Electronic Cigarettes: How Will They Impact Human Health?

Prue Talbot
TRDRP Electronic Cigarette Webinar
10-3-2013
• Conflict of Interest: none

• Disclosures:
  • Our lab receives funding from TRDRP, training grants, and Fellowships and Internships from NIH, NSF, TRDRP, CIRM and support for a shared Stem Cell Core Facility from CIRM
Health Risks Linked to Conventional Smoking

<table>
<thead>
<tr>
<th>Smoking</th>
<th>Secondhand Smoke Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancers</td>
<td>Children</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>Stroke</td>
</tr>
<tr>
<td>Larynx</td>
<td>Blindness, cataracts</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Periodontitis</td>
</tr>
<tr>
<td>Trachea, bronchi, and lung</td>
<td>Acute anemia</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>Atherosclerotic peripheral vascular disease</td>
</tr>
<tr>
<td>Stomach</td>
<td>Chronic obstructive pulmonary disease, asthma, and other respiratory effects</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Hip fractures</td>
</tr>
<tr>
<td>Kidney and ureter</td>
<td>Reproductive effects in women (including reduced fertility)</td>
</tr>
<tr>
<td>Cervix</td>
<td>Bladder</td>
</tr>
</tbody>
</table>

Risks From Smoking During Pregnancy

Smoking can cause problems for a woman trying to become pregnant or who is already pregnant, and for her baby before and after birth.

Effects on Mothers
- Difficulty getting pregnant
- Placenta separates from the womb too early, causing bleeding
- Placenta covers the cervix, causing complications
- Water breaks too early

Effects on Babies
- Baby born too small
- Baby born too early
- Sudden infant death syndrome
- Fetal death
- Infant death
- Miscarriage
- Certain birth defects, such as:
  - Cleft lip/palate
  - Clubfoot
  - Gastrochisis
  - Some heart defects
  - Cryptorchidism

ACTIVE SMOKER | PASSIVE SMOKER | PRENATAL EXPOSURE
Do EC Present Health Benefits/Risks?

Are EC safer than conventional cigarettes?

Do EC reduce the risk of cancer and other adverse effects linked to conventional cigarettes?

Do any EC health effects overlap those of conventional cigarettes?

Do EC produce their own set of positive/negative health effects?
Health Effects of Electronic Cigarettes

In vitro studies using cells models
Animal studies
Human studies/Clinical Trials

Types of study design

- Experimental
  - Randomised Controlled Trial (RCT)
  - Cohort (longitudinal)
  - Case-control
  - Cross-sectional
- Observational
  - Ecological (population-based)

Epidemiological/Infodemiological Studies
In Vitro Cytotoxicity of EC Refill Fluids

Cytotoxicity = ability of a chemical to kill cells

IC$_{50}$ = dose that kills half the cells

Purpose: 1. Compare relative cytotoxicity of different refill fluid products
2. Determine if cytotoxicity varies with different cells types

Study was motivated by EC users who asked us to evaluate refill fluids that made them ill.
Strategy for Cytotoxicity Screen

- Two humectants
- Five products that made users ill
- 34 Refill fluids from 4 companies

Bahl et al 2012 Reproductive Toxicology 34:529
### Hierarchy of Cytotoxicity for 41 Refill Fluids

