

**Responses to FDA Questions on E-Cigarettes and Public Health  
Docket Number FDA-2014-N-1936**

**UCSF TCORS Investigators<sup>1</sup>**

April 13, 2015

At the start of the first workshop in a series of public workshops to gather information on e-cigarettes, the FDA announced the opening of a docket for submission of written comments. The full list of questions appears at <http://www.fda.gov/TobaccoProducts/NewsEvents/ucm428317.htm>

This comment provides responses to these questions from the UCSF TCORS investigators. When a response appears below several questions, the response is to the questions as a group.

**Toxicological considerations**

- 1. How can toxicological evaluations of the short and long-term effects of e-cigarettes in users be approached?**
- 2. What are the potential roles of nonclinical models (e.g., *in silico*, *in vitro*, and *in vivo*) and human clinical studies?**
- 3. What *in vitro* and *in vivo* models can be utilized for comparing toxicity between tobacco products?**
- 4. What panel of biomarkers of exposure and toxicity in animal studies can be used to evaluate the toxicity of short and long-term e-cigarette use?**

While *in vitro* and *in silico* models certainly have an important role in mechanistic and pathogenesis-oriented studies of the impact of e-cigarette exposure on lung biology, in general, these models are most useful when combined with *in vivo* and/or human clinical studies, particularly when the primary concern is extrapolation to the impact of e-cigarette exposures on human health. These models will also be most useful when they are based on an understanding of the underlying pathways through which the toxins contained in e-cigarette aerosol exhibit biological effects. While there is some understanding of these mechanisms from existing studies of cigarettes and occupational and environmental exposures, the fact that the FDA has been reluctant to support “mechanistic” studies as part of its effort to develop tobacco regulatory science severely restricts the effective use of such models.

***To effectively answer these questions the FDA needs to reconsider its reluctance to support studies that investigate the mechanisms by which exposure to tobacco***

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***products causes disease, so long as the development of this understanding will support the development of regulations in the intermediate term.***

### ***The importance of cardiovascular and pulmonary outcomes***

Studies of the acute cardiovascular and respiratory effects in active e-cigarette users will be informative because these changes occur much faster than changes associated with cancer. In addition, the risk profile of e-cigarette aerosol is likely to be higher for cardiovascular and non-cancer pulmonary effects than for cancer because e-cigarettes do not burn tobacco and so produce lower levels of carcinogens than conventional cigarettes.

It may not be appropriate to study e-cigarette use in subjects who do not already use them. There is the potential for these non-users to become addicted to nicotine, and it is possible that non-experienced e-cigarette users do not use e-cigarettes in the same manner that experienced users do. In smokers of traditional cigarettes and in populations exposed to air pollution, cardiovascular health effects are rapid, with changes seen within minutes of use or exposure, followed by respiratory effects, with changes seen within hours. Thus, the preliminary toxicological evaluation of e-cigarettes should first focus on acute cardiovascular and respiratory responses in experienced e-cigarette users.

Myocardial infarction in middle age and older adults is a well-established health risk of smoking. Myocardial infarction is associated with endothelial dysfunction, inflammation, oxidative stress, abnormal sympathetic neural signaling and increased coagulation of the blood. Studies that analyze biomarkers of all five of these five contributing domains will provide the best and most complete assessment of the acute cardiovascular risks of e-cigarettes. UCSF TCORS Project 5 is currently testing response to e-cigarette use, in human subjects.

Flow-mediated dilation is a noninvasive test that is the gold standard for measuring changes in endothelial function. Impaired flow-mediated dilation of the brachial artery predicts risk of myocardial dysfunction.<sup>2</sup> If we find that e-cigarette impairs endothelial function, flow-mediated dilation may become an important biomarker for testing the health effects of e-cigarettes. In evaluating inflammation, it is important to test markers of both mild, acute phase inflammation (like interleukin 6, IL-6) and more severe acute phase inflammation (like tumor necrosis factor alpha, TNF- $\alpha$ ).

### ***Focus on the most sensitive endpoints in the most susceptible subgroups***

The fact that e-cigarette products are rapidly evolving complicates problems of assessing the health impacts of e-cigarettes in general. At present, it is not clear how best to expose animals to e-cigarette aerosol, including assessing the most appropriate species to assess the effects of e-cigarettes aerosol on different biological outcomes, how to deliver e-cigarette aerosol, which devices/brands/juices to use, and how to insure that the model system accurately mimics human exposure characteristics (many of which are still under study themselves) to the greatest degree possible. Until there is a clear consensus on the best way to

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<sup>2</sup> Yeboah J, Folsom AR, Burke GL, Johnson C, Polak JF, Post W, Lima JA, Crouse JR, Herrington DM. Predictive Value of Brachial Flow-Medicated Dilation for Incident Cardiovascular Events in a Population-Based Study. *Circulation*. Aug 11, 2009;120:502-9.

expose animals to e-cigarette aerosol the exposure method that produces the largest biological effect should be used.

One potential approach in human clinical studies is to analyze the effects of e-cigarette exposures on lung health is the use of controlled exposures to e-cigarettes followed by flexible bronchoscopy. These studies could allow analysis of the acute effects of e-cigarette exposure on both the airways and alveolar compartment of the lung. For acute lung injury in particular, these studies could be further enhanced by lipopolysaccharide inhalation, a well-established model of acute lung injury in humans.<sup>3</sup> Ethical considerations would likely dictate that these studies compare current users of e-cigs to current non-users, since it may be harmful to healthy non-using subjects to randomize them to e-cigarette exposure.

A high priority should be development of a smoking (vaping) machine for e-cigarettes, including allowing for control of “vaping” parameters, including puff parameters and power delivered to the e-cigarette coils, and methodology for collecting particulate matter and gas-phase components in the aerosol. A range of protocols will probably be necessary to reflect the wide range of e-cigarette types and use patterns because, as of this writing, there is no “standard” way of using an e-cigarette that mimics “average” patterns. A programmable machine capable of varying puff parameters to mimic individual vaping behavior and including a power supply to vary the power delivered to the coils would be desirable.

***In order to meet the FDA’s mandate to protect the public health, given the wide variety of products and use patterns, toxicological and risk assessments should be based on the highest risk pattern of use of a given device when used by the most sensitive members of the population. These settings and susceptible individuals may vary depending on the disease outcome.***

**5. What panels of biomarkers of exposure and toxicity allow for cross-species comparisons (i.e., between animals and humans)? What are the limitations of scaling from animal to human studies?**

#### ***Follow Well-Established Procedures from Environmental Risk Assessment***

Dealing with these questions has been common in the development of environmental regulations related to control of ambient air pollutants. The body of peer-reviewed scientific work and associated regulations provides a strong scientific and legal precedent for the FDA’s use of combined animal and human exposure data, including how to handle issues of cross-species extrapolation, exposure levels and times, and selection of species and end points for assessment. The FDA should follow these well-established procedures and require that the tobacco companies do so in the preparation of materials submitted to the FDA.

In particular, the FDA should conduct risk assessments of tobacco products, including e-cigarettes, using approaches and policies following those developed by the Office of Environmental Health Hazard Assessment (OEHHHA) at the California Environmental Protection

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<sup>3</sup> Shyamsundar M, McAuley DF, Ingram RJ, Gibson DS, O’Kane D, McKeown ST, Edwards A, Taggart C, Elborn JS, Calfee CS, Matthay MA, O’Kane CM. Keratinocyte growth factor promotes epithelial survival and resolution in a human model of lung injury. *Am J Respir Crit Care Med*. 2014 Jun 15; 189(12):1520-9. doi: 10.1164/rccm.201310-1892OC. PMC4226011.

Agency. These methods and the associated risk values have been developed through a rigorous scientific process that included extensive public comments from interested parties, including industry, and were subject to independent external scientific peer review by the California State Scientific Review Panel on Toxic Air Contaminants.

Most important, the risk numbers are developed for ambient rather than occupational exposures. The practice of setting risk levels based on susceptible subpopulations is also important for developing and implementing health-protective standards.

The OEHHA Technical Support Document for the Non-cancer Reference Exposure Levels (REL) and approved values for RELs is available at [http://www.oehha.ca.gov/air/chronic\\_rels/index.html](http://www.oehha.ca.gov/air/chronic_rels/index.html).

The document describing methods for developing cancer potency factors, the consideration of early exposures and the current cancer potency factors is available at [http://www.oehha.ca.gov/air/hot\\_spots/tsd052909.html](http://www.oehha.ca.gov/air/hot_spots/tsd052909.html).

There are look-up tables for the RELs and for the cancer potency factors that are towards the top of the pages in the links listed above.

Like OEHHA, FDA should follow the Hazard Index approach for mixtures where a chemical impacts the same target organ rather than looking at each chemical separately. The Hazard Index approach sums the ratio of the exposure to the Reference Exposure Level for each chemical impacting the same target organ. This is described on page 9 of the REL document (see Table of contents).

For mixtures of carcinogens, the cancer risk assessment adds the risks from each regardless of target site. Also, OEHHA applies age sensitivity factors for exposures to infants and children rather than simply multiplying exposure times potency. It is important that FDA consider early in life exposures when considering exposure to the cardiovascular and pulmonary toxins and carcinogens in e-cigarette aerosol.

The identification of biomarkers of toxicity that allow for cross-species comparisons of the role of tobacco products in acute lung injury is a major goal of UCSF TCORS Project 4.

## **6. What panel of biomarkers of exposure and toxicity could be useful for monitoring exposure and toxicity in humans across different tobacco products?**

Nicotine and its metabolites have high specificity for tobacco and nicotine-containing medications, and are useful for assessing nicotine exposure, pharmacologic effects, and addiction liability. Nicotine metabolites in urine, also called “total nicotine equivalents” (TNE), is one of the best measures of nicotine intake.<sup>4</sup> Cotinine in plasma, saliva, and urine also performs

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<sup>4</sup>Benowitz NL, Jacob P 3rd, Fong I, and Gupta S. Nicotine metabolic profile in man: Comparison of cigarette smoking and transdermal nicotine. *J. Pharmacol. Exp. Ther.* 1994; 268:296-303.

<sup>5</sup>Benowitz NL and P. Jacob, P 3rd. Metabolism of nicotine to cotinine studied by a dual stable isotope method. *Clin. Pharmacol. Exp. Ther.* 1994; 268:296-303; Benowitz NL and Jacob P 3rd. Daily intake of nicotine during cigarette smoking. *Clin. Pharmacol. Ther.* 1984, 35: 499-504.

well in this regard.<sup>5</sup>

The main classes of carcinogens in tobacco and tobacco smoke are nitrosamines, in particular tobacco specific nitrosamines (TSNA), polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and certain volatile organic compounds (VOCs).<sup>6</sup> Volatile organic compounds present in tobacco smoke may cause damage to the cardiovascular or respiratory systems. Carbon monoxide exposure increases the risk of acute cardiovascular events. All of these have useful biomarkers of exposure, either a metabolite or the parent compound that can be measured in biofluids or other sample types such as hair or nail clippings. Of these, only the TSNA have high specificity for tobacco; the others have dietary and/or environmental sources as well. However, the others, being combustion products, generally result in biomarker concentrations in smokers that are elevated compared to the levels found in non-smokers.

The most generally useful biomarker for the TSNA class of carcinogens is 4-methylnitrosamino-1-(3-pyridyl)-1-butanol (NNAL), a metabolite of the lung selective carcinogen 4-methylnitrosamino-1-(3-pyridyl)-1-butanone (NNK).<sup>7</sup> It can be measured in urine, hair, and in toenail clippings.<sup>8</sup> It has a long biological half-life in urine, about 10 days.<sup>9</sup> For that reason, NNAL can detect tobacco use occurring over relatively long periods, but it is not very sensitive to short-term changes in usage. N'-nitrosonornicotine (NNN) is another carcinogenic TSNA that can be used as a biomarker,<sup>10</sup> but its measurement is difficult and it is not widely used. Because TSNA are present in unburned tobacco, they are important biomarkers of exposure for both smoked and smokeless products.

Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous environmental contaminants produced by incomplete combustion of organic materials. The most potent carcinogens in this class, such as benzo[a]pyrene are present in such small quantities and are so expensively metabolized that biomarkers are very difficult to measure and are not often used. However, metabolites of some of the more plentiful PAHs, such as naphthalene, fluorene, phenanthrene,

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<sup>6</sup>Hoffmann I, El-Bayoumy K. The less harmful cigarette: a controversial issue. A tribute to Ernst L. Wynder. *Chem. Res. Toxicol.* 2001;14, 767-790.

<sup>7</sup>Hecht SS. Tobacco smoke carcinogens and lung cancer. *J Natl Cancer Inst.* 1999 Jul 21;91(14):1194-210.

<sup>8</sup>Jacob P 3rd, Havel C, Lee DH, Yu L, Eisner MD, Benowitz NL. Subpicogram per milliliter determination of the tobacco-specific carcinogen metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol in human urine using liquid chromatography-tandem mass spectrometry. *Anal Chem* 2008; 80:8115-21; Yao L, Yang J, Guan YF, Liu BZ, Zheng SJ, Wang WM, Zhu XL, Zhang ZD. Development, validation, and application of a liquid chromatography-tandem mass spectrometry method for the determination of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol in human hair. *Anal Bioanal Chem.* 2012 Nov;404(8):2259-66; Stepanov I, Hecht SS, Lindgren B, Jacob P 3rd, Wilson M, Benowitz NL. Relationship of human toenail nicotine, cotinine, and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol to levels of these biomarkers in plasma and urine. *Cancer Epidemiol Biomarkers Prev.* 2007 Jul;16(7):1382-6.

<sup>9</sup>Goniewicz ML, Havel CM, Peng MW, Jacob P 3rd, Dempsey D, Yu L, Zielinska-Danch W, Koszowski B, Czogala J, Sobczak A, Benowitz NL. Elimination kinetics of the tobacco-specific biomarker and lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol. *Cancer Epidemiol Biomarkers Prev.* 2009;18:3421-5.

<sup>10</sup>Yuan JM, Knezevich AD, Wang R, Gao YT, Hecht SS, Stepanov I. Urinary levels of the tobacco-specific carcinogen N'-nitrosonornicotine and its glucuronide are strongly associated with esophageal cancer risk in smokers. *Carcinogenesis.* 2011 Sep;32(9):1366-71.

and pyrene are more easily measured in urine, and metabolites of these can serve as biomarkers of exposure to the PAH class of carcinogens.<sup>11</sup> Although PAH exposure has dietary and environmental sources, metabolite concentrations in urine are generally elevated in smokers compared to non-smokers.<sup>12</sup> Because they are combustion products, PAH metabolites are most appropriate as biomarkers in smokers, but studies have reported significant levels of PAHs in smokeless products.<sup>13</sup>

As with the PAHs, VOCs are formed by incomplete combustion of organic materials, and have environmental and dietary sources. Likewise, their levels are generally elevated in urine of smokers as compared to non-smokers. Many toxic VOCs are metabolized to mercapturic acids that are useful biomarkers of exposure.<sup>14</sup> Acrolein, benzene, and 1,3-butadiene are VOCs of particular concern that are present in tobacco smoke. Acrolein can cause cardiovascular or lung damage. Benzene is a human carcinogen (IARC class 1A) that is known to cause leukemia. Acrolein results from heating glycerol (glycerin) or fats derived from glycerol, e.g., triglycerides. For this reason, acrolein is of particular interest with regard to e-cigarette use, because glycerol ("vegetable glycerin", VG) is commonly used in the vehicle or humectants of e-cigarette fluids. Benzene exposure from hookah use may be higher than from cigarette smoking, possibly due to the burning charcoal generally placed on top of the moist fruit-tobacco mixture.<sup>15</sup> 1, 3-Butadiene is considered a human carcinogen. Mercapturic acid biomarkers that are useful in tobacco studies are listed in Table 1.

