev et al. 2016). E-cigarettes are recognized as a new source of submicron-sized particles, leading to possible high exposure to these particles in users. Concentrations in the range of 10^9 particles $\times$ cm^{-3} were measured in the mainstream of e-cigarette aerosols (Fuoco et al. 2014). An in vitro study by Zhang and colleagues (2013) found that under the conditions of a single-puff experiment, an e-cigarette generated an aerosol having particle sizes in the range of 100–600 nm (nanometers), similar to that of conventional cigarettes. Mikheev and colleagues (2016) reported that the size distribution of e-cigarette aerosol differs from that of combustible tobacco smoke and that e-cigarettes normally exhibit a bimodal particle size distribution: nanoparticles (11–25 nm count median diameter) and submicron particles (96–175 nm count median diameter). Each mode has comparable number concentrations (10^7–10^8 particles/cm^3). Goel and colleagues (2015) detected radicals in aerosols from all e-cigarettes and e-liquids tested (2.5–10.3 x10^{13} radicals per puff at 3.3 V [voltage]), from e-liquid solvents PG and VG, and from "dry puffing" (overheating of e-liquid) (Farsalinos et al. 2015c).

Because the aerosols deriving from e-liquids are mainly made of droplets that are expected to dissolve as they reach the lung's epithelium, not only the number but also the volume (size) of particles needs to be considered. Manigrasso and colleagues (2015) found that e-cigarettes are a source of extremely high doses of particles in the human respiratory system. On average, 6.25 $\times 10^{10}$ particles were deposited in the respiratory tree after a single 2-second puff, an estimated 30% of the daily doses of particles for a nonsmoking person. After 10 puffs, the relevant mean-layer thickness of the e-liquid on the lung epithelium was comparable to the thickness of surfactant layer covering the alveolar and bronchial regions, suggesting a higher susceptibility to irritant endpoints (Manigrasso et al. 2015). These results demonstrate that e-cigarettes produce submicron-sized particles and highly oxidizing free radicals that may present a potential toxicologic risk to e-cigarette users.

Aerosolized Flavorants

Little is known about the flavorants used in e-cigarettes, and more than 7,700 unique flavors are on the market (Zhu et al. 2014b). Flavored e-cigarette products are popular with adult users, and sweet and candy-like flavors may make these products attractive to children and adolescents (Villanti et al. 2013; Farley et al. 2014; King et al. 2014). Many of the chemicals used in e-liquid flavorings are "generally recognized as safe" for ingesting (e.g., in food). However, these substances have not been tested adequately for safety when heated at various temperatures when inhaled in aerosolized form (Barrington-Trimis et al. 2014). The Flavor and Extract Manufacturers Association of the United States (2015), in an official statement, notes that ingredients in flavors are evaluated for exposure through ingestion only; thus, any results cannot be extrapolated to use through inhalation. Further, flavoring compounds often remain undeclared on e-cigarette and e-liquid packaging (Tierney et al. 2016).

CDC tested 36 e-cigarette products for 10 flavor compounds commonly used as additives in tobacco products (Lisko et al. 2015). Measurable levels of eucalyptol and pulegone were found in the menthol-flavored varieties for all manufacturers. Menthol concentrations ranged from 3,700 to 12,000 µg/g in flavored e-liquids, levels similar to those found in the filler of conventional cigarettes. Interestingly, menthol was found at low concentrations in 40% of the tobacco-flavored nonmenthol products tested. Other flavor compounds found were camphor, methyl, salicylate, pulegone, cinnamaldehyde (CAD), and eugenol (Lisko et al. 2015).

Tierney and colleagues (2016) analyzed 30 e-cigarette products on the U.S. market and found 13 products contained more than 1% flavor chemicals by weight. Among the chemicals identified were aldehydes (e.g., benzaldehyde and vanillin), which are categorized as primary irritants of the respiratory tract (Roberts et al. 2015). Tierney and colleagues (2016) also found that tobacco-flavored e-liquids were derived from confection-flavored chemicals (e.g., bubble gum and cotton candy flavoring) rather than tobacco extract.

Some chemicals in e-cigarettes, although approved for ingestion, have established adverse health effects when inhaled. In vitro studies of cytotoxicity suggest that different flavored e-cigarette products may vary in their potential to adversely affect health. Bahl and colleagues (2012) reported cytotoxic effects of the solutions used in e-cigarettes that were not attributable to the nicotine but to the concentration of chemicals employed as flavors. These effects were most pronounced on mouse neural stem cells and human embryonic stem cells compared to human pulmonary fibroblast (Bahl et al. 2012).

Similar findings were reported by Behar and colleagues (2014) who found a greater cytotoxic effect of flavored e-liquid solutions on human embryonic stem cells compared to human pulmonary fibroblast. Further, two cinnamon-related chemicals, CAD and 2-methoxycinnamaldehyde, were particularly cytotoxic at doses found in the refill liquids (Behar et al. 2014). CAD, which is derived from the essential oil of cinnamon bark, is a highly bioactive compound (Jayaprakasha and Rao 2011). It has been used as an anticancer agent (Nagle et al. 2012), an insecticide (Cheng et al. 2009), and a bactericide (Nostro et al. 2012), and it is employed commercially as an additive in many foods and fragrances (Cocchiara et al. 2005).

Farsalinos and colleagues (2014a) analyzed 159 e-liquids obtained from a variety of manufacturers and retailers in Europe and the United States for the presence of two flavorings: diacetyl (DA) and acetyl propionyl (AP). The study revealed that these substances were present in the majority of the samples tested, with a significant proportion containing both chemicals. Furthermore, Allen and colleagues (2016) detected DA above the laboratory limit of detection in 39 of 51 flavors tested. DA, also known as 2, 3-butanedione, is a member of a general class of organic compounds referred to as diketones, α-diketones, or α-dicarbonyls. It provides a characteristic buttery flavor, is naturally found in various foods, and is used as a synthetic flavoring agent in food products such as butter, caramel, cocoa, coffee, dairy products, and alcoholic beverages. Although it is generally recognized as safe when ingested, it has been associated with a decline in respiratory function in persons exposed to it through inhalation (Egilman et al. 2011; Clark and Winter 2015). Inhaling DA and artificial butter-flavored powders and aerosols can cause fixed obstructive lung disease in exposed workers (Chaisson et al. 2010). In addition, it has been implicated in the development of bronchiolitis obliterans, an irreversible respiratory disease also called "popcorn lung disease" (Harber et al. 2006). AP, also called 2, 3-pentanedione, is a α-diketone that is chemically and structurally similar to DA. Although it has become a popular replacement for DA, acute inhalation exposure to AP has been shown to cause airway epithelial damage similar to DA (Hubbs et al. 2012).

The analysis by Farsalinos and colleagues (2014a) found that 74.2% of the sample contained one or both of these chemicals, with 69.2% of the sample containing DA. Both DA and AP were found in 28.3% of the sample e-liquids. These chemicals were detected even in samples coming from manufacturers that stated these flavorings were not present in their products. However, exposure to DA and AP was 100 and 10 times lower, respectively, than exposure to these chemicals from cigarette smoking. Few studies have examined safe levels of DA and AP via tobacco product; however, 47.3% of DA- and 41.5% of AP-containing samples exposed consumers to levels higher than the safety limits outlined by the National Institute for Occupational Safety (NIOSH) for occupational exposure. This exposure threshold outlined by NIOSH is not intended to suggest exposure at or below that limit should be considered sufficiently safe (Hubbs et al. 2015).

Aerosolized Adulterants

TSNAs, potent carcinogens identified in tobacco and tobacco smoke, include N-nitrosonornicotine (NNN), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), N-nitrosoanabasine (NAB), and N-nitrosoanatabine (NAT) (Hecht 1998, 1999; USDHHS 2010, 2014). NNN and NNK are classified by the International Agency for Research on Cancer (IARC) as Group 1 human carcinogens (IARC 2004). Their presence in e-liquids is mostly attributable to the processes used in extracting nicotine from tobacco leaves or the addition of tobacco flavorings (Kim and Shin 2013; Cheng 2014). These compounds are formed from their alkaloid precursors and from nitrite or nitrate, predominantly during tobacco curing, fermentation, and aging. NNN, NAB, and NAT are formed primarily from their corresponding secondary amines (nornicotine, anatabine, and anabasine) in the early stages of tobacco curing and processing, while the majority of NNK is formed from the tertiary amine nicotine at the later stages of tobacco curing and fermentation (Hecht 1998). Nitrosation reactions of corresponding amines can occur in e-liquids, especially during inadequate storage or manufacturing processes; inadequate storage is believed to increase the levels of NNN as a consequence of the nitrosation of nornicotine converted from nicotine in liquids (Kim and Shin 2013).

Some studies have identified traces of TSNAs in e-liquids, but at levels far below those seen in combustible tobacco (Trehy et al. 2011; Farsalinos et al. 2015a). Further, Goniewicz and colleagues (2014b) found that the aerosol of some e-cigarettes contains traces of the carcinogenic nitrosamines NNN and NNK, but neither was detected in aerosol from the Nicorette inhalator (an NRT product).

Several studies have reported the presence of other hazardous compounds in e-liquids or in the aerosol produced by e-cigarettes (Exponent Inc. 2009; Hadwiger et al. 2010; Lim and Shin 2013; Uchiyama et al. 2013; Williams et al. 2013; Bekki et al. 2014; Goniewicz et al. 2014a,b; Kosmider et al. 2014; Jensen et al. 2015; Kavvalakis et al. 2015; Laugesen 2015; Oh and Shin 2015; Varlet et al. 2015; Khlystov and Samburova 2016). For example, an FDA study detected the presence of amino-tadalafil and rimonabant in e-liquids (Hadwiger et al. 2010); amino-tadalafil is a structural analogue of tadalafil, the active pharmaceutical ingredient in Cialis, a prescription drug approved in the United States for treatment of erectile dysfunction. Rimonabant (trade name Zimulti) was approved in Europe for the treatment of obesity, but its marketing authorization was withdrawn by the European Medicines Agency in 2009. FDA approval of this drug has been withheld because of unresolved issues involving rimonabant therapy and increased frequencies of psychiatric adverse events, including suicide and an ill-defined constellation of neurologic symptoms and seizures (FDA 2007). The presence of unapproved active pharmaceutical ingredients suggests that some e-cigarettes may expose users to pharmacologically active substances with undocumented and unknown effects.

Oh and Shin (2015) conducted a study to identify and quantify the presence of diethyl phthalate (DEP) and diethylhexyl phthalate (DEHP) in e-liquids. DEP is used as a solvent to bind cosmetics and fragrances and in various industrial applications, including plasticizers, detergent bases, and aerosol sprays. DEHP is used widely as a plasticizer in the manufacture of articles made of polyvinylchloride. DEP and DEHP were detected in 47.6% and 79.1% of e-liquids, respectively, with concentration ranges of 0.01–1745.20 mg/L and 0.06–81.89 mg/L (Oh and Shin 2015). Both DEP and DEHP have estrogenic and antiandrogenic activity that cause premature breast development in girls. DEHP is classified by IARC as a possible carcinogen in humans (IARC 2000). Although the amounts of the two phthalates detected in this study were lower than the safety levels, the source of these toxicants is unknown, perhaps coming from packaging materials and the production procedure.

Carbonyls are present in e-cigarettes, and levels increase with device voltage (Kosmider et al. 2014; Jensen et al. 2015). Long-term exposure to carbonyl compounds, such as formaldehyde, acetaldehyde, and acrolein, increases the risk of cancer. IARC and the U.S. Environmental Protection Agency (EPA) have classified formaldehyde as "carcinogenic to humans" (USDHHS 1999; IARC 2009). EPA has set the acceptable daily intake (ADI) of formaldehyde as 0.2 mg/kg (kilograms) body weight and has warned of the potential adverse health effects of exceeding ADI. Acetaldehyde is also toxic, an irritant, and a probable carcinogen (USDHHS 1999). Acrolein is toxic through all routes of administration and may cause respiratory and ocular irritation (Faroon et al. 2008; Bein and Leikauf 2011). Acrolein in cigarette smoke has been linked to several pulmonary diseases, including increased risk of lung cancer (Feng et al. 2006), as well as asthma and chronic obstructive pulmonary disease (Bein and Leikauf 2011). One study found an association between acrolein exposure and risk of cardiovascular disease (DeJarnett et al. 2014).

Lim and Shin (2013) detected formaldehyde and acetaldehyde in 225 replacement liquids for e-cigarettes purchased in Korea, with ranges of 0.02–10.09 mg/L (mean 2.16 mg/L) and 0.10–15.63 mg/L (mean = 4.98 mg/L). Although the amounts of formaldehyde and acetaldehyde detected in replacement liquids for e-cigarettes are relatively low compared to conventional cigarettes, they should be controlled to the lowest possible concentrations in raw materials, as they may be formed when e-liquids are heated. Furthermore, as larger capacity batteries and heating mechanisms are developed (Farsalinos et al. 2014b; Sleiman et al. 2016), users will be exposed to higher concentrations of formaldehyde, acetaldehyde, acrolein, and other carbonyls (Kosmider et al. 2014). Jensen and colleagues (2015) reported formaldehyde concentrations higher than conventional cigarettes in high-voltage e-cigarettes. Havel and colleagues (2016) reported acetaldehyde, acrolein, and formaldehyde generation increased markedly at voltages at or above 5 volts. Geiss and colleagues (2016) reported that formaldehyde exceeded safety levels at the lowest wattage (5 watts), which is the wattage applied in most second generation e-cigarettes.

Summary

Although some typical constituents of the e-cigarette aerosol have been identified, the potential short- and long-term health consequences of inhalation of the heated and aerosolized constituents of the e-liquids, including solvents, flavorants, and toxicants, still require further investigation to quantify health effects. Commercial and custom-mixed e-liquids are produced with undisclosed manufacturing procedures, packaging materials, and purity standards for their constituents, increasing the risks of potential health consequences. E-cigarettes are a source of extremely high doses of fine particles (e.g., aerosol) in the human respiratory system. Fine particles are emitted when the solvents PG and VG are aerosolized, and mild respiratory effects have been documented, but adequate assessments are lacking. An additional concern is the aerosolization and inhalation of flavor additives in e-liquids. While some of the chemicals used may be generally recognized as safe for use in foods, they have not been thoroughly tested for their potential

sensitizing, toxic, or irritating characteristics when inhaled. Further, given the extent of possible variations in the ratio of flavor additives, with up to 7,700 unique e-liquid varieties available (Zhu et al. 2014b), these chemicals may be toxic in the concentrations present in manufactured or do-it-yourself e-liquids. Finally, other hazardous compounds and carcinogens have been detected in e-liquids, or in the heated aerosol produced by e-cigarettes, including formaldehyde, acetaldehyde, and acrolein.

Effects of Toxicants Produced During Aerosolization

A primary reason for investigating the health effects of heated and aerosolized e-liquids is that, under such conditions, chemical reactions may result in the formation of new compounds (Sleiman et al. 2016). In some devices, the temperature in the center of a heating coil can exceed 350°C, causing changes in the chemical components of the e-liquid. When carbonyl compounds are present in the refill liquids, heating can enhance their concentrations in the aerosol (Talih et al. 2015). Carbonyl compounds result from dehydration and fragmentation of VG and PG, which can be oxidized to formaldehyde and acetaldehyde during heating. Hutzler and colleagues (2014) applied headspace gas chromatography-mass spectrometry to enable incubation of liquids at various temperatures. At 150°C, the levels of acetaldehyde and formaldehyde were found to be up to 10-fold higher than they were at ambient temperatures for samples in which PG was a main component. The generation of carbonyl compounds seems to increase when liquids touch the heating element inside an e-cigarette, which is indicated by a color change around the wire, as has been reported in some devices (Uchiyama et al. 2013). Evidence suggests when e-liquid touches the heating element (heated nichrome wire), it is oxidized to formaldehyde, acetaldehyde, acrolein, glyoxal, and methylglyoxal in the presence of oxygen (Bekki et al. 2014; Goniewicz et al. 2014b; Kosmider et al. 2014).

Several studies have reported that short-chain aldehydes, such as formaldehyde, acetaldehyde, or acrolein, are produced during heating. Uchiyama and colleagues (2013) measured carbonyl compounds in e-cigarette aerosols generated according to the Canadian "intense regimen" (55mL puff volume, 2-second puff duration, 30 seconds between puffs, and a total of 10 puffs). Thirteen brands of e-cigarettes were assessed, and investigators detected several carbonyl compounds, such as formaldehyde, acetaldehyde, acetone, acrolein, propanol, crotonaldehyde, and butanol. They also detected two other harmful carbonyl compounds that had not been detected in the mainstream smoke from conventional cigarettes: glyoxal and methylglyoxal. Jensen and colleagues (2015) observed that formaldehyde-containing hemiacetals can be formed during the aerosolization process. These molecules are known to release formaldehyde and are used as industrial biocides, but it is not currently known how formaldehyde-releasing agents affect the respiratory tract.

The amount of carbonyl compounds in e-cigarette aerosols varies substantially, not only among different brands but also among different samples of the same products (Ohta et al. 2011; Bekki et al. 2014; Kosmider et al. 2014; Jensen et al. 2015), from 100-fold less than tobacco to nearly equivalent values. Notably, the amount of voltage the battery puts out affects the concentration of the carbonyl compounds in the emission. Some e-cigarettes allow users to increase aerosol production and nicotine delivery by raising the battery's output voltage. In addition, some users elect to directly drip e-liquid onto an exposed heater coil, reportedly for greater aerosol production and "throat hit." Talih and colleagues (2015) showed that use of such direct-drip atomizers may involve greater exposure to toxic carbonyls, including formaldehyde, because of the potentially higher temperatures reached by the coil. The adverse effects of acrolein (2-propenal), an unsaturated aldehyde, depend on dose and cell type and are influenced by experimental conditions (Bein and Leikauf 2011). In vitro studies found that acrolein inhibits DNA repair and forms acrolein-deoxyguanosine DNA adducts that are mutagenic (Wang et al. 2009, 2012; Tang et al. 2011). Despite the known DNA-damaging effects of acrolein, its mutagenicity in mammalian cells remains uncertain, and according to an evaluation by the IARC, there is inadequate evidence for carcinogenicity in humans or animals (IARC 1995). Because of its extreme toxicity, acrolein has been difficult to characterize in standard animal carcinogenicity tests. Animal experiments showed that acrolein can have a range of adverse effects, including a role in carcinogenesis (Cohen et al. 1992); excessive mucus production and macrophage and neutrophil accumulation with consequent production of proinflammatory cytokines and proteases (Moretto et al. 2012); damage to neurons and myelin disruption (Shi et al. 2011); and it may play a role in the progression of atherosclerosis and cardiovascular disease (Park and Taniguchi 2008; DeJarnett et al. 2014).

