Public Health Consequences of E-Cigarettes

January 23, 2018
Committee

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Statement of Task

• Evaluate the available evidence of the health effects related to the use of electronic nicotine delivery systems (ENDS)
• Identify future federally funded research needs
Terminology: What are E-Cigarettes?

• Heterogeneous group of products that are referred to using a widely variably terminology (e.g., ENDS, electronic cigarettes, vaporizers, mods, tanks)
• May or may not contain nicotine*
• Excludes heat-not-burn products*

*As clarified by Mitchell Zeller, Director of FDA Center for Tobacco Products, at the committee’s first meeting
Report Organization

Section I: E-Cigarette Devices, Constituents, and Exposures

Section II: Effects of E-Cigarettes on Health

Section III: Public Health Implications of E-Cigarettes
Committee Approach

• Literature Search
  – February 1, 2017 to August 31, 2017
  – 6 databases
  – Approximately 4,200 unique results identified; over 800 reviewed for the report

• Literature Review and Quality Assessment

• Approach to Assessing Causality
  – Evidence Synthesis (Hill’s criteria)

• Levels of Evidence and Conclusions
Approach to Assessing Causality

• First examined evidence on distal health outcomes [E], then moved up the causal chain to intermediate/short-term outcomes, mechanisms/modes of action, and exposures.

• Considered human data most relevant and animal data supportive.

• In vitro data useful for hypothesis generation and understanding mechanisms, but relevance for establishing human health risk uncertain.

Source: Figure 2-1
Levels of Evidence Framework

- Conclusive
- Substantial
- Moderate
- Limited
- Insufficient
- No available
  (not evidence of no effect)

- More, higher quality studies (e.g., randomized and non-randomized controlled studies)
- Conclusions can be made
- Greater confidence that limitations (including chance, bias, and confounding factors) can be ruled out
Devices, Uses, and Exposures

* shown to demonstrate approximate scale

a. Generic Combustible Tobacco Cigarette
b. First Generation E-Cigarette
c. Second Generation E-Cigarette
d. Third Generation E-Cigarette

Source: Figure 3-1

DISCLAIMER
These illustrations are intended to be generic representations of a device within each of the depicted categories. They are not meant to represent or endorse any specific product or manufacturer.
Toxicology of Constituents

• **Conclusive evidence that ...**
  – *most e-cigarette products contain and emit numerous potentially toxic substances.* [5-1]
  – *the number, quantity, and characteristics of [these] substances emitted ... is highly variable and depends on product characteristics ... and how the device is operated.* [5-2]

• **Substantial evidence that ... under typical conditions of use, exposure to potentially toxic substances from e-cigarettes is significantly lower compared with combustible tobacco cigarettes.* [5-3]
Nicotine

• *Conclusive evidence* that exposure to nicotine from e-cigarettes is highly variable and depends on product characteristics ... and how the device is operated. [4-1]

• *Substantial evidence* that nicotine intake from e-cigarette devices among experienced adult e-cigarette users can be comparable to that from combustible tobacco cigarettes.[4-2]
Metals

- **Substantial evidence** that e-cigarette aerosol contains metals [5-4]
- **Limited evidence** that the number of metals in e-cigarette aerosol could be greater than the number of metals in combustible tobacco cigarettes.* [5-5]

*Except for cadmium, which is markedly lower in e-cigarettes compared with combustible tobacco cigarettes
Health Effects Evaluated

• Modes of Action
  – Endothelial Cell Dysfunction
  – Oxidative Stress

• Dependence & Abuse Liability

• Cardiovascular Diseases

• Cancers

• Respiratory Diseases

• Oral Diseases

• Reproductive & Developmental Effects

• Injuries & Poisonings
Approach to Evaluation of Health Effects

• Characterization of Disease Endpoints and Intermediate Outcomes
• Optimal Study Design
• Questions Addressed by the Literature
  • Considered comparisons to unexposed and to smokers as appropriate
• Evidence Review
• Synthesis and Conclusions
• Vulnerable/Susceptible Populations
Dependence & Abuse Liability

• **Substantial evidence** that e-cigarette use results in symptoms of dependence on e-cigarettes[8-1]

• **Moderate evidence** that
  – risk and severity of dependence are lower for e-cigarettes than combustible tobacco cigarettes [8-2]
  – variability in e-cigarette product characteristics ... is an important determinant of risk and severity [8-3]
Cardiovascular Diseases

• **No available evidence** whether or not e-cigarette use is associated with clinical cardiovascular outcomes ... and subclinical atherosclerosis [9-1]

• Substantial evidence that heart rate increases after nicotine intake from e-cigarettes [9-2]

• Moderate evidence that diastolic blood pressure increases after nicotine intake from e-cigarettes [9-3]
Cardiovascular Diseases