Aromatic amines, such as 2-naphthylamine and 4-aminobiphenyl are carcinogenic combustion products that can be measured in urine,<sup>16</sup> or in blood as hemoglobin adducts.<sup>17</sup>

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<sup>11</sup> Jacob P 3rd, Wilson M, Benowitz NL. Determination of phenolic metabolites of polycyclic aromatic hydrocarbons in human urine as their pentafluorobenzyl ether derivatives using liquid chromatography-tandem mass spectrometry. *Analytical Chemistry* 2007; 79:587-98; Carmella SG, Ming X, Olvera N, Brookmeyer C, Yoder A, Hecht SS. High throughput liquid and gas chromatography-tandem mass spectrometry assays for tobacco-specific nitrosamine and polycyclic aromatic hydrocarbon metabolites associated with lung cancer in smokers. *Chem Res Toxicol.* 2013; 19:26:1209-1.

<sup>12</sup> St Helen G, Goniewicz ML, Dempsey D, Wilson M, Jacob P 3rd, Benowitz NL. Exposure and Kinetics of Polycyclic Aromatic Hydrocarbons (PAHs) in Cigarette Smokers. *Chem Res Toxicol.*, 2012;25:952-64

<sup>13</sup> Hearn BA, Renner CC, Ding YS, Vaughan-Watson C, Stanfill SB, Zhang L, Polzin GM, Ashley DL, Watson CH. Chemical analysis of Alaskan Iq'mik smokeless tobacco. *Nicotine Tob Res.* 2013;15:1283-8.

<sup>14</sup> Alwis KU, Blount BC, Britt AS, Patel D, Ashley DL. Simultaneous analysis of 28 urinary VOC metabolites using ultra high performance liquid chromatography coupled with electrospray ionization tandem mass spectrometry (UPLC-ESI/MSMS). *Anal Chim Acta.* 2012;750:152-60; Carmella SG, Chen M, Han S, Briggs A, Jensen J, Hatsukami DK, Hecht SS. Effects of smoking cessation on eight urinary tobacco carcinogen and toxicant biomarkers. *Chem Res Toxicol.* 2009;22:734-41; Jacob P 3rd, Abu Raddaha AH, Dempsey D, Havel C, Peng M, Yu L, Benowitz NL. Comparison of Nicotine and Carcinogen Exposure with Waterpipe and Cigarette Smoking. *Cancer Epidemiol Biomarkers Prev.* 2013;22:765-72.

<sup>15</sup> Jacob P 3rd, Abu Raddaha AH, Dempsey D, Havel C, Peng M, Yu L, Benowitz NL. Comparison of Nicotine and Carcinogen Exposure with Waterpipe and Cigarette Smoking. *Cancer Epidemiol Biomarkers Prev.* 2013;22:765-72.

<sup>16</sup> Yu J, Wang S, Zhao G, Wang B, Ding L, Zhang X, Xie J, Xie F. Determination of urinary aromatic amines in smokers and nonsmokers using a MIPs-SPE coupled with LC-MS/MS method. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2014;958:130-5.

<b>Table 1. Volatile Organic Compounds (VOCs) and Their Biomarkers</b>		
<b>VOC</b>	<b>Biomarker</b>	<b>Abbreviation</b>
Acrolein	3-Hydroxypropylmercapturic acid	3-HPMA
Acrylamide	2-Carbamoylethylmercapturic acid (Acrylamide Mercapturic Acid)	AAMA
Acrylonitrile	2-Cyanoethylmercapturic acid	CNEMA
Benzene	Phenylmercapturic acid	PMA
1,3-Butadiene	2-Hydroxy-3-buten-1-yl-mercapturic acid	MHBMA-3
Crotonaldehyde	3-Hydroxy-1-methyl-1-propylmercapturic acid	HMPMA
Ethylene, Ethylene Oxide	2-Hydroxyethylmercapturic acid	HEMA
Methylating Agents	Methylmercapturic acid	MMA
Propylene, Propylene Oxide	2-Hydroxypropylmercapturic acid	2-HPMA

Exposure to aromatic amines is associated with an increased risk of bladder cancer, as is cigarette smoking. Biomarker levels are generally increased in smokers as compared to non-smokers.

Carbon monoxide is formed by incomplete combustion of organic materials and is prevalent in the environment due to its presence in motor vehicle exhaust. A simple measure of exposure is in exhaled breath, which is often used to distinguish smokers from non-smokers, but due to its presence in the environment it is not useful for detecting light smoking. CO exposure can also be determined by measuring carboxyhemoglobin in blood.<sup>18</sup> CO will not be useful for assessing exposure to e-cigarettes because there is no combustion. Generally useful biomarkers for tobacco studies are listed in Table 2.

<b>Table 2. Biomarkers and Applications</b>	
<b>Biomarker</b>	<b>Applications</b>
Nicotine and cotinine (plasma, saliva, urine)	Nicotine exposure and effects, verify tobacco use or abstinence
Multiple nicotine metabolites = TNE (urine)	One of the best measures of nicotine intake
Nicotine in hair	Long term tobacco or nicotine exposure
NNAL (urine)	Tobacco carcinogen (NNK) exposure
PAH Metabolites (urine)	Carcinogen Exposure
Mercapturic acids (urine)	Toxic VOC exposure, including acrolein, 1,3-butadiene, benzene
Aromatic Amines (urine or hemoglobin adducts)	Carcinogen Exposure
CO (expired breath or carboxyhemoglobin)	Carbon Monoxide exposure or verify smoking status

<sup>17</sup> Seyler TH, Reyes LR, Bernert JT. Analysis of 4-aminobiphenyl hemoglobin adducts in smokers and nonsmokers by pseudo capillary on-column gas chromatography- tandem mass spectrometry. *J Anal Toxicol.* 2010;34:304-11.

<sup>18</sup> SRNT Subcommittee on Biochemical Verification. Biochemical verification of tobacco use and cessation. *Nicotine Tob. Res.* 2002; 4, 149-159.

**7. Where are aerosols delivered or deposited in humans?**

Having clear answers about where e-cigarette aerosols are deposited is crucial to assessing the effectiveness of e-cigarettes as nicotine delivery devices, their addictive potential, and the toxicity of aerosol constituents, empirical data are not yet available. It is known that aerosol size is critical in determining deposition in the airways. Ongoing studies in other labs show that e-cigarette particles have a bimodal distribution, with particles in the sub-micron and nano size ranges. We assume that larger particles are deposited in the head region and nanoparticles are expected to be deposited lower in the respiratory tract, including the alveoli. Other approaches involving the use of computational fluid dynamic models based on the physical properties of e-cigarette aerosols to model e-cigarette aerosol behavior in the respiratory tract are being done.

Although characterizing e-cigarette particle size distribution is important, and computational models can be useful, these approaches are limited and complicated by the fact that e-cigarette particles are dynamic in the airways (hygroscopic growth of the particles is significant) and user behaviors such as depth of inhalation and aerosol swallowing cannot be ignored in assessing deposition. Studies with human subjects should be conducted to answer this question.

Based on pilot data from a pharmacokinetic study of experienced e-cigarette users, in which the UCSF TCORS assessed nicotine intake, systemic retention, and plasma nicotine levels after 15 puffs, there are identify three distinct plasma nicotine pharmacokinetic profiles suggestive of three main areas of aerosol deposition/delivery. These include the lung, with its characteristic rapid nicotine absorption; buccal cavity and/or upper airways, characterized by slower, sustained nicotine absorption; and the gastrointestinal tract, which showed delayed nicotine absorption likely due to ion trapping of nicotine in the stomach.

While we speculate on the site of aerosol deposition based on plasma nicotine pharmacokinetic profiles, a superior alternative to identifying where the aerosols are deposited is through utilization of imaging techniques such as PET scans (with labeled <sup>11</sup>C-nicotine). This technique has been used to accurately determine sites of nicotine aerosol deposition from use of nicotine inhalers. Given that nicotine is primarily in the particulate phase, one limitation is it may not reflect where gas phase constituents are delivered. But given that a majority of e-cigarette aerosol constituents are in the particulate phase, imaging of nicotine deposition and absorption can be used to as a proxy for other constituents.

**8. What methods most effectively measure aerosol delivery/deposition/absorption?**

**9. What is the impact of local and systemic exposure (of e-liquid and aerosol)?**

**10. What aerosol constituents (e.g., chemicals, toxicants, flavorants, other additives) are delivered to users? Are there differences in delivery of aerosol constituents between new and experienced users?**

**11. What are the levels of aerosol constituents delivered to the experienced user?**

**12. How do levels of toxicant exposure compare to those in users of other tobacco or nicotine containing products (e.g., traditional cigarettes, other combusted tobacco products, smokeless tobacco, nicotine replacement therapy)?**

13. What are the toxicological concerns associated with long-term inhalation of aerosols containing propylene glycol, glycerin and flavorings?
14. What is known about the toxicities of inhaled flavorings? Are some inhaled flavorings more toxic than others?
15. What strategies can be used to evaluate the potential toxicity of inhaled flavorings in humans?
16. What strategies can be used to demonstrate that an individual flavor ingredient additive does not increase the inherent toxicity of the e-liquid and aerosol?

Analysis of toxicant exposure is a vital part of the evaluation of e-cigarette toxicity. E-cigarette aerosol is currently known to contain respirable particles, nicotine,<sup>19</sup> volatile organic compounds like formaldehyde,<sup>20</sup> and metals.<sup>21</sup> E-cigarette aerosol chemistry depends on the composition of the e-liquid and the wire used in the heating coil and the temperature of the heating coil. Higher coil temperature has been shown to increase the concentration of particles, nicotine and volatile organic compounds in the aerosol. Temperature of the coil is dependent on both the voltage of the battery and the resistance of the coil. Both of these factors should be consistently measured in toxicological studies of e-cigarettes. It is not enough to simply measure the voltage of the battery. The resistance of the coil must also be measured and the total wattage calculated.  $Watts = \frac{Battery\ Voltage^2}{Coil\ resistance\ (ohms)}$

Given the great variety of flavorings used in e-cigarette juice, it seems appropriate to screen individual flavorings in vitro and follow up on positive and negative results with in vivo investigations. It is important to remember when testing flavorings that they will be heated and inhaled. It is therefore necessary to generate e-cig aerosol containing the flavoring of interest and test the aerosol. The aerosol should be generated both a moderate wattage, such as 5 watts and a more extreme wattage, such as 9 watts. It is also possible for a synergistic toxic effect between the flavoring and nicotine to occur, so all flavorings should be screened both with and without nicotine. Cell lines that are particularly appropriate for in vitro testing include embryonic stem cells and neural stem cells.<sup>22</sup>

The cytotoxicity of e-cigarette liquids and aerosols with different flavors have been tested on human embryonic fibroblasts, mouse embryonic fibroblasts and rat cardiomyoblasts. Toxicity has been shown to be flavor-dependent, with some flavors exhibiting toxicity and others not.<sup>23</sup>

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<sup>19</sup> 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 Tob Res.* 2015 Feb;17(2):150-7.

<sup>20</sup> Jensen RP<sup>1</sup>, Luo W, Pankow JF, Strongin RM, Peyton DH. Hidden formaldehyde in e-cigarette aerosols. *N Engl J Med.* 2015 Jan 22;372(4):392-4.

<sup>21</sup> Williams M<sup>1</sup>, 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.

<sup>22</sup> Bahl, V., Lin, S., Xu, N., Davis, B., Wang, Y., Talbot, P. Comparison of electronic cigarette refill fluid cytotoxicity using embryonic and adult models. *Reproductive Toxicology.* 2012 Dec;34(4):529-37.

<sup>23</sup> Bahl, V., Lin, S., Xu, N., Davis, B., Wang, Y., Talbot, P. Comparison of electronic cigarette refill fluid cytotoxicity using embryonic and adult models. *Reproductive Toxicology.* 2012 Dec;34(4):529-37;

The answers to Health Effects in Users Question 2 are also relevant here; those responses are included to the responses to these questions by reference.

***The FDA should require convincing evidence from adequately power studies proof from e-cigarette manufacturers that specific additives do not increase the toxicity of e-cigarette liquid and aerosol.***

The fact that the FDA has recognized an additive as Generally Recognized as Safe (GRAS) when ingested should not be accepted as justification that an additive is safe when inhaled.<sup>24</sup>

### **Topography**

- 1. How are e-cigarettes used in terms of actual use patterns (frequency of use) and topography (number of puffs per session, puff volume, puff duration, velocity)?**
- 2. How can e-cigarette topography be evaluated to accurately capture user behaviors?**
- 3. What factors impact e-cigarette topography? For example, how is topography affected by the type of device, reason(s) for use, or user subpopulation (e.g., polytobacco users, experienced users, youth)?**
- 4. What strategies can be used to quantitate e-cigarette use? How can quantitative measures of e-cigarette use be compared to the use of other tobacco or nicotine containing products?**

There are a few studies in existence attempting to answer questions 1-3 related to topography of e-cigarette use.<sup>25</sup> Studies have assessed puff duration using smoking machines, self-reported data, and images of people using conventional cigarettes and e-cigarettes on

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Farsalinos, K. E., Romagna, G., Alliffranchini, E., Ripamontil, E., Bocchietto, E., Todeschi, S., Tsiapras, D., Kyrzopoulos, S. & Voudris, V. Comparison of the Cytotoxic Potential of Cigarette Smoke and Electronic Cigarette Vapour Extract on Cultured Myocardial Cells. *International Journal of Environmental Research and Public Health*, 2013; 10, 5146-5162; Farsalinos, K. E., 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: Research and Treatment*, 2013; 7, 139.

<sup>24</sup> Flavor and Extract Manufacturers Association (2013, 3/3/2015). *Safety Assessment and Regulatory Authority to Use Flavors: Focus on E-cigarettes*. Retrieved 4/8/2015, 2015, from <https://www.femaflavor.org/safety-assessment-and-regulatory-authority-use-flavors-focus-e-cigarettes>.

