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September 30, 2015

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane  
Rockville, MD 20852

Re: Docket No. FDA-2015-N-1514

Dear Sir or Madam:

On behalf of the American Heart Association (AHA), including the American Stroke Association (ASA) and more than 30 million volunteers and supporters, we appreciate the opportunity to provide comments on nicotine warnings and child-resistant packaging for liquid nicotine, nicotine-containing e-liquids, and other tobacco products.

AHA is pleased that the Food and Drug Administration (FDA) is examining methods to decrease accidental exposures to nicotine. However, we are disappointed that the Agency chose to address this issue by issuing an Advanced Notice of Proposed Rulemaking (ANPRM) – the earliest possible step in the rulemaking process. Moving from an ANPRM to a proposed rule and ultimately to a final regulation could take a year or longer. During that time, poisonings associated with liquid nicotine will only continue to climb. To protect children, the FDA needs to move quickly and require both child-resistant packaging and a warning statement advising consumers to keep these products away from children. We encourage the Agency to release the rules as soon as possible, and require newly deemed products to comply no later than six months after the effective date of the final deeming rule. As our comments below illustrate, this is one area where moving a regulation forward swiftly is a necessity.

## **Nicotine Exposure Warnings**

### ***Should FDA require nicotine exposure warning(s) on liquid nicotine?***

Yes. Liquid nicotine can be extremely toxic if ingested or absorbed through the skin. Common signs of nicotine intoxication include dizziness, nausea, vomiting, pallor, tachycardia, and sweating.<sup>1</sup> Severe cases of nicotine exposure can also cause confusion, agitation, lethargy, convulsions, and death, likely due to respiratory arrest.<sup>2</sup> E-cigarette liquids (also known as e-liquid or e-juice), in particular, pose a significant risk of toxicity because there is no limit on the amount of nicotine an e-liquid can contain and base solutions with as much as 100mg/ml of nicotine for “do-it-yourself” e-liquid formulation are available for purchase on the Internet.

As the Agency is well aware, poison control centers have experienced a dramatic spike in the number of calls for accidental exposure to e-cigarette liquid. Calls jumped from 271 in 2011 to 3,783 in 2014, and slightly more than half of the calls involved children under the age of six,<sup>3</sup> including one 18-month-old boy who, last December, became the first child to die after drinking from an unsecured bottle of e-liquid.<sup>4</sup>

We can assume that some, if not all of these accidents occurred because consumers are unaware that e-liquids can pose substantial risks. To prevent accidental exposures, consumers must be warned that nicotine is toxic and advised to keep e-liquids away from children and pets.

### ***Should FDA require nicotine exposure warning(s) on other tobacco products, including, but not limited to, novel tobacco products?***

Yes. Any tobacco product that contains nicotine presents a risk of nicotine toxicity. Many children experience toxic exposures to cigarettes, e-cigarettes, and other tobacco products each year, and it is likely we will see the number of exposures to novel tobacco products increase as they become more prevalent in the market. Novel tobacco products may have a heightened appeal for children as many of the dissolvables resemble candy, gum or mints, and nicotine lotions and drinks may easily be confused with non-nicotine versions of these products. It is therefore reasonable to include a warning on a wide range of tobacco products, including novel tobacco products.

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<sup>1</sup> Bhatnagar A, et al. on behalf of the American Heart Association Advocacy Coordinating Committee, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Quality of Care and Outcomes Research. Electronic cigarettes: a policy statement from the American Heart Association. *Circulation*. 2014;130:1418-1436.

<sup>2</sup> Ibid.

<sup>3</sup> American Association of Poison Control Centers. E-Cigarette Devices and Liquid Nicotine. <http://www.aapcc.org/alerts/e-cigarettes/>.

<sup>4</sup> K. Clukey. Case Closed in Fort Plain Liquid Nicotine Death: Police: 18-month-old boy accidentally consumed e-cigarette ingredients. Times Union. April 13, 2015. <http://www.timesunion.com/news/article/Case-closed-in-Fort-Plain-liquid-nicotine-death-6195411.php>.

