

## E-Cigarettes: The Vapor This Time?

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E-Cigarettes (EC) have exploded onto the world's nicotine delivery scene, bringing in their wake millions of new users (Tobacco Vapor Electronic Cigarette Association, 2013), their own subculture (Alderman, 2013) and challenges to existing indoor smoking ordinances. Most importantly, e-cigarettes raise a wide range of important research questions from the toxicology and carcinogenicity, through abuse liability, addictive potential and cessation efficacy, to prevalence among different demographic sectors of society (Etter et al., 2011).

A debate has erupted in the tobacco control field around how to characterize and regulate e-cigarettes and how, when and who should or should not use them; are they harm reduction devices? (Cahn and Siegel, 2010). And while there has been an uptick in peer-reviewed research over the past few years, many of these findings have been contradictory at best; some finding that toxicants at much lower concentrations than in regular tobacco cigarettes and carry little if any risk to human health (McAuley et al., 2012; Goniewicz et al., 2013) while other research shows equal and even higher concentrations of toxicants that would be harmful to the public's health (Williams et al., 2013). Disconcertingly, many of the varying findings are probably true, given the unregulated and variable production processes and quality among e-cigarette brands.

That e-cigarette use, marketing and research are exploding is an understatement; nonetheless, much more research is needed. Given the magnitude of e-cigarette popularity and increasing amount of media exposure, the public health community is faced with a daunting task of responding to the aggressive marketing of e-cigarettes and advocating for policies without having all the answers, scientific or otherwise.

Nonetheless, this paper is not a complete review of the topic but will be limited instead to four areas: 1) The history of e-cigarettes and their current regulatory status in the United States and California; 2) what is known today about the chemical composition of the e-cigarette "juice" and the inhaled and the ambient vapors; 3) what is known today about e-cigarettes as a cessation device and harm reducer; and 4) the recent game changing entrance of the tobacco industry into the e-cigarette business. To conclude this article, the meaning of the title of this paper "E-cigarettes: The vapor this time?" will be discussed. Borrowing from James Baldwin's *The Fire Next Time*, we will explore how nicotine addiction could evolve in the 21<sup>st</sup> century and highlight TRDRP's upcoming webcast on this "*burning issue*".

### **From Whence E-Cigarettes?**

Chinese pharmacist Hon Lik developed the first marketable electronic cigarette in 2004 (Wikipedia, 2013). However, over the past 50 years a number of attempts have been made to create and market tobacco/nicotine products that use pyrolysis (heating) as opposed to combustion (burning). From Herbert Gilbert's "smokeless non-tobacco cigarette" in 1963, through RJ Reynolds *Premier* in 1989 and *Eclipse Cigarettes* in 2000, to Philip Morris' Platforms 1, 2, and 3 heated tobacco products of today, the cigarette companies have long been in search of non-combustible cigarette alternatives (Inventor Inc; Wikipedia, 2013). As early as 1979 Dr. Norman L. Jacobson presented a paper at a meeting of the American College of Chest Physicians in Houston entitled *Non-Combustible Cigarettes-"Vaping"* (UCSF, Documents Library, 2013) an uncannily prescient description of e-cigarettes today:

“This presentation describes a practical and apparently satisfying method of administering nicotine by nicotine vapor inhalation via a non-combustible cigarette, hereafter referred to as an NCC. To our knowledge, a method of inhaling pure nicotine vapor has not been reported previously. To simplify description, we will hereafter refer to nicotine vapor inhalation through an NCC as vaping and people who inhale nicotine vapor as vapers” (UCSF Documents Library, 2013)

Not only was Jacobson’s NCC device the same size as a regular cigarette, but by measuring certain biological parameters including 24 hour cotinine measures, serum nicotine totals and carbon hemoglobin amounts, he was able to establish that the vapor was actually delivering nicotine to study participants, though a somewhat lower levels than conventional tobacco cigarettes. Cotinine levels varied between the six test subjects, with more experienced vapers getting more nicotine from the “NCC” (UCSF Documents Library, 2013). This creation ultimately became the Nicotine Inhaler that we have today (Leischow, 1994; Leischow et al., 1996),

Fast-forwarding to the 21<sup>st</sup> century, e-cigarettes are not just an idea but also a growing economic concern. In 2004 Golden Dragon Holdings, the company where he was employed, marketed Hon Lik’s device; the company subsequently changed its name to Ruyan Group (holdings) Ltd Beijing (Wikipedia, 2013). It is interesting to note that the name Ruyan in Chinese, 如烟, means “resembling smoking” (Wikipedia, 2013). Another important note is that in its inception and still today Ruyan and other e-cigarette companies in China and elsewhere market their products as smoking reduction and cessation devices.

### **The Wild, Wild West**

When e-cigarettes appeared in the United States in 2007, they quickly came under Food and Drug Administration (FDA) scrutiny. Given the rapid rise in use and the underdetermined nature of these products, the FDA blocked the importation of e-cigarettes in 2008 as unapproved drug delivery devices. (Riker et al., 2012). Concomitantly, the FDA launched a series of investigations, into the content of these new products and found that e-cigarettes were potentially hazardous to the public’s health, given the discovery of tobacco specific nitrosamines and other volatile organic compounds in e-cigarette vapor (Westenberger, 2009). Meanwhile, in May 2009, the FDA seized shipments of Sottera Inc. e-cigarettes (NJOY parent company) along with other e-cigarette producers merchandise at U.S. Customs. In response to the FDA actions, Sottera challenged the FDA and sued, arguing that e-cigarettes served the same purpose as regular cigarettes and thus should be regulated under the Family Smoking Prevention and Tobacco Control Act (FSPTCA) of 2009 as a tobacco product, not as a drug (Gonzales, 2012).