<sup>25</sup> Etter, J. F., Bullen, C. Electronic cigarette: users profile, utilization, satisfaction and perceived efficacy. *Addiction* 2011; 106(11), 2017-2028; Evans, S. E., & Hoffman, A. C. Electronic cigarettes: abuse liability, topography and subjective effects. *Tobacco Control* 2014; 23(suppl 2), ii23-ii29; Farsalinos, K. E., Romagna, G., Tsiapras, D., Kyrzopoulos S, Voudris V. Evaluation of 2013b. Evaluating nicotine levels selection and patterns of electronic cigarette use (vaping) topography and estimation in a group of liquid consumption: implications for research protocol standards definition and for public health authorities’ regulation. *International Journal “vapers” who had achieved complete substitution of environmental research smoking. Substance Abuse: Research and public health* 2013; 10(6), 2500-2514. *Treatment*; Yip H, Talbot P. Mining data on usage of electronic nicotine delivery systems (ENDS) from YouTube videos. *Tobacco Control*, 2013; 22(2), 103-106.

YouTube. Generally these studies indicate that e-cigarette users tend to engage in longer puff duration than cigarette smokers. Additionally, experienced users of e-cigarettes tend to puff longer than do novice users. These studies illustrate that e-cigarette topography can be evaluated in a variety of ways including self-report, lab settings, and video.

E-cigarette use patterns and topography are highly variable across individuals. It is not altogether clear that researchers have figured out how to measure use patterns. Initially, users were asked to give the number of puffs taken over a day. Realizing that many users take hundreds of puffs a day and are likely to mischaracterize their puffing, a new approach is to ask subjects to assume that one 'time' consists of about 15 puffs or lasts about 10 minutes and they are then asked to estimate the number of 'times' they used the e-cigarette. Subjects age and use patterns is also likely important. Even this approach is challenging in a number of ways. First, many e-cigarette users puff continuously for extended periods of time and have no identifiable breaks to lump into a 'time.' In a pilot study where the UCSF TCORS used videotape to analyze use patterns during a 90-minute *ad libitum* session, some subjects took as many as 120 puffs during that session (average of 1.3 puffs per minute), including long segments of continuous puffing. Second, puffing behavior is highly dependent on the type of e-cigarette and its performance. There can be considerable within-user variation in use patterns and topography. Users seem to maintain a certain behavior while using a specific e-cigarette at a given power setting. Their behavior changes if the e-cigarette is changed or if a setting is changed, such as change in battery voltage, changed battery.

Despite the challenges with characterizing use patterns, available data and the UCSF TCORS pilot data suggest that on average puff duration is about 4 seconds long. Puff duration and puff volume have been shown to affect nicotine delivery while puff velocity has no effect on nicotine delivery.

In order to fully understand and quantify topography we need to have standardized metrics of both the device and use patterns. Ideally, devices would measure length and duration of puff, frequency of puff, and amount of aerosol and nicotine inhaled. More research is also needed to assess how experienced users use e-cigarettes vs novice users. Additional work is also needed to assess how factors such as flavorants and nicotine level affect topography. Early studies focused on first generation devices that are now known to be poor nicotine delivery devices; there is a need to conduct more research on topography of e-cigarettes using the most current devices, and to determine whether and how topography varies by type of device, amount of nicotine, and flavorants. We also need more studies that examine topography among different age groups (youth, young adults, older adults), and among new initiates versus those with a history of using e-cigarettes as well as other tobacco product use especially cigarettes.

Currently, there are no ecological momentary assessments published assessing e-cigarette use. Such studies have already been done on adults and adolescents with regards to conventional cigarettes.<sup>26</sup> This type of study, which would allow for in depth tracking of patterns of use, could provide very important information regarding both patterns of use and what environmental and personal factors influence these patterns of use.

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<sup>26</sup> Piasecki, T. M., Trela, C. J., Hedeker, D., Mermelstein, R. J. Smoking antecedents: Separating between-and within-person effects of tobacco dependence in a multiwave ecological momentary assessment investigation of adolescent smoking. *Nicotine & Tobacco Research*, 2014; 16(Suppl 2), S119-S126; Serre, F., Fatseas, M., Swendsen, J., & Auriacombe, M. Ecological Momentary Assessment in the Investigation of Craving and Substance Use in Daily Life: A Systematic Review. *Drug and Alcohol Dependence* 2015; March (148) 1-20.

## **Clinical Pharmacology and Abuse Liability**

### **1. What are the pharmacokinetics and the pharmacodynamic effects of nicotine delivered via e-cigarettes?**

A number of studies have assessed the pharmacokinetics of e-cigarettes to determine their effectiveness as nicotine delivery devices. Earlier reports showed that e-cigarettes did not deliver nicotine effectively but studies published in the past two years have shown that nicotine is absorbed rapidly, with peak plasma nicotine levels within 2 to 5 minutes of puffing. Given this rapid absorption of nicotine from e-cigarettes, it is expected that users will be able to modify their behavior to titrate their blood nicotine levels for the desired pharmacological/psychoactive effects, thus making e-cigarettes addictive. The pharmacodynamic effects of e-cigarettes are determined in large part by the peak plasma nicotine levels. UCSF TCORS pilot data showed a range from 3 ng/mL to 20 ng/mL within 5 minutes of puffing. It is expected that a user with 20 ng/mL would experience cigarette-like psychoactive effects from nicotine whereas one with 3 ng/mL would experience nicotine's effects to a much lesser extent, if at all. These issues are further complicated by inaccurate labeling of nicotine contents of e-cigarette cartridges and refill solutions.<sup>27</sup>

***As a result, it is vital that the FDA require nicotine concentration labels on all e-cigarettes and e-cigarette accessories, as well as require documented evidence that labels accurately reflect device contents.***

### **2. How do the pharmacokinetic and pharmacodynamic properties of e-cigarettes differ in specific subpopulations (e.g., experienced users, naïve users, dual users, youth)?**

There are marked differences in e-cigarette pharmacokinetics in naïve and experienced users. Studies on nicotine pharmacokinetics in naïve users showed low nicotine delivery (low peak plasma) in contrast to experienced users.

Pharmacokinetic and pharmacodynamics studies of e-cigarettes in dual users have not been fully investigated. The best approach to understanding how e-cigarette pharmacokinetics differ in dual users is to conduct a crossover study in which they switch between cigarettes and e-cigarettes. Given that most e-cigarette users are dual-users with cigarettes, it is important that this type of study be conducted.

For ethical reasons, pharmacokinetic studies on youth have not been conducted. However, pharmacokinetic studies on naïve young adult users can inform e-cigarette pharmacokinetic youth. This is a critical issue because it is easier for youth to become addicted to nicotine and do so earlier and with less overall nicotine usage compared to adults.<sup>28,29</sup>

It is vital that the FDA regulate e-cigarettes and enforce age requirements for purchasing

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<sup>27</sup> Goniewicz, M. L., Kuma, T., Gawron, M., Knysak, J., Kosmider, L. Nicotine Levels in Electronic Cigarettes. *Nicotine & Tobacco Research*. 2013; 15 (1): 158-166. doi: 10.1093/ntr/nts103.

<sup>28</sup> DiFranza, J. R., Riggs, N., Pentz, M.A. Time to re-examine old definitions of nicotine dependence. *Nicotine & Tobacco Research*, 2008; 10(6): 1109-1111.

<sup>29</sup> Scragg, R., Wellman, R.J., Laugense, M., DiFranza, J.R. Diminished autonomy over tobacco can appear with the first cigarettes. *Addictive Behavior*, 2008; 33(5): 689-698.

(including on-line) and prohibit advertising that is likely to reach youth in order to avoid further youth exposure to nicotine.

**3. To what extent do e-cigarettes deliver nicotine via pulmonary absorption?**

No comments.

**4. What are the primary subjective effects associated with e-cigarette use?**

The primary subjective effects associated with e-cigarettes may be influenced by whether or not the e-liquid has nicotine and/or flavorants, the type of device being used (for example if it is an efficient nicotine delivery device (second or third generation versus first generation) and the context in which the user is using the product (for example if the individual is a youth using an e-cigarette in a social setting versus if the individual is an older adult who smokes cigarettes and is trying to use e-cigarettes to quit smoking). In order to fully determine primary subjective effects, studies need to be conducted in which you inquire about appeal, positive and negative experiences of using the product, perspective on the flavors if used, desire to continue to use the product, and so on. These studies would need to be conducted amongst people who have and have not previously used cigarettes, among people using different levels of nicotine and flavorants, and the type of device used.

**5. How do the subjective effects associated with e-cigarette use differ in specific subpopulations (e.g., experienced users, naive users, dual users, youth)?**

Studies have identified different reasons for use depending on the individual. For example, in a qualitative assessment of adolescents, novice e-cigarette users cited curiosity, flavors, and peer influence as reasons for experimenting with e-cigarettes. E-cigarette users who also smoked cigarettes, on the other hand, cited reasons such as their perceptions that they could be used anywhere and that e-cigarettes could help them quit smoking as reasons for using these products.<sup>30</sup> Recent qualitative research<sup>31</sup> showed that adolescents were very unclear about the effects of using e-cigarettes, compared to other tobacco products.

**6. What are the reinforcing effects of e-cigarettes? How do these compare to traditional cigarettes in smokers as well as to other combusted products, smokeless tobacco or nicotine replacement therapy?**

***Based on the available evidence it is reasonable to assume that e-cigarettes play a reinforcing role similar to other nicotine delivery products.***

In a national web-based survey among older adult cigarette smokers (N=454), aged 45+ years, participants were asked to think about and rate the potential risks and benefits associated with using e-cigarettes on a scale from -10 (risks) to 10 (benefits). Those who reported past 30-day electronic cigarette use (n=120) perceived electronic cigarettes to be a benefit (1.7, SD=5.6). In comparison, cigarette smokers perceived traditional cigarettes to be a risk (-4.2, SD=6.9). These data suggest that those who use these respective products perceive

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<sup>30</sup> Kong G, Cavallo D, Hyland A, Cummings KM, Krishnan-Sarin S. Trends in use of electronic nicotine delivery systems by adolescents. *Addictive Behavior*. 2014;39:338-40.

<sup>31</sup> Roditis, M.L., Halpern-Felsher, B. Adolescents' perceptions of risks and benefits of conventional cigarettes, e-cigarettes and marijuana: A qualitative analysis. *Journal of Adolescent Health* (in press).

traditional cigarettes as risk and electronic cigarettes as a benefit, which could motivate electronic cigarette users to continue using electronic cigarettes even if they are using them to aide in cessation of traditional cigarettes.<sup>32</sup>

## **7. What measures or methods can be used for assessing the reinforcing effects of e-cigarettes in users?**

Tracking how use progresses over time, both with regards to type of product used and frequency of use, will be an important study to assess the reinforcing effects of e-cigarettes in users and the role flavors play in reinforcing the effects of e-cigarettes. Studies done with conventional cigarettes and cigars, for example, have tracked how the tobacco companies used flavored products, including menthol, as starter products, with the intention of targeting these milder products to new or younger smokers.<sup>33</sup> There are initial studies with e-cigarettes showing that individuals move from first generation “cigalike” e-cigarettes to more advanced e-cigarettes, and that both nicotine delivery capabilities and flavor choices impact individuals’ decisions to change devices.<sup>34</sup>

## **8. Are there ways that flavorings may enhance the abuse liability of e-cigarettes?**

***There is strong and consistent evidence that flavors are a major driver of tobacco sales in the youth market, and that youth want strong and intense flavors in the products they consume.***

The 2012 Surgeon General report, *Preventing Tobacco Use Among Youth and Young Adults*,<sup>35</sup> concluded that the use of tobacco products such as cigars and smokeless tobacco that are available in flavors have increased among high school students. The cigars preferred most by adolescents and young adults are flavored (peach, grape, apple, and chocolate). Tobacco manufacturers have used menthol and cherry flavored smokeless products as part of a “graduation strategy” with low free nicotine content to encourage new users to start with particular products and progress to others with higher levels of free nicotine.<sup>35</sup> With many of these flavored products available on the market, smokeless tobacco use has been increasing among adolescents.<sup>36</sup> Mint flavored smokeless tobacco products play a role in the initiation and maintenance of smokeless tobacco use.<sup>37</sup> A majority of first and current choice of smokeless

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<sup>32</sup> Wang, J.B. & Cataldo, J.K. (2015) Perceptions of e-cigarettes among older adult smokers. Unpublished raw data.

<sup>33</sup> Hersey, J. C., Nonnemaker, J. M., Homsy, G. Menthol Cigarettes Contribute to the Appeal and Addiction Potential of Smoking for Youth. *Nicotine & Tobacco Research*, 2010; 12(suppl 2), S136-S146. doi: 10.1093/ntr/ntq173; Kostygina, G., Glantz, S. A., Ling, P. M. Tobacco industry use of flavours to recruit new users of little cigars and cigarillos. *Tobacco control*, 2014, tobaccocontrol-2014-051830. [epub ahead of print]

<sup>34</sup> Yingst, J. M., Veldheer, S., Hrabovsky, S., Nichols, T. T., Wilson, S. J., Foulds, J. Factors associated with electronic cigarette users’ device preferences and transition from first generation to advanced generation devices. *Nicotine & Tobacco Research*. 2015, doi: 10.1093/ntr/ntv052.

<sup>35</sup> U.S. Department of Health and Human Services. “Preventing Tobacco Use Among Youth and Young Adults.” A Report of the Surgeon General, “Preventing Tobacco Use Among Youth and Young Adults.” A Report of the Surgeon General, 2012.

<sup>36</sup> Johnston LOM, PM; Bachman, JG; Schulenberg, JE. . *Monitoring the Future national survey results on drug use, 1975-2010. Volume I: Secondary school students*. Ann Arbor: Institute for Social Research, The University of Michigan 2011.

<sup>37</sup> Oliver AJ, Jensen JA, Vogel RI, Anderson AJ, Hatsukami DK.. Flavored and nonflavored smokeless tobacco products: rate, pattern of use, and effects. *Nicotine & Tobacco Research* 2013;15(1):88-92.

tobacco products was flavored, and a significant number of those who initiated use with unflavored products eventually switched to flavored products, specifically mint or wintergreen, to sustain use.<sup>37</sup> With increased manufacture of flavored moist snuff by 72% between 2005 and 2011, flavored moist snuff products contributed to 59.4% of the growth.<sup>38</sup>

E-cigarette companies use the same methods that cigarette companies (all of whom are now selling e-cigarettes) used to entice kids into a lifelong addiction to cigarettes.<sup>39,40</sup> These include widespread marketing of fruit, candy, mint and even alcohol flavors), with spending on advertising rising from \$5.6 million in 2010 to \$82.1 million in 2013.<sup>41</sup> As reported in a systematic content analysis of e-cigarette website marketing: "Candy, fruit, and coffee flavors were offered on most sites. Youthful appeals included images or claims of modernity (73%); increased social status (44%); enhanced social activity (32%); romance (31%); and use by celebrities (22%)."<sup>42</sup>

The advertising techniques currently used by e-cigarette companies are increasing interest in trying e-cigarettes among adults.<sup>8</sup> Ads that emphasize the differences between e-cigarettes and cigarettes are particularly effective, especially those that advertise e-cigarettes as healthier than cigarettes, less expensive, or helpful to quit smoking. E-cigarette companies are marketing e-cigarettes as healthier than cigarette smoking and for smoking cessation.<sup>43</sup> Many adult e-cigarette users say they are using e-cigarettes to stop smoking.<sup>44</sup>

In addition to the use of flavors that appeal to youth e-cigarette companies are aggressively promoting their products to young people. Even tobacco companies and e-cigarette manufacturers admit that flavored e-cigarettes are a problem because of their appeal

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<sup>38</sup> Delnevo CD, Wackowski OA, Giovenco DP, Manderski MT, Hrywman M, Ling PM.. Examining market trends in the United States smokeless tobacco use: 2005–2011. *Tobacco Control* 2014;23(2):107-12.