- Limited evidence that e-cigarette use is associated with a short-term increase in systolic blood pressure, changes in biomarkers of oxidative stress, increased endothelial dysfunction and arterial stiffness, and autonomic control. [9-4]

- Insufficient evidence that e-cigarette use is associated with long-term changes in heart rate, blood pressure, and cardiac geometry and function. [9-5]
Cancers

- **Limited evidence from in vivo animal studies using intermediate biomarkers of cancer to support the hypothesis that long-term e-cigarette use could increase the risk of cancer** [but] **no available evidence whether or not e-cigarette use is associated with intermediate cancer endpoints in humans** * [10-1, 10-2]

*True for comparisons with both combustible tobacco cigarettes and with no use of tobacco products*
Cancers

- **No available evidence** from adequate long-term animal bioassays of e-cigarette aerosol exposures to inform cancer risk [10-2]
- **Limited evidence** that e-cigarette aerosol can be mutagenic or cause DNA damage in humans, animal models, and human cells in culture [10-3]
- **Substantial evidence** that some chemicals present in e-cigarette aerosols are capable of causing DNA damage and mutagenesis* ... Whether or not the levels of exposure are high enough to contribute to human carcinogenesis remains to be determined [10-4]

*Supports the biological plausibility that long-term exposure to e-cigarette aerosols could increase risk of cancer and adverse reproductive outcomes
Respiratory Diseases

• **No available evidence whether or not e-cigarettes cause respiratory diseases in humans** [11-1]
• *Moderate evidence for increased cough and wheeze in adolescents who use e-cigarettes and an association with e-cigarette use and an increase in asthma exacerbations* [11-4]
• *Limited evidence of adverse effects of e-cigarette exposure on the respiratory system from animal and in vitro studies* [11-5]
Respiratory Diseases

• Limited evidence for
  – improvement in lung function and respiratory symptoms among adult smokers with asthma who switch to e-cigarettes completely or in part (dual use) [11-2]
  – reduction of COPD exacerbations among adult smokers with COPD who switch to e-cigarettes completely or in part (dual use) [11-3]
Injuries & Poisonings

- Conclusive evidence that...
  - e-cigarette devices can explode and cause burns and projectile injuries ... [especially] when batteries are of poor quality, stored improperly, or are being modified by users [14-1]
  - intentional or accidental exposure to e-liquids (from drinking, eye contact, or dermal contact) can result in adverse health effects ... and can be fatal [14-2, 14-3]
Public Health Implications of E-Cigarettes

• Smoking among Youth and Young Adults
• Smoking Cessation among Adults
• Harm Reduction
• Modeling of E-Cigarette Use
Youth & Young Adult Smoking: Ever Use

• **Substantial evidence** that e-cigarette use increases risk of ever using combustible tobacco cigarettes among youth and young adults [16-1]
Youth & Young Adult Smoking: Smoking Progression

Among youth and young adult e-cigarette users who ever use combustible tobacco cigarettes:

- **Moderate evidence** that e-cigarette use increases the frequency and intensity of subsequent combustible tobacco cigarette smoking [16-2]

- **Limited evidence** that e-cigarette use increases, in the near term, the duration of subsequent combustible tobacco cigarette smoking [16-3]
Adult Smoking Cessation

**Limited evidence that e-cigarettes may be effective aids to promote smoking cessation overall**\(^a\, b\) [17-1]

\(^a\) Very little data from randomized controlled trials

\(^b\) Results of trials and observational studies often differ
Adult Smoking Cessation

• **Moderate evidence** from randomized controlled trials that e-cigarettes with nicotine are more effective than e-cigarettes without nicotine for smoking cessation [17-2]

• **Insufficient evidence** from randomized controlled trials about the effectiveness of e-cigarettes as cessation aids compared with no treatment or to FDA-approved smoking cessation treatments [17-3]

• **Moderate evidence** from observational studies that more frequent use of e-cigarettes is associated with increased likelihood of cessation [17-4]
Harm Reduction: Complete Switching

• **Conclusive evidence** that completely substituting e-cigarettes for combustible tobacco cigarettes reduces users’ exposure to numerous toxicants and carcinogens present in combustible tobacco cigarettes [18-1]

• **Substantial evidence** that completely switching from regular use of combustible tobacco cigarettes to e-cigarettes results in reduced short-term adverse health outcomes in several organ systems [18-2]
Harm Reduction: Dual Use

• **No available evidence** whether or not long-term e-cigarette use among smokers (dual use) changes morbidity or mortality compared with those who only smoke combustible tobacco cigarettes [18-3]

• **Insufficient evidence** that e-cigarette use changes short-term adverse health outcomes in several organ systems in smokers who continue to smoke combustible tobacco cigarettes (dual users) [18-4]
Secondhand Exposure