The court found in Sottera’s favor, and the FDA appealed to the US Court of Appeals for the District of Columbia, which in December 2010 in a 3-0 vote, the court ruled for Sottera, stating that the FDA can and should regulate these products under the FSPTCA and not as drug devices, *unless therapeutic claims are made* (Gonzales, 2012). In April 2011, the FDA wrote a letter to its stakeholders, [Regulation of E-Cigarettes and Other Tobacco Product](#), signed by Lawrence R. Deyton, M.S.P.H., M.D., then Director of the Center for Tobacco Products and Janet Woodcock, M.D., Director of the Center for Drug Evaluation and Research, which stated in part: “that products made or derived from tobacco can be regulated under the Tobacco Control Act unless they are “marketed for therapeutic purposes,” in which case they are regulated as drugs and/or devices. The Agency is considering whether to issue guidance and/or a regulation on “therapeutic claims” (FDA/CTP, 2011). As of this writing, the FDA has not issued such guidance.

The United Kingdom has gone in the exact opposite direction, as their Medicines and Healthcare Products Regulatory Agency has called for the regulation of e-cigarettes as medical devices for cessation by 2016. This has touched off a discussion of what this will mean in the context of the European Union (Nature, 2013; Medicines and Healthcare Products Regulatory Agency, 2013).

At the same time, UK public health advocates have urged their government to reserve its judgment on e-cigarettes until the impacts and consequences of what some would call “excessive” regulation can be properly assessed in light of e-cigarettes potential public health benefit (Bates and Stimson 2013). Others point out that if e-cigarettes are regulated as medical devices it would lead to cost increases and less product innovation; at bottom it would protect the “market monopoly of cigarettes” (Hajek, 2013)

Today, more than 2 years after the April 2011 letter, the FDA has not acted to regulate neither the product requirements nor the marketing of e-cigarettes. Instead, we have an assortment of local and state ordinances, laws and regulations defining where and who can use e-cigarettes. In California, currently there is only one statewide law on e-cigarettes, which, as of 2011, makes it unlawful for a person to sell or otherwise furnish an electronic cigarette to persons less than 18 years of age; California Health and Safety Code § 119405 (West 2013). (See [E-Cigs Code](#)). In addition, the University of California is set to enact a system wide smoking policy that would ban smoking, including e-cigarettes on its 10 campuses. The University of California, Los Angeles (UCLA) and University of California, San Francisco (UCSF) already have restrictions on smoking anywhere on campuses, indoors and outdoors and these policies both include e-cigarettes.

In the absence of statewide legislation, some local California jurisdictions have taken up the task of regulating e-cigarettes themselves. In March 2013, Contra Costa County took the lead and enacted an ordinance that explicitly states that, “E-cigarettes will no longer be permitted in places where smoking is prohibited within the county” (CCC, 2013). However, when a similar law was attempted to be enacted at the State level, the outcome was quite different. Senator Ellen Corbett proposed a bill that would regulate e-cigarettes just like regular tobacco cigarettes, thereby restricting their use in the indoor environment, among other things. However, the bill (Corbett SB 648) that had passed out of 3 Senate sub-committees met stiff opposition in the California Assembly’s Governmental Organization committee and was pulled from consideration in May 2013 before a vote could be taken (ALA, 2013).

For more background on the regulatory options see: [Regulatory Options for Electronic Cigarettes](#) For a list of e-cigarette laws and regulations by state see:



### **It is Only Water Vapor . . .**

This assertion is ubiquitous on e-cigarette vendor and purveyor websites (Tobacco Vapor Electronic Cigarette Association, 2011). While e-cigarette liquids contain nicotine, propylene glycol, and flavorants among other things, e-cigarette vapor emissions are not solely water vapor. As the studies reviewed below show, e-cigarette vapor often contains among other things, propylene glycol, heavy metals, volatile organic compounds and tobacco specific nitrosamines, albeit generally in lower concentrations than regular tobacco cigarettes. The health hazard associated with this level of exposure has not yet been determined and doing so will likely take years, since people will have to use e-cigarettes for some time before the effects of long-term exposure can be assessed.

Before reviewing these issues, it is important to point out that one of the problems with analyzing e-cigarettes and its vapor is the absence of product standards and regulation; e-cigarette cartridges often contain variable levels of nicotine solution; so generalizing between and among studies of different brands or even different e-cigarettes within the same brand is problematic.

Trehy et al., working in the Food and Drug Administration’s Division of Pharmaceutical Analysis “found that (1) the nicotine content labeling was not accurate with some manufacturers, (2) nicotine is present in the “smoke” from electronic cigarettes, and (3) nicotine related impurities contents in cartridges and refills were found to vary by electronic cigarette manufacturer.” Similarly, Cameron and colleagues in assessing seven different e-cigarette nicotine solutions found that “ the amount of nicotine present

(mg/ml) was equivalent to or lower than what was marked or expected given the manufactures concentration ranges provided (Cameron, et al., 2013). Other research shows that aerosol density of e-cigarette vapor decreased as a person vaped, necessitating users to inhale more deeply and take in greater amounts of vapor to achieve the desired nicotine content while vaping one e-cigarette (Trtchourain, Williams and Talbot, 2010). As the nicotine declines with every puff and the number of puffs increase “the efficacy of nicotine vaporization varies not only between brands but also within brands for one use to the next” (Germany study, 2013; Goniewicz (a), et al., 2013). Even under clinical laboratory conditions, e-cigarette users were not always exposed to measurable levels of nicotine (Vansickel, et al., 2010).