<sup>39</sup> Grana R, Ling P. Smoking Revolution? A content analysis of electronic cigarette retail websites. *American Journal of Preventive Medicine*. 2014;46(4):395-403.

<sup>40</sup> Andrade M, Hastings G, Angus K. Promotion of electronic cigarettes: tobacco marketing reinvented? *BMJ*. 2013;347:f7473.

<sup>41</sup> American Legacy Foundation, (May 2014). *Vaporized: E-Cigarettes, Advertising, and Youth*. Available at: [http://legacyforhealth.org/content/download/4542/63436/version/1/file/LEG-Vaporized-E-cig\\_Report-May2014.pdf](http://legacyforhealth.org/content/download/4542/63436/version/1/file/LEG-Vaporized-E-cig_Report-May2014.pdf).

<sup>42</sup> Grana R, Ling P. Smoking Revolution? A content analysis of electronic cigarette retail websites. *American Journal of Preventive Medicine* 2014; 46(4):395-403.

<sup>43</sup> Lee S., Kimm H., Yun J.E., Lee, S.H. Public Health Challenges of Electronic Cigarettes in South Korea. *Journal of Preventive Medicine and Public Health*, 2011;44(6): 235-241; de Andrade and Hastings, 2013, The Marketing of E-Cigarettes: A UK Snapshot *BMJ Group Blogs*, <http://blogs.bmj.com/tc/2013/04/06/the-marketing-of-e-cigarettes-a-uk-snapshot>; Yamin, C. K., CK, Bitton, A., &, Bates, D. W. E-cigarettes: a rapidly growing Internet phenomenon. *Annals of internal medicine*, 2010; 153(9), 607-609. *DW*, 153 (9): 607-609. Grana R, Ling P. Smoking Revolution? A content analysis of electronic cigarette retail websites. *American Journal of Preventive Medicine* 2014; 46(4):395-403.

<sup>44</sup> Etter. Electronic cigarettes: a survey of users. *BMC Public Health*, 2010;10:231; Pearson JL, Richardson A, Niaura RS, Vallone DM, Abrams DB, E-Cigarette Awareness, Use, and Harm Perceptions in US Adults. *American Journal of Public Health*, 2012;102(9): 1758-1766; P, Fagan P, Little MA, Kawamoto CT, Herzog TA; Pokhrel, P., Fagan, P., Little, M. A., Kawamoto, C. T., & Herzog, T. A. Smokers who try e-cigarettes to quit smoking: findings from a multiethnic study in Hawaii. *American Journal of Public Health*, 2013; 103(9), e57-e62., 102(9): 1758-1766; Vickerman KA, Carpenter KM, Altman T, Nash CM, Zbikowski SM. Use of Electronic Cigarettes Among State Tobacco Cessation Quitline Callers. *Nicotine & Tobacco Research*. 2013;15(10):1787-1791.

to youth. In fact, Lorillard, makers of Blu, warned parents on “Real Parents. Real Questions”, a subsite of Lorillard’s Youth Smoking Prevention Program website, that “Kids may be particularly vulnerable to trying e-cigarettes due to an abundance of fun flavors such as cherry, vanilla, pina-colada and berry.”<sup>45</sup> The company also noted “For the first time, ‘smoking’ ads are returning to TV with advertising campaigns for e-cigarettes” and “More than 1.78 million middle school and high school students have tried e-cigarettes since 2012.” Lorillard’s Real Parents. Real Questions website also stated that the “Use of e-cigarettes has recently doubled among teens with 4.7% using them in 2011 and 10% using them in 2012.”

These estimates are for US high school students in the National Youth Tobacco Survey (NYTS). NYTS estimates ever e-cigarette use prevalence among middle school students was 1.4% in 2011 and 2.7% in 2012.<sup>46</sup> Current e-cigarette use for both middle and high school students was 1.1% in 2011 and 2.1% in 2012. E-cigarette advertising uses the same appeals that cigarette companies have used to entice kids into a lifelong addiction to cigarettes.<sup>47</sup> Along with the widespread marketing of fruit, candy, mint and even alcohol flavors, these include romantic or sexual imagery, celebrity endorsements, event sponsorships, and the use of social media. In April 2013, Congressional House and Senate leaders released a report showing this, as did the Legacy Foundation, created to educate youth about the risks and consequences of tobacco use.<sup>48</sup>

With the use and integration of the traditional marketing into social media, these messages may be increasingly effective at targeting youth and young adults as they appear to come from peers or celebrity figures, rather than the manufacturer or retailer.

E-cigarette advertising also uses media channels frequented by youth. Increased spending on TV advertising by e-cigarette companies has resulted in higher exposure of adolescents (12 to 17 years old) and young adults (18 to 24 years old) to e-cigarette TV ads in the U.S.<sup>49</sup> Between 2012 and 2013, e-cigarette ads appeared on several TV programs that were rated among the top 100 youth programs for that year.

E-cigarette advertising is also prevalent on other media formats frequented by youth,

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<sup>45</sup> Lorillard Inc. Youth Smoking Prevention Program. Real Parents Real Questions (2014). <http://www.realparentsrealanswers.com/what-you-need-to-know-about-e-cigarettes-infographic/> Accessed May 31, 2014. (A copy of this website has been submitted to the FDA as a public comment, tracking number 1jy-8cep-qnbj).

<sup>46</sup> Corey C, Wang B, Johnson SE, Apelberg B, Husten C, King BA, McAfee TA, Bunnell R, Arrazola RA, Dube SR . Electronic cigarette use among middle and high school students- United States, 2011-2012. *Morbidity and Mortality Weekly Report*. 2013;62(35):729-730.

<sup>47</sup> Grana R, Ling P. Smoking Revolution? A content analysis of electronic cigarette retail websites. *American Journal of Preventive Medicine* 2014; 46(4):395-403; Andrade M, Hastings G, Angus K. Promotion of electronic cigarettes: tobacco marketing reinvented? *BMJ* 2013; 347:f7473; American Legacy Foundation, (May 2014). *Vaporized: E-Cigarettes, Advertising, and Youth*. Available at: [http://legacyforhealth.org/content/download/4542/63436/version/1/file/LEG-Vaporized-E-cig\\_Report-May2014.pdf](http://legacyforhealth.org/content/download/4542/63436/version/1/file/LEG-Vaporized-E-cig_Report-May2014.pdf)

<sup>48</sup> Senate and House Report (April 14, 2014) *Gateway to Addiction? A Survey of Popular Electronic Cigarette Manufacturers and Targeted Marketing to Youth*. Available at: [http://www.durbin.senate.gov/public/index.cfm/files/serve?File\\_id=81d14ff7-f2f6-4856-af9d-c20c0b138f8f](http://www.durbin.senate.gov/public/index.cfm/files/serve?File_id=81d14ff7-f2f6-4856-af9d-c20c0b138f8f)

<sup>49</sup> Duke J C, Lee YO, Kim AE, Watson KA, Arnold KY, Nonnemaker JM, Porter L. Exposure to electronic cigarette television advertisements among youth and young adults. *Pediatrics* 2014; 134: e29-e36.

such as the internet and social media sites such as Twitter. Over 73,000 tweets posted by 23,700 separate users mentioned e-cigarettes between May 1 and June 30 of 2012.<sup>50</sup> 89.7% of these tweets were commercial (as opposed to organic). Although data on users under 18 is scarce -- 26% of internet users 18 to 29 years old are members of Twitter -- nearly double the percentage of users between 30 and 49.<sup>51</sup> An analysis of over 17,500 adults ages 18 and older found that much of the exposure to e-cigarette advertising is not sought out by the user.<sup>52</sup> While only 5% of participants had searched for information on e-cigarettes online and through other avenues, over 50% had been exposed to e-cigarette ads on TV, radio, in print or online between February and March of 2013, and 66% of those who had been exposed were exposed through TV.

Preliminary data from the UCSF TCORS indicates the following: Among urban 9<sup>th</sup> and 12<sup>th</sup> grade adolescents, those who reported having ever used an e-cigarette, most initiated with fruit flavored e-cigarettes, followed by with mint or menthol and dessert flavored.<sup>53</sup> Among male high school baseball athletes in rural California, flavored tobacco products were overwhelmingly preferred over unflavored products.<sup>54</sup>

***Given that e-cigarette companies (which are increasingly owned by large tobacco companies) are using well-established advertising techniques that have been shown to increase tobacco use by youth, it is crucial that the FDA regulate and restrict the marketing of e-cigarettes in the same way that cigarette marketing is restricted as part of the current rule making process.***

## **9. What non-nicotine constituents in e-cigarette aerosols may contribute to e-cigarette use and dependence?**

It is known that the acetaldehyde in conventional cigarettes as well as menthol reinforce the addictive nature of conventional cigarettes.<sup>55</sup> It will be important to assess addictiveness of products that contain both flavorants and nicotine versus those that contain nicotine alone, as well as those with and without menthol, to assess if flavorants reinforce use behavior on their own. Regarding questions 6 and 8 and any other concerns regarding flavorings in e-cigarettes

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<sup>50</sup> Huang J, Kornfield R, Szczypka G, Emery SL. A cross-sectional examination of marketing of electronic cigarettes on Twitter. *Tobacco Control* 2014;23(suppl 3):iii26-iii30

<sup>51</sup> Bullas J. Pew Report: The demographics of Twitter users. 2012; [http://www.ragan.com/Main/Articles/Pew\\_Report\\_The\\_demographics\\_of\\_Twitter\\_users\\_44999.aspx](http://www.ragan.com/Main/Articles/Pew_Report_The_demographics_of_Twitter_users_44999.aspx). Accessed 8/4/2014, 2014.

<sup>52</sup> Emery SL, Vera L, Huang J, Szczypka G. Wanna know about vaping? Patterns of message exposure, seeking and sharing information about e-cigarettes across media platforms. *Tobacco Control* 2014;23(suppl 3):iii17-iii25

<sup>53</sup> Halpern-Felsher and Roditis. (2015). Preliminary data collection on adolescents' initiation of e-cigarettes and flavored e-cigarettes.

<sup>54</sup> Chaffee BW, Couch ET, Essex G, Gansky SA, Cheng J, Kavanagh C, Murray J, Hill J, Glantz SA, Benowitz N, Walsh MM. Use of Flavored Tobacco Products Among High School Males in California, Preliminary Findings. NIH Tobacco Centers of Regulatory Science Grantee Meeting (poster). Bethesda, MD. November 2014.

<sup>55</sup> Ahijevych, K., Garrett, B. E. The Role of Menthol in Cigarettes as a Reinforcer of Smoking Behavior. *Nicotine & Tobacco Research*, 2010; 12(suppl 2), S110-S116. doi: 10.1093/ntr/ntq203

Belluzzi, J. D., Wang, R., Leslie, F. M. Acetaldehyde enhances acquisition of nicotine self administration in adolescent rats. *Neuropsychopharmacology*, 2005; 30(4), 705-712.

Rose, J. E. Nicotine and nonnicotine factors in cigarette addiction. *Psychopharmacology*, 2006; 184(3 4), 274-285.

it is important to take a step back and recognize the considerable information currently available that clearly shows 1) the active pursuit by the tobacco companies of young customers;<sup>56</sup> and 2) the use of flavoring and other strategies to lure youth to use these products.<sup>57</sup> Using flavors to attract youth to tobacco products is a well-documented tactic of the tobacco industry.

In a national web-based survey among older adult cigarette smokers (N=454), aged 45+ years, those who were also using flavored electronic cigarettes (n=44) vs. non-flavored electronic cigarettes (n=64) in the past 30 days were more likely to report “still using because it’s too hard to quit (45% vs. 18%; p=.05). The multivariate model was adjusted for age, gender, education, race/ethnicity, and total Fagerstrom Test for Nicotine Dependence score. The single-item is from the Hooked on Nicotine Checklist<sup>58</sup> in which each of the 10 items has face validity as an indicator of diminished autonomy (for tobacco).<sup>59</sup>

***While it will be useful to collect data on flavored e-cigarettes, the evidence to date indicates that the FDA should assume that the use of these flavors in e-cigarettes has similar effects as in cigarettes and prohibit their use until such time as there is strong and convincing evidence that flavors in e-cigarettes function differently than flavors in other tobacco products.***

#### **10. What unique abuse liability risks may exist for e-cigarette users in specific subpopulations (e.g., former smokers, youth, polytobacco users)?**

E-cigarettes represent a very specific type of abuse liability for youth in that youth may not just become addicted to e-cigarettes, they may also be more likely to start using conventional cigarettes as well. Recent studies show that e-cigarette use among adolescents represents a new form of childhood experimentation with nicotine. Adolescents who use e-cigarettes have higher intentions to smoke conventional cigarettes and are more susceptible to smoking conventional cigarettes in the next 2 years.<sup>60</sup>

This pattern is not limited to the US; adolescents are initiating nicotine exposure with e-

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<sup>56</sup> Ling, P. M., Glantz, S. A. Why and how the tobacco industry sells cigarettes to young adults: evidence from industry documents. *American Journal of Public Health* 2002; 92(6), 908-916.

<sup>57</sup> Kostygina, G., Glantz, S. A., Ling, P. M. Tobacco industry use of flavours to recruit new users of little cigars and cigarillos. *Tobacco Control* 2014, tobaccocontrol-2014-051830.; Kreslake, J. M., Wayne, G. F., Alpert, H. R., Koh, H. K., Connolly, G. N. Tobacco industry control of menthol in cigarettes and targeting of adolescents and young adults. *American Journal of Public Health*, 2008; 98(9), 1685; Ling, P. M., Glantz, S. A. Why and how the tobacco industry sells cigarettes to young adults: evidence from industry documents. *American Journal of Public Health*, 2002; 92(6), 908-916; Pollay, R. W. Targeting youth and concerned smokers: evidence from Canadian tobacco industry documents. *Tobacco Control*, 2000; 9(2), 136-147.

<sup>58</sup> Wellman RJ, DiFranza JR, Savageau JA, Godiwala S, Friedman K, Hazelton J. Measuring adults’ loss of autonomy over nicotine use: the Hooked on Nicotine Checklist. *Nicotine Tob Res.* 2005;7(1):157-161. doi:10.1080/14622200412331328394.

<sup>59</sup> Wang, J, Cataldo JK. (2014, November). Preliminary findings on flavored tobacco products and e-cigarette use in older adult cigarette smokers. Poster presentation at the Grantee Meeting of the NIH Tobacco Centers of Regulatory Sciences, Bethesda, Maryland).

