

Public Comment submitted to FDA on

**Nicotine Exposure Warnings and Child-Resistant Packaging for Liquid Nicotine, Nicotine-Containing E-Liquid(s), and Other Tobacco Products; Request for Comments**

Docket No. FDA-2015-N-1514

Submitted by

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California Poison Control System<sup>2</sup>

August 12, 2015

Background (from ANPRM): FDA intends to use the information submitted in response to this ANPRM to further inform its thinking about options for issuing potential regulations that would require nicotine exposure warnings and/or child-resistant packaging for some tobacco products, as articulated in this document. For the purposes of the questions in this ANPRM:

- “Liquid nicotine and nicotine-containing e-liquid(s) (liquid nicotine combined with colorings, flavorings, and/or potentially other ingredients)” are generally referred to as liquid nicotine.
- “Liquid nicotine” (as used throughout this document) refers to liquid nicotine that is made or derived from tobacco and intended for human consumption.
- “Novel tobacco products” (as used throughout this document) refers to products such as dissolvables, lotions, gels, and drinks

**A. Nicotine Exposure Warnings**

**1. Should FDA consider requiring nicotine exposure warning(s) text on liquid nicotine? If so, why?**

Yes.

Because liquid nicotine (which area solution that generally contain 1-2% nicotine in propylene glycol [PG], glycerol [vegetable glycerin, VG] or a mixture of the two) can be readily absorbed

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through intact skin, accidental exposures are considerably more hazardous for e-cigarettes than for conventional tobacco products. It is likely that the liquids pose a much greater ingestion hazard than conventional tobacco products as well, since nicotine in the liquids is likely to be absorbed much more rapidly than nicotine in a solid tobacco product. Large quantities of liquid nicotine can be purchased over the Internet, increasing the likelihood of serious accidental poisonings.

Calls to Poison Center in the U.S. have been increasing steadily since 2010, with calls per month increasing from one in September 2010 to 512 in February 2014.<sup>3</sup> Exposures were most commonly ingestions (68.9%), followed by inhalations (16.8%), eye exposures (8.5%) and skin exposures (5.9%). E-cigarette calls involves children age 5 or less (51.1%), with 42.0% calls from people > 20years. E-cigarette calls were more likely to report and adverse effect (57.6%) compared to cigarette ingestions (36.0%). The most common adverse effects were vomiting, nausea and eye irritation, with one suicide death from intravenous injection.

Given these findings, the FDA should require package inserts for liquid nicotine similar to those provided with prescription drugs that describe their hazards of liquid nicotine. Since the products in question are widely available, rather than prescription drugs intended for use under professional supervision, this information needs to be presented in a nontechnical way that all or almost all users can easily notice and understand, including use of graphics and simple language.

Warning labels should include the dermal absorption hazard, a statement that the amount of nicotine in e-liquids can be substantial and pose a serious risk, especially for small children, and that care should be taken to keep products out of the reach of children and pets.

Here are the relevant sections of the information from safety data sheets<sup>4</sup> required of chemical suppliers:

## 2.2 GHS [Globally Harmonized System] Label elements, including precautionary statements

Pictogram



Signal word Danger

Hazard statement(s)

H300 + H310

Fatal if swallowed or in contact with skin

H410

Very toxic to aquatic life with long lasting effects.

<sup>3</sup> Chatham-Stephens K, Law R, Taylor E, Melstrom P, Bunnell R, Wang B, Apelberg Bnad Schier J; Calls to Poison Centers for Exposures to Electronic Cigarettes – United States, September 2010 – February 2014: MMWR 63: 292-293, 2014; Vakkalanka J, Hardison L and Holstege C.; Epidemiological trends in electronic cigarette exposures reported to U.S. Poison Centers: Clinical Toxicology, 2014; Bartschat S, Mercer-Chalmers-Bender K, Beike J, Rothschild A and Jubner M; Not only smoking is deadly: fatal ingestion of e-juice – a case report. Int J Legal Med, 2014; Bassett R, Osterhoudt K and Brabazon T; Nicotine poisoning in an infant: NEJM 370; 23, 2014.

<sup>4</sup> Sigma-Aldrich Safety Data Sheet, (-)-Nicotine

<http://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&language=en&productNumber=N3876&brand=SIGMA&PageToGoToURL=%2Fsafety-center.html>

Precautionary statement(s)	
P262	Do not get in eyes, on skin, or on clothing.
P264	Wash skin thoroughly after handling.
P270	Do not eat, drink or smoke when using this product.
P273	Avoid release to the environment.
P280	Wear protective gloves/ protective clothing.
P301 + P310	IF SWALLOWED: Immediately call a POISON CENTER or doctor/physician.
P302 + P350	IF ON SKIN: Gently wash with plenty of soap and water.
P310	Immediately call a POISON CENTER or doctor/ physician.
P361	Remove/Take off immediately all contaminated clothing.
P363	Wash contaminated clothing before reuse.
P391	Collect spillage.
P405	Store locked up.
P501	Dispose of contents/ container to an approved waste disposal plant.

FDA should also collaborate with the Department of Transportation to ensure that appropriate packaging for a hazardous substance is being used when e-liquids are shipped.

**2. Should FDA consider requiring nicotine exposure warning(s) text on tobacco products other than liquid nicotine, including, but not limited to, novel tobacco products? If so, which products and why?**

These warnings should appear on all tobacco products that contain nicotine, not just liquid nicotine.

Children frequently ingest tobacco products. Cigarettes are most frequently ingested, followed by smokeless tobacco products.<sup>5</sup> As new tobacco products continue to proliferate, it is likely that children will increasingly ingest them as well, as is the case of the rapidly rising calls to poison control centers for e-cigarette poisoning. Most reports to poison control centers related to ingestion of tobacco products by children involve very young children, particularly infants and toddlers less than 1 year old.<sup>6</sup> New tobacco products, especially flavored products, are appealing to children toddlers. These products include dissolvables and other smokeless tobacco products that may be appealing to children and youth and that may be alternatives to cigarette smoking among pregnant women.

Warnings about nicotine exposure on all tobacco products will educate parents, help protect children and pets from poisoning, and inform users about the products.

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<sup>5</sup> Novotny TE, Hardin SN, Hovda LR, Novotny DJ, McLean MK, Khan S. Tobacco and cigarette butt consumption in humans and animals. *Tobacco Control*. 2011;20(Suppl 1):i17-i20; Connolly GN, Richter P, Aleguas A, Jr., Pechacek TF, Stanfill SB, Alpert HR. Unintentional child poisonings through ingestion of conventional and novel tobacco products. *Pediatrics*. May 2010;125(5):896-899.

<sup>6</sup> Connolly GN, Richter P, Aleguas A, Jr., Pechacek TF, Stanfill SB, Alpert HR. Unintentional child poisonings through ingestion of conventional and novel tobacco products. *Pediatrics*. May 2010;125(5):896-899.

It is important to emphasize that children are not the only population who need and deserve protection from the nicotine exposure in e-cigarettes and other novel tobacco products. E-cigarette use is increasing among older adults, creating the need for nicotine warnings and protection against accidental nicotine exposure for all individuals to protect this group as well.

Among U.S. adults 45-64, ever use of e-cigarettes rose from 1.6% in 2010 to 12.2% in 2013, a net change of 542%. For adults 65+, ever use increased from 0.4% in 2010 to 4.8% in 2013, a net change of 167%. Current use of e-cigarettes showed similar increases for 45-64 year olds, 0.6% in 2010 to 5.5 % in 2013, more than an eight-fold increase.<sup>7</sup> During the same time, there was a nearly 20-fold increase in e-cig users among former smokers (0.3% to 5.4%).<sup>8</sup> A study of the prevalence of ever use, current use, and a newly created category of “established use” in a nationally representative web survey of current and former cigarette smokers and found that former smokers were 3.24 times more likely than daily smokers to be established users of e-cigarettes (95% CI=1.13, 9.30, p<0.05).<sup>9</sup>

Older adults are at risk for nicotine toxicity/poisoning because: 1) adults and older adults are increasingly using e-cigarettes,<sup>5</sup> 2) CDC poison center calls for nicotine poisoning have increased from 0.3 percent in September 2010 to 41.7 percent in February 2014, and 42% of those calls were from users greater than 20 years old<sup>10</sup> and 3) the disposition and pharmacodynamic responsiveness to nicotine changes with age.<sup>11,12</sup> General changes in absorption, distribution, and elimination of drugs are consistent with known physiologic changes in the aging population (e.g., reduced liver mass and liver blood flow).<sup>10</sup> Nicotine is a high hepatic extraction drug and about 80% of nicotine clearance is accounted for by metabolic clearance, with oxidation of nicotine to cotinine as the quantitatively major metabolic pathway.<sup>13</sup> As a consequence of the age-related reduction of hepatic blood flow, there is a reduced non-renal clearance of nicotine and body composition might affect the volume of distribution because nicotine is primarily distributed in lean body tissue.<sup>14</sup>

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<sup>7</sup> McMillen RC, Gottlieb MA, Whitmore Shaefer RM, et al. Trends in Electronic Cigarette Use Among U.S. Adults: Use is Increasing in Both Smokers and Nonsmokers. *Nicotine Tob Res.* 2014; ntu213.

<sup>8</sup> Blackwell DL, Lucas JW, Clarke TC. Summary health statistics for US adults: National Health Interview survey, 2012. Vital and health statistics. Series 10, Data from the National Health Survey. 2014(260):1-161; Molander L, Hansson A, Lunell E. Pharmacokinetics of nicotine in healthy elderly people. *Clin Pharmacol Ther.* Jan 2001;69(1):57-65.

<sup>9</sup> Giovenco DP, Lewis MJ, Delnevo CD. Factors associated with e-cigarette use: a national population survey of current and former smokers. *Am J Prev Med.* 2014;47(4):476-480.