Keeping in mind the variability in product quality, many studies on e-cigarettes reveal a host of other chemicals, metals, VOCs, and carcinogens contained in e-cigarette vapor, most often at lower levels than in regular cigarette tobacco products. In one of the first studies to look at the content of the e-vapor, Westenberger at the FDA found detectable levels of nicotine specific nitrosamines in e-cigarette vapor, though at lower levels than cigarettes; this finding prompted the FDA to restrict the importation of e-cigarettes (see above). Westenberger also found diethylene glycol, a poisonous organic compound, in one cartridge of e-liquid (Westenberger, 2009). To date no other studies have found this compound in an e-cigarette liquid. Nonetheless, given the lack of product standards in the field, it is sobering that a product tainted by a potentially deadly chemical could be purchased by an unsuspecting consumer. At the same time that Westenberger produced his report, Murray Laugesen, working for Ruyan E-Cigarettes, presented a poster at the Society for Research on Nicotine and Tobacco that showed in this brand that there were 50 cigarette smoke toxicants, however none were found above “trace” amounts (Laugesen, 2009). Romagna et al., in a poster presented at the European meeting of the SRNT, found that, compared to cigarettes, which produced nicotine, acrolein, toluene, exylone and PAHs, e-cigarette emissions had none of these chemicals, when measured in the indoor environment (Romagna, et al, 2012). In the subsequently published paper investigating the cytotoxicity of e-cigarette emissions, the authors found that of “21 commercially available EC liquids we tested in vapor form, only one was found to have cytotoxic effects on cultured mammalian fibroblast cells according to ISO 10993-5 definition” (Romagna et al., 2013).

Other published studies have found numerous chemicals in e-cigarette vapor again at lower levels than that in conventional cigarettes. Comparing pollutant concentrations, including volatile organic compounds (VOCs), carbonyls, Polycyclic Aromatic Hydrocarbons (PAHs), nicotine TSNA and glycol between e-cigarettes and regular cigarettes, McAuley et al., found that “No-Significant Risk” from vapor samples of e-cigarettes was detected (McAuley, 2012). It must be noted here that there may be serious flaws in this paper. Dr. Stanton Glantz, among others, noticed that in the McAuley’s article that “they did not detect any benzo(a)pyrene in the conventional cigarette smoke despite the fact that it has been established for over half a century that benzo(a)pyrene is an important carcinogen in cigarette smoke.” Additionally, Glantz points out that “The most amazing conclusion in the paper (on page 855, second column, 11 lines from the top), however, is that “neither vapor from e-liquids **or cigarette smoke** analytes posed a condition of ‘Significant Risk’ of harm to human health via the inhalation route of exposure” (Glantz Blog, 2013).

Another major e-cigarette study by Maciej Goniewicz, and colleagues, entitled, *Levels of selected carcinogens and toxicants in vapour from electronic cigarettes*, has demonstrated that e-cigarette vapor contains VOCs, at much lower levels than in regular tobacco smoke (Goniewicz, et al, 2013). The authors found “that the e-cigarette vapours contained some toxic substances. The levels of the toxicants were 9-450 times lower than in cigarette smoke . . .” The authors state that “Our findings are consistent with the idea that substituting tobacco cigarettes with e-cigarettes may substantially reduce exposure to selected tobacco-specific toxicants.” (Goniewicz, et al, 2013). Formaldehyde, acrolein, toluene, NNN, NNK or heavy metals in e-cigarette were found in substantially lower concentrations than in regular tobacco smoke. The authors do note that carbonyl compounds have been shown to be toxic;

formaldehyde is a known carcinogen and acrolein has been shown to “cause irritation of the nasal cavity, and damage to the lining of the lungs and is thought to contribute to cardiovascular disease in cigarette smokers” (Goniewicz, et al, 2013). The afore mentioned article also compared e-cigarette vapor to a nicotine inhaler and found that while NNN and NNK were found in the e-cigarette vapor, none of these carcinogens were found in the nicotine inhaler.

Other researchers have found other toxicants in e-cigarette liquids and vapor at much higher concentrations. Williams et al., in looking at metal and silicate particles in electronic cigarette cartomizer fluid and aerosol, found that “The concentrations of nine of eleven elements in the EC aerosol were *higher than or equal to* the corresponding concentrations in conventional cigarette smoke. Many of the elements identified in EC aerosol are known to cause respiratory distress and disease” (Williams, et al., 2013). Specifically, this team found elevated readings in e-cigarette aerosol for tin, silver, iron, nickel aluminum and silicate nanoparticles (Williams et al., 2013). Moreover, tin whiskers and particles were found in the cartomizer fluid and upon testing determined to be cytotoxic in assays using human pulmonary fibroblasts (Williams et al., 2013).

Not only are metals, carcinogens and VOCs inhaled by e-cigarette users but these chemicals are being released into the indoor environment, and as it would be expected, secondhand vaping takes place. It has been reported that e-cigarette vapor interacts with the human lung causing changes in the sizes of the aerosol particles; these particles enter the lung larger than when they are exhaled (Schripp et al., 2012). Schripp and colleagues, in their article, *Does e-cigarette consumption cause passive vaping?* answers the question decisively:

“The consumption of e-cigarettes causes emissions of aerosols and VOCs, such as 1,2-propanediol, flavoring substances, and nicotine, into indoor air. During inhalation of e-cigarette vapor, the aerosol size distribution alters in the human lung and leads to an exhalation of smaller particles. This effect is caused by the evaporation of the liquid particles in the lung and in the environment after exhalation. The quantity of the inhaled vapor could be observed to depend on the “liquid” delivery system of the e-cigarette in use. Overall, the e-cigarette is a new source of VOCs and ultrafine/fine particles in the indoor environment. Therefore, the question of “passive vaping” can be answered in the affirmative. However, with regard to a health-related evaluation of e-cigarette consumption, the impact of vapor inhalation into the human lung should be of primary concern” (Schripp et al., 2013)