Other volatile organic compounds (VOCs) found in e-cigarette aerosol include a variety of chemicals (e.g., aliphatic and aromatic hydrocarbons), some of which may have short- or long-term adverse health effects. Benzene (classified as group 1 by IARC) and other solvents (toluene, xylenes, and styrene) could be present in e-cigarettes because of their use in the extraction of nicotine from tobacco leaves. Goniewicz and colleagues (2014b) detected both toluene and m- and p-xylene in

e-cigarette aerosols. A wide variety of other VOCs in e-cigarette liquids produce aromas and flavor through heating (Tierney et al. 2016).

Heavy metals such as tin, lead, and nickel were discovered by Williams and colleagues (2013) in a brand of e-liquids and the resulting aerosols. Those researchers analyzed the contents of e-cigarette cartomizers (a polyfill wrapped heating coil capable of longer puff durations than an atomizer) and the aerosols by using light and electron microscopy, x-ray microanalysis, particle counting, and inductively coupled plasma optical emission spectrometry. The aerosol contained particles >1 μm that were composed of tin, silver, iron, nickel, aluminum, and silicate, and nanoparticles (<100 nm) of tin, chromium, and nickel. Small particles composed of various elements (tin, other metals, semimetals, and silicates) passed through the cartomizer fibers and were present in aerosols. These particles likely originated from parts of the device (i.e., atomizer/cartomizer) (Williams et al. 2013).

Concentrations of 9 of the 11 elements in e-cigarette aerosol identified by Williams and colleagues (2013) were higher than or equal to concentrations in conventional cigarette smoke. Many of the metals identified in e-cigarette aerosol, such as lead and cadmium (Farsalinos et al. 2015b), are known to cause respiratory distress and disease (Zalups and Ahmad 2003). These metals are produced by the aerosolization of e-liquids (Farsalinos et al. 2015b) and by flaws in e-cigarette heating mechanisms and poor quality control (Williams et al. 2013; Farsalinos et al. 2015b; Mikheev et al. 2016). While these initial analyses indicate potential exposures, additional measures are needed because of challenges in measuring trace levels of metals.

Summary

E-liquids produce chemical reactions that may result in the formation of new, harmful compounds. Carcinogens (e.g., formaldehyde, acetaldehyde, and acrolein) and toxic heavy metals (e.g., lead and cadmium) have been found in e-cigarette aerosols in laboratory tests conducted at temperatures within the range of most e-cigarette products. These chemicals and metals have been detected in e-liquids and e-cigarette aerosols, signifying the need for further study on the potential short- and long-term health ramifications.

A limitation to understanding the health impact of chemical reactions is the heterogeneity of e-cigarette devices (e.g., voltage), e-liquids (e.g., quality, content), and use behaviors (e.g., puff duration), as emissions may be altered by any combination of these mechanical and behavioral differences. Further, it is difficult to fully contextualize the carcinogenic emissions of e-cigarette aerosol given the diversity of products currently available, as well as those that may become available as the devices continue to evolve (Farsalinos et al. 2014b).

Effects Not Involving Inhalation of Aerosol by the E-Cigarette User

Health effects not attributable to direct inhalation of e-cigarette aerosol include explosion or fire associated with malfunctioned devices, poisoning through contact exposure or intentional or unintentional ingestion of e-liquid, and exposure to secondhand aerosol or its condensate.

Health Effects Attributable to Explosions and Fires Caused by E-Cigarettes

Most reports of explosions and fires caused by e-cigarettes have appeared in print and online media and on televised programs. From August 2009 to March 2014, a search of U.S. media by the U.S. Fire Administration (2014) found 25 reports of e-cigarette explosions or fires. These data suggest that the number of such events is small when compared with the number of e-cigarette users. Of the 25 incidents found in the search, 2 caused serious harm, and there were no deaths attributable to explosions. In most cases, the resulting fires did not spread far from the site of the explosion. However, in one case an entire bedroom was lost to fire (U.S. Fire Administration 2014). As for explosions, several have occurred during an e-cigarette's use, causing severe facial damage or injuries to bodies and hands (Brennan 2015; Corona and Marcus 2015; Duranty 2015; Fox 5 Digital Team 2015; Goff and Schwartz 2015; Jablow and Sexton 2015; Shastry and Langdorf 2016), but most occurred while the device's batteries were being charged. Overcharging lithium batteries can lead to thermal runaway, causing the e-cigarette battery or container to be propelled, often with portions catching fire (U.S. Fire Administration 2014; Bohr et al. in press).

Health Effects Caused by Ingestion of E-Cigarette Liquids

The liquids in both e-cigarettes and the containers used to refill them can cause nicotine poisoning. Consequences of nicotine intoxication in the e-liquid include nausea, vomiting, headaches, dizziness, and diarrhea at low doses; seizures; tachycardia; abdominal pain; confusion; and even death (Cervellin et al. 2013). The amount of nicotine needed to cause death in humans is uncertain and, according to a reevaluation, may be higher than previously thought (Mayer 2014). The total amount

of nicotine in refill liquids varies and can be as high as 1,000 mg/10 mL in do-it-yourself bottles (Davis et al. 2015), which could be lethal if consumed (Mayer 2014).

The increase in poisonings prompted enactment of the *Child Nicotine Poisoning Prevention Act of 2015* (2016) in January 2016. This law requires any container of liquid nicotine sold, manufactured, distributed, or imported into the United States be placed in special packaging that is difficult to open by children under 5 years of age. Although labels may indicate the concentrations of nicotine, such labels can be incomplete, confusing, or inaccurate (Trtchounian and Talbot 2011; Cameron et al. 2014), and some bottles have not been labeled at all (Davis et al. 2015). Of most concern, some bottles of e-cigarette refill liquids labeled "no nicotine" have been found to contain significant amounts of that substance (e.g., 25.6 mg/mL; Trehy et al. 2011). Regardless, many e-cigarette users may not be aware of the toxic effects of nicotine and may not know that refill liquids should be kept away from toddlers and children. These liquids are often sold in colorful bottles with flavors that are attractive to children (Bahl et al. 2012). The liquids usually come in small dropper bottles that can be mistaken for bottles containing food dye or eye drops. Finally, many refill liquids are made in local "vape shops," which have only recently come under FDA regulation (*Federal Register* 2016), with no uniform training process for mixers, a lack of standards and protections, and unknown concentrations of nicotine.

The rapid growth in popularity of e-cigarettes and the ease with which refill liquids can be purchased have made e-cigarettes an increasingly common item in many households, thereby elevating the possibility of accidental nicotine poisoning. Instances of related case reports, often involving children or infants, are increasing. For example, an 18-month-old girl was treated at an emergency room for hypertension and tachycardia after drinking about 2 mL of refill liquid from a bottle on a nightstand (Shawn and Nelson 2013). Unintentional exposure to nicotine can occur through ingestion, absorption through the skin, inhalation, or dropping refill liquids into one's eyes (Cantrell 2014).

Figure 3.2 shows data from 2011 to 2016 on exposures to e-cigarettes or liquid nicotine (i.e., any contact with e-cigarettes or liquid nicotine, not necessarily resulting in any health effects) (American Association of Poison Control Centers 2016). These data show a dramatic increase in exposures through 2014 with a slight reduction of exposures in 2015. Fifty-one percent of the calls to poison control centers regarding exposures to e-cigarettes involved children 5 years of age or younger (CDC 2014). Increased e-cigarette exposures have also been reported by state and local poison centers (Banerji et al. 2014; Cantrell 2014; Guttenburg et al. 2014; Lee et al. 2014; California Department of Public Health 2015).

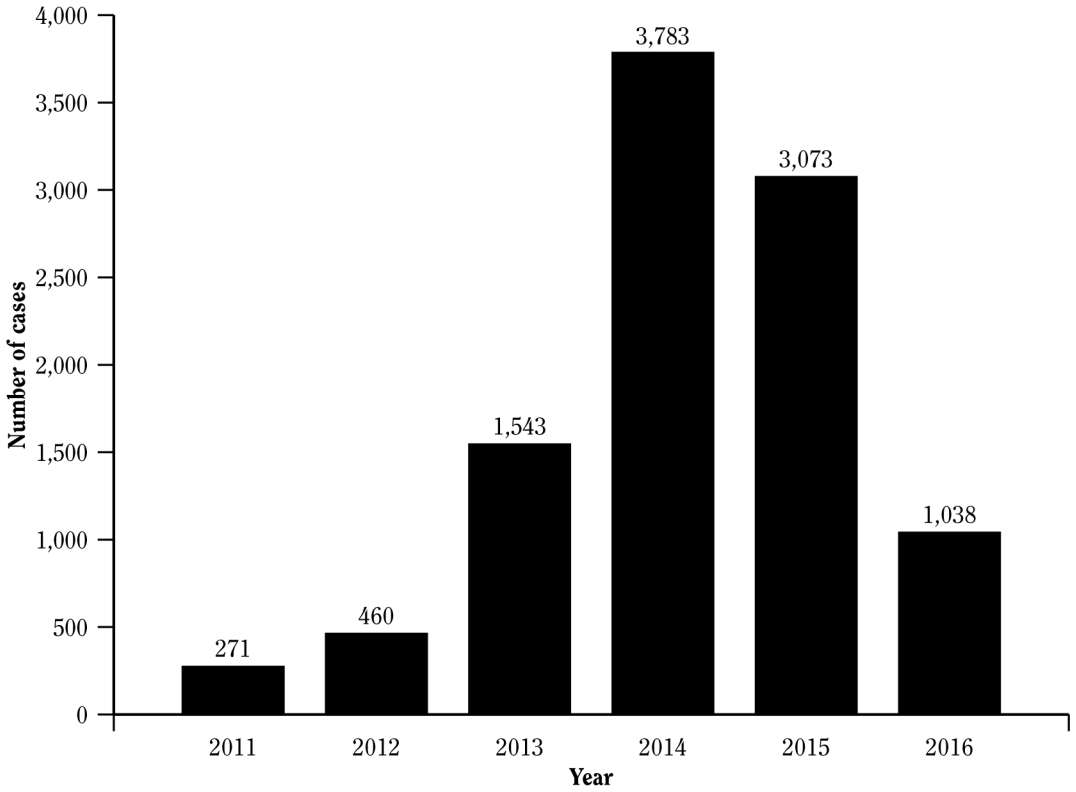
Secondhand Exposure to the Constituents of E-Cigarette Aerosol

Exposure to secondhand smoke from combustible tobacco products is a known cause of morbidity and mortality (USDHHS 2006). Secondhand smoke, a mixture of the sidestream smoke from a smoldering cigarette and the mainstream smoke exhaled by a smoker, is known to contaminate both indoor and outdoor environments. In addition, when the constituents of smoke deposit on surfaces, nonsmokers can be exposed to them via touch, ingestion, or inhalation. These deposited constituents of combustible smoke are known as "thirdhand smoke" (Matt et al. 2011; Protano and Vitali 2011). E-cigarettes represent another potential source of exposure to toxicants for nonusers, via secondhand or thirdhand exposure to aerosol.

Exposure to Nonusers

In contrast to combustible tobacco products, e-cigarettes do not produce sidestream emissions; aerosol is produced during activation of the device. Some of this aerosol is subsequently exhaled into the environment where nonusers may be exposed through inhalation, ingestion, or dermal contact. As previously described in this chapter, constituents of the emissions may include nicotine, carbonyl compounds, VOCs, polyaromatic hydrocarbons, TSNAs, heavy metals, and glycols. It is not clear how much of inhaled e-cigarette aerosol is exhaled into the environment where nonusers can be exposed. Some studies have used machines to produce e-cigarette aerosols and measured the pollutants emitted (McAuley et al. 2012; Czogala et al. 2014; Geiss et al. 2015); others have involved the use by one or more persons of an e-cigarette and measured the change in pollutants in either a room or a test chamber after use (Schripp et al. 2013; Schober et al. 2014). One study measured airborne nicotine in the homes of e-cigarette users (Ballbe et al. 2014). The concentration of e-cigarette aerosol in a given microenvironment depends primarily on the strength of the source or the number of e-cigarettes used and the emission rate of the aerosol for that device. E-cigarettes, however, are heterogeneous in their design and in the liquids used, and the specific product combination significantly affects the secondhand emissions (Kosmider et al. 2014; Geiss et al. 2015). The number of puffs and depth of inhalation may be particularly relevant to the amount exhaled by the user and may also affect e-cigarette emissions (Talih et al. 2016).

Figure 3.2 Data showing exponential increase in the number of cases of human exposure to e-cigarette products and liquid nicotine between 2011 and 2016



Source: American Association of Poison Control Centers (2016).
Note: These numbers reflect the closed human exposures to e-cigarettes and liquid nicotine reported to poison centers as of July 31, 2016. The numbers may change as cases are closed and additional information is received.

Movement of E-Cigarette Aerosol

Similar to the case with secondhand tobacco smoke, e-cigarette aerosol is an inherently dynamic mixture that changes over time in terms of constituents and concentrations. Czogala and colleagues (2014) demonstrated a significant signal from a laser photometer indicating the presence of ambient aerosol in a room after e-cigarette use. However, this aerosol disappeared in just seconds to a few minutes as it either evaporated to the gas phase or deposited on surfaces in the room. In contrast, in the same study, secondhand cigarette smoke exhibited a particulate phase that stayed suspended in the room at high concentrations for more than 30 minutes. For the VOCs in e-cigarette aerosol, such as formaldehyde, acrolein, and acetaldehyde, the source strength and ventilation rate will largely determine their concentration in indoor air. Semi-VOCs, such as nicotine and TSNAs, are also largely affected by sorption on and subsequent desorption from surfaces and dust in a room (Singer et al. 2002, 2003; Goniewicz and Lee 2015). The extent of this type of thirdhand contamination from e-cigarettes in real-world settings has not been established but would be of particular concern for children living in homes of e-cigarette users, as they spend more time indoors, are in proximity to and engage in greater activity in areas where dust collects and may be resuspended (e.g., carpets on the floor), and insert non-food items in their mouths more frequently (EPA 2008; Matt et al. 2011).

Exposure to E-Cigarette Aerosol and Considerations of Dose

A large body of studies has measured exposure to secondhand and thirdhand smoke from conventional cigarettes using personal or area air monitoring, surface testing, and dust testing. Studies of the exposure of e-cigarette aerosol to nonusers, however, are limited. Schripp and colleagues (2013) observed small increases of fine and ultrafine particles and some VOCs, including PG,

flavoring substances, and nicotine, indicating passive inhalation of e-cigarette aerosols by nonusers in the presence of e-cigarette users. Those authors demonstrated that the distribution in the sizes of the aerosol's component particles changes in the lungs and results in the exhalation of smaller particles, likely caused by the evaporation of the liquid particles in the lungs and in the environment after exhalation. Schober and colleagues (2014) found substantially higher amounts of PG, VG, particulate matter (PM), and nicotine in a 45-m^3 chamber during e-cigarette use sessions with volunteers compared to controlled sessions. They also found a 20% increase in the level of polycyclic aromatic hydrocarbons (PAHs) and a 2.4-fold increase in aluminum concentrations.

Williams and colleagues (2013) demonstrated contamination by metal and silicate particles in e-liquid and its aerosol using scanning electron microscopy. In a different study measuring machine-generated secondhand e-cigarette aerosol in an emission chamber, Geiss and colleagues (2015) found significant levels of PG, VG, and nicotine in the chamber's air. Carbonyl compounds of concern (e.g., formaldehyde, acetaldehyde, acrolein, and acetone) were below the limits of detection in this study. O'Connell and colleagues (2015), who assessed secondhand e-cigarette emissions in a small meeting room (12.8 m^2) with three e-cigarette users during a 165-minute session, found a significant increase in PG but did not see the expected increase in VG or nicotine. This study reported no increase in PAHs, trace metals, TSNAs, or acrolein, but did find an increase in total VOCs, formaldehyde, and acetaldehyde. However, the compounds were found at levels below guidelines for the quality of indoor air from the World Health Organization or European Union. Ruprecht and colleagues (2014) found significantly lower concentrations and counts for particles from an e-cigarette used in a 50-m^3 room compared with conventional cigarettes. Interestingly, they also found that nicotine-free e-cigarettes produced higher particle levels than e-cigarettes containing nicotine. Saffari and colleagues (2014) found that total particulate exposure was 10-fold lower in e-cigarettes than it was in conventional cigarettes. Emissions of heavy metals from e-cigarettes were also dramatically less, with the exception of nickel, zinc sulfide, and silver, which showed higher emission rates from e-cigarettes. PAH levels were not elevated by e-cigarette use in this study.

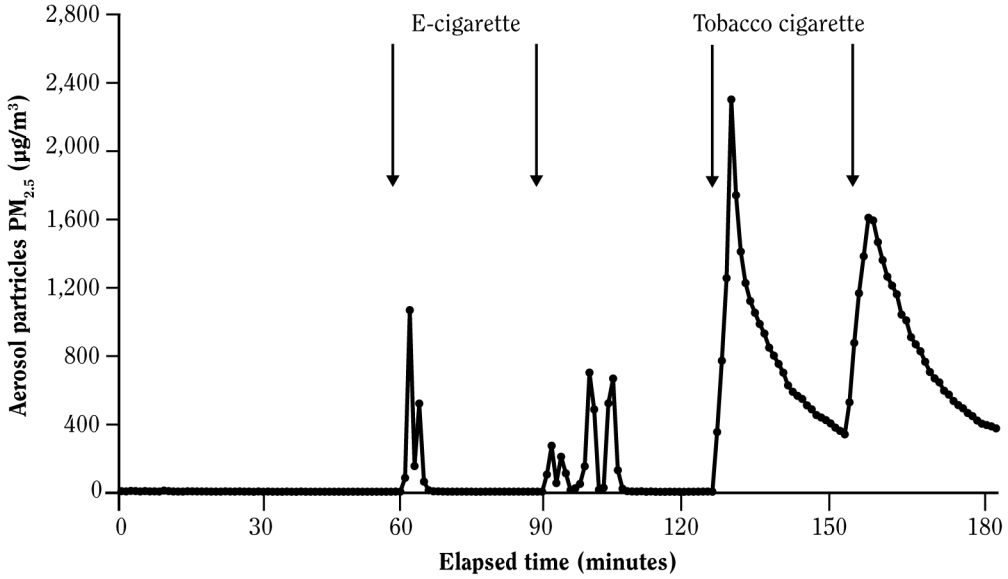
Concentrations of PM, especially $PM_{2.5}$, which is fine PM, and nicotine are the two most common markers used to measure exposure to secondhand smoke (Avila-Tang et al. 2010; Apelberg et al. 2013). Indirect measures of the mass concentration of PM from secondhand smoke using real-time particle monitors are well validated in terms of the accuracy of these measurements in relation to other constituents of secondhand smoke and to health effects (Hyland et al. 2008; Apelberg et al. 2013). These same types of particle monitors are often used in studies of e-cigarette aerosol to compare PM levels from conventional cigarettes with those from e-cigarettes, though PM findings may not directly relate to the short- and long-term health effects of each product (Czogala et al. 2014; Schober et al. 2014).