<sup>10</sup> Chatham-Stephens K, Law R, Taylor E, et al. Notes from the field: calls to poison centers for exposures to electronic cigarettes--United States, September 2010-February 2014. *MMWR Morb Mortal Wkly Rep.* 2014;63(13):292-293.

<sup>11</sup> Molander L, Hansson A, Lunell E. Pharmacokinetics of nicotine in healthy elderly people. *Clin Pharm Ther.* Jan 2001;69(1):57-65.

<sup>12</sup> Hämmerlein A, Derendorf H, Lowenthal DT. Pharmacokinetic and pharmacodynamic changes in the elderly. *Clin Pharm.* 1998;35(1):49-64.

<sup>13</sup> Benowitz NL, Jacob P. Individual differences in nicotine kinetics and metabolism in humans. *NIDA Res Monogr.* 1997;173(4864):13; Benowitz NL, Jacob P, Jones RT, Rosenberg J. Interindividual variability in the metabolism and cardiovascular effects of nicotine in man. *Journal of Pharmacology and Experimental Therapeutics.* 1982;221(2):368-372.

<sup>14</sup> Benowitz NL, Jacob P. Individual differences in nicotine kinetics and metabolism in humans. *NIDA Res Monogr.* 1997;173(4864):13; Benowitz NL, Jacob P, Jones RT, Rosenberg J. Interindividual variability in the metabolism

Warnings and protective packaging are essential, and attention needs to be paid to the readability and noticeability of the warnings, particularly for people whose eyesight is often limited. Large warnings with large and bold text as well as graphics are needed.

**3. On what basis (e.g., physical characteristics or appearance of the product or packaging, product risks, form of marketing, route of exposure, type of packaging) should FDA determine which products should be required to carry the warning(s)? What data or information would be helpful to demonstrate the need for a warning or warnings?**

All tobacco-related and/or nicotine-containing products should carry warning labels. Highest priority should be liquid products that have high nicotine content and that are flavored to smell/taste like candy or are packaged to look like candy, making them attractive to children. Liquids are important to focus on because nicotine is absorbed quickly and more completely in its liquid form than in tobacco. High priority should be placed on traditional tobacco products that contain high levels of nicotine (10 mg/gm or more) versus products (e.g., compressed nicotine tablets) with much lower levels of nicotine (1 mg).

In addition to liquids, which may pose the highest risk of poisonings, products that are chewed and can be consumed in their entirety such as dissolvables may also be a source of nicotine overdose and poisoning and should carry warning labels. High priority should also be placed on products that are likely to be used by women as substitutes for tobacco cigarettes during pregnancy due to the possible effects on the developing fetus and pregnant woman.

Products should be required to carry warning(s) regardless of the form of marketing, and whether sold over the internet or at local vape shops.

**4. If FDA were to require nicotine exposure warning(s) text for liquid nicotine, what issues should the warning(s) address and what wording should be used? Please consider: (a) Whether the warning(s) should be broad, or directed at specific dangers; (b) whether the warning(s) should specifically address oral, ocular, and dermal exposure dangers; (c) whether the warning(s) should focus exclusively on the risks to children and youth, or include the risks to vulnerable populations, such as pregnant women, adults with medical conditions, and pets; (d) whether the warning(s) should contain instructions to avoid the dangers altogether, such as “keep out of the reach of children”; (e) whether there are other dangers of liquid nicotine exposure that should be covered by the warning(s); and (f) whether information about what to do in the case of an accidental exposure to liquid nicotine should be included (e.g., when to seek medical attention, when to contact a Poison Control Center). Please submit data or evidence to support your position.**

All nicotine-containing products should carry warnings that are presented in a way that is understandable, highly visible, and salient to the user. Leaving warning labels off some nicotine-containing products conveys the information that the unlabeled product is safe. For example, in a

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and cardiovascular effects of nicotine in man. *Journal of Pharmacology and Experimental Therapeutics*. 1982;221(2):368-372.

qualitative study, “There was also a perception among parents that we live in a protective society; subsequently parental awareness of toxicity was strongly linked to the packaging of the product. Many parents were surprised to discover that products without warning labels or CRCs [child resistant containers] could be dangerous for children.”<sup>15</sup> (This study was conducted in Australia; similar perceptions are held by the American adults.<sup>16</sup>)

**(a) Whether the warning(s) should be broad, or directed at specific dangers; and (b) whether the warning(s) should specifically address oral, ocular, and dermal exposure dangers;**

Drawing on the evidence from cigarette warnings and World Health Organization recommendations, warnings should be specific rather than broad and generic,<sup>17</sup> and the warnings should also be specifically directed at certain health risks. Warnings that are overly broad will likely be dismissed by individuals who may be at risk. Broad messages such as “Keep out of reach of children” are necessary but not adequate. They are too generic and just tell parents and caregivers what to do without specifying why.

Further, messages should specifically address the danger when ingested or when they come in contact with skin or eyes. In addition to risks to children, risks to other vulnerable populations (e.g., older adults) should also be mentioned.

Moreover, aside from potential damage to oral, ocular, or other types of tissues from direct, accidental exposure (e.g., spills or ingestion), there is evidence to suggest damaging oral health effects from chronic exposure to the nicotine even when nicotine-containing products are used as intended. Tobacco smoking is the most critical modifiable risk factor in the development of periodontal (gum) disease,<sup>18</sup> of which mild to severe disease affects nearly half of all American adults.<sup>19</sup> Nicotine itself may contribute to the development and persistence of periodontal disease, separate from the potentially damaging effects of other toxicants found in tobacco smoke. This major impact of smoking on poor gum health has been mechanistically implicated to the nicotine contained in cigarette smoke.<sup>20</sup> Nicotine impairs the ability of human gingival fibroblasts to adhere to tooth root surfaces,<sup>21</sup> which is essential for inflamed periodontal tissues

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<sup>15</sup> Gibbs L, Waters E, Sherrard J, et al. Understanding parental motivators and barriers to uptake of child poison safety strategies: a qualitative study. *Injury Prevention*. 2005;11(6):373-377.

<sup>16</sup> Cataldo JK, Petersen AB, Hunter M, Wang J, Sheon N. E-cigarette Marketing and Older Smokers: Road to Renormalization. *American Journal of Health Behavior*. 2015;39(3):361-371.

<sup>17</sup> World Health Organization Framework Convention on Tobacco Control. Elaboration of guidelines for implementation of Article 11 of the Convention 2008.

<sup>18</sup> Johnson GK, Guthmiller JM. The impact of cigarette smoking on periodontal disease and treatment. *Periodontol* 2000. 2007;44:178-94.

<sup>19</sup> Eke PI, Dye BA, Wei L, et al. Update on Prevalence of Periodontitis in Adults in the United States: NHANES 2009 to 2012. *J Periodontol*. 2015;86(5):611-22.

<sup>20</sup> Wendell KJ, Stein SH. Regulation of cytokine production in human gingival fibroblasts following treatment with nicotine and lipopolysaccharide. *J Periodontol*. 2001;72(8):1038-44; Darby IB, Hodge PJ, Riggio MP, et al. Clinical and microbiological effect of scaling and root planing in smoker and non-smoker chronic and aggressive periodontitis patients. *J Clin Periodontol*. 2005;32(2):200-6.

<sup>21</sup> Tanur E, McQuade MJ, McPherson JC, Al-Hashimi IH, Rivera-Hidalgo F. Effects of nicotine on the strength of attachment of gingival fibroblasts to glass and non-diseased human root surfaces. *J Periodontol*. 2000;71(5):717-22.

to heal after therapy, and nicotine may suppress the cytodifferentiation and mineralization capacity of periodontal ligament cells.<sup>22</sup> Therefore, any nicotine-containing product has the potential to damage oral tissues, and the FDA should consider oral health related warnings for all nicotine-containing products.

Warnings on liquids should contain specific information, such as the concentration of nicotine in the liquid and the amount of liquid in commonly understood measures (like teaspoons) as well as in that the more technical measures (mL) that could poison or kill an infant.. For example - a recent estimate of the oral LD50 for nicotine is 6.5-13 mg/kg.<sup>23</sup> For a 15 kg child a potentially lethal dose is less than 100 mg. When the lethal dose is stated on the label, users of these liquids may take the warnings more seriously since they can visualize how much liquid constitutes a potentially lethal dose. Further, research shows that adolescents do not understand broad concepts such as “addiction”<sup>24</sup>), and other research<sup>25</sup> indicates that broad messages are not as effective as specific messages especially with youth, making it clear that warning messages need to be directed at specific dangers. Explaining the toxic effects of nicotine is more educational and effective. For example, it would be helpful to state: “wear gloves when handling liquid nicotine” or, more specifically, “wear protective gloves when refilling your e-cigarettes.” (See response to Question A1). Warnings should also address specific groups such as children (risk of poisoning), pregnant women (potential effects on the developing fetus), and people with risk of cardiovascular disease (effects of nicotine on heart rate variability), among other at-risk groups.

Given how new electronic cigarette products are, and how little information is available to the public regarding the health effects of e-cigarettes (and other newly emerging products) on people in general or vulnerable populations, it is critical to include as much information as possible.

At the same time, the FDA should be cognizant of the fact that if you provide too much information people will ignore it (for example full drug labels handed out with medications). For greatest impact need to select most important warnings and make them easy to see and digest. It is important that not all information is provided at once, and instead, the warnings rotate to provide absorbable amounts of information in each warning. A major concern with warning labels is message fatigue, and studies show that health warnings have their greatest impact shortly after implementation and decline in effectiveness over time.<sup>26</sup> The FDA should regularly update and refresh warning labels for maximum educational impact and to reflect the latest available information.

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<sup>22</sup> Yanagita M, Kojima Y, Kawahara T, Kajikawa T, Oohara H, Takedachi M, Yamada S, Murakami S. Suppressive effects of nicotine on the cytodifferentiation of murine periodontal ligament cells. *Oral Dis.* 2010;16(8):812-7.

