The "Continuum of Risk" Must Include Cardiovascular Disease

Comment Submitted in Response to FDA Regarding Proposed Rule
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; Regulations on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products
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Most of the discussion of "continuum of risk" that the FDA states that it intends to use in its rulemaking (p 23144) has been focused on cancer. While e-cigarettes deliver lower levels of carcinogens than conventional cigarettes, the ultrafine particles and nicotine that these products deliver have important effects on the development of cardiovascular disease and triggering of cardiac events that are likely to be as large as for inhalation of combusted tobacco products.

Cancer is not the only important health risk to consider for tobacco use. Indeed, cardiovascular disease accounts for 40.50 % of smoking-induced deaths (U.S. Department of Health and Human Services, Centers for Disease Control and Prevention et al. 2014). Nicotine itself also has important adverse health effects on several other biological systems that the FDA must consider.

The idea of a "spectrum of risk" or "continuum of risk" among tobacco and nicotine delivery products is logical. However at this time it is a hypothesis lacking sufficient empirical evidence to use as a basis for regulatory decisions. There have been many instances in the history of the tobacco epidemic when similar logical hypotheses have been proven to be wrong. It was logical to believe that filtered cigarettes would be safer than unfiltered cigarettes. It was logical to believe that light cigarettes would be safer than full-flavor cigarettes. It was logical to believe that the risk of cardiovascular disease from exposure to secondhand cigarette smoke would be 10-100 times less than that of active smoking. Each one of these logical hypotheses has been proven wrong, at an immense cost to the public health (U.S. Department of Health and Human Services, U.S. Public Health Service et al. 2001, Institute of Medicine 2010, U.S. Department of

Health and Human Services, Centers for Disease Control and Prevention et al. 2014). The FDA should not predicate regulatory actions on the assumption that any tobacco or nicotine delivery product is substantially safer than another until the improved safety profile has been demonstrated by a substantial body of peer-reviewed scientific research.

E-cigarette Particles May Cause Substantial Cardiovascular and Pulmonary Disease

Like combustible tobacco products, E-cigarettes deliver nicotine in an aerosol of ultrafine respirable particles to the user. Exposure to respirable particles causes cardiovascular morbidity and mortality (Institute of Medicine 2010). In both cardiovascular and pulmonary disease, increasing evidence supports a non-linear dose-response relationship between cigarette smoke exposure and toxicity. For instance, in cardiovascular disease, mortality increases in a logarithmic fashion with increasing exposure to even small amounts of cigarette smoke and airborne fine particulate matter (Pope et al, Circulation 2009). Likewise, a similar pattern of rapid increases in risk at low levels of exposure has been demonstrated in the association between cigarette smoke exposure and acute lung injury after severe blunt trauma (Calfee, Matthay et al. 2011). Thus, even if e-cigarettes or other tobacco products deliver lower doses of specific toxins compared with traditional cigarettes, they cannot necessarily be presumed to be safer, since substantial risk may be present with even low levels of exposure.

The mechanisms by which particle exposure causes a near-immediate increase in the risk of myocardial infarction and the chemical and physical properties of particles that convey this risk are not fully understood. It is possible that e-cigarette aerosol particles are less harmful to cardiovascular health than combustion particles. However, until research has shown that e-cigarette particles do not cause the same kinds of acute changes in biomarkers of cardiovascular disease risk or increase the incidence of cardiovascular disease at the population level as exposure to combustion particles does, protection of public health requires treating them as being as dangerous as similar size particles in primary and secondhand smoke.

Dual Use Can Increase Cardiovascular Disease Risk

If there are differences in the health risks associated with combustible and non-combustible tobacco and nicotine delivery products, it is still unlikely that regulating the products presumed to be least harmful less stringently will result in improvements in the public health. The FDA is only one contributor to the array of communications on tobacco that is dominated by the tobacco industry. If the FDA indicates that one tobacco product is safer than another, it is likely to increase dual use by nonusers. The concomitant use of two or more tobacco products, can exacerbate dependence on nicotine among light-to-medium consumption smokers (Timberlake 2008). The INTERHEART study (Teo, Ounpuu et al. 2006) suggests that dual use may be more dangerous than continued smoking alone. In this international study of 52 countries, current

smoking was associated with a greater risk of non-fatal AMI (odds ratio [OR] 2.95, 95% CI 2.77-3.14, p<0.0001) compared with never smoking; chewing tobacco alone was associated with OR 2.23 (1.41-3.52), and dual users (smokers who also chewed tobacco) had the highest increase in risk (4.09, 2.98-5.61). Furthermore, according to Mejia, Ling, & Glantz (Mejia, Ling et al. 2010), promoting smokeless tobacco as a harm reduction strategy would lead to changes in use patterns of tobacco products, including initiation and dual use. Mejia et al. used a decision tree analysis to provide a quantitative prediction of the net health effects that could be expected from promoting smokeless tobacco (particularly snus) as a harm reduction strategy in the USA. Their analysis indicates that, even if an individual switching entirely from smoked to smokeless tobacco experienced a reduction in individual risk, this strategy would be unlikely to result in health benefits to the average individual. Significantly, the Mejia et al, model assumed that dual use was less risky than continuing smoking alone. The INTERHEART study suggests that, if anything, the Mejia et al. model underestimates the negative health impact of promoting smokeless tobacco as a harm reduction strategy.