Only a few reports have been published indicating that e-cigarettes have immediate effects on the user. Vardavas and his team in their article, *Short-term Pulmonary Effects of Using an Electronic Cigarette*, found that only after 5 minutes of use, e-cigarettes had immediate adverse physiologic effects, similar to some of the effects seen with tobacco smoking, including decreased Fractional exhaled Nitric Oxide (FeNO). FeNo shows the retardation of lung function, which accounts for people reporting difficulty in breathing. This measure is often used in assessing person with asthma. Vardavas and his team also found that using e-cigarettes increased respiratory resistance; both the FeNO and respiratory findings were statistically significantly different comparing e-cigarettes with nicotine to a control group of e-cigarettes without nicotine in them (Vardavas, 2012).

In another report, Drs. McCauley, Markin and Hosmer found some unexpected consequences of e-cigarette use. One patient of theirs had been reporting over a 7-month period, dispnea, coughing and fever and even after numerous antibiotic treatments the patient’s symptom continued. After hospitalization and a thorough medical work up, the doctors discovered that the patient had lipoid pneumonia occasioned by the regular inhalation of vaporized nicotine. The patient was instructed to avoid the use of e-cigarettes and her symptoms improved. The authors state that this was the first time that they had observed lipoid pneumonia from inhaled vaporized nicotine; nor is there extant literature on this phenomenon. “Prior discussion regarding the safety of e-cigarettes has primarily focused on nicotine

and other carcinogenic compounds. Certainly the risk of lipid pneumonia adds another dimension to the super-charged social, political, and medical debate surrounding the regulation and legality of e-cigarette use” (McCauley, Markin and Hosmer, 2011).

Propylene glycol is found in a number of FDA approved products, including foods, cosmetics and the Nicotine Inhaler (FDA, 1982). However, even the FDA data sheet warns that propylene glycol causes eye and respiratory irritation and exposure should be limited. There are a few studies indicating that the mist has acute respiratory and ocular effects. Wielander and colleagues exposed 27 subjects to propylene glycol mist, for 1 minute and found that even at that short duration that a person’s “tear film stability decreased, ocular and throat symptoms increased, forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) was slightly reduced, and self rated severity of dyspnoea was slightly increased” (Wielander, Norback and Lindfren, 2001). Similarly, though not e-cigarettes, Varughese and team measured personal exposure of stage performers to propylene glycol; subjects reported reduced lung function the closer they were to the fog (Varughese, et al., 2005). Even though propylene glycol is FDA approved for use in some products, the inhalation of vaporized nicotine in propylene glycol is not. Some studies show that heating propylene glycol changes its chemical composition producing small amounts of propylene oxide, a known carcinogen (Henderson et al., 1981). Clearly, more study is needed to see if these changes occur when propylene glycol is heated in e-cigarettes.

In a 2013 review, Igor Burstyn (Burstyn 2013) examined the extant of literature using as a basis for comparison “ the most universally recognized workplace exposure standards, Threshold Limit Values (TLVs), ... (and) conducted under “worst case” assumptions about both chemical content of aerosol and liquids as well as behavior of vapors. Emphasizing the benign nature of e-cigarettes, Burstyn, in his 2013 article, *Peering through the mist: What does the chemistry of contaminants in electronic cigarettes tell us about health risks?* The author found that:

“an analysis of current state of knowledge about chemistry of liquids and aerosols associated with electronic cigarettes indicates that there is no evidence that vaping produces inhalable exposures to *contaminants* of the aerosol that would warrant health concerns by the standards that are used to ensure safety of workplaces. However, the aerosol generated during vaping as a whole (*contaminants plus declared ingredients*), if it were an emission from industrial process, creates personal exposures that would justify surveillance of health among exposed persons in conjunction with investigation of means to keep health effects as low as reasonably achievable. Exposures of bystanders are likely to be orders of magnitude less, and thus pose no apparent concern” (Burstyn, 2013).

Criticism immediately arose concerning the author’s use of Threshold Limit Values. Commenting on this paper Dr. Stanton Glantz suggested that:

“TLVs are for occupational exposures. Occupational exposures are generally much higher than levels considered acceptable for ambient or population-level exposures. Occupational exposures also do not consider exposure to sensitive subgroups, such as people with medical conditions, children and infants, who might be exposed to secondhand e-cigarette emissions. Finally, even when setting allowable occupational exposures, regulatory agencies like OSHA often establish tighter standards than TLVs, and often those tighter levels have been criticized as not being health protective” (Glantz blog, Aug, 2013).

### **Fetal Exposure . . .**

There are many studies that demonstrate the relationship between smoking cigarettes by the mother and poor health outcomes for both the mother and the fetus. Many of these have been summarized in a journal article by Wickstrom (2007). On the other hand, at present there are virtually no studies on e-

cigarettes and pregnancy. To complicate matters further, cigarette smoke contains thousands of toxic chemicals, most at greater concentrations than those in e-cigarettes. Moreover, nicotine concentrations in e-cigarette aerosol are less than nicotine concentrations in regular nicotine cigarettes. Nonetheless, some studies have isolated the effects of nicotine, the active ingredient in e-cigarettes from other toxins in regular cigarettes.