<sup>13</sup> Roditis, M.L., Lee, J., & Halpern-Felsher, B. Adolescent (Mis)Perceptions about Nicotine Addiction: Results from a Mixed-Methods Study. *Health Education & Behavior.* In Press.

<sup>23</sup> Mayer B, How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self-experiments in the nineteenth century. *Arch Toxicol* 88: 5-7, 2014.

<sup>24</sup> Roditis, M.L., Lee, J., & Halpern-Felsher, B. Adolescent (Mis)Perceptions about Nicotine Addiction: Results from a Mixed-Methods Study. *Health Education & Behavior.* In Press.

<sup>25</sup> World Health Organization Framework Convention on Tobacco Control. Elaboration of guidelines for implementation of Article 11 of the Convention 2008.

<sup>26</sup> Hammond D. Health warning messages on tobacco products: A review. *Tobacco Control.* 2011;20(5):327-337.

Do not use “WARNING” in all messages. While the word “warning” can function as a signal word, it can also function as a “stop” word in which the individual reads the word “warning,” but nothing after it. It also takes up space, which is limited, thereby requiring the remaining information in the warning to be in smaller type.

We suggest the following warning statements for nicotine-containing products (related specifically to nicotine; this list does not include other items related to the consumption of tobacco products):

- This product can cause and maintain nicotine addiction
- Nicotine is a poison: Do not drink the liquid in this product
- Nicotine is a poison: Do not let the liquid touch your skin
- Nicotine is a poison, even in very small amounts.
- Nicotine is a poison: less than a teaspoon can kill you.
- To prevent poisoning keep this product away from babies and children and pets
- Wear gloves when handling liquid nicotine
- Wear protective gloves when refilling your e-cigarettes
- Pregnant women should not consume nicotine in any form due to its harmful effects on the developing fetus.

**(c) Whether the warning(s) should focus exclusively on the risks to children and youth, or include the risks to vulnerable populations, such as pregnant women, adults with medical conditions, and pets;**

Warnings should address risks to children and youth, but any warnings should not be exclusive to one subsection of the population, given that nicotine-containing products present substantial risks to numerous population groups. The FDA should develop warnings that are specifically be directed at children (risk of poisoning), as well as warnings that address risks to pregnant women (potential effects on the developing fetus), people with risk of cardiovascular disease (effects of nicotine on heart rate variability), and other at-risk groups, including pets. In fact, there is sufficient evidence to conclude that nicotine exposure increases the risk for other adverse health effects for all individuals, including otherwise healthy adults. Thus, the FDA should not restrict its warnings to only children and youth, which could lead some consumers to believe erroneously that nicotine-containing products pose risks only to children.

Along with other, more recent evidence, the FDA should consider the following conclusions from the 2014 Report of the U.S. Surgeon General<sup>27</sup> to guide the development of specific warning messages that address the findings of this report on nicotine:

1. The evidence is sufficient to infer that at high-enough doses nicotine has acute toxicity.
2. The evidence is sufficient to infer that nicotine activates multiple biological pathways through which smoking increases risk for disease.
3. The evidence is sufficient to infer that nicotine exposure during fetal development, a critical window for brain development, has lasting adverse consequences for brain development.
4. The evidence is sufficient to infer that nicotine adversely affects maternal and fetal health during pregnancy, contributing to multiple adverse outcomes such as preterm delivery and stillbirth.
5. The evidence is suggestive that nicotine exposure during adolescence, a critical window for brain development, may have lasting adverse consequences for brain development.
6. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to nicotine and risk for cancer.

**(d) Whether the warning(s) should contain instructions to avoid the dangers altogether, such as “keep out of the reach of children”;**

Drawing on the evidence from cigarette warnings and World Health Organization recommendations, warnings should be specific rather than broad and generic,<sup>28</sup> and the warnings should also be specifically directed at certain health risks. Warnings that are overly broad will likely be dismissed by individuals who may be at risk. Broad messages such as “Keep out of reach of children” are too generic. They tell parents and caregivers what to do without specifying why. Further, messages should specifically address the danger when ingested or when they come in contact with skin or eyes. In addition to risks to children, risks to other vulnerable populations (e.g., older adults) should also be mentioned.

The serious risk of acute toxicity from nicotine<sup>29</sup> adequately justifies instructions that children avoid any contact, ingestion, or handling of nicotine or nicotine-containing products. Any warning that contains instructions less clear or less strongly worded than “keep out of the reach of children” would falsely suggest that it is appropriate for children to handle nicotine.

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<sup>27</sup> U.S. Department of Health and Human Services. *The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.

<sup>28</sup> World Health Organization Framework Convention on Tobacco Control. Elaboration of guidelines for implementation of Article 11 of the Convention 2008.

<sup>29</sup> U.S. Department of Health and Human Services. *The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014

**e) Whether there are other dangers of liquid nicotine exposure that should be covered by the warning(s)**

The most serious acute poisonings have occurred with oral exposure, but there are also risks of ocular and dermal exposure to nicotine – all three exposures should be mentioned in warning labels. Including specific warning about symptoms of nicotine toxicity -- nausea, vomiting, sweating, palpitations, dizziness, loss of consciousness, seizures, respiratory arrest, and death – is important.<sup>30</sup>

A 2015 report in *Tobacco Control*<sup>31</sup> noted that e-cigarette users often combine different flavored e-cigarette that they presume to be nicotine free. Labels should be on all products that contain nicotine and warn that if the product is ingested, it could cause addiction, poisoning and/or death.

**(f) whether information about what to do in the case of an accidental exposure to liquid nicotine should be included (e.g., when to seek medical attention, when to contact a Poison Control Center).**

Based on qualitative research conducted at UCSF parents sometimes first call vape shops for advice on what to do when their child ingests liquid nicotine. This is inappropriate and dangerous, since vape shops' interest is in selling their products rather than promoting public health. E-cigarettes are often promoted by sellers as having only “harmless water vapor,” yet studies show that the aerosol delivered by these products includes toxic chemicals.<sup>32</sup> Moreover, phone calls to poison control regarding nicotine poisoning or nicotine exposure to the skin have increased dramatically since these products have emerged on the market.<sup>33</sup> Including specific warning about symptoms of nicotine toxicity -- nausea, vomiting, sweating, palpitations, dizziness, loss of consciousness, seizures, respiratory arrest, and death – is important as well as instructions on what to do in case of accidental exposure, either through skin or ingestion, including calling the local Poison Control Center.

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<sup>30</sup> Chatham-Stephens K, Law R, Taylor E, Melstrom P, Bunnell R, Wang B, Apelberg Bnad Schier J; Calls to Poison Centers for Exposures to Electronic Cigarettes – United States, September 2010 – February 2014. *MMWR* 63: 292-293, 2014; Vakkalanka J, Hardison L and Holstege C.; Epidemiological trends in electronic cigarette exposures reported to U.S. Poison Centers: *Clinical Toxicology*, 2014; Bartschat S, Mercer-Chalmers-Bender K, Beike J, Rothschild A and Jubner M; Not only smoking is deadly: fatal ingestion of e-juice – a case report. *Int J Legal Med* 2014; Bassett R, Osterhoudt K and Brabazon T; Nicotine poisoning in an infant: *NEJM* 370; 23, 2014.

<sup>31</sup> Davis, B., A. Razo, E. Nothnagel, M. Chen, and P. Talbot. 2015 Jul 27. pii: tobaccocontrol-2015-052468. doi: 10.1136/tobaccocontrol-2015-052468. [Epub ahead of print] Unexpected nicotine in Do-it-Yourself electronic cigarette flavourings: *Tob Control*. 2015 Jul 27. pii: tobaccocontrol-2015-052468. doi: 10.1136/tobaccocontrol-2015-052468. [Epub ahead of print]

<sup>32</sup> Grana R, Benowitz N, Glantz SA. E-cigarettes a scientific review. *Circulation*. 2014;129(19):1972-1986. Goniewicz ML, Knysak J, Gawron M, Kosmider L, Sobczak A, Kurek J, et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tobacco Control*. 2013. Chatham-Stephens K, Law R, Taylor E, Melstrom P, Bunnell R, Wang B, et al. Notes from the field: Calls to poison centers for exposures to electronic cigarettes—united states, september 2010–february 2014. *MMWR Morbidity and Mortality Weekly Report*. 2014;63(13):292-293.

<sup>33</sup> Chatham-Stephens K, Law R, Taylor E, Melstrom P, Bunnell R, Wang B, et al. Notes from the field: Calls to poison centers for exposures to electronic cigarettes—United States, September 2010–February 2014. *MMWR Morbidity and Mortality Weekly Report*. 2014;63(13):292-293.

**5. With preceding question 4 in mind, should there be multiple textual warnings that randomly display to convey different dangers, or should there be a single, consistent textual warning that covers all of the different dangers? Please submit data or evidence to support your position.**

As stated in response to Question A4, the warnings should contain a variety of information; however, including a lengthy warning also means that parents and other people are not likely to read it in its entirety. Short rotating warnings would be more effective. It is well-established that warning labels on cigarettes “wear off” over time if not changed<sup>34</sup> and people stop noticing them. To ensure effective communication with users and the general public, multiple and changing warnings are necessary.

In addition to warning labels on the outside of bottles and other packages, there should be inserts that list all major hazards and precautions. Based on our answer to Question A1, these inserts should include the following information:

**2.2 GHS Label elements, including precautionary statements**

Pictogram



Signal word Danger

Hazard statement(s):

Can be fatal if swallowed or in contact with skin

Very toxic to aquatic life with long lasting effects.

Precautionary statement(s):

Do not get in eyes, on skin, or on clothing.

Wash skin thoroughly after handling.

Do not eat, drink or smoke when transferring this product.

Avoid release to the environment.\*

Wear protective gloves

Wear protective clothing if handling large quantities\*

IF SWALLOWED: Immediately call a POISON CENTER or doctor/physician.