Caution is warranted when interpreting the results of PM measurements comparing e-cigarettes with conventional cigarettes. The aerosols produced are fundamentally different, with the former resulting from aerosolization of liquid and the latter resulting from combustion of organic matter. The true $PM_{2.5}$ mass concentration of e-cigarette aerosol from commonly used light-scattering instruments (Czogala et al. 2014) cannot be determined without calibrating the device to a reference standard for the aerosol in question. Even this calibration would be questionable given the highly volatile nature of e-cigarette aerosol, making it difficult to capture and accurately determine the mass. Real-time $PM_{2.5}$ measurements such as this are useful, however, to determine the presence of an aerosol and to see the *relative* changes in this aerosol over time and under various conditions, such as changing source strength. Figure 3.3 shows the significant increase in aerosol concentration from e-cigarettes after about 1 hour and the subsequent rapid decline, presumably from initial aerosolization and deposition of this aerosol. There may still be significant amounts of this e-cigarette aerosol in the environment, but the particle monitor can no longer measure it, as it is either in the aerosol phase or deposited on surfaces. For these reasons, it is important not to rely solely on PM mass concentrations for determining exposure to e-cigarette aerosol and for making comparisons with conventional cigarettes. Measurement of the individual toxicants of concern in the aerosol phase and on surfaces is warranted.

Health Effects of Secondhand Exposure to E-Cigarette Aerosols

Flouris and colleagues (2012, 2013) conducted two clinical studies of the health effects of secondhand exposure to e-cigarette aerosol. The researchers found no short-term change in markers of complete blood count after 1 hour of exposure to e-cigarette aerosol in a group of 15 nonsmokers (Flouris et al. 2012). Similarly, the same exposure caused no significant change in short-term lung function, although the results were of borderline statistical significance (Flouris et al. 2013). However, these studies demonstrated that passive exposure to e-cigarettes causes an increase in serum cotinine that is similar to that from passive exposure to cigarette smoke, suggesting the need to

Figure 3.3 Changes in aerosol particle $PM_{2.5}$ concentrations during experiment of e-cigarette use and tobacco cigarette smoking in an exposure chamber



Source: Czogala et al. (2014).
Note: **PM** = particulate matter.

examine the impact of passive aerosolized nicotine inhalation on long-term lung function. Furthermore, limited effects would likely occur in the short exposure observed through the methodologies used by Flouris and colleagues (2012, 2013), as these studies did not account for prolonged and persistent passive exposure to e-cigarette aerosols.

Several researchers have modeled the health risks of passive exposure to e-cigarettes (Colard et al. 2015) on the basis of the limited exposure data available and have come to various conclusions. Offermann (2015) concluded that, for indirect exposure, two chemicals—nicotine and PG—exceeded California EPA exposure level standards for noncarcinogenic health effects. Burstyn (2014), who compared e-cigarette aerosol exposure to workplace exposure standards, concluded that only PG and VG warrant attention in e-cigarette users while, for bystanders, none of the constituents of e-cigarette aerosol pose apparent concern. It is important to note that standards for workplace exposure are typically not appropriate to apply to the population as a whole, as they are intended for a healthy working population during a typical work day, not accounting for the risks to children, pregnant women, or those with preexisting health conditions. Further, standards for workplace exposure are very different in concentration and duration than what is to be expected from e-cigarette use.

An additional consideration for regulating e-cigarettes in indoor environments is the potential for allergic reactions in nonusers. Dermal and oral PG exposures are known causes of dermatitis and allergic sensitization (Warshaw et al. 2009; Al Jasser et al. 2011). Several e-liquids contain flavorants derived from nuts and in fact have labels cautioning persons who have nut allergies not to use these products. Research has not evaluated whether nonusers can have allergic reactions from these potential allergens in e-cigarette aerosol, but this is a risk that should be explored as 8% of U.S. children have food allergies (Gupta et al. 2011).

Evidence Summary

E-cigarette use among youth and young adults in the United States has increased considerably in recent years (see Chapter 2). There is little doubt that the use of e-cigarettes by youth and young adults represents self-administration of the drug nicotine, and this self-administration of nicotine puts youth at risk for addiction and many related harmful consequences. Animal research indicates adolescent brains are particularly sensitive to nicotine's effects, such that subsequent self-administration is more likely, and that same literature indicates that this age group is at risk for a constellation of nicotine-induced neural and behavioral alterations. Studies of the effects of maternal smoking of conventional cigarettes during pregnancy, coupled with preclinical literature examining the effects of maternal self-administration of nicotine during pregnancy, suggest that e-cigarette use by mothers during pregnancy presents a wide variety of risks to fetal, infant, and child brain development.

Users of e-cigarettes risk respiratory exposure to a variety of aerosolized chemicals, including solvents and flavorants added intentionally to e-liquids, adulterants added unintentionally, and other toxicants produced during the heating/aerosolization process. The health impacts of frequent exposure to the toxicants in e-cigarette aerosol are not well understood, though several are known carcinogens. As highlighted previously in this chapter, the detection and level of these carcinogens depend on several factors, including the concentration of the e-liquid and the strength of the heating device. Although e-cigarettes have been used as a cessation device, the evidence supporting the effectiveness of e-cigarettes as an aid for quitting conventional cigarettes remains extremely weak for adults (Bullen et al. 2013; Caponnetto et al. 2013; Grana et al. 2014; Kalkhoran and Glantz 2016) and untested and nonexistent among youth.

Further research is warranted to focus on the characteristics of e-cigarette devices, the constituents of e-liquids, and the user behaviors that can influence the yield of nicotine and other toxicants (Shihadeh and Eissenberg 2015). This close focus includes providing details of devices (e.g., voltage of the power supply, heating element resistance) and components of e-liquids (e.g., propylene glycol, vegetable glycerin, other additives), and measuring user puff topography. Standardization of procedures for producing and delivering the aerosol is likely a necessary component of at least some in vivo and in vitro work. Preclinical work examining the effects of e-cigarette aerosols is a clear research need and, again, the standardization of procedures for production and delivery of the aerosol is necessary. To enhance relevance, the parameters of aerosol production should span the range of those seen with humans (Shihadeh and Eissenberg 2011).

The huge variety of products of different origin and design, the rapid emergence of new products, and the varied ways in which consumers use these products make the development of standard measurement conditions challenging (Famele et al. 2015). Accordingly, research is needed to understand how different design features relate to potential toxicity—for example, if the compounds in e-cigarettes are affected by heating, changes in chemical composition, or pH; if these compounds are absorbed into the bloodstream; and how additives to the e-liquid affect the bioavailability of these compounds, among other considerations. Research is also needed to understand whether potential health risks may be ameliorated by changes in product engineering.

Conclusions

1. Nicotine exposure during adolescence can cause addiction and can harm the developing adolescent brain.

2. Nicotine can cross the placenta and has known effects on fetal and postnatal development. Therefore, nicotine delivered by e-cigarettes during pregnancy can result in multiple adverse consequences, including sudden infant death syndrome, and could result in altered corpus callosum, deficits in auditory processing, and obesity.

3. E-cigarettes can expose users to several chemicals, including nicotine, carbonyl compounds, and volatile organic compounds, known to have adverse health effects. The health effects and potentially harmful doses of heated and aerosolized constituents of e-cigarette liquids, including solvents, flavorants, and toxicants, are not completely understood.

4. E-cigarette aerosol is not harmless "water vapor," although it generally contains fewer toxicants than combustible tobacco products.

5. Ingestion of e-cigarette liquids containing nicotine can cause acute toxicity and possibly death if the contents of refill cartridges or bottles containing nicotine are consumed.

References

Adriani W, Macri S, Pacifici R, Laviola G. Peculiar vulnerability to nicotine oral self-administration in mice during early adolescence. *Neuropsychopharmacology* 2002;27(2):212–24.

Agrawal A, Scherrer JF, Grant JD, Sartor CE, Pergadia ML, Duncan AE, Madden PA, Haber JR, Jacob T, Bucholz KK, et al. The effects of maternal smoking during pregnancy on offspring outcomes. *Preventive Medicine* 2010;50(1–2):13–8.

Al Jasser M, Mebuke N, de Gannes GC. Propylene glycol: an often unrecognized cause of allergic contact dermatitis in patients using topical corticosteroids. *Skin Therapy Letter* 2011;16(5):5–7.

Al Mamun A, O'Callaghan FV, Alati R, O'Callaghan M, Najman JM, Williams GM, Bor W. Does maternal smoking during pregnancy predict the smoking patterns of young adult offspring? A birth cohort study. *Tobacco Control* 2006;15(6):452–7.

Allen JG, Flanigan SS, LeBlanc M, Vallarino J, MacNaughton P, Stewart JH, Christiani DC. Flavoring chemicals in e-cigarettes: diacetyl, 2, 3-pentanedione, and acetoin in a sample of 51 products, including fruit-, candy-, and cocktail-flavored e-cigarettes. *Environmental Health Perspectives* 2016;124(6):733–9.

American Association of Poison Control Centers. *Electronic Cigarettes and Liquid Nicotine Data,* 2016; <https://aapcc.s3.amazonaws.com/files/library/E-cig__Nicotine_Web_Data_through_09.2016.pdf>; accessed: September 7, 2016.

American College of Obstetricians and Gynecologists. Committee opinion number 503: tobacco use and women's health. *Obstetrics and Gynecology* 2011;118(3):746–50.

American E-liquid Manufacturing Standards Association. *E-liquid Manufacturing Standards (Version 1.8)*, 2014; <http://www.aemsa.org/wp-content/uploads/2014/02/AEMSA-Standards_Version-1-8.pdf>; accessed: May 21, 2015.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington (VA): American Psychiatric Association, 2013.

Anderson RC, Harris PN, Chen KK. Toxicological studies on synthetic glycerin. *Journal of the American Pharmaceutical Association* 1950;39(10):583–5.

Aoyama Y, Toriumi K, Mouri A, Hattori T, Ueda E, Shimato A, Sakakibara N, Soh Y, Mamiya T, Nagai T, et al. Prenatal nicotine exposure impairs the proliferation of neuronal progenitors, leading to fewer glutamatergic neurons in the medial prefrontal cortex. *Neuropsychopharmacology* 2016;41(2):578–89.

Apelberg BJ, Hepp LM, Avila-Tang E, Gundel L, Hammond SK, Hovell MF, Hyland A, Klepeis NE, Madsen CC, Navas-Acien A, et al. Environmental monitoring of secondhand smoke exposure. *Tobacco Control* 2013;22(3):147–55.

Aramakis VB, Hsieh CY, Leslie FM, Metherate R. A critical period for nicotine-induced disruption of synaptic development in rat auditory cortex. *Journal of Neuroscience* 2000;20(16):6106–16.

Avila-Tang E, Travers MJ, Navas-Acien A. Promoting smoke-free environments in Latin America: a comparison of methods to assess secondhand smoke exposure. *Salud Publica de México* 2010;52(Suppl 2):S138–S148.

Azam L, Chen Y, Leslie FM. Developmental regulation of nicotinic acetylcholine receptors within midbrain dopamine neurons. *Neuroscience* 2007;144(4):1347–60.

Bahl V, Lin S, Xu N, Davis B, Wang YH, Talbot P. Comparison of electronic cigarette refill fluid cytotoxicity using embryonic and adult models. *Reproductive Toxicology* 2012;34(4):529–37.

Bailey CD, Tian MK, Kang L, O'Reilly R, Lambe EK. Chrna5 genotype determines the long-lasting effects of developmental in vivo nicotine exposure on prefrontal attention circuitry. *Neuropharmacology* 2014;77:145–55.

Ballbe M, Martinez-Sanchez JM, Sureda X, Fu M, Perez-Ortuno R, Pascual JA, Salto E, Fernandez E. Cigarettes vs. e-cigarettes: Passive exposure at home measured by means of airborne marker and biomarkers. *Environmental Research* 2014;135:76–80.

Banerji S, Bikkumalla S, Cozza A, Guttenberg A, Bronstein AC. Kids and vapor: a 4-year analysis of pediatric exposures to electronic cigarettes. *Clinical Toxicology* 2014;52:743–4.

Bao W, Michels KB, Tobias DK, Li S, Chavarro JE, Gaskins AJ, Vaag AA, Hu FB, Zhang C. Parental smoking during pregnancy and the risk of gestational diabetes in the daughter. *International Journal of Epidemiology* 2016;45(1):160–9.

Barrington-Trimis JL, Samet JM, McConnell R. Flavorings in electronic cigarettes: an unrecognized respiratory health hazard? *JAMA: the Journal of the American Medical Association* 2014;312(23):2493–4.

Behar RZ, Davis B, Wang Y, Bahl V, Lin S, Talbot P. Identification of toxicants in cinnamon-flavored electronic cigarette refill fluids. *Toxicology in Vitro* 2014;28(2):198–208.

Behl M, Rao D, Aagaard K, Davidson TL, Levin ED, Slotkin TA, Srinivasan S, Wallinga D, White MF, Walker VR, et al. Evaluation of the association between maternal smoking, childhood obesity, and metabolic disorders: a national toxicology program workshop review. *Environmental Health Perspectives* 2013;121(2):170–80.

Bein K, Leikauf GD. Acrolein—a pulmonary hazard. *Molecular Nutrition & Food Research* 2011;55(9):1342–60.

Bekki K, Uchiyama S, Ohta K, Inaba Y, Nakagome H, Kunugita N. Carbonyl compounds generated from electronic cigarettes. *International Journal of Environmental Research and Public Health* 2014;11(11):11192–200.

Belluzzi JD, Lee AG, Oliff HS, Leslie FM. Age-dependent effects of nicotine on locomotor activity and conditioned place preference in rats. *Psychopharmacology* 2004;174(3):389–95.

Bennett DS, Mohamed FB, Carmody DP, Bendersky M, Patel S, Khorrami M, Faro SH, Lewis M. Response inhibition among early adolescents prenatally exposed to tobacco: an fMRI study. *Neurotoxicology and Teratology* 2009;31(5):283–90.

Benowitz NL, Burbank AD. Cardiovascular toxicity of nicotine: Implications for electronic cigarette use. *Trends in Cardiovascular Medicine* 2016;26(6):515–23.

Bergstrom HC, McDonald CG, French HT, Smith RF. Continuous nicotine administration produces selective, age-dependent structural alteration of pyramidal neurons from prelimbic cortex. *Synapse* 2008;62(1):31–9.

Bernheim A, Halfon O, Boutrel B. Controversies about the enhanced vulnerability of the adolescent brain to develop addiction. *Frontiers in Pharmacology* 2013;4:118.

Bhatnagar A. E-cigarettes and cardiovascular disease risk; evaluation of evidence, policy implications, and recommendations. *Current Cardiovascular Risk Reports* 2016;10(7):24.

Biederman J, Monuteaux MC, Mick E, Wilens TE, Fontanella JA, Poetzl KM, Kirk T, Masse J, Faraone SV. Is cigarette smoking a gateway to alcohol and illicit drug use disorders? A study of youths with and without attention deficit hyperactivity disorder. *Biological Psychiatry* 2006;59(3):258–64.

Blank MD, Disharoon S, Eissenberg T. Comparison of methods for measurement of smoking behavior: mouthpiece-based computerized devices versus direct observation. *Nicotine & Tobacco Research* 2009;11(7):896–903.

Boden JM, Fergusson DM, Horwood LJ. Cigarette smoking and depression: tests of causal linkages using a longitudinal birth cohort. *British Journal of Psychiatry* 2010;196(6):440–6.

Bohr S, Almarzouqi F, Pallua N. Extensive burn injury caused by fundamental electronic cigarette design flaw. *Annals of Burns and Fire Disasters*, in press.

Bohrer J. Stealth vaping, 2015; <http://vapenewsmagazine.com/october-2014/stealth-vaping>; accessed: May 23, 2015.

Boutwell BB, Beaver KM. Maternal cigarette smoking during pregnancy and offspring externalizing behavioral problems: a propensity score matching analysis. *International Journal of Environmental Research and Public Health* 2010;7(1):146–63.

Brady S, Siegel G, Albers RW, Price D, editors. *Basic neurochemistry: principles of molecular, cellular and medical neurobiology*. Amsterdam: Elsevier, 2012.

Brennan C. Man sues e-cigarette store for $1 million after batteries explode in his cargo shorts and give him second degree burns on his crotch. *Daily Mail*, March 12, 2015; <http://www.dailymail.co.uk/news/article-2991815/Man-sues-e-cigarette-store-1million-batteries-explode-cargo-shorts-send-sparks-flying-crotch-kickball-game.html>; accessed: April 21, 2015.

Brielmaier JM, McDonald CG, Smith RF. Immediate and long-term behavioral effects of a single nicotine injection in adolescent and adult rats. *Neurotoxicology and Teratology* 2007;29(1):74–80.

Britton AF, Vann RE, Robinson SE. Perinatal nicotine exposure eliminates peak in nicotinic acetylcholine receptor response in adolescent rats. *Journal of Pharmacology and Experimental Therapeutics* 2007;320(2):871–6.

Bronisch T, Hofler M, Lieb R. Smoking predicts suicidality: findings from a prospective community study. *Journal of Affective Disorders* 2008;108(1–2):135–45.

Brook JS, Balka EB, Ning Y, Brook DW. Trajectories of cigarette smoking among African Americans and Puerto Ricans from adolescence to young adulthood: associations with dependence on alcohol and illegal drugs. *American Journal on Addictions* 2007;16(3):195–201.

Bruin JE, Gerstein HC, Holloway AC. Long-term consequences of fetal and neonatal nicotine exposure: a critical review. *Toxicological Sciences* 2010;116(2):364–74.

Buettner-Schmidt K, Miller DR, Balasubramanian N. Electronic cigarette refill liquids: child-resistant packaging, nicotine content, and sales to minors. *Journal of Pediatric Nursing* 2016;31(4):373–9.

Buka SL, Shenassa ED, Niaura R. Elevated risk of tobacco dependence among offspring of mothers who smoked during pregnancy: a 30-year prospective study. *American Journal of Psychiatry* 2003;160(11):1978–84.

Bullen C, Howe C, Laugesen M, McRobbie H, Parag V, Williman J, Walker N. Electronic cigarettes for

smoking cessation: a randomised controlled trial. *Lancet* 2013;382(9905):1629–37.

Bullen C, McRobbie H, Thornley S, Glover M, Lin R, Laugesen M. Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. *Tobacco Control* 2010;19(2):98–103.

Burstyn I. Peering through the mist: systematic review of what the chemistry of contaminants in electronic cigarettes tells us about health risks. *BMC Public Health* 2014;14:18.

California Department of Public Health. *State Health Officer's Report on E-cigarettes: A Community Health Threat*, 2015; <http://www.cdph.ca.gov/programs/tobacco/Documents/Media/State%20Health-e-cig%20report.pdf>; accessed: April 28, 2015.

Cameron JM, Howell DN, White JR, Andrenyak DM, Layton ME, Roll JM. Variable and potentially fatal amounts of nicotine in e-cigarette nicotine solutions. *Tobacco Control* 2014;23(1):77–8.

Cantrell FL. Adverse effects of e-cigarette exposures. *Journal of Community Health* 2014;39(3):614–6.