The "Spectrum of Risk" is a Useful Marketing Tool for the Tobacco Industry

Tobacco companies have a strong motivation to exploit the market potential of alternative nicotine products to generate new profits, without cannibalizing existing profits from cigarettes, by creating new forms of nicotine and tobacco use (Peeters and Gilmore 2013). For instance, in 2009, Reynolds American acquired the Swedish company Niconovum AB, which makes nicotine replacement therapy (NRT) products, including nicotine gum and oral spray (Craver 2013, CSP News 2013). In September 2012, Altria announced the launch of Tju "chewing tobacco gum" in Denmark and of Verve tobacco-derived nicotine discs, which are currently being test-marketed in Virginia (Altria Group Inc. 2013). Although not directly promoted as smoking cessation aids, these tobacco products resemble NRT products and so may be perceived as analogous to NRT gums and lozenges in regards to product safety. The resulting effects on the health of the population are unknown.

Nicotine Presents Significant Cardiovascular Health Risks

E-cigarettes deliver both particles and nicotine. In addition to being highly addictive, nicotine also has numerous pathological effects (Bruin, Gerstein et al. 2010, Mills, Thorlund et al. 2014, Samet 2014). A meta-analysis of 63 randomized clinical trials of smoking cessation therapies found that the use of nicotine replacement therapy was associated with an elevated risk of cardiovascular disease events (RR, 2.29%; 95% CI, 1.39-3.82), when compared to the use of buproprion or varenicline (Mills, Thorlund et al. 2014, Samet 2014). When the studies with only 12 months of follow up were excluded, the increased risk for all cardiovascular disease events increased to 3.03 (95% confidence interval, 2.04-4.67) (Samet 2014). Nicotine has wide-ranging and potentially persistent effects on cardiovascular disease risk.

Myocardial infarctions are caused by the rupture of atherosclerotic plaques in the coronary arteries. Pathology in the endothelial cells that line arteries and enhanced blood supply to the plaques within arteries contribute to myocardial infarction. Endothelial cell function can be measured by a technique called flow-mediated dilation of the brachial artery. Briefly, the diameter of the main artery in the arm is measured by ultrasound before and after a significant increase in blood flow. When blood flow increases, healthy endothelial cells secrete nitric oxide which relaxes the muscles in the arteries causing dilation. Unhealthy endothelial cells cannot do this. The use of smokeless tobacco and nicotine nose spray both decrease endothelial function as measured by flow-mediated dilation of the brachial artery (Neunteufl, Heher et al. 2002, Granberry, Smith et al. 2003).

Angiogenesis, the growth of new capillaries, is another essential part of the development and rupture of atherosclerotic plaques (Moulton 2006). Heeschen et al. showed that subcutaneous nicotine doubled the local growth of capillaries in mice (Heeschen, Jang et al. 2001). At clinically relevant concentrations (similar to those of a light to moderate smoker), nicotine promotes endothelial cell migration, poliferation, survival, tube formation and nitric oxide production in vivo (Heeschen, Jang et al. 2001). Nicotine also accelerates the growth of lung tumors in a mouse model (Heeschen, Jang et al. 2001), an effect also produced by secondhand smoke exposure (Zhu, Heeschen et al. 2003). Potential mechanisms include the development and mobilization of endothelial progenitor cells (Heeschen, Chang et al. 2006, Yu, Liu et al. 2011). It is important to note that all the animal studies cited in these comments used nicotine concentrations comparable to those found in the plasma and follicular fluid of light to moderate smokers.

Reproductive and Developmental Effects of Nicotine

Exposure to nicotine in utero has significant and life-long effects on the heart, lungs, brain, reproductive systems and metabolism (Maritz 2008, Bruin, Gerstein et al. 2010). Children of women who smoke have hypertension (Beratis, Panagoulias et al. 1996, Blake, Gurrin et al. 2000). Animal studies suggest that nicotine alone can cause hypertension. Fetal and neonatal nicotine exposure causes increased blood pressure during adulthood in normotensive rats and spontaneously rats (Pausova, Paus et al. 2003, Gao, Holloway et al. 2008). Nicotine exposure changed the composition and quantity of perivascular fat and impaired the ability of the perivascular fat tissue to modulate the contraction of blood vessels (Gao, Holloway et al. 2005, Gao, Lu et al. 2007).