<table>
<thead>
<tr>
<th>Electronic cigarette refill fluid name</th>
<th>Company</th>
<th>Nicotine (mg/ml)</th>
<th>hESC IC$_{50}$</th>
<th>NOAEL</th>
<th>mNSC IC$_{50}$</th>
<th>NOAEL</th>
<th>hPF IC$_{50}$</th>
<th>NOAEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propylene Glycol</td>
<td>FS-USA²</td>
<td>&gt;1</td>
<td>0.3</td>
<td>&gt;1</td>
<td>0.3</td>
<td>&gt;1</td>
<td>&gt;1</td>
<td></td>
</tr>
<tr>
<td>Vegetable Glycerin</td>
<td>FS-USA</td>
<td>&gt;1</td>
<td>&gt;1</td>
<td>&gt;1</td>
<td>&gt;1</td>
<td>&gt;1</td>
<td>&gt;1</td>
<td></td>
</tr>
<tr>
<td>Bubblegum</td>
<td>FS-USA</td>
<td>24mg</td>
<td>&gt;1</td>
<td>0.3</td>
<td>&gt;1</td>
<td>0.3</td>
<td>&gt;1</td>
<td></td>
</tr>
<tr>
<td>Butterscotch</td>
<td>FS-USA</td>
<td>0mg</td>
<td>&gt;1</td>
<td>0.3</td>
<td>&gt;1</td>
<td>0.1</td>
<td>&gt;1</td>
<td>0.001</td>
</tr>
<tr>
<td>Butterscotch</td>
<td>FS-USA</td>
<td>6mg</td>
<td>&gt;1</td>
<td>0.1</td>
<td>&gt;1</td>
<td>0.1</td>
<td>&gt;1</td>
<td></td>
</tr>
<tr>
<td>Caramel</td>
<td>FS-USA</td>
<td>0mg</td>
<td>&gt;1</td>
<td>0.3</td>
<td>&gt;1</td>
<td>0.1</td>
<td>&gt;1</td>
<td></td>
</tr>
<tr>
<td>Caramel</td>
<td>FS-USA</td>
<td>6mg</td>
<td>&gt;1</td>
<td>0.3</td>
<td>&gt;1</td>
<td>0.3</td>
<td>&gt;1</td>
<td></td>
</tr>
<tr>
<td>Chocolate Biscotti</td>
<td>FS-USA</td>
<td>24mg</td>
<td>&gt;1</td>
<td>0.3</td>
<td>&gt;1</td>
<td>0.3</td>
<td>&gt;1</td>
<td></td>
</tr>
<tr>
<td>Caramel</td>
<td>Global Smoke</td>
<td>18mg</td>
<td>0.75</td>
<td>0.1</td>
<td>&gt;1</td>
<td>0.3</td>
<td>0.41</td>
<td>0.01</td>
</tr>
<tr>
<td>Butterfinger</td>
<td>FS-USA</td>
<td>24mg</td>
<td>0.51</td>
<td>0.1</td>
<td>&gt;1</td>
<td>0.3</td>
<td>&gt;1</td>
<td></td>
</tr>
<tr>
<td>Menthol Arctic</td>
<td>FS-USA</td>
<td>0mg</td>
<td>0.45</td>
<td>0.3</td>
<td>&gt;1</td>
<td>&gt;1</td>
<td>0.45</td>
<td>0.3</td>
</tr>
<tr>
<td>Wisconsin Frost</td>
<td>Red Oak</td>
<td>18mg</td>
<td>0.37</td>
<td>0.1</td>
<td>0.61</td>
<td>0.3</td>
<td>&gt;1</td>
<td></td>
</tr>
<tr>
<td>Domestic</td>
<td>Red Oak</td>
<td>18mg</td>
<td>0.37</td>
<td>0.1</td>
<td>0.31</td>
<td>0.1</td>
<td>&gt;1</td>
<td></td>
</tr>
<tr>
<td>JC Original</td>
<td>Johnson Creek</td>
<td>18mg</td>
<td>0.38</td>
<td>0.03</td>
<td>0.45</td>
<td>0.3</td>
<td>&gt;1</td>
<td></td>
</tr>
<tr>
<td>Coconut</td>
<td>FS-USA</td>
<td>0mg</td>
<td>0.35</td>
<td>0.1</td>
<td>0.68</td>
<td>0.3</td>
<td>&gt;1</td>
<td>0.3</td>
</tr>
<tr>
<td>Peanut Buttercup</td>
<td>FS-USA</td>
<td>24mg</td>
<td>0.36</td>
<td>0.03</td>
<td>0.8</td>
<td>0.3</td>
<td>0.18</td>
<td>0.01</td>
</tr>
<tr>
<td>French Vanilla</td>
<td>Johnson Creek</td>
<td>18mg</td>
<td>0.34</td>
<td>0.1</td>
<td>0.37</td>
<td>0.1</td>
<td>0.97</td>
<td>0.3</td>
</tr>
<tr>
<td>Vanilla Tahiti</td>
<td>FS-USA</td>
<td>0mg</td>
<td>0.36</td>
<td>0.1</td>
<td>0.35</td>
<td>0.1</td>
<td>0.19</td>
<td>0.03</td>
</tr>
<tr>
<td>Tennessee cured</td>
<td>Johnson Creek</td>
<td>18mg</td>
<td>0.26</td>
<td>0.01</td>
<td>0.32</td>
<td>0.1</td>
<td>&gt;1</td>
<td>0.3</td>
</tr>
<tr>
<td>Tennessee cured</td>
<td>Red Oak</td>