IF ON SKIN: Gently wash with plenty of soap and water.

Immediately call a POISON CENTER or doctor/ physician.

Remove/Take off immediately all contaminated clothing.

Wash contaminated clothing before reuse.

Collect spillage.\*

Store locked up.\*

Dispose of contents/ container to an approved waste disposal plant.\*

\*Most appropriate for containers of large quantities handled by wholesalers and retailers, i.e. greater than the one ounce or so bottles generally sold to consumers.

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<sup>34</sup> Hammond D. Health warning messages on tobacco products: a review. *Tobacco Control*. 2011;20:327-337.

The FDA should require nicotine exposure warnings be placed on product packaging and that prominent, strong warnings be placed at the physical locations where nicotine-containing products are sold, including point-of-sales as well as on any websites of online retailers. Restricting warning messages to product packaging only would limit the reach of those warnings. Prominent warnings in retail locations have the potential to educate the public broadly and to inform consumers' decision-making before they have committed to purchasing a nicotine-containing product. Prominent point-of-sale anti-smoking warnings in Australia have been associated with smokers' interest in quitting and future quit attempts.<sup>35</sup> In New York City, implementation of point-of-sale signs with graphic health warnings greatly increased awareness of smoking-related health risks and increased smokers' quitting contemplation.<sup>36</sup> In implementing new exposure warnings related to nicotine-containing products, the FDA should not limit the placement of such warnings to the products or their packaging alone.

**6. If FDA were to require nicotine exposure warning(s) text for tobacco products other than liquid nicotine, including, but not limited to, novel tobacco products, what issues should the warning(s) address and what wording should be used? Please consider: (a) Whether the warning(s) should be broad, or directed at specific dangers; (b) whether the warning(s) should specifically address oral, ocular, and dermal exposure dangers; (c) whether the warning(s) should focus exclusively on the risks to children and youth, or include the risks to vulnerable populations, such as pregnant women, adults with medical conditions, and pets; (d) whether the warning(s) should contain instructions to avoid the dangers altogether, such as “keep out of the reach of children”; (e) whether there are other dangers of nicotine exposure that should be covered by the warning(s); and (f) whether information about what to do in the case of an accidental exposure to liquid nicotine should be included (e.g., when to seek medical attention, when to contact a Poison Control Center). Please submit data or evidence to support your position.**

All the same points made in answer to Question A4 apply here and are included by reference in this answer.

In addition, earlier studies conducted at UCSF qualitatively<sup>37</sup> and quantitatively<sup>38</sup> evaluated a print ad designed to discourage smokers from starting to use smokeless tobacco. The results of this research are relevant to the question FDA is posing here.

The two versions of the ad are below:

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<sup>35</sup> Li L, Borland R, Yong HH, Hitchman SC, Wakefield MA, Kasza KA, Fong GT. The association between exposure to point-of-sale anti-smoking warnings and smokers' interest in quitting and quit attempts: findings from the International Tobacco Control Four Country Survey. *Addiction*. 2012;107(2):425-33.

<sup>36</sup> Coady MH, Chan CA, Auer K, Farley SM, Kilgore EA, Kansagra SM. Awareness and impact of New York City's graphic point-of-sale tobacco health warning signs. *Tob Control*. 2013;22(e1):e51-6.

<sup>37</sup> Popova L, Kostygina G, Sheon NM, Ling PM. A qualitative study of smokers' responses to messages discouraging dual tobacco product use. *Health Education Research*. 2014:cyt150.

<sup>38</sup> Popova L, Neilands TB, Ling PM. Testing messages to reduce smokers' openness to using novel smokeless tobacco products. *Tob Control*. Jul 2014;23(4):313-321.

**Are you or a family member using smokeless or “dissolvable” tobacco?**

**Keep this Poison Control Hotline number in your phone: 1-800-222-1222**



Nicotine is poison. Children 6-24 months old who put a cigarette butt, snus or dissolvable smokeless product in their mouths will require immediate medical attention.

Snus look like candy in a wrapper. Dissolvables look like mints. So if you have smokeless in the house, keep these toxics in a childproof container, out of reach.

And be ready to call the Poison Control Hotline.

**Smokeless.  
Risky for you.  
Poison for them.**

**Do YOU or a family member use  
smokeless or “dissolvable” tobacco?**



**Keep this Poison Control number  
in your phone: 1-800-222-1222.**

Nicotine is poison. Toddlers who put a cigarette butt, snus or dissolvable smokeless product in their mouths need immediate medical attention. Snus look like candy in a wrapper. Dissolvables look like mints. Always keep these toxic products out of kids' reach. And be ready to call Poison Control.

**SMOKELESS TOBACCO.**

Risky for you. Poison for them.

A message from your Public Health Department

Our qualitative research found that participants evaluated this ad as effective:

“Wow the one with the baby is impactful”

“Great ad. No matter what you think of tobacco, keep it away from kids!”

“Seeing a young child reaching for the dish is enough to make me read the whole advertisement”

“Educational”

“It makes sense!”

“As a parent I would be less likely to even try the product out of fear of my child getting a hold of it”

“This ad does not offend; it is helpful and I believe it”

For some, the idea that children can get poisoned by a smokeless tobacco product was new:

“I didn't think of chew as a poison”

“Never thought about young children putting snus in their mouths”

As we wrote in our paper reporting these results,<sup>39</sup> those who tried smokeless tobacco before tended to discount this ad as an anti-tobacco ad, saying that it is strictly for parents who have little children and does not deter smokers from using the products:

Interviewer: “Do you think this would make someone less likely to take up smokeless tobacco?”

“No, I just think that it will make them more aware of securing the tobacco out of the reach of children”

“No because it is not aimed at the dangers to the person using it. Does underage drinking stop adults from doing it?”

“I think not, just make them be more careful about it.”

Although one person said, “I would think twice before ever bringing smokeless product inside my home after seeing this ad. It worked for me!”

In our quantitative study with a nationally representative sample of current and recently former smokers,<sup>40</sup> this advertisement (the color version) significantly increased perceptions of harm of snus from 4.73 at pretest to 5.00 at posttest ( $p < .01$ ) measured with the question “In your opinion, how harmful are new smokeless tobacco products, such as snus, to general health?” on a 9-point scale with 1 – not at all harmful and 9 – extremely harmful.

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<sup>39</sup> Popova L, Kostygina G, Sheon NM, Ling PM. A qualitative study of smokers' responses to messages discouraging dual tobacco product use. *Health Education Research*. 2014;cyt150.

<sup>40</sup> Popova L, Neilands TB, Ling PM. Testing messages to reduce smokers' openness to using novel smokeless tobacco products. *Tob Control*. Jul 2014;23(4):313-321.

This research indicates that warning labels could use statements informing that “Nicotine is poison,” urging to “Always keep these toxic products out of kids’ reach” and to “Keep the poison control number in your phone: 1-800-222-1222.” These statements peak parents’ attention and broadly raise perceptions of harm of these products.

**7. With preceding question 6 in mind, please respond to the following questions: Should there be multiple textual warnings that randomly display to convey different dangers, or should there be a single, consistent textual warning that covers all of the different dangers? Should different types of tobacco products carry different warnings? If so, which type(s) of tobacco products should carry what warning(s) and what is the reasoning for different warnings for different types of tobacco products? Please submit data or evidence to support your position.**

As noted above, there should be warnings on all nicotine-containing products.

There should be no comparative risk warnings, such as “This product is a safer alternative to cigarettes.” “Safer” is understood as “safe.” We conducted a study with a national US sample of non-users of tobacco, smokers, and dual users, exposing them to advertisements for moist snuff, snus, and e-cigarettes with different warning labels. The data from non-users of tobacco have been published in *BMC Public Health*.<sup>41</sup> In brief, we found that the comparative warning label (“WARNING: No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes”):

- 1) significantly lowered perceptions of harm of moist snuff among non-users of tobacco
- 2) significantly lowered perceptions of harm of snus among exclusive smokers
- 3) significantly increased positive attitudes towards moist snuff among dual users

Warnings should be based on the harms of each product rather than comparative (lower or higher) harms.

The FDA should require that nicotine exposure warnings be placed on product packaging, and that prominent, strong warnings be placed at the physical locations where nicotine-containing products are sold, including point-of-sales as well as the websites of online retailers. Restricting warning messages only to product packaging would limit the reach of those warnings. Prominent warnings in retail locations have the potential to educate the public broadly and to inform consumers’ decision-making before they have committed to purchasing a nicotine-containing product. Prominent point-of-sale anti-smoking warnings in Australia have been associated with smokers’ interest in quitting and future quit attempts.<sup>42</sup> In New York City, implementation of point-of-sale signs with graphic health warnings greatly increased awareness of smoking-related

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<sup>41</sup> Popova L, Ling PM. Nonsmokers' responses to new warning labels on smokeless tobacco and electronic cigarettes: an experimental study. *BMC Public Health*. 2014;14(1):997.

<sup>42</sup> Li L, Borland R, Yong HH, Hitchman SC, Wakefield MA, Kasza KA, Fong GT. The association between exposure to point-of-sale anti-smoking warnings and smokers' interest in quitting and quit attempts: findings from the International Tobacco Control Four Country Survey. *Addiction*. 2012;107(2):425-33.

health risks and increased smokers' quitting contemplation.<sup>43</sup> In implementing new exposure warnings related to nicotine-containing products, the FDA should not limit the placement of such warnings to the products or their packaging alone.

**8. If FDA were to require nicotine exposure warning(s) text for liquid nicotine, should FDA consider requiring color(s) or graphic elements, such as symbols, as part of the warning(s)? If so, what color or graphic elements should FDA consider? (a) Are there data on graphic elements and/or colors that would be most effective in communicating the dangers associated with nicotine exposure? If so, please provide these data. (b) Would a graphic element alone (as opposed to text alone or any combination of text, color, or graphic elements) be sufficient to effectively communicate the dangers associated with nicotine exposure? Please provide data or evidence to support your position. (c) How could the warning(s) text and graphic image(s) add to or detract from each other?**

FDA should require nicotine exposure warnings for *all* tobacco products, including liquid nicotine and novel products, and should require color and graphic elements in addition to text in all nicotine exposure warnings.