<sup>60</sup> Moore, G. F., Littlecott, H. J., Moore, L., Ahmed, N., & Holliday, J. E-cigarette use and intentions to smoke among 10-11-year-old never-smokers in Wales. *Tobacco Control*, 2014 tobaccocontrol 2014-052011.

cigarettes on an international level.<sup>61</sup>

Adolescent e-cigarette users are more likely to be cigarette smokers. Among adolescent cigarette experimenters (smoked at least one puff), ever e-cigarette use was associated with higher odds of ever smoking cigarettes (smoked more than 100 cigarettes; odds ratio [OR] = 6.31; 95%CI, 5.39-7.39) and current cigarette smoking (OR = 5.96; 95%CI, 5.67-6.27), more likely to have progressed from experimenting with cigarettes to becoming established smokers, tend to be heavier cigarette smokers, and are less likely to have stopped smoking even though they are more likely to intend to quit smoking in the future.<sup>62</sup> This pattern is the opposite of what we would observe if e-cigarettes were discouraging cigarette smoking and increasing cigarette smoking cessation among youth.

While the precise fraction of youth who initiate nicotine use with e-cigarettes and go on to become cigarette smokers will not be known until longitudinal studies (which, because of their very nature, take time, often years) are completed, in order to comply with its mandate to protect public health the FDA should assume that a substantial fraction of youth who use e-cigarettes go on to use cigarettes for purposes of regulation of e-cigarette products and, more important, marketing.

***Even among youth who do not progress from e-cigarette use to cigarette use, increasing the number of youth using nicotine is itself a serious adverse public health outcome.***

#### **11. What is the impact of e-cigarette use on nicotine addiction (e.g., how may e-cigarette use increase, support or decrease nicotine addiction)?**

There are now 11 published studies<sup>63</sup> that compare quitting smoking among smokers who use e-cigarettes compared to smokers who do not use e-cigarettes (counting the two

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<sup>61</sup> Dutra, L. M., Glantz S.A. "High international electronic cigarette use among never smoker adolescents." *Journal of Adolescent Health* 2014; 55: 595-597.

<sup>62</sup> Dutra, L. M., Glantz S.A. "Electronic cigarettes and conventional cigarette use among US adolescents a cross-sectional study." *JAMA Pediatrics* 2014; 168(7): 610-617; Lee S, Grana R, Glantz SA. Electronic-cigarette use among Korean adolescents: Market penetration, dual use, and relationship to quit attempts and former smoking. *J. Adolesc. Health* Available online 22 November 2013 <http://dx.doi.org/10.1016/j.jadohealth.2013.11.003>

<sup>63</sup> Grana R, Popova L, Ling P. A longitudinal analysis of electronic cigarette use and smoking cessation. *JAMA Internal Medicine*. 2014;174(5):812-813; Adkison SE, O'Connor RJ, Bansal-Travers M, Hyland A, Borland R, Yong H, Cummings MK, McNeill A, Thrasher JF, Hammond D, Fong GT. Electronic Nicotine Delivery Systems: International Tobacco Control Four-Country Survey. *American Journal of Preventive Medicine*. 2013;44(3):207-215; Vickerman KA, Carpenter KM, Altman T, Nash CM, Zbikowski SM. Use of Electronic Cigarettes Among State Tobacco Cessation Quitline Callers. *Nicotine & Tobacco Research*. 2013;15(10):1787-1791; Choi K, Forster JL. Beliefs and experimentation with electronic cigarettes: a prospective analysis among young adults. *Am J Prev Med*. 2014;46(2):175-178; Choi K, Forster JL. Response to letter to the editor regarding "Beliefs and experimentation with electronic cigarettes: a prospective analysis among young adults". *Am J Prev Med*. 2014; 46(6):e58-9. doi: 10.1016/j.amepre.2014.02.013. Popova L, Ling PM. Alternative Tobacco Product Use and Smoking Cessation: A National Study. *American Journal of Public Health*. 2013;103(5):923-930; Borderud SP, Li Y, Burkhalter JE, Sheffer CE, Ostroff JS. Electronic cigarette use among patients with cancer: Characteristics of electronic cigarette users and their smoking cessation outcomes. *Cancer*. 2014;120(22):3527-3535; Brown J, Beard E, Kotz D, Michie S, West R. Real-world effectiveness of e-cigarettes when used to aid smoking cessation: a cross-sectional population study. *Addiction*. 2014;109(9):1531-1540; Biener L, Hargraves JL. A longitudinal study of electronic cigarette use among a

analyses Lois Biener<sup>64</sup> did, one for intense e-cigarette users and one for intermittent e-cigarette users, as separate estimates) as they are used in the real world.

In particular, there are three recent large longitudinal studies on adults that indicate that e-cigarette users, on average, are less likely to quit smoking. Using the 2010 Tobacco Use Supplement to the Current Population Survey (TUS-CPS), Shi et al<sup>65</sup> found that cigarette smokers who were using e-cigarettes for smoking cessation were less likely to be abstinent from smoking at follow-up than those who used pharmaceutical aids. Similarly, Pavlov et al<sup>66</sup> found that those who adopted e-cigarettes while enrolled in a primary care smoking cessation program (counseling and nicotine replacement therapy) were less likely to have quit three months later than those who never adopted e-cigarettes. McMillen and colleagues<sup>67</sup> found that adult never and former smokers were both susceptible to using e-cigarettes in the future, combatting the argument that never cigarette smokers are not using e-cigarettes.

These real-world population estimates of the effects of e-cigarette use on smoking cessation are more appropriate for assessing the impact of e-cigarettes on smoking behavior than randomized clinical trials<sup>68</sup> of e-cigarettes as a cessation device because e-cigarettes are being mass marketed as a consumer product not as medicine for smoking cessation. (If at some point, e-cigarette companies propose FDA approval of e-cigarettes as a therapeutic device the randomized trials will have more relevance, particularly if e-cigarettes are made available by prescription similar to a nicotine inhaler.)

Using all these estimates in a random effects meta-analysis (see figure below) shows a significant drop in quitting with an odds ratio of 0.723 (with a 95% confidence interval ["margin of error"] of 0.531 to 0.983). Thus, smokers who use e-cigarettes are about 30% less likely to quit smoking than smokers who do not use e-cigarettes.

The FDA should consider this overall effect on behavior among all smokers when assessing the likely population health impacts of e-cigarettes. ***It is likely that this substantial depression in quitting behavior will overwhelm any possible benefits of use as a***

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population-based sample of adult smokers: association with smoking cessation and motivation to quit. *Nicotine Tob Res.* 2015;17(2):127-133; Shi Y, Pierce J, White M, Wilson C, Conway K, Hartman A, Vijayaraghavan M, Messer K. E-Cigarette Use, Smoking Cessation and Change in Smoking Intensity in the 2010/2011 TUS-CPS Longitudinal Cohort. Abstract presented at Society for Research on Nicotine and Tobacco, Philadelphia, 2015; Pavlov D, Ivanova A, Hussain S, Selby P, Zawertailo L. Adoption of e-cigarettes during tobacco dependence treatment is associated with poorer quit outcomes. Abstract presented at Society for Research on Nicotine and Tobacco, Philadelphia, 2015.

<sup>64</sup> Biener L, Hargraves JL. A longitudinal study of electronic cigarette use among a population-based sample of adult smokers: association with smoking cessation and motivation to quit. *Nicotine Tob Res.* 2015;17(2):127-133.

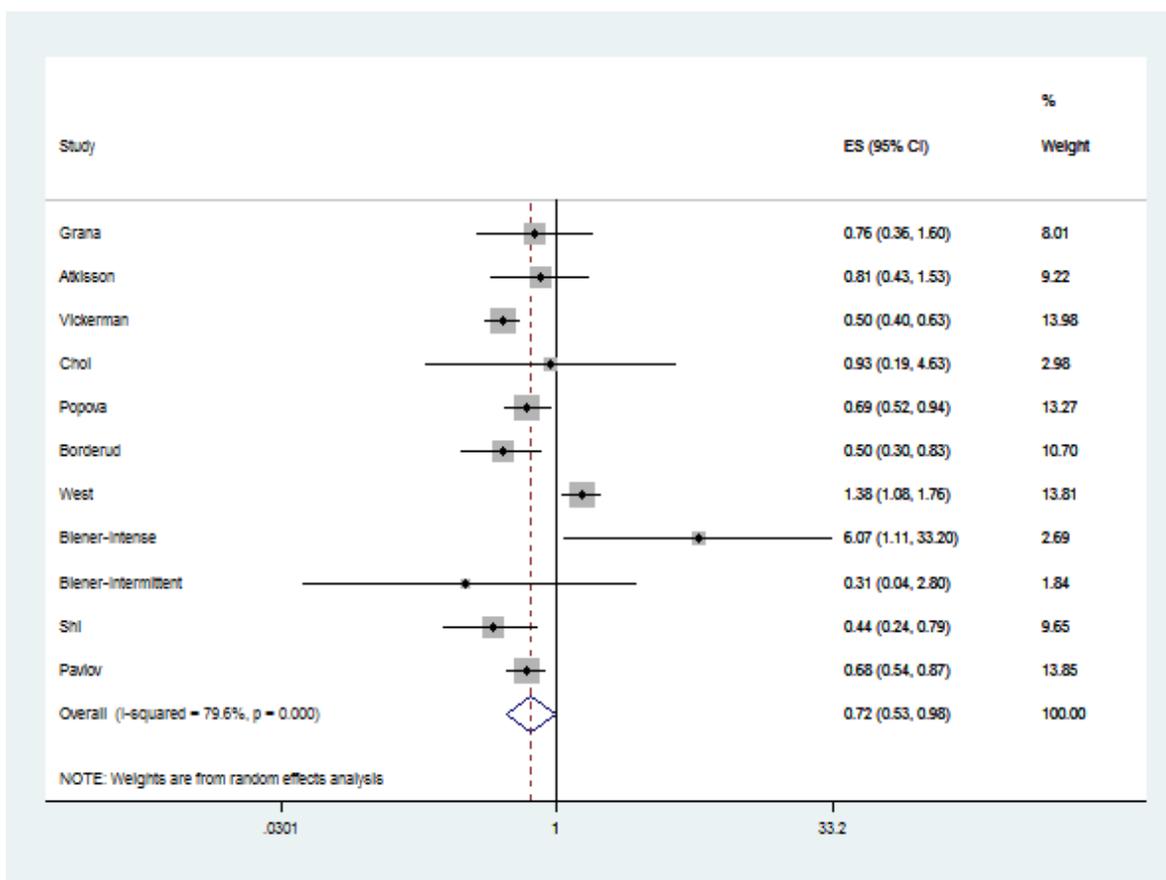
<sup>65</sup> Shi, Y., Pierce J, White M, Wilson C, Conway K, Hartman A, Vijayaraghavan M, Messer K. et al. E-cigarette use, smoking cessation and change in smoking intensity in the 2010/2011 TUS-CPS longitudinal cohort. 2015 Society for Research on Nicotine and Tobacco. Philadelphia, PA.

<sup>66</sup> Pavlov, D, Ivanova A, Hussain S, Selby P, Zawertailo L. Adoption of e-cigarettes during tobacco dependence treatment is associated with poorer quit outcomes. 2015 Society for Research on Nicotine and Tobacco. Philadelphia, PA.

<sup>67</sup> McMillen R Tanski S, Wilson K, Shaefer RM, Klein J, Winickoff J.. Susceptibility To Electronic Cigarette Use Among Current Nonsmoker. 2014 American Public Health Association. New Orleans, LA.

<sup>68</sup> Rahman MA, Hann N, Wilson A, Mnatzaganian G, Worrell-Carter L. E-cigarettes and smoking cessation: Evidence from a systematic review and meta-analysis. *PLoS One* 2015. doi:2-1371/journal.pone.0122544.

**cessation aid among some smokers or the fact that some smokers switch entirely from combusted cigarettes to e-cigarettes.**



**12. What strategies can be used to evaluate the potential for an e-cigarette withdrawal syndrome? What strategies can be used to characterize e-cigarette withdrawal?**

**13. What are the characteristics of e-cigarettes that may affect uptake and use by nonusers, former smokers, and youth?**

There are several characteristics of e-cigarettes that may affect uptake and use by nonusers, former smokers, and youth. The first characteristic is that e-cigarettes are viewed as classy or trendy, with youth talking about the fact that e-cigarettes have great hype, particularly in comparison to conventional cigarettes. Second, given that e-cigarettes come in so many flavors that are appealing to youth (e.g., fruit, dessert, mint, candy), it is likely that you will initiate e-cigarettes just to experience these flavors. Finally, adolescents perceive that e-cigarettes are less harmful than other tobacco products.

Adolescents and young adults believe that e-cigarettes are significantly less likely to result in social risks, compared to the other products. E-cigarettes are also believed to be less likely to result in health risks, followed by smokeless tobacco. E-cigarettes are also believed to be significantly less addictive than other tobacco products. Conversely, e-cigarettes were rated as the product most likely to help someone fit in and are rated just as likely as cigarettes and

cigars to make them look cool.<sup>69</sup> Finally, e-cigarettes are heavily marketed, with extensive advertisement online, through TV and other ads increasing dramatically in the last few years, and youth report seeing such ads for e-cigarettes.<sup>70</sup>

## **Health Effects in Users**

### **1. What are the known short and long-term health effects of e-cigarettes in experienced users? What are potential other short and long-term health effects of e-cigarettes in users that should be evaluated?**

There is an immediate reduction in pulmonary function following use of e-cigarettes.<sup>71</sup>

As described in the response to Toxicological Considerations Question 2, there is good reason to expect substantial adverse cardiovascular effects caused by e-cigarette use. The answer to that question is incorporated by reference as part of the answer to this question.

### **2. What are the potential short and long-term health effects of inhaling humectants (e.g., propylene glycol, glycerin), flavorings and other e-liquid additives?**

The use of propylene glycol (with or without glycerin) as the liquid base for e-cigarettes and related “vaping” products causes an additional layer of both confusion and potential toxicity. Propylene glycol is approved by the FDA for ingestion (eating) in food. This fact is widely promoted to e-cigarette users and leads to the general impression that the propylene glycol component of the aerosol is harmless. However, propylene glycol is not harmless when inhaled.<sup>72</sup> According to the Dow Chemical Company’s Safety Data Sheet<sup>73</sup> for propylene glycol, “mist may cause irritation of upper respiratory tract (nose and throat).”

The American Chemistry Council<sup>74</sup> has also warned of potential respiratory and eye irritation resulting from propylene glycol exposure. Chronic exposure to propylene glycol can also cause depression of the central nervous system.<sup>75</sup>

The popular but inaccurate characterization of e-cigarette aerosol as “vapor” creates confusion even at this level, as Dow’s safety sheet mentions that “at room temperature, exposure to vapor is minimal due to low volatility.” That is, the gas that would form from evaporation of propylene glycol does not present a problem at room temperature because very

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<sup>69</sup> Halpern-Felsher, B., Roditis, M.L., Cash, D. (2015) Adolescents Perceive Significantly Less Risks but Similar Benefits in E-cigarettes vs Cigarettes. Presented at the Society for Research on Nicotine and Tobacco (SRNT) annual conference.