<td>18mg</td>
<td>0.32</td>
<td>0.1</td>
<td>0.09</td>
<td>&gt;1</td>
<td>&gt;1</td>
<td>0.03</td>
</tr>
<tr>
<td>Island</td>
<td>Red Oak</td>
<td>18mg</td>
<td>0.24</td>
<td>0.01</td>
<td>0.30</td>
<td>0.1</td>
<td>&gt;1</td>
<td></td>
</tr>
<tr>
<td>Pure Nicotine</td>
<td>FS-USA</td>
<td>100mg</td>
<td>0.23</td>
<td>0.01</td>
<td>0.31</td>
<td>0.1</td>
<td>0.35</td>
<td>0.001</td>
</tr>
<tr>
<td>Valencia</td>
<td>Red Oak</td>
<td>18mg</td>
<td>0.22</td>
<td>0.03</td>
<td>0.31</td>
<td>0.1</td>
<td>&gt;1</td>
<td>0.03</td>
</tr>
<tr>
<td>Tiramisu</td>
<td>FS-USA</td>
<td>0mg</td>
<td>0.12</td>
<td>0.001</td>
<td>0.54</td>
<td>0.01</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Mint Chocolate</td>
<td>Johnson Creek</td>
<td>18mg</td>
<td>0.12</td>
<td>0.01</td>
<td>0.28</td>
<td>0.1</td>
<td>&gt;1</td>
<td>0.1</td>
</tr>
<tr>
<td>Swiss Dark</td>
<td>Red Oak</td>
<td>18mg</td>
<td>0.11</td>
<td>0.03</td>
<td>0.16</td>
<td>0.03</td>
<td>0.30</td>
<td>0.1</td>
</tr>
<tr>
<td>Caramel</td>
<td>FS-USA</td>
<td>0mg</td>
<td>0.1</td>
<td>0.03</td>
<td>0.14</td>
<td>0.03</td>
<td>0.22</td>
<td>0.01</td>
</tr>
<tr>
<td>RY4</td>
<td>Global Smoke</td>
<td>18mg</td>
<td>0.09</td>
<td>0.03</td>
<td>0.09</td>
<td>0.03</td>
<td>&gt;1</td>
<td></td>
</tr>
<tr>
<td>Espresso</td>
<td>Johnson Creek</td>
<td>18mg</td>
<td>0.08</td>
<td>0.01</td>
<td>0.30</td>
<td>0.1</td>
<td>&gt;1</td>
<td>0.3</td>
</tr>
<tr>
<td>Mercado</td>
<td>Red Oak</td>
<td>18mg</td>
<td>0.08</td>
<td>0.01</td>
<td>0.09</td>
<td>0.03</td>
<td>0.82</td>
<td>0.3</td>
</tr>
<tr>
<td>Simply Strawberry</td>
<td>Johnson Creek</td>
<td>18mg</td>
<td>0.06</td>
<td>0.01</td>
<td>0.43</td>
<td>0.3</td>
<td>&gt;1</td>
<td>0.1</td>
</tr>
<tr>
<td>Arctic Menthol</td>
<td>Johnson Creek</td>
<td>18mg</td>
<td>0.05</td>
<td>0.01</td>
<td>0.19</td>
<td>0.1</td>
<td>&gt;1</td>
<td>0.3</td>
</tr>
<tr>
<td>Butterscotch</td>
<td>FS-USA</td>
<td>0mg</td>
<td>0.06</td>
<td>0.03</td>
<td>0.22</td>
<td>0.03</td>
<td>0.26</td>
<td>0.03</td>
</tr>
<tr>
<td>Summer Peach</td>
<td>Johnson Creek</td>
<td>18mg</td>
<td>0.04</td>
<td>0.01</td>
<td>0.45</td>
<td>0.1</td>
<td>&gt;1</td>
<td>0.3</td>
</tr>
<tr>
<td>Black Cherry</td>
<td>Johnson Creek</td>
<td>18mg</td>
<td>0.05</td>
<td>0.01</td>
<td>0.16</td>
<td>0.1</td>
<td>&gt;1</td>
<td>0.3</td>
</tr>
<tr>
<td>JC Original</td>
<td>Johnson Creek</td>
<td>11mg</td>
<td>0.04</td>
<td>0.01</td>
<td>0.46</td>
<td>0.1</td>
<td>&gt;1</td>
<td></td>
</tr>
<tr>
<td>Chocolate Truffle</td>
<td>Johnson Creek</td>
<td>18mg</td>
<td>0.03</td>
<td>0.01</td>
<td>0.26</td>
<td>0.03</td>
<td>&gt;1</td>
<td></td>
</tr>
<tr>
<td>Tennessee cured</td>
<td>Johnson Creek</td>
<td>11mg</td>
<td>0.03</td>
<td>0.01</td>
<td>0.30</td>
<td>0.1</td>
<td>&gt;1</td>
<td>0.001</td>
</tr>
<tr>
<td>Cinnamon Ceylon</td>
<td>FS-USA</td>
<td>0mg</td>
<td>0.01</td>
<td>0.01</td>
<td>0.04</td>
<td>0.01</td>
<td>0.07</td>
<td>0.03</td>
</tr>
<tr>
<td>Butterscotch²</td>
<td>Freedom Smoke</td>
<td>0mg</td>
<td>-</td>
<td></td>
<td>0.58</td>
<td>0.3</td>
<td>0.26</td>
<td>0.03</td>
</tr>
</tbody>
</table>