Cao J, Dwyer JB, Mangold JE, Wang J, Wei J, Leslie FM, Li MD. Modulation of cell adhesion systems by prenatal nicotine exposure in limbic brain regions of adolescent female rats. *International Journal of Neuropsychopharmacology* 2011;14(2):157–74.

Cao J, Wang J, Dwyer JB, Gautier NM, Wang S, Leslie FM, Li MD. Gestational nicotine exposure modifies myelin gene expression in the brains of adolescent rats with sex differences. *Translational Psychiatry* 2013;3:e247.

Caponnetto P, Campagna D, Cibella F, Morjaria JB, Caruso M, Russo C, Polosa R. EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. *PloS One* 2013;8(6):e66317.

Casey BJ, Tottenham N, Liston C, Durston S. Imaging the developing brain: what have we learned about cognitive development? *Trends in Cognitive Sciences* 2005;9(3):104–10.

Cavalca E, Kong G, Liss T, Reynolds EK, Schepis TS, Lejuez CW, Krishnan-Sarin S. A preliminary experimental investigation of peer influence on risk-taking among adolescent smokers and non-smokers. *Drug and Alcohol Dependence* 2013;129(1–2):163–6.

Centers for Disease Control and Prevention. Projected smoking-related deaths among youth—United States. *Morbidity and Mortality Weekly Report* 1996;45(44):971–4.

Centers for Disease Control and Prevention. Notes from the field: calls to poison centers for exposures to electronic cigarettes—United States, September 2010–February 2014. *Morbidity and Mortality Weekly Report* 2014;63(13):292–3.

Centers for Disease Control and Prevention. Tobacco use among middle and high school students—United States, 2011–2014. *Morbidity and Mortality Weekly Report* 2015;64(14):381–5.

Centers for Disease Control and Prevention. Tobacco use among middle and high school students—United States, 2011–2015. *Morbidity and Mortality Weekly Report* 2016;65(14):361–7.

Cervellin G, Luci M, Bellini C, Lippi G. Bad news about an old poison: a case of nicotine poisoning due to both ingestion and injection of the content of an electronic cigarette refill. *Emergency Care Journal* 2013;9(18):53–4.

Chaisson NF, Kreiss K, Hnizdo E, Hakobyan A, Enright PL. Evaluation of methods to determine excessive decline of forced expiratory volume in one second in workers exposed to diacetyl-containing flavorings. *Journal of Occupational and Environmental Medicine* 2010;52(11):1119–23.

Chang GQ, Karatayev O, Leibowitz SF. Prenatal exposure to nicotine stimulates neurogenesis of orexigenic peptide-expressing neurons in hypothalamus and amygdala. *Journal of Neuroscience* 2013;33(34):13600–11.

Chen H, Matta SG, Sharp BM. Acquisition of nicotine self-administration in adolescent rats given prolonged access to the drug. *Neuropsychopharmacology* 2007;32(3):700–9.

Chen WJ, Kelly RB. Effect of prenatal or perinatal nicotine exposure on neonatal thyroid status and offspring growth in rats. *Life Sciences* 2005;76(11):1249–58.

Cheng SS, Liu JY, Huang CG, Hsui YR, Chen WJ, Chang ST. Insecticidal activities of leaf essential oils from Cinnamomum osmophloeum against three mosquito species. *Bioresource Technology* 2009;100(1):457–64.

Cheng T. Chemical evaluation of electronic cigarettes. *Tobacco Control* 2014;23(Suppl 2):ii11–ii17.

Child Nicotine Poisoning Prevention Act of 2015, Public Law 114-116, (2016).

Chistyakov V, Patkina N, Tammimaki A, Talka R, Salminen O, Belozertseva I, Galankin T, Tuominen R, Zvartau E. Nicotine exposure throughout early development promotes nicotine self-administration in adolescent mice and induces long-lasting behavioural changes. *European Journal of Pharmacology* 2010;640(1–3):87–93.

Choi H, Schmidbauer N, Sundell J, Hasselgren M, Spengler J, Bornehag CG. Common household chemicals and the allergy risks in pre-school age children. *PloS One* 2010;5(10):e13423.

Clark S, Winter CK. Diacetyl in foods: a review of safety and sensory characteristics. *Comprehensive Reviews in Food Science and Food Safety* 2015;14(5):634–43.

Cobb CO, Hendricks PS, Eissenberg T. Electronic cigarettes and nicotine dependence: evolving products, evolving problems. *BMC Medicine* 2015;13:119.

Cocchiara J, Letizia CS, Lalko J, Lapczynski A, Api AM. Fragrance material review on cinnamaldehyde. *Food and Chemical Toxicology* 2005;43(6):867–923.

Cohen G, Roux JC, Grailhe R, Malcolm G, Changeux JP, Lagercrantz H. Perinatal exposure to nicotine causes deficits associated with a loss of nicotinic receptor function. *Proceedings of the National Academy of Sciences of the United States of America* 2005;102(10):3817–21.

Cohen SM, Garland EM, St John M, Okamura T, Smith RA. Acrolein initiates rat urinary bladder carcinogenesis. *Cancer Research* 1992;52(13):3577–81.

Colard S, O'Connell G, Verron T, Cahours X, Pritchard JD. Electronic cigarettes and indoor air quality: a simple approach to modeling potential bystander exposures to nicotine. *International Journal of Environmental Research and Public Health* 2015;12(1):282–99.

Colby SM, Tiffany ST, Shiffman S, Niaura RS. Are adolescent smokers dependent on nicotine? A review of the evidence. *Drug and Alcohol Dependence* 2000;59(Suppl 1): S83–S95.

Coleman T, Chamberlain C, Davey MA, Cooper SE, Leonardi-Bee J. Pharmacological interventions for promoting smoking cessation during pregnancy. *Cochrane Database of Systematic Reviews* 2012, Issue 9. Art. No.: CD010078. DOI: 10.1002/14651858.CD010078.

Cornelius MD, Leech SL, Goldschmidt L, Day NL. Is prenatal tobacco exposure a risk factor for early adolescent smoking? A follow-up study. *Neurotoxicology and Teratology* 2005;27(4):667–76.

Corona M, Marcus E. Electronic cigarette blamed for Sparks High gym explosion. *USA Today*, January 13, 2015; <http://www.usatoday.com/story/news/nation-now/2015/01/13/electronic-cigarette-gym-explosion-nevada/21699097/>; accessed: April 21, 2015.

Counotte DS, Goriounova NA, Li KW, Loos M, van der Schors RC, Schetters D, Schoffelmeer AN, Smit AB, Mansvelder HD, Pattij T, et al. Lasting synaptic changes underlie attention deficits caused by nicotine exposure during adolescence. *Nature Neuroscience* 2011;14(4):417–9.

Counotte DS, Spijker S, Van de Burgwal LH, Hogenboom F, Schoffelmeer AN, De Vries TJ, Smit AB, Pattij T. Long-lasting cognitive deficits resulting from adolescent nicotine exposure in rats. *Neuropsychopharmacology* 2009;34(2):299–306.

Cowperthwaite B, Hains SM, Kisilevsky BS. Fetal behavior in smoking compared to non-smoking pregnant women. *Infant Behavior & Development* 2007;30(3):422–30.

Czogala J, Goniewicz ML, Fidelus B, Zielinska-Danch W, Travers MJ, Sobczak A. Secondhand exposure to vapors from electronic cigarettes. *Nicotine & Tobacco Research* 2014;16(6):655–62.

D'Onofrio BM, Rickert ME, Langstrom N, Donahue KL, Coyne CA, Larsson H, Ellingson JM, Van Hulle CA, Iliadou AN, Rathouz PJ, et al. Familial confounding of the association between maternal smoking during pregnancy and offspring substance use and problems. *Archives of General Psychiatry* 2012;69(11):1140–50.

D'Onofrio BM, Van Hulle CA, Waldman ID, Rodgers JL, Harden KP, Rathouz PJ, Lahey BB. Smoking during pregnancy and offspring externalizing problems: an exploration of genetic and environmental confounds. *Development and Psychopathology* 2008;20(1):139–64.

Dahl RE. Adolescent brain development: a period of vulnerabilities and opportunities. Keynote address. *Annals of the New York Academy of Sciences* 2004;1021:1–22.

Dao JM, McQuown SC, Loughlin SE, Belluzzi JD, Leslie FM. Nicotine alters limbic function in adolescent rat by a 5-HT1A receptor mechanism. *Neuropsychopharmacology* 2011;36(7):1319–31.

Davis B, Dang M, Kim J, Talbot P. Nicotine concentrations in electronic cigarette refill and do-it-yourself fluids. *Nicotine & Tobacco Research* 2015;17(2):134–41.

Dawkins L, Corcoran O. Acute electronic cigarette use: nicotine delivery and subjective effects in regular users. *Psychopharmacology* 2014;231(2):401–7.

Dawkins LE, Kimber CF, Doig M, Feyerabend C, Corcoran O. Self-titration by experienced e-cigarette users: blood nicotine delivery and subjective effects. *Psychopharmacology* 2016;233(15-16):2933–41.

DeJarnett N, Conklin DJ, Riggs DW, Myers JA, O'Toole TE, Hamzeh I, Wagner S, Chugh A, Ramos KS, Srivastava S, et al. Acrolein exposure is associated with increased cardiovascular disease risk. *JAMA: the Journal of the American Medical Association* 2014;3(4):e000934.

Dickson PE, Miller MM, Rogers TD, Blaha CD, Mittleman G. Effects of adolescent nicotine exposure and withdrawal on intravenous cocaine self-administration during adulthood in male C57BL/6J mice. *Addiction Biology* 2014;19(1):37–48.

Dierker L, Swendsen J, Rose J, He J, Merikangas K. Transitions to regular smoking and nicotine dependence in the Adolescent National Comorbidity Survey (NCS-A). *Annals of Behavioral Medicine* 2012;43(3):394–401.

Dierker LC, Donny E, Tiffany S, Colby SM, Perrine N, Clayton RR. The association between cigarette smoking and DSM-IV nicotine dependence among first

year college students. *Drug and Alcohol Dependence* 2007;86(2-3):106–14.

Dietz PM, England LJ, Shapiro-Mendoza CK, Tong VT, Farr SL, Callaghan WM. Infant morbidity and mortality attributable to prenatal smoking in the U.S. *American Journal of Preventive Medicine* 2010;39(1):45–52.

Dietz PM, Homa D, England LJ, Burley K, Tong VT, Dube SR, Bernert JT. Estimates of nondisclosure of cigarette smoking among pregnant and nonpregnant women of reproductive age in the United States. *American Journal of Epidemiology* 2011;173(3):355–9.

DiFranza JR, Savageau JA, Rigotti NA, Fletcher K, Ockene JK, McNeill AD, Coleman M, Wood C. Development of symptoms of tobacco dependence in youths: 30 month follow up data from the DANDY study. *Tobacco Control* 2002;11(3):228–35.

Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ* 2004;24;328(7455):1519.

Doura MB, Gold AB, Keller AB, Perry DC. Adult and periadolescent rats differ in expression of nicotinic cholinergic receptor subtypes and in the response of these subtypes to chronic nicotine exposure. *Brain Research* 2008;1215:40–52.

Duncan JR, Paterson DS, Kinney HC. The development of nicotinic receptors in the human medulla oblongata: inter-relationship with the serotonergic system. *Autonomic Neuroscience* 2008;144(1–2):61–75.

Durante AS, Ibidi SM, Lotufo JP, Carvallo RM. Maternal smoking during pregnancy: impact on otoacoustic emissions in neonates. *International Journal of Pediatric Otorhinolaryngology* 2011;75(9):1093–8.

Duranty A. OCFA: man injured after e-cigarette explodes near his face in Santa Ana apartment. *The Orange County Register*, March 9, 2015; <http://www.ocregister.com/articles/fire-653537-concialdi-ocfa.html>; accessed: April 21, 2015.

Dutra LM, Glantz SA. High international electronic cigarette use among never smoker adolescents. *Journal of Adolescent Health* 2014;55(5):595–7.

Dwyer JB, Broide RS, Leslie FM. Nicotine and brain development. *Birth Defects Research. Part C: Embryo Today* 2008;84(1):30–44.

Egilman DS, Schilling JH, Menendez L. A proposal for a safe exposure level for diacetyl. *International Journal of Occupational and Environmental Health* 2011;17(2):122–34.

Ehlinger DG, Bergstrom HC, Burke JC, Fernandez GM, McDonald CG, Smith RF. Adolescent nicotine-induced dendrite remodeling in the nucleus accumbens is rapid, persistent, and D1-dopamine receptor dependent. *Brain Structure & Function* 2016;221(1):133–45.

Eissenberg T. Electronic nicotine delivery devices: Ineffective nicotine delivery and craving suppression after acute administration. *Tobacco Control* 2010;19(1):87–8.

Ekblad M, Korkeila J, Lehtonen L. Smoking during pregnancy affects foetal brain development. *Acta Paediatrica* 2015;104(1):12–8.

England LJ, Bunnell RE, Pechacek TF, Tong VT, McAfee TA. Nicotine and the developing human: a neglected element in the electronic cigarette debate. *American Journal of Preventive Medicine* 2015;49:286.

Ernst M, Fudge JL. A developmental neurobiological model of motivated behavior: anatomy, connectivity and ontogeny of the triadic nodes. *Neuroscience and Biobehavioral Reviews* 2009;33(3):367–82.

Estabrook R, Massey SH, Clark CAC, Burns JL, Mustanski TB, Cook EH, O'Brien TC, Makowski B, Espy KA, Wakschlag LS. Separating family-level and direct exposure effects of smoking during pregnancy on offspring externalizing symptoms: bridging the behavior genetic and behavior teratologic divide. *Behavioral Genetics* 2015;18:1–14.

Etter JF. A longitudinal study of cotinine in long-term daily users of e-cigarettes. *Drug and Alcohol Dependence* 2016;160:218–21.

Etter JF. Explaining the effects of electronic cigarettes on craving for tobacco in recent quitters. *Drug and Alcohol Dependence* 2015;148:102–8.

Etter JF, Eissenberg T. Dependence levels in users of electronic cigarettes, nicotine gums and tobacco cigarettes. *Drug and Alcohol Dependence* 2015;147:68–75.

Etter JF, Zather E, Svensson S. Analysis of refill liquids for electronic cigarettes. *Addiction* 2013;108(9):1671–9.

Exponent Inc. *NJOY E-Cigarette Health Risk Assessment*, 2009; <http://truthaboutecigs.com/science/5.php>; accessed: May 21, 2015.

Falk L, Nordberg A, Seiger A, Kjaeldgaard A, Hellstrom-Lindahl E. Smoking during early pregnancy affects the expression pattern of both nicotinic and muscarinic acetylcholine receptors in human first trimester brainstem and cerebellum. *Neuroscience* 2005;132(2):389–97.

Famele M, Ferranti C, Abenavoli C, Palleschi L, Mancinelli R, Draisci R. The chemical components of electronic cigarette cartridges and refill fluids: review of analytical methods. *Nicotine & Tobacco Research* 2015;17(3):271–9.

Farley SM, Seoh H, Sacks R, Johns M. Teen use of flavored tobacco products in New York City. *Nicotine & Tobacco Research* 2014;16(11):1518–21.

Faroon O, Roney N, Taylor J, Ashizawa A, Lumpkin MH, Plewak DJ. Acrolein health effects. *Toxicology and Industrial Health* 2008;24(7):447–90.

Farsalinos KE, Gillman G, Poulas K, Voudris V. Tobacco-specific nitrosamines in electronic cigarettes: comparison between liquid and aerosol levels. *International Journal of Environmental Research and Public Health* 2015a;12(8):9046–53.

Farsalinos KE, Kistler KA, Gillman G, Voudris V. Evaluation of electronic cigarette liquids and aerosol for the presence of selected inhalation toxins. *Nicotine & Tobacco Research* 2014a;17(2):168–74.

Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Voudris V. Evaluating nicotine levels selection and patterns of electronic cigarette use in a group of "vapers" who had achieved complete substitution of smoking. *Substance Abuse* 2013a;7:139–46.

Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Voudris V. Evaluation of electronic cigarette use (vaping) topography and estimation of liquid consumption: implications for research protocol standards definition and for public health authorities' regulation. *International Journal of Environmental Research and Public Health* 2013b;10(6):2500–14.

Farsalinos KE, Spyrou A, Tsimopoulou K, Stefopoulos C, Romagna G, Voudris V. Nicotine absorption from electronic cigarette use: comparison between first and new-generation devices. *Scientific Reports* 2014b;4:4133.

Farsalinos KE, Voudris V, Poulas K. Are metals emitted from electronic cigarettes a reason for health concern? A risk-assessment analysis of currently available literature. *International Journal of Environmental Research and Public Health* 2015b;12(5):5215–32.

Farsalinos KE, Voudris V, Poulas K. E-cigarettes generate high levels of aldehydes only in 'dry puff' conditions. *Addiction* 2015c;110(8):1352–6.

Federal Register. U.S. Department of Health and Human Services, Food and Drug Administration. Deeming Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Restrictions on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products. 81 *Fed. Reg.* 28974 (2016); <https://federalregister.gov/a/2016-10685>; accessed: May 16, 2016.

Feng Z, Hu W, Hu Y, Tang MS. Acrolein is a major cigarette-related lung cancer agent: preferential binding at p53 mutational hotspots and inhibition of DNA repair. *Proceedings of the National Academy of Sciences of the United States of America* 2006;103(42):15404–9.

Fergusson DM, Woodward LJ, Horwood LJ. Maternal smoking during pregnancy and psychiatric adjustment in late adolescence. *Archives of General Psychiatry* 1998;55(8):721–7.

Ferrari M, Zanasi A, Nardi E, Morselli Labate AM, Ceriana P, Balestrino A, Pisani L, Corcione N, Nava S. Short-term effects of a nicotine-free e-cigarette compared to a traditional cigarette in smokers and non-smokers. *BMC Pulmonary Medicine* 2015;15:120.

Fewell JE, Smith FG. Perinatal nicotine exposure impairs ability of newborn rats to autoresuscitate from apnea during hypoxia. *Journal of Applied Physiology* 1998;85(6):2066–74.

Fiore MC, Jaén CR, Baker TB, Bailey W, Benowitz N, Curry S, Dorfman S, Froehlicher E, Goldstein M, Healton C, et al. *Treating Tobacco Use and Dependence: 2008 Update—Clinical Practice Guidelines*. Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, 2008.

Flavor and Extract Manufacturers Association of the United States. *The Safety Assessment and Regulatory Authority to Use Flavors—Focus on E-Cigarettes*, 2015; <http://www.femaflavor.org/sites/default/files/FEMAGRAS_Ecig_March_3_2015.pdf>; accessed: May 21, 2015.

Flouris AD, Chorti MS, Poulianiti KP, Jamurtas AZ, Kostikas K, Tzatzarakis MN, Wallace Hayes A, Tsatsakis AM, Koutedakis Y. Acute impact of active and passive electronic cigarette smoking on serum cotinine and lung function. *Inhalation Toxicology* 2013;25(2):91–101.