<sup>70</sup> Bar, S., Roditis, M. L., & Halpern-Felsher, B. A Look into 9th and 12th Graders' Access to Electronic Cigarettes. *Journal of Adolescent Health* 2015; 56 (2), S30-S31. (Presentation at the Society for Adolescent Health and Medicine Annual Conference.

<sup>71</sup> 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.

<sup>72</sup> Grana, R., Benowitz, N.L., Glantz, S.A. E-cigarettes: a scientific review. *Circulation* 2014; 129(19): 1972-1986.

<sup>73</sup> The Dow Chemical Company (2013). Propylene Glycol USP/EP. [Safety Data Sheet](#). Issue date 3/25/2013, print date 2/27/2014, section 11 regarding toxicological information.

<sup>74</sup> The American Chemistry Council. Propylene glycol: considerations against use in theatrical fogs. July 2001. <http://www.lyondellbasell.com/techlit/techlit/2280.pdf>. Accessed November 21, 2013.

<sup>75</sup> Sciencelab.com, Inc. Material Data Safety Sheet: Propylene Glycol. Updated May 21, 2013. Sciencelab.com, Inc., Houston, TX.

little has evaporated; but theoretically if it did evaporate into a gas, and practically as it is actively delivered to the airway via aerosolization, propylene glycol presents potential hazards to respiratory health regardless of what other chemicals might accompany it.

Although some of the flavors used in e-cigarettes have been deemed Generally Recognized As Safe (GRAS) when ingested (eaten) the Flavor and Extract Manufacturers Association has emphasized that this designation only applies to the use of these flavors in food and stated that claims that flavors used in e-cigarettes are FEMA GRAS are misleading.<sup>76</sup>

***FDA regulation and warning labels are necessary to educate the public about the presence of potentially harmful ingredients in e-cigarettes in addition to nicotine.***

### **3. What strategies can be used to evaluate the short and long-term health effects of e-cigarettes in users?**

In addition to animal and human testing and epidemiology, mathematical models have the potential to inform regulatory decision making. Indeed, only such models can be used to predict future effects of the expansion of the e-cigarette market.

Any such model, however, by necessity, includes assumptions about the structure of the changes that will take place as well as the many parameters that are embedded in any model. These assumptions are often implicit and, given the complexity of some models, hard to locate and assess.

Philip Morris International has published the theoretical framework for a Markov model to assess the health impacts of modified risk tobacco products (MRTP),<sup>77</sup> which would include e-cigarettes. Their model reasonably relates the risks of a new product to cigarettes on a 0 to 100% scale and accounts for transitions between non-use, cigarette use, MRTP use, and quitting. The use of a Markov model, if structured appropriately and based on reliable inputs, is also a reasonable approach.

There are, however, several serious problems with the PMI model which make it inappropriate for assessment of the long-term population impact of e-cigarette use:

- Most important, it does not, however, account for dual use of e-cigarettes and cigarettes, which is the most common use pattern and which has substantial health impacts.
- The PMI model also does not explicitly model changes in use patterns (youth initiation, depressed quitting cigarettes) which can be more important than the relative toxicity of the product itself.
- The PMI model also only considers morbidity not mortality effects and ignores premature deaths over age 75.

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<sup>76</sup> Flavor and Extract Manufacturers Association. *Safety Assessment and Regulatory Authority to Use Flavors: Focus on E-cigarettes*. Retrieved 8 Apr 2015 from <https://www.femaflavor.org/safety-assessment-and-regulatory-authority-use-flavors-focus-e-cigarettes>.

<sup>77</sup> Weitkunat R, Lee PN, Baker G, Sponsiello-Wang Z, Gonzalez-Zuloeta Ladd AM, Ludicke F. A novel approach to assess the population health impact of introducing a Modified Risk Tobacco Product. *Regul Toxicol Pharmacol* 2015;72(1):87-93.

- While a potential advantage of the PMI model is that it allows modeling of how the health impact of a MRTP evolves over time for different age groups and genders, but doing so requires making hundreds, if not thousands, of assumptions about precisely how risks evolve over time.
- PMI suggests using risk estimates prepared by industry consultant Peter N. Lee, who has a long history of producing low estimates of health effects of smoking and secondhand smoke.<sup>78</sup>

While the detail in models like the one PMI proposed is appealing, in practice there is rarely the data necessary to reliably estimate all or even most of the parameters in the model, while creates the opportunity to manipulate the results through selection of the assumed parameters.

This example illustrates several important principles that the FDA should follow when evaluating any mathematical model used in risk assessment:

- The model should be as simple as possible.
- The model should explicitly account for changes in the use patterns of all relevant products, including effects on starting, stopping, and dual use.
- The health risk numbers should be based on broad consensus estimates, such as those in Surgeon General Reports or produced by authoritative bodies like the California Environmental Protection Agency.
- Where health risks are not known, a wide range of possible risks should be considered.

***Regulatory decision making based on models should follow a health-protective approach, where risks to susceptible subgroups are considered and, in the face of uncertainty, the highest plausible risks should be used. The FDA should follow the scientifically peer-reviewed policies developed by the California Environmental Protection Agency (described in detail under Toxicological Issues, Question 5 and incorporated here by reference) should be used to deal with these uncertainties.***

#### **4. What biomarkers and clinical endpoints can be used to assess the impact of e-cigarettes on user health?**

There is an immediate reduction in pulmonary function following use of e-cigarettes.<sup>79</sup>

As noted above, studies of the acute cardiovascular and respiratory effects of active e-cigarette users, will be informative because these changes occur much faster than changes associated with cancer. In addition, the risk profile of e-cigarette aerosol is likely to be higher for

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<sup>78</sup> Hong MK, Bero LA. How the tobacco industry responded to an influential study of the health effects of secondhand smoke. *BMJ* 2002;325(7377):1413-6 (PMC 1124865); Yano E. Japanese spousal smoking study revisited: how a tobacco industry funded paper reached erroneous conclusions. *Tob Control* 2005;14(4):227-33; discussion 33-5 (PMC 1748079).

<sup>79</sup> 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.

cardiovascular and non-cancer pulmonary effects than for cancer because e-cigarettes do not burn tobacco and so produce lower levels of carcinogens than conventional cigarettes.

Myocardial infarction in middle age and older adults is a well-established health risk of smoking. Myocardial infarction is associated with endothelial dysfunction, inflammation, oxidative stress, abnormal sympathetic neural signaling and increased coagulation of the blood. Studies that analyze biomarkers of all five of these five contributing domains will provide the best and most complete assessment of the acute cardiovascular risks of e-cigarettes. UCSF TCORS Project 5 is currently testing the response of these mechanisms to e-cigarette use, in human subjects.

Flow-mediated dilation is a noninvasive test that is the gold standard for measuring changes in endothelial function. Impaired flow-mediated dilation of the brachial artery predicts risk of myocardial dysfunction.<sup>80</sup> If we find that e-cigarette impairs endothelial function, flow-mediated dilation may become an important biomarker for testing the health effects of e-cigarettes. In evaluating inflammation, it is important to test markers of both mild, acute phase inflammation (like interleukin 6, IL-6) and more severe acute phase inflammation (like tumor necrosis factor alpha, TNF- $\alpha$ ).

Another area in which there are likely to be adverse health effects is oral health. Tobacco, in many forms, has well-characterized deleterious effects on the tissues of the oral cavity, notably as a major independent risk factor for oral cancer - the eighth most common cause of cancer deaths worldwide.<sup>81</sup> However, tobacco also has been implicated in multiple non-neoplastic oral conditions, including oral mucosal lesions and periodontal breakdown in users of smokeless tobacco (even recognized by tobacco industry consultants)<sup>82</sup> and impaired postoperative wound healing among smokers.<sup>83</sup> Nicotine stomatitis, a form of hyperkeratosis of the hard palate associated with salivary gland inflammation and salivary duct metaplasia, is caused by exposure to heat and smoke among pipe and cigar users.<sup>84</sup> It is unknown whether prolonged direct contact with the heated aerosol from electronic cigarettes has the potential to induce oral tissue changes. The possible impact of nicotine, flavorants, or other aerosol constituents delivered to the oral cavity by electronic cigarettes has not been explored. There is a pressing need for further research, including both basic laboratory science and epidemiologic investigations to characterize the distribution of oral conditions among electronic cigarette users.

## **5. What evidence is available that e-cigarettes promote current smokers to completely switching as compared to continuing dual or polytobacco use? What data are**

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<sup>80</sup> Yeboah J, Folsom AR, Burke GL, Johnson C, Polak JF, Post W, Lima JA, Crouse JR, Herrington DM. Predictive value of brachial flow-mediated dilation for incident cardiovascular events in a population-based study: the multi-ethnic study of atherosclerosis. *Circulation* 2009;120(6):502-9.

<sup>81</sup> Johnson NW, Jayasekara P, Amarasinghe AA. Squamous cell carcinoma and precursor lesions of the oral cavity: epidemiology and aetiology. *Periodontol* 2000. 2011;57:19-37.

<sup>82</sup> Kallischnigg G, Weitkunat R, Lee PN. Systematic review of the relation between smokeless tobacco and non-neoplastic oral diseases in Europe and the United States. *BMC Oral Health*. 2008;8:13.

<sup>83</sup> Jones JK, Triplett RG. The relationship of cigarette smoking to impaired intraoral wound healing: a review of evidence and implications for patient care. *J Oral Maxillofac Surg*. 1992;50:237-40.; Trombelli L, Scabbia A. Healing response of gingival recession defects following guided tissue regeneration procedures in smokers and non-smokers. *J Clin Periodontol*. 1997;24:529-33.

<sup>84</sup> Regezi JA, Sciubba JJ, Jordan RCK. *Oral pathology: clinical pathologic considerations*, 4th ed. WB Saunders, Philadelphia. 2003:81-2.

**available that indicate the characteristics of e-cigarettes that may enhance the potential for complete switching and how do these characteristics compare to approved cessation aids?**

With regards to youth, there is concern that youth who would normally not use tobacco products may start using e-cigarettes and then move on to other tobacco products as well. For example, a recent study has found that, among middle school students who had used e-cigarettes, 51.2% initiated any tobacco use with e-cigarettes.<sup>85</sup> Additionally, a recent study assessing risk status and tobacco use suggest that e-cigarettes are being used by medium-risk adolescents, a group that traditionally would be considered less susceptible to tobacco product use. This same study saw reported rates of e-cigarette use alone of 17%, conventional cigarette use alone of 3% and dual use of 12%, suggesting high rates of dual use among adolescents.<sup>86</sup>

***Regarding youth e-cigarettes use, current evidence suggests that youth who use e-cigarettes are more likely to start using conventional cigarettes, with youth who use e-cigarettes having higher intentions to smoke conventional cigarettes and being more susceptible to smoking conventional cigarettes in the next 2 years.<sup>87</sup> These studies point to the idea that e-cigarettes may be the initiation point for youth to begin to use not just e-cigarettes, but conventional cigarettes and possibly other tobacco products as well.***

### **Considerations for Health Effects in Specific User Populations**

#### **1. What populations of users may be at lower or higher risk of adverse effects related to e-cigarette use?**

The populations known to be at highest risk of adverse health effects of traditional tobacco products are the old, the young, the unborn and those with pre-existing respiratory or cardiovascular disease. It is important to consider testing the health effects of e-cigarettes in some of these high risk populations. Clinical research with adult asthmatics who use e-cigarettes and older adults with mild cardiovascular disease may reveal health effects that are not apparent in healthy young adults.

#### **2. What factors could be considered in the evaluation of risk in vulnerable populations?**

#### **3. What are the health effects in dual users (i.e., users of e-cigarettes and traditional cigarettes or other combusted products)?**

#### **4. What unique issues could be considered in the evaluation of the short and long-term health effects in users of e-cigarettes in combination with traditional cigarettes, other combusted products, and smokeless tobacco?**

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<sup>85</sup> Krishnan-Sarin, S., Morean, M., Camenga, D., Cavallo, D. A., Kong, G. E-cigarette Use among High School and Middle School Adolescents in Connecticut. *Nicotine & Tobacco Research* 2014, doi: 10.1093/ntr/ntu243.

<sup>86</sup> Wills, T. A., Knight, R., Williams, R. J., Pagano, I., Sargent, J. D. Risk factors for exclusive e-cigarette use and dual e-cigarette use and tobacco use in adolescents. *Pediatrics*, 2015; 135(1), e43-e51.

<sup>87</sup> Moore, G. F., Littlecott, H. J., Moore, L., Ahmed, N., Holliday, J. E-cigarette use and intentions to smoke among 10-11-year-old never-smokers in Wales. *Tobacco Control* 2015 tobaccocontrol-2014-052011.

**5. What unique health effects may be of concern for users with underlying disease (e.g., chronic obstructive pulmonary disease, cardiovascular disease, diabetes mellitus, cancers, mental health disorders)?**

No comments.

**6. What unique health effects may be of concern in youth e-cigarette users?**

E-cigarette market penetration is higher among youth than adults<sup>88</sup>, including youth who have never smoked a cigarette and have low risk for initiating nicotine use with cigarettes. Thus, e-cigarettes are a pathway to initiate nicotine addiction among youth who would likely never smoke. In addition, e-cigarette use is associated with increased susceptibility to future cigarette smoking.<sup>89</sup>

E-cigarette use thus could have the effect of prolonging and expanding the nicotine addiction epidemic.

***FDA needs to give these issues, including the general ineffectiveness of youth access restrictions and the importance of marketing and promotion, in developing regulations to prevent youth use of e-cigarettes.***

**7. How can health risks associated with youth initiation and ongoing use be evaluated?**

There are a number of important ways that health risks associated with youth initiation and ongoing use should be evaluated, including longitudinal mixed methods studies incorporating both surveys and qualitative assessments and ecological momentary assessments of youth who use e-cigarettes. It is important to have studies that track youth before they begin initiation in order to assess what factors influence initiation. Additionally, along with use of e-cigarettes, such studies should also ask questions pertaining to use of other tobacco products as well.

The sudden arrival of electronic cigarettes into the global tobacco marketplace has been followed by a rapid rise in youth initiation.<sup>90</sup> Questions remain as to the precise extent to which youth initiation leads to long-term use of electronic cigarettes, dual-use with other tobacco products, or initiation of cigarette smoking among individuals who would not have been drawn to tobacco otherwise. Epidemiologic studies are well suited to address such questions. However, it is crucial such studies take age, period, and cohort effects into account. Age effects occur when age is strongly related to outcome or exposure: e.g., 12th-graders are more likely to smoke cigarettes than 8th-graders. Period effects occur when time is a key determinant of overall exposure or outcome occurrence: e.g., electronic cigarettes were not widely available in 2010

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<sup>88</sup> Grana, R., Benowitz, N.L., Glantz, S.A. E-cigarettes: a scientific review. *Circulation* 2014; 129(19): 1972-1986.

<sup>89</sup> Moore, G. F., Littlecott, H. J., Moore, L., Ahmed, N., & Holliday, J. E-cigarette use and intentions to smoke among 10-11-year-old never-smokers in Wales. *Tobacco Control*, 2014 tobaccocontrol 2014-052011.