***On what basis should FDA determine which products should be required to carry the warning(s)?***

We recommend that the FDA focus on the following factors: 1) how much nicotine a product contains and its relative toxicity to children; 2) how quickly the nicotine could be absorbed or metabolized in its existing form; and 3) the likelihood that the product will appeal to children (i.e., child-friendly flavors, images, colors, resemblance to food, drink or candy).

Liquids, especially those that are high in nicotine content, should be required to carry an exposure warning, because a small amount – even a few milliliters – can cause harm.<sup>5</sup> The nicotine in liquids is also absorbed quickly and more completely than nicotine contained in solid form, and the effects of exposure begin within a short timeframe – usually within 15 minutes when ingested.<sup>6</sup> In addition, liquid nicotine is often sold in fruit and candy flavors and many are packaged using bright colors, graphics, and cartoon characters, all of which are appealing to children and increase the likelihood of accidental exposure.

Novel products such as dissolvables and nicotine-laced gels, lotions, and drinks may also be very appealing to children. As noted previously, dissolvables are often packaged to resemble candy or mints and could be mistaken for such. Nicotine gels and lotions are similar in appearance to more innocuous household products such as liquid soap or hydrating lotion. And nicotine drinks may look like regular water. Children or unsuspecting adults could easily misidentify these products and unintentionally be exposed to harmful levels of nicotine.

***What issues should the warning(s) address and what wording should be used?***

The warning should be focused on the risks of nicotine toxicity, address all routes of exposure (oral, dermal, and ocular), and include the symptoms of nicotine toxicity. It should also clearly advise consumers to keep these products away from children and pets, and provide information about what to do in case of accidental exposure. Consumers are used to warning statements that follow this model which is frequently used on common household products such as cleaners or pesticides.

We provide the following warning as an example for the Agency's consideration:

**WARNING: Keep this product away from children and pets.**

**This product contains nicotine. Nicotine can be harmful when swallowed or absorbed through the skin. Do not swallow, do not get on skin or in eyes. Nicotine can cause nausea, vomiting, sweating, heart palpitations, dizziness, convulsions, breathing difficulty, and death.**

**Contact a poison control center (1-800-222-1222) for treatment advice.**

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<sup>5</sup> Bhatnagar A. Ibid.

<sup>6</sup> Ibid.

***Should there be multiple textual warnings that randomly display to convey different dangers, or should there be a single, consistent textual warning?***

We recommend using one consistent warning that – following our suggestions above – warns consumers of the risk of nicotine poisoning, lists the specific symptoms, advises consumers to keep the product away from children and pets, and directs consumers to call a poison control center if exposure occurs. All of these elements should be included in a nicotine exposure warning.

Removing any of these elements or allowing a rotating warning to highlight only one (or a few) potential dangers at a time may decrease the effectiveness of the warning statement. For instance, a warning that only lists nausea, vomiting, and sweating as potential signs of nicotine poisoning may not be taken as seriously as a warning that also mentions convulsions, breathing difficulty, and death. Likewise, a warning that only addresses the risk of ingestion is not appropriate if the product can also be absorbed through the skin. Thus, we strongly encourage the FDA to use one consistent warning that includes all of the most common dangers.

***Should FDA require color or graphic elements, such as symbols, as part of the warning(s)? What color or graphic warnings should FDA consider?***

Yes, the FDA should consider requiring a graphic element in addition to the text-based warning statement. Studies show that colorful, graphic warnings are a marked improvement over plain text warnings. For example, a recent meta-analysis found that when compared to text-only warnings, pictorial warnings on cigarette packages were better at 1) attracting and holding attention; 2) generating strong cognitive and emotional reactions; 3) eliciting negative attitudes toward smoking; and 4) increasing intentions to not start smoking and to quit smoking.<sup>7</sup>

A graphic symbol may also be useful in communicating the risk of danger to children or low-literate adults. Many children have been taught that graphic symbols, such as Mr. Yuk™<sup>8</sup> or a skull and crossbones, mean that a product is poisonous or dangerous and should be left alone. Including one of these symbols on e-liquids and novel tobacco products may discourage children from touching, playing with, or ingesting these products if they find one within reach. We encourage the FDA to consider requiring a symbol similar to Mr. Yuk™, a skull and crossbones, or another graphic symbol that might be understood by children to indicate that the product is dangerous and should be left alone. Before selecting a specific symbol, the Agency should test the graphics with both children and adults as effectiveness may vary by audience.