Graphic elements such as pictures and imagery may be more effective than text-only messages at communicating health risks of tobacco products.<sup>44</sup> Studies have found that users and non-users rate warnings with graphic images as more effective than text-only warnings.<sup>45</sup> A 2015 meta-analysis of experiments and international literature examining the impact of pictorial cigarette pack warnings found that pictorial warnings are more effective than text-only warnings. (see The WHO Framework Convention on Tobacco Control (FCTC)<sup>46</sup> and the FCTC Article 11.<sup>47</sup>) In

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<sup>43</sup> Coady MH, Chan CA, Auer K, Farley SM, Kilgore EA, Kansagra SM. Awareness and impact of New York City's graphic point-of-sale tobacco health warning signs. *Tob Control*. 2013;22(e1):e51-6.

<sup>44</sup> Noar SM, Hall MG, Francis DB, Ribisl KM, Pepper JK, Brewer NT. Pictorial Cigarette Pack Warnings: A Meta-Analysis of Experimental Studies. *Tob Control* 2015; ;0:1–14. doi:10.1136/tobaccocontrol-2014-051978; Fong G, Hammond D, Hitchman S. The Impact of Pictures on the Effectiveness of Tobacco Warnings. *Bull World Health Organ* 2009; 87:640-3.

<sup>45</sup> Noar SM, Hall MG, Francis DB, Ribisl KM, Pepper JK, Brewer NT. Pictorial Cigarette Pack Warnings: A Meta-Analysis of Experimental Studies. *Tob Control* 2015;0:1–14. doi:10.1136/tobaccocontrol-2014-051978; Cameron, LD, Pepper, JK, Brewer, NT. Responses of young adults to graphic warning labels for cigarette packages. *Tob Control* 2015; 24(e1):e14-22; O'Hegarty M, Pederson LL, Nelson DE, *et al*. Reactions of young adult smokers to warning labels on cigarette packages. *Am J Prev Med* 2006; 30:467–73; O'Hegarty M, Pederson LL, Nelson DE, *et al*. Reactions of young adult smokers to warning labels on cigarette packages. *Am J Prev Med* 2006;30:467–73; Bansal-Travers M, Hammond D, Smith P, *et al*. The impact of cigarette pack design, descriptors, and warning labels on risk perception in the US. *Am J Prev Med* 2011; 40:674–82; Kees J, Burton S, Andrews JC, *et al*. Tests of graphic visuals and cigarette package warning combinations: implications for the framework convention on tobacco control. *J Public Policy Marketing* 2006; 25:212–23; Pepper JK, Cameron LD, Reiter PL, *et al*. Non-smoking male adolescents' reactions to cigarette warnings. *PLoS ONE* 2013; 8:e65533.

<sup>46</sup> World Health Organization. *WHO Framework Convention on Tobacco Control*. Geneva, Switzerland. 2003.

<sup>47</sup> World Health Organization. *Guidelines for implementation of Article 11 of the WHO Framework Convention on Tobacco Control (Packaging and labeling of tobacco products)* 2009; Noar SM, Hall MG, Francis DB, Ribisl KM, Pepper JK, Brewer NT. Pictorial Cigarette Pack Warnings: A Meta-Analysis of Experimental Studies. *Tob Control* 2015;0:1–14. doi:10.1136/tobaccocontrol-2014-051978.

particular, compared with text-only warnings, pictorial warnings attracted and held attention better.<sup>48</sup>

The tobacco companies' extensive research on colors provides information that is useful for designing nicotine exposure warning labels that would adequately attract and hold consumers' attention. In the 1950s, psychologist and marketing pioneer Louis Cheskin used scientific testing to analyze the nature, psychological aspects, and impact of color on consumers and explained how color could be used to design effective packaging,<sup>49</sup> and Philip Morris hired Cheskin and his Color Research Institute (CRI) to help redesign its Marlboro pack.<sup>50</sup> When designing nicotine exposure warnings, FDA should choose colors that are known to the tobacco companies to make packages more visually prominent and salient.<sup>51</sup> Additionally studies show that a black border directs individuals' eyes to text, so including such a border would also improve the warning messages.<sup>52</sup>

Tobacco industry documents show that black and red are also visually prominent.<sup>53</sup>

Based on the tobacco companies' research, black text on a light background provides better contrast than white text on a dark background,<sup>54</sup> so color schemes using black text on a white background or white text on a black background are not as effective.<sup>55</sup>

Based on the tobacco companies' research cited above, ***FDA should require nicotine exposure warnings to use a color scheme of black text on a bright yellow background.***

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<sup>48</sup> Noar SM, Hall MG, Francis DB, Ribisl KM, Pepper JK, Brewer NT. Pictorial Cigarette Pack Warnings: A Meta-Analysis of Experimental Studies. *Tob Control* 2015;0:1–14. doi:10.1136/tobaccocontrol-2014-051978; Nonnemaker J, Farrelly M, Kamyab K, *et al.* Experimental Study of Graphic Cigarette Warning Labels: Final Results Report. Prepared for Center for Tobacco Products, Food and Drug Administration. 2010.

<sup>49</sup> Cheskin L. *Color Guide for Marketing Media*. 1954. Brown & Williamson.  
<http://legacy.library.ucsf.edu/tid/yjb14f00>

<sup>50</sup> Marlboro - *The Pack the People Picked*. RJ Reynolds. <http://legacy.library.ucsf.edu/tid/joz51c00>. Wall Street Journal, Sept. 18, 1995. *Red Packages Lure Shoppers like Capes Flourished at Bulls -- Marlboro, Coca-Cola, Colgate Wear Most Popular Color On Global Market Shelves*. Philip Morris.  
<http://legacy.library.ucsf.edu/tid/kpn39h00>

<sup>51</sup> [No author] *Color Scheming*. 1990. Philip Morris. <http://legacy.library.ucsf.edu/tid/wkn86c00>; Wagner C. *Color Cues*. 1990. Philip Morris. <http://legacy.library.ucsf.edu/tid/xkn86c00>; Bockweg T, Chapple N, Cornell C, Swaim WF. *Color Documentation for Doral Packaging Colors*. 16 Jan. 2001. RJ Reynolds.  
<http://legacy.library.ucsf.edu/tid/hsu14j00>.

<sup>52</sup> Hammond D. Health warning messages on tobacco products: A review. *Tob Control* 2011; 20(5):327-337.

<sup>53</sup> Bockweg T, Chapple N, Cornell C, Swaim WF. *Color Documentation for Doral Packaging Colors*. 16 Jan. 2001. RJ Reynolds. <http://legacy.library.ucsf.edu/tid/hsu14j00>*et al.*, (2001); Miller L. Principles of Measurement of Visual Standout in Pack Design: Report No Rd 2039. 23 May. 1986. British American Tobacco.  
<http://legacy.library.ucsf.edu/tid/ihb34a99>; [No author] Product Communication. British American Tobacco.  
<http://legacy.library.ucsf.edu/tid/okz16a99>.

<sup>54</sup> Bockweg T, Chapple N, *et al.*, (2001) Bockweg T, Chapple N, Cornell C, Swaim WF. *Color Documentation for Doral Packaging Colors*. 16 Jan. 2001. RJ Reynolds. <http://legacy.library.ucsf.edu/tid/hsu14j00>

<sup>55</sup> [No author] *Color Scheming*. 1990. Philip Morris. <http://legacy.library.ucsf.edu/tid/wkn86c00>; Miller L. Principles of Measurement of Visual Standout in Pack Design: Report No Rd 2039. 23 May. 1986. British American Tobacco.

Further, the FDA should require nicotine warnings to have a black border, and tobacco companies should be prohibited from changing their packaging so that it blends in with the new bright yellow and black warning messages because studies show that warning messages that are visually distinct from the packaging of a product are more noticeable.<sup>56</sup>

See also answers to questions A1, A2, A3, A4, A5, A6, A7, and A12, which are integrated by reference into our answer to this question.

**9. If FDA were to require nicotine exposure warning(s) text for tobacco products other than liquid nicotine, including, but not limited to, novel tobacco products, should FDA consider requiring color(s) or graphic elements as part of the warning(s)? If so, what color or graphic elements should FDA consider? (a) Are there data on graphics and/or colors that would be most effective in communicating the dangers associated with nicotine exposure? If so, please provide these data. (b) Would a graphic image alone be sufficient to effectively communicate the dangers associated with nicotine exposure? Please provide data or evidence to support your position. (c) How could the warning(s) text and graphic image(s) add to or detract from each other? (d) Should different tobacco products carry different color or graphic elements? If so, what criteria should FDA use to determine which type of tobacco products should carry what color or graphic elements?**

See answers to questions A1, A3, A4, and A8.

**10. If FDA were to require a nicotine exposure warning(s) (text and any applicable color or graphic element) for liquid nicotine, should FDA adopt a different nicotine exposure warning(s) requirement based on the packaging/containers (e.g., a brief/abbreviated warning(s) for liquid nicotine in small packaging/containers, omit the warning(s) if the tobacco product is in a child-resistant package)? If so, how should the warning(s) differ? Please submit data or evidence to support your position.**

All packages should require prominent, easy-to-read and understand text and graphical warnings. If the nicotine container is small, it can be packaged attached to a larger piece of cardboard or other packaging that is large enough to communicate the warning effectively. Such packaging is common for small items (often to deter theft).

Warnings regarding nicotine poisoning should be fixed in color so as not to convey degrees of danger. The text should also be fixed.