<sup>90</sup> Arrazola RA, Neff LJ, Kennedy SM, Holder-Hayes E, Jones CD; Centers for Disease Control and Prevention (CDC). Tobacco use among middle and high school students--United States, 2013. *MMWR Morb Mortal Wkly Rep.* 2014;63:1021-6.; Camenga DR, Delmerico J, Kong G, Cavallo D, Hyland A, Cummings KM, Krishnan-Sarin S.. Trends in use of electronic nicotine delivery systems by adolescents. *Addict Behav.* 2014;39:338-40.

but are relatively easy to acquire in 2015. Finally, cohort effects are related to events at particular times that “carry forward” with each age group: e.g., the graduating high school class of 2015 will always be individuals that began high school just as electronic cigarettes were emerging, while each subsequent high school class represents a potentially different experience.

Therefore, any study to recruit individuals of different ages and/or over multiple years must adjust for time-related factors in the analysis. For example, it would be inappropriate to compare the first tobacco experiences of 12th-graders and 8th-graders, without accounting for the time period at which those experiences occurred. Likewise, if only a small fraction of college-age cigarette smokers were to report tobacco initiation with electronic cigarettes, this could merely reflect a low availability of electronic cigarettes when these individuals were in their mid-teens. Longitudinal epidemiologic studies have the capacity to answer critical questions regarding the long-term implications of electronic cigarette initiation among youth. In considering the evidence, the FDA must assess whether age, period, cohort effects have been taken into account appropriately.

Answering specific questions specific to the health risks associated with both youth initiation and ongoing use of e-cigarettes will require an exploration of both toxicant exposures and longitudinal investigations into the uptake of e-cigarettes among non-traditional cigarette smokers. Methods for collecting specimens (i.e., urine) from participants will need to be developed to account for the relatively short half-life of relevant toxicants. Furthermore, in order to avoid the cross-contamination of specimens from tobacco smoking, study participants will have to abstain from all smoking (e.g., cigars, traditional cigarettes and marijuana) for a set time prior to collection. Focusing studies on e-cigarette-only smokers (i.e., never tobacco smokers) will allow for the longitudinal investigation of the effect of these products on the uptake of traditional cigarette smoking (and/or marijuana smoking or “vaping”). Given that the uptake of e-cigarettes among youth has been skyrocketing along with the fact that adolescents may be more susceptible to the effects of nicotine, this should be a critical area for FDA.

In the meantime, in order to fulfill its mandate to protect the public health the FDA should not wait for definitive longitudinal studies – which will take years -- to be conducted. The available cross sectional studies show substantial use of e-cigarettes by youth, including many youth who have never smoked a cigarette.

While youth initiation of nicotine use is a serious public health problem regardless of the precise fraction of youth who initiate nicotine use with e-cigarettes, FDA should also base regulatory decisions on reasonable interpretations of the available cross-sectional studies and information linking e-cigarette use with susceptibility to future cigarette smoking.

The cost of nicotine and cigarette initiation is very high and must be prevented. In the meantime, e-cigarette use will continue to rise among youth, as well nicotine addiction.

**8. What are the short and long-term health effects of e-cigarette use during pregnancy? What is the impact of e-cigarette use during pregnancy on the pregnant woman and on the fetus?**

Nicotine use has well-documented adverse effects on fetal development.<sup>91</sup>

Despite these adverse effects, nicotine replacement therapy is warranted among pregnant women because smoking cigarettes exposes the developing fetus to a wide range of other toxins.<sup>92</sup> The risk profile of e-cigarettes, however, is different from FDA approved pharmaceuticals and, as noted above, e-cigarettes have not been approved by the FDA as a form of nicotine replacement therapy.

Until such time as there is affirmative evidence that nicotine from e-cigarettes does not have the same adverse effects as nicotine delivered from other tobacco products, the FDA should assume that e-cigarette use has similar adverse effects as other tobacco products that deliver nicotine.

Indeed, Philip Morris voluntarily includes the following warning on its *Mark Ten* e-cigarettes:

WARNING: This product is not a smoking cessation product and has not been tested as such. This product is intended for use by persons of legal age or older, and not by children, women who are pregnant or breast-feeding, or persons with or at risk of heart disease, high blood pressure, diabetes, or taking medicine for depression or asthma. Nicotine is addictive and habit forming, and it is very toxic by inhalation, in contact with the skin, or if swallowed. Nicotine can increase your heart rate and blood pressure and cause dizziness, nausea, and stomach pain. Inhalation of this product may aggravate existing respiratory conditions. Ingestion of the non-vaporized concentrated ingredients in the cartridges can be poisonous.

CA Proposition 65 Warning: This product contains nicotine, a chemical known to the state of California to cause birth defects or other reproductive harm.<sup>93</sup>

As Philip Morris notes, nicotine is on the California Proposition 65 list as a substance known to cause birth defects or reproductive harm.<sup>94</sup> The process of listing a chemical on the Proposition 65 list requires extensive research and independent scientific peer review.

***The FDA should treat nicotine as an established reproductive toxin.***

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<sup>91</sup> England LJ, Bunnell RE, Pechacek TF, Tong VT, McAfee TA. Nicotine and the Developing Human: A Neglected Element in the Electronic Cigarette Debate. *Am J Prev Med.* 2015 Mar 7. pii: S0749-3797(15)00035-5. doi: 10.1016/j.amepre.2015.01.015. [Epub ahead of print]

<sup>92</sup> Dempsey DA, Benowitz NL. Risks and benefits of nicotine to aid smoking cessation in pregnancy. *Drug Saf.* 2001;24(4):277-322.

<sup>93</sup> Philip Morris Mark Ten website. [https://www.markten.com/gconnect/login\\_input.action](https://www.markten.com/gconnect/login_input.action) (accessed 11 April 2015).

<sup>94</sup> California Environmental Protection Agency Office of Environmental Health Hazard Assessment. Proposition 65. <http://www.oehha.ca.gov/prop65.html> (accessed 11 April 2015).

## **8. How can the short and long-term effects of e-cigarette use during pregnancy be evaluated?**

To date, the FDA has directed little attention toward the potential health effects of e-cigarette use in non-users. This is a scientific and strategic mistake. Like combustible tobacco products, e-cigarettes release chemicals into the environment and expose non-users. The respirable particles, volatile organic compounds, metals and potentially toxic flavorants inhaled by the user are not all retained. Exhaled secondhand aerosol may pose a health risk to non-users. Research has shown that nicotine from e-cigarette aerosol can deposit and sorb onto surfaces.<sup>95</sup>

E-cigarettes also present a significant risk of spills and leaks that also release nicotine into the environment. Research has shown that nicotine spreads from skin and clothing into indoor environments through dermal contact and evaporation.

Sorbed nicotine can react with ambient oxidants to form 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and 1-(N-methyl-N-nitrosamino)-1-(3-pyridinyl)-4-butanal (NNA).<sup>96</sup>

NNK is a known carcinogen and NNA is a related, tobacco-specific nitrosamine. E-cigarette use will expose non-users to both NNK and NNA. This is an important part of the health effects of e-cigarette use.

### **Human Factors**

#### **1. What adverse events have been associated with e-cigarette use in users?**

The Center for Tobacco Products (CTP) discloses e-cigarette adverse events (AE) that have been reported to FDA on its CTP FOIA Electronic Reading Room website.<sup>97</sup> (As of April 3, 2015, FDA disclosed three separate collections of e-cigarette AE reports totaling 252 pages: the first collection (“Report 1”, 116 pages) covers AE reports dated June 22, 2009 through June 25, 2013;<sup>98</sup> the second collection (“Report 2”, 21 pages) covers AE reports dated June 25, 2013 through October 5, 2013;<sup>99</sup> and the third collection (“Report 3”, 114 pages) covers AE reports dated October 5, 2013 through March 12, 2014.<sup>100</sup>

It is likely that many more adverse events related to e-cigarette use have occurred than are documented in these three reports; as CTP notes in the introduction to Report 1, since AE

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<sup>95</sup> Goniewicz ML, Lee L. Electronic cigarettes are a source of thirdhand exposure to nicotine. *Nicotine Tob Res.* 2015; (2):256-8. doi: 10.1093/ntr/ntu152. Epub 2014 Aug 30.)

<sup>96</sup> Sleiman M, Gundel LA, Pankow JF, Jacob P 3rd, Singer BC, Destailats H., Formation of carcinogens indoors by surface-mediated reactions of nicotine with nitrous acid, leading to potential thirdhand smoke hazards. *Proc Natl Acad Sci U S A.* 2010;107(15):6576-81.)

<sup>97</sup><http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/AbouttheCenterforTobaccoProducts/ucm221165.htm>

<sup>98</sup><http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/AbouttheCenterforTobaccoProducts/UCM361437.pdf>

<sup>99</sup><http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/AbouttheCenterforTobaccoProducts/UCM379475.pdf>

<sup>100</sup><http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/AbouttheCenterforTobaccoProducts/UCM393323.pdf>

reports are submitted to CTP voluntarily, “[g]enerally only a small fraction of adverse events associated with any product is reported” (Report 1). Moreover, with the skyrocketing growth of e-cigarette use, it is likely that many more adverse events occurred in the year since the most recent AE report dated March 12, 2014.

In a study published in 2013, Chen summarized the 47 adverse event reports that had been filed with CTP between 2008 and early 2012,<sup>101</sup> and found that “8 of the 47 adverse events were serious health issues including hospitalizations due to congestive heart failure, hypotension, pneumonia, chest pain, and “possible infant death secondary to choking on e-cig cartridge.”

Since Chen’s report, many more serious adverse events (SAEs) have been documented. Four SAEs were reported in Report 1, including two deaths. Five SAE’s were reported in Report 2, including severe burns sustained by a 3-year-old boy whose clothing caught fire when he was strapped in a car seat because his mother’s e-cigarette exploded while recharging it, and hospitalizations for hearing loss, blood clots, blacking out, and pneumonia (Report 2). Five SAE’s were reported in Report 3, including injuries sustained by an e-cigarette user (a broken upper palate, cracked upper denture, and 1st and 2nd degree burns) when a fire erupted after a coil shorted, which then caused the battery to explode; an explosion and fire harming a person with home oxygen; and hospitalizations for a seizure, a severe allergic reaction, and a psychotic episode. (Report 3).

In addition to these reported SAEs, the most common AE complaints reported to CTP included respiratory problems, shortness of breath, and coughing and lung problems; chest pain and heart irregularities including unusually fast or slow heart rates, palpitations, and arrhythmias; throat constriction and allergies; flu symptoms, vomiting, and nausea; severe headaches; stomach pain, diarrhea, constipation, and bloating; eye and mouth irritations; and memory loss, anxiety, dizziness, confusion, and/or disorientation (Reports 1, 2, and 3) For example, attached is a spreadsheet that details the AEs disclosed in Report 1. Many of the AEs reported, especially those documented in Report 3, were submitted by individuals who did not themselves smoke e-cigarettes, but described health problems resulting from exposure to second-hand e-cigarette smoke from co-workers or family members (Report 3).

In addition to the AEs reported to FDA and disclosed on CTP’s website, nicotine poisonings and injuries from explosions and fires have been reported to poison control centers and in the national media. An April 2014 CDC study found a dramatic increase in e-cigarette related calls to poison centers.<sup>102</sup> Serious burns and injuries have resulted from explosions and fires, not all of which are reported in CTP’s posted AE reports.<sup>103</sup> Grana et al. describe

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<sup>101</sup> Chen, I.L. 2013. FDA Summary of Adverse Events on Electronic Cigarettes. *Nicotine & Tobacco Research*, 15, 615-616.

<sup>102</sup> Centers for Disease Control and Prevention. New CDC study finds dramatic increase in e-cigarette-related calls to poison centers, April 3, 2014. <http://www.cdc.gov/media/releases/2014/p0403-e-cigarette-poison.html>.

<sup>103</sup> CBS NEWS. Electronic Cigarette Explodes in Man’s Mouth, Causes Serious Injuries. February 16, 2012: Available from: [http://www.cbsnews.com/8301-504763\\_162-57379260-10391704/electronic-cigarette-explodes-in-mans-mouth-causes-serious-injuries](http://www.cbsnews.com/8301-504763_162-57379260-10391704/electronic-cigarette-explodes-in-mans-mouth-causes-serious-injuries); Strickland J. Woman Says E-Cigarette Exploded, Shot Flames 4 Feet across Living Room. WSB-TV [serial on the Internet]. 2013: Available from: <http://www.wsbtv.com/news/news/local/woman-says-e-cigarette-exploded-shot-flames-4-feet/nZkCX/>.

significant adverse events related to e-cigarettes in their Background Paper on E-cigarettes prepared for the World Health Organization.<sup>104</sup>

## **2. How are e-cigarette products modified by users and what are the inherent risks or consequences of the various modifications?**

Almost every design feature of e-cigarettes can be modified by users who are motivated to do so. YouTube videos demonstrate how to re-fill disposable cartridges that were designed for single use or how to build coils in clearomizers that were not designed to be modifiable. Rebuildable atomizers (RBAs) are highly modifiable. Users are able to experiment with multiple coils. While most RBAs are designed for 1 or 2 coils, users have found ways to add 3 or 4 coils to RBAs. The use of various metals in coils is also gaining popularity. One such metal is pure nickel, a low resistance wire.

Easy modification against product design highlights the challenges involved in regulating e-cigarettes as well as present potential risks. Re-use of disposable cartridges introduces the possibility of exposure to oxidized contaminants from worn out coils. Modification of coils, low resistance wires, and higher number of coils in devices can lead to battery explosion and user injuries.

## **3. What strategies can be used to mitigate risks related to human factors?**

FDA needs to integrate e-cigarettes into its national educational campaign that message on the risks of e-cigarettes. There is good evidence that such large scale messaging campaigns can significantly impact adolescent initiation; for example, the Florida Tobacco Control Program's "truth" campaign that featured commercials and countermarketing strategies describing the tobacco industry's purposeful marketing to teens of cigarettes alongside information regarding the addictive and harmful nature of cigarettes was associated with a decrease in youth smoking rates.<sup>105</sup>

In March 2015 the California Department of Health Services initiated an evidence-based mass media educational campaign on e-cigarettes.<sup>106</sup> The FDA should integrate similar messaging and themes into its public education efforts.

Such strategies (specifically strategies that describe the role of the tobacco industry while also discussing the harmful and addictive nature of these products) should be expanded to e-cigarettes as well as, it is important to note, messaging on the risks of conventional cigarettes without messaging on risks related to e-cigarettes may be viewed by adolescents as implicitly condoning use of these products or meaning that there is no harm related to the use of these other products. This is particularly important in the case of e-cigarettes, which are heavily marketed via a number of media sites, including television commercials. For example, research

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<sup>104</sup> Grana R, Benowitz N, Glantz S. *Electronic Nicotine Delivery Systems*, prepared for the World Health Organization in December 2013. Available at <http://escholarship.org/uc/item/13p2b72n>.