• **Conclusive evidence** that e-cigarette use increases airborne concentrations of particulate matter and nicotine in indoor environments compared with **background** levels [3-1]

• **Moderate evidence** that secondhand exposure to nicotine and particulates is lower from e-cigarettes compared with **combustible tobacco cigarettes** [18-5]

• **Limited evidence** that e-cigarette use increases levels of nicotine and other e-cigarette constituents on a variety of indoor surfaces compared with background levels. [3-2]
Modeling of E-cigarette Use

- Mendez-Warner model of smoking prevalence and health effects
- Range of assumptions about e-cigarette effects on:
  - Smoking initiation rate (0, 5, 10, 25, and 50% increase),
  - Smoking cessation rate (-5, 0, 5, 10, and 15% increase), and
  - Relative harm of e-cigarettes compared to combustible tobacco cigarettes (0, 10, 25, and 50% as harmful)
- Period: 2015-2050 and 2015-2070
- Outcomes: life years lost/gained because of e-cigarettes compared to the status-quo (no e-cigarette effects)
## Modeling of E-cigarette Use

### 2015-2050

**Life-years lost due to e-cigs (in Millions)**

E-cigs = 10% x risk of combustibles

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### 2015-2070

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Cessation Increases by

-5%  0%  5%  10%  15%
Modeling of E-cigarette Use

If e-cigarettes increase smoking initiation by 5% and smoking cessation by 15% from 2015 on, there would be a net 3.1 million cumulative life-years saved by the year 2050.
### Modeling of E-cigarette Use

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If e-cigarettes increase smoking initiation by 50% and decrease smoking cessation by 5% from 2015 on, there would be a net 9.3 million cumulative life-years lost by the year 2070.

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If e-cigarettes increase smoking initiation by 5% and smoking cessation by 15% from 2015 on, there would be a net 3.1 million cumulative life-years saved by the year 2050.
## Modeling of E-cigarette Use

### Life-years lost due to e-cigs (in Millions)

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Modeling of E-cigarette Use

• In all scenarios where e-cigarettes increase the smoking cessation rate, the modeling projects that use of these products will generate a net public health benefit at least in the short run (by 2050)

• The harms from increased initiation by youth will take time to manifest, occurring decades after the benefits of increased cessation are seen
Modeling of E-cigarette Use

• For long-range projections (e.g., 50 years out), the net public health benefit is substantially less, and is negative under some scenarios due to the harms from increased initiation.

• If e-cigarette use does not increase the smoking cessation rate, the model projects that there would be net public health harm in the short and long term
Modeling of E-cigarette Use

• While there is uncertainty about the relative harm of e-cigarettes compared to combustible tobacco and their effect on smoking initiation and cessation, the available evidence suggests that:
  – E-cigarettes are likely to be substantially less harmful than combustible tobacco
  – E-cigarette use is not likely to increase the smoking initiation rate by more than 10%
  – E-cigarette use is likely to increase the smoking cessation rate within the 5% - 15% range
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Note: The values in parentheses indicate the decrease in life-years lost due to e-cigs compared to combustibles.
Modeling of E-cigarette Use

• The modeling results suggest that, under likely scenarios, the use of e-cigarettes in the population will result in a net public health benefit.

• Under extreme adverse assumptions, the modeling projects a net public health loss
Moving Forward

• More and better research is needed to clarify the short-and long-term health effects of e-cigarettes in individuals and populations

• The committee’s approach to evaluating the health effects of e-cigarettes provides a generalizable template for future evaluations of the evidence
Research Needs

This is not an intractable problem; See Handout

Each of the three major sections of the report ends with a chapter on research needs with specific suggestions to:

1. Address Gaps in Substantive Knowledge
2. Improve Research Methods and Quality
Research Needs, for example

• Research into e-cigarette device and liquid characteristics to inform product standards
• Cohort studies to compare clinical and subclinical heath outcomes among e-cigarette users vs. combustible tobacco users
• Observational studies to assess the relationship between youth use of e-cigarettes and subsequent progression to regular smoking of combustible tobacco products
• Randomized controlled trials of the effectiveness of e-cigarettes as cessation aids, especially compared with FDA-approved smoking cessation aids
Summary

• While e-cigarettes are not without health risks, they are likely to be far less harmful than combustible tobacco cigarettes.

• E-cigarettes contain fewer numbers and lower levels of toxic substances than conventional cigarettes

• The long-term health effects of e-cigarettes are not yet clear.
Summary

• Using e-cigarettes may help adults who smoke combustible tobacco cigarettes quit smoking, but more research is needed.

• Among youth, e-cigarette use increases the risk of initiating smoking combustible tobacco cigarettes.
Visit [nationalacademies.org/eCigHealthEffects](nationalacademies.org/eCigHealthEffects) to download the full report.

For more information, Kathleen Stratton (kstratton@nas.edu)

Thank you!