Nicotine easily crosses the placental barrier and studies have found that “fetal circulation [of nicotine] at levels exceeding maternal concentrations by 15%, and amniotic fluid concentrations of nicotine...88% higher than maternal plasma” (Wickstrom, 2007; Luck, et al., 1985; Pastrakuljic et al., 1998). Nicotine also accumulates in breast milk, extending the nicotinic exposure to the postnatal period during breastfeeding (Wickstrom, 2007). Studies have shown there is a negative impact of nicotine on the developing human brain both among fetuses and in kids, is a result of the existence of nicotine receptors in the brain during the first trimester (Helstrom, Nordber, 2002). In an animal model, exposing developing rats to extremely low doses of nicotine in utero causes learning, attention, and memory deficits consistent with cognitive deficits seen in ADHD; deficits that seem to extend into adulthood (Levine, et al., 1993). Other research has shown that: “lowering the dose of nicotine in rats to the point where growth impairment vanishes, and where plasma levels match those of moderate smokers, still produces all the signs of fetal brain damage that are seen at higher doses (Slotkin, 1998). This finding has high clinical relevance since intrauterine growth retardation is the most commonly used predictor of adverse perinatal outcome in offspring of smokers (DiFranza JR, Lew RA., 1995)

Furthermore nicotine may raise the risk of pre-eclampsia in the mother through effects on the cardiovascular system, for example by causing endothelial dysfunction or raising blood pressure” (Quoted in Wickstrom, 2007 from England, et al., 2003). Pre-eclampsia is a dangerous condition that can lead to seizure, stroke, multiple organ failure and death of the mother and/or baby. Given the adverse effects of nicotine on growth and neurological development in the fetus and the increased risk of pre-eclampsia risk in the mother, it is safe to assume that e-cigarette use, like conventional cigarette use, alcohol and caffeine, should be contraindicated for pregnant women. It might be prudent to restrict the public exposure of “secondhand” e-cigarette vapor, especially given nicotine potential negative fetal outcomes.

This was a short and abbreviated review of the toxicological literature concerning e-cigarettes. All studies seem to agree that there are many toxic chemicals in e-cigarettes. Correspondingly, most studies would agree for the most part, toxins in e-cigarettes are at concentrations lower than in regular tobacco cigarettes. However, the idea that e-cigarette emissions are just water vapor should be laid to rest.

### **A Cessation Device; a Harm Reducer . . .**

Most, if not all, e-cigarette proponents argue that this device is a ‘harm reduction product’ and that if people simply replaced all cigarettes with e-cigarettes (and nothing else changed) the lives saved and the betterment of the public’s health would be substantial (Cahn Z, Siegel M., 2010). I would hope that this would be the case, too. However, the available data does not support this hope. The cessation studies show that while there have been reductions in person’s regular tobacco cigarette consumption, what we see more often than not is that individuals persist in using both e-cigarettes and regular cigarettes, what is commonly called “dual use”.

In 2011, Polosa et al., reported “sustained 50% reduction in number of cig/day at week-24 was shown in 13/40 (32.5% participants; their median of 25 cigs/day decreasing to 6 cigs/day ( $p < 0.001$ )” The authors go on to point out that “sustained 80% reduction was shown in 5/40(12.5%) participants; their median of 30 cigs/day decreasing to 3 cigs/day ( $p = 0.043$ ). Sustained smoking abstinence at week-24 was observed in 9/40(22.5%) participants, with 6/9 still using the e-cigarette by the end of the study. Combined

sustained 50% reduction and smoking abstinence was shown in 22/40 (55%) participants, with an overall 88% fall in cigs/day.”

In another study, Caponnette et. al., comparing three different groups; Group A received 7.2 mgs of e-nicotine, Group B for the first 6 weeks received 7.2 but after that received 5.4 mgs of e-nicotine and Group C received no nicotine cartridges in their e-cigarettes. Collapsing the three groups together, the authors report that “smoking reduction was documented in 22.3% and 10.3% at week-12 and week-52 respectively. Complete abstinence from tobacco smoking was documented, again collapsing groups, in 10.7% and 8.7% at week-12 and week-52 respectively. (Caponnette et al., 2013). These authors go on to report that there were significant reductions in cigarettes used per day amongst the 3 groups; baseline to week 52 saw declines in group A from 19 to 11; in group B from 21 to 10; and in Group C regular cigarette use drop from 22 to 12 (Caponnette, et al., 2013).

These findings from these two studies are not surprising; a small percentage of people quit and another larger group reduced their regular tobacco cigarette use. However, let us train another lens on the findings reported above. In the Polosa study, only nine of the 40 people stopped smoking altogether, while 31 of the people (77.5%) continued to smoke regular tobacco cigarettes, albeit at a reduced level. Similarly in the Caponnette study, there were substantial reductions in regular tobacco use across groups; still at the end of the day 162 people of the remaining 183 people at week-52 were smoking cigarettes, or 89% of participants; most of them a half a pack a day.

In a recent 4 country survey, Sarah Adkison, et al., found that the “Prevalence of trying ENDS [Electronic Nicotine Delivery System] was higher among younger, nondaily smokers with a high income and among those who perceived ENDS as less harmful than traditional cigarettes. Current use was higher among both nondaily and heavy ( $\geq 20$  cigarettes per day) smokers. In all, 79.8% reported using ENDS because they were considered less harmful than traditional cigarettes; 75.4% stated that they used ENDS to help them reduce their smoking; and 85.1% reported using ENDS to help them quit smoking.” These authors concluded that since the majority of their sample was non-daily smokers and people interesting in quitting, that e-cigarettes “may have the potential to serve as a cessation aid” (Adkison, et al., 2013).

