

Department of Pharmaceutical Sciences
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July 3, 2019

The Honorable Raja Krishnamoorthi
Chairman, Subcommittee on Economic and
Consumer Policy
Committee on Oversight and Reform
U.S. House of Representatives
Washington, DC 20515

Dear Chairman Krishnamoorthi,

As a Professor of Pharmaceutical Sciences and Anatomy & Neurobiology at the University of California, Irvine, I am writing to express concern over the rapid increase in e-cigarette use among youth and to emphasize the profound, lasting dangers of nicotine exposure during adolescence. I have done research on the effects of nicotine exposure during critical periods of brain development since 1998, and am speaking for myself and not the University.

Epidemiological research has demonstrated a consistent progression in drug use from nicotine and alcohol, to marijuana, and then to illicit substances such as cocaine and opioids. Decades of clinical human and preclinical animal research support a major contribution of nicotine, in particular, as an underlying factor for this “gateway” theory of drug addiction. My lab has focused on the effects of nicotine during critical periods of development, including adolescence.

Adolescence is a protracted, critical period of brain development that is not complete until around 25 years of age, and is when use of nicotine-containing products typically begins. The hallmark of adolescence is a profound reorganization of brain regions necessary for mature cognitive and executive function, working memory, emotional regulation, reward processing, and motivated behavior. One of the central regulators of these maturational changes in pathways regulating addiction, mood, and cognition are neuronal nicotinic receptors, which are also activated by nicotine.

Animal studies on nicotine’s effects in the developing brain - which allow for ethical experimentation, optimal control of experimental conditions, and the ability to evaluate neurobiological mechanisms – have provided critical insight into the inherent vulnerability of teen brains to drugs of abuse, and nicotine in particular¹. We – and other NIH-funded labs across the country - have consistently shown that nicotine exerts very different effects on the brain during adolescence compared to adulthood. For example, adolescents find low doses of nicotine more rewarding than adults. At the same time, the aversive effects of nicotine are less pronounced and the adult-typical stress response after nicotine exposure is absent, resulting in a net shift towards pro-addictive responses to nicotine during adolescence. Similarly, after chronic exposure to nicotine, if the drug is removed or nicotinic receptors are blocked, animals typically experience unpleasant physical and emotional symptoms of withdrawal. However, these symptoms are less severe in younger animals. It is important to note here that human research finds that teenagers become dependent on nicotine/tobacco products more quickly than adults and have less success quitting. This may be due to non-nicotine constituents in tobacco smoke.

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In order to model the initial, intermittent e-cigarette use patterns by teenagers, we have created a model where early adolescent animals are given a brief, low-dose nicotine treatment – equivalent to 2 e-cigarettes per day over four days. This brief nicotine exposure produces long-lasting alterations in the adolescent brain, making it more sensitive to the rewarding effects of other drugs of abuse such as cocaine, methamphetamine, and alcohol. Importantly, this same nicotine exposure has no effect in adults. We have also shown that combinations of nicotine and alcohol are highly rewarding to adolescent males but not adults, because a neuroprotective mechanism emerges later in development². Other research groups have shown long-lasting decrements in cognitive function and attention span, as well as increased impulsivity, anxiety and fear, and a depression-like state after adolescent nicotine exposure.

In sum, the perception that electronic cigarettes are safe is incorrect. Extensive preclinical research demonstrates that nicotine use during critical periods of development, including adolescence, can have long-term deleterious effects on the brain that negatively impact cognition and increase the risk of psychiatric disorders and drug dependence. Coupled with the alarming exponential rise in e-cigarette use among teenagers, I agree that the Subcommittee should investigate JUUL's role in the e-cigarette epidemic.

I appreciate the opportunity to provide these comments. To discuss this matter further, please contact me at (949)824-6351.

Sincerely,



Frances Leslie, Ph. D.

Professor of Pharmaceutical Sciences and Anatomy & Neurobiology

¹ Yuan, M., Cross, S. J., Loughlin, S. E., & Leslie, F. M. (2015). Nicotine and the adolescent brain. *The Journal of physiology*, 593(16), 3397-3412.

² Lárraga, A., Belluzzi, J. D., & Leslie, F. M. (2017). Nicotine increases alcohol intake in adolescent male rats. *Frontiers in behavioral neuroscience*, 11, 25.