Warning labels should not vary or be altered because of differences in packages or even stated differences in nicotine levels. For example, numerous studies show that there is a great deal of variation between the stated amount of nicotine in these products and the actual amount, with

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<sup>56</sup> Wogalter MS, Conzola VC, Smith-Jackson TL. Research-based guidelines for warning design and evaluation. *Applied Ergonomics* 2002; 33(3):219-230.

studies showing instances of e-cigarette products being labeled as zero nicotine and actually containing nicotine.<sup>57</sup>

Given the risk to children from the accidental ingestion of these products, the warnings should remain on the label even when the vial is child resistant since by definition, it is only resistant not child-proof and the dangers are significant.<sup>58</sup> There could be cases where child resistance fails.

A dog who ate an e-cigarette cartridge died as a result.<sup>59</sup> The Pet Poison Helpline has encountered a sharp uptick in calls concerning cases of nicotine poisoning in pets that ingested e-cigarettes or liquid nicotine refill solution. In six months in 2014, cases more than doubled, indicating that along with their increased popularity, e-cigarettes are becoming a more significant threat to pets. While dogs account for the majority of cases, nicotine in e-cigarettes and liquid refill solution is toxic to cats as well.<sup>60</sup>

**11. With respect to tobacco products other than liquid nicotine, including, but not limited to, novel tobacco products, if FDA were to require a nicotine exposure warning(s) (text and any applicable color or graphic element), should FDA adopt a different nicotine exposure warning(s) requirement based on the packaging/containers (e.g., a brief/abbreviated warning(s) for tobacco products in small packaging, omit the warning(s) if the tobacco product is in a child-resistant package)? If so, how should the warning(s) differ? Please submit data or evidence to support your position.**

No. The FDA should not allow a means for manufacturers of tobacco products to sidestep or minimize the size and prominence of warnings by manipulating the product packaging. Packages can be increased in size to accommodate effective warning labels.

**12. Are you aware of data or information that would support any required font sizes, formatting, and display considerations for nicotine exposure warnings (textual and/or graphic)? If so, please provide that evidence.**

The FDA should not limit any proposed warnings to text-only messages that are small in size. A systematic review of 94 qualitative and quantitative research studies concluded that small, text-

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<sup>57</sup>Goniewicz ML, Kuma T, Gawron M, Knysak J, Kosmider L. Nicotine levels in electronic cigarettes. *Nicotine & Tobacco Research*. 2013;15(1):158-166. Trehy ML, Ye W, Hadwiger ME, Moore TW, Allgire JF, Woodruff JT, et al. Analysis of electronic cigarette cartridges, refill solutions, and smoke for nicotine and nicotine related impurities. *Journal of Liquid Chromatography & Related Technologies*. 2011;34(14):1442-1458.

<sup>58</sup> Poisoning cases related to e-cigarettes keep spiraling upward. Campaign for Tobacco-Free Kids website. [http://www.tobaccofreekids.org/tobacco\\_unfiltered/post/2014\\_09\\_26\\_e-cig](http://www.tobaccofreekids.org/tobacco_unfiltered/post/2014_09_26_e-cig). Published September 26, 2014. Accessed November 9, 2014.

<sup>59</sup> Gander, K. "Dog dies after coming into contact with e-cigarette fluid." *The Independent*. <http://www.independent.co.uk/news/uk/home-news/dog-dies-after-coming-into-contact-with-ecigarette-9139535.html> Published February 19, 2014. Accessed August 12, 2015.

<sup>60</sup> <http://www.petpoisonhelpline.com/2014/09/e-cigarettes-pets-mix/>

only messages are less effective at conveying information to consumers than large warning with pictures.<sup>61</sup>

While we are not aware of work that examines nicotine exposure warnings directly, the general consensus is the bigger the warning the better, and visual elements are more impactful (visual salience, knowledge, and behavioral intentions) than text warnings.<sup>62</sup> There is also evidence that improved warning labels reduce health disparities.<sup>63</sup>

The University of Waterloo has conducted a number of studies on this topic, including research using the International Tobacco Control surveys to compare findings in the US, Canada, the UK, and Australia.<sup>64</sup> They found that larger warnings and rotating warnings were most effective. Graphic health warnings included in cigarette advertisements increase attention compared to text-only warnings.<sup>65</sup>

The Australian government has conducted research into plain packaging, and the resulting research reports are available online.<sup>66</sup> They report that dark olive is the preferred color for plain-packaged cigarettes because it was perceived as “being less appealing, containing cigarettes that were perceived to be more harmful to health, lower quality, and harder to quit.”<sup>67</sup> They also found that the font should be at least 14 point, and recommended the use of Lucida Sans. Larger front of pack graphic warnings were determined to be more effective because they were more noticeable, and they recommended that the graphic cover 75% of the pack front. Similar results were found for roll your own cigarettes, cigarillos, and premium cigars.<sup>68</sup>

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<sup>61</sup> Hammond D. Health warning messages on tobacco products: a review. *Tob Control*. 2011;20(5):327-37.

<sup>62</sup> Hammond D, Fong G, McDonald P, Cameron R, Brown K. Impact of the graphic Canadian warning labels on adult smoking behaviour. *Tob Control*. 2003; 12: 391 - 95. Borland R, Wilson N, Fong G, Hammond D, Cummings K, Yong H, et al. Impact of graphic and text warnings on cigarette packs: Findings from four countries over five years. *Tobacco Control*. 2009; 18: 358-64.

<sup>63</sup> Thrasher JF, Carpenter MJ, Andrews JO, Gray KM, Alberg AJ, Navarro A, et al. Cigarette warning label policy alternatives and smoking-related health disparities. *American Journal of Preventive Medicine*. 2012; 43: 590-600.

<sup>64</sup> <http://davidhammond.ca/projects/packaging-warnings/health-warnings-research/>. Hammond D. Health warning messages on tobacco products: a review. *Tobacco Control* 2011;20(5):327-337. Hammond D. Tobacco labelling and packaging toolkit: a guide to FCTC Article 11. Waterloo: University of Waterloo, Department of Health Studies 2009. Hammond D, Fong G, Borland R, et al. Text and Graphic Warnings on Cigarette Packages: Findings from the International Tobacco Control Four Country Study. *American Journal of Preventive Medicine* 2007;**32**(3):202-209. Hammond D, Fong G, McNeill A, et al. Effectiveness of cigarette warning labels in informing smokers about the risks of smoking: findings from the International Tobacco Control (ITC) Four Country Survey. *Tob Control* 2006;15 Suppl 3:iii19 - iii25.

<sup>65</sup> Klein EG, Shoben AB, Krygowski S, et al. Does Size Impact Attention and Recall of Graphic Health Warnings? *Tobacco Regulatory Science* 2015;**1**(2):175-185. Fong GT, Hammond D, Hitchman SC. The impact of pictures on the effectiveness of tobacco warnings. *Bulletin of the World Health Organization*. 2009; 87: 640-3.

<sup>66</sup> <http://www.health.gov.au/internet/main/publishing.nsf/Content/mr-plainpack>

<sup>67</sup> Parr V, Tan B, Eli P, Miller K. August 2011. Market research to determine effective plain packaging of tobacco products. Sydney, Australia: GfK Blue Moon. Available at <http://www.health.gov.au/internet/main/publishing.nsf/Content/mr-plainpack>

<sup>68</sup> Parr V, Tan B, Eli P. December 2011. Market research to determine impact of plain packaging on other tobacco products. Sydney, Australia: GfK Blue Moon. Available at <http://www.health.gov.au/internet/main/publishing.nsf/Content/mr-plainpack>

A study of legibility or reading speed of warning labels in the context of plain packaging concluded that, “Among experimenters and weekly smokers, plain packaging increases visual attention to health warnings and away from branding. Daily smokers, even relatively early in their smoking careers, seem to avoid the health warnings on cigarette packs. Adolescent never-smokers attend the health warnings preferentially on both types of packs, a finding which may reflect their decision not to smoke.”<sup>69</sup>

**13. Should FDA require the inclusion of the American Association of Poison Control Centers' telephone number on the container labeling and/or packaging of liquid nicotine and tobacco products other than liquid nicotine? Why or why not?**

Yes. The AAPC number will forward callers to local poison control centers.

**14. Are there any nicotine exposure warnings (textual and/or graphic) for liquid nicotine required by authorities at the local, State, or Federal (i.e., other agencies) level, or by foreign governments that you particularly would like to highlight? If so, which ones and why? Are there any data regarding the effectiveness or utility of these warnings? If so, please provide these data.**

California requires a warning about the reproductive risks of nicotine under its Proposition 65, but these warnings are not particularly effective. Businesses decide whether to place a warning label based upon their understanding of the chemicals in the product. Additionally, the manufacturer is not required to provide the California Office of Health Hazard Assessment with information about the products and the labels only indicate there's a chemical that might cause cancer or affect reproduction. There is no additional information for the consumer.

Guernsey (a Channel Island) tested a warning on nicotine products but it was not implemented.<sup>70</sup> Suffolk County, NY requires liquid nicotine warning notices posted at cash registers where the product is sold but labels are not required on bottles.<sup>71</sup> In 2014, Suffolk County proposed a bill that would have required the listing of ingredients for nicotine products. A few bills have been introduced by city and state legislative bodies around warning labels on products and Farmington Connecticut introduced a bill requiring child-proof containers for liquid nicotine.

**15. Are there any nicotine exposure warnings (textual and/or graphic) for tobacco products other than liquid nicotine required by authorities at the local, State, or Federal (i.e., other agencies) level, or by foreign governments that you particularly would like to highlight? If**

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<sup>69</sup> Maynard OM, Attwood A, O'Brien L, Brooks S, Hedge C, Leonards U, Munafò MR. Avoidance of cigarette pack health warnings among regular cigarette smokers. *Drug Alcohol Depend.* 2014 Mar 1;136:170-4. doi: 10.1016/j.drugalcdep.2014.01.001. Epub 2014 Jan 15.