Again, as in the two previous studies, this study showed a reduction in cigarette use by e-cigarette users, hinting at the potential as a cessation device. However, as the authors point out: “Notably, 85% (n=146) of current ENDS users stated that they used ENDS as a tool to help them quit smoking, although only 11% of current ENDS users report having quit since Wave 7. Quitting did not differ between users and non-users, chi-square (2, n=4136) = 0.442 (P=0.516).” (Adkison, et al., 2013). These cessation results directly contradict the widely made claim that e-cigarettes are an effective aid for cessation. There was no difference in cessation between the people using e-cigarettes and those who were not using them. Hence, here is the dilemma in a nutshell: after a year of using e-cigarettes as a cessation device, the vast majority, 89%, had not quit and were still using regular cigarettes.

In another study, Vickerman and colleagues looked at e-cigarette use among tobacco cessation quitline callers (Vickerman et al., 2013). This six state survey collected data on 2758 treatment seekers at baseline and then again a 7 months. The authors found that: “Nearly one third (30.9%) of respondents reported ever using or trying e-cigarettes; most used for a short period of time (61.7% for less than 1 month). The most frequently reported reasons for use were to help quit other tobacco (51.3%) or to replace other tobacco (15.2%).” The authors also found that “Both e-cigarette user groups were significantly less likely to be tobacco abstinent at the 7-month survey compared with participants who had never tried e-cigarettes (30-day point prevalence quit rates: 21.7% and 16.6% vs. 31.3%,  $p < .001$ ) (Vickerman et al., 2013). In other words, people using e-cigarettes were significantly *less* likely (by about 1/3) to have quit cigarettes at follow-up.

Most recently, Christopher Bullen and his team published the results of a randomized controlled clinical trial in *Lancet* comparing e-cigarettes, Nicotine Replacement Treatment (NRT) and e-cigarettes without nicotine. The authors found no significant difference in cessation rates between the NRT and nicotine e-cigarettes. Even though at 6-months 7.3% of e-cigarette users remained abstinent compared to 5.8% of those using NRT, the difference between conditions was not statistically significant: “Achievement of abstinence was substantially lower than we anticipated for the power calculation, thus we had insufficient statistical power to conclude superiority of nicotine e-cigarettes to patches or to placebo e-cigarettes . . . E-cigarettes, with or without nicotine, were modestly effective at helping smokers to quit, with similar achievement of abstinence as with nicotine patches, and few adverse events” (Bullen, et al., 2013)

Dual use is a major issue, since numerous research studies have shown that smoking as few as 1 to 4 cigarettes a day significantly increases the chances of disease and mortality. Bjartveit and Tverdal have shown in a sample of 23 521 men and 19 201 women, aged 35–49 years, screened for cardiovascular disease risk factors in the mid 1970s and followed throughout 2002, that “smoking 1–4 cigarettes per day was associated with a significantly higher risk of dying from ischaemic heart disease and from all causes, and from lung cancer in women” (Bjartveit and Tverdal, 2005). Shane, Ling and Glantz in a review of the literature found 16 peer-reviewed articles that showed that light and or intermediate smokers were still at significant risk for a whole host of maladies, including cardiovascular disease, lung, gastric, and esophageal cancer (Shane, Ling and Glantz, 2010). Thus, even though e-cigarette users appear to reduce their regular tobacco cigarette consumption while using e-cigarettes, this may not confer any real reductions in the risk of tobacco-induced disease.

It is important to note that most cessation regimens and the studies that report on them have similar findings; the majority of people are not successful. It should be kept in mind that a nicotine patch does not deliver any VOCs or heavy metals, while the toxicological consequences of e-cigarette constituents and vapor are yet to be determined. This point should not be lost on clinicians and users alike. On the other hand, the lower cost; the freedom from prescription; the accepted mode of delivery of nicotine; the more satisfying user experience reported; and social cachet of e-cigarettes as compared to the nicotine patch may make them preferable to consumers and more culturally acceptable (Etter and Bullin, 2011; Barbeau, Borda and Siegel, 2013).

### **Enter the Merchants of Death**

With Lorillard’s acquisition of Blu Electronic Cigarettes in April of 2012 for a mere \$135 million, the tobacco industry is moving to harness the e-cigarette business and its profits and tie it inextricably to the existing tobacco industry. Let us be clear, smokable tobacco is responsible for most of the deaths globally and in the United States and the corporations responsible are increasingly assuming production and marketing of e-cigarettes. Given industry history, these strategic moves in and of themselves clearly warrant heightened scrutiny by industry watchdogs and regulators

These strategic moves have already begun generating increased revenue for Lorillard, where Blu contributed \$61 million in total sales, responsible for a 10% increase in profits in the second quarter of 2013 (News & Record, September 2013), just a year after Lorillard bought Blu. The acquisition of Blu by Lorillard appears to have forced the hands of other major regular tobacco cigarette makers. Recognizing the warning sign, British American Tobacco (BAT) has begun to put its imprimatur on the e-cigarette business in the United Kingdom, hence worldwide. With the acquisition of CN Creative, a Manchester based e-cigarette company, and with the announcement that Nicotventures (a BAT subsidiary), BAT launched its own e-cigarette, Vype in July, thus placing itself squarely in the e-cigarette business (Vapor Ranks, July 2013). The Chief Financial Officer (CFO) for BAT stated, “The size of the market for tobacco alternatives could account for as much as 40% of BAT’s revenues in 20 years’ time” (Vapor Ranks, April 2013). Not to be outdone, RJ Reynolds (RJR), the 2<sup>nd</sup> largest cigarette

maker in the United States entered the fray. In June 2013, Reynolds's CEO and President announced that RJR would be test marketing their own e-cigarette, Vuse. Reynolds intends that Vuse will be distinguished from its competitors through its "technical" superiority; its digital technology will ensure "a perfect puff, first time, every time" (Felberbaum, June, 6, 2013). Not only is the Reynolds product microprocessor-driven, tobacco experts are also and most importantly developing it! Please view the Vuse commercial, it is a must see: [Vuse ad](#).