**Cytotoxicity**

- **Low** (IC$_{50}$ > 1%)  
- **Moderate** (0.1% < IC$_{50}$ < 1%)  
- **High** (IC$_{50}$ < 0.1%)

Bahl et al 2012
Cytotoxicity of Refill Fluids from Four Companies

Bahl et al. 2012

Products ranged over all three categories of cytotoxicity for all the cell types.

- Most products were highly/moderately cytotoxic to stem cells and non-cytotoxic to hPF.
Follow-up On Cinnamon-Flavored Refill Fluids

Gas Chromatography-Mass Spectrometry was Used to Identify Chemicals in Cinnamon Ceylon

Cinnamaldehyde  2-Methoxycinnamaldehyde  Dipropylene glycol  Vanillin

HIGH  HIGH  LOW  LOW

MTT Assay Was Used to Evaluate Cytotoxicity of Authentic Standards

Behar et al
Doses Were Prepared So Fluids and Aerosols Could Be Compared

Refill fluid

Culture Medium

Aerosol
Cytotoxicity of Aerosol vs Fluids – hPF
19 Products Compared

68%: Refill fluids and aerosols were equally cytotoxic. N = 13

11%: Refill fluid was more cytotoxic than the aerosol. N = 2

21%: Aerosol was more cytotoxic than the refill fluid. N = 4
Cytotoxicity Done on European EC Products