Flouris AD, Poulianiti KP, Chorti MS, Jamurtas AZ, Kouretas D, Owolabi EO, Tzatzarakis MN, Tsatsakis AM, Koutedakis Y. Acute effects of electronic and tobacco cigarette smoking on complete blood count. *Food and Chemical Toxicology* 2012;50(10):3600–3.

Foulds J, Veldheer S, Yingst J, Hrabovsky S, Wilson SJ, Nichols TT, Eissenberg T. Development of a questionnaire for assessing dependence on electronic cigarettes among a large sample of ex-smoking e-cigarette users. *Nicotine & Tobacco Research* 2015;17(2):186–92.

Fox 5 Digital Team. E-cigarette explodes in man's face, *Fox 5 News*, 2015; <http://fox5sandiego.com/2015/02/09/e-cigarette-explodes-in-mans-face/>; accessed: April 21, 2015.

Franco P, Groswasser J, Hassid S, Lanquart JP, Scaillet S, Kahn A. Prenatal exposure to cigarette smoking is associated with a decrease in arousal in infants. *Journal of Pediatrics* 1999;135(1):34–8.

Franke RM, Park M, Belluzzi JD, Leslie FM. Prenatal nicotine exposure changes natural and drug-induced reinforcement in adolescent male rats. *European Journal of Neuroscience* 2008;27(11):2952–61.

Fuoco FC, Buonanno G, Stabile L, Vigo P. Influential parameters on particle concentration and size distribution in the mainstream of e-cigarettes. *Environmental Pollution* 2014;184:523–9.

Galvan A, Schonberg T, Mumford J, Kohno M, Poldrack RA, London ED. Greater risk sensitivity of dorsolateral

prefrontal cortex in young smokers than in nonsmokers. *Psychopharmacology* 2013;229(2):345–55.

Gao YJ, Holloway AC, Zeng ZH, Lim GE, Petrik JJ, Foster WG, Lee RM. Prenatal exposure to nicotine causes postnatal obesity and altered perivascular adipose tissue function. *Obesity Research* 2005;13(4):687–92.

Gaysina D, Fergusson DM, Leve LD, Horwood J, Reiss D, Shaw DS, Elam KK, Natsuaki MN, Neiderhiser JM, Harold GT. Maternal smoking during pregnancy and offspring conduct problems: evidence from 3 independent genetically sensitive research designs. *JAMA Psychiatry* 2013;70(9):956–63.

Gehricke JG, Loughlin SE, Whalen CK, Potkin SG, Fallon JH, Jamner LD, Belluzzi JD, Leslie FM. Smoking to self-medicate attentional and emotional dysfunctions. *Nicotine & Tobacco Research* 2007;9(Suppl 4):S523–S536.

Geiss O, Bianchi I, Barahona F, Barrero-Moreno J. Characterisation of mainstream and passive vapours emitted by selected electronic cigarettes. *International Journal of Hygiene and Environmental Health* 2015;218(1):169–80.

Geiss O, Bianchi I, Barrero-Moreno J. Correlation of volatile carbonyl yields emitted by e-cigarettes with the temperature of the heating coil and the perceived sensorial quality of the generated vapours. *International Journal of Hygiene and Environmental Health* 2016;219(3):268–77.

Giedd JN, Rapoport JL. Structural MRI of pediatric brain development: what have we learned and where are we going? *Neuron* 2010;67(5):728–34.

Gilman SE, Gardener H, Buka SL. Maternal smoking during pregnancy and children's cognitive and physical development: a causal risk factor? *American Journal of Epidemiology* 2008;168(5):522–31.

Goel R, Durand E, Trushin N, Prokopczyk B, Foulds J, Elias RJ, Richie JP Jr. Highly reactive free radicals in electronic cigarette aerosols. *Chemical Research in Toxicology* 2015;28(9):1675–7.

Goff K, Schwartz G. Anaheim Hills teen injured by exploding e-cig, *NBC Los Angeles*, 2015; <http://www.nbclosangeles.com/news/local/Anaheim-Hills-Teen-Injured-Exploding-E-Cig-291489711.html>; accessed: April 21, 2015.

Goniewicz ML, Gawron M, Nadolska J, Balwicki L, Sobczak A. Rise in electronic cigarette use among adolescents in Poland. *Journal of Adolescent Health* 2014a;55(5):713–5.

Goniewicz ML, Gupta R, Lee YH, Reinhardt S, Kim S, Kim B, Kosmider L, Sobczak A. Nicotine levels in electronic cigarette refill solutions: a comparative analysis of products from the U.S., Korea, and Poland. *International Journal on Drug Policy* 2015;26(6):583–8.

Goniewicz ML, Knysak J, Gawron M, Kosmider L, Sobczak A, Kurek J, Prokopowicz A, Jablonska-Czapla M, Rosik-Dulewska C, Havel C, et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tobacco Control* 2014b;23(2):133–9.

Goniewicz ML, Lee L. Electronic cigarettes are a source of thirdhand exposure to nicotine. *Nicotine & Tobacco Research* 2015;17(2):256–8.

Gorini C, Jameson H, Woerman AL, Perry DC, Mendelowitz D. Prenatal nicotine exposure enhances the trigeminocardiac reflex via serotonin receptor facilitation in brainstem pathways. *Journal of Applied Physiology* 2013;115(4):415–21.

Goriounova NA, Mansvelder HD. Nicotine exposure during adolescence leads to short- and long-term changes in spike timing-dependent plasticity in rat prefrontal cortex. *Journal of Neuroscience* 2012;32(31):10484–93.

Grana R, Benowitz N, Glantz S. *Background Paper on E-Cigarettes (Electronic Nicotine Delivery Systems)*. San Francisco (CA): Center for Tobacco Control Research and Education, University of California, San Francisco, December 2013.

Grana RA, Popova L, Ling PM. A longitudinal analysis of electronic cigarette use and smoking cessation. *JAMA Internal Medicine* 2014;174(5):812–3.

Greenland S, Satterfield MH, Lanes SF. A meta-analysis to assess the incidence of adverse effects associated with the transdermal nicotine patch. *Drug Safety* 1998;18(4):297–308.

Griesler PC, Hu MC, Schaffran C, Kandel DB. Comorbid psychiatric disorders and nicotine dependence in adolescence. *Addiction* 2011;106(5):1010–20.

Griesler PC, Kandel DB, Davies M. Maternal smoking in pregnancy, child behavior problems, and adolescent smoking. *Journal of Research on Adolescence* 1998;8:159–85.

Grove KL, Sekhon HS, Brogan RS, Keller JA, Smith MS, Spindel ER. Chronic maternal nicotine exposure alters neuronal systems in the arcuate nucleus that regulate feeding behavior in the newborn rhesus macaque. *Journal of Clinical Endocrinology and Metabolism* 2001;86(11):5420–6.

Gulley JM, Juraska JM. The effects of abused drugs on adolescent development of corticolimbic circuitry and behavior. *Neuroscience* 2013;249:3–20.

Gunnerbeck A, Wikstrom AK, Bonamy AK, Wickstrom R, Cnattingius S. Relationship of maternal snuff use and cigarette smoking with neonatal apnea. *Pediatrics* 2011;128(3):503–9.

Gupta RS, Springston EE, Warrier MR, Smith B, Kumar R, Pongracic J, Holl JL. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics* 2011;128(1):e9–e17.

Guttenburg A, Banerji S, Cozza A, Bikkumalla S, Bronstein AC. E-cigarette exposure: regional poison center exposure trends. *Clinical Toxicology* 2014;52:808–9.

Hadwiger ME, Trehy ML, Ye W, Moore T, Allgire J, Westenberger B. Identification of amino-tadalafil and rimonabant in electronic cigarette products using high pressure liquid chromatography with diode array and tandem mass spectrometric detection. *Journal of Chromatography A* 2010;1217(48):7547–55.

Haghighi A, Schwartz DH, Abrahamowicz M, Leonard GT, Perron M, Richer L, Veillette S, Gaudet D, Paus T, Pausova Z. Prenatal exposure to maternal cigarette smoking, amygdala volume, and fat intake in adolescence. *JAMA Psychiatry* 2013;70(1):98–105.

Hahn EJ, Rayens MK, Chaloupka FJ, Okoli CT, Yang J. *Projected Smoking-Related Deaths Among U.S. Youth: A 2000 Update*. Lexington (KY): University of Kentucky, 2002; <http://uknowledge.uky.edu/cgi/viewcontent.cgi?article=1000&context=nursing_reports>; accessed: September 12, 2016.

Hajek P, Goniewicz ML, Phillips A, Myers Smith K, West O, McRobbie H. Nicotine intake from electronic cigarettes on initial use and after 4 weeks of regular use. *Nicotine & Tobacco Research* 2015;17(2):175–9.

Hall BJ, Wells C, Allenby C, Lin MY, Hao I, Marshall L, Rose JE, Levin ED. Differential effects of non-nicotine tobacco constituent compounds on nicotine self-administration in rats. *Pharmacology, Biochemistry and Behavior* 2014;120:103–8.

Hamilton BE, Martin JA, Ventura SJ. Births: preliminary data for 2011. *National Vital Statistics Reports* 2012;61(5):1–18.

Hamilton BE, Martin JA, Ventura SJ. Births: preliminary data for 2012. *National Vital Statistics Reports* 2013;62(3):1–20.

Hanna EZ, Yi HY, Dufour MC, Whitmore CC. The relationship of early-onset regular smoking to alcohol use, depression, illicit drug use, and other risky behaviors during early adolescence: results from the youth supplement to the third national health and nutrition examination survey. *Journal of Substance Abuse* 2001;13(3):265–82.

Hanna ST. Nicotine effect on cardiovascular system and ion channels. *Journal of Cardiovascular Pharmacology* 2006;47(3):348–58.

Hansson J, Galanti MR, Hergens MP, Fredlund P, Ahlbom A, Alfredsson L, Bellocco R, Eriksson M, Hallqvist J, Hedblad B, et al. Use of snus and acute myocardial infarction: pooled analysis of eight prospective observational studies. *European Journal of Epidemiology* 2012;27(10):771–9.

Harber P, Saechao K, Boomus C. Diacetyl-induced lung disease. *Toxicological Reviews* 2006;25(4):261–72.

Harrod CS, Fingerlin TE, Chasan-Taber L, Reynolds RM, Glueck DH, Dabelea D. Exposure to prenatal smoking and early-life body composition: the healthy start study. *Obesity* 2015;23(1):234–41.

Havel CM, Benowitz NL, Jacob P, Helen GS. An electronic cigarette vaping machine for the characterization of aerosol delivery and composition. *Nicotine & Tobacco Research*. 2016.

Hecht SS. Biochemistry, biology, and carcinogenicity of tobacco-specific N-nitrosamines. *Chemical Research in Toxicology* 1998;11(6):559–603.

Hecht SS. Tobacco smoke carcinogens and lung cancer. *Journal of the National Cancer Institute* 1999;91(14):1194–210.

Hellstrom-Lindahl E, Gorbounova O, Seiger A, Mousavi M, Nordberg A. Regional distribution of nicotinic receptors during prenatal development of human brain and spinal cord. *Brain Research: Developmental Brain Research* 1998;108(1–2):147–60.

Holbrook BD. The effects of nicotine on human fetal development. *Birth Defects Research. Part C, Embryo Today: Reviews* 2016;108(2):181–92.

Holloway AC, Lim GE, Petrik JJ, Foster WG, Morrison KM, Gerstein HC. Fetal and neonatal exposure to nicotine in Wistar rats results in increased beta cell apoptosis at birth and postnatal endocrine and metabolic changes associated with type 2 diabetes. *Diabetologia* 2005;48(12):2661–6.

Horst NK, Heath CJ, Neugebauer NM, Kimchi EY, Laubach M, Picciotto MR. Impaired auditory discrimination learning following perinatal nicotine exposure or beta2 nicotinic acetylcholine receptor subunit deletion. *Behavioural Brain Research* 2012;231(1):170–80.

Hua M, Yip H, Talbot P. Mining data on usage of electronic nicotine delivery systems (ENDS) from YouTube videos. *Tobacco Control* 2013;22(2):103–6.

Huang YY, Kandel DB, Kandel ER, Levine A. Nicotine primes the effect of cocaine on the induction of LTP in the amygdala. *Neuropharmacology* 2013;74:126–34.

Hubbs AF, Cummings KJ, McKernan LT, Dankovic DA, Park RM, Kreiss K. Comment on Farsalinos et al. "evaluation of electronic cigarette liquids and aerosol for the presence of selected inhalation toxins." *Nicotine & Tobacco Research* 2015;17(10):1288–9.

Hubbs AF, Cumpston AM, Goldsmith WT, Battelli LA, Kashon ML, Jackson MC, Frazer DG, Fedan JS, Goravanahally MP, Castranova V, et al. Respiratory and olfactory cytotoxicity of inhaled 2,3-pentanedione in Sprague-Dawley rats. *American Journal of Pathology* 2012;181(3):829–44.

Hutzler C, Paschke M, Kruschinski S, Henkler F, Hahn J, Luch A. Chemical hazards present in liquids and

vapors of electronic cigarettes. *Archives of Toxicology* 2014;88(7):1295–308.

Hyland A, Travers MJ, Dresler C, Higbee C, Cummings KM. A 32-country comparison of tobacco smoke derived particle levels in indoor public places. *Tobacco Control* 2008;17(3):159–65.

Iliadou AN, Koupil I, Villamor E, Altman D, Hultman C, Langstrom N, Cnattingius S. Familial factors confound the association between maternal smoking during pregnancy and young adult offspring overweight. *International Journal of Epidemiology* 2010;39(5):1193–202.

Inamdar AS, Croucher RE, Chokhandre MK, Mashyakhy MH, Marinho VC. Maternal smokeless tobacco use in pregnancy and adverse health outcomes in newborns: a systematic review. *Nicotine & Tobacco Research* 2015;17(9):1058–66.

Ingebrethsen BJ, Cole SK, Alderman SL. Electronic cigarette aerosol particle size distribution measurements. *Inhalation Toxicology* 2012;24(14):976–84.

Iniguez SD, Warren BL, Parise EM, Alcantara LF, Schuh B, Maffeo ML, Manojlovic Z, Bolanos-Guzman CA. Nicotine exposure during adolescence induces a depression-like state in adulthood. *Neuropsychopharmacology* 2009;34(6):1609–24.

Ino T. Maternal smoking during pregnancy and offspring obesity: meta-analysis. *Pediatrics International* 2010;52(1):94–9.

International Agency for Research on Cancer. Acrolein. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* 1995;63:337–72.

International Agency for Research on Cancer. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 77: Some Industrial Chemicals*. Lyon (France): World Health Organization and International Agency for Research on Cancer, 2000.

International Agency for Research on Cancer. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: A Review of Human Carcinogens*. Part F: Chemical agents and related occupations. Vol. 100F. Lyon (France): International Agency for Research on Cancer, 2009.

International Agency for Research on Cancer. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Tobacco Smoke and Involuntary Smoking*. Vol. 83. Lyon (France): International Agency for Research on Cancer, 2004.

Isensee B, Wittchen HU, Stein MB, Hofler M, Lieb R. Smoking increases the risk of panic: findings from a prospective community study. *Archives of General Psychiatry* 2003;60(7):692–700.

Jablow LM, Sexton RJ. Spontaneous electronic cigarette explosion: a case report. *American Journal of Medical Case Reports* 2015;3(4):93–4.

Jacob P 3rd, Yu L, Shulgin AT, Benowitz NL. Minor tobacco alkaloids as biomarkers for tobacco use: comparison of users of cigarettes, smokeless tobacco, cigars, and pipes. *American Journal of Public Health* 1999;89(5):731–6.

Jacobsen LK, Krystal JH, Mencl WE, Westerveld M, Frost SJ, Pugh KR. Effects of smoking and smoking abstinence on cognition in adolescent tobacco smokers. *Biological Psychiatry* 2005;57(1):56–66.

Jacobsen LK, Picciotto MR, Heath CJ, Frost SJ, Tsou KA, Dwan RA, Jackowski MP, Constable RT, Mencl WE. Prenatal and adolescent exposure to tobacco smoke modulates the development of white matter microstructure. *Journal of Neuroscience* 2007a;27(49):13491–8.

Jacobsen LK, Slotkin TA, Mencl WE, Frost SJ, Pugh KR. Gender-specific effects of prenatal and adolescent exposure to tobacco smoke on auditory and visual attention. *Neuropsychopharmacology* 2007b;32(12):2453–64.

Jacobsen LK, Slotkin TA, Westerveld M, Mencl WE, Pugh KR. Visuospatial memory deficits emerging during nicotine withdrawal in adolescents with prenatal exposure to active maternal smoking. *Neuropsychopharmacology* 2006;31(7):1550–61.

Jacobson JT, Morehouse CR. A comparison of auditory brain stem response and behavioral screening in high risk and normal newborn infants. *Ear and Hearing* 1984;5(4):247–53.

Jamal M, Does AJ, Penninx BW, Cuijpers P. Age at smoking onset and the onset of depression and anxiety disorders. *Nicotine & Tobacco Research* 2011;13(9):809–19.

Jasinska AJ, Zorick T, Brody AL, Stein EA. Dual role of nicotine in addiction and cognition: a review of neuroimaging studies in humans. *Neuropharmacology* 2014;84:111–22.

Jauniaux E, Gulbis B, Acharya G, Thiry P, Rodeck C. Maternal tobacco exposure and cotinine levels in fetal fluids in the first half of pregnancy. *Obstetrics and Gynecology* 1999;93(1):25–9.

Jayaprakasha GK, Rao LJ. Chemistry, biogenesis, and biological activities of Cinnamomum zeylanicum. *Critical Reviews in Food Science and Nutrition* 2011;51(6):547–62.

Jensen RP, Luo W, Pankow JF, Strongin RM, Peyton DH. Hidden formaldehyde in e-cigarette aerosols. *New England Journal of Medicine* 2015;372(4):392–4.

John U, Meyer C, Rumpf HJ, Hapke U. Self-efficacy to refrain from smoking predicted by major depression and nicotine dependence. *Addictive Behaviors* 2004;29(5):857–66.

Kable JA, Coles CD, Lynch ME, Carroll J. The impact of maternal smoking on fast auditory brainstem responses. *Neurotoxicology and Teratology* 2009;31(4):216–24.

Kalkhoran S, Glantz SA. E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. *The Lancet Respiratory Medicine* 2016;29;4(2):116–28.

Kandel D, Kandel E. The Gateway Hypothesis of substance abuse: developmental, biological and societal perspectives. *Acta Paediatrica* 2015;104(2):130–7.

Kandel DB, Hu MC, Griesler PC, Schaffran C. On the development of nicotine dependence in adolescence. *Drug and Alcohol Dependence* 2007;91(1):26–39.

Kandel DB, Udry JR. Prenatal effects of maternal smoking on daughters' smoking: nicotine or testosterone exposure? *American Journal of Public Health* 1999;89(9):1377–83.