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<sup>7</sup> Noar SM, et. Pictorial Cigarette Pack Warnings: A Meta-Analysis of Experimental Studies. *Tob Control* 2015;0:1-14. doi:10.1136/tobaccocontrol-2014-051978.

<sup>8</sup> Mr. Yuk™ was created by the Pittsburgh Poison Center in 1971 and is still in use today. See <http://www.upmc.com/Services/poison-center/Pages/about-yuk.aspx>.

***Should the FDA require the inclusion of the American Association of Poison Control Centers' (AAPCC) telephone number on the container labeling and/or packaging?***

Yes. Warning consumers about the dangers of nicotine exposure is key, but it is an incomplete message if it does not also provide guidance on what to do if an exposure occurs. Including the AAPCC phone number is a simple and brief way to direct consumers to a resource that can provide treatment instructions.

Providing the AAPCC phone number would also be in-line with other consumer products, such as household cleaners, that contain warning statements. Many of these products already include the AAPCC phone number as part of their product label. Consequently, consumers have come to expect that warning statements will be accompanied by treatment instructions. The FDA should hold e-liquids and novel tobacco products to the same standard and require the inclusion of the AAPCC phone number.

**Child-Resistant Packaging**

***Should FDA require child-resistant packaging for liquid nicotine?***

Yes. The poison control center data speaks for itself – almost 3,800 people reported exposures to e-cigarette devices and liquid nicotine last year, and more than half of these exposures occurred in young children under the age of six. Many of these children “became very ill; some even requiring ER visits”, and at least one child died.<sup>9</sup> The numbers for 2015 are no better with over 1,700 exposures reported during the first six months of the year alone. The good news is that child-resistant packaging can help reverse this trend.

Child-resistant packaging is an effective means of reducing exposures to hazardous substances. Since the Poison Prevention Act of 1970 became law, child-resistant packaging has been required for a wide-range of household substances, from oral medications and mouthwash to furniture polish and turpentine; and studies show that requiring child-resistant packaging for these products works. For example, from 1958 to 1963, there were an average of 120 fatal aspirin poisonings *each year* involving children under five.<sup>10</sup> But the mortality rate experienced a 34% reduction after a 1972 child-resistant packaging requirement was implemented, resulting in approximately 90 fewer deaths between 1973 and 1990.<sup>11</sup> When the child-resistant packaging requirement was extended two years later to include oral prescription drugs, the mortality rate dropped by 45%, saving a projected 460 children between 1974 and 1992.<sup>12</sup>

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<sup>9</sup> American Association of Poison Control Centers. E-Cigarette Devices and Liquid Nicotine. <http://www.aapcc.org/alerts/e-cigarettes/>.

<sup>10</sup> Rodgers, GB. The Effectiveness of Child-Resistant Packaging for Aspirin. *Arch Pediatr Adolesc Med.* 2002; 156:929-933.

<sup>11</sup> Ibid.

<sup>12</sup> Rodgers, GB. The Safety Effects of Child-Resistant Packaging for Oral Prescription Drugs: Two Decades of Experience. *JAMA*, June 5, 1996. Volume 275.

We expect that child-resistant packaging of liquid nicotine will have a similar result – a significant decrease in the number of nicotine poisonings. We urge the FDA to follow the lead of Minnesota, New York, and Vermont, which have all implemented their own child-resistant packaging requirements, and require child-resistant packaging for all e-liquids. There is no question that child-resistant packaging is appropriate – and desperately needed – for these products.

***Should FDA require child-resistant packaging for liquid nicotine if the product is not intended to be opened by the consumer?***

Yes, the FDA should require child-resistant packaging for all liquid nicotine products. Even products that are not intended to be opened by the consumer, such as permanently sealed, prefilled, and disposable e-cigarette cartridges, can pose a poison risk. Children or pets may still find a way to access the liquid nicotine in a way the manufacturer did not intend.