<sup>105</sup> Farrelly, Davis, Haviland, Messeri, & Healton, Evidence of a Dose-Response Relationship between "truth" Antismoking Ads and Youth Smoking Prevalence *American Journal of Public Health*, 2005; 95(3), 425-431; Niederdeppe, Farrelly, & Haviland. Confirming "truth": More Evidence of a Successful Tobacco Countermarketing Campaign in Florida. *American Journal of Public Health* 2004, 94 (2), 255-257. Roditis, M., Cash D., and Halpern-Felsher B. (in prep). Adolescents Perceptions of Long and Short Term Risks and Benefits across Tobacco Products.

<sup>106</sup> <http://www.tobaccofreeca.com/> and <http://stillblowingsmoke.org/> (accessed 11 April 2015).

youth shows that between 2011 and 2013 there was a 256% increase in youth exposure to e-cigarette advertising on television.<sup>49, 103</sup>

#### **4. What information do consumers need to adequately understand the product and mitigate risk?**

In order to begin answering the question what information consumers need to adequately understand the product, the regulatory agency needs to establish what it means to “understand the product.” For example, it is not sufficient for a consumer to know that cigarettes cause mouth cancer but believe that that would not happen to them.

Chapman and Liberman’s 2005 paper<sup>107</sup> gives a good overview on what it means to have an “adequately informed” consumer. They created a useful typology of “being informed” with four levels:

Level 1: having heard that smoking increases health risks

Level 2: being aware that specific diseases are caused by smoking

Level 3: accurately appreciating the meaning, severity, and probabilities of developing tobacco related diseases

Level 4: personally accepting that the risks inherent in levels 1–3 apply to one’s own risk of contracting such diseases

The same levels can be applied to being informed about electronic cigarettes, with a few specific caveats.

Consumers should have **information about the contents** of the product. For e-cigarettes, this would be the contents of e-liquid, but also the components (e.g., what the heating element is made of, container, etc.).

Consumers should be informed about the **effects of these contents on the user**. In describing the potential effects of these components, it is not appropriate to use classifications designed for other methods of use, such as the standards established for food. For example, the Flavor and Extract Manufacturers Association of America (FEMA) issued a statement that it is inappropriate to use food standards for flavors (generally recognized as safe – GRAS) or occupational exposure limits (OELs) when examining the contents of e-cigarettes.<sup>108</sup> E-cigarette companies should not be allowed to use the GRAS or OELs standards when disclosing the contents of their products.

***In the absence of information about effects of e-cigarette contents and components on users, FDA should include the fact that no information is available about the health effects on humans of inhaling the ingredients used in e-cigarettes is presently available in its mass media public education campaign.***

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<sup>107</sup> Chapman S, Liberman J. Ensuring smokers are adequately informed: reflections on consumer rights, manufacturer responsibilities, and policy implications. *Tobacco Control*. 2005;14(suppl 2):ii8-ii13. doi: 10.1136/tc.2005.012591 [http://tobaccocontrol.bmj.com/content/14/suppl\\_2/ii8.full.pdf+html](http://tobaccocontrol.bmj.com/content/14/suppl_2/ii8.full.pdf+html).

<sup>108</sup> The Safety Assessment and Regulatory Authority to Use Flavors – Focus on E-Cigarettes, revised March 3, 2015, available at <https://www.femaflavor.org/safety-assessment-and-regulatory-authority-use-flavors-focus-e-cigarettes>.

***FDA should also require e-cigarette companies to prominently disclose this information in all advertising and marketing materials as well as on the product packaging itself.***

***Giving no information conveys the idea to the consumers that since there is no information disclosed, the products must be safe.***

When the information about the contents is presented, it should be presented in the absolute way, rather than in comparison to cigarettes.

Consumers should also be informed about **effects of these products on bystanders** (effects of second-hand and third-hand aerosol).

Chapman and Liberman conclude, “At the very least, we should be looking towards regulation that creates environments in which, as far as possible, smokers are adequately informed. This would entail ensuring that adequate information is actively communicated by manufacturers, the regulation of other communication likely to affect smokers’ understanding of the risks such as industry marketing and attractive packaging, and constructing environments in ways that do not dilute understanding of the products’ risks, such as regulating where products can be sold.”<sup>109</sup>

Consumers get information about products from a variety of sources: information in the media (including on social media), communication with friends and family, information on products themselves (such as brand and promotional materials on the package or warning labels), and advertising. Much of the information consumers get is actually misinformation. Advertisements explicitly or implicitly claim that using e-cigarettes will make consumers healthy, popular, and wealthy. ***And in communicating these claims tobacco companies are using appeals to emotions because they know they are more effective than simply listing statistical information or facts.***

An adequate informational campaign about a product should also contain elements of a countermarketing campaign, dismantling the claims industry makes about these products. To be more effective, this campaign should appeal to the same emotions product advertisements appeal to.

Another source of information about products is the place where the products are sold. If the products are sold in convenience stores next to candy or in pharmacies under “smoking cessation” title, that conveys an idea to the consumers that these products are as safe as other things sold in the same stores. When consumers see e-cigarettes sold in the “smoking cessation” section (like in this picture taken in Walgreens in Denver, CO in Aug 2014), they will believe that these products are cessation devices.

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<sup>109</sup> Chapman S, Liberman J. Ensuring smokers are adequately informed: reflections on consumer rights, manufacturer responsibilities, and policy implications. *Tobacco Control*. 2005;14(suppl 2):ii8-ii13. doi: 10.1136/tc.2005.012591 [http://tobaccocontrol.bmj.com/content/14/suppl\\_2/ii8.full.pdf+html](http://tobaccocontrol.bmj.com/content/14/suppl_2/ii8.full.pdf+html), p. ii11.



When establishing evidence for regulatory action concerning adequately informing the consumers, regulatory agencies should be careful not rely on industry's claims that consumers are already well-informed or overestimate risks of products. Tobacco and e-cigarette companies would argue that because in the studies measuring perceptions of risk of e-cigarettes many consumers rate them "equally as risky as cigarettes," consumers should instead be educated that e-cigarettes are safer. However, as we found in our study on perceptions of risk of snus among U.S. smokers,<sup>110</sup> perceptions of relative risk depend on the way questions are asked.

One way is to measure the relative risk directly, by asking a single question, such as "Compared to cigarettes, is smokeless tobacco less harmful, as harmful as, or more harmful?" Another way is to ask about perceived risk of cigarettes and smokeless tobacco separately. In a study, only 22.1% of the nationally representative sample of smokers said smokeless tobacco was less harmful than cigarettes when we used a single question, but 51.6% gave lower ratings of harm to smokeless tobacco when two separate questions were asked. Thus, assessing perceived relative harm with a single question dramatically underestimates actual understanding of perceived risks. Yet this approach is frequently used and in their petitions tobacco companies predominantly cite studies that use single question, thus likely underestimating the true

<sup>110</sup> Popova L, Ling PM. Perceptions of Relative Risk of Snus and Cigarettes Among US Smokers. *American Journal of Public Health* 2013;103: e21–e23. doi:10.2105/AJPH.2013.301547.

proportion of consumers who believe that smokeless tobacco is less harmful than cigarettes.<sup>111</sup>

***FDA should implement regulatory strategies for minimizing exposure of youth and nonsmoking adults to e-cigarette marketing and promotion***

As soon as FDA successfully achieves regulatory authority over e-cigarettes it should implement the policies suggested in the paper "Effectively Regulating E-Cigarettes and Their Advertising— and the First Amendment" by Eric Lindblom.<sup>112</sup> This paper notes that there are two possible justifications for allowing e-cigarettes on the market:

1. *They might help current smokers quit cigarettes.*
2. *They might be an effective harm reduction strategy for current smokers.*

It also notes that there are several ways in which e-cigarettes could result in increased harm:

3. *Kids who would not otherwise have smoked cigarettes start using e-cigarettes and become addicted to nicotine.*
4. *Former smokers take up e-cigarettes.*
5. *Former smokers relapse to smoking cigarettes again.*

While the first two points about the potential benefits of e-cigarettes are controversial, the last three are not. Indeed, the major challenge to e-cigarette enthusiasts is how to craft a policy/regulatory environment in which the possible benefits of e-cigarettes can occur without the collateral damage of promoting increased nicotine addiction in never or former smokers.

This article presents a sensible and practical solution: ***Limit e-cigarette advertising and promotion to highly targeted direct-to-consumer contact materials that only go to confirmed current smokers.***

- This is something that companies can do given their databases of current smokers.
- This highly focused advertising would get e-cigarette advertisements out of mass media (including the internet) and greatly reduce exposure to nonsmokers.
- This article carefully assesses the First Amendment issues and shows how the FDA could use its existing enforcement authority without any new rule-making.
- This approach would not only allow action much faster - years faster - than using rule-making, but it would also be easier to defend in court.

If it turns out that e-cigarettes do not help smokers quit, keep people smoking (which, at a population level, is their effect in studies to date<sup>113</sup> or that they turn out to be more dangerous

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<sup>111</sup> R.J. Reynolds. Citizen petition. 2011. Available at: <http://www.regulations.gov/#!documentDetail;D=FDA-2011-P-0573-0001>; Swedish Match MRTP application. 2014. Available at <http://www.regulations.gov/#!documentDetail;D=FDA-2014-N-1051-0003>.

<sup>112</sup> Lindblom E. Effectively Regulating E-Cigarettes and Their Advertising— and the First Amendment. *Food and Drug Law Journal* 2015; 70(1): 57-94; available at [http://www.law.georgetown.edu/oneillinstitute/news/documents/March10-LindblomFDLJ\\_001.pdf](http://www.law.georgetown.edu/oneillinstitute/news/documents/March10-LindblomFDLJ_001.pdf).

<sup>113</sup> Grana R, Benowitz N, Glantz SA. (2014). "E-cigarettes: a scientific review." *Circulation* 129(19): 1972-1986.

than the optimists think (i.e. if assumptions 1 and/or 2 turn out to be wrong), the FDA can adjust its rules. But the damage will only be done to current smokers, and the significant collateral damage listed in items 3, 4, and 5 will have been avoided.

## 6. What labeling strategies could be considered?

The following response draws on the June 2014 public comment by ML Roditis, BL Halpern-Felsher, LK Lempert, SA Glantz, L Popova, JK Cataldo, *FDA's Proposed Warning Statements Are Weak and Ineffective both in Form and Content and Should Be Replaced with Effective Messages* submitted to docket FDA-2014-N-0189.<sup>114</sup> That comment is integrated into this response by reference.)

The FDA should implement the following strategies when implementing warning labels for electronic cigarettes:

- 1) **Do not use the word “Warning.”** For textual warnings, the word “warning” serves as a signal (especially to smokers who are very familiar with them) to stop reading. It also takes up valuable space. Therefore, the textual label should just include the statement, without the word “Warning.”
- 2) **Use large warning labels** (at least 50% of surface area). Larger warning messages are more memorable and perceived as more impactful by both youth and adults.<sup>115</sup> Warnings that cover at least 50% of the surface area are recommended by the FCTC and are becoming the international standard.
- 3) **Do not exempt nicotine-free products from labeling.** Studies show that the stated and actual amount of nicotine in e-cigarettes varies greatly, with studies showing instances of e-cigarette products being labeled as zero nicotine and actually containing nicotine.<sup>116</sup>
- 4) **Switch warning labels and their placement frequently.** Warning labels are most effective when they are novel and their effectiveness diminishes with time.<sup>117</sup>
- 5) **Use graphic labels to attract attention and communicate better.** Studies consistently show superiority of graphic labels over text for attention, recall, and changes in attitudes, beliefs, and behavioral intentions.<sup>118</sup>

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<sup>114</sup> Available at <http://tobacco.ucsf.edu/sites/tobacco.ucsf.edu/files/u9/FDA-comment-warning%20label%20comments%20for%20proposed%20deeming%20rule%20part%201%20June%202012-1jy-8cmm-zjhq.pdf>.

<sup>115</sup> Hammond D, Fong GT, Borland R, Cummings KM, McNeill A, Driezen P. Text and graphic warnings on cigarette packages: findings from the international tobacco control four country study. *American Journal of Preventive Medicine*. 2007;32(3):202-9.

<sup>116</sup> Goniewicz ML, Kuma T, Gawron M, Knysak J, Kosmider L. Nicotine levels in electronic cigarettes. *Nicotine & Tobacco Research*. 2013;15(1):158-66.; Trehy ML, Ye W, Hadwiger ME, Moore TW, Allgire JF, Woodruff JT, Ahadi SS, B;acl KC & Westemberger 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.

<sup>117</sup> Hammond D. Health warning messages on tobacco products: a review. *Tobacco Control*. 2011;20:327-37.

<sup>118</sup> Hammond D. Health warning messages on tobacco products: a review. *Tobacco Control*. 2011;20:327-37.

6) **Counteract industry's claims.** In the absence of regulation, e-cigarettes are aggressively advertised as “harmless water vapor” and even beneficial to health.<sup>119</sup> To counteract these claims, warning labels could be used. For example:

- “Not harmless water vapor. Contains toxins and carcinogens”
- “Contains chemicals that cause cancer”
- This product can cause and maintain nicotine addiction
- This product irritates your lungs
- This product pollutes the air others breathe
- E-cigarettes have been known to explode
- Nicotine is a poison: Do not drink the liquid in this product
- Nicotine is a poison: Do not let the liquid touch your skin
- To prevent poisoning keep this product away from babies and children

7) **Encourage quitting.** Research on fear appeals shows that in order to be effective, threatening messages need to be coupled with efficacy-enhancing messages.<sup>120</sup> When depicting the dangers of using tobacco products (including e-cigarettes), it is essential to pair up the fear-inducing textual or graphic message with an efficacy enhancing component so that consumers will be able to do something to stay away from these products and feel capable of doing it.

Currently, **smokers are driven by hope** spurred by the anecdotal evidence that e-cigarettes help some smokers quit and the e-cigarette advertisements implicitly and explicitly promoting e-cigarettes as smoking devices. **Public health agencies need to harness this hope and encourage smokers to make a quit attempt** and to keep making them. One option is to use a label saying that “this product will not help you quit” or the current warning on Altria’s MarkTen (“This product is not a smoking cessation product and has not been tested as such”). Yet this might reduce smokers’ quitting self-efficacy.

***A better strategy would be to prominently display a quitline number along with the factual statement “Smokers who get help from the Quitline are twice as likely to quit for good.”***

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<sup>119</sup> Grana R, Ling PM. “Smoking Revolution”: A Content Analysis of Electronic Cigarette Retail Websites. *American Journal of Preventive Medicine*. 2014;46(4):395-403.

<sup>120</sup> Witte K. Fear as motivator, fear as inhibitor: Using the extended parallel process model to explain fear appeal successes and failures. In: Anderson PA, Guerrero LK, editors. *Handbook of communication and emotion: Research, theory, applications, and contexts*. San Diego, CA: Academic Press; 1998. p. 423-50; Witte K, Allen M. A meta-analysis of fear appeals: Implications for effective public health campaigns. *Health Education & Behavior*. 2000;27(5):591-615. doi: Doi 10.1177/109019810002700506; Ruiter RA, Kessels LT, Peters GJY, Kok G. Sixty years of fear appeal research: Current state of the evidence. *International journal of psychology*. 2014;49(2):63-70.