Kandel DB, Wu P, Davies M. Maternal smoking during pregnancy and smoking by adolescent daughters. *American Journal of Public Health* 1994;84(9):1407–13.

Kandel DB, Yamaguchi K, Chen K. Stages of progression in drug involvement from adolescence to adulthood: further evidence for the gateway theory. *Journal of Studies on Alcohol* 1992;53(5):447–57.

Kandel ER, Kandel DB. Shattuck Lecture. A molecular basis for nicotine as a gateway drug. *New England Journal of Medicine* 2014;371(10):932–43.

Kardia SL, Pomerleau CS, Rozek LS, Marks JL. Association of parental smoking history with nicotine dependence, smoking rate, and psychological cofactors in adult smokers. *Addictive Behaviors* 2003;28(8):1447–52.

Katbamna B, Klutz N, Pudrith C, Lavery JP, Ide CF. Prenatal smoke exposure: effects on infant auditory system and placental gene expression. *Neurotoxicology and Teratology* 2013;38:61–71.

Kavvalakis MP, Stivaktakis PD, Tzatzarakis MN, Kouretas D, Liesivuori J, Alegakis AK, Vynias D, Tsatsakis AM. Multicomponent analysis of replacement liquids of electronic cigarettes using chromatographic techniques. *Journal of Analytical Toxicology* 2015;39(4):262–9.

Key AP, Ferguson M, Molfese DL, Peach K, Lehman C, Molfese VJ. Smoking during pregnancy affects speech-processing ability in newborn infants. *Environmental Health Perspectives* 2007;115(4):623–9.

Khlystov A, Samburova V. Flavoring compounds dominate toxic aldehyde production during e-cigarette vaping. *Environmental Science & Technology* 2016. DOI: 10.1021/acs.est.6b05145.

Kim HJ, Shin HS. Determination of tobacco-specific nitrosamines in replacement liquids of electronic cigarettes by liquid chromatography-tandem mass spectrometry. *Journal of Chromatography A* 2013;1291:48–55.

King BA, Tynan MA, Dube SR, Arrazola R. Flavored-little-cigar and flavored-cigarette use among U.S. middle and high school students. *Journal of Adolescent Health* 2014;54(1):40–6.

Kisilevsky BS, Chambers B, Parker KC, Davies GA. Auditory processing in growth-restricted fetuses and newborns and later language development. *Clinical Psychological Science* 2014;2(4):495–513.

Kisilevsky BS, Davies GA. Auditory processing deficits in growth restricted fetuses affect later language development. *Medical Hypotheses* 2007;68(3):620–8.

Klein LC, Stine MM, Pfaff DW, Vandenbergh DJ. Maternal nicotine exposure increases nicotine preference in periadolescent male but not female C57B1/6J mice. *Nicotine & Tobacco Research* 2003;5(1):117–24.

Kleykamp BA, Jennings JM, Sams C, Weaver MF, Eissenberg T. The influence of transdermal nicotine on tobacco/nicotine abstinence and the effects of a concurrently administered cigarette in women and men. *Experimental and Clinical Psychopharmacology* 2008;16(2):99–112.

Kohlmeier KA. Nicotine during pregnancy: changes induced in neurotransmission, which could heighten proclivity to addict and induce maladaptive control of attention. *Journal of Developmental Origins of Health and Disease* 2015;6(3):169–81.

Korres S, Riga M, Balatsouras D, Papadakis C, Kanellos P, Ferekidis E. Influence of smoking on developing cochlea. Does smoking during pregnancy affect the amplitudes of transient evoked otoacoustic emissions in newborns? *International Journal of Pediatric Otorhinolaryngology* 2007;71(5):781–6.

Kosmider L, Sobczak A, Fik M, Knysak J, Zaciera M, Kurek J, Goniewicz ML. Carbonyl compounds in electronic cigarette vapors: effects of nicotine solvent and battery output voltage. *Nicotine & Tobacco Research* 2014;16(10):1319–26.

Kota D, Martin BR, Robinson SE, Damaj MI. Nicotine dependence and reward differ between adolescent and adult male mice. *Journal of Pharmacology and Experimental Therapeutics* 2007;322(1):399–407.

Kristjansson AL, Mann MJ, Sigfusdottir ID. Licit and illicit substance use by adolescent e-cigarette users compared with conventional cigarette smokers, dual users, and non users. *Journal of Adolescent Health* 2015;57(5):562–4.

Kristjansson EA, Fried PA, Watkinson B. Maternal smoking during pregnancy affects children's vigilance performance. *Drug and Alcohol Dependence* 1989;24(1):11–9.

Krous H. Sudden Infant Death Syndrome (SIDS), Sudden Unexpected Death in Infancy (SUDI), and Sudden Unexplained Death in Childhood (SUDC). In: Collins KA, Byard RW, editors. *Forensic Pathology of Infancy and Childhood*. 1st ed. New York: Springer-Verlag, 2014:193–206.

Kuja-Halkola R, D'Onofrio BM, Larsson H, Lichtenstein P. Maternal smoking during pregnancy and adverse outcomes in offspring: genetic and environmental sources of covariance. *Behavior Genetics* 2014;44(5):456–67.

La Merrill MA, Cirillo PM, Krigbaum NY, Cohn BA. The impact of prenatal parental tobacco smoking on risk of diabetes mellitus in middle-aged women. *Journal of Developmental Origins of Health and Disease* 2015;6(3):242–9.

Lacy RT, Hord LL, Morgan AJ, Harrod SB. Intravenous gestational nicotine exposure results in increased motivation for sucrose reward in adult rat offspring. *Drug and Alcohol Dependence* 2012;124(3):299–306.

Lacy RT, Morgan AJ, Harrod SB. IV prenatal nicotine exposure increases the reinforcing efficacy of methamphetamine in adult rat offspring. *Drug and Alcohol Dependence* 2014;141:92–8.

Lai S, Lai H, Page JB, McCoy CB. The association between cigarette smoking and drug abuse in the United States. *Journal of Addictive Diseases* 2000;19(4):11–24.

Langley K, Heron J, Smith GD, Thapar A. Maternal and paternal smoking during pregnancy and risk of ADHD symptoms in offspring: testing for intrauterine effects. *American Journal of Epidemiology* 2012;176(3):261–8.

Langley K, Rice F, van den Bree MB, Thapar A. Maternal smoking during pregnancy as an environmental risk factor for attention deficit hyperactivity disorder behaviour. A review. *Minerva Pediatrica* 2005;57(6):359–71.

Latimer K, Wilson P, Kemp J, Thompson L, Sim F, Gillberg C, Puckering C, Minnis H. Disruptive behaviour disorders: a systematic review of environmental antenatal and early years risk factors. *Child: Care, Health and Development* 2012;38(5):611–28.

Lau D, Baldus S. Myeloperoxidase and its contributory role in inflammatory vascular disease. *Pharmacology and Therapeutics* 2006;111(1):16–26.

Laugesen M. Nicotine and toxicant yield ratings of electronic cigarette brands in New Zealand. *New Zealand Medical Journal* 2015;128(1411):77–82.

Lavigne JV, Hopkins J, Gouze KR, Bryant FB, LeBailly SA, Binns HJ, Lavigne PM. Is smoking during pregnancy a risk factor for psychopathology in young children? A methodological caveat and report on preschoolers. *Journal of Pediatric Psychology* 2011;36(1):10–24.

Lee S, Kimm H, Yun JE, Jee SH. Public health challenges of electronic cigarettes in South Korea. *Journal of Preventive Medicine and Public Health* 2011;44(6):235–41.

Lee SC, Stokkeland KL, Cole JB, Bangh SA. Electronic cigarettes: A safe way to light up? *Clinical Toxicology* 2014;52:777.

Lee YH, Gawron M, Goniewicz ML. Changes in puffing behavior among smokers who switched from tobacco to electronic cigarettes. *Addictive Behaviors* 2015;48:1–4.

Leech SL, Richardson GA, Goldschmidt L, Day NL. Prenatal substance exposure: effects on attention and impulsivity of 6-year-olds. *Neurotoxicology and Teratology* 1999;21(2):109–18.

Lejuez CW, Aklin W, Bornovalova M, Moolchan ET. Differences in risk-taking propensity across inner-city adolescent ever- and never-smokers. *Nicotine & Tobacco Research* 2005;7(1):71–9.

Lenroot RK, Giedd JN. Brain development in children and adolescents: insights from anatomical magnetic resonance imaging. *Neuroscience and Biobehavioral Reviews* 2006;30(6):718–29.

Leslie FM. Multigenerational epigenetic effects of nicotine on lung function. *BMC Medicine* 2013;11:27.

Leventhal AM, Zvolensky MJ. Anxiety, depression, and cigarette smoking: a transdiagnostic vulnerability framework to understanding emotion-smoking comorbidity. *Psychological Bulletin* 2015;141(1):176–212.

Levin ED, Lawrence S, Petro A, Horton K, Seidler FJ, Slotkin TA. Increased nicotine self-administration following prenatal exposure in female rats. *Pharmacology, Biochemistry and Behavior* 2006;85(3):669–74.

Levin ED, Rezvani AH, Montoya D, Rose JE, Swartzwelder HS. Adolescent-onset nicotine self-administration modeled in female rats. *Psychopharmacology* 2003;169(2):141–9.

Levin ED, Slotkin TA. Developmental neurotoxicity of nicotine. In: Slikker W, Chang LW, editors. *Handbook of Developmental Neurotoxicity*. New York: Academic Press, 1998:587–616.

Lewinsohn PM, Rohde P, Brown RA. Level of current and past adolescent cigarette smoking as predictors of future substance use disorders in young adulthood. *Addiction* 1999;94(6):913–21.

Liang K, Poytress BS, Chen Y, Leslie FM, Weinberger NM, Metherate R. Neonatal nicotine exposure impairs nicotinic enhancement of central auditory processing and auditory learning in adult rats. *European Journal of Neuroscience* 2006;24(3):857–66.

Lieb R, Schreier A, Pfister H, Wittchen HU. Maternal smoking and smoking in adolescents: a prospective community study of adolescents and their mothers. *European Addiction Research* 2003;9(3):120–30.

Lim HH, Shin HS. Measurement of aldehydes in replacement liquids of electronic cigarettes by headspace gas chromatography-mass spectrometry. *Bulletin of the Korean Chemical Society* 2013;34(9):2691–6.

Lindsay GB, Rainey J. Psychosocial and pharmacologic explanations of nicotine's "gateway drug" function. *Journal of School Health* 1997;67(4):123–6.

Linnet KM, Dalsgaard S, Obel C, Wisborg K, Henriksen TB, Rodriguez A, Kotimaa A, Moilanen I, Thomsen PH, Olsen J, et al. Maternal lifestyle factors in pregnancy risk of attention deficit hyperactivity disorder and associated behaviors: review of the current evidence. *American Journal of Psychiatry* 2003;160(6):1028–40.

Lisko JG, Tran H, Stanfill SB, Blount BC, Watson CH. Chemical composition and evaluation of nicotine, tobacco alkaloids, pH, and selected flavors in e-cigarette cartridges and refill solutions. *Nicotine & Tobacco Research* 2015;17(10):1270–8.

Lopez AA, Hiler MM, Soule EK, Ramôa CP, Karaoghlanian NV, Lipato T, Breland AB, Shihadeh AL, Eissenberg T. Effects of electronic cigarette liquid nicotine concentration on plasma nicotine and puff topography in tobacco cigarette smokers: A preliminary report. *Nicotine & Tobacco Research* 2016;18(5):720–3.

Lotfipour S, Ferguson E, Leonard G, Perron M, Pike B, Richer L, Seguin JR, Toro R, Veillette S, Pausova Z, et al. Orbitofrontal cortex and drug use during adolescence: role of prenatal exposure to maternal smoking and BDNF genotype. *Archives of General Psychiatry* 2009;66(11):1244–52.

Lotfipour S, Leonard G, Perron M, Pike B, Richer L, Seguin JR, Toro R, Veillette S, Pausova Z, Paus T. Prenatal exposure to maternal cigarette smoking interacts with a polymorphism in the alpha6 nicotinic acetylcholine receptor gene to influence drug use and striatum volume in adolescence. *Molecular Psychiatry* 2010;15(1):6–8.

Luck W, Nau H, Hansen R, Steldinger R. Extent of nicotine and cotinine transfer to the human fetus, placenta and amniotic fluid of smoking mothers. *Developmental Pharmacology and Therapeutics* 1985;8(6):384–95.

Lydon DM, Wilson SJ, Child A, Geier CF. Adolescent brain maturation and smoking: what we know and where we're headed. *Neuroscience and Biobehavioral Reviews* 2014;45:323–42.

Manigrasso M, Buonanno G, Fuoco FC, Stabile L, Avino P. Aerosol deposition doses in the human respiratory tree of electronic cigarette smokers. *Environmental Pollution* 2015;196:257–67.

Mao J, Liu J, Pang X, Li M, Song J, Han C, Wu D, Wang S. Nicotine induces the expression of C-reactive protein via MAPK-dependent signal pathway in U937 macrophages. *Molecules and Cells* 2012;34(5):457–61.

Marini S, Buonanno G, Stabile L, Ficco G. Short-term effects of electronic and tobacco cigarettes on exhaled nitric oxide. *Toxicology and Applied Pharmacology* 2014;278(1):9–15.

Mark KS, Farquhar B, Chisolm MS, Coleman-Cowger VH, Terplan M. Knowledge, attitudes, and practice of electronic cigarette use among pregnant women. *Journal of Addiction Medicine* 2015;9(4):266–72.

Marsot A, Simon N. Nicotine and cotinine levels with electronic cigarette a review. *International Journal of Toxicology* 2016;35(2):179–85.

Massey SH, Reiss D, Neiderhiser JM, Leve LD, Shaw DS, Ganiban JM. Maternal personality traits associated with patterns of prenatal smoking and exposure: implications for etiologic and prevention research. *Neurotoxicology and Teratology* 2016;53:48–54.

Matt GE, Quintana PJ, Destaillats H, Gundel LA, Sleiman M, Singer BC, Jacob P, Benowitz N, Winickoff JP, Rehan V, et al. Thirdhand tobacco smoke: emerging evidence and arguments for a multidisciplinary research agenda. *Environmental Health Perspectives* 2011;119(9):1218–26.

Mayer B. How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self-experiments in the nineteenth century. *Archives of Toxicology* 2014;88(1):5–7.

McAuley TR, Hopke PK, Zhao J, Babaian S. Comparison of the effects of e-cigarette vapor and cigarette smoke on indoor air quality. *Inhalation Toxicology* 2012;24(12):850–7.

McCartney JS, Fried PA, Watkinson B. Central auditory processing in school-age children prenatally exposed to cigarette smoke. *Neurotoxicology and Teratology* 1994;16(3):269–76.

McCrory C, Layte R. Prenatal exposure to maternal smoking and childhood behavioural problems: a quasi-experimental approach. *Journal of Abnormal Child Psychology* 2012;40(8):1277–88.

McNair LF, Kohlmeier KA. Prenatal nicotine is associated with reduced AMPA and NMDA receptor-mediated rises in calcium within the laterodorsal tegmentum: a pontine nucleus involved in addiction processes. *Journal of Developmental Origins of Health and Disease* 2015;6(3):225–41.

McQuown SC, Belluzzi JD, Leslie FM. Low dose nicotine treatment during early adolescence increases subsequent cocaine reward. *Neurotoxicology and Teratology* 2007;29(1):66–73.

Mikheev VB, Brinkman MC, Granville CA, Gordon, SM, Clark PI. Real-time measurement of electronic cigarette aerosol size distribution and metals content analysis. *Nicotine & Tobacco Research* 2016;18(9):1895–1902.

Mills KL, Tamnes CK. Methods and considerations for longitudinal structural brain imaging analysis across development. *Developmental Cognitive Neuroscience* 2014;9:172–90.

Mojica CY, Dao JM, Yuan M, Loughlin SE, Leslie FM. Nicotine modulation of adolescent dopamine receptor signaling

and hypothalamic peptide response. *Neuropharmacology* 2014;77:285–93.

Moore D, Aveyard P, Connock M, Wang D, Fry-Smith A, Barton P. Effectiveness and safety of nicotine replacement therapy assisted reduction to stop smoking: systematic review and meta-analysis. *BMJ* 2009;338:b1024.

Moretto N, Volpi G, Pastore F, Facchinetti F. Acrolein effects in pulmonary cells: relevance to chronic obstructive pulmonary disease. *Annals of the New York Academy of Sciences* 2012;1259:39–46.

Morgan AJ, Harrod SB, Lacy RT, Stanley EM, Fadel JR. Intravenous prenatal nicotine exposure increases orexin expression in the lateral hypothalamus and orexin innervation of the ventral tegmental area in adult male rats. *Drug and Alcohol Dependence* 2013;132(3):562–70.

Morris CD, May MG, Devine K, Smith S, DeHay T, Mahalik J. Multiple perspectives on tobacco use among youth with mental health disorders and addictions. *American Journal of Health Promotion* 2011;25(5 Suppl):S31–S37.

Mourtakos SP, Tambalis KD, Panagiotakos DB, Antonogeorgos G, Arnaoutis G, Karteroliotis K, Sidossis LS. Maternal lifestyle characteristics during pregnancy, and the risk of obesity in the offspring: a study of 5,125 children. *BMC Pregnancy and Childbirth* 2015;15(1):66.

Moylan S, Jacka FN, Pasco JA, Berk M. Cigarette smoking, nicotine dependence and anxiety disorders: a systematic review of population-based, epidemiological studies. *BMC Medicine* 2012;10:123.

Moylan S, Jacka FN, Pasco JA, Berk M. How cigarette smoking may increase the risk of anxiety symptoms and anxiety disorders: a critical review of biological pathways. *Brain Behavior* 2013;3(3):302–26.

Muller KU, Mennigen E, Ripke S, Banaschewski T, Barker GJ, Buchel C, Conrod P, Fauth-Buhler M, Flor H, Garavan H, et al. Altered reward processing in adolescents with prenatal exposure to maternal cigarette smoking. *JAMA Psychiatry* 2013;70(8):847–56.

Munafo MR, Araya R. Cigarette smoking and depression: a question of causation. *British Journal of Psychiatry* 2010;196(6):425–6.

Munafo MR, Wileyto EP, Murphy MF, Collins BN. Maternal smoking during late pregnancy and offspring smoking behaviour. *Addictive Behaviors* 2006;31(9):1670–82.

Munakata M. Exhaled nitric oxide (FeNO) as a non-invasive marker of airway inflammation. *Allergology International* 2012;61(3):365–72.

Muneoka K, Nakatsu T, Fuji J, Ogawa T, Takigawa M. Prenatal administration of nicotine results in dopaminergic alterations in the neocortex. *Neurotoxicology and Teratology* 1999;21(5):603–9.

Musso F, Bettermann F, Vucurevic G, Stoeter P, Konrad A, Winterer G. Smoking impacts on prefrontal attentional network function in young adult brains. *Psychopharmacology* 2007;191(1):159–69.