Within weeks of the introduction of Vuse, Altria presented the public with its own e-cigarette, MarkTen. Being test marketed in the fall of 2013 in Indiana, Altria expects that Mark Ten along with other e-cigarettes will come under FDA regulation in the not too distant future. The company promotes the fact that liquid nicotine in the Mark Ten is derived directly from tobacco leaves and is not synthetic. Many industry observers were initially expecting Altria to buy out one of the existing e-cigarette companies, like NJOY, currently second as market leader, but for now that does not seem to be the case. While the conventional wisdom says that Altria is very late to the game, and alternative hypothesis has arisen suggesting that it was in their long-term best interest to enter late and gradually. Tobacco and Beverages analyst, Bonnie Herzog at Wells Fargo securities suggests that, "Despite the perception MO's [Altria's] MarkTen is somewhat of a "me too" product and that MO was late to the e-cig party, we are now more confident MO has the ability to leverage its war chest of cash, its sizeable infrastructure, its deep understanding of the tobacco consumer, and its entrenched position at retail." She further states, "we increasingly believe that MO's strategy to enter more slowly could prove to be quite shrewd as it 'rides on the coattails' of LO [Lorillard], and others, as they spend millions of dollars to develop the category." (Herzog, September, 2013).

The American banking, securities and marketing sectors, are quite bullish on e-cigarettes. Herzog has mentioned many times over the past few months that Wells Fargo believes that e-cigarettes will surpass regular cigarettes in sales in the next decade (by 2023) (Herzog, 2013). Moreover, in her June 2013 forecast, she suggests that:

"We now anticipate the e-cig market will approach \$2B in retail sales (including online) by the end of 2013 and eclipse \$10B by 2017. Importantly, our analysis indicates that e-cigs could be margin enhancing to the combined category in the near term and by 2017, we predict e-cig margins could approach the mid 40% range, higher than current conventional cig margins of approximately 40%. Furthermore, we increasingly believe the entrance of the "Big 3" tobacco manufacturers could catapult the growth of the e-cig category driving the total conventional cig and e-cig profit pool up by a CAGR [Compound Annual Growth Rate] of 7% over the next decade" (Herzog, 2013).

It is important to underscore that the banking and investment sectors are forecasting that e-cigarettes are going to push both e-cigarette and conventional cigarette profits up across the board. It is not a stretch to assume that the corporate strategy that is unfolding involves marketing e-cigarettes as a "lite" nicotine alternative while also continuing to offer the "stronger" alternative (regular cigarettes). Where have we seen this strategy before?

The entry of the tobacco industry into the e-cigarette arena should be a wake-up call to the FDA and tobacco control advocates alike. Regulation of e-cigarettes, production standardization, quality control polices and mitigation of e-waste from these devices is essential if they are to become, as some would hope, a way to reduce the toll of disease and death from smoking. The public health community might want to consider e-cigarettes in the "end-game" discussions; e-cigarettes *may* be a key to ending the dominance and resulting death from conventional cigarettes. This possibility should not be dismissed out-of-hand without substantive research and discussion. At the same time harm reductionist should be cautioned about their association with the tobacco industry in this endeavor and their consequences, should e-cigarettes be found detrimental to the public's health in the long term.

## **E-Cigarettes: The Vapor This Time?**

The vapor had been with us for more or less 10 years now. While a plethora of local regulations abound, we are ending 2013 without any national regulations on the fastest rising product on the nicotine market. We know that e-cigarette emissions are much more than just water vapor. At the same time, the long-term effects of these products remain unknown.

The 21<sup>st</sup> century poses a daunting task for those of us in tobacco control. If we are to believe the investment experts that nicotine from e-cigarettes that is vaporized will be the norm within the next 10 years, a revolutionary shift in nicotine consumption has begun. Keep in mind that this revolution could be short lived, if studies continue to show dual use on the part of e-cigarette consumers. Still, e-cigarettes are already beginning to change some cultural norms and standards. It will not be “smoke getting in her eyes,” ala the 20th century, rather, will it be the vapor this time in the 21<sup>st</sup> century? The question mark is important; this is a decision that not only smokers, often teens and pre-teens, are now making. The recent findings by the Centers for Disease Control and Prevention were sobering in this regard to say the least: Among Middle and High School Students, e-cigarette use doubled rising from 4.7 percent in 2011 to 10.0 percent in 2012 for those who had ever used these products. Additionally, e-cigarette use rose from 1.5 percent to 2.8 percent for teens reporting use in the past 30 days. The CDC estimates that in 2012 more than 1.78 million middle and high school students nationwide had tried e-cigarettes. Moreover, most problematic, 76.3% of youth who used e-cigarettes within the past 30 days also smoked conventional cigarettes in the same period (MMWR, CDC, 2013).

As tobacco control advocates and scientists, we must understand sooner rather than later what e-cigarette consumption means for public health; for the average e-cigarette consumer. The challenge is mustering the will and ability to make sensible policy decisions before all the questions have been answered which will, as noted above, take many years. It was not too long ago that doctors along with tobacco companies were advancing claims that cigarette smoking was harmless. People around the world rapidly embraced this and smoking became the norm. You could drive a car, operate machinery, hold a conversation and, AND also be addicted to a drug. It took decades, following their mass introduction during and following WWI, to discover that cigarettes were the main purveyors of disease and death worldwide. We sit here in the second decade of the 21<sup>st</sup> century confronted with a similar and equally important question: Is it the Vapor this Time and what should be done?