***Should FDA require child-resistant packaging on other tobacco products, including, but not limited to, novel tobacco products?***

Yes. All tobacco products pose a risk of nicotine poisoning. Consider Camel Orbs, Sticks, and Strips with a nicotine content ranging between 0.6mg and 3.1mg. Or Nic Lite, the flavored nicotine drink, which has 4mg of nicotine per eight ounce bottle. Because young children can suffer ill effects after consuming as little as 1mg of nicotine,<sup>13</sup> one lozenge (or less) or a small amount of nicotine water could be enough to cause nicotine poisoning.

Many of these products are also attractive to children. Children may mistake dissolvable tobacco products for candy, gum, or mints because of their appearance, colorful packaging, and product flavors. Other novel products such as nicotine water, gel, and lotion closely resemble non-nicotine versions and may be mistaken for such. In addition, young children who've seen an adult drink from a bottle of nicotine water or pop an orb into their mouth may be inclined to imitate that behavior.

To decrease the chance that children will be exposed to the nicotine in these products, the FDA must require child-resistant packaging. There is no valid reason not to. Consumers are used to child-resistant packaging; it is ubiquitous throughout the marketplace – from medications and mouthwash to cleaners and pesticides. Consumers should also expect to see it here given the real threat of nicotine poisoning that novel tobacco products pose.

***If FDA were to require child-resistant packaging, what type of exposure risks (e.g., oral, ocular, dermal) should FDA seek to mitigate?***

We recommend that FDA require manufacturers of liquid nicotine, e-liquid, and novel tobacco products to utilize packaging designed to mitigate all three routes of exposure: oral, dermal, and ocular. According to a review of AAPCC data, all three routes of exposure are problematic, with oral exposures to e-liquid reported as the most frequent (68.9%), followed

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<sup>13</sup> Connolly GN, et al. Unintentional Child Poisonings Through Ingestion of Conventional and Novel Tobacco Products. *Pediatrics* 2010;125:896–899.

by ocular (8.9%) and dermal (5.9%).<sup>14</sup> The remaining 16.8% of exposures are from inhalations, which we assume, may be the result of using the products as intended. To be effective, child-resistant packaging should be designed to keep children from opening the product or obtaining a toxic or harmful amount regardless of the route of exposure.

***If FDA were to require child-resistant packaging for liquid nicotine, how should the requirement be articulated?***

AHA recommends that the FDA consult with the U.S. Consumer Product Safety Commission (CPSC) regarding the standards for child-resistant packaging. The CPSC already has “special packaging” standards that require products to meet specific child-resistance performance standards. And, as we understand it, the FDA and CPSC have previously worked together to prevent child poisonings from prescription drug containers. It may be appropriate to base the requirements for nicotine-containing products on the same standards currently in use for medications.

***Are there other factors FDA should consider to further prevent or discourage people from inadvertently consuming or being exposed to liquid nicotine?***

Yes, the FDA should consider the impact that flavors, fragrances, and packaging have on children.

As the Agency is aware, liquid nicotine is available in a wide range of candy and fruit flavors, many of which are attractive to children, such as strawberry, chocolate, graham cracker, and gummy bear. Other flavors share the same names as children’s cereals or children’s cartoon characters. Liquid nicotine is also frequently packaged in bright, colorful packages with appealing images of fruit, candy, or other food items, or cartoon characters. Many of the advertising techniques used to market e-cigarettes and e-liquids also appear to target, or at least reach, a lot of youth.

Appealing flavors, fragrances, and colors make it more likely that children will want to touch, play with, or put liquid nicotine into their mouth. This appeal has likely been a contributing factor to the 7,500+ reports of liquid nicotine exposure since 2011.<sup>15</sup> Packets of concentrated laundry detergent are another example of the effect that bright colors and fun packaging have on infants and children. In 2014, poison control centers received almost 12,000 calls for exposures in children under the age of five.<sup>16</sup> According to the AAPCC, children are attracted to single-use detergent packets “[b]ecause they are colorful and squishy... they look like candy or something fun to play with.”<sup>17</sup> We are very concerned that we are on a similar path with both liquid and novel nicotine products.

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<sup>14</sup> Chatham-Stephens K, et al. Calls to Poison Centers for Exposures to Electronic Cigarettes – United States September 2010- February 2014. CDC MMWR: April 4, 2014, Vol. 63, No. 13.