Mychasiuk R, Muhammad A, Gibb R, Kolb B. Long-term alterations to dendritic morphology and spine density associated with prenatal exposure to nicotine. *Brain Research* 2013;1499:53–60.

Nagle AA, Gan FF, Jones G, So CL, Wells G, Chew EH. Induction of tumor cell death through targeting tubulin and evoking dysregulation of cell cycle regulatory proteins by multifunctional cinnamaldehydes. *PloS One* 2012;7(11):e50125.

Natarajan R, Wright JW, Harding JW. Nicotine-induced conditioned place preference in adolescent rats. *Pharmacology, Biochemistry and Behavior* 2011;99(3):519–23.

Natividad LA, Torres OV, Friedman TC, O'Dell LE. Adolescence is a period of development characterized by short- and long-term vulnerability to the rewarding effects of nicotine and reduced sensitivity to the anorectic effects of this drug. *Behavioural Brain Research* 2013;257:275–85.

Navarro HA, Seidler FJ, Whitmore WL, Slotkin TA. Prenatal exposure to nicotine via maternal infusions: effects on development of catecholamine systems. *Journal of Pharmacology and Experimental Therapeutics* 1988;244(3):940–4.

Nelson EE, Leibenluft E, McClure EB, Pine DS. The social re-orientation of adolescence: a neuroscience perspective on the process and its relation to psychopathology. *Psychological Medicine* 2005;35(2):163–74.

Newman MB, Shytle RD, Sanberg PR. Locomotor behavioral effects of prenatal and postnatal nicotine exposure in rat offspring. *Behavioural Pharmacology* 1999;10(6–7):699–706.

Nides MA, Leischow SJ, Bhatter M, Simmons M. Nicotine blood levels and short-term smoking reduction with an electronic nicotine delivery system. *American Journal of Health Behavior* 2014;38(2):265–74.

Nomura Y, Gilman SE, Buka SL. Maternal smoking during pregnancy and risk of alcohol use disorders among adult offspring. *Journal of Studies on Alcohol and Drugs* 2011;72(2):199–209.

Norton KJ, June KM, O'Connor RJ. Initial puffing behaviors and subjective responses differ between an electronic nicotine delivery system and traditional cigarettes. *Tobacco Induced Diseases* 2014;12(1):17.

Nostro A, Scaffaro R, D'Arrigo M, Botta L, Filocamo A, Marino A, Bisignano G. Study on carvacrol and cinnamaldehyde polymeric films: mechanical properties, release kinetics and antibacterial and antibiofilm

activities. *Applied Microbiology and Biotechnology* 2012;96(4):1029–38.

O'Brien TC, Mustanski BS, Skol A, Cook EH Jr, Wakschlag LS. Do dopamine gene variants and prenatal smoking interactively predict youth externalizing behavior? *Neurotoxicology and Teratology* 2013;40:67–73.

O'Callaghan FV, Al Mamun A, O'Callaghan M, Alati R, Najman JM, Williams GM, Bor W. Maternal smoking during pregnancy predicts nicotine disorder (dependence or withdrawal) in young adults—a birth cohort study. *Australian and New Zealand Journal of Public Health* 2009;33(4):371–7.

O'Connell G, Colard S, Cahours X, Pritchard JD. An assessment of indoor air quality before, during and after unrestricted use of e-cigarettes in a small room. *International Journal of Environmental Research and Public Health* 2015;12(5):4889–907.

O'Dell LE, Bruijnzeel AW, Smith RT, Parsons LH, Merves ML, Goldberger BA, Richardson HN, Koob GF, Markou A. Diminished nicotine withdrawal in adolescent rats: implications for vulnerability to addiction. *Psychopharmacology* 2006;186(4):612–9.

O'Loughlin J, DiFranza J, Tyndale RF, Meshefedjian G, McMillan-Davey E, Clarke PB, Hanley J, Paradis G. Nicotine-dependence symptoms are associated with smoking frequency in adolescents. *American Journal of Preventive Medicine* 2003;25(3):219–25.

O'Loughlin J, Dugas EN, Brunet J, DiFranza J, Engert JC, Gervais A, Gray-Donald K, Karp I, Low NC, Sabiston C, et al. Cohort profile: the Nicotine Dependence in Teens (NDIT) study. *International Journal of Epidemiology* 2015;44(5):1537–46.

Offermann FJ. Chemical emissions from e-cigarettes: direct and indirect (passive) exposures. *Building and Environment* 2015;93(Part 1):101–5.

Oh JA, Shin HS. Identification and quantification of several contaminated compounds in replacement liquids of electronic cigarettes by gas chromatography-mass spectrometry. *Journal of Chromatographic Science* 2015;53(6):841–8.

Ohta K, Uchiyama S, Inaba Y, Nakagome H, Kunugita N. Determination of carbonyl compounds generated from the electronic cigarette using coupled silica cartridges impregnated with hydroquinone and 2,4-dinitrophenylhydrazine. *Bunseki Kagaku* 2011;60:791–7.

Oken E, Levitan EB, Gillman MW. Maternal smoking during pregnancy and child overweight: systematic review and meta-analysis. *International Journal of Obesity* 2008;32(2):201–10.

Oncken C, McKee S, Krishnan-Sarin S, O'Malley S, Mazure C. Gender effects of reported in utero tobacco exposure on smoking initiation, progression and nicotine dependence in adult offspring. *Nicotine & Tobacco Research* 2004;6(5):829–33.

Oncken CA, Litt MD, McLaughlin LD, Burki NA. Nicotine concentrations with electronic cigarette use: effects of sex and flavor. *Nicotine & Tobacco Research* 2015;17(4):473–8.

Osterman MJ, Martin JA, Curtin SC, Matthews TJ, Wilson EC, Kirmeyer S. Newly released data from the revised U.S. birth certificate, 2011. *National Vital Statistics Reports* 2013;62(4):1–22.

Park YS, Taniguchi N. Acrolein induces inflammatory response underlying endothelial dysfunction: a risk factor for atherosclerosis. *Annals of the New York Academy of Sciences* 2008;1126:185–9.

Pauly JR, Sparks JA, Hauser KF, Pauly TH. In utero nicotine exposure causes persistent, gender-dependant changes in locomotor activity and sensitivity to nicotine in C57Bl/6 mice. *International Journal of Developmental Neuroscience* 2004;22(5–6):329–37.

Paus T, Nawazkhan I, Leonard G, Perron M, Pike GB, Pitiot A, Richer L, Veillette S, Pausova Z. Corpus callosum in adolescent offspring exposed prenatally to maternal cigarette smoking. *Neuroimage* 2008;40(2):435–41.

Paus T, Pausova Z. Prenatal exposure to maternal cigarette smoking, addiction, and the offspring brain. In: Feldstein Ewing SW, Witkiewitz K, Filbey FM, editors. *Neuroimaging and Psychosocial Addiction Treatment: An Integrative Guide for Researchers and Clinicians*. UK: Palgrave Macmillan, 2015:212–30.

Peace MR, Baird TR, Smith N, Wolf CE, Poklis JL, Poklis A. Concentration of nicotine and glycols in 27 electronic cigarette formulations. *Journal of Analytical Toxicology* 2016;40(6):403–7.

Peck JD, Neas B, Robledo C, Saffer E, Beebe L, Wild RA. Intrauterine tobacco exposure may alter auditory brainstem responses in newborns. *Acta Obstetricia et Gynecologica Scandinavica* 2010;89(4):592–6.

Pentel PR, Keyler DE, Chen Y, LeSage MG, Dufek MB, Le C, Leslie FM. Vaccination against nicotine does not prevent nicotine-induced changes in fetal nicotinic receptor binding and c-fos mRNA expression in rats. *Neurotoxicology and Teratology* 2006;28(5):589–96.

Peto R, Lopez AD, Boreham J, Thun M, Heath C Jr. *Mortality from Smoking in Developed Countries, 1950–2000: Indirect Estimates from National Vital Statistics*. Oxford (UK): Oxford University Press, 1994.

Pickens LR, Rowan JD, Bevins RA, Fountain SB. Sex differences in adult cognitive deficits after adolescent nicotine exposure in rats. *Neurotoxicology and Teratology* 2013;38:72–8.

Pipkin JA, Kaplan GJ, Plant CP, Eaton SE, Gil SM, Zavala AR, Crawford CA. Nicotine exposure beginning in adolescence enhances the acquisition of methamphetamine

self-administration, but not methamphetamine-primed reinstatement in male rats. *Drug and Alcohol Dependence* 2014;142:341–4.

Poon K, Leibowitz SF. Consumption of substances of abuse during pregnancy increases consumption in offspring: possible underlying mechanisms. *Frontiers in Nutrition* 2016;3:11.

Poorthuis RB, Mansvelder HD. Nicotinic acetylcholine receptors controlling attention: behavior, circuits and sensitivity to disruption by nicotine. *Biochemical Pharmacology* 2013;86(8):1089–98.

Porath AJ, Fried PA. Effects of prenatal cigarette and marijuana exposure on drug use among offspring. *Neurotoxicology and Teratology* 2005;27(2):267–77.

Portugal GS, Wilkinson DS, Turner JR, Blendy JA, Gould TJ. Developmental effects of acute, chronic, and withdrawal from chronic nicotine on fear conditioning. *Neurobiology of Learning and Memory* 2012;97(4):482–94.

Powell GL, Gaddy J, Xu F, Fregosi RF, Levine RB. Developmental Nicotine Exposure disrupts dendritic arborization patterns of hypoglossal motoneurons in the neonatal rat. *Developmental Neurobiology* 2016.

Protano C, Vitali M. The new danger of thirdhand smoke: why passive smoking does not stop at secondhand smoke. *Environmental Health Perspectives* 2011;119(10):A422.

Proulx E, Piva M, Tian MK, Bailey CD, Lambe EK. Nicotinic acetylcholine receptors in attention circuitry: the role of layer VI neurons of prefrontal cortex. *Cellular and Molecular Life Sciences* 2014;71(7):1225–44.

Quaranta L, Sabatelli M, Madia F, Lippi G, Conte A, Gazzetta F, Tonali P. Expanding the nosology of hypermelinating neuropathies: description of two new entities. *Journal of the Peripheral Nervous System* 2002;7(1):82–3.

Ramôa CP, Hiler MM, Spindle TR, Lopez AA, Karaoghlanian N, Lipato T, Breland AB, Shihadeh A, Eissenberg T. Electronic cigarette nicotine delivery can exceed that of combustible cigarettes: a preliminary report. *Tobacco Control* 2016;25(e1):e6–e9.

Renne RA, Wehner AP, Greenspan BJ, Deford HS, Ragan HA, Westerberg RB, Buschbom RL, Burger GT, Hayes AW, Suber RL, et al. 2-week and 13-week inhalation studies of aerosolized glycerol in rats. *Inhalation Toxicology* 1992;4(2):95–111.

Richardson HL, Walker AM, Horne RS. Maternal smoking impairs arousal patterns in sleeping infants. *Sleep* 2009;32(4):515–21.

Richardson SA, Tizabi Y. Hyperactivity in the offspring of nicotine-treated rats: role of the mesolimbic and nigrostriatal dopaminergic pathways. *Pharmacology, Biochemistry and Behavior* 1994;47(2):331–7.

Roberts KH, Munafo MR, Rodriguez D, Drury M, Murphy MF, Neale RE, Nettle D. Longitudinal analysis of the effect of prenatal nicotine exposure on subsequent smoking behavior of offspring. *Nicotine & Tobacco Research* 2005;7(5):801–8.

Roberts SM, James RC, Williams PL, editors. *Principles of Toxicology: Environmental and Industrial Applications*. 3rd ed. Hoboken (NJ): Wiley, 2015.

Robertson OH, Loosli CG, et al. Tests for the chronic toxicity of propylene glycol and triethylene glycol on monkeys and rats by vapor inhalation and oral administration. *Journal of Pharmacology and Experimental Therapeutics* 1947;91(1):52–76.

Rose JS, Dierker LC, Donny E. Nicotine dependence symptoms among recent onset adolescent smokers. *Drug and Alcohol Dependence* 2010;106(2-3):126–32.

Rosenberg J, Benowitz NL, Jacob P, Wilson KM. Disposition kinetics and effects of intravenous nicotine. *Clinical Pharmacology and Therapeutics* 1980;28(4):517–22.

Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology*. 3rd ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2008.

Rubinstein ML, Luks TL, Moscicki AB, Dryden W, Rait MA, Simpson GV. Smoking-related cue-induced brain activation in adolescent light smokers. *Journal of Adolescent Health* 2011;48(1):7–12.

Ruprecht AA, De Marco C, Pozzi P, Munarini E, Mazza R, Angellotti G, Turla F, Boffi R. Comparison between particulate matter and ultrafine particle emission by electronic and normal cigarettes in real-life conditions. *Tumori* 2014;100(1):e24–e27.

Rydell M, Cnattingius S, Granath F, Magnusson C, Galanti MR. Prenatal exposure to tobacco and future nicotine dependence: population-based cohort study. *British Journal of Psychiatry* 2012;200(3):202–9.

Rydell M, Granath F, Cnattingius S, Magnusson C, Galanti MR. In-utero exposure to maternal smoking is not linked to tobacco use in adulthood after controlling for genetic and family influences: a Swedish sibling study. *European Journal of Epidemiology* 2014;29(7):499–506.

Saffari A, Daher N, Ruprecht A, De Marco C, Pozzi P, Boffi R, Hamad SH, Shafer MM, Schauer JJ, Westerdahl D, et al. Particulate metals and organic compounds from electronic and tobacco-containing cigarettes: comparison of emission rates and secondhand exposure. *Environmental Science: Processes & Impacts* 2014;16(10):2259–67.

Santanam N, Thornhill BA, Lau JK, Crabtree CM, Cook CR, Brown KC, Dasgupta P. Nicotinic acetylcholine receptor signaling in atherogenesis. *Atherosclerosis* 2012;225(2):264–73.

Schneider S, Diehl K. Vaping as a catalyst for smoking? An initial model on the initiation of electronic cigarette use and the transition to tobacco smoking among adolescents. *Nicotine & Tobacco Research* 2016;18(5):647–53.

Schneider T, Bizarro L, Asherson PJ, Stolerman IP. Hyperactivity, increased nicotine consumption and impaired performance in the five-choice serial reaction time task in adolescent rats prenatally exposed to nicotine. *Psychopharmacology* 2012;223(4):401–15.

Schober W, Szendrei K, Matzen W, Osiander-Fuchs H, Heitmann D, Schettgen T, Jorres RA, Fromme H. Use of electronic cigarettes (e-cigarettes) impairs indoor air quality and increases FeNO levels of e-cigarette consumers. *International Journal of Hygiene and Environmental Health* 2014;217(6):628–37.

Schochet TL, Kelley AE, Landry CF. Differential expression of arc mRNA and other plasticity-related genes induced by nicotine in adolescent rat forebrain. *Neuroscience* 2005;135(1):285–97.

Schripp T, Markewitz D, Uhde E, Salthammer T. Does e-cigarette consumption cause passive vaping? *Indoor Air* 2013;23(1):25–31.

Seidenberg AB, Jo CL, Ribisl KM. Differences in the design and sale of e-cigarettes by cigarette manufacturers and non-cigarette manufacturers in the USA. *Tobacco Control* 2016;25(e1):e3–e5.

Selya AS, Wakschlag LS, Dierker LC, Rose JS, Hedeker D, Mermelstein RJ. Exploring alternate processes contributing to the association between maternal smoking and the smoking behavior among young adult offspring. *Nicotine & Tobacco Research* 2013;15(11):1873–82.

Shastry S, Langdorf MI. Electronic vapor cigarette battery explosion causing shotgun-like superficial wounds and contusion. *Western Journal of Emergency Medicine* 2016;17(2):177.

Shawn L, Nelson LS. Smoking cessation can be toxic to your health. *Emergency Medicine* 2013;45(1):7–9, 19.

Shenassa ED, Papandonatos GD, Rogers ML, Buka SL. Elevated risk of nicotine dependence among sib-pairs discordant for maternal smoking during pregnancy: evidence from a 40-year longitudinal study. *Epidemiology* 2015;26(3):441–7.

Shi R, Rickett T, Sun W. Acrolein-mediated injury in nervous system trauma and diseases. *Molecular Nutrition & Food Research* 2011;55(9):1320–31.

Shihadeh A, Eissenberg T. Electronic cigarette effectiveness and abuse liability: predicting and regulating nicotine flux. *Nicotine & Tobacco Research* 2015;17(2):158–62.

Shihadeh AL, Eissenberg TE. Significance of smoking machine toxicant yields to blood-level exposure in water pipe tobacco smokers. *Cancer Epidemiology, Biomarkers and Prevention* 2011;20(11):2457–60.

Shram MJ, Funk D, Li Z, Le AD. Periadolescent and adult rats respond differently in tests measuring the rewarding and aversive effects of nicotine. *Psychopharmacology* 2006;186(2):201–8.

Shram MJ, Funk D, Li Z, Le AD. Acute nicotine enhances c-fos mRNA expression differentially in reward-related substrates of adolescent and adult rat brain. *Neuroscience Letters* 2007;418(3):286–91.

Singer BC, Hodgson AT, Guevarra KS, Hawley EL, Nazaroff WW. Gas-phase organics in environmental tobacco smoke. 1. Effects of smoking rate, ventilation, and furnishing level on emission factors. *Environmental Science & Technology* 2002;36(5):846–53.

Singer BC, Hodgson AT, Nazaroff WW. Gas-phase organics in environmental tobacco smoke: 2. Exposure-relevant emission factors and indirect exposures from habitual smoking. *Atmospheric Environment* 2003;37(39–40):5551–61.

Slawecki CJ, Gilder A, Roth J, Ehlers CL. Increased anxiety-like behavior in adult rats exposed to nicotine as adolescents. *Pharmacology, Biochemistry and Behavior* 2003;75(2):355–61.

Sleiman M, Logue JM, Montesinos VN, Russell ML, Litter MI, Gundel LA, Destaillats H. Emissions from electronic cigarettes: key parameters affecting the release of harmful chemicals. *Environmental Science & Technology* 2016;50(17):9644–51.

Slotkin TA. Fetal nicotine or cocaine exposure: which one is worse? *Journal of Pharmacology and Experimental Therapeutics* 1998;285(3):931–45.

Slotkin TA, Lappi SE, McCook EC, Lorber BA, Seidler FJ. Loss of neonatal hypoxia tolerance after prenatal nicotine exposure: implications for sudden infant death syndrome. *Brain Research Bulletin* 1995;38(1):69–75.

Slotkin TA, Seidler FJ. Nicotine exposure in adolescence alters the response of serotonin systems to nicotine administered subsequently in adulthood. *Developmental Neuroscience* 2009;31(1-2):58–70.

Slotkin TA, Skavicus S, Card J, Stadler A, Levin ED, Seidler FJ. Developmental neurotoxicity of tobacco smoke directed toward cholinergic and serotonergic systems: more than just nicotine. *Toxicological Sciences* 2015;147(1):178–89.