- Examined aerosol from 21 EC products – compared to cigarette smoke.
- Used mouse/BALB 3T3 cells –a mouse embryonic fibroblast line
- Incubated 24 hours with test dilutions of aerosol or smoke.
- Used IC₃₀ to define cytotoxicity.
- Found cigarette smoke more cytotoxic than EC aerosol.
- Found one EC aerosol (Coffee flavor) that was cytotoxic.
Examples of Studies Done With Human EC Users
Complete Blood Cell Count Markers Not Affected in EC Users and Those Passively Exposed

Flouris et al 2012 Food and Chemical Toxicology

- Effect of EC and CC use on complete blood cell count.

- Blood cell count increased in those actively or passively smoking tobacco cigarettes.

- Blood cell count was not significantly affected in those actively or passively using EC.
Safety Assessment of EC in Smokers

• 32 smokers used EC for 4 weeks (more than 150 EC puffs/day)

• No abnormal changes in:
  • Blood pressure
  • Hematological data
  • Blood chemistry

No severe adverse events were observed.

Concluded this EC may be a safe alternative to smoking.
Reviews recent EC peer reviewed and “grey” literature and makes predictions about compliance with occupational exposure limits.

Concluded individual and combined exposures to contaminants in EC fall below thresholds for concern for compounds with known toxicity, including:
- volatile organic chemicals (VOCs),
- tobacco specific nitrosamines (TSNA), polycyclic aromatic hydrocarbons (PAHs),
- metals.

Recommends monitoring health effects related to propylene glycol and glycerin. Magnitude of the exposure is novel and at levels for concern given the lack of data on inhalation of these chemicals at levels found in EC aerosol.

Does not consider inhalation of flavoring chemicals.
Adverse Events Reported to the FDA
Chen 2012 Nicotine & Tobacco Research

N = 47 since 2008

- Hospitalization for:
  - pneumonia,
  - congestive heart failure,
  - disorientation,
  - seizure,
  - hypotension,
  - aspiration pneumonia,
  - second degree burns to face (explosion),
  - chest pain and rapid heart beat,
  - possible infant death secondary to choking on EC,
  - loss of vision requiring surgery

N = 8

- False advertising
- Headache/migraine
- Chest pain
- Cough/sputum
- Nausea/vomiting
- Dizziness
- Sleepy/tired
- Feeling sick
- Confusion/stupor
- Sore throat
- Shortness of breath
- Abdominal pain
- Pleurisy
- Blurry vision

N = 39

https://www.accessdata.fda.gov/scripts/medwatch/
Short Term Pulmonary Effects Using an EC

Evaluation of immediate effects of EC aerosol inhalation on airway mechanics

- 30 healthy smokers – ad lib use of EC for 5 minutes
- Controls used EC with cartridge removed
- Four parameters of lung physiology were adversely affected by 5 minutes of inhalation of EC aerosol
- Concluded short term EC use produce adverse effects similar to those seen with conventional cigarettes
- Above changes were statistically different in controls and EC users but may not be of major clinical importance
EC: Do They have a Role in Smoking Cessation?
Odum et al 2012 Journal of Pharmacy Practice 25: 611

