EDITORIAL
E-CIGARETTES

Should we worry about children's exposure to third-hand by-products generated from electronic nicotine delivery systems?

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Children and other individuals sharing spaces with END users frequently become exposed to first-, second- and third-hand chemicals. This editorial discusses the findings from a recent study exploring the impact of third-hand exposure. https://bit.ly/3cogiw0

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Despite electronic nicotine delivery systems (ENDS), such as e-cigarettes, being readily available for the past decade, we still know very little about the long-term effects on the user, and the second- and third-hand impact on non-users. Approximately 7% of former smokers quit tobacco smoking by switching to ENDS [1]. However, a high number of young adults become addicted to nicotine by using ENDS products, which could influence addiction to other nicotine products. The safety of ENDS is now in question [2], especially with the recent vaping-associated pulmonary injury outbreak and growing evidence of potential harmful effects of vaping [3] and mounting data on ENDS evaluated in animal models [4]. Earlier this year the U.S. Food and Drug Administration (FDA) issued an enforcement policy on unauthorised flavoured cartridges in ENDS, with particular emphasis on targeting minors [5]. Most are not aware of the potential impact of third-hand exposure, which is residual chemicals left on surfaces and clothing following vaping that can subsequently be a source of exposure *via* touching these contaminated areas or breathing in the off-gassing from these surfaces. Here we will outline what we need to consider for third-hand exposure for minors.

Toxic first-hand ingestion of ENDS liquid in infants is reported [6]. Frequently, children and other individuals sharing spaces with ENDS users could become exposed to first-, second- and third-hand chemicals. Equally, there are extensive guidelines for the protection of children from exposure to cigarette smoke generated by tobacco products, including the Clinical Effort Against Second-hand Smoke Exposure (CEASE) Intervention [7]. Prior to establishing guidelines for ENDS products, we need to consider the impact of third-hand surface residuals generated from ENDS products and whether these chemicals alter homeostasis and development, especially in children and young adults. Where would you envision finding potential third-hand ENDS vapour exposure? We need to look at the homes of current vapours, homes previously occupied by vapours, areas where vaping is permitted, second-hand or rented vehicles, hotel rooms and any other indoor location where vaping could have occurred. Equally, vapour residual sedimentation from ENDS products can be influenced by the ventilation rate within the dwelling, air quality, rural or urban environments, the number of individuals living with the dwelling, socioeconomic

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status, the presence of pets, cleanliness of the dwelling, presence of allergens, nutrition status, and obesity. Equally, we need to utilise animal models and clinical studies to determine whether by-products generated by ENDS are safe and what biological changes could occur. Overall, utilising knowledge the scientific community gained while investigating the biological impact of cigarette smoke, generated by tobacco products, on disease pathology can be applied to determine whether ENDS are safe for the user and anyone in close proximity, especially children.

The liquid within ENDS typically contains propylene glycol (PG), vegetable glycerin (VG), glycerol, an assortment of flavours and nicotine. Researchers have reported between 60 to 113 chemicals in multiple brands of ENDS liquids generated during the vaporisation process [8, 9]. Several of these chemicals and particles are known to be toxic or carcinogenic. Equally, these chemicals are linked to multiple respiratory and cardiac diseases. The frequently observed chemicals generated by vaping are formaldehyde, acetaldehyde, acrolein, glyoxal, acetone, propanal, crotonaldehyde, butanal and methylglyoxal [10–12]. Whether all of these chemicals coat surfaces to generate third-hand ENDS exposure is unknown. A recent study by Chen *et al.* [13] investigated the impact of third-hand vaping in young mice. The investigators placed a towel that was exposed to ENDS vapour without or with nicotine within the animal's enclosure for 8 days [13]. These investigators identified the chemical components generated in ENDS vapour, such as formaldehyde, acetaldehyde, benzene, phenol and benzaldehyde. However, only nicotine and PG were detected on the vapour-coated towel [13].