Slotkin TA, Tate CA, Cousins MM, Seidler FJ. Prenatal nicotine exposure alters the responses to subsequent nicotine administration and withdrawal in adolescence: Serotonin receptors and cell signaling. *Neuropsychopharmacology* 2006;31(11):2462–75.

Smith LN, McDonald CG, Bergstrom HC, Brielmaier JM, Eppolito AK, Wheeler TL, Falco AM, Smith RF. Long-term changes in fear conditioning and anxiety-like

behavior following nicotine exposure in adult versus adolescent rats. *Pharmacology, Biochemistry and Behavior* 2006;85(1):91–7.

Smith RF, McDonald CG, Bergstrom HC, Ehlinger DG, Brielmaier JM. Adolescent nicotine induces persisting changes in development of neural connectivity. *Neuroscience and Biobehavioral Reviews* 2015;55:432–43.

Sokolov BP. Oligodendroglial abnormalities in schizophrenia, mood disorders and substance abuse. Comorbidity, shared traits, or molecular phenocopies? *International Journal of Neuropsychopharmacology* 2007;10(4):547–55.

Somerville LH, Casey BJ. Developmental neurobiology of cognitive control and motivational systems. *Current Opinion in Neurobiology* 2010;20(2):236–41.

Sorenson CA, Raskin LA, Suh Y. The effects of prenatal nicotine on radial-arm maze performance in rats. *Pharmacology, Biochemistry and Behavior* 1991;40(4):991–3.

Spear LP. The adolescent brain and age-related behavioral manifestations. *Neuroscience and Biobehavioral Reviews* 2000;24(4):417–63.

Spear LP. *The Behavioral Neuroscience of Adolescence*. New York: W.W. Norton, 2010.

Spear LP. Rewards, aversions and affect in adolescence: emerging convergences across laboratory animal and human data. *Developmental Cognitive Neuroscience* 2011;1(4):392–400.

Spindle TR, Breland AB, Karaoghlanian NV, Shihadeh AL, Eissenberg T. Preliminary results of an examination of electronic cigarette user puff topography: the effect of a mouthpiece-based topography measurement device on plasma nicotine and subjective effects. *Nicotine & Tobacco Research* 2015;17(2):142–9.

Spindel ER, McEvoy CT. The Role of Nicotine in the Effects of Maternal Smoking during Pregnancy on Lung Development and Childhood Respiratory Disease. Implications for Dangers of E-Cigarettes. *American Journal of Respiratory and Critical Care Medicine* 2016;193(5):486–94.

St. Helen G, Havel C, Dempsey D, Jacob P 3rd, Benowitz NL. Nicotine delivery, retention, and pharmacokinetics from various electronic cigarettes. *Addiction* 2016;111(3):535–44.

Steinberg L. A social neuroscience perspective on adolescent risk-taking. *Developmental Review* 2008;28(1):78–106.

Stevens HE, Vaccarino FM. How animal models inform child and adolescent psychiatry. *Journal of the American Academy of Child and Adolescent Psychiatry* 2015;54(5):352–9.

Stroud LR, Papandonatos GD, Shenassa E, Rodriguez D, Niaura R, LeWinn KZ, Lipsitt LP, Buka SL. Prenatal glucocorticoids and maternal smoking during pregnancy independently program adult nicotine dependence in daughters: a 40-year prospective study. *Biological Psychiatry* 2014;75(1):47–55.

Suter MA, Mastrobattista J, Sachs M, Aagaard K. Is there evidence for potential harm of electronic cigarette use in pregnancy? *Birth Defects Research Part A: Clinical and Molecular Teratology* 2015;103(3):186–95.

Talih S, Balhas Z, Eissenberg T, Salman R, Karaoghlanian N, El Hellani A, Baalbaki R, Saliba N, Shihadeh A. Effects of user puff topography, device voltage, and liquid nicotine concentration on electronic cigarette nicotine yield: measurements and model predictions. *Nicotine & Tobacco Research* 2015;17(2):150–7.

Talih S, Balhas Z, Salman R, Karaoghlanian N, Shihadeh A. "Direct dripping": a high-temperature, high-formaldehyde emission electronic cigarette use method. *Nicotine & Tobacco Research* 2016;18(4):453–9.

Tang MS, Wang HT, Hu Y, Chen WS, Akao M, Feng Z, Hu W. Acrolein induced DNA damage, mutagenicity and effect on DNA repair. *Molecular Nutrition & Food Research* 2011;55(9):1291–300.

Task Force on Sudden Infant Death Syndrome, Moon RY. SIDS and other sleep-related infant deaths: expansion of recommendations for a safe infant sleeping environment. *Pediatrics* 2011;128(5):1030–9.

Taylor AE, Howe LD, Heron JE, Ware JJ, Hickman M, Munafo MR. Maternal smoking during pregnancy and offspring smoking initiation: assessing the role of intrauterine exposure. *Addiction* 2014;109(6):1013–21.

Taylor DR, Pijnenburg MW, Smith AD, De Jongste JC. Exhaled nitric oxide measurements: clinical application and interpretation. *Thorax* 2006;61(9):817–27.

Tehranifar P, Liao Y, Ferris JS, Terry MB. Life course socioeconomic conditions, passive tobacco exposures and cigarette smoking in a multiethnic birth cohort of U.S. women. *Cancer Causes and Control* 2009;20(6):867–76.

Thapar A, Rice F, Hay D, Boivin J, Langley K, van den Bree M, Rutter M, Harold G. Prenatal smoking might not cause attention-deficit/hyperactivity disorder: evidence from a novel design. *Biological Psychiatry* 2009;66(8):722–7.

Tierney PA, Karpinski CD, Brown JE, Luo W, Pankow JF. Flavour chemicals in electronic cigarette fluids. *Tobacco Control* 2016;25(e1):e10–e15.

Tjora T, Hetland J, Aaro LE, Wold B, Wiium N, Overland S. The association between smoking and depression from adolescence to adulthood. *Addiction* 2014;109(6):1022–30.

Tong VT, Dietz PM, Morrow B, D'Angelo DV, Farr SL, Rockhill KM, England LJ, Centers for Disease Control

and Prevention. Trends in smoking before, during, and after pregnancy—Pregnancy Risk Assessment Monitoring System, United States, 40 sites, 2000–2010. *Morbidity and Mortality Weekly Report: Surveillance Summaries* 2013;62(6):1–19.

Toro R, Leonard G, Lerner JV, Lerner RM, Perron M, Pike GB, Richer L, Veillette S, Pausova Z, Paus T. Prenatal exposure to maternal cigarette smoking and the adolescent cerebral cortex. *Neuropsychopharmacology* 2008;33(5):1019–27.

Torres OV, Tejeda HA, Natividad LA, O'Dell LE. Enhanced vulnerability to the rewarding effects of nicotine during the adolescent period of development. *Pharmacology, Biochemistry and Behavior* 2008;90(4):658–63.

Trehy ML, Ye W, Hadwiger ME, Moore TW, Allgire JF, Woodruff JT, Ahadi SS, Black JC, Westenberger BJ. Analysis of electronic cigarette cartridges, refill solutions, and smoke for nicotine and nicotine related impurities. *Journal of Liquid Chromatography & Related Technologies* 2011;34(14):1442–58.

Treur JL, Willemsen G, Bartels M, Geels LM, van Beek JH, Huppertz C, van Beijsterveldt CE, Boomsma DI, Vink JM. Smoking during adolescence as a risk factor for attention problems. *Biological Psychiatry* 2015;78(9):656–63.

Trtchounian A, Talbot P. Electronic nicotine delivery systems: is there a need for regulation? *Tobacco Control* 2011;20(1):47–52.

U.S. Department of Health, Education, and Welfare. *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service*. Washington: U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, 1964. PHS Publication No. 1103.

U.S. Department of Health, Education, and Welfare. *Smoking and Health. A Report of the Surgeon General*. Washington: U.S. Department of Health, Education, and Welfare, Office of the Assistant Secretary for Health, Office on Smoking and Health, 1979. DHEW Publication No. (PHS) 79-50066.

U.S. Department of Health and Human Services. *The Health Consequences of Smoking: Nicotine Addiction. A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1988. DHHS Publication No. (CDC) 88-8406.

U.S. Department of Health and Human Services. *Preventing Tobacco Use Among Young People: A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1994.

U.S. Department of Health and Human Services. *Toxicological Profile for Formaldehyde*. Atlanta (GA): Public Health Service, Agency for Toxic Substances and Disease Registry, 1999.

U.S. Department of Health and Human Services. *The Health Consequences of Smoking: A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2004.

U.S. Department of Health and Human Services. *The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General*. 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.

U.S. Department of Health and Human Services. *How Tobacco Smoke Causes Disease—The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2010.

U.S. Department of Health and Human Services. *Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2012.

U.S. Department of Health and Human Services. *Smoking—50 Years of Progress: A Report of the Surgeon General*. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.

U.S. Environmental Protection Agency. *Child-Specific Exposure Factors Handbook (Final Report)*. Washington (DC): National Center for Environmental Assessment, Office of Research and Development, 2008.

U.S. Fire Administration. *Electronic Cigarette Fires and Explosions*, 2014; <https://www.usfa.fema.gov/downloads/pdf/publications/electronic_cigarettes.pdf>; accessed: July 22, 2015.

U.S. Food and Drug Administration. *Briefing Document for the Endocrinologic and Metabolic Drugs Advisory Committee Meeting*. Silver Spring (MD): U.S. Food and Drug Administration, 2007.

U.S. Food and Drug Administration. FDA 101: smoking cessation products, 2015; <http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM331925.pdf>; accessed: October 25, 2015.

U.S. Pharmacopeia. Nicotine, n.d.; <www.pharmacopeia.cn/v29240/usp29nf24s0_m56620.html>; accessed: May 21, 2015.

Uchiyama S, Ohta K, Inaba Y, Kunugita N. Determination of carbonyl compounds generated from the e-cigarette using coupled silica cartridges impregnated with hydroquinone and 2,4-dinitrophenylhydrazine, followed by high-performance liquid chromatography. *Analytical Sciences: The International Journal of the Japan Society for Analytical Chemistry* 2013;29(12):1219–22.

Vansickel AR, Cobb CO, Weaver MF, Eissenberg TE. A clinical laboratory model for evaluating the acute effects of electronic "cigarettes": nicotine delivery profile and cardiovascular and subjective effects. *Cancer Epidemiology, Biomarkers and Prevention* 2010;19(8):1945–53.

Vansickel AR, Eissenberg T. Electronic cigarettes: effective nicotine delivery after acute administration. *Nicotine & Tobacco Research* 2013;15(1):267–70.

Vansickel AR, Weaver MF, Eissenberg T. Clinical laboratory assessment of the abuse liability of an electronic cigarette. *Addiction* 2012;107(8):1493–500.

Vardavas CI, Anagnostopoulos N, Kougias M, Evangelopoulou V, Connolly GN, Behrakis PK. Short-term pulmonary effects of using an electronic cigarette: impact on respiratory flow resistance, impedance, and exhaled nitric oxide. *Chest* 2012;141(6):1400–6.

Varlet V, Farsalinos K, Augsburger M, Thomas A, Etter JF. Toxicity assessment of refill liquids for electronic cigarettes. *International Journal of Environmental Research and Public Health* 2015;12(5):4796–815.

Vastola BJ, Douglas LA, Varlinskaya EI, Spear LP. Nicotine-induced conditioned place preference in adolescent and adult rats. *Physiology and Behavior* 2002;77(1):107–14.

Villanti AC, Richardson A, Vallone DM, Rath JM. Flavored tobacco product use among U.S. young adults. *American Journal of Preventive Medicine* 2013;44(4):388–91.

Vleeming W, Rambali B, Opperhuizen A. The role of nitric oxide in cigarette smoking and nicotine addiction. *Nicotine & Tobacco Research* 2002;4(3):341–8.

Wagner FA, Anthony JC. Into the world of illegal drug use: exposure opportunity and other mechanisms linking the use of alcohol, tobacco, marijuana, and cocaine. *American Journal of Epidemiology* 2002;155(10):918–25.

Wakschlag LS, Henry DB, Blair RJ, Dukic V, Burns J, Pickett KE. Unpacking the association: Individual differences in the relation of prenatal exposure to cigarettes and disruptive behavior phenotypes. *Neurotoxicology and Teratology* 2011;33(1):145–54.

Wakschlag LS, Kistner EO, Pine DS, Biesecker G, Pickett KE, Skol AD, Dukic V, Blair RJ, Leventhal BL, Cox NJ, et al. Interaction of prenatal exposure to cigarettes and MAOA genotype in pathways to youth antisocial behavior. *Molecular Psychiatry* 2010;15(9):928–37.

Wang HT, Hu Y, Tong D, Huang J, Gu L, Wu XR, Chung FL, Li GM, Tang MS. Effect of carcinogenic acrolein on DNA repair and mutagenic susceptibility. *Journal of Biological Chemistry* 2012;287(15):12379–86.

Wang HT, Zhang S, Hu Y, Tang MS. Mutagenicity and sequence specificity of acrolein-DNA adducts. *Chemical Research in Toxicology* 2009;22(3):511–7.

Warshaw EM, Botto NC, Maibach HI, Fowler JF Jr, Rietschel RL, Zug KA, Belsito DV, Taylor JS, DeLeo VA, Pratt MD, et al. Positive patch-test reactions to propylene glycol: a retrospective cross-sectional analysis from the North American Contact Dermatitis Group, 1996 to 2006. *Dermatitis* 2009;20(1):14–20.

Weden MM, Miles JN. Intergenerational relationships between the smoking patterns of a population-representative sample of U.S. mothers and the smoking trajectories of their children. *American Journal of Public Health* 2012;102(4):723–31.

Wei J, Wang J, Dwyer JB, Mangold J, Cao J, Leslie FM, Li MD. Gestational nicotine treatment modulates cell death/survival-related pathways in the brains of adolescent female rats. *International Journal of Neuropsychopharmacology* 2011;14(1):91–106.

Weiss RB, Baker TB, Cannon DS, von Niederhausern A, Dunn DM, Matsunami N, Singh NA, Baird L, Coon H, McMahon WM, et al. A candidate gene approach identifies the CHRNA5-A3-B4 region as a risk factor for age-dependent nicotine addiction. *PLoS Genetics* 2008;4(7):e1000125.

Weissman MM, Warner V, Wickramaratne PJ, Kandel DB. Maternal smoking during pregnancy and psychopathology in offspring followed to adulthood. *Journal of the American Academy of Child and Adolescent Psychiatry* 1999;38(7):892–9.

Weng SF, Redsell SA, Swift JA, Yang M, Glazebrook CP. Systematic review and meta-analyses of risk factors for childhood overweight identifiable during infancy. *Archives of Disease in Childhood* 2012;97(12):1019–26.

Werley MS, McDonald P, Lilly P, Kirkpatrick D, Wallery J, Byron P, Venitz J. Non-clinical safety and pharmacokinetic evaluations of propylene glycol aerosol in Sprague-Dawley rats and Beagle dogs. *Toxicology* 2011;287(1–3):76–90.

Wieslander G, Norback D, Lindgren T. Experimental exposure to propylene glycol mist in aviation emergency training: acute ocular and respiratory effects. *Occupational and Environmental Medicine* 2001;58(10):649–55.

Wilens TE, Vitulano M, Upadhyaya H, Adamson J, Sawtelle R, Utzinger L, Biederman J. Cigarette smoking associated with attention deficit hyperactivity disorder. *Journal of Pediatrics* 2008;153(3):414–9.

Williams CM, Kanagasabai T. Maternal adipose tissue response to nicotine administration in the pregnant rat: effects on fetal body fat and cellularity. *British Journal of Nutrition* 1984;51(1):7–13.

Williams M, Villarreal A, Bozhilov K, Lin S, Talbot P. Metal and silicate particles including nanoparticles are present in electronic cigarette cartomizer fluid and aerosol. *PloS One* 2013;8(3):e57987.

Wills TA, Knight R, Williams RJ, Pagano I, Sargent JD. Risk factors for exclusive e-cigarette use and dual e-cigarette use and tobacco use in adolescents. *Pediatrics* 2015;135(1):e43–e51.

Wills TA, Sargent JD, Knight R, Pagano I, Gibbons FX. E-cigarette use and willingness to smoke: a sample of adolescent non-smokers. *Tobacco Control* 2016;25(e1):e52–e59.

Wong MK, Barra NG, Alfaidy N, Hardy DB, Holloway AC. Adverse effects of perinatal nicotine exposure on reproductive outcomes. *Reproduction* 2015;150(6):R185–R193.

Xiao D, Xu Z, Huang X, Longo LD, Yang S, Zhang L. Prenatal gender-related nicotine exposure increases blood pressure response to angiotensin II in adult offspring. *Hypertension* 2008;51(4):1239–47.

Yan XS, D'Ruiz C. Effects of using electronic cigarettes on nicotine delivery and cardiovascular function in comparison with regular cigarettes. *Regulatory Toxicology and Pharmacology* 2015;71(1):24–34.

Yuan M, Cross SJ, Loughlin SE, Leslie FM. Nicotine and the adolescent brain. *Journal of Physiology* 2015;593(16):3397–412.

Zacny JP, Stitzer ML. Cigarette brand-switching: effects on smoke exposure and smoking behavior. *Journal of Pharmacology and Experimental Therapeutics* 1988;246(2):619–27.

Zalups RK, Ahmad S. Molecular handling of cadmium in transporting epithelia. *Toxicology and Applied Pharmacology* 2003;186(3):163–88.

Zhan W, Dierker LC, Rose JS, Selya A, Mermelstein RJ. The natural course of nicotine dependence symptoms among adolescent smokers. *Nicotine & Tobacco Research* 2012;14(12):1445–52.

Zhang K, Wang X. Maternal smoking and increased risk of sudden infant death syndrome: a meta-analysis. *Legal Medicine* 2013;15(3):115–21.

Zhang Y, Sumner W, Chen DR. In vitro particle size distributions in electronic and conventional cigarette aerosols suggest comparable deposition patterns. *Nicotine & Tobacco Research* 2013;15(2):501–8.

Zhu J, Lee KP, Spencer TJ, Biederman J, Bhide PG. Transgenerational transmission of hyperactivity in a mouse model of ADHD. *Journal of Neuroscience* 2014a;34(8):2768–73.

Zhu J, Zhang X, Xu Y, Spencer TJ, Biederman J, Bhide PG. Prenatal nicotine exposure mouse model showing hyperactivity, reduced cingulate cortex volume, reduced dopamine turnover, and responsiveness to oral methylphenidate treatment. *Journal of Neuroscience* 2012;32(27):9410–8.

Zhu SH, Sun JY, Bonnevie E, Cummins SE, Gamst A, Yin L, Lee M. Four hundred and sixty brands of e-cigarettes and counting: implications for product regulation. *Tobacco Control* 2014b;23(Suppl 3):iii3–iii9.