Table 1. Undesirable Side Effects of E-Cigarettes

<table>
<thead>
<tr>
<th>Design</th>
<th>Survey(^{15a})</th>
<th>Survey(^{16b})</th>
<th>Randomized Cross-over</th>
<th>Observational(^{19c})</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>81</td>
<td>3037</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Duration</td>
<td>N/A</td>
<td>N/A</td>
<td>9 hours Per product</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Throat</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth and/or throat</td>
<td>26.2%</td>
<td>26.2%</td>
<td>N/A</td>
<td>8.8%</td>
</tr>
<tr>
<td>Burning/sore throat</td>
<td>N/A</td>
<td>22.1%</td>
<td>N/A</td>
<td>11.8%</td>
</tr>
<tr>
<td>Mouth and throat irritation</td>
<td>N/A</td>
<td>N/A</td>
<td>38%</td>
<td>N/A</td>
</tr>
<tr>
<td>Mouth irritation</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>20.6%</td>
</tr>
<tr>
<td>Throat irritation</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>32.4%</td>
</tr>
<tr>
<td>Dry cough</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>32.4%</td>
</tr>
<tr>
<td>Central nervous system</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertigo, headache, nausea</td>
<td>11.5%</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Vertigo/dizziness</td>
<td>N/A</td>
<td>N/A</td>
<td>21%</td>
<td>14.7%</td>
</tr>
<tr>
<td>Headache</td>
<td>N/A</td>
<td>N/A</td>
<td>18%</td>
<td>11.8%</td>
</tr>
<tr>
<td>Nausea</td>
<td>N/A</td>
<td>N/A</td>
<td>29%</td>
<td>14.7%</td>
</tr>
</tbody>
</table>

Abbreviation: N/A, not applicable or not reported.
\(^{a}\)Values reflect percentage of comments of undesirable effects, not the percentage of patients due to the open-ended question format of the survey. The remaining values in the table reflect percentage of patients.
\(^{b}\)Values reported are for the 16 mg nicotine e-cigarette.
\(^{c}\)Values reported are at week 4.

Bullen et al 2010 Tob Control 19:98
Etter and Bullen 2011 Addiction 106: 2017
Etter 2010 BMC Public Health 10:231

- Case study of 18 month old girl who drinks about 2ml of EC refill fluid
- Rushed to emergency room with signs of nicotine poisoning
- Was given IV fluids and monitored 24 hours
- Her tachycardia and hypertension resolved
- Was discharged and appeared to be ok
- Parents were educated about safe storage of EC refill fluids.
EC Use Linked to Exogenous Lipoid Pneumonia

• EC user presented with exogenous lipoid pneumonia
  • Had been using EC about 7 months

• Inflammation caused by deposition of lipid in the lungs

• Chest CT showed opacities consistent with lipoid pneumonia.

• Macrophages in bronchoalveolar lavage fluid were loaded with lipid.

• Patient stopped using EC and her condition improved.

• Hypothesized condition may have been caused by inhaling EC aerosol.
• Infodemiological Approach

• Total number of EC users = 492

• 405 different symptoms reported

• 78 positive symptoms

• 326 negative symptoms

• 12 Systems affected in EC users

Hua et al 2013 JIMR 15: e59.
Do EC Reduce the Risk of Cancer?

• This hypothesis is supported by lower levels of carcinogens (TSNA and PAHs) in EC aerosol than in cigarette smoke. (e.g. Goniewicz 2013 Tob Control)

• It will take long-term studies to know if using EC reduces the risk of cancer.

• Because many individuals use EC, these studies could begin now.
Other Public Health Concerns

• EC may be a viable harm reduction product that reduces health risks in individuals who use EC instead of conventional cigarettes.

• Current smokers may become addicted to EC rather than quit smoking.

• EC may be gateway products that attract young non-smokers.

• Use of EC in public places is being debated.
Overall Summary

- EC products vary in their cytotoxicity, and flavorings should be tested carefully, as they can contribute to cytotoxicity.

- Stem cells were more sensitive to refill fluids than differentiated adult cells.

- Experimental and infodemiological studies and surveys report both positive and negative health effects associated with EC use.

- It will be a number of years until we know the long-term health effects of EC, including their effect on cancer. Cancer is a major public health question. But it is not the only question.

- Much more work needs to be done on EC and their health effects.
Thanks to:

- Dr. Sabrina Lin
- Vasu Bahl
- Barbara Davis
- Rachel Behar
- Crystal Hua
- Yuhuan Wang
- Nicole Xu
- Mina Alfi
- Alex Razo
- Michael Dang
- Anna Trtchounian
- Monique Williams

Funding provided by TRDRP
UCR Deans Fellowships
Cornelius Hopper Fellowships

mNSC provided by Dr. Evan Snyder