TRDRP’s e-cigarette webcast “The Vapor This Time?”, the title adapted from James Baldwin’s excellent account of the brewing storm in the United States African American community in the 1960’s, is the program’s attempt to bring the discussion of e-cigarettes, both pro and con, to a broader audience. Understanding and listening to varied viewpoints can only help us all make the right decisions in the future.

Minimally, we must learn from the past. I’ll add my personal perspective here and use James Baldwin’s excellent account of the brewing storm in the United States African American community in the 1960’s, as an analogy. In 1963, distinguished Black author James Baldwin, published a quite prophetic novel, *The Fire Next Time* (Baldwin, 1963). While it focused on a biblical passage: God gave Noah the rainbow sign, said the fire next time, it was alerting all of us to the impending fire about to explode and rage across United States in the years to come. Baldwin’s prediction was spot on; inner city Black communities erupted in protest and fought back against the racial and oppressive conditions that they had faced since day one in this country. *The Fire Next Time* was published in 1963, by 1964, Harlem was ablaze in the summer; Watts erupted in the summer of 1965; and Detroit and Newark among a host of other cities followed suit in the fight for Black freedom and equality.

What does this have to do with e-cigarettes? Everything! James Baldwin's, *The Fire Next Time* was a warning; *The Vapor this Time* is too. In a perfect world, e-cigarettes would be highly effective cessation devices, weaning smokers off lethal tobacco cigarettes. However, what appear to be clear warning signs are visible: many people are opting to be dual users; the nicotine released in the vapor is likely to be hazardous to pregnant women; and regardless of whether you are using regular cigarettes or e-cigarettes, the tobacco industry's entrance into the global e-cigarette market place should give us all pause. The cigarette companies are clear and we should be too, the tobacco industry's venture into the e-cigarette market is solely to accelerate its profits, not save lives. Bonnie Herzog, from Wells Fargo put the matter succinctly:

“. . . we increasingly believe the entrance of the “Big 3” tobacco manufacturers could catapult the growth of the e-cig category driving the total conventional cig and e-cig profit pool up by a CAGR of 7% over the next decade” [emphasis in the original] (Herzog, 2013) [CAGR: Compound Annual Growth Rate]

Lest we forget the bottom line . . .

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### **The Tobacco Related Disease Research Program live webcast: E-Cigarettes: The Vapor This Time?**

This event will take place Thursday, October 3, 2013 from 1pm to 4pm PDT at University of California San Francisco, Health Sciences West, 301. The following leaders in the field of e-cigarette research will serve as panelists for this most important discussion:

Monique Williams, ABD, from the Environmental Toxicology Department University of California, Riverside will lead off the webcast. Her presentation entitled: *E-Cigarette Liquids and Vapors: Is it Harmless Water Vapor?* Ms. Williams' talk will review what is in electronic cigarette cartridge fluid and refill fluid as well as the inhaled and exhaled aerosol. While some claim e-cigarettes emit only water vapor, Ms. Williams' own research and that of others suggest the situation is more complex.

Prudence Talbot, Ph.D. is the Director of the UCR Stem Cell Center and Stem Cell Core Facility University of California Riverside and will follow Ms Williams. Dr. Talbot's presentation is entitled: *Electronic Cigarettes: How Will They Impact Human Health?* Dr. Talbot's presentation will focus on the personal and public health effects of e-cigarettes. Clearly, there is no literature on the long-term health effects since these products are just now coming into general use. Dr. Talbot will review the few studies that have assessed the immediate health impact of these products. Dr. Talbot will also suggest some things that users should be concerned about going forward.

Natalie Walker, Ph.D., is a Heart Foundation Douglas Senior Fellow in Heart Health (Prevention), National Institute for Health Innovation, School of Population Health, University of Auckland, New Zealand. Following Dr. Talbot, Dr. Walker's talk is entitled: *E-Cigarettes: A 21st Century Cessation Device?; A Review of the Literature.* Dr. Walker will present a review of the literature on the use of e-cigarettes for smoking cessation. She will discuss how successful these products are as a cessation aid, and how they compare to other cessation methods. Dr. Walker is a co-author of the recently published trial “*Electronic cigarettes for smoking cessation: a randomised controlled trial* (Bullen C, et al., *Lancet* 2013). She will report on the findings of this trial in her presentation.

Jean-François Etter, Ph.D., is Professor of Public Health and Faculty of Medicine at the Institute of Social & Preventive Medicine at the University of Geneva, Switzerland  
Dr. Etter's presentation: *The Profile of Vapers and How E-Cigarettes Should be Regulated* will be streamed in Live from Geneva. Dr. Etter will review the surveys of e-cigarette users and describe the profile of 'vapers', their reasons for using e-cigarettes and perceived effects. He will also summarize the current regulation on e-cigarettes and how, ideally, these products should be regulated. Dr. Etter is arguably an internationally recognized proponent for e-cigarettes.

Stanton Glantz, Ph.D., is the Director at the Center for Tobacco Control Research & Education University of California San Francisco. Another world-renowned speaking, Dr. Glantz will close the presentation part of the webcast as a Discussant with remarks about: E-cigarettes: Where are we; Where Should We Go? Dr. Glantz has been asked to comment on and reflect on the four panelists and their presentations, particularly pointing out where the field needs to go as it relates to e-cigarettes. Increasingly, Dr. Glantz has been speaking out both publically and through his Blog on the necessity to regulate e-cigarettes just like regular tobacco cigarettes.

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