Maternal smoking during pregnancy increases the risk of asthma in childhood, adolescence and adulthood and is associated with diminished lung function (Gilliland, Berhane et al. 2000, Gilliland, Li et al. 2001, Gilliland, Berhane et al. 2003, Li, Langholz et al. 2005, Lannero, Wickman et al. 2006). Animals studies testing the effects of pure nicotine have shown that it can change

airway structure and reduce pulmonary function in fetal monkeys. Perinatal nicotine exposure impairs alveolarization in rats (Maritz, Scott et al. 1993, Maritz and van Wyk 1997, Maritz and Dennis 1998, Maritz and Windvogel 2003) and accelerates aging of the lungs, resulting in decreased internal surface for gas exchange (Maritz 2002, Maritz and Windvogel 2003).

Epidemiological studies have demonstrated that prenatal tobacco exposure is associated with adverse neurobehavioral outcomes including attention-deficit hyperactivity disorder, learning disabilities, behavioral problems and increased risk of nicotine addiction (reviewed in (Pauly and Slotkin 2008, Winzer-Serhan 2008, Dwyer, McQuown et al. 2009)). Prenatal exposure to nicotine alone causes similar problems in rodent models (Pauly and Slotkin 2008, Winzer-Serhan 2008, Dwyer, McQuown et al. 2009).

There is a significant association between smoking and reduced fertility among both women (Hughes and Brennan 1996, Augood, Duckitt et al. 1998, Shiverick and Salafia 1999, Hull, North et al. 2000, Greenlee, Arbuckle et al. 2003) and men (Vine 1996, Kunzle, Mueller et al. 2003, Fuentes, Munoz et al. 2010). Data from animal studies suggest that nicotine exposure is a critical contributor to the infertility observed in women who smoke. Female rats exposed to nicotine during fetal and neonatal development had reduced fertility, dysregulation of ovarian steroidogenesis, and altered follicle dynamics. Developmental nicotine exposure also resulted in reduced granulosa cell proliferation, increased ovarian cell death, and decreased blood vessel development in the ovary during adulthood (Holloway, Kellenberger et al. 2006, Petrik, Gerstein et al. 2009).

Epidemiological studies have shown a strong relationship between maternal smoking and subsequent obesity and metabolic diseases, including hypertension and type-2 diabetes, in children (Montgomery and Ekbom 2002, Power and Jefferis 2002, Toschke, Koletzko et al. 2002, von Kries, Toschke et al. 2002, Bergmann, Bergmann et al. 2003, Wideroe, Vik et al. 2003, Oken, Levitan et al. 2008, Syme, Abrahamowicz et al. 2010). Of the 6000+ chemicals in cigarette smoke, animal studies suggest that fetal exposure to nicotine alone may result in postnatal metabolic changes associated with obesity, type-2 diabetes and hypertension. Maternal nicotine exposure during pregnancy and lactation in rats causes increased fat mass and increased body mass, altered perivascular fat composition and function, elevated blood pressure and impaired glucose homeostasis postnatally (Gao, Holloway et al. 2005, Holloway, Kellenberger et al. 2006, Gao, Lu et al. 2007, Gao, Holloway et al. 2008, Somm, Schwitzgebel et al. 2008).

Other Direct Adverse Effects of Nicotine

Nicotine causes macular degeneration. Growth of blood vessels into the choroid of the eye causes retinal edema, hemorrhage and fibrosis which lead to loss of central vision. Mice that

received nicotine orally had greater growth of blood vessels in the choroid after an experimental injury to Bruch's membrane (Kiuchi, Matsuoka et al. 2008). Nicotine also increases cerebrovascular permeability and this effect can be blocked by an antagonist to the nicotinic acetylcholine receptors (nAChR) (Suner, Espinosa-Heidmann et al. 2004).

Indeed, the FDA has categorized NRT as a category D drug during pregnancy because of the nicotine. The FDA recognizes that "There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks" (Briggs, Freeman et al. 2011). While this risk is tolerable for people using *therapeutic* nicotine, it is not acceptable for *recreational* nicotine.

The FDA should also develop its regulations in full cognizance of the conclusions in the 2104 Surgeon General's report (U.S. Department of Health and Human Services, Centers for Disease Control and Prevention et al. 2014) regarding nicotine:

> 1. The evidence is sufficient to infer that at high-enough doses nicotine has acute toxicity.
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> 2. The evidence is sufficient to infer that nicotine activates multiple biological pathways through which smoking increases risk for disease.
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> 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.
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> 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.

Taken together, these studies demonstrate unequivocally that products and devices that deliver respirable particles and nicotine are inherently dangerous. The "Spectrum of Risk" is an unproven hypothesis with potentially deadly effects on the public health. FDA should not deem any tobacco or nicotine product to be safer than another, until it is proven to be safer through a substantial and consistent body of peer-reviewed scientific research.

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