Chen *et al.* [13] reported that third-hand ENDS vapour reduced lung inflammatory responses such as CCL1, 2, 4 and 7, tumour necrosis factor and nicotine in ENDS vapour-enhanced CCL11 levels. Third-hand ENDS vapour also subdued macrophage infiltration into airways, airway resistance, spleen and brain weight [13]. Therefore, immune responses and organ development were altered by acute third-hand exposure to ENDS. Animal nicotine exposure studies after the prenatal period suggest that nicotine has damaging effects on the brain, including cognitive deficits [13]. Therefore, third-hand exposure to nicotine and other compounds in ENDS may result in brain development complications in infants. Equally, sustained exposure to nicotine results in extramedullary haematopoiesis in the spleen of mice due to inhibition of rolling and migration of enriched haematopoietic stem cells across bone marrow endothelial cells *in vitro* and decreased expression of β2 integrin on the surface of these cells [14]. Many of the changes described by Chen *et al.* [13] were attributed to the non-nicotine components, likely PG. Despite PG being considered to be safe, PG toxicity can occur and exposure concentration and duration must be considered. PG is known to induce elevated apoptosis in the developing brain [15]. Dermal application of PG is also known to induce allergy symptoms in certain individuals [16]. It is important to note that certain populations will process PG differently to the general population, especially patients with underlying kidney disease, or impaired alcohol dehydrogenase enzyme systems (such as children aged <4 years, pregnant women and hepatic disease patients). These populations are all prone to PG accumulation [17]. Therefore, infants may be more susceptible to chemicals deemed non-toxic, compared to healthy adults. Although PG is considered safe by the US FDA, PG can accumulate and cause lactic acidosis, central nervous system depression, coma, hypoglycaemia, seizures and haemolysis [18]. This could also be true for other chemicals present in ENDS, beyond PG. The scientific community recognises the importance of ageing in disease processes but we must also be mindful of children responding differently than adults to stimuli. One major limitation in the study by Chen *et al.* [13] is the use of only male animals [13]. Therefore, we need to address whether this is a sex-dependent phenotype. Equally, would better ventilation within the dwelling, or reducing the number of individuals living within the dwelling, or reduced surrounding allergens or nutrition status alter these outcomes? Inflammation, respiratory infections, asthma symptoms and short-term sick leave increase with lower ventilation rates in the work setting [19], and we anticipate reduced exposure to ENDS by-products with higher ventilation levels. In a study with a ventilation level comparable to residential properties, the PG levels rose from $0.5\ \mu g \cdot m^{-3}$ to $203.6\ \mu g \cdot m^{-3}$ during vaping [20]. Equally, the air quality within the dwelling, whether in a rural or urban environment, could further complicate the potential exposure risks to children. Depending on the location of the dwelling, third-hand ENDS by-products could coat the surface in combination with animal, dander, mould, dust mites, cockroaches and mice [21]. The flavouring in ENDS alters allergy responses to human dust mite in mice [22]. However, further studies are required for third-hand exposure and infant ingestion.

The vapour of a combination of PG and VG in ENDS does increase lipid accumulation in alveolar macrophages due to alteration in type II pneumocytes surfactant homeostasis, which is independent of nicotine [3]. This is achieved by inhibition of *ABCA1* and *ABCG1*, transporter molecules responsible for removal of excess intracellular cholesterol and phospholipid, and thereby phospholipids accumulate within cells and interfere with surfactant homeostasis [3]. This accumulation of phospholipids also coincided with an abundance of M2 macrophages that exhibit reduced inflammation, such as *Tlr7*, *Il1b* and *Tnfa* [3]. Loss of *Tlr7* responses makes the lungs more susceptible to viral infections, including influenza [3] and human rhinovirus [23]. These immune changes all occur with products (*i.e.* PG and VG) which are deemed safe [24].

Despite the mounting evidence suggesting that ENDS are unsafe, one cannot rule out their usefulness as a tobacco smoke cessation product. However, more studies are required to explore all facets of vaping exposure, especially when considering the health of children. A recent study demonstrated that multiple ENDS users congregating in a poorly ventilated area can result in indoor air pollution with PM_{10} (particles with a 50% cut-off aerodynamic diameter of 10 μm), air nicotine and volatile organic compounds and air nicotine concentration ($125\ \mu g \cdot m^{-3}$) equivalent to concentrations measured in bars and nightclubs [25]. However, the level of exposure will differ between ENDS products and improved ventilation may minimise exposure, as seen in second-hand vaping [26]. Finally, we want to outline other topics that were not discussed here but are important in relation to the safety of ENDS to children and the unborn. ENDS usage is linked to DNA methylation changes, immune responses and neurological changes to offspring *in utero* in animal models [27, 28]. This may be partially due to young women metabolising nicotine faster than the rest of the population [29]. Importantly, the impact of third-hand nicotine exposure is still to be fully elucidated and should also be investigated clinically in infants and young adults. In research, we examine one variable; however, what is the likelihood that people use the nicotine-free liquid in their ENDS? Despite the impact of ENDS vapour with or without nicotine, we should expect most inhaled vaping liquids to contain nicotine. Therefore, many questions remain when discussing the possible impact of third-hand exposure to by-products generated by ENDS, especially to children. Unfortunately, it is extremely difficult to fully elucidate the questions outlined due to the many complex variables but we should consider third-hand ENDS exposure as a possible health problem for children.

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