<sup>70</sup> Guernsey 2011 Quitting - addiction, efficacy. 2011. Health Warning Labels.

Available at <http://www.publichealthwatchdog.com/new-yorks-suffolk-county-enacts-liquid-nicotine-warning/>

<sup>71</sup> Available at <http://longisland.news12.com/news/suffolk-lawmakers-propose-liquid-nicotine-ingredient-disclosure-requirement-at-retailers-1.9448414>. Available at <http://longisland.news12.com/news/suffolk-lawmakers-propose-liquid-nicotine-ingredient-disclosure-requirement-at-retailers-1.9448414>. Available at <http://connecticut.cbslocal.com/2014/08/19/warning-of-nicotine-poisoning-threat-from-e-cigarette-liquid/>

**so, which ones and why? Are there any data regarding the effectiveness or utility of these warnings? If so, please provide these data.**

See answer to question A4.

**16. Are you aware of any existing evidence regarding whether warnings(text and any applicable color or graphic element) are effective for mitigating the risks of nicotine exposure? If so, please provide that evidence.**

We do not know of any specific studies on this point, but, as noted in response to Question A4, there are some specific principles that should be applied to the labels.

## **B. Child-Resistant Packaging**

**1. Should FDA require child-resistant packaging for liquid nicotine? If so, why?**

Yes. As noted above, there is a growing number of accidental poisoning cases among children.<sup>72</sup> In addition, it is likely that young children may find little vials of “kid friendly” flavorings enticing enough to try.

**2. Should FDA require child-resistant packaging for liquid nicotine if the liquid nicotine product is not intended to be opened by the consumer (e.g., liquid nicotine in permanently sealed, prefilled, and/or disposable cartridges)?**

All liquid nicotine products (and, in fact, all nicotine products) should be in child-resistant containers. The intent of the manufacturer is not the question; it is the ability of children to consume the product in a way that can lead to poisoning.

**3. Should FDA consider requiring child-resistant packaging for tobacco products other than liquid nicotine, including, but not limited to, novel tobacco products? If so, which ones and why?**

Yes. All nicotine containing products should be in childproof containers to prevent accidental poisoning. The mini-lozenges are in child-proof containers since they look like candy (Tic-Tacs), but regular size lozenges should also be child-proofed since, unlike gum, there is the potential to bite and swallow a lozenge.

**4. If FDA were to require child-resistant packaging for liquid nicotine (including for those products that are not intended to be opened by the consumer), what type of exposure risks (e.g., oral, ocular, dermal) should FDA seek to mitigate with the requirement?**

As described in response to Questions A1, A3, A4, A8, all these routes should be mitigated.

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<sup>72</sup> Poisoning cases related to e-cigarettes keep spiraling upward. Campaign for Tobacco-Free Kids website. [http://www.tobaccofreekids.org/tobacco\\_unfiltered/post/2014\\_09\\_26\\_e-cig](http://www.tobaccofreekids.org/tobacco_unfiltered/post/2014_09_26_e-cig). Published September 26, 2014. Accessed November 9, 2014

**5. If FDA were to require child-resistant packaging for tobacco products other than liquid nicotine, including, but not limited to, novel tobacco products, what risks (e.g., oral, ocular, dermal) should FDA seek to mitigate with the requirement?**

For the reasons described in the answers to questions A1, A3, A4, A8, child resistant packing should be required for all nicotine products.

**6. If FDA were to require child-resistant packaging for liquid nicotine, how should the requirement be articulated? Please consider: (a) Whether the requirement should be based on mandated physical characteristics of the packaging (e.g., must have a squeeze-to-turn lid, flow restrictor); (b) whether the requirement should be performance based (e.g., unable to be opened by 80 percent or more of 5-year-olds who try to open the package, and more than 90 percent of adults on average between the ages of 50-70 can successfully open the package); or (c) whether the requirement should be based on a combination of (a) and (b), or is there some other basis for the requirement that FDA should consider? Is your proposal technically feasible? Please submit data or evidence to support your position.**

We do not have any response to this question.

**7. If FDA were to require child-resistant packaging for tobacco products other than liquid nicotine, including, but not limited to, novel tobacco products, how should the requirement be articulated? Please consider: (a) Whether the requirement should be based on mandated physical characteristics of the packaging (e.g., must have a squeeze-to-turn lid, child-resistant cap, blister packaging); (b) whether the requirement should be performance based (e.g., unable to be opened by 80 percent or more of 5-year-olds who try to open the package, and more than 90 percent of adults on average between the ages of 50-70 can successfully open the package); or (c) whether the requirement should be based on a combination of (a) and (b), or is there some other basis for the requirement that FDA should consider? Is your proposal technically feasible? Please submit data or evidence to support your position.**

We do not have any data on this question, but it seems logical to package dissolvable lozenges in blister packs and squeeze-to-turn lids on oral and nasal snuff and snus products.

**8. Are there other factors FDA should consider to further prevent or discourage people (especially infants and children) from inadvertently consuming or being exposed to liquid nicotine? If so, please explain. Examples of other factors may include: attractiveness of the product or packaging (e.g., appealing images, fragrance, flavors), resemblance of packaging to food and drink items (e.g., candy, fruit), color of the product (e.g., resemblance to beverages such as juice), resemblance of packaging to that of medications (e.g., eye drops).**

Since the attractive, kid friendly labeling can be alluring to children, we recommend that vials of nicotine should be plain black and white with information identifying percent or mg nicotine and name of flavor but without pictures of said flavors or colors. Flavors should be assigned

alphanumeric codes, such as Z34, instead of descriptive flavor names that may appeal to children, such as cherry.

**9. If FDA were to require child-resistant packaging, what should FDA consider and what actions should FDA take to mitigate the risk that users of products with child-resistant packaging will defeat the purpose of the packaging by leaving the packaging open, by disabling the protection mechanism, or by moving the product to a different container?**

The warnings we have outlined will reinforce the dangers of this product in combination with child resistant packaging.

### **C. Other Actions and Considerations**

**1. With respect to liquid nicotine, should FDA require both nicotine exposure warnings (text and/or any applicable color or graphic element) and child-resistant packaging, or should only one and not the other be required? Please explain your reasoning and provide data or evidence to support your position.**

Both warnings and child-resistant packaging are needed. Warnings serve to educate parents. Child-resistant packaging provides additional line of defense if parents forget to safeguard the product.

In addition, adults can read and may not be aware of the dermal absorption hazard, which should be emphatically stated. Child-resistant packaging is needed to protect young children.

**2. With respect to tobacco products other than liquid nicotine, including, but not limited to, novel tobacco products, should FDA require both nicotine exposure warnings (text and/or any applicable color or graphic element) and child-resistant packaging, or should only one and not the other be required? Please explain your reasoning and provide data or evidence to support your position.**

A combination of warning labels and child resistant packaging should be used for all products for the previously stated reasons.

**3. With respect to liquid nicotine and the dangers of nicotine poisoning, should FDA consider requiring any additional warnings beyond a nicotine exposure warning (text and/or any applicable color or graphic element)? If so, please describe the warning(s) (textual and/or graphic) and provide evidence or data to support your recommendation.**

Yes. This issue was addressed in detail in our public comment on the FDA deeming rule, which is adapted below and submitted as a formal response to this question.

***The FDA's Proposed Warnings on Addiction are Inadequate and Do Not Reflect Current Understanding of Appropriate Messaging on Addiction***

Docket No. FDA-2014-N-0189

ML Roditis, BL Halpern-Felsher, LK Lempert, SA Glantz, L Popova, JK Cataldo

Warning statements on addiction should include messages that account for the fact that nicotine addiction is a complicated concept, process and disease and needs to be communicated to youth and young adults using different language than for adults.

***The warnings should address how easily addiction occurs, especially among youth, and the fact that addiction is a complicated process that may be difficult to understand.***

The FDA conducted extensive research for its "The Real Cost" campaign on how to communicate the concept of addiction; this knowledge should be reflected in the warning messages that the FDA requires on tobacco products, including liquid nicotine and novel tobacco products.

Evidence shows that both youth and adults have difficulty quitting smoking. The 2007 Youth Risk Behavior Survey, for example, found that while 60.9% of high school daily smokers have tried to quit, only 12.2% were successful.<sup>73</sup> In adult populations, 70% of current smokers reported wanting to quit, 44% attempting to quit, and between 4-7% being successful.<sup>74</sup>

The process of addiction can happen well before the onset of daily smoking.<sup>75</sup> Despite clear evidence that adolescents and adults become addicted to nicotine,<sup>76</sup> and do so well before regular daily tobacco use, both adults and children show confusion over the term addiction, and both adolescents and adults display skepticism about whether becoming addicted will and can happen.<sup>77</sup>

60% of adult smokers and close to half of adolescent smokers believe that they can smoke for a few years and then quit,<sup>78</sup> though actual quit rates are much lower.

Qualitative research shows that adolescents display optimism regarding their ability to quit smoking as well as skepticism over the seriousness of nicotine addiction.<sup>79</sup> Qualitative studies

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<sup>73</sup>Malarcher A, Jones S, Morris E, Kann L, Buckley R. High school students who tried to quit smoking cigarettes: United States, 2007. *MMWR*. 2009;58(16):428-431.

<sup>74</sup>Centers for Disease Control. Quitting smoking among adults--United States, 2001-2010. *MMWR Morbidity and Mortality Weekly Report*. 2011;60(44):1513.

<sup>75</sup>DiFranza JR, Riggs N, Pentz MA. Time to re-examine old definitions of nicotine dependence. *Nicotine & Tobacco Research*. 2008;10(6):1109-1111. Scragg R, Wellman RJ, Laugesen M, DiFranza JR. Diminished autonomy over tobacco can appear with the first cigarettes. *Addictive Behaviors*. 2008;33(5):689-698.