<sup>15</sup> AAPCC. E-Cigarette Devices and Liquid Nicotine. <http://www.aapcc.org/alerts/e-cigarettes/>

<sup>16</sup> AAPCC. Poison Exposure Report. <http://www.aapcc.org/alerts/laundry-detergent-packets/>

<sup>17</sup> AAPCC. Laundry Detergent Packets Fact Sheet.

[https://aapcc.s3.amazonaws.com/pdfs/topics/Laundry\\_packet\\_factsheet\\_5.2012.pdf](https://aapcc.s3.amazonaws.com/pdfs/topics/Laundry_packet_factsheet_5.2012.pdf)

To decrease the likelihood that infants and children will be exposed to liquid nicotine, the FDA should prohibit the use of non-tobacco flavorings, limit the use of cartoon characters and other graphics that appear to target children, and extend existing advertising and marketing restrictions to these products. The Agency should also examine whether tactics used by other countries – such as requiring plan packaging for tobacco products – are warranted here.

***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?***

We recommend that the FDA consider requiring flow restrictors on containers of liquid nicotine. Flow restrictors can limit a child's ability to access liquid nicotine even if the child-resistant device is disabled or misused. A study of flow restrictors on liquid medicine found that young children (3-4 years old) were able to remove less liquid from bottles with flow restrictors.<sup>18</sup> The children also required more time to access the liquid, which "may provide an opportunity for caregiver intervention before substantial amounts are removed."<sup>19</sup> A flow restrictor may also discourage a user from moving the product to a different container because of the additional time and effort that would be required.

**Other Actions and Considerations**

***Should FDA require both nicotine exposure warnings and child-resistant packaging, or should only one and not the other be required?***

The FDA should require both a nicotine exposure warning and child-resistant packaging for all liquid nicotine and novel tobacco products. As discussed above, child-resistant packaging has a proven history of reducing harm to children. It may be the most effective, single strategy to combat poisoning since limiting a child's ability to open or access a product results in an immediate reduction in risk.

However, child-resistant packaging should not be used alone; child-resistant packaging can fail or be defeated. Thus, making consumers aware of the risks and encouraging them to keep tobacco products away from children and pets should remain the first line of defense. A nicotine exposure warning, ideally coupled with a consumer education campaign, can help raise awareness and encourage behavior change.

***Should FDA consider any additional measures to mitigate nicotine exposure risks for people beyond nicotine exposure warnings and child-resistant packages?***

As noted above, we recommend that FDA embark on a consumer education campaign to raise awareness of nicotine toxicity and the dangers associated with accidental exposure. The campaign should emphasize the need to keep these products out of the reach of children and pets. Pregnant women should also be advised to avoid contact with these products.

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<sup>18</sup> Lovegrove MC, et al. Efficacy of Flow Restrictors in Limiting Access of Liquid Medications by Young Children. *J Pediatr* 2013; 163:1134-39.

<sup>19</sup> Ibid.

We encourage the Agency to begin the education campaign immediately; there is no need to wait until regulatory requirements are in place.

**Conclusion**

In closing, we appreciate the Agency's decision to examine the issue of acute nicotine toxicity and the need for a warning statement and child-resistant packaging. Accidental exposure to nicotine has become a significant problem as demonstrated by the recent surge in calls to poison control centers, more than half of which were for children. Unfortunately this dangerous trend will continue unless the FDA takes action to prevent future poisonings.

To protect the most vulnerable members of our society, the FDA must require liquid nicotine, e-liquid, and other tobacco products, including novel tobacco products, to bear a nicotine exposure warning and use child-resistant packaging. A warning statement is needed to inform tobacco users of the dangers these products pose when left within reach of a child or pet, and to advise them what to do if an accidental exposure occurs. However, a warning statement alone is not enough; there is no guarantee that it will change consumer behavior. That is why child-resistant packaging must be used in conjunction with an exposure warning.

We urge the FDA to move quickly on this issue. Each product sold without child-resistant packaging and an exposure warning places another child at risk.

Thank you for consideration of our comments.

Sincerely,

A handwritten signature in black ink that reads "Nancy A. Brown". The signature is written in a cursive style with a long horizontal flourish at the end.

Nancy A. Brown  
Chief Executive Officer  
American Heart Association