<sup>76</sup>Fagerstrom KO, Heatherton TF, Kozlowski L. Nicotine addiction and its assessment. *Ear Nose Throat J*. 1990;69(11):763-5.

<sup>77</sup>DiFranza JR, Savageau JA, Fletcher K, O'Loughlin J, Pbert L, Ockene JK, et al. Symptoms of tobacco dependence after brief intermittent use: The development and assessment of nicotine dependence in youth-2 study. *Archives of Pediatrics & Adolescent Medicine*. 2007;161(7):704-710.

<sup>78</sup>Arnett JJ. Optimistic bias in adolescent and adult smokers and nonsmokers. *Addictive Behaviors*. 2000;25(4):625-632.

<sup>79</sup>Moffat BM, Johnson JL. Through the haze of cigarettes: Teenage girls' stories about cigarette addiction. *Qualitative Health Research*. 2001;11(5):668-681. Roditis, M.L., Lee, J., & Halpern-Felsher, B. Adolescent

also show that while youth and young adults are aware of the risk of nicotine addiction, they display a great deal of uncertainty over what nicotine addiction actually entails. In particular, adolescents do not realize that "addiction" means it is very difficult to quit using these products,<sup>80</sup> and that many of the "pleasures" of tobacco use, such as relaxation, are simply the results of self-medication (with nicotine) to treat the symptoms of acute nicotine withdrawal.<sup>81</sup> These findings about adolescents' and adults' misperceptions about nicotine are particularly important for warning messages on tobacco products. If individuals think they can start using these products and quit whenever they wish, then warnings regarding the long- and even short-term health consequences become moot as individuals will think they can choose to quit smoking before ever having to deal with these health effects.

Given the evidence that adults and adolescents do not understand addiction, it is vitally important to provide comprehensive, detailed messages on nicotine addiction. These messages need to recognize youth and young adults' lack of understanding and skepticism of addiction and need to provide detailed examples and definitions of addiction in order to be effective.

Extensive research shows that youth and young adults do not just underestimate the risk of addiction. Adolescent smokers and those who eventually become smokers perceive significantly less risk of many health consequences, including long-term consequences such as heart attack and lung cancer, as well as short-term consequences such as having trouble breathing.<sup>82</sup> Such perceptions predict subsequent smoking.<sup>83</sup>

Warnings that are comprehensive and engage the reader emotionally are significantly more effective at transmitting information than warning labels that present the information alone.<sup>84</sup>

The FDA should utilize its own research when finalizing the warning labels and tie warnings to its research-based "The Real Cost" educational campaign. Results from the FDA's qualitative research used to design the Real Cost campaign<sup>85</sup> shows that many youth and young adults smoke in emotionally charged situations, such as when they are stressed, mad, or frustrated and that teens respond the best to campaigns that focus on concepts such as "Why Let a Cigarette Tell You What to Do" and "Cigarettes are not the Answer." Additionally, the FDA's own work indicates that effective portrayals of nicotine addiction should be straight forward, but also portray addiction as a sinister and unwanted presence in one's life.<sup>96</sup>

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(Mis)Perceptions about Nicotine Addiction: Results from a Mixed-Methods Study. *Health Education & Behavior*. In Press.

<sup>80</sup>Haines RJ, Poland BD, Johnson JL. Becoming a 'real' smoker: Cultural capital in young women's accounts of smoking and other substance use. *Sociology of Health & Illness*. 2009;31(1):66-80.

<sup>81</sup>Silverstein B. Cigarette smoking, nicotine addiction, and relaxation. *Journal of Personality and Social Psychology*. 1982;42(5):946.

<sup>82</sup>Halpern-Felsher BL, Biehl M, Kropp RY, Rubinstein ML. Perceived risks and benefits of smoking: Differences among adolescents with different smoking experiences and intentions. *Preventive Medicine*. 2004;39(3):559-567.

<sup>83</sup>Song AV, Morrell HE, Cornell JL, Ramos ME, Biehl M, Kropp RY, et al. Perceptions of smoking-related risks and benefits as predictors of adolescent smoking initiation. *American Journal of Public Health*. 2009;99(3):487.

<sup>84</sup>Hammond D. Health warning messages on tobacco products: A review. *Tobacco Control*. 2011;20(5):327-337.

<sup>85</sup>Sacksteder K. FDA teen experimenter qualitative researcher (foiad material): *Tru Insight*; 2013.

The messages that the FDA created for the Real Cost Campaign from these findings effectively communicate important information by being visually stimulating and graphic; for example, images of a young man pulling out his own tooth or a young woman peeling at her skin as payment for a cigarette (FOIA material). The Real Cost Campaign's website, for example, argues for messages that "highlights consequences that youth and young adults are concerned about, such as cosmetic health effects and loss of control due to addiction."<sup>86</sup>

Warnings should speak to the lack of control associated with addiction. This understanding should be reflected in the FDA's warning labels on tobacco products and liquid nicotine.

For these reasons we suggest the following warning messages regarding addiction:

- 85% of smokers wish they had never started smoking. Nicotine is highly addictive.
- 70% of smokers want to stop smoking. Nicotine is highly addictive.
- The process of nicotine addiction starts well before you are smoking every day. Nicotine is highly addictive.
- Tobacco can be harder to quit than heroin or cocaine. Nicotine is highly addictive.
- Most smokers smoke for years longer than they want. Nicotine is highly addictive.
- Most smokers take 6-11 attempts to quit. Nicotine is highly addictive.
- 75% of teens who smoke are still smoking five years later. Nicotine is highly addictive.
- Addiction is the disease. Smoking is the symptom. Nicotine is highly addictive.

In addition to the points raised in our earlier public comment, there are known dangers of inhaling certain compounds in flavorings. Specifically, research has found a link between lung disease and lung function abnormalities and diacetyl, the keytone responsible for buttery flavors.<sup>87</sup> The FDA should require warning labels for e-liquid nicotine (and non-nicotine) solutions that contain this compound.

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<sup>86</sup> Food and Drug Administration. The real cost campaign. 2014 [cited 2014 June 10th]; Available from: <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/AbouttheCenterforTobaccoProducts>

<sup>87</sup> Cichocki JA, Smith GJ, Morris JB. Tissue sensitivity of the rat upper and lower extrapulmonary airways to the inhaled electrophilic air pollutants diacetyl and acrolein. *Toxicol Sci.* 2014 Nov;142(1):126-36. doi: 10.1093/toxsci/kfu165. Epub 2014 Aug 21; Cummings KJ, Boylstein RJ, Stanton ML, Piacitelli CA, Edwards NT, LeBouf RF, Kreiss K. Respiratory symptoms and lung function abnormalities related to work at a flavouring manufacturing facility. *Occup Environ Med.* 2014 Aug;71(8):549-54. doi: 10.1136/oemed-2013-101927. Epub 2014 Jun 2; Kelly FL, Sun J, Fischer BM, Voynow JA, Kummarapurugu AB, Zhang HL, Nugent JL, Beasley RF, Martinu T, Gwinn WM, Morgan DL, Palmer SM. Diacetyl induces amphiregulin shedding in pulmonary epithelial cells and in experimental bronchiolitis obliterans. *Am J Respir Cell Mol Biol.* 2014 Oct;51(4):568-74. doi: 10.1165/rcmb.2013-0339OC.

**4. With respect to tobacco products other than liquid nicotine, including, but not limited to, novel tobacco products, and the dangers of nicotine poisoning, should FDA consider requiring any additional warnings beyond a nicotine exposure warning (text and/or any applicable color or graphic element)? If so, for which products? Also, please describe the warning(s) (textual and/or graphic) and provide evidence or data to support your recommendation.**

Although at this point we have no evidence regarding the long-term health effects of novel tobacco products, lack of warnings are often perceived as absence of danger by the users. Therefore, it is necessary to include warning labels on all nicotine products.

**5. Should FDA consider any additional measures to mitigate nicotine exposure risks for people (especially infants and children) beyond nicotine exposure warnings (text and any applicable color or graphic element) and child-resistant packaging? If so, what measures should FDA consider and why? Please provide evidence or data to support your recommendation.**

There are occupational exposure concerns for nicotine. Vape shops have bottles containing multiple gallons of concentrated nicotine solutions. If such a bottle were to break, there is substantial nicotine exposure potential – particularly dermal exposure and possibly inhalation exposure for employees and clients. All liquid nicotine products should have warning labels.

Commercial settings require different and more stringent regulations due to large quantities that are handled. Employees need to be properly trained if they work with large containers of nicotine solution. Complete safety data sheets, SOPs, and documentation of employee training should be required, as EH&S here requires of lab personnel using hazardous chemicals. OSHA inspections, federal or state, should be required of businesses handling large quantities.

There is considerable evidence that nicotine harms and changes the developing brain during adolescence.<sup>88 89,90</sup> Adolescents tend to respond more to messages regarding how a drug affects their development than messages about overall harm. Thus, the FDA should develop messages that discuss the impact that nicotine has on the developing brain.

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<sup>88</sup> Casey, B., and R. M. Jones. Neurobiology of the adolescent brain and behavior: Implications for substance use disorders. *Journal of the American Academy of Child and Adolescent Psychiatry* 2010; 49(12):1189-1201.

<sup>89</sup> Dwyer JB, McQuown SC, Leslie FM. The dynamic effects of nicotine on the developing brain. *Pharmacology & Therapeutics*. 2009;122(2):125-139.

<sup>90</sup> Lydon, D. M., S. J. Wilson, A. Child, and C. F. Geier. Adolescent brain maturation and smoking: What we know and where we're headed. *Neuroscience and Biobehavioral Reviews* 2014; 45:323-342; England LJ, Bunnell RE, Pechacek TF, Tong VT, McAfee TA. Nicotine and the Developing Human: A Neglected Element in the Electronic Cigarette Debate. *American Journal of Preventive Medicine*. 2015 Aug;49(2):286-93. doi: 10.1016/j.amepre.2015.01.015. Epub 